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Approaches to the synthesis of 9-member C-C rings through novel benzofuranyl C-glycosides

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Approaches to the synthesis of 9-member C-C rings through novel Benzofuranyl C-Glycosides

by

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10th Sept. 1993
Date

Chair of Examining Committee

Sept. 14, 1993
Date

Executive Officer

Supervisory Committee

The City University of New York

Abstract

Approaches to the Synthesis of 9-member C-C rings through novel Benzofuranyl C-Glycosides

by

Panayiotis C. Meleties

Advisor: Professor Vernon G. S. Box

The novel non natural 6-C-benzofuranylglycosides were synthesized from 4-bromobenzofuran derivatives and protected carbohydrate lactones. An intramolecular nucleophilic reaction between the benzofuranyl moiety (position 3) and the anomeric carbon will lead to the 9-member C-C ring.

The synthesis of the 4-bromobenzofuran derivatives was achieved either by [3,3] aromatic Claisen rearrangement or by condensation of salicylaldehyde derivatives with α-haloketones. The 2-acylbenzofuran derivatives were deoxygenated either directly or after reduction and methylation by a novel application of the $TMSCl/NaBH_3CN$ reagent. Bromine-lithium exchange yielded the 4-lithiated benzofuran derivatives, which were used for the synthesis of the 6-C-benzofuranyl glycosides.

Protected derivatives of glucurono-6,3-lactone, and idofurano-6,3-lactone were synthesized and allowed to react with the 4-lithiated benzofuran derivatives to produce the novel 6-C-benzofuranyl glycosides. Reduction and dehydration yielded a pair of diastereomeric 6-endo or exo-C-benzofuranyl-[1,4:3,6]-difuranosides. Deprotection of the difuranosides with the I_2/MeOH reaction led to the mixture of the four possible diastereomeric 1-methoxy-6-C-benzofuranyl-[1,4:3,6]-difurano-2,5-diols arising from the anomeric center and the scrambling of the stereogenic center at C_6.

This thesis is dedicated to my mother and father.

Acknowledgements

I would like to extend my sincere thanks to the persons who in many ways invested time and effort contributing to the accomplishment of this work:

Professor Vernon Box, my thesis advisor who introduced me to the world of scientific research, expanded my intellectual capabilities and provided a constant stimulation and interest for this research.

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I would also like to thank professor Theodore Axenrod and his graduate students, for acquiring the ^1H NOE and ^1H COSY NMR spectra.

The research facilities and the financial support provided by the City College are greatly appreciated. Mr. Ramsey Pal was very helpful in the acquisition of all the mass spectra.

I would also like to thank my wife Niki for typing the entire manuscript and for her patience, endurance and understanding that helped complete this work.

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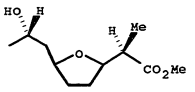
Introduction

Carbohydrates have been widely used for the total syntheses[1-3] of a plethora of natural products. Many natural products have complex structures involving extended carbon chains with long sequences of stereogenic centers bearing hydroxy groups. This suggests that chiral templates, synthesized from simple carbohydrate molecules, would be useful precursors. Examples of molecules that are attractive targets for such syntheses are the families of Erythronolide[3] and Tylonide[1] antibiotics. Natural products with structures less complicated have also been totally synthesized starting with carbohydrate molecules. In such simpler cases like the Multistratin pheromone it is not an extended chiral C-chain that is provided by the carbohydrate, but a crucial stereogenic center (sch. 1).

The C-chains bearing various combinations of carbinol stereogenic centers, that can be used for the introduction of a large number of functional groups, establish the carbohydrate molecules as a unique and invaluable synthetic unit. The incorporation of such a molecule in a synthetic scheme usually leads to an intermediate with high chirality per carbon and high functionality content. Such chiral template - intermediates usually need only minor modifications, achieved by simple high yield chemical reactions, to reach the synthetic target.

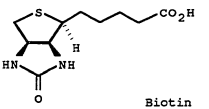
Scheme 1

D-Ribose



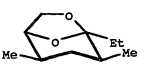
(-)-Methyl nonacetate

D-Mannose



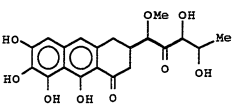
Biotin

D-Mannitol



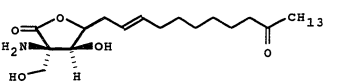
(-))-Multistratin

D-Arabinose



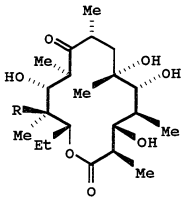
Chromomycinone

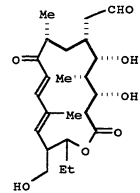
L-Arabinose



(-)-Anhydromyrocin

D-Glucose



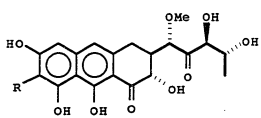


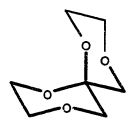
R = OH Erythronolide A
R = H Erythronolide B

Tylonide

D-Galactose

D-Fructose



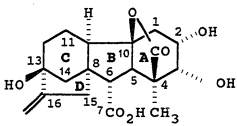


OLIVIN

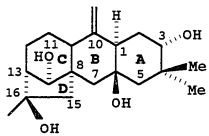
[2,2]-spirotetrahydro pyran(sex pheromone of the olive fruit fly)

Structures obtained from ref. 1.

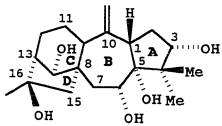
Scheme 2



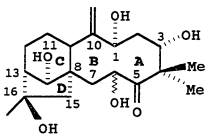
Gibberellic acid GA8



Leucothol



Grayanotoxin II



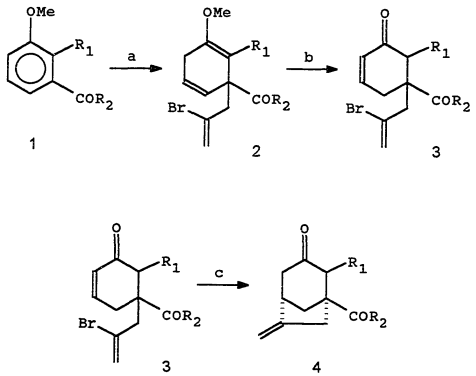
Grayanol A 6(S)
Grayanol B 6(R)

The sequence of the stereogenic centers and the functional groups present on the rings A, B in the gibberellin GA8[4,5], grayanotoxin II, grayanols A, B and leucothol D[6,7], encourage the use of a carbohydrate fragment in a novel synthetic approach. A synthetic scheme which unlike to the reported syntheses[8] would be based on a chiral template derived from a C-glycoside.

Retrosynthetic analysis

The most profound common characteristics in all four molecules are the fused rings C,D. It has been demonstrated that such a system could be obtained by a Birch reduction-alkylation[9,10], followed by a free radical cyclization[11] of the intermediate halide 3 (sch. 3).

Scheme 3



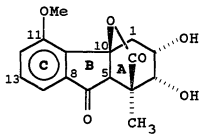
1 2 3 3 4

a) Li, NH_3, 2,3-dibropropene, b) H^+, H_2O, c) Bu_3SnH, AIBN.

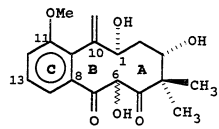
By substituting for the C, D fused rings the appropriately substituted parent aromatic ring, the intermediates 5 from GA8 and 6 from the grayanols are obtained

(sch. 4). The grayanols A, B are considered to be the parent compounds to grayanotoxin II and leucothol D.

Scheme 4



5



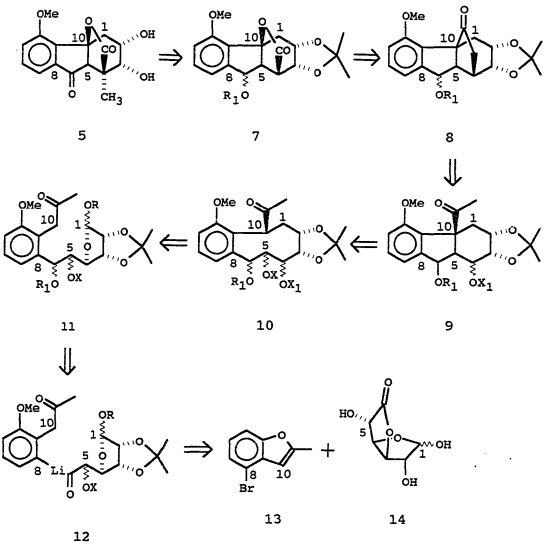
6

Retrosynthetic approach to the gibberellin skeleton

The carbonyl group on C_6 is necessary to control the Birch reduction-alkylation step. A protected oxygen functionality could be the parent group for that. The hydroxy-groups on carbons 2, 3 would also be protected. The syn conformation favors an acetal protecting group, 7 (sch. 5).

The lactone bridge of 5 could be constructed by a Baeyer-Villiger oxidation[12] of the corresponding ketone 8. An extra carbon may be used to generate a cyclopentanone ring 8 instead of the actual cyclobutanone precursor of 7. That extra carbon could be removed after the six member ring lactone is formed by degradative oxidation[12] to the 5-member ring lactone.

Scheme 5



The cyclopentanone bridge of intermediate 8 could be formed from the intramolecular reaction of the silyl enolate of methyl ketone 9 with an oxygen functionality at C_4 under Lewis Acid catalysis. The same ketone group is the key group that is to be used to form the C_{10}-C_1 and C_{10}-C_5 bonds. The C_{10}-C_5 bond could be formed from the intramolecular reaction of the corresponding enolate of the ketone 10

with an activated oxygen good leaving group at C_5, under Lewis Acid catalysis if necessary. The C_{10}-C_1 bond could be formed from the reaction of the corresponding enolate of ketone 11 with an activated electrophilic center at C_1. Combining the need for an activated C_1 and the need to have a protected oxygen functionality at C_4 until the later stages of the synthetic scheme a carbohydrate furanose ring could be the best choice. The anomeric center of 11 being the C_1 would be the first to be activated.

Cleavage of the C_6-aromatic ring bond of 11 generates the two major synthons. The aromatic ring has the 3-position activated as Grignard (lithium) reagent and bears a 2-alkyl chain. The need for the 3-methoxy on the benzene ring (Birch reduction, sch. 3, pg 5), and the 2-alkyl chain with a β-carbonyl group, which would participate in two intramolecular C-C bond formations through its enolate, could be combined into a 4-bromobenzofuran 13.

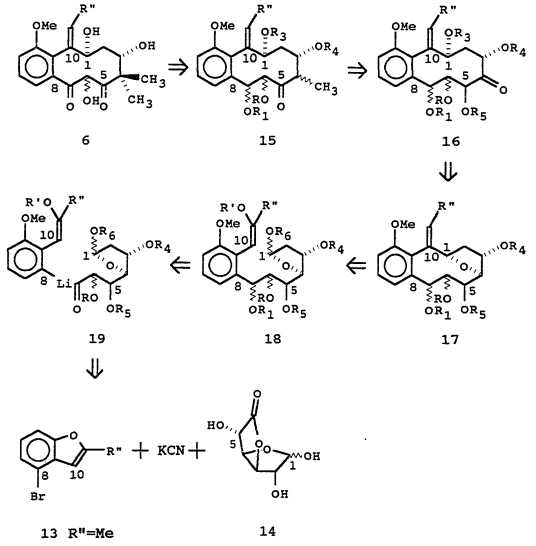
The non aromatic synthon could be a 6-carbon carbohydrate molecule with two initially active sides, the anomeric center at C_1 and a carbonyl group at C_6. The chosen carbohydrate is 6,3-glucofuranuronolactone 14.

Retrosynthetic approach to the grayanol skeleton

The grayanotoxin intermediate 6 (sch. 6) could be obtained from a methylation reaction of the enolate derived from the ketone 15. The first methyl group at C_4 could be introduced by a Wittig reaction (followed by hydrogenation) on the ketone 16. The ketone 16 could be the product of oxidation of a hydroxy group at C_4. That hydroxy group and the protected hydroxy at C_1 could be the basis for the 1,4-furanose ring protecting both at the same time (17).

The C_{10}-C_1 bond could be formed from an intramolecular reaction between an enolate of the side chain from the aromatic ring and the activated hydroxy group on C_1 (18), such as an anomeric center of a carbohydrate furanose ring.

Scheme 6



The resulting carbonyl from that enolate would be reduced to alcohol and dehydrated to the double bond. The need for the 3-methoxy (Birch reduction, sch. 3, pg 5) and the 2-enolate on the benzene ring could be combined best in a benzofuranyl unit. For R" = CH_3 the 4-bromobenzofuran derivative 13, proposed from the approach to GA8 could also be used. The extra carbon could be removed by degradative oxidation[12].

The C_7-C_8 bond would be formed by an intermolecular reaction from an aromatic anionic species, such as a Grignard reagent, and a carbonyl group on C_7. This reaction has identified the two synthons required. The aromatic which could be obtained from a 4-bromo-benzofuran derivative and a 7-carbon carbohydrate unit. That unit could be obtained from the reaction of a 6-carbon carbohydrate molecule and KCN. The 6-carbon unit could also be, the 6,3-glucofuranuronolactone 14. The deoxygenation of C_2 could be easily achieved by a simple Barton deoxygenation.

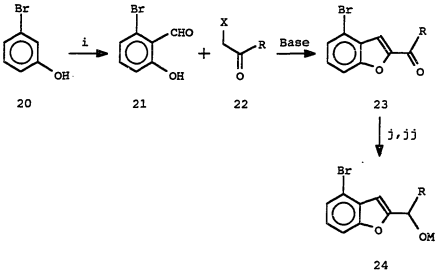
The retrosynthetic analyses for intermediates 5 and 6 point out to two key step reactions. The initial intermolecular reaction between the aromatic synthon and the carbohydrate carbonyl group and the intramolecular glycosidation reaction to form the macrocyclic glycosides 10 (sch. 5) and 17 (sch. 6). Those macrocyclic glycosides are the key chirai-templates that the synthesis of the molecular skeleta and finally the total synthesis of the natural products would be based on. The cyclic glycoside 10 is the primary synthetic target of this endeavor.

Synthetic plan

Synthesis of 4-bromobenzofuran

The proposed synthetic plan for the synthesis of the chiral templates 10 and 17 begins with the synthesis of the benzofuran 13. Meta bromophenol 20 can be formylated[13] to the 6-bromo salicylaldehyde 21. Aldehyde 21 undergoes cyclization with α-haloketone[14] 22 to give the 2-acyl-benzofuran 23. Reduction and methylation reactions should lead to benzofuran 24 (sch. 7).

Scheme 7



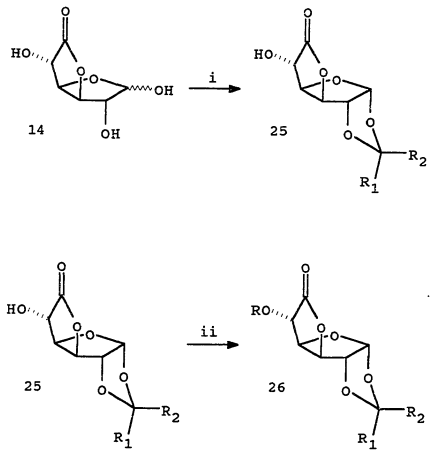
20 21 22 23 24

i) $CHCl_3$, NaOH 50%, j) $NaBH_4$, jj) Methylation (Me_2SO_4).

Protection of glucofuranurono-6,3-lactone

Glucuruno-6,3-lactone 14 is to be protected as 1,2-O,O-benzylidene or 1,2-O,O-isopropylidene acetal 25. The remaining free 5-OH would be protected as a silyl ether to obtain the substrate 26 (sch. 8).

Scheme 8



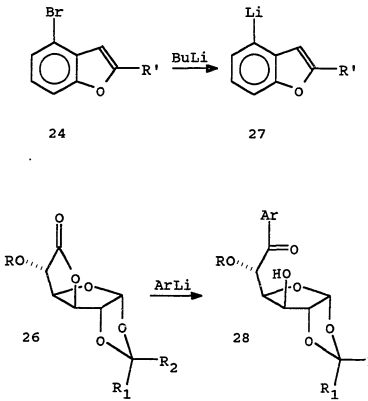
i) Acetone, con.H_2SO_4 (R_1 = R_2 = Me), or benzaldehyde, $ZnCl_2$ (R_1 = H, R_2 = Ph),

ii) TBDMSCl, Imidazole, DMF (R = TBDMS).

Synthesis of the C-glycosides

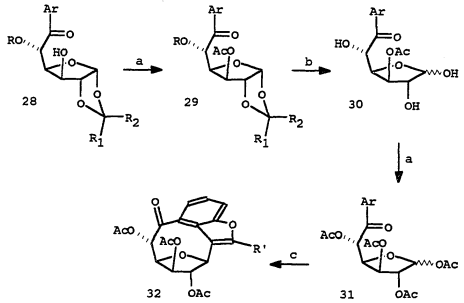
A bromine-lithium exchange on 4-bromobenzofuran 24 would generate the lithiated intermediate 27. That will react with the protected lactone 26 to form the keto-alcohol 28 (sch. 9).

Scheme 9



24=ArLi, R_1=R_2=Me, or R_1=H, R_2=Ph, R=TBDMS

Scheme 10

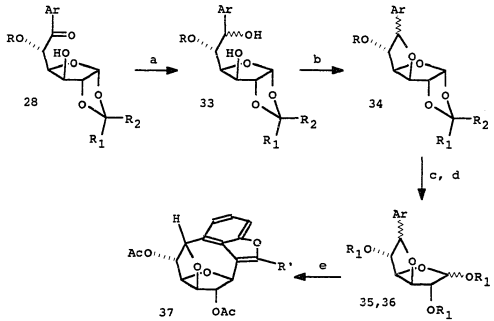


a) Ac_2O, pyridine, b) i) TBAF, ii) AcOH 80%, c) $SnCl_4$
(R_1=R_2=Me, or R_1=H, R_2=Ph, R=TBDMS).

Ketoalcohol 28 will be the beginning compound for two reaction sequences that will lead to the final substrates, on which the macrocyclic cyclization will be attempted.

Acetylation of ketoalcohol 28 will yield the acetate 29. Cleavage of the silylether with fluoride ions and hydrolysis of the acetal in 80% acetic acid should yield triol 30. Triol 30 will be acetylated to the tetraacetate 31. Treatment of the tetraacetate 31 with Lewis Acid catalysts[15-19], particularly $SnCl_4$, is expected to force the cyclization to compound 32 (sch. 10).

Scheme 11



a) $NaBH_4$, b) dehydration, c) i) TBAF, ii) AcOH 80%, d) Ac_2O, pyridine, e) $SnCl_4$, ($R_1 = R_2 =$ Me, or $R_1 =$ H, $R_2 =$ Ph, R =TBDMS).

Reduction of the ketoalcohol 28 should produce diol 33. Cyclization by dehydration of the diol 33 is expected to give a mixture of glycosides 34. Deprotection with fluoride ions of the silyl ether followed by acidic hydrolysis of the acetal will lead to the mixture of triols 35. Acetylation will yield the corresponding triacetates 35, 36. Treatment of the triacetates 36 with Lewis Acid catalysts[15-19] will be expected to force the cyclization of the 6-C- glycoside with the right stereochemistry at C_6 to the compound 37 (sch. 11).

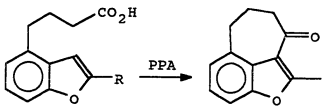
Both cyclizations to be attempted will generate the same C-C ring size, but the second takes a more controlled approach. By generating the 6,3-oxygen bridge one of the two diastereomers will have the benzofuran at an endo position, placing it close to

the anomeric center C_1, minimizing the rotational movements needed so the two reacting centers come at a reaction distance.

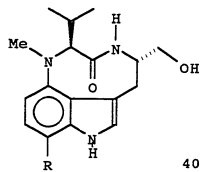
Encouraging reactions supporting such an approach to the macrocyclic templates 10 and 17 have already been reported (sch. 12). The intramolecular cyclization[14] of the benzofuran derivative 38 to the 7-member ring ketone 39 and the construction intramolecularly[20-22] of the 9-member ring teleocidin skeleton 40 from indole show that that size of rings are feasible. Intramolecular aromatic glycosidation[15-19] of the carbohydrate 41 under Lewis Acid catalysis has also been demonstrated (sch. 12).

In conclusion the synthesis of the chiral templates 10 and 17 which as discussed could serve as the origin for the synthesis of gibberellins and grayanols is proposed, beginning from 6,3-glucuronolactone 14 and 4-bromobenzofuran 13. The synthetic approach would lead to novel 6-benzofuranyl-C-glycosides. The intramolecular cyclization of these aryl-glycosides would generate a macrocyclic 9-member ring, joined by one O-bridge (32) or two O-bridges (37). The stereochemistry at the anomeric center C_1 dictated by the direction of the cyclization would be the right one to initiate the synthesis of the natural products. The 10-member ring that is needed for grayanols could be approached the same way from a heptose substrate.

Scheme 12



38 39



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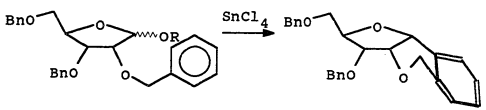
Teleocidin Skeleton



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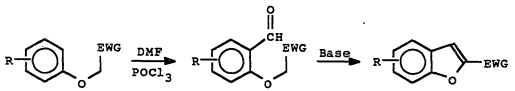
Syntheses of Benzofuran derivatives

The wide range of natural products[1] incorporating the benzofuran skeleton and their important biological and medical activity has prompted the development of a large number of synthetic methods[2-18].

Alkyl aryl ethers 1 derived from 2-hydroxy benzaldehydes (salicylaldehydes), bearing an electron withdrawing group (EWG), on the methylene attached to the phenolic oxygen, such as nitrile, nitro, carbonyl, undergo intramolecular aldol condensation to yield the benzofuran 2 in a basic environment[2-5]. The method can also be modified to include a formylation step. Alkyl aryl ether 3 undergoes a classic Vilsmeier-Haak reaction[6] with DMF/$POCl_3$ to yield the aldehyde 1 which then cyclizes to benzofuran 2 (sch. 1).

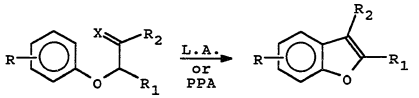
Scheme 1



3 1 2

Appropriately substituted alkyl aryl ethers 4 with an electrophilic center on the alkyl group undergo intramolecular electrophilic cyclization[7,8] to produce the corresponding benzofurans 5, under Lewis Acid or strong mineral acid catalysis (sch. 2).

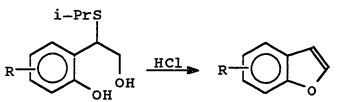
Scheme 2



4 5

Ortho-alkyl substituted phenols 6 have been cyclized to benzofurans[9,10]. Phenol 6 in 2-methoxy ethanol in the presence of HCl cyclizes to yield benzofuran 7 (sch. 3).

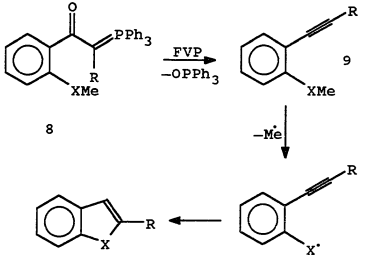
Scheme 3



6 7

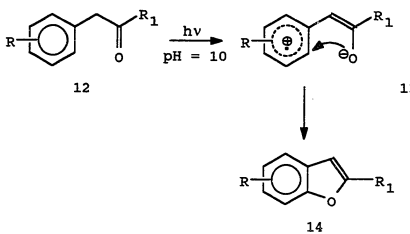
Employing harsher conditions even 2-substituted methyl phenyl ethers 8 have been cyclized to benzofurans. Triphenylphosphonium-ylid 8 under flash vacuum pyrolysis[11] (FVP) eliminated triphenylphosphine oxide to give 2-alkynyl-phenyl-methyl ether 9. Dissociation to methyl and phenoxy radicals 10 leads to a radical cyclization giving the 2-substituted benzofuran 11 (sch. 4).

Scheme 4



11 X = O, S. 10

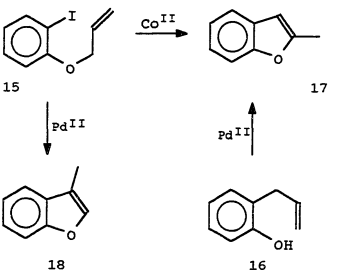
Scheme 5



Ketone 12 was cyclized to benzofuran 14 through the enolate radical cation[12] 13. The enolate ion was produced under irradiation of the parent ketone in a strongly basic environment pH = 10 (sch. 5).

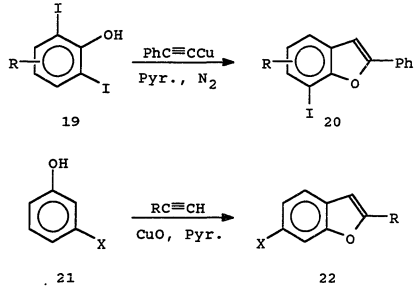
Transition metal catalysts are also effective tools for the synthesis of benzofurans. 2-Iodophenyl allyl ethers 15 and 2-allyl phenols 16 undergo cyclizations[13,14,15] in the presence of Co^{II} and Pd^{II} to the benzofurans 17 and 18 (sch. 6).

Scheme 6



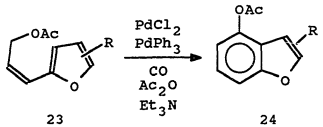
Reaction of the diiodophenol 19 with phenyl ethynyl cuprate yielded the 7-iodobenzofuran[16] 20. In a similar manner the 3-substituted phenol 20 in the presence of cuprous oxide in pyridine underwent coupling reaction[17] with an alkyne to form the 6-substituted benzofuran 22 (sch. 7).

Scheme 7

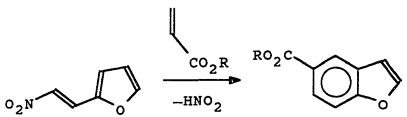


The synthetic methods presented have focused on the construction of the furan ring, starting from a suitable aryl substrate through either intramolecular or intermolecular reactions. An entirely different approach is the construction of the benzene ring using a substituted furan derivative as substrate. Cyclocarbonylation[18a] of the furan 23 with $PdCl_2$ as catalyst has been reported to generate the 4-acetyloxy-benzofuran 24. On the other hand vinyl-substituted furan 25 underwent a Diels-Alder reaction[18b] with an acrylate ester to yield the 5-substituted benzofurans 26 through HNO_2 elimination (sch. 8).

Scheme 8



23 24

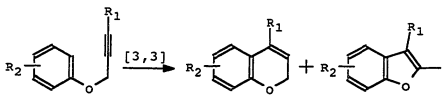


25 26

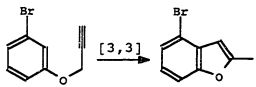
Substituted benzofurans 29 were also synthesized as side products during the [3,3]-Claisen rearrangement[19] of the aryl propargyl ethers 27, in non polar solvents. The main products were the benzochromene derivatives 28. Changing the solvent to a more polar and more basic the benzofurans became the main product[20] (sch. 9).

The [3,3]-Claisen rearrangement of the 3-bromophenyl-propargyl ether 30 and the condensation of the 6-bromosalicylaldehyde 32 with an α-haloketone were the methods chosen. Both of them are expected to yield the 4-bromobenzofuran derivatives. The 4-bromobenzofuran derivative is the aromatic fragment that will be used for the synthesis of the C-glycosides. Direct bromination of non-substituted benzofurans cannot be used, because the 4-bromo derivative coulnot be obtained[21]. Instead products from bromine addition to the furan double bond are formed[21]. Polymerization of the benzofurans also is catalyzed by the halogenation reactions[21].

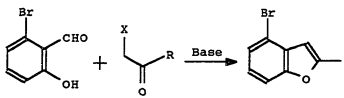
Scheme 9



27 28 29



30 31



32 33

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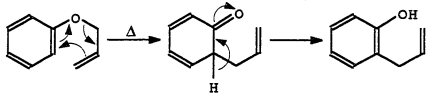
Synthesis of 4-halo-benzofurans by [3,3] Claisen rearrangement

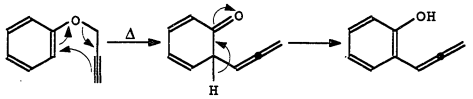
[3,3] Claisen rearrangement of the aryl allyl and aryl alkynyl ethers

Aryl allyl 1 or propargyl 2 ethers undergo thermal [3,3] Claisen rearrangement to form the 2-substituted allyl 3 and allenyl 4 cyclohexadienones[1-6]. Both cyclohexa dienones are enolized to the corresponding allyl (5) and allenyl (6) phenols (sch. 1).

Scheme 1



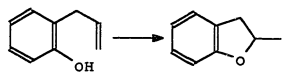
1 3 5



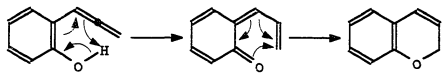
2 4 6

The 2-substituted phenols under the reaction conditions can undergo further intramolecular transformations. Allyl phenol 5 can be cyclized to the dihydrobenzofuran 7[8]. Allenyl phenol 6 can undergo a [1,5] H-shift to the dienylcyclohexadienone 8 which with an electrocyclic rearrangement forms the chromene 9[1-7] (sch. 2).

Scheme 2



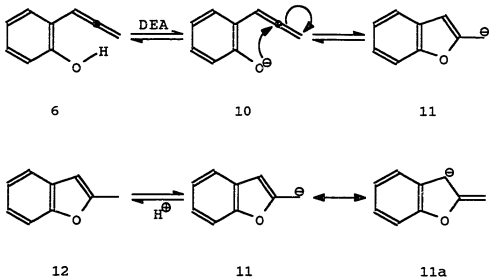
5 7



6 8 9

The thermal rearrangement of the propargyl ether to the allenyl phenol, and finally the chromene is favored in non-polar and non-basic solvents[1] such as decalin. Changing the solvent into a basic and a polar one, such as diethylaniline (DEA), in the presence of a basic salt, such as K_2CO_3, changes the course of the reaction through a solvent participation scheme[1]. Allenyl phenol 6 becomes the phenoxide 10 under the basic and polar conditions in refluxing DEA/K_2CO_3. The phenoxide 10 undergoes an electrocyclic reaction to the anion 11 which by taking a proton from the solvent becomes the 2-methyl-benzofuran 12 (sch. 3).

Scheme 3



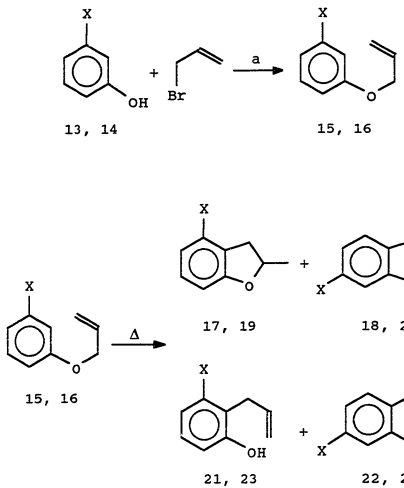
6 10 11

12 11 11a

[3,3] Claisen rearrangement of the 3-halophenyl allyl ethers

The 4-halo-2-methyl benzofuran can be prepared from a disubstituted phenol. 3-Chloro (13) and 3-bromo (14) phenols (sch. 4) in refluxing acetone in the presence of K_2CO_3 and allylbromide were transformed to the corresponding allyl phenol ethers 15 and 16[8]. Allyl ether 15 heated under N_2 at temperatures 160-170°C was rearranged to two pairs of products, a pair of dihydro-benzofurans[7,8] 17, 18 and a pair of allyl phenols 21, 22. 3-Bromophenyl allyl ether 16 under the same reaction conditions yielded similarly the dihydro benzofurans 19, 20 and the allyl phenols 23, 24. In both cases for the chlorophenyl and the bromophenyl allyl ether the predominant rearranged product is the 4-halo-2-methyl-2,3-dihydro-benzofuran 17, 19 and the 3-halo-2-allyl-phenol 21, 23 (table 1, sch. 4).

Scheme 4



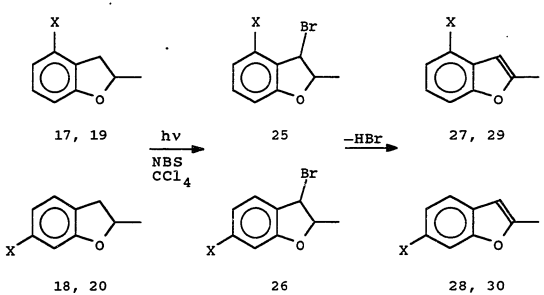
a) refl. acetone K_2CO_3

Table 1

Comp.	X	Prod.	Y%
13	Cl	15	93.0
14	Br	16	89.4
15	Cl	17	11.9*
15	Cl	18	5.9*
15	Cl	21	48.6*
15	Cl	22	28.2*
16	Br	19	11.1*
16	Br	20	8.1*
16	Br	23	47.6*
16	Br	24	22.5*

* ^{1}H NMR

Scheme 5



Bromination of the pairs of the dihydro benzofurans 17, 18 and 19, 20 with NBS produced the 3-bromo-dihydro derivatives 25, 26 which were not isolated, but under the

reaction conditions HBr was eliminated to yield the corresponding mixture of the 4-halo, 6-halo-2-methyl benzofurans 27, 28 and 29, 30 (sch. 5).

[3,3] Claisen rearrangement of the aryl propargyl ethers

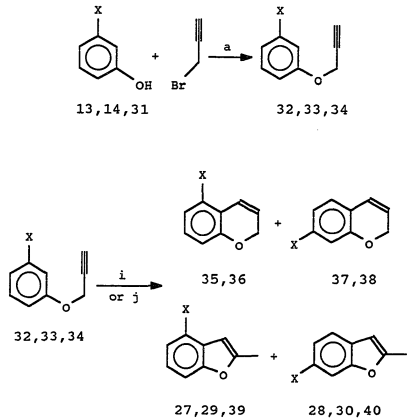
The rearrangement of the 3-halo 32, 33 and 3-nitro propargyl phenyl ethers 34 followed the same pattern (sch. 6). The propargyl ethers were obtained in refluxing acetone in the presence of K_2CO_3 from the propargyl bromide and the corresponding 3-chloro, bromo and nitro- phenols[8] 13, 14, 31.

Table 2

Comp.	X	Product	Y%	method[1,7,8]
13	Cl	32	92.9	a
14	Br	33	98.4	a
31	NO_2	34	92.6	a
32	Cl	27	24.0*	i
32	Cl	28	16.0*	i
33	Br	29	32.8*	i
33	Br	30	17.2*	i
32	Cl	35	32.3*	j
32	Cl	37	16.2*	j
33	Br	36	32.4*	j
33	Br	38	16.2*	j
34	NO_2	39	30.0	i
34	NO_2	40	2.0	i

(a, i, j sch. 6, * ^{1}H NMR)

Scheme 6



a) refl. acetone K_2CO_3, i) refl. DEA, K_2CO_3, N_2, j) refl. DEA, N_2.

3-Chlorophenyl and 3-bromophenyl propargyl ethers 32 and 33 under N_2 in refluxing DEA were rearranged to the corresponding pairs of chromenes[4-6] 35, 37 and 36, 38 with the predominant isomer from each pair being the 5-chloro and 5-bromo chromene 35 and 36 respectively (table 2). On the other hand the rearrangement of all three of them 32, 33, 34 under N_2 in refluxing DEA/K_2CO_3 led to the corresponding 2-methyl-4-(chloro, bromo, nitro)-benzofuran 27, 29, 39 and 2-methyl-6-(chloro, bromo, nitro)-benzofurans 28, 30, 40. The predominant benzofuran was again the 4-substituted product (table 2). The pairs of the halobenzofurans were inseparable as well as those of the halochromenes. The nitrobenzofurans were separated by column

chromatography. The halobenzofurans were contaminated by traces of the corresponding chromenes as shown from the respective ^1H NMR spectra of the mixtures.

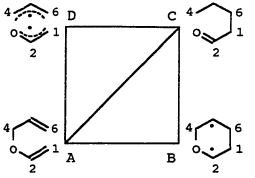
Regioselectivity of the [3,3] Claisen rearrangement

The [3,3] Claisen rearrangement of the 3-halophenyl-propargyl ethers offers an easy access to the 4-halobenzofurans, although the final mixture of products cannot be separated by column chromatography. The predominance of the 4-substituted benzofurans, 5-substituted chromenes, and 3-substituted halophenols over their isomers (tables 1 and 2), almost 2/1 preference, was attributed conventionally to the electronic effect of the substituents[6] on the aromatic ring. Obviously in intramolecular cyclizations like the present ones the steric hindrance factor is unimportant. Even if it were important the predominant product would have not been favored.

The traditional approach to describe the [3,3] Claisen rearrangement is based on a concerted synchronous mechanism[9,10]. By this mechanism the reaction takes place in a single kinetic step (concerted). During that step the chemical bonds are breaking and forming at the same rate at the same time (synchronous). This has been supported by orbital symmetry considerations[11] (Woodward-Hoffman rules).

The concerted synchronous mechanism has come recently under scrutiny[9,12-19]. It is recognized that the rearrangement is not at all synchronous although it maintains to a certain degree the concerted character. By not being synchronous, the bond breaking and the bond forming occur at different rates before and after the transition state. The two events taking place at the same time generate the concerted character of the reaction. This separation of the reaction to two chemical simple events is best described by a More O' Ferrall-Jencks diagram[14,15] (sch. 7).

Scheme 7



The More O' Ferrall-Jencks diagramm presents the possible mechanistic paths being considered. The AC path corresponds to a concerted synchronous mechanism. The AD path corresponds to the bond breaking event preceding to the bond forming and the AB to the bond forming preceding to the bond breaking event.

The initial event in the thermal [3,3] Claisen rearrangement that is triggering the mechanism is the thermal distortion of the unsaturated bond of the alkenyl or the propargyl part. The thermal distortion of the unsaturated bond is translated to a geometric distortion from planarity[20]. Distortion of the singlet ground state S_0 of the alkenes could take them to the first triplet excited state T_1. The vibrational states of the S_0 and the T_1 are overlapping making it possible for an alkene to cross from S_0 to T_1, where the alkenes are considered to be [1,2] diradicals[20].

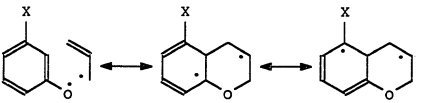
The next event is the one that determines the mechanistic path. The reaction being exothermic suggests an early more reactant like transition state[13-15], with the bond breaking beginning before the bond forming. This mechanistic pathway is supported by isotope effect experiments[13-15,18,19]. The transition state being in the ACD area could be described better as a pair of two radicals. The pair of the two radicals is loosely held together, and according to substitution could even lead to the extreme

pair[13-15] D. Experimental data[4,7,10] have proved that the new σ-bond is formed always between C_1 and C_6. No product has ever been isolated to have the new σ-bond formed between C_1 and C_4 indicating that a bonding interaction between C_1 and C_6 must be in progress. Actually that is the argument that was used to propose a chair transition state that conforms with the molecular orbital symmetry.

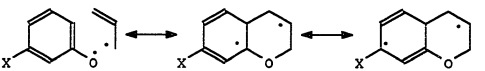
Considering the bond forming as the event taking place first, the transition state should be described better in the ABC area. According to substitution the extreme transition state[13-15] B could also be possible. At that point B the new σ-bond has been formed without any bond broken yet. Semiempirical calculations[9] have pointed out that the σ-C_4-O bond becomes only little longer while the new σ-C_1-C_6 bond is already very short. Further it has been observed that subsituents[14,16] at position 2 (Ireland-Claisen), and 5, the positions that radicaloid character is developed, are increasing the rate of the reaction.

The inability to determine through the experimental and theoretical data the real nature of the transition state makes the proposed More O' Ferral-Jencks diagramm the best approach[13-15] to it. The transition state should be a resonance intermediate[9] with both extreme situations B and D contributing. The contribution of each should vary according to substitution. The contribution from B is zero only at the extreme point D, at every other point the transition state should exhibit a certain degree of biradicaloid character.

Scheme 8



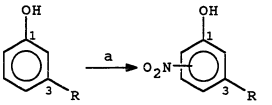
41 42a 42b



43 44a 44b

The 1,3-disubstituted aromatic ring is giving two products, with [1,2,3] and [1,2,5] substitution patterns on the benzene ring (position 1 is the O-position) . These products are obtained from the corresponding transition states. The best approximation to analyze the regioselectivity is through the extreme resonance structures participating in those transition states (sch. 8). The pair of radicals 41 or 43 would give rise to the [1,2,5] substituted benzene ring rather than the [1,2,3]. The product of the radical coupling has been proved to be determined by the distribution of the unpaired electron spin density of the phenoxy radical[21]. Theoretical data predicted[21] that the electron density should be higher at C_4 followed by C_6 and smaller at C_2 (table 3).

Scheme 9



45 46

a) $NaNO_3$, H_2SO_4 3M, catalyst $NaNO_2$, CH_2Cl_2, room temperature, 48h.

Table 3

	Unpaired electron density			Nitration product Y%		
R	C_2	C_4	C_6	2-NO_2	4-NO_2	6-NO_2
MeO	0.1639	0.3959	0.2697	18.9	45.8	31.2
Cl	0.1680	0.3971	0.2607	19.5	45.9	30.2
CN	0.1939	0.3853	0.2432	22.4	44.6	28.1
NO_2	0.2133	0.3733	0.2339	24.7	43.3	27.1
CHO	0.2028	0.3852	0.2297	23.4	44.5	26.5
COMe	0.1993	0.3877	0.2304	23.0	44.8	26.6

data taken from ref.21b

Experimental results obtained from the nitration of the corresponding phenols under free radical conditions confirmed these predictions[21] (table 3). The approach to the regioselectivity through the recombination of the pair of radicals 41 or 43 (D on the More O Ferrall-Jencks diagramm) suggests that the non-favored regioselectivity should have been obtained. The remaining probabilities for the transition state are the ones having a certain degree of radicaloid character. The extreme 42 and 44 structures should be a good aproximation in determining whether the radicaloid character is the

factor controlling the regioselectivity of the reaction. The 3-substituents on the aromatic ring, whether electron donating or withdrawing group, exhibit a stabilization effect[22,23] on the dienyl radicals 42a,b and 44a,b. The radicals become more stable when the substituent X is an electron withdrawing group due to the synergetic captodative effect[22-25]. The electron withdrawing groups are stabilizing more the radical centers than the electron donating groups[22,25] making the 42b and 44b the dominant structures. The same stuctures 42b, 44b are also more stable[22,25] when the substituent is a halide due to the stronger inductive effect. The linearly conjugated radical 42b being more stable[22] than the cross conjugated 43b should be the preferred pathway to the final product. That is the pathway leading to the preferred regioselectivity. The radicaloid rising from contribution of the radical 42b should be the preferred pathway for the reaction to follow. That pathway leads to the observed regioselectivity (table 4).

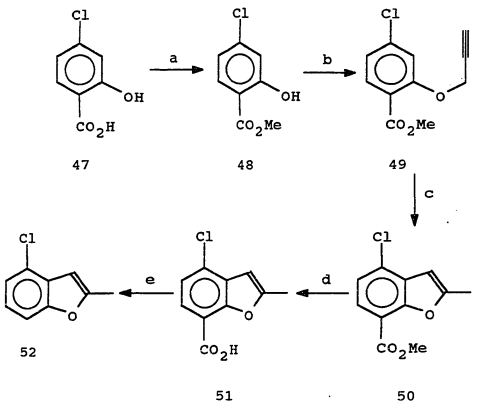
Table 4

X	Ether	[1,2,3]	[1,2,5]	Ref.
OMe	Propargyl	54	46	5,6
OBz	Propargyl	63%	-	5
Me	Allyl	56	44	7,8
F_3C	Allyl	63	37	7
Br	Allyl	64	36	7,8
C_4H_8	Allyl	74	26	7
NHAc	Allyl	46	40	8
Cl	Allyl	65	35	8
OBz	Allyl	77	23	8
CN	Allyl	70	30	8
Cl	Allyl	24	16	-
Br	Allyi	32.8	17.2	-
Cl	Propargyl	32.3	16.2	-
Br	Propargyl	32.4	16.2	-
NO_2	Propargyl	30%	2%	-

Synthesis of the 4-chloro-2-methylbenzofuran

The 4-chlorobenzofuran finally was synthesized from the commercially available 4-chlorosalicylic acid 47 (sch. 10). Refluxing the 4-chlorosalicylic acid in methanol with con. H_2SO_4 as catalyst the methyl salicylate 48 was prepared. The methyl salicylate 48 reacted with propargyl bromide in refluxing acetone and K_2CO_3 to yield the ether 49. The ether 49 was cyclized in refluxing DEA under N_2 in the presence of K_2CO_3 to yield the methyl-4-chloro-2-methylbenzofuroate 50.

Scheme 10



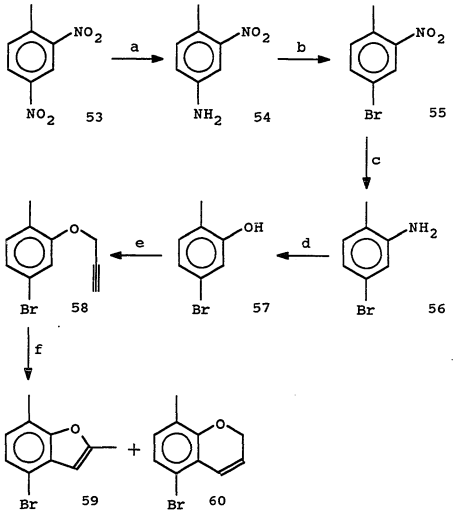
a) refl. MeOH, con. H_2SO_4 (86.4%), b) refl. Acetone, K_2CO_3 (95.3%), c) refl. DEA, K_2CO_3, N_2, d) NaOH, refl. EtOH 95% (87.9% from b), refl. isoquinoline, Cu_2O, N_2, (63.3%).

The benzofuroate 50 was never isolated but instead it was hydrolyzed to the corresponding benzofuroic acid (white amorphous solid after purification) 51, in 95% ethanol and NaOH. The benzofuroic acid 51 was decarboxylated[26] by Cu_2O in refluxing isoquinoline for 20 min. The 4-chloro-2-methyl benzofuran 52 was the product.

Synthesis of the 4-bromo-2,7-dimethylbenzofuran

The 4-bromobenzofuran was synthesized from 2,4-dinitrotoluene 53 (sch. 11). Selective reduction of the 4-nitro group by ammonium polysulfide at room temperature yielded the 4-amino-2-nitrotoluene 54 (yellow solid). Diazotization of the aniline 54 with $NaNO_2$ and H_2SO_4, and subsequent treatment of the diazonium with a solution of freshly made Cu_2Br_2 (not exposed to the atmosphere) in hydrobromic acid yielded the 4-bromo-2-nitro-toluene 55 (pale yellow solid). The 4-bromo-2-nitrotoluene was reduced to the 4-bromo-2-aminotoluene 56 with $SnCl_2$ in hydrochloric acid. Diazotization of the toluidine 56 with $NaNO_2$ and H_2SO_4 at 0-5°C and treatment of the diazonium with hot 50% H_2SO_4 yielded the 4-bromo-2-hydroxytoluene 57. The phenol 57 in refluxing acetone with propargyl bromide, K_2CO_3 became the propargyl ether 58. The propargyl ether 58 was cyclized in refluxing DEA under N_2 in the presence of K_2CO_3 to yield the 4-bromo-2,7-dimethylbenzofuran 59 and the 5-bromo-8-methylchromene 60 as the minor product. They were separated by column chromatography (cyclohexane as solvent).

Scheme 11



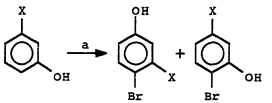
a) Ammonium polysulfide (99.2%), b) i) $NaNO_2$, H_2SO_4, 0-5°C, ii) Cu_2Br_2, HBr, room temperature (79.6%), c) $SnCl_2$, 95% EtOH, HCl (92.5%), d) $NaNO_2$, H_2SO_4, 65°C (84.2%), e) Propargyl bromide, refl. acetone, K_2CO_3 (80.2%), f) refl. DEA, K_2CO_3, N_2 59(23.7%), 60(8.6%).

Reimer-Tiemann formylation of the 3-bromophenol

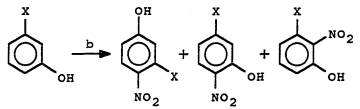
Bromination and nitration[21,27] of the 3-halo phenols yielded predominantly the [1,2,5] and the [1,3,4] trisubstituted products. The [1,2,3] product was obtained in small

amounts from the nitration reaction (sch. 12, table 5). The Reimer-Tiemann[28] formylation of the 3-bromophenol yielded as major product the [1,2,3] trisubstituted product. The other two isomers, obtained roughly in equal amounts, were the minor products (sch. 12, table 5).

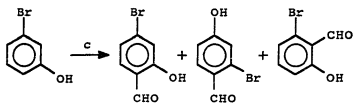
Scheme 12



13,14 61,62 63,64



13,14 65,66 67,68 69,70



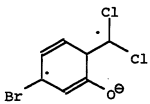
14 71 72 73

a) Br_2, CCl_4, b) HNO_3, AcOH, c) $CHCl_3$, NaOH 50%, Δ, N_2.

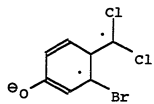
Table 5

	X	Product (y%)			method
		[1,3,4]	[1,2,5]	[1,2,3]	
13	Cl	61 (31.1)	63 (31.1)	-	a
14	Br	62 (27.4)	64 (37.3)	-	a
13	Cl	65 (40.7)	67 (18.5)	69 (11.1)	b
14	Br	66 (32.9)	68 (19.6)	70 (11.9)	b
14	Br	71 (14.6)	72 (12.3)	73 (23.2)	c

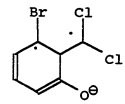
Scheme 13



74



75



76

The regioselectivity observed for the Reimer-Tiemann formylation of the 3-bromo phenol could also be explained by a mechanism involving radical species generated from the dichlorocarbene[29]. The radical addition of the dichlorocarbene to the 3-bromophenoxide generates the corresponding diradical species. The linearly conjugated diradical 76 is expected to be more stable[22] than the cross conjugated 74, 75 (sch. 13). The more stable intermediate generates the predominant product.

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Synthesis of 4-bromo-benzofuran derivatives from substituted salicylaldehydes

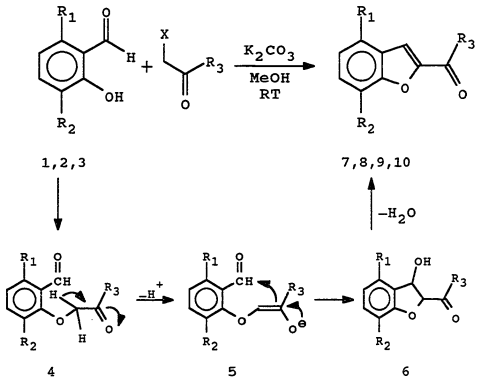
Synthesis and bromination reactions of the 2-acylbenzofuran derivatives

Salicylaldehyde 1, 6-bromosalicylaldehyde 2 and o-vanillin 3, in methanol, at room temperature, in the presence of K_2CO_3 underwent reaction with α-halo-ketones, (bromo-acetophenone[1], chloroacetone[2,3]) to yield the corresponding 2-acyl benzofurans 7-10. Initially the halide of the α-halo ketone is diplaced[4] by the phenoxide to provide the α-keto aryl ether 4. The ether 4 in the basic environment of the reaction enolizes to enolate 5, which, in an intramolecular aldol condensation reaction with the 2-carbonyl group produces the 2-acyl-benzofuran derivatives through dehydration of the intermediate alcohol 6 (sch. 1).

The target 4-bromobenzofuran 8 had been obtained in a single reaction step from 6-bromosalicylaldehyde 2. The salicylaldehyde 2 was obtained from the formylation of 3-bromophenol in only 20% yield as one of three isomers (ch. 3). The other two isomers account for another 20% of the total yield. Bromination of the other 2-acyl benzofurans is an alternative route to the 4-bromo benzofuran.

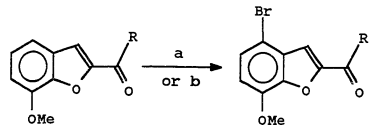
Bromination of the 2-benzoyl-benzofuran 7 does not lead to substitution on the benzene ring, but to a mixture of products from the addition of bromine to the double bond of the furan ring[5,6,7,8]. The introduction of an electron donating group on the benzene ring of the benzofuran leads to electrophilic substitution on the benzene ring[5,9] instead of addition to the double bond of the furan ring.

Scheme 1

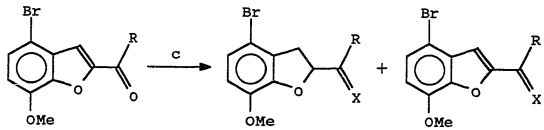


Ald.	R_1	R_2	R_3	X	Bzf.	y%
1	H	H	Ph	Br	7	66.3
2	Br	H	Ph	Br	8	74.3
3	H	OMe	Ph	Br	9	79.4
3	H	OMe	Me	Cl	10	89.5

Scheme 2



9,10 11,12,13



12 14 15

Comp.	R	Prod.	R	X	Y%	method
9	Ph	11	Ph	-	91.4*	a, b*
10	Me	12	CH_nBr_{3-n}	-	86.7	a
10	Me	13	Me	-	86.3	b
12	CH_nBr_{3-n}	14	CH_3	O, (H, H), (H, OH)	-	c
			CH_2OAc	H, OAc	-	c
		15	CH_3	O, (H, H), (H, OH)	-	c

a) Br_2, CCl_4, K_2CO_3, room temperature, b) Br_2, 95% t-ButOH, K_2CO_3, room temperature, c) Zn, refl. AcOH. *obtained from b.

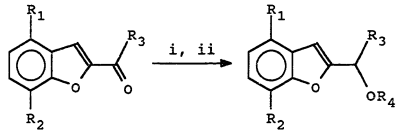
Bromination of the 7-methoxy-2-benzoyl benzofuran 9 in CCl_4 led to the 4-bromo benzofuran 11. The 7-methoxy-2-acetyl benzofuran 10 undergoing the same reaction led to a mixture of 4-bromo substituted benzofurans 12 that were formed from the haloform reaction of the 2-acetyl group with bromine[2]. The mixture included mono, di and tri bromo acetyl-4-bromo-benzofuran derivatives (12) (86.7% total). Attempted dehalogenation of the α-bromo-acetyl group with Zn in refluxing acetic acid yielded a more complicated mixture of products. The dehalogenation was successful, but partial hydrogenation[10] of the carbonyl group and the furan ring had occurred. A mixture of at least six compounds was detected from the ^1H NMR spectrum (sch. 2).

Considering that the haloform reaction is catalyzed by HBr generated *in situ* during the bromination of the benzene ring, the solvent of the reaction was changed to 95% t-butanol, with solid K_2CO_3, basic mixture which instantly neutralized the generated HBr. Under these conditions the bromination of the 7-methoxy-2-acetyl benzofuran 10 was successful and the 4-bromo benzofuran 13 was the only product isolated.

Reduction and methylation reactions of the 2-acylbenzofuran derivatives

The intended use of the 4-bromo benzofurans to generate Grignard reagents introduced the need to render the 2-acyl substituent inert towards Grignard reaction conditions.The 2-acyl-benzofurans 7, 8, 10, 11, 13 were reduced to the corresponding alcohols 16, 17, 18, 19, 20 in ethanol at room temperature with sodium borohydride. The alcohols underwent a two phase transfer[11] methylation reaction in benzene, and 50% NaOH solution with 1.6 eq. dimethyl sulfate and catalytic amount of tetrabutyl-ammonium iodide, at room temperature, to form the corresponding methyl ethers 21, 22, 23, 24, 25 (sch.3).

Scheme 3

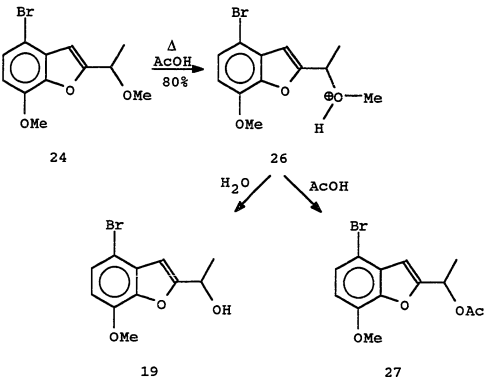


			Ketone	Alcohol		Ether	
R_1	R_2	R_3		R_4 = H	y%	R_4 = Me	y%
H	H	Ph	7	16	93.7	21	84.7
Br	H	Ph	8	17	87.1	22	85.2
H	OMe	Me	10	18	97.0	23	84.8
Br	OMe	Me	13	19	90.1	24	87.8
Br	OMe	Ph	11	20	86.7	25	91.7

i) $NaBH_4$, EtOH, room temperature, ii) Me_2SO_4, C_6H_6, NaOH 23%, TBAI, room temperature.

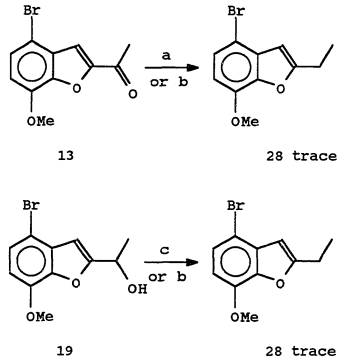
The benzofuranyl alcohols 16, 17, 18, 19, 20 and the corresponding methyl ethers suffered polymerization upon standing at room temperature over a long time period. The polymerization was more extensive for samples that had a significant amount of impurities (crude samples). The facile polymerization of benzofurans makes them ideal substrates for polymerization and copolymerization under various conditions and catalysts, like acids or Lewis acids[12]. The presence of the oxygen functionality on the 2-substituent increases the rate of polymerization by forming a carbocation through elimination of the oxygen bearing group, which is stabilized by the furan ring.

Scheme 4



Heating benzofuran 24 in 80% acetic acid hydrolyzed the methyl ether yielding the corresponding alcohol 19 and the corresponding acetate 27. Clearly a protonation of the 2-substituent-methoxy group led to oxonium ion 26 which underwent a displacement of a methanol molecule, by water to give the alcohol 19 (19.3%) and by the acetic acid to give the acetate 27 (19.5%) (sch. 5).

Scheme 5



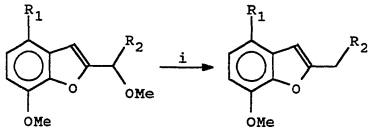
a) $AlCl_3$, $LiAlH_4$, Et_2O, b) Et_3SiH, CF_3CO_2H, c) Et_3SiH, $BF_3.Et_2O$.

Deoxygenation reactions of the 2-alkyl chain of the benzofurans

To minimize the risk of polymerization, deoxygenation of the 2-substituent of the 4-bromobenzofurans was undertaken. Attempted deoxygenation of the ketone 13 with $AlCl_3/LiAlH_4$[13] in ether at 0°C, under N_2, produced only trace amounts of the desired 2-ethyl-4-bromo-7-methoxybenzofuran 28. A white solid of polymeric nature was obtained as the major product. A second attempt on the same substrate with triethylsilane[14] in trifluroacetic acid yielded only a polymer. Similarly, with $Et_3SiH/BF_3.Et_2O$ at room temperature, the corresponding alcohol 19 again gave the desired deoxygenated benzofuran 28 in trace amounts, with the major product being a polymer.

An alternative deoxygenation of the 2-acetyl-benzofuran 13 is to employ the Wolff Kishner reaction[12]. Treating 13 with hydrazine at high temperature would produce 28. But considering the facile polymerization of the oxygenated-benzofurans 20, 19 and recognizing that this is the result of the easy formation of the carbocation at that position, demonstrated by the hydrolysis of the methyl ether 24 under heating with 80% acetic acid, a new approach was attempted on the methyl ether 24.

Scheme 6



a b

R_1	R_2	Ether	Bzf.	y%
H	Me	23	29	80.3
Br	Me	24	28	84.8
Br	Ph	25	30	77.2

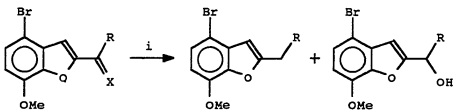
i) 6eq. $NaBH_3CN$, 6 eq. TMSCl, CH_3CN, N_2, mol. sieves 3Å, room temperature..

The methyl ether 24 was treated with 1eq of trimethylchlorosilane and 1eq. $NaBH_3CN$, in dry acetonitrile, under N_2, in the presence of molecular sieves 3Å, at room temperature[15]. The substrate was recovered unchanged after 24h stirring. When the amounts of TMSCl and $NaBH_3CN$ were increased to 6eq. each, stirring the reaction for the same amount of time under the same conditions gave an 80% yield of the 2-ethyl benzofuran 28. Trace amounts of the ether 24 also were detected. For larger scale

reactions the reaction time was extended appropriately. Under these conditions the methyl ethers 23, 25 were also reduced to the corresponding products 29, 30 (sch. 6).

The deoxygenation of the 2-side chain under these conditions was not limited to the ethers 23, 24, 25. Also the ketone 13 was reduced yielding the alcohol 20 (48.6%) along with the benzofuran 30 (48.6%). The acetate 27 under the same conditions yielded the alcohol 19 (trace amounts) and the corresponding deoxygenated product 28 (trace amounts, detected by the ^{1}H NMR) (sch. 7).

Scheme 7



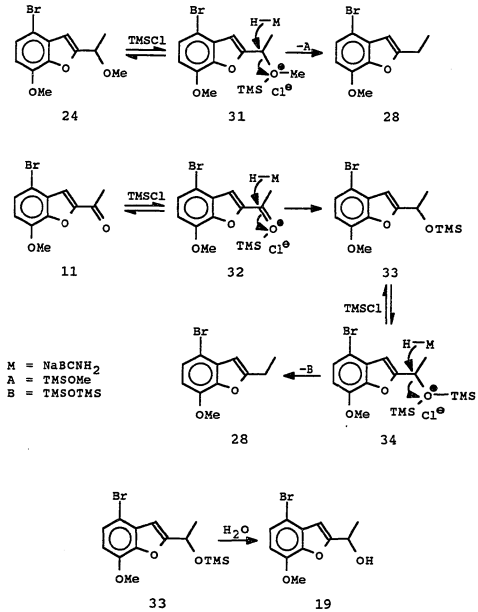
a b c

R	X	a	b	y%	c	y%
Ph	O	13	20	48.6	30	48.6
Me	H, OAc	27	28		19	

i) 6eq. $NaBCNH_3$, 6 eq. TMSCl, CH_3CN, N_2, mol. sieves 3Å, room temperature.

The excess of TMSCl presumably reacts reversibly to give the oxonium ion 31. The oxonium 31 then undergoes hydride attack from the $NaBH_3CN$ to yield the deoxygenated product 28 and methyl trimethylsilyl ether (sch. 8).

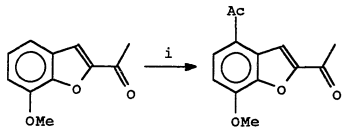
Scheme 8



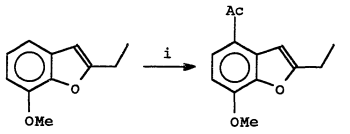
The ketone 11 forms the oxonium ion 32 from the association of the TMSCl with the carbonyl group. At first hydride delivery produces the silyl ether 33. The silyl ether 33 then goes through the same mechanism like the methyl ether to yield the

deoxygenated product and the bis-trimethyl silyl ether. The same mechanism also applies for the acetate. The stepwise reduction of the ketones through the silyl ether 33 is supported from the isolated alcohols 19, 20 as side products (sch. 8).

Scheme 9



10 35



29 36

i) Ac_2O, $BF_3.Et_2O$, CH_3CN, N_2, room temperature.

Friedel-Craft acetylation of the 7-methoxy benzofuran derivatives

The acetylation of the ketone 10 and the 2-ethyl benzofuran 29 in dry acetonitrile at room temperature with acetic anhydride and $BF_3.Et_2O$ as catalyst yielded the 4-acetyl derivatives 35 (32.8%), 36 (40.0%) in both cases as expected[16,17] (sch. 9).

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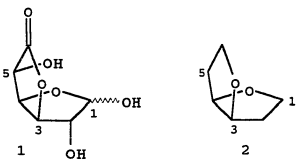
Protected derivatives of D-glucofuranurono-6,3-lactone

Protection and reduction reactions of the glucofuranurono-6,3-lactone

D-Glucofurano-6,3-lactone 1 is commercially obtained by catalytic oxidation[1] of D-glucose with Pt/O_2. The molecular skeleton is a 2,6-dioxabicyclo [3.3.0] octane 2 which has a C_3 and C_4 syn-configuration (sch. 1).

Scheme 1

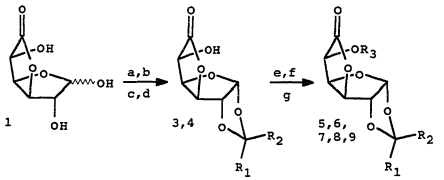


The dioxabicyclooctane skeleton divides the three hydroxyl functions, to two groups, the anomeric OH and the 2-OH belong to the first and the 5-OH to the second. The first group was protected by an acetal group and the second by a silyl ether formation (sch. 2).

Glucofurano-6,3-lactone 1 produced the 1,2-O-benzylidene[2,8] derivative 3 either by reaction with benzaldehyde dimethyl acetal in refluxing THF, or DMF with a catalytic amount of PTSA, or with benzaldehyde and $ZnCl_2$. The benzylidene group introduced a new stereogenic carbon and the mixture of the exo- and the endo-phenyl diastereomers 3 was obtained. The exo-phenyl was the major diastereomer and was obtained in 40% yield from the benzaldehyde and $ZnCl_2$ reaction[8]. A mixture of exo-, endo-phenyl isomers was also obtained in 32% yield from the same reaction. The

introduction of the new stereocenter at the benzylidene group and the need for a separation of the mixture of the two diastereomers prompted the consideration of an achiral protecting acetal group. D-glucofurano-6,3-lactone 1 in dry acetone with a catalytic amount of conc. H_2SO_4 was protected as the 1,2-O-isopropylidene-6,3-lactone[3] 4 (sch. 2).

Scheme 2



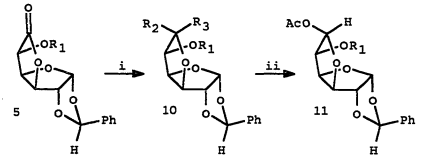
Comp.	R_1	R_2	R_3	React. cond.	y%
3 exo	H	Ph	H	a, b, c	33, 36, 56
3 endo	Ph	H	H	a, b, c	11, 32, 16
4	Me	Me	H	d	70
5	H	Ph	TBDMS	e	80.3
6	Me	Me	TBDMS	e	84.0
7	H	Ph	Trityl	f	80.3
8	H	Ph	$ClSiMe_2$	g(i)	/
9	H	Ph	t-BuOSiMe$_2$	g(ii)	72.2

a) $C_6H_5CH(OMe)_2$, PTSA, refl. THF, b) $C_6H_5CH(OMe)_2$, PTSA, DMF, room temperature, c) C_6H_5CHO, $ZnCl_2$, room temperature, d) Acetone, con. H_2SO_4, room temperature, e) TBDMSCl, Imidazole, DMF, room temperature, f) Trityl bromide, refl. pyridine, g(i)) Cl_2SiMe_2, pyridine, benzene, N_2, room temperature, g(ii)) t-BuOH, pyridine, benzene, 65°C.

The remaining free 5-OH group was protected as a t-butyldimethylsilyl ether[4] (TBDMS). Benzylidene 3-exo and acetonide 4 derivatives of the D-6,3-glucofurano lactone in dry DMF with 1.2eq TBDMSCl and 2.4eq imidazole at room temperature were protected as the corresponding silyl ethers 5 and 6 respectively.

Alternative methods to protect the 5-OH group were also investigated. The exo-phenyl benzylidene derivative 3 in refluxing pyridine with triphenylmethyl bromide (trityl bromide) yielded the tritylated[5] product 7. The same derivative 3 in benzene with dichlorodimethyl silane[6] at room temperature, in the presence of pyridine yielded the chlorodimethyl silyl ether 8. The t-butoxydimethylsilyl ether 9 was obtained at higher temperatures from the reaction of 8 with t-butanol[6]. The conversion from 3 to 9 is a one pot reaction performed under N_2.

Scheme 3



Comp.	R_1	R_2	R_3
5	TBDMS	-	-
10 exo	TBDMS	OH	H
10 endo	TBDMS	H	OH
11 exo	TBDMS	OAc	H

i) DIBAH, diethyl ether, -78°C, N_2, 80% (endo/exo = 3/1), ii) pyridine, acetic anhydride, 99.8%.

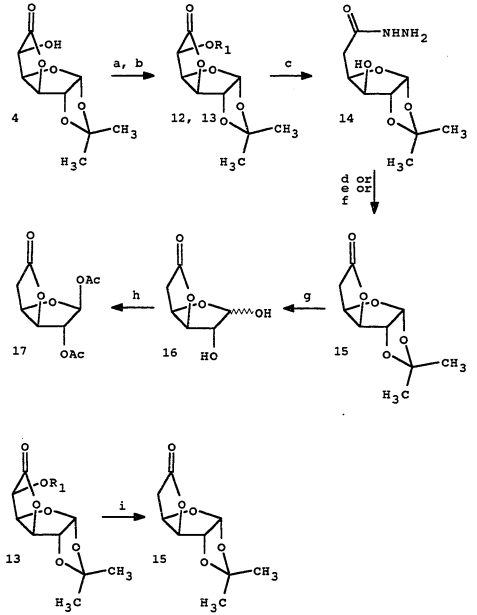
Reduction of the 5-t-butyldimethylsilyl-1,2-O-benzylidene lactone 5 with diisobutyl aluminum hydride[7] (DIBAH) at -78°C in ether under N_2 yielded the hemiacetal 10. The acetate 11 was obtained[8] from 10 by acetylation with pyridine and acetic anhydride at room temperature (sch. 3).

Deoxygenation at C_5 of the glucofurano-6,3-lactone

Deoxygenation of the carbon-5 of the 6,3-glucofuranolactone is also an effective method for rendering inactive that site of the molecule. Methylsulfonate ester 12 and the p-toluenesulfonate ester 13 were obtained from the reaction of the 1,2-O-isopropy lidene-glucofurano-6,3-lactone 4 with the corresponding sulfonyl chlorides[9,10] in pyridine, under N_2, at 0°C.

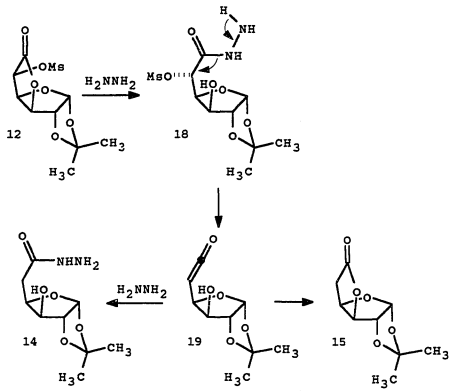
The acyl hydrazide 14 was formed by treating the methylsulfonate ester 12 with excess of hydrazine[9] in dry dioxan. The hydrazide then underwent cyclization with N-bromosuccinimide[11,12] (NBS), or ceric ammonium nitrate[13] (CAN), or $CuCl_2$[14] to produce small amounts of the 5-deoxyfurano lactone 15. The low yields of 15 were attributed to the hydrolysis of the isopropylidene protecting group under the reaction conditions. The final pH of the reaction solution was strongly acidic (pH = 3). In fact concentration of the reaction mixture of the NBS/MeOH(solvent) reaction and direct acetylation of the residue yielded the anticipated diacetate 17, obviously obtained from diol 16 which was the product of the acidic hydrolysis of 15 (sch. 4).

Scheme 4



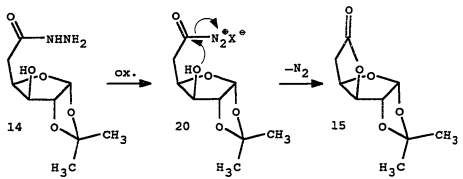
a) MsCl, pyridine, diethyl ether, N_2, 0°C, 72% (R_1 = Ms, 12), b) TsCl, pyridine, diethyl ether, 0°C, N_2, 81.2% (R_2 = Tos, 13), c) hydrazine, dioxane, 0°C, N_2, d) CAN, aq. acetonitrile, 25°C, 14%, e) NBS, MeOH, 25°C, 10%, f) $CuCl_2.2H_2O$, THF, 25°C, 18h, 12%, g) H^+, H_2O, h) pyridine, acetic anhydride, 25°C, 20%, i) NaI, AIBN, Bu_3SnH, refl. DMeOEt, N_2.

Scheme 5



Initially nucleophilic attack of hydrazine on the 5-methylsulfonate-1,2-O-iso propylidenefurano-6,3-lactone 12 forms the hydrazide 18. The hydrazide 18 undergoes intramolecular elimination of the methylsulfonate to form the ketene 19. In the excess of hydrazine, ketene 19 undergoes another nucleophilic attack to form the isolated hydrazide 14. Ketene 19 in the absence of the excess of hydrazine could cyclize directly to the 5-deoxy-lactone 15, undergoing an intramolecular[9,11] nucleophilic attack from the 3-hydroxyl group (sch. 5).

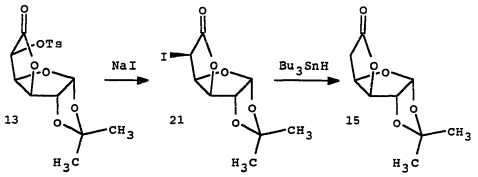
Scheme 6



The oxidation[12,13] of the hydrazide 14 forms eventually the diazonium salt 20, which undergoes intra-molecular cyclization by displacement of the N_2 from the 3-OH group to the lactone 15 (sch. 6).

The very low yields of the hydrazine deoxygenation and the hydrolysis of the 1,2-O-isopropylidene protecting group dictated a non aqueous environment reaction. The tosylate ester 13 was reduced to the deoxygenated lactone 15, 38.9%, by refluxing with NaI, Bu_3SnH and AIBN[15] in dimethoxy ethane under N_2. Presumably the tosylate 13 underwent nucleophilic dispiacement by the iodide to form the intermediate iodide 21. The iodide 21 formed *in situ* was immediately reduced by the Bu_3SnH to the deoxy-lactone 15. Attempted isolation of the iodide 21 in a stepwise reaction resulted only in decomposition products. Decomposition may also be the reason for the not so good yield of the reaction (sch. 7).

Scheme 7

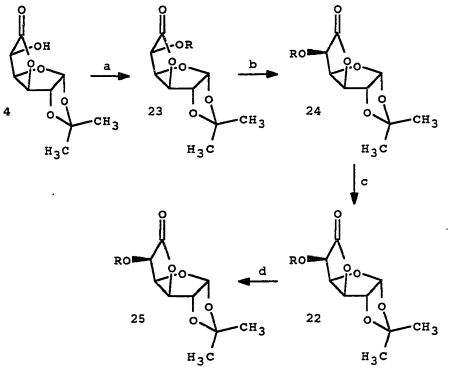


Synthesis of idofuranurono-6,3-lactone derivatives from glucofuranurono-6,3-lactone

Idofurano-6,3-lactone 22, the epimer of glucofurano-6,3-lactone 4, at C-5, has been synthesized by various multistep reaction methods[17]. The shorter synthesis of it, is by direct configuration inversion at C-5 of the glucofurano lactone[19,20,21]. The facile nucleophilic displacement[16] the sulfonic esters could undergo with inversion of configuration in an Sn2 reaction made them the substrate of choice. The tendency of the carbohydrate substrate to undergo elimination reactions[1,20] requires that the reaction conditions be very mild. A very good leaving group was chosen, the trifluoromethane sulfonate, which made the displacement possible by a nucleophile as weak as the sodium trifluoroacetate. Glucofurano-6,3-lactone 4 in dry methylene chloride at -20°C was converted to the triflate[18] 23 in the presence of pyridine, under N_2 in high yields. The triflate group underwent Sn2 displacement[20] by sodium trifluoroacetate in DMF at room temperature to yield the trifluoroacetate ester 24, which was not isolated. Methanolysis of the ester 24, by passing a solution of it in methanol through a celite column yieided the idofurano-6,3-lactone 22 at 75-80% yield from the glucofurano-6,3-lactone 4. The hydrolysis of the ester 24 must take place under very

mild conditions, almost neutral. Use of other esters like benzoates led to eliminations[20] during their hydrolysis. Lower yields could be obtained if the Sn2 displacement had taken place with KNO_2[21] (sch. 8).

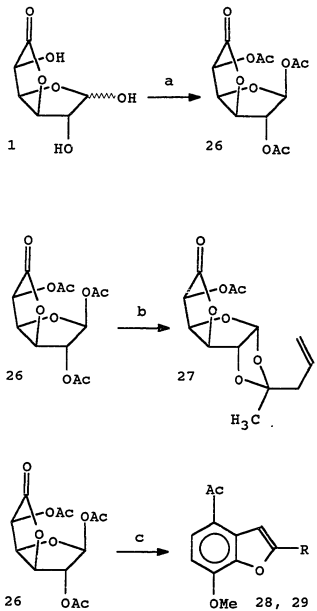
Scheme 8



a) Tf_2O, pyridine, CH_2Cl_2, -20°C, N_2, 90.4%, (R=Tf, 23), b) F_3CCO_2Na, DMF, room temerature, (R=F_3CCO, 24), c) MeOH, celite, room temperature, 88.7%, (R=H), d) TBDMSCl, imidazole, DMF, room temperature, 80.9%, (R=TBDMS).

Idofurano-6,3-lactone 22 was further protected to the 5-t-butyldimethylsilyl ether 25 under standard conditions.

Scheme 9

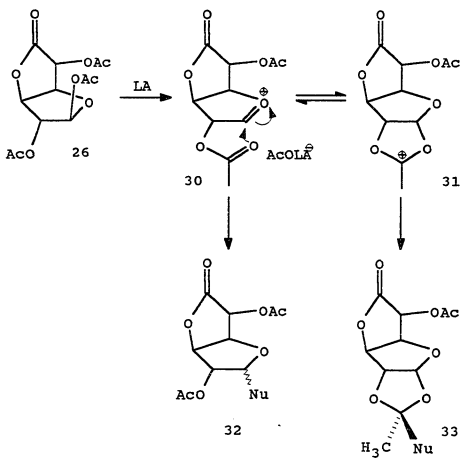


a) Ac_2O, $BF_3.Et_2O$, R. T.,78.8%, b) AllTMS, $BF_3.Et_2O$, CH_3CN, room temperature, N_2, 88%, c) 2-ethyl-7-methoxy-benzofuran, or 2-acetyl-7-methoxy-benzofuran, $BF_3.Et_2O$, CH_3CN, room temperature., N_2, traces of 28(R = Et), 29(R = Ac).

C-glycosidation reactions of the glucofurano-6,3-lactone derivatives

Glucofurano-6,3-lactone 1 was converted to the β-triacetate 26 in acetic anhydride at room temperature with $BF_3.Et_2O$ as catalyst[1,22]. The triacetate 26 was treated in acetonitrile with 1eq. of $BF_3.Et_2O$ and excess of allyltrimethylsilane in a standard approach[23,24] to form the 1-C-allyl-glycoside. Instead the product 27 was obtained. Similar treatment of the triacetate 26 in the presence of 2-ethyl-7-methoxy-benzofuran or 2-acetyl-7-methoxy-benzofuran yielded traces of the corresponding 4-acetyl-benzofuran derivatives 28 and 29 respectively (sch. 9).

Scheme 10



The carbocation 30 is the intermediate that is generated from the reaction of the $BF_3.Et_2O$ with the anomeric acetate. Anchimeric participation from the 2-OAc leads to the cation 31. Although the anomeric cation 30 is the more stable and should be the one undergoing the nucleophilic attack to generate the standard product 32, that did not happen. Both directions of the nucleophilic attack on the cation 30 are sterically hindered, the endo from the 6,3-lactone ring and the 5-OAc, the exo from the syn 2-acetate enforced by the neighbouring group participation. However, the cationic center on the structure 31 is not sterically hindered, accessible by the nucleophile from the exo-face to yield the obtained product 33 (sch. 10).

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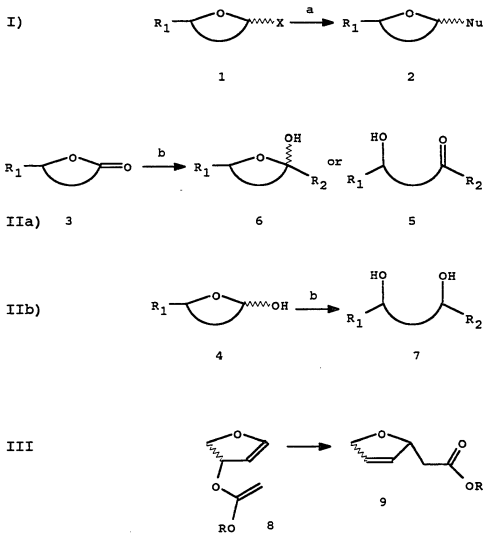
Synthesis of 6-C-4'-benzofuranyl glycosides

General methods for the synthesis of C-glycosides

C-Glycosides have been prepared by three major methods[1,2]. I) An activated carbohydrate substrate 1 under Lewis Acid or other strong acid catalysis undergoes a nucleophilic attack to form a mixture of α and β-C-glycosides[1] 2. II) A glycosidic C-C bond through a reaction between a carbohydrate lactone 3, or other carbohydrate carbonyl group 4 and a Grignard reagent[2]. The product is either a keto alcohol 5, a hemiacetal 6, or a diol 7. The acyclic glycoside undergoes then a sequence of reduction and dehydration reactions to yield the cyclic glycoside 2. III) The Claisen rearrangement is a less employed alternative to the other two. Suitably substituted carbohydrate[1a] 8 undergoes easily rearrangement to the C- glycoside 9 (sch. 1).

The synthesis of the 6-C-arylglycosides from the glucofurano-6,3-lactone could in principle be done by both methods, I and II. The first method would have required an extra reduction step of the carbonyl group in order to activate it . The second method, IIa, in one reaction step yields the 6-C-aryl glycoside. The uncyclized product 5 is the beginning compound for the synthesis of the macrosyclic C-glycoside (ch. 1, synthetic plan). The method, IIa (sch. 1) was applied for the synthesis of the 6-C-arylglycosides.

Scheme 1



a) Lewis Acid, Nucleophile, b) R_2M (M = Li, MgX).

Synthesis of the 6-C-arylglycosides

4-Bromobenzofuran derivatives 10 were subjected to bromine-lithium exchange reaction[3] with butyl lithium in dry THF at -78°C under N_2 to obtain the corresponding lithiated intermediates 11 (sch. 2).

The protected D-glucofurano and idofurano-6,3-lactones 12 (10, ch. 4) were the carbohydrate substrates[4]. The reaction between the lactones 12 and the aryl lithium 11 yielded the ketoalcohols 13 which were acetylated to the corresponding acetate esters 14 (sch. 2).

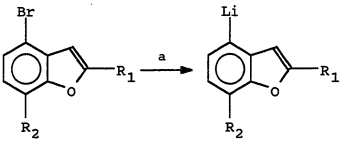
Table 1

Ar	R_1	R_2	R_3	R_4	13	y%	14	y%
Ph	H	Ph	OTBDMS	H	a	83.5	a	100
Ph	Me	Me	OTBDMS	H	b	80.9	b	-
Ph	H	Ph	OTrityl	H	c	88.1	c	-
Ar1	H	Ph	OTBDMS	H	d	77.7	d	90.7
Ar2	Me	Me	OTBDMS	H	e	67.5	e	91.5
Ar3	Me	Me	OTBDMS	H	f	65.8	f	86.5
Ar3	H	Ph	OTBDMS	H	g	74.4	g	95.6
Ar2	H	Ph	OTBDMS	H	h	70.5	h	-
Ar2	Me	Me	H	OTBDMS	i	91.2	i	92.6

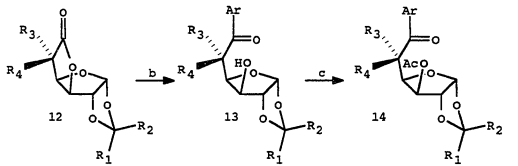
(Ar1, Ar2, Ar3 sch. 2)

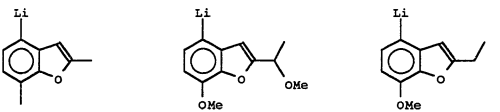
The ketoalcohols 13 are not easily purified. They suffered extensive decomposition (charring) upon standing at room temperature exposed to the atmosphere for a long time. On the other hand the acetates 14 were much more easily purified and they survived longer under these conditions.

Scheme 2



10 11

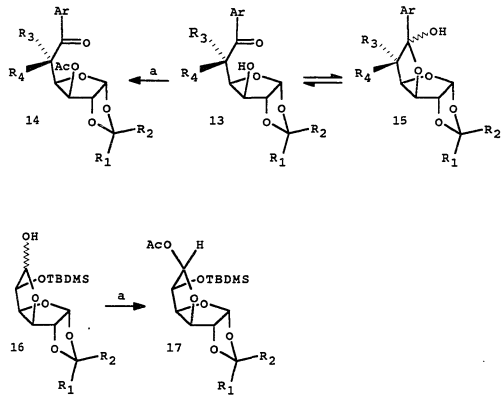




Ar1Li Ar2Li Ar3Li

a) t-BuLi, THF, N_2, -78°C, b) ArLi, THF, N_2, -78°C, c) Ac_2O, pyridine.

Scheme 3



a) Ac_2O, pyridine, room temperature.

Evidence from the IR and ^1H NMR spectra suggest that an equilibrium between the ketoalcohol form 13 and the lactol form 15 exists. In fact IR spectra taken for samples obtained by concentration of chloroform solutions showed no carbonyl group absorption. The ^1HNMR spectra of the same diluted samples in deuterated chloroform showed chemical shifts for the $Hs(H_5)$ of the benzofuranyl moiety corresponding to the ketoalcohol form 13. The complexity of the ^1HNMR spectra indicate that to some extent both forms are present in solution.

Assuming the same equilibrium existing in pyridine both isomeric forms are exposed to the acetic anhydride. The 6-hydroxyl group of the lactol 15 being sterically

more hindered than the 3-hydroxyl of the ketoform 13 was not acetylated. The acetate 14 was obtained shifting the equilibrium towards the ketoform. The acetylation under the same conditions of the lactol 16(mixture 3/1 = endo/exo) yielded exclusively the 6-exo-acetate 17 showing that steric factors are important in controlling the outcome of the reaction under such conditions.The lack of the aromatic group allowed the lactol ring to survive (sch. 3).

Reduction and 3,6-dehydration reactions of the 6-C-arylglycosides

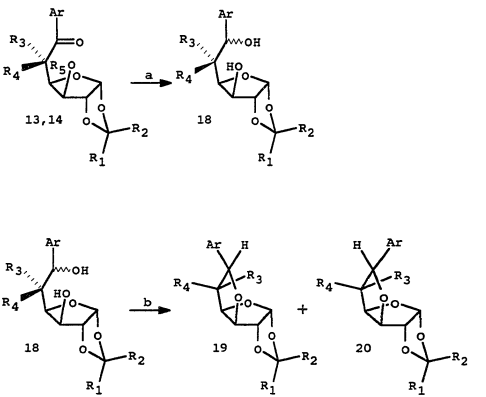
The ketoalcohols 13 and the corresponding ketoacetates 14 were reduced to the same diol 18 with $NaBH_4$ in ethanol at room temperature at high yields. The diols 18 were cyclized[5a,2f] by dehydration with SO_2X_2/Py at room temperature, under N_2 to a mixture of 6-exo 19 and 6-endo-C-aryl-glycosides 20. The glucofurano-derivatives and the 5-deoxy derivatives yielded as a major cyclized product the 6-exo–C-arylglycoside[6] 19. The idofurano derivative yielded as a major product the 6-endo-C-arylglycoside[6] 20 (sch. 4).

Table 2

Ar	R_1	R_2	R_3	R_4	R_5	18	y%	X	y%	19/20
Ph	H	Ph	OR	H	Ac	a	96.5	Br	96.5	2/1
Ar1	H	Ph	OR	H	Ac	b	96.8	Br	86.2	2/1
Ar1	H	Ph	OR	H	H	b	99.6			
Ar2	Me	Me	OR	H	Ac	c	92.2	Br	82.5	1.6/1
Ar3	H	Ph	OR	H	Ac	d	82.9	Br	75.6	2.1/1
Ar3	H	Ph	OR	H	H	d		Cl	79.2	2.3/1
Ar3	Me	Me	OR	H	Ac	e	97.1	Cl	73.0	1.3/1
Ar3	Me	Me	H	OR	H	f	86.7	Cl	79.4	1/1.2
Ar3	Me	Me	H	H	H	g	90.4	Cl	94.7	2/1
Ar3	Me	Me	H	H	Bz	g	50.8			

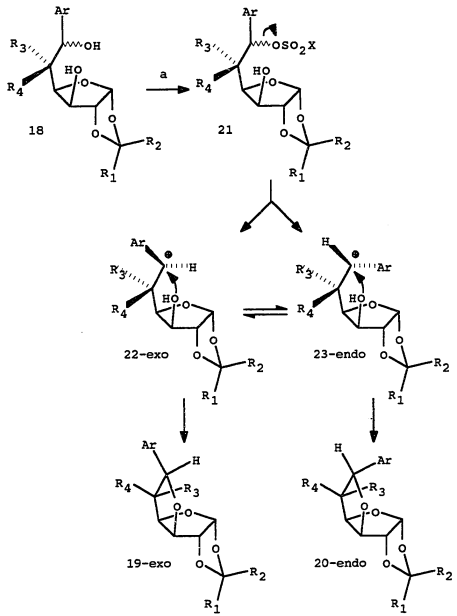
(R=TBDMS, Ar1, Ar2, Ar3 sch. 2)

Scheme 4



a) $NaBH_4$, EtOH, room temperature, b) SO_2X_2, Pyridine, N_2, room temperature.

Scheme 5



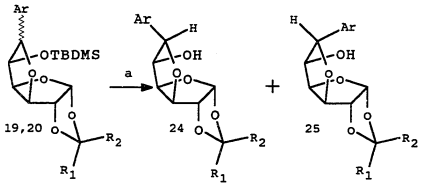
a) SO_2X_2 (X=Cl, Br), Pyridine, N_2, room temperature.

The different steric environment at the two hydroxyl groups of the diol 18 allowed for selective reaction of the 6-OH. Thus the incoming thionyl halide (chloride, or bromide) reacted first with the 6-OH to form the halosulfite ester 21. The 3-OH group is so sterically hindered that even when excess of thionyl halide was used, its rate of reaction was low enough not to give measurable product besides the observed reaction. The halosulfite ester 21 cyclizes to the 6-C-arylglycosides 19 and 20 through the carbocations 22 and 23 which are formed by elimination of the halosulfite moiety (sch. 5).

The exo-conformation 22 is favored by glucofurano (R_3=OTBDMS, R_4=H) and the 5-deoxy-furano (R_3=R_4=H) derivatives and led to the major 6-exo-C-aryl-glucoside 19. The endo-conformation 23 is favored by the idofurano series and led to the 6-endo-C-arylglycoside 20. For both series the favored conformation of the cation and the major product places the Ar-group and the OTBDMS group (R_3 for the glucofurano, R_4 for the idofurano derivatives) in the anti-position rather than the syn-position assumed by the minor product.

The Sn1 nature of the mechanism was demonstrated from the cyclization of the 5-deoxy-furano diols (R_3=R_4=H) 18g. The two diastereomeric diols separately underwent cyclization to yield identical mixtures of 6-exo 19g and 6-endo-C-aryl-5-deoxyglycosides 20g, with the exo 19g being the major product. The mixtures of the 6-C-arylglycosides 19 and 20 were not easily separated, specifically the 6-C-aryl-5-deoxy glycosides 19g and 20g were inseparable. Better separation for some of the 6-C-aryl-glucofurano derivatives was achieved when the silyl ether group (R_3=OTBDMS) was cleaved with tetrabutylammonium fluoride (TBNF) in THF, room temperature under N_2, to produce the alcohols 24 and 25 (sch. 6).

Scheme 6



19/20	Ar	R_1	R_2	Prod.	y%
19a/20a	Ph	H	Ph	24, 25	78.7
20e	Ar3	Me	Me	25*	91.5
19e	Ar3	Me	Me	24	87.8
20e	Ar3	Me	Me	25	87.9

*isolated as an acetate

a) TBAF, THF, N_2, room temperature.

Each diastereomer from the mixtures of the 6-exo 19 and 6-endo-C-aryl-glycosides 20 was identified based on its ^{1}HNMR spectrum. Extrapolating from simpler compounds based on the same [1,4: 6,3]-difuranose system reported in the literature[6], a consistent pattern was observed. The diastereomer with the 6-substituent placed exo 19 showed the smaller coupling constant between the H_5-H_6 for the glucodifurano series. The diastereomer with the 6-substituent placed endo 20 showed larger coupling constant between the H_5-H_6 (table 3).

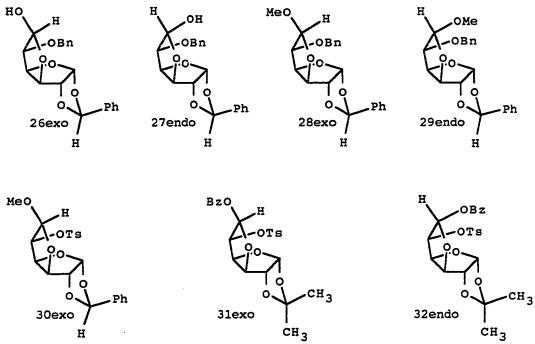
Table 3

Comp.	H_1	H_2	H_3	H_4	H_5	H_6
26*exo	6.19 d *3.7*	/	/	/	3.88 dd *4.7, 4.7*	5.23 dd
27*endo	6.13 d *3.7*	/	/	/	3.87 dd *4.7, 5.6*	5.38 dd
28*exo	6.17 d *3.7*	4.82 d *4.5*	4.71 d	4.93 dd *4.5, 2.8*	3.92 dd *2.8*	4.96 d
29*endo	6.23 d	4.77 d *3.5*	4.70 d *5.0*	4.87 dd	3.67 dd *4.5, 4.5*	4.72 d *4.5*
30*exo	6.06 d *3.5*	4.79 d	4.70 d *4.5*	4.98 dd	4.70 dd *4.5, 1.8*	4.96 d *1.8*
31*exo	5.82 d	4.51 d *3.7*	4.61 d *3.6*	4.79 dd *4.6*	4.94 dd *3.3*	6.12 d *3.3*
32*endo	6.01 d	4.61 d *3.5*	4.73 d *4.3*	4.98 dd	4.87 dd *4.5, 4.5*	6.25 d *4.5*
16endo	6.16 d *3.7*	4.94 d *3.7*	4.63 d *4.1*	4.70 dd	4.15 dd *4.6, 4.6*	5.11 d *4.4*
16exo	6.12 d *3.7*	4.96 d	4.96 d	4.77 dd *3.5, 4.3*	4.04 dd *4.3, 1.7*	5.23 d *1.9*
17exo	6.13 d *3.7*	4.79d	4.79 d	4.92 dd *4.9, 5.1*	4.17 dd *4.7, 1.9*	5.96 dd *1.9*
20a-endo	6.02 d 3.9	4.71 d 3.8	4.99 d 2.9	4.36 dd *3.3, 4.6*	4.14 dd *5.6*	5.02 d *6.2*
19a-exo	6.14 d	4.74 d	4.46 d	4.54 dd	4.54 dd	4.90 d

	3.9	*3.9*	*3.0*			*3.7*
19b-exo	6.15 d	4.85 d	4.59 d	4.61 dd	4.73 dd	5.21 d
	3.7	*3.7*	*3.9*	*3.8, 6.5*	*3.8, 6.5*	*3.8*
20b-endo	6.05 d	4.83 d	5.14 d	4.55 dd	4.12 dd	5.26 d
	3.8	*3.8*	*3.5*	*3.5, 5.7*	*5.6, 5.6*	*5.5*
20c-endo	5.89 d	4.64 d	4.97 d	4.22 dd	4.36 dd	5.29 d
	3.6	*3.7*	*2.9*	*2.7, 4.5*	*4.2, 7.5*	*6.4*
19c-exo	6.00 d	4.66 d	4.49 d	4.69 dd		5.15 d
	3.6	*3.6*	*3.2*	*3.1, 5.9*		*3.5*
20e-endo	5.88 d	4.63 d	4.97 d	4.33 dd	4.21 dd	5.28 d
	3.7	*3.7*	*2.8*	*2.9, 4.3*	*4.4, 6.5*	*6.6*
19e-exo	6.00 d	4.65 d	4.48 d	4.71 dd	4.62 dd	5.15 d
	3.6	*3.4*	*3.1*	*3.2 5.9*	*5.9, 3.6*	*3.6*
20f-endo	5.98 d	4.46 d	4.71 d	3.97 d	4.98 d	5.11 d
	3.5	*3.5*	*1.9*		*7.7*	
19f-exo	6.05 d	4.55 d	4.63 d	3.41 d	4.63 d	5.18 d
	3.4	*3.4*	*2.3*	*2.3*		*8.5*
19g-exo	6.02 d	4.73 d	4.77 d	5.10 dd	2.48 dd	5.22 dd
	3.8	*3.7*	*3.2*	*3.2, 3.4*	*5.1, 13.6*	*5.1, 10.7*
					(5endo, 2.00 ddd *3.6, 10.2 14.0*)	
20g-endo	6.00 d	4.79 d	4.45 d	5.02 dd	2.33 dd	5.10 dd
	3.8	*3.8*	*3.2*	*3.6, 5.6*	*7.3 14.2*	
					(5endo, 2.00 ddd *3.6, 10.2, 14*)	

*data obtained from ref. 6, plain letters δ(ppm), italics j(Hz), d doublet.

Scheme 7

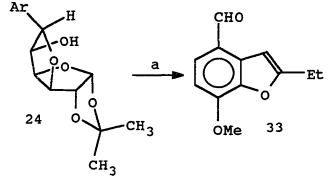


Oxidation reactions of the 6-C-benzofuranylglycosides

The alcohols 24 and 25 also underwent extensive decomposition upon prolonged exposure to the atmosphere. In fact attempted oxidation[7] of the alcohol 24 with DMSO and Ac_2O yielded not the expected ketone but traces of the 4-benzofuranyl aldehyde 33 along with unidentified carbohydrate decomposition[9] products (sch. 8).

The ketoalcohol 13f on the other hand underwent smooth oxidation with DMSO/Ac_2O to the corresponding diketone 34, the acetate 14f was the side product obtained. DMSO/$(COCl)_2$[8] also provided the diketone 34 from the ketoalcohol 13f. Attempted desilylation of the diketone 34 under standard conditions and then acetylation to the corresponding acetate, yielded decompositon products and traces of the 4-benzofuranyl aldehyde 33 (sch. 9).

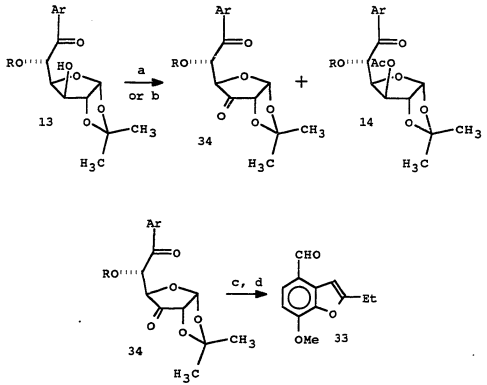
Scheme 8



a) Ac_2O, DMSO, room temperature, (Ar = 2-ethyl-7-methoxy-benzofuran).

The 4-benzofuranyl aldehyde 33 was formed in both cases under strong basic conditions, by cleavage of the C_5-C_6 carbon bond from the carbohydrate moiety. Strong basic conditions favor and initiate eliminations on carbohydrate substrates[10-12], especially those bearing carbonyl groups. Presumably the alcohol 24 was oxidized to the corresponding ketone 35. The ketone 35 could undergo ring opening of the 6,3-oxygen bridge facilitated by the DMSO towards the acetate 36. Nucleophilic attack by the acetic anhydride on the 5-carbonyl group leads to the alcoxide 37, which easily undergoes elimination to the obtained aldehyde 33 and presumably the mixed anhydride 37 which was not isolated due to further degradation reactions (sch. 10).

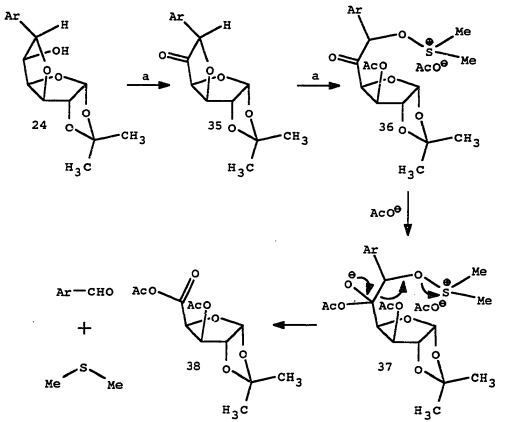
Scheme 9



a) Ac_2O, DMSO, room temperature, (34, 43.4%, 14f, 26.8%), b) $(COCl)_2$, DMSO, -78°C, (34, 53%), c) TBAF, THF, N_2, room temperature, d) Ac_2O, Pyridine, (Ar = 2-ethyl-2methoxy benzofuran, R=TBDMS).

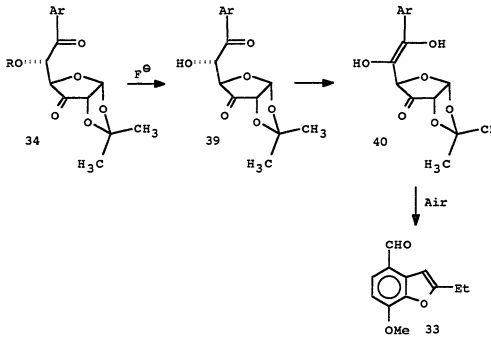
Desilylation of the diketone 34 with fluoride ions leads to the alcohol 39. The initially formed α-hydroxy diketone 39 could undergo rearrangement to the enolate form 40. The enolate 40 in the presence of air could be further oxidized[13], resulting to the C_5-C_6 bond cleavage. The benzofuranylaldehyde 33, is one of the products of such oxidation isolated in trace amounts (sch. 11). The carbohydrate residue was not isolated due to further decomposition.

Scheme 10



a) DMSO, Ac_2O, room temperature, (Ar = 2-ethyl-7-methoxy benzofuran).

Scheme 11



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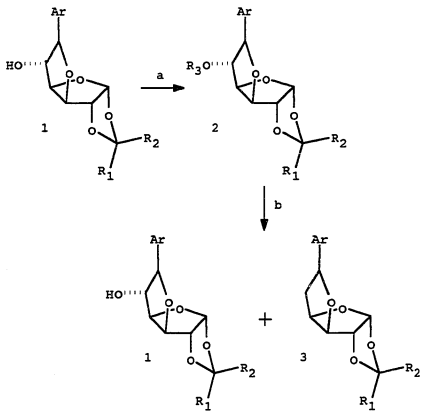
Deoxygenation of the 6-C-benzofuranyl glycosides

Deoxygenation reaction at C_5 of the 6-C-benzofuranylgluco-[1,4:3,6] difuranoglycoside

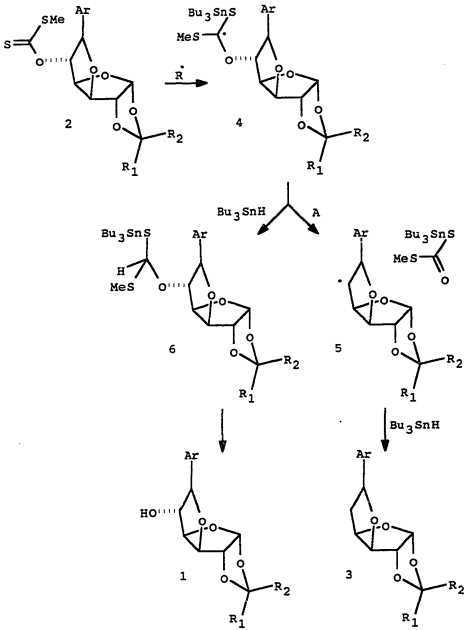
The 5-hydroxyl group of the carbohydrate moiety of the 6-benzofuranyl glycosides 1 was substituted by a hydrogen in a free radical deoxygenation reaction[1,2,3], (Barton deoxygenation[4-10]). The stereochemistry at the newly formed stereocenter at C_5 of the parent 6-C-aryl- glycoside was proved unambiguously by the 5-deoxyglycoside.

Scheme 1



a) NaH, Imidazole, CS_2, MeI, N_2, THF, (2 R_3=MeSCS), b) Bu_3SnH, AIBN, N_2, refl. toluene, (R_1=H, R_2=Ph, 3 (34.7%), 1 (29.7%)), (R_1=R_2=Me, 3 (53.7%), 1 (17.1%)), Ar=2-ethyl-7-methoxybenzofuran.

Scheme 2



The 6-exo-C-benzofuranylglycoside 1 was converted to the corresponding xanthate ester 2 at high yields, in dry THF (by NaH, CS_2, methyl iodide and imidazole as a

catalyst[8], under N_2). The xanthate ester 2 was deoxygenated by refluxing in dry toluene with Bu_3SnH, under N_2, and AIBN as a free radical initiator (sch. 1). The 5-deoxyglycoside 3 was obtained along with the parent alcohol 1. Apparently the intermediate radical 4 underwent fragmentation[1,2] to the alkyl radical 5, which led to the 5-deoxy-glycoside 3. On the other hand [1,2] addition of Bu_3SnH to the radical 4 forms the dithioorthoformate 6 which finaly was hydrolyzed to the parent alcohol[1,2]. The major product was the 5-deoxyglycoside 3 (sch. 2).

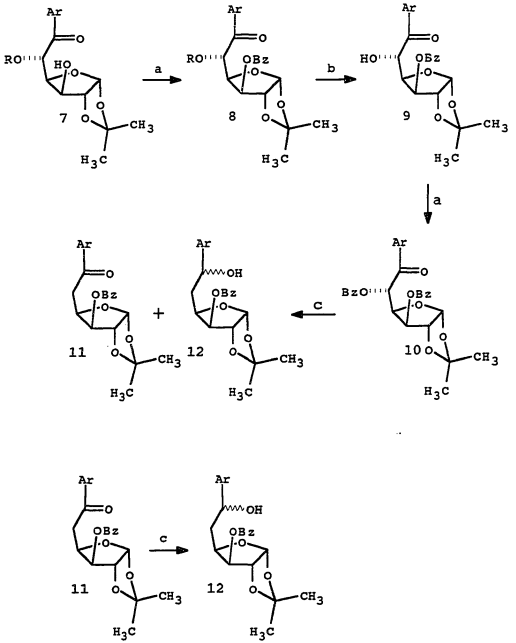
Deoxygenation at C_5 of the 6-C-benzofuranylgluco-[1,4]-furanoglycoside

A similar deoxygenation could also be performed on the acyclic glycoside 10. The immediate product from the Grignard reaction (ch.5), ketoalcohol 7, underwent benzoylation in pyridine at room temperature. The product, benzoate ester 8, underwent desilylation with TBNF in THF under N_2, to the alcohol 9. The alcohol 9 was never isolated or purified but immediately was subjected to benzoylation under standard conditions to afford dibenzoate 10 (sch. 3).

The dibenzoate 10 was refluxed in dry toluene with excess of Bu_3SnH and catalytic amount of AIBN, under N_2. A mixture of products was obtained, the expected[1,12] 5-deoxy-6-keto-benzofuranylglycoside 11 and the 5-deoxy alcohol 12 (sch. 3). The alcohol 12 was obtained from the reduction[13,14] of the primary product, the ketone 11, by the Bu_3SnH.

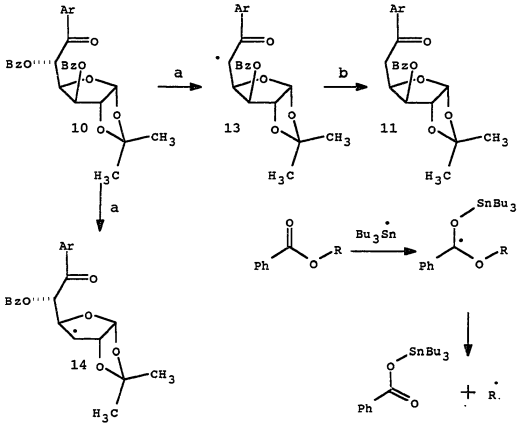
Both benzoate groups could have reacted with the tributyltin radical to generate the corresponding intermediates 13 and 14. The stability of the radicals 13 and 14 is the factor[1] that determines the selectivity. The alkyl radicals 13 and 14 are the fragmentation product of a carbonyl radical that is formed first, and then decomposes to the corresponding alkyl radical and the tributyltin benzoate. The relative stability of the radicals 13 and 14 determines which benzoate undergoes the radical cleavage[1]. The alkyl radical 13, being alpha to the 6-keto-group, is the more stable (sch. 4).

Scheme 3



a) Benzoyl chloride, pyridine, room temperature, b) TBAF, THF, N_2, room temperature, 8 (77.8%), 10 (96.3% from 8), (7, 8 R=TBDMS), c) Bu_3SnH, AIBN, refl. toluene, N_2, 11 (39.2%), 12 (41.4%), (Ar=2-ethyl-7-methoxybenzofuran).

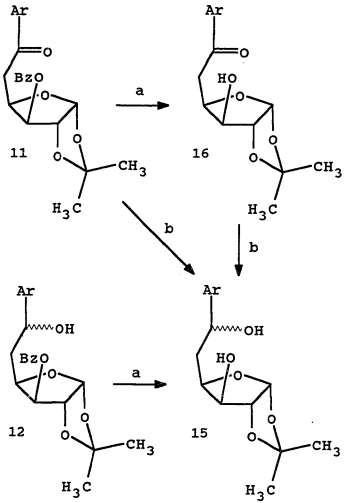
Scheme 4



a) $Bu_3Sn^{\cdot}$, b) Bu_3SnH, (Ar=2-ethyl-7-methoxybenzofuran).

The 3-benzoate-6-hydroxyl glycoside 12 was a mixture of two diastereomers. Basic hydrolysis of the benzoate group led to the diol 15, which was separated into the two diastereomers. Hydrolysis of the benzoate 11 to the keto alcohol 16, followed by reduction of 16 with $NaBH_4$ in EtOH produced the same diol mixture 15. This mixture 15 was also obtained by direct reduction of the keto benzoate 11 with $NaBH_4$/EtOH (sch. 5).

Scheme 5



a) NaOH, MeOH, room temperature, b) $NaBH_4$, EtOH, room temperature, 15 (70.3%, (44.7/25.6), from 12, 81.1%, from 11), Ar=2-ethyl-7-methoxybenzofuran.

Cyclization of each diastereomer of 15 individually, or of the mixture itself, with thionyl chloride with pyridine, or Et_2O, or THF as solvents yielded the same mixture of 5-deoxyglycosides pointing to an intramolecular Sn1reaction type (ch.6).

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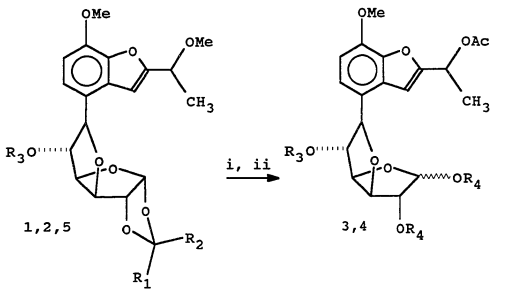
Hydrolysis of the 6-C-benzofuranyl glycosides

The synthesis of the 6-C-benzofuranylglycosides 1 was the first part of the outlined plan. The second part is a direct attempt to form the nine member C-C ring by an intramolecular cyclization between the C_1 carbon of the carbohydrate part and the C_3 carbon of the benzofuranyl part.

The 1,2-hydroxyl groups of the carbohydrate had been protected with a common protecting group as benzylidene or isopropylidene[1]. The intramolecular nucleophilic attack from the benzofuranyl ring to the anomeric carbon could not be attempted while the anomeric hydroxyl group is protected with the rather inert acetalic function. Therefore the hydrolysis of the acetals and possible activation of the anomeric hydroxyl group became imperative.

The 5-hydroxyl-6-C-benzofuranylglycosides 1 were easily converted to the corresponding acetates 2 under standard conditions. Attempted hydrolysis by refluxing for 5h in 80% acetic acid[1], resulted in a complex mixture of diols 3. Acetylation of the crude triol product yielded a mixture of four diastereomeric tetraacetates 4 at 45.7% overall. The four diastereomeric tetraacetates could not be separated. Nevertheless cyclization of the mixture of the tetraacetates was attempted under Lewis Acid catalysis. The mixture of tetraacetates 4 was treated with $SnCl_4$ at room temperature under N_2 in CH_2Cl_2 or CH_3CN. A polymer was formed and precipitated within 30 min. The formation of the polymer was attributed to the acetate group attached on the α-C of the 2-ethyl group of the benzofuran. The ease of exchange of the methoxy group to hydroxy or acetate at that position, reflecting the ease of the carbocation formation is well documented (ch. 4).

Scheme 1



	R_1	R_2	R_3	R_4
1	H	Ph	H	-
2	H	Ph	Ac	-
3	-	-	Ac	H
4	-	-	Ac	Ac
5	H	Ph	TBDMS	H

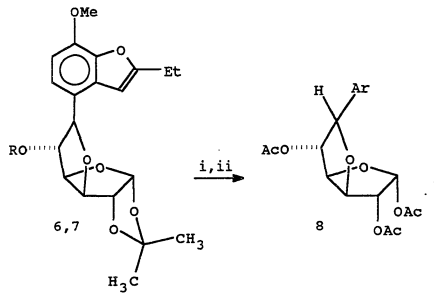
i) a) refl. 80% AcOH, or b) AcOH, Ac_2O, (1/1), cat. H_2SO_4, ii) Ac_2O, pyridine.

A second method of cleavage of the benzylidene group was the acetolysis[3] (Ac_2O/AcOH = 50/50, cat. H_2SO_4) of the silylether 5. The acetolysis was followed by acetylation of the product under standard conditions to yield only traces of the expected tetraacetate 4.

The demonstrated sensitivity of the α-oxygenated group of the 2-alkyl substituent of the benzofuran toward acids and Lewis Acid catalysts prompted the use of the corresponding deoxygenated benzofuran.

The 5-hydroxyl glycoside 6 was converted to the acetate 7 under standard conditions. Attempted hydrolysis of the isopropylidene group of acetate 7 with BCl_3 resulted only in traces of the anticipated triacetate 8, after acetylation of the crude product, accompanied by other unidentified products. Unidentified polymeric products only were also obtained by treating the acetate 7 with $AlCl_3$.

Scheme 2

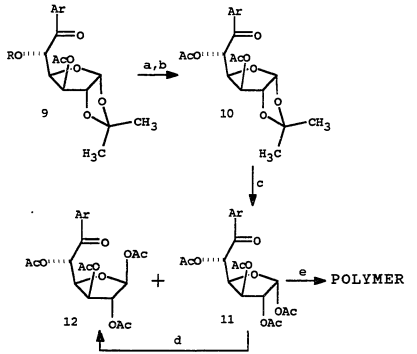


i) BCl_3, CH_2Cl_2, N_2, 0°C, 2min. (6 R=H, 7 R=Ac), ii) Ac_2O, pyridine, room temperature.

The glycoside 9 was converted to the 6-keto-3,5-diacetate 10 in two steps. Cleavage of the 5-t-butylsilyl ether group was followed by acetylation of the alcohol, which was not isolated. The ketodiacetate 10 was subjected to acetolysis[3] (Ac_2O/AcOH

= 50/50, cat. H_2SO_4). The isopropylidene group was cleaved completely. Two products were isolated, the α-tetraacetate 11 25.2%, and the β-tetraacetate 12 34.3%.

Scheme 3



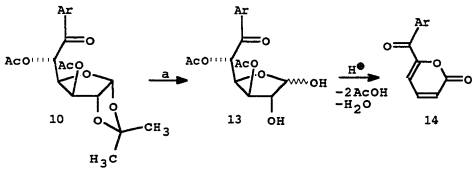
a) TBAF, THF, N_2, room temperature, (R=TBDMS) b) Ac_2O, pyridine, room temperature, c) Ac_2O, AcOH, (1/1), cat.H_2SO_4, d) $BF_3.Et_2O$, CH_2Cl_2, N_2, room temperature, e) $SnCl_4$, CH_2Cl_2, N_2, room temperature .

Attempted intramolecular cyclization of 11 by treating it with $BF_3.Et_2O$[5] in CH_2Cl_2 under N_2 resulted only in isomerization at the C_1. Attempted cyclization[2] of the α-tetraacetate 11 with $SnCl_4/CH_2Cl_2$ under N_2 at room temperature led to polymerization.

However when the keto diacetate 10 was treated with PTSA, H_2O, MeOH, THF at room temperature, elimination reactions[6] ocurred, finally yielding the lactone 14.

Apparently an initial protonation of the isopropylidene led to its hydrolysis. The hemiacetal 13 is the presumed product. The hemiacetal 13 under acidic catalysis underwent elimination of two acetic acid molecules and dehydration to eventually form the α-pyrone 14 (sch. 4).

Scheme 4



a) PTSA, H_2O, methanol, THF, room temperature.

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Synthesis of the 6-C-benzofuranyl-1-methoxy glycosides

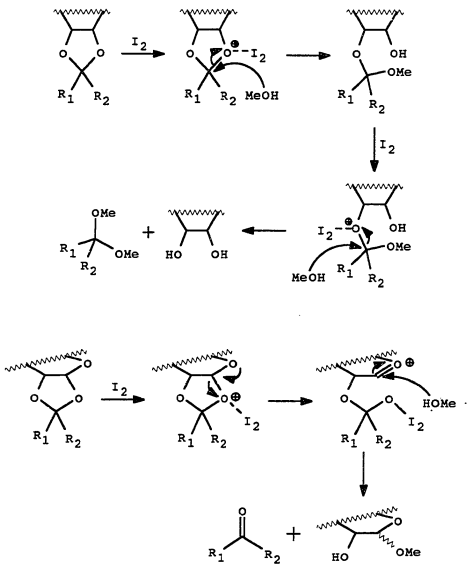
The I_2 catalyzed methanolysis of acetals

The hydrolysis of the benzylidene and isopropylidene protective groups of 1,2 diols could be effected by a large number of methods[1]. A variety of reagents ranging from very mild to very strong acids and Lewis Acid catalysts are available. The established sensitivity of the benzofuran moiety towards strong acids and Lewis acids, suggested that milder methods should be used. Milder methods such as hydrogenolysis[2], TMSX (X = Br, I) cleavage[3], TMSCl/$NaBH_3CN$ cleavage[4], or even NBS reaction[5] on the benzylidene could not be applied without complications. The C_6 of the carbohydrate unit that is bearing the benzofuranyl moiety is obviously benzylic.

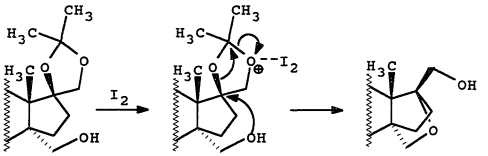
An alternative method for cleavage of the acetals is their methanolysis[6], catalyzed by I_2. Standard conditions[6] of the method is to stir the acetal in a dilute solution of I_2 (0.5-1%) in methanol either at room temperature or at reflux. The soft acid I_2 forms a complex with one of the oxygens of the dioxolane ring activating the formation of the oxonium ion on the acetal carbon. Nucleophilic attack from methanol takes place on the oxonium ion and the product is the diol and presumably the dimethyl ketal. When the anomeric center is involved the nucleophilic attack from methanol generated the corresponding methyl glycoside (sch. 1).

The method is not limited to O-acetals. Thioacetals also could undergo the same cleavage. Reported applications of the reaction showed that appropriately substituted molecules like the steroid 1 underwent intramolecular cyclization[7] under these conditions to the corresponding product 2 (sch. 2).

Scheme 1



Scheme 2



1 2

The I_2 catalyzed methanolysis of the 6-C-benzofuranylglycosides

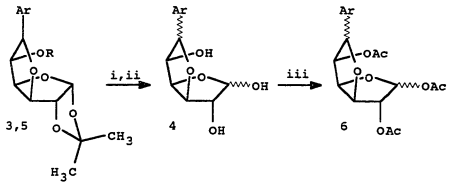
The mixture of 6-(exo, endo)-C-benzofuranyl-5-acetate-glucodifuranosides 3 was subjected to the I_2/MeOH reaction. ^1H NMR spectrum of the crude product of the reaction indicated the formation of at least four methyl glycosides. Also extensive cleavage of the 5-acetate group was observed. Further hydrolysis of the crude product with 80% acetic acid at 80°C yielded an inseparable mixture of the four triols 4. The same mixture of the four triols 4 was obtained from the reaction of the corresponding 5-hydroxyl-6-C-benzofuranyl glycosides 5 (sch. 3).

The mixture of triols 4 was acetylated to the corresponding mixture of triacetates 6. Attempted intramolecular cyclization with $SnCl_4$ in CH_2Cl_2 failed, yielding only polymeric products.

The cleavage of the 5-acetate group suggested an anchimeric participation to the carbocation generated at the anomeric center 7. Nucleophilic attack from methanol takes place apparently first at the 5-acetate group which is transformed to the orthoacetate ester 8. Reaction of the ester 8 with I_2 eventually leads to the anomeric

cation 10 with elimination of methyl acetate. Nucleophilic attack from methanol on the cation 10 generated the mixture of the 1-methyl glycosides 11 (sch. 4).

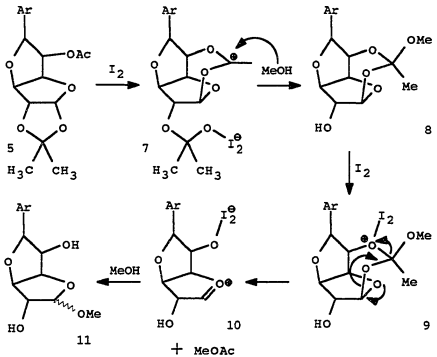
Scheme 3



i) I_2, refl. MeOH, ii) AcOH 80%, 80°C, (R=Ac 3, R=H 5).

The cleavage of the 5-acetate group during the I_2/MeOH reaction dictated that the parent alcohols should be used. Pure 6-exo-C-benzofuranyl glycosides 12, 13 and 6-endo-C-benzofuranyl glycosides 14, 15 (benzylidene 12, 14, isopropylidene 13, 15) gave identical mixtures of four 1-methyl-6-C-benzofuranyl glycosides (19, 20, 21, 22). Separation of the mixture by column chromatography ($CHCl_3$/EtOAc = 6/4) succeeded in isolating 19 (6-exo-C-aryl-1-α-methyl-glycoside) and 22 (6-endo-C-aryl-1-β-methyl glycoside) while the 20 (6-exo-C-aryl-1-β-methyl glycoside) and 21 (6-endo-C-aryl-1- α-methyl glycoside) were obtained as an inseparable mixture (sch. 5, table 2).

Scheme 4

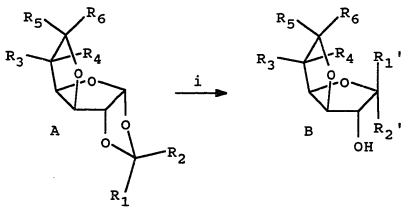


The idodifuranoglycosides 16(6-exo-C-aryl) and 17(6-endo-C-aryl-5-O-t-butyldimethylsilyl-1,2-O-isopropylidene) gave glycosides 23(6-exo-C-aryl-1-α-methyl), 24(6-exo-C-aryl-1-β-methyl), 25(6-endo-C-aryl-1-α-methyl), 26(6-endo-C-aryl-1-β-methyl-idodifuranoside). Separation of this mixture was similar to the separation of the glucofurano derivatives. The 23 and 26 were obtained pure, the 24 and the 25 as an inseparable mixture (sch. 5, table 2).

The 5-deoxy-6-exo-C-benzofuranyl glycoside 18 undergoing the same reaction yielded also a similar mixture of four methyl glycosides 27(6-exo-C-aryl-1-α-methyl), 28(6-exo-C-aryl-1-β-methyl), 29(6-endo-C-aryl-1-α-methyl), 30(6-endo-C-aryl-1-β-methyl), which could not be separated (sch. 5, table 2).

The formation of the 1-α, or β-methyl glycosides was expected. The scrambling of the stereochemistry at C_6 was attributed to the benzylic character of that carbon. The stereochemistry at C_5 determines which carbocation is favored. The idoglycosides favored the exo-carbocation 29, the 5-deoxy and the glucoglycosides the endo-carbocation 30 (sch. 6).

Scheme 5



i) I_2, refl. MeOH.

Table 1

A	R_1	R_2	R_3	R_4	R_5	R_6
12	H	Ph	H	OH	Ar	H
13	Me	Me	H	OH	Ar	H
14	H	Ph	H	OH	H	Ar
15	Me	Me	H	OH	H	Ar
16	Me	Me	OR	H	Ar	H
17	Me	Me	OR	H	H	Ar
18	Me	Me	H	H	Ar	H

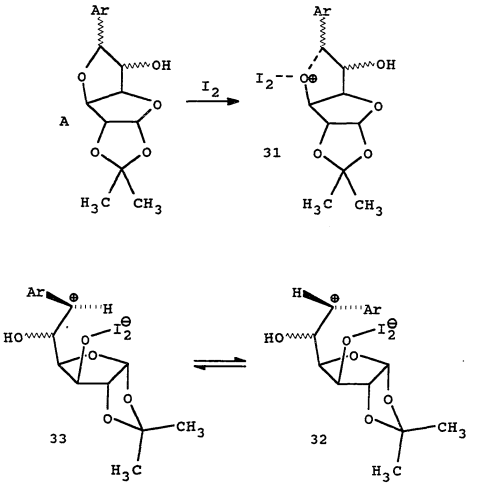
R=TBDMS

Table 2

B	R'_1	R'_2	R_3	R_4	R_5	R_6	B y% from A			
							12	13	14	15
19	H	OMe	H	OH	Ar	H	24.2	19.8	21.1	19.6
20	OMe	H	H	OH	Ar	H	21.5*	13.2*	14.1*	19.6*
21	H	OMe	H	OH	H	Ar	10.8*	6.6*	7.0*	9.8*
22	OMe	H	H	OH	H	Ar	12.1	10.5	16.9	19.6
								16		17
23	H	OMe	OH	H	Ar	H		10.2		10.4
24	OMe	H	OH	H	Ar	H		11.2*		8.5*
25	H	OMe	OH	H	H	Ar		29.6*		17.0*
26	OMe	H	OH	H	H	Ar		37.9		41.1
								18		
27	H	OMe	H	H	Ar	H		12.2*		
28	OMe	H	H	H	Ar	H		26.8*		
29	H	OMe	H	H	H	Ar		3.0*		
30	OMe	H	H	H	H	Ar		9.0*		

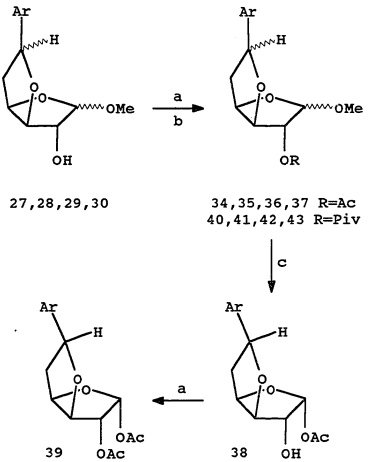
* ^{1}H NMR integration

Scheme 6



The possibility that the carbocations 32 and 33 could undergo nucleophilic attack by the solvent methanol to form the corresponding methoxy compounds should be excluded because no such side product was detected. On the other hand intramolecular cyclization[7] is much faster and predominates over the intermolecular nucleophilic attack from methanol, especially at positions with increased steric demand.

Scheme 7



a) Ac_2O, pyridine, room temperature, (R=Ac), b) PivCl, pyridine, room temperature, (R=Piv 91.3%), c) AcOH 80%, 80°C.

Hydrolysis of the 1-methoxy-6-C-benzofuranyl-5-deoxy-gluco-[1,4:3,6]-difuranoglycosides

The mixture of the four 5-deoxy-6-C-benzofuranyl-1-(α, β)-methyl glycosides (27, 28, 29, 30) was acetylated under standard conditions to the mixture of the corresponding acetates (34, 35, 36, 37, 91.8%). Attempted hydrolysis of the 1-methyl-glycoside unit with 80% AcOH at 80°C led to acetate migration. The 1-α-acetyl-

glycoside 38 was isolated pure, being the major component of the mixture. Acetylation of the acetyl glycoside 38 yielded the diacetate 39 (sch. 7).

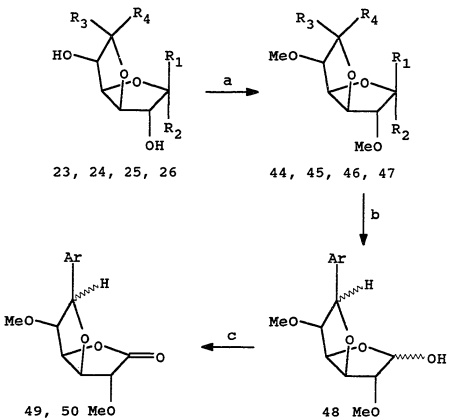
The mixture of the four 1-(α, β)-methyl glycosides 27, 28, 29, 30 yielded the corresponding pivaloate esters under treatment with pivaloyl chloride in pyridine at room temperature. The mixture of the obtained pivaloate esters 40, 41, 42, 43 could not be separated.

The [1,2] acetate migration suggested that groups not prone to migration under acidic hydrolysis conditions should be used to protect the free hydroxyl groups.

Hydrolysis of the 1,2,5-trimethoxy-6-C-benzofuranyl-ido-[1,4:3,6]-difurano glycosides

The idodifuranodiols 23, the mixture of 24 and 25 and the 26 were methylated[8] to the corresponding trimethyl derivatives 44, 45 and 46, 47 respectively, with NaH, MeI in THF under N_2. The trimethyl derivatives were then hydrolyzed with 80% acetic acid at 80°C for 48h. The trimethyl derivatives 44, the mixture of 45 and 46, and the 47 gave the same mixture 48 of four hemiacetals. The mixture of the hemiacetals 48 was oxidized[9] with DMSO/Ac_2O to the corresponding lactones. The product of the oxidation was an inseparable mixture of two lactones 49 and 50 (49/50 = 2.6/1 ^1H NMR integration, sch. 8). The 6-endo-C-benzofuranyl lactone 49 was the major component corresponding to the favored conformation 51 of the intermediate cation formed from the ring opening-closing during the hydrolysis step at C_6 (sch. 9).

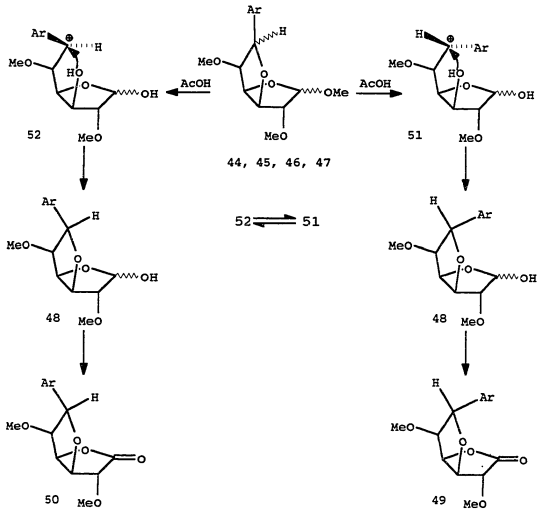
Scheme 8



diol	R_1	R_2	R_3	R_4	Prod.	y%	48%
23	H	OMe	Ar	H	44	75.2	64.0
24	OMe	H	Ar	H	45	83.3	64.9
25	H	OMe	H	Ar	46	83.3	64.9
26	OMe	H	H	Ar	47	79.4	69.2

a) NaH, THF, MeI, N_2, b) AcOH 80%, 80°C, c) Ac_2O, DMSO, room temperature (50.2%).

Scheme 9



The mixture of hemiacetals 48 was treated with $BF_3.Et_2O$ at room temperature for 48h. The anticipated cyclization did not ocurr, the hemiacetals 48 were recovered. The mixture of the lactones 49 and 50 was also recovered when it was treated with $BF_3.Et_2O$ or $AlCl_3$ at room temperature for 48h.

The 1-O-methyl-6-C-aryl glycosides were identified on the basis of their ^1H NMR spectra (table 3). The H_1 and the H_2 of the 1-β-O-methyl glycosides showed no coupling, pointing out the respective diastereomers. The stereochemistry at C_6 was determined based on the j-value of the coupling between the H_5 and H_6. The 6-endo-C-glucodifuranosides showed larger values than the 6-exo-C-aryl isomers due to the syn-conformation of the H_5 and H_6. The stereochemistry at C_6 for the 6-endo-C-idoglycosides was determined from the interaction of the $H_{3'}$ from the 6-benzofuranyl group and the 1-β-methoxy group. Particularly for the 6-endo-C-benzofuranyl-1-β-methyl idoglycoside the $H_{3'}$ is shifted to higher δ values than the corresponding $H_{3'}$ of the other isomers. The trimethyl 6-exo-C-aryl-idoglycosides in which the benzofuranyl moiety is syn to the 5-methoxy group, were identified by the shielding effect of the aromatic group on that methoxy group, shifting the corresponding chemical shift to lower values (data analysis based on the same references as in ch. 6).

Table 3

Comp.	H_1	H_2	H_3	H_4	H_5	H_6	$H_{3'}$	1-MeO
19	4.67	4.67	4.67	4.27 dd *2.1, 4.3*	4.04 dd *4.8*	5.10 d *4.4*	6.48	3.51
20	/	/	/	/	/	5.13 d *4.4*	6.47	3.52
21	/	/	/	/	/	5.20 d *7.8*	6.37	3.51
22	4.98	4.26	4.63 d *4.8*	4.84 dd *5.0*	4.07 dd *5.3, 8.3*	4.92 d *8.3*	6.41	3.48

23	5.23 d *2.7*	4.30 d *2.7*	4.73 d *4.7*	4.81 dd *4.7, 2.3*	4.26 dd *2.3, 4.3*	5.05 d *4.5*	6.46	3.53
24	4.97	/	/	4.70 dd *5.0, 2.1*	4.60 dd *1.8, 4.9*	5.15 d *4.5*	6.51	3.51
25	5.60 d *2.9*	/	4.80 d *4.5*	/	/	4.85 d *6.7*	6.40	3.47
26	5.00	4.40	4.58 d *8.6*	4.21 dd *8.7, 3,6*	4.89 dd *3.5, 6.2*	4.49 d *6.3*	6.85	3.40
34	5.24 d *4.3*	4.94 dd *4.1, 3.9*	5.02 dd *3.5, 5.2*	4.89 dd *5.4*	2.38 dd *4.7, 13.6* 1.93 ddd, *5.4, 13.7, 11.1*	5.14 dd *11.1*	6.45	3.41
35	5.19	4.97	4.75 d *4.8*	5.12 dd *5.2*	2.45 dd *5.4,13.7* 2.05 ddd, *5.4, 10.7, 13.9*	5.45 dd *5.4, 10.7*	6.39	3.49
37	5.34	4.99	5.04 d *4.1*	4.88 dd *5.5, 11.5*	2.50 ddd *5.4, 8.4, 13.8* 2.10ddd *5.4, 12.0*	5.40 dd *5.4, 10.7*	6.86	3.45
44	5.13	/	4.73	4.90	/	5.08	6.49	3.00*
45	5.00	3.86	4.82 d *4.8*	4.88 d *4.9*	3.90 d *3.5*	5.48 *3.4*	6.43	3.00*
46	4.90 d *7.4*	/	4.70 dd *2.5, 5.6*	4.77 dd *2.1, 5.7*	/	5.24 d *4.5*	6.52	3.34*

47	5.10	4.00	4.61 d *6.3*	4.89 dd *3.4, 6.3*	3.88 dd *3.4, 8.5*	4.70 d *8.5*	6.89	3.34*
49	/	4.92 d *6.4*	/	/	4.68 d *4.3*	5.09 dd *1.0, 4.3*	6.36	3.40*
50	/	5.23 d *3.2*	/	/	4.88 d *4.1*	5.16 d *3.9*	6.41	3.00*

* 5MeO, plain letters δ-values, italics j-values

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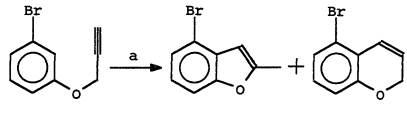
Discussion and conclusions

The synthesis of medium size carbocyclic units is an important part of the total synthesis of more complicated natural products[1]. The utilization of a carbohydrate substrate to provide the 6-carbon fragment with high stereochemical and functional content in combination with another molecular fragment providing 3-carbons was the conceptual basis for the outlined research plan. The use of this approach was demonstrated by applying the concept on the retrosynthetic analysis of the gibberellin and grayanol molecular skeleta. An appropriately substituted benzofuran was chosen as the source for the 3-carbon fragment. The benzene ring of the benzofuran could serve to build rings C, D of the gibberellin and the grayanol skeleta (ch.1).

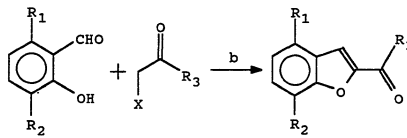
The synthesis of the 4-bromobenzofuran derivatives

The synthesis of the 4-bromobenzofuran derivatives was the first part of the synthetic approach. Essentially two methods succeeded in producing the 4-bromo benzofuran. The first was the thermal [3,3] Claisen rearrangement of the corresponding propargyl-aryl-ether 1 to yield the 4-bromo-2,7-dimethylbenzofuran 2 along with its isomer 5-bromo-8-methylchromene 3. The second method and more important was the basic condensation of a salicylaldehyde 4 with an α-halo-ketone to the corresponding 2-acylbenzofuran 5. The 4-bromobenzofuran derivative could be obtained directly with this method by using the 6-bromosalicylaldehyde 4a. The 6-bromosalicylaldehyde was prepared by formylation of 3-bromophenol in 20% yield, one of three isomeric aldehydes. The 4-bromobenzofuran derivative could also be obtained by bromination of the 2-acylbenzofuran, that was produced by condensation of the o-vanillin 4b with the α-halo-ketones (sch. 1).

Scheme 1



1 2 3



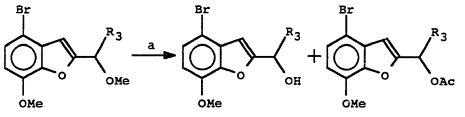
4a,4b 5a,5b

a) refl. DEA, K_2CO_3, N_2, b) MeOH, K_2CO_3, room temperature.
(a R_1=Br, R_2=H, b R_1=H, R_2=OMe, R_3=Me or Ph)

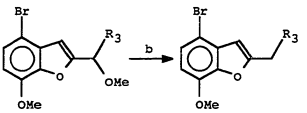
Benzofurans undergo facile polymerization[2] in the presence of Lewis Acid catalysts even at temperatures as low as -78°C. The 2-acyl group of 5 and the derivatives of it, the corresponding alcohol 6 and the methyl ether 7 facilitated the polymerization. Attempted deoxygenation using a combination of Lewis Acid catalysts ($AlCl_3$, $BF_3.OEt_2$) or strong acids (CF_3CO_2H) with hydride donors ($LiAlH_4$, Et_3SiH) led only to polymerization. The deoxygenated derivative 9 was obtained only in trace amounts. The sensitivity of the methyl ether 7 towards acids was clearly demonstrated, by

heating it at 80°C for 1 hour in 80% AcOH. It was cleaved to the corresponding alcohol 6 19% and transformed to the corresponding acetate 8 19%, (sch. 2).

Scheme 2



7 6 8



7 9

a) 80% AcOH, 80°C, b) $NaBH_3CN$, TMSCl, mol.sieves 3Å, N_2, room temperature, (R_3=Ph or Me).

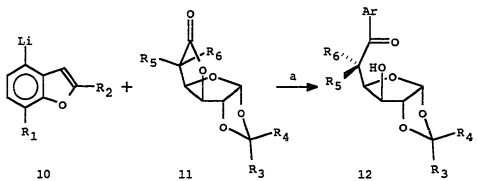
The acidic and Lewis Acid sensitivity of the benzofuran derivatives with an α-oxygenated 2-alkyl chain prompted the consideration of a milder reduction method. A novel application of Garreg's reaction[3] ($NaBH_3CN$, TMSCl), from carbohydrate chemistry proved to be successful in yielding the deoxygenated product 9 80% yield. The reaction was tested with all the α-oxygenated-2-alkyl-benzofuran derivatives (5, 6, 7, 8). The deoxygenated product 9 was the product from all of them although the yield

was varied and depended on the reaction time. Partial reduction products were also obtained at various yields.

Synthesis of the 6-C-benzofuranyl glycosides

The synthesis of the 6-C-benzofuranyl glycosides 12 was achieved using the 4-lithiated benzofuran 10, obtained from the 4-bromobenzofuran by Br-Li exchange, and the protected furano-6,3-lactone 11. Thus in one step producing novel non natural 6-C-glycosides in yields near 80% (sch. 3).

Scheme 3



a) THF, -78°C, N_2, (R_3=H, R_4=Ph) or (R_3=R_4=Me),(a R_5=H, R_6=OTBDMS), (b R_5=R_6=H), (c R_5=OTBDMS, R_6=H), (R_1=R_2=Me), (R_1=OMe, R_2=CH(OMe)CH_3), (R_1=OMe, R_2=Et).

Both benzylidene and the isopropylidene acetals were used. The introduction of a benzylidene group produced two isomers due to the stereogenic acetal center introduced. Because there was no advantage in cleaving it, it was eventually abandoned in favor of isopropylidene.

The 6-C-benzofuranyl difuranose glycosides were obtained in two steps in high yields from the keto alcohol 12 or the corresponding keto acetate 13. Reduction of 12

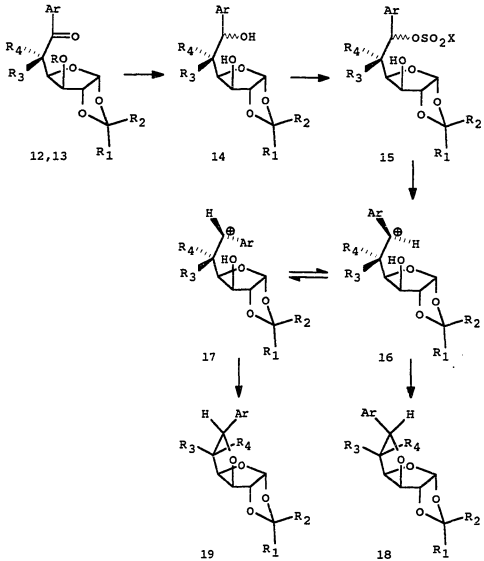
or 13 with $NaBH_4$, in EtOH at room temperature led to the diols 14 which were cyclized by intra-molecular dehydration in pyridine, with the action of thionyl halides (Br or Cl). The cyclization followed an intramolecular Sn1 mechanism. It is assumed that the carbocation 16 was formed stabilized by the 6-aryl group and then the cyclization takes place to yield the product. The cyclization led to two 6-C-aryl-difuranose glycosides 18, 19. For some derivatives the pair could not be separated by column chromatography (sch. 4).

The glucofuranose and the deoxy glucofuranose diols yielded as the major product the 6-exo-C-aryl-difuranose glycoside 18(a, b), while the 6-endo-C-aryl-difuranose glycoside 19(a, b) was the minor (roughly 2/1=exo/endo). The idofuranose yielded the 6-endo-C-aryl-difuranose glycoside 19c as the major product, the 6-exo 18c was the minor (exo/endo=1/1.2). The orientation of the intermediate carbocation is the factor determining the product. The aryl group of the glucofuranose and deoxy-gluco-furanose is predominantly oriented anti to the 5-O-t-butyldimethylsilyl and away from the 1,4-furanose ring. Changing the stereochemistry at C_5 to the idofuranose series the orientation of the aryl group away from the 1,4-furanose ring is not feasible any more, because it is being placed syn to the 5-O-t-butyldimethylsilyl. This orientation becomes the less favored and gives rise to the minor glycoside 18c. The epimer gives rise to the major glycoside 19c (sch. 4, ch. 6, table 2).

The Sn1 mechanism was demonstrated from the dehydration of the deoxy-diols 14b. Those were able to be separated to the two different isomers based on the 6-C stereochemistry. Cyclization of each diastereomer individually, or their mixture, in different solvents such as pyridine, or ether or THF with pyridine as base, yielded identical mixtures of the 6-exo, endo-glycosides 18b, 19b. The cyclization of the diol instead of the exchange of the OH-groups with halides from the thionyl halide is attributed to the sterically protected, less reactive 3-OH. That enables the formation of

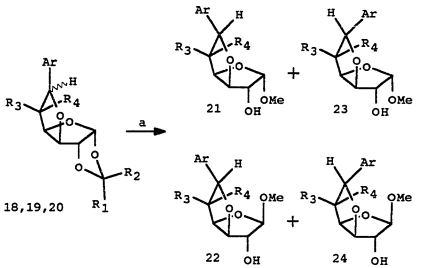
the halosulfite ester 15 which by elimination of the halosulfite moiety generates the carbocations 16, 17 (sch. 4).

Scheme 4



(R_1=H, R_2=Ph) or (R_1=R_2=Me), (a R_3=H, R_4=OTBDMS), (b R_3=R_4=H), (c R_3=OTBDMS, R_4=H)

Scheme 5

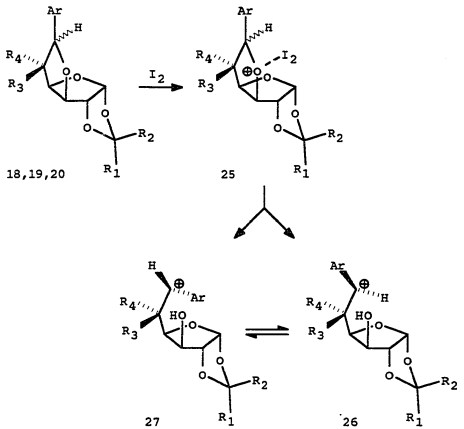


a) I_2, MeOH, 18, 19 (R_1=H, R_2=Ph) or (R_1=R_2=Me),
(a R_3=H, R_4=OH, R_4=OAc 20), (b R_3=R_4=H), (c R_3=OTBDMS, R_4=H),
21, 22, 23, 24 (a R_3=H, R_4=OH), (b R_3=R_4=H), (c R_3=OH, R_4=H)

Synthesis of the 1-methoxy-6-C-benzofuranyl-[1,4:3,6]-difuranoglycosides

The deprotection of the difuranosides 18 and 19 could be done either stepwise by removing first the silyl ether group and then hydrolyzing the alcohol or in one step doing both at the same time. The application of the I_2, MeOH reaction[4] made the deprotection possible in one step. Stepwise reaction removing the silyl ether first and then applying the I_2, MeOH reaction does not give any benefit or change the results of the reaction. The use of the 5-acetates 20 in order to differentiate between the 2 and 5-hydroxyl groups did not help either since the acetate group was cleaved during the application of the I_2, MeOH reaction (sch. 5).

Scheme 6

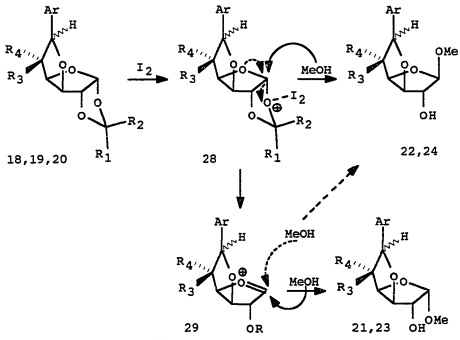


(R_1=H, R_2=Ph) or (R_1=R_2=Me), (a, R_3=H, R_4=OH), (b, R_3=R_4=H), (c, R_3=OTBDMS, R_4=H)

The 1-O-methyl-6-C-aryl difuranosides obtained showed a similar distribution to the intramolecular dehydration. The major product for the glucofuranosides and the deoxy furanosides was the 6-exo-aryl 21(a, b), 22(a, b), the 6-endo-aryl 23c, 24c was the major product for the idofurano compounds. The same identical mixture of the difuranosides 21, 22, 23, 24 was obtained independently from either the exo 18 or the endo 19 or any mixture of them.

The ratio of the products at the C_6 stereocenter is dictated again by the favored conformation of the intermediate carbocation. The conformation 26 that produces the 6-exo-aryl isomer is favored by the glucofurano and the 5-deoxyglucofurano compounds. The 6-endo-aryl isomer is favored for the idofurano compounds and is obtained through conformation 27 (sch. 6, ch. 9, table 2).

Scheme 7

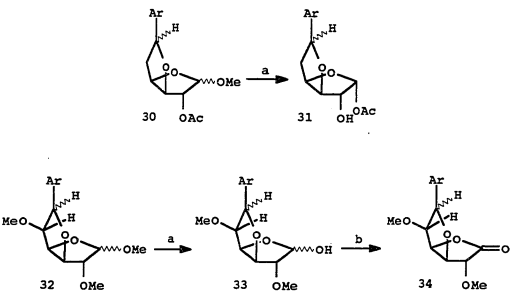


(R_1=H, R_2=Ph) or (R_1=R_2=Me), (a R_3=H, R_4=OH), (b, R_3=R_4=H), (c, R_3=OTBDMS, R_4=H)

The intramolecular ring opening and closure without the involvement of the solvent methanol must be the predominant reaction path since the intramolecular reaction is faster and no 6-methoxy product was detected. Clearly the mechanism of the reaction at C_6 followes an Sn1 path. However the mechanism of the reaction at the anomeric

center should follow more likely an Sn2 path. By the Sn2 like mechanism the 1-O-methylglycoside obtained should have been the β. The nucleophilic attack from methanol takes place from the direction opposite to the leaving acetal 28. But significant amounts of the 1-α-O-methylglycosides 21 and 23 were obtained for the 6-exo and 6-endo isomers. That fact by itself suggested steric hindrance on the incoming methanol molecule so the Sn2-like mechanism must shift to a significant part to become Sn1-like, where a carbocation at the anomeric center 29 is formed and stabilized to undergo nucleophilic attack from both faces leading to α and β nucleosides (sch. 7).

Scheme 8



a) 80% AcOH, 80°C, b) Ac_2O, DMSO, room temperature.

The I_2, methanol reaction demonstrated the sensitivity of the 6,3-O-bridge to acids. In fact attempted hydrolysis of the 1-methyl glycosides with 80% AcOH at 80°C always led to a mixture of four triols beginning from either the 6-exo or 6-endo-aryl glycosides.

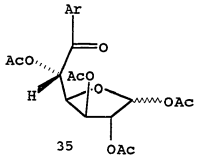
The migration of the 2-acetate group to the anomeric center during the attempted hydrolysis of the 1-O-methylglycoside 30 prompted the introduction of protecting groups less sensitive to the hydrolysis conditions, therefore not likely to migrate. The trimethylated idodifuranosides 32 were hydrolyzed to the hemiacetals 33 which were oxidized to the lactones 34 (sch. 8).

Attempted intramolecular reactions to form a macrocyclic glycoside

The 6-benzofuranyl glycoside was the substrate on which the cyclization to form the 9-carbon ring was attempted. Numerous attempts on the tetraacetate-6-ketobenzofuranoside 35 with Lewis Acid catalysts ($SnCl_4$, $AlCl_3$, $BF_3.Et_2O$) yielded only products of polymeric nature, or just effected isomerization at the anomeric center. Attempted cyclization on the 6-aryl-difuranoside yielded similar products. Particularly the triacetate mixture 36 was polymerized with $SnCl_4$. The hemiacetal 37 being treated with $BF_3.OEt_2$ at room temperature for 2 days did not react. The mixture of lactones 38 with $BF_3.OEt_2$ or $AlCl_3$, also did not change (37, 38 the isomers from the corresponding mixtures were expected to cyclize, sch. 9).

Apart from these specific attempts other reactions involved in the synthesis of the glycosides could have effected the cyclization. In other words every time a carbocation was formed at the anomeric center there was a probability for the cyclization to occur. The acetolysis of the diacetate 39 was the first such possibility. The expected tetraacetates 40 were obtained. Under these conditions the rearrangement of benzylidene acetal 41 was reported[5] to occur. That led to the product 44, involving a nucleophilic reaction from the dichlorophenyl conjugated double bond to the cation generated on the benzylic carbon 42 (sch. 10).

Scheme 9



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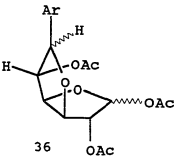

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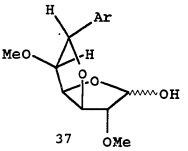
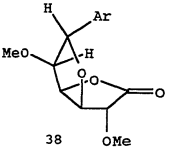


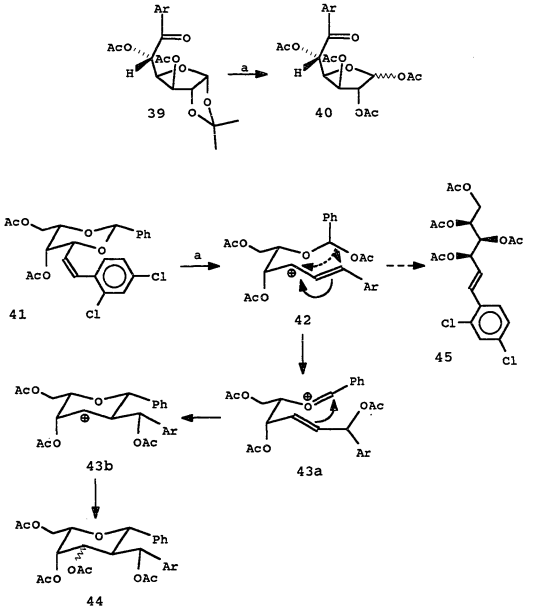
37



38

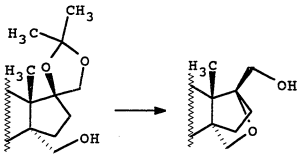
The other reaction was the BCl_3-hydrolysis of the isopropylidene which gave a complicated mixture of products. The carbocation at the anomeric center was also generated during the I_2, MeOH reaction, but cyclization was not observed. Intramolecular cyclization[6] under the I_2, MeOH reaction was also reported (sch. 11).

Scheme 10



a) AcOH, Ac_2O, cat. con. H_2SO_4.

Scheme 11

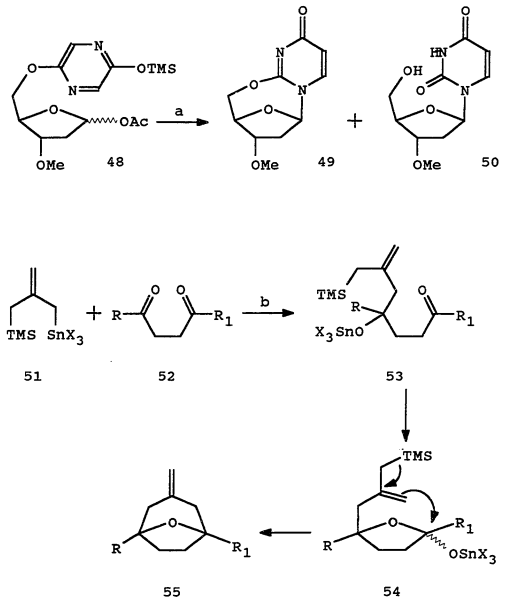


46 47

a) I_2, MeOH.

Cyclizations based on a similar concept have recently been reported. The cyclization of carbohydrate derivative[7] 48 to the 7-member ring nucleoside 49 and its hydrolysis product 50, was reported as a method for the exclusive preparation of β-glycosides. The condensation[8] of allylsilane 51 with the dicarbonyl 52 and the subsequent cyclization of the intermediates 53 and 54 to the product 55 was introduced as a method for generating 7 and 8-membered carbocyclic rings (sch. 12).

Scheme 12

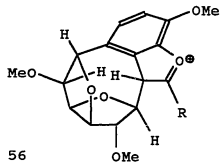


a) TMSOTf, CD_3CN, -78°C, (49 19%, 50 24%), b) TMSOTf, CH_2Cl_2, -78°C.

Examination of the reported cyclizations show that more reactive substrates were used along with the powerful reaction promoter trimethylsilyl trifluoromethylsulfonate (TMSOTf). The second characteristic is that there are no substituents on the newly formed ring and the cyclization is based on a single 1,4-furan ring. On the other hand the attempted cyclizations of the 6-C-benzofuranylglycoside is hindered by the 5-OR which is oriented syn to the path of the desired cyclization. The benzofuranyl moiety in both glucofurano 35, 36, 28a, 29a and 5-deoxyglucofurano 28b, 29b series is oriented away from the 1,4-furan ring bearing the anomeric center, that is to undergo nucleophilic attack by the 3-position of the benzofuran. The orientation of the benzofuran away from the 1,4-furan ring increased the distance between the two anticipated reaction centers (anomeric cation and the position 3' from the benzofuran), so the intramolecular nucleophilic reaction could not take place. Instead the benzofuran itself exposed also to the Lewis Acid catalysts underwent presumably polymerization, participating in intermolecular reactions.

Changing the stereochemistry at C_5 did not help either. Although for the most promising isomer 24c the situation looks ideal the cyclization did not take place, even though the distance of the $C_{3'}$ (benzofuran) to the anomeric center is at minimum, (judged from the shifting of the δ $H_{3'}$ = 6.9 instead of 6.4) place. First the existence of the 6,3-O-bridge generates a rigid difuranose system that does not allow flexibility as in the reported examples. The benzofuranyl group, given its size, might not be the right one to couple the C_6 and C_1 of the generated difuranose system. A steric effect is also introduced by the 2'-alkyl (benzofuran) side chain. The major factor could be that the required intermediate 56 which should introduce a saturated center at $C_{3'}$ (benzofuran) increasing further the steric demand (sch. 13).

Scheme 13



56

Apparently the intermediate 56 was never formed. The methods reported do not involve a saturated intermediate nor a difuranose base system. The nucleophilic attack in both methods was initiated by an enolate 48 and by a silane group 54. The favored conformation required for cyclization in both cases was not achieved by a 6,3-O-bridge but was induced by the two lone pairs of the oxygen, intermediate-48, and by the bulky silane group, intermediate-54, thus achieving the necessary flexibility and the right conformation and distance.

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Experimental section

^1H NMR spectra, ^1H NOE and ^1H COSY were recorded on a 300MHz FT NMR NR/300 Bruker instrument in $CDCl_3$, unless otherwise specified. IR spectra were recorded on a Perkin-Elmer 247 instrument, samples were placed between NaCl plates either neat or as Nujol mulls. Mass spectra were recorded on a Finnigan MAT SSQ70 using either EI or CI (NH_3). Melting points were taken on a Melt Temp instrument. They are uncorrected. Solvents and chemicals were bought from Fisher Scientific Co. and Aldrich Chemical Co., Inc.. THF was distilled over Na under N_2, other solvents were purified following standard procedures (Vogel, Practical Organic Chemistry, second edition) when necessary.

Chapter 3

General procedure for the preparation of Allyl-Aryl-Ethers: 3-Chlorophenol (5.0g, 38.9mmol) was dissolved in acetone (reagent grade 25mL), K_2CO_3 (5.4g, 39.1mmol) was added, followed by allyl bromide (5.0g, 3.6mL, 40.6 mmol). The solution was stirred under reflux until TLC analysis showed the consumption of the phenol (8 hours). The solution was cooled to room temperature and diluted with water. It was extracted with ether four times (25mL each time). The ether extracts were combined and washed twice with 10% aqueous NaOH (30mL each). The organic phase was washed once with water 30mL, dried over $MgSO_4$ and concentrated to yield the liquid allyl 3-chlorophenyl-ether **15** (6.1g, 93%).

3-Chlorophenyl allyl ether 15: (C_9H_9OCl), (93%), ^1H NMR (300 MHz): δ 7.15-7.20 (dd, 1H, H-5, $J_{5\text{-}4}$ = 9.0Hz, $J_{5\text{-}6}$ = 7.8Hz), 6.90-6.93 (d, 1H, H-6, $J_{6\text{-}5}$= 7.5Hz), 6.90 (s, 1H, H-2), 6.78-6.8 (d, 1H, H-4, $J_{4\text{-}5}$ = 9.3Hz), 5.96-6.08 (o, 1H, H-2', $J_{2'\text{-}1'a}$ = 17.1Hz, $J_{2'\text{-}1'b}$ =

10.4Hz, $J_{2'-3'}$ = 5.2Hz), 5.43-5.37 (d, 1H, H-1'a, $J_{1'a-2'}$ = 17.6Hz), 5.27-5.31 (d, 1H, H-1'b, $J_{1'b-2'}$ = 9.9Hz), 4.49-4.5 (d, 2H, H-3', $J_{3'-2'}$ = 5.1Hz).

3-Bromophenyl allyl ether 16: (C_9H_9OBr), (89.4%), ^1H NMR (300MHz): δ 7.08-7.11 (1H, H-5, J_{5-4} = 7.9Hz), 7.05-7.07 (1H- H-6, J_{6-5} = 4.7Hz), 7.07 (s, 1H, H-2), 6.80-6.84 (d, 1H, H-4, J_{4-5} = 7.9Hz), 5.95-6.07 (o, 1H, H-2', $J_{2-3'}$ = 5.1Hz, $J_{2'-1'a}$ = 17.2Hz, $J_{2'-1'b}$ = 10.5Hz), 5.36-5.42 (d, 1H, H-2'a, $J_{1'a-2'}$ = 17.2Hz), 5.26-5.30 (d, 1H, H-1'b, $J_{1'b-2'}$ = 10.5Hz), 4.47-4.49 (d, 1H, H-3', $J_{3'-2'}$ = 5.2Hz).

IR: 1572(s), 1575(s), 2860(w), 3070(w).

General procedure for the [3,3] Claisen rearrangement of allyl 3-halophenyl ethers and subsequent cyclization to the 2,3-dihydrobenzofurans: 3-Chlorophenyl allyl ether **15** (5.6g 33.2mmol) was heated neat under N_2 at temperatures 190-200°C for 3h. The reaction mixture was cooled to room temperature, and aqueous NaOH (5M, 56mL) was added. The aqueous solution was extracted three times with petroleum ether (25mL each time). The petroleum ether extracts were combined and washed with 30mL of water, then dried over $MgSO_4$ and concentrated to yield a residue composed of a 2/1 mixture of chloro-2,3-dihydrobenzofurans **17** and **18** (1.0g, 17.8%). The aqueous basic solution was acidified with hydrochloric acid (5M) to pH = 3. Then it was extracted with ether three times (25mL each time). The ether extracts were combined, washed with 30mL of water, dried over $MgSO_4$ and concentrated to yield a 2/1 mixture of chloro-allylphenols **21/22** (4.3g, 76.8%).

Mixture of chloro-allylphenols 21, 22: (C_9H_9OCl), 76.8%, (93/54), ^1H NMR (300 MHz): δ 6.93-7.00 (overlapping, d from 21 H-4, H-5, d from 22 H-5), 6.82-6.85 (dd, 1H from 22, H-4, J_{4-5} = 8.0Hz, J_{4-2} = 2.0Hz), 6.77-6.78 (s, 1H from 22, H-2, J_{2-4} = 2.0Hz), 5.85-6.00 (overlapping 2 octets, and s 1H from 21, H-2', 1H from 22, H-2' , 1H s, 1H from 22, H-OH), 5.02-5.13 (overlapping dd, 2H from 21, H-1', 2H from 22, H-1), 3.54-3.57 (d,

2H from 21, H-3', $J_{3'-2'}$ = 5.9Hz), 3.30-3.32 (d, 2H from 22, H-3', $J_{3'-2'}$ = 6.2Hz), 2.67 (s, 1H from 21, H-OH).

IR: 1585(s), 1635(m), 2920(w), 2975(w), 3075(w), 3450(s).

Mixture of chloro-2-methyl-2,3-dihydrobenzofurans 17, 18: (C_9H_9OCl), 17.8% (2/1), ^{1}H NMR (300 MHz): δ 6.99-7.04 (overlapping dd, 1H, H-6 from 17, d 1H, H-5, s 1H, H-7 from 18), 6.73-6.8 (overlapping d, 1H, H-4 from 17, J_{4-5} = 8.0Hz, d, 1H, H-4, from18, J_{4-5} = 8.3 Hz), 6.61-6-63 (d, 1H, H-7 from 17, J_{7-6}=8.0Hz), 4.9-5.0 (overlapping multiplets, 1H, H-2 from 18), 3.2-3.37 (overlapping dd, 1H, H-3a from 17, J_{3a-2} = 8.9Hz, J_{3a-3b} = 16.0Hz, 1H, ftom 18, H-3a, J_{3a-2} = 8.9Hz, J_{3a-3b} = 15.8Hz), 2.7-2.86 (overlapping dd, 1H, from 17, H-3b, J_{3b-2} = 7.5Hz, J_{3b-3a} = 16.0Hz, 1H, from 18 H-3b, J_{3b-2} = 7.4Hz, J_{3b-3a} = 15.8Hz), 1.42-1.47 (overlapping d, 3H from 17, 2-Me J_{Me-2} = 6.7Hz, 3H from 18, 2-Me, J_{Me-2} = 6.9Hz).

IR: 1590(s), 1605(s), 2860(w), 2925(m), 2970(m), 3500(w).

Mixture of bromo-allylphenols 23, 24: (C_9H_9OBr), 70.1% (76/36): ^{1}H NMR (300 MHz): δ 7.0-7.13 (d/d, 1H from 23, H-4, J_{4-5} = 8.0Hz, J_{4-6} = 1.1Hz), 6.95-6..99 (dd, 1H from 24, H-4, J_{4-5} = 8.3Hz, J_{4-6} = 1.8Hz), 6.85-6.92 (overlapping, s, 1H from 24, H-2, dd, 1H from 24, H-6, t, 1H from 23, H-5, $J_{5-4,6}$ = 8.0Hz), 6.67-6.70 dd, 2H from 23, H-7, J_{7-6} = 8.0Hz, J_{7-5} = 1.0Hz), 5.85-6.1 (overlapping, m, 1H from 23, H-2', m, 1H from 24, H-2', 1H from 23, H-OH), 5.02-5.12 (overlapping dd, 2H from 23, H-1', 2H' from 24, H-1'), 3.55-3.58 (d, 2H from 23, H-3', $J_{3'-2'}$ = 5.9Hz), 3.27-3.29 (d, 2H from 24, H-3', $J_{3'-2'}$ = 6.3Hz), 2.8 (s,1H from 24, H-OH).

IR: 1580(s), 1600(m), 1635(m), 2810(w), 2975(w), 3000(w),3.075(w), 3475(s).

Mixture of bromo-2,3-dihydro-2-methylbenzofurans 19, 20: (C_9H_9OBr), 19.2% (19/14) : ^{1}H NMR (300 MHz): δ 7.28-7.33 (overlapping d), 6.88-7.07 (overlapping), 6.65-6.67 (overlapping), 4.88-5.00 (overlapping multiplets, 1H from 19, H-2, 1H from 20, H-2), 3.18-3.4 (overlapping dd, 1H from 19, H-3a, J_{3a-2} = 8.7Hz, J_{3a-3b} = 15.8Hz, 1H from 20, H3a, J_{3a-2} = 8.8Hz, J_{3a-3b} = 15.5Hz), 2.68-2.84 (dd overlapping, 1H from 19, H-3b,

J_{3b-2} = 7.5Hz, J_{3b-3a} = 15.9Hz, 1H from 20, H-3b, J_{3b-3a} = 15.6Hz, J_{3b-2} = 7.6Hz), 1.42-1.47 (overlapping d, 3H from 19, 2-Me, J_{Me-2} = 7.5Hz, 3H from 20, 2-Me, J_{Me-2} = 7.7Hz). IR: 1580(s), 1605(s),1655(w), 2920(s), 2980(s), 3070(w), 3500(w).

Bromination with NBS of the 2,3-dihydro-2-methyl benzofurans: A 100mL round bottom flask equipped with a reflux condenser was charged with a solution of a 2/1 mixture 4 and 7-chloro-2,3-dihydro-2-methylbenzofurans **17**, **18** (0.9g, 5.34mmol) in 30mL of dry carbon tetrachloride.N-Bromosuccinimide(NBS, 1.0g, 6.0mmol) was added. The solution was irradiated with a Sylvania 300 watt light source for 2 hours (until succinimide was floating on the surface of the solvent). During the irradiation the solvent was refluxing and vapors of HBr were detected with wet litmus paper, escaping the condenser. The reaction was cooled to room temperature. The solid succinimide was removed by suction filtration. The filtrate was concentrated. The remaining residue (0.85g, 86%) was a 2/1 mixture of 4-chloro and 6-chloro-2-methylbenzofurans **27**, **28**.

General Procedure for the preparation of the propargyl aryl ethers: A solution of 3-chlorophenol (5.0g, 38.9mmols) in acetone (50mL) was refluxed in the presence of K_2CO_3 (5.9g, 42.7mmols) and propargyl bromide (5.1g, 42.8mmols, 4.8mL 80% solution). The reaction was refluxed until TLC analysis showed that the phenol had completely reacted (5h). The reaction was then cooled to room temperature, diluted with water and extracted with ether three times (50mL each). The ether extracts were combined and washed with 10% aqueous of NaOH (30mL) and water (30mL). The organic phase was dried over $MgSO_4$, and concentrated to yield the propargyl 3-chlorophenyl ether **32** (6.0g 92.9%). The product was pure enough to be used for the next reaction.

3-Chlorophenyl propargyl ether 32: (C_9H_7OCl), 92.9%: ^1H NMR (300 MHz): δ 7.16-7.21 (t, 1H, H-5, J_{5-6} = 8.6Hz), 6.94-6.97 (overlapping, s, 1H, H-2, d 1H, H-4), 6.82-

6.86(d, 1H, H-6, J_{6-5} = 8.4Hz), 4.63-4.64 (d, 2H, H-3', $J_{3'-1'}$ = 2.4Hz), 2.52-2.54 (t, 1H, H-1', $J_{1'-3'}$ = 2.5Hz).

IR: 1580(s), 1595(s), 2020(w), 2865(w), 2910(w), 3060(w), 3300(s).

MS(ci): m/z 167(MH^+), 169(M+2)H^+).

3-Bromophenyl proparglyl ether 33: (C_9H_7OBr), 98.4%: ^1H NMR (300 MHz): δ 7.10-7.15 (overlapping, 3H, s, 1H, H-2, d 1H, H-3, dd 1H, H-5), 6.88-6.92 (dt, 1H, H-6, J_{6-4} = 2.3Hz, J_{6-5} = 7.4Hz), 4.65-4.66 (d, 2H, H-3', $J_{3'-1}$ = 2.4Hz), 2.53-2.55 (t, 1H, H-1', $J_{1'-3'}$ = 2.4Hz).

IR: 1585(s), 1720(w), 1820(w), 1920(w), 2025(w), 2120(m), 2860(m), 2910(m), 3060(w), 3300(s).

MS(ei): m/z 210(M^+), 212(M+2$^+$).

3-Nitro-phenyl propargyl ether 34: ($C_9H_7NO_3$), pale yellow crystalls, mp 67-69°C, 92.6%: ^1H NMR (300 MHz): δ 7.84-7.88 (d, 1H, H-4, J_{4-5} = 8.8Hz), 7.80-7.82 (t, 1H, H-2, J_{2-6} = 2.3Hz), 7.43-7.49 (t, 1H, H-5, J_{5-6} = 8.2Hz), 7.29-7.33 (dd, 1H, H-6, J_{6-5} = 8.4Hz, J_{6-2} = 2.4Hz), 4.78-4.79 (d, 2H, H-3', $J_{3'-2'}$ = 2.3Hz), 2.59-2.60 (t, 1H, H-1', $J_{1'-3'}$ = 2.3Hz).

IR (Nujol mull): 1350(m), 1360(m), 1585(m), 1620(w), 3285(w).

MS(ei): m/z 177(M^+).

4-Chloro-3-propargyloxy-methylbenzoate-7 49: ($C_{11}H_9O_3Cl$), white amorphous solid, 95.3%, ^1H NMR (300 MHz): δ 7.75-7.78 (d, 1H, H-6, J_{6-5} = 8.4Hz), 7.12-7.13 (d, 1H, H-3, J_{3-5} = 1.8Hz), 7.00-7.04 (dd, 1H, H-5, J_{5-6} = 8.4Hz, J_{5-3} = 1.8Hz), 4.78-4.79 (d, 2H, H-3', $J_{3'-1'}$ = 2.4Hz), 3.88, (5,3,H, H-Me), 2.59-2.61 (t, 1H, H-1', $J_{1'-3'}$ = 2.4Hz).

IR (Nujol mull): 1595(s), 1700(s), 1715(s), 1920(w), 2035(w), 2120(m), 3250(m).

3-Bromo-6-methylphenyl propargyl ether 58: ($C_{10}H_9OBr$), 80.23%: ^1H NMR (300 MHz): δ 7.00-7.06 (overlapping 3H, H-3, 5, 6), 4.67-4.69 (d,2H, H-3', $J_{3'-1'}$ = 2.4Hz), 2.52-2.54 (t, 1H, H-1', $J_{1'-3}$ = 2.4Hz), 2.17(5, 3 H, H-Me).

IR: 1690(s), 1740(w), 1865(w), 1920(w), 2020(w), 2120(m), 2860(m), 2920(s), 2955(s), 3025(m), 3065(m), 3300(s).

MS(ei): m/z 224(M^+), 226($M+2^+$).

Generral procedure for the [3,3] Claisen rearrangement of the propargyl aryl ethers: Procedure A: A solution of the 3-chlorophenyl propargyl ether **32** (2.0g, 12.0mmols), in diethylaniline (DEA, 10mL) was refluxed under N_2 for 3 hours. The reaction was cooled to room temperature. The DEA was removed under vacuum (B.p. = 68°C). The residue was dissolved in ethyl acetate (50mL). The organic phase was washed with 10% solution of HCl (3 times, 30mL each), dried over $MgSO_4$, concentrated and chromatographed to yield a 2/1 mixture of chlorochromenes **35**, **37** (0.97g, 48.5%) with traces of chloro-2-methylbenzofurans **27**, **28**.

Procedure B: A solution of 3-chlorophenyl propargyl ether **32** (2.0g, 12.0mmols) in DEA (10mL) was refluxed (200°C) under N_2 in the presence of K_2CO_3 (1.7g, 12.3mmols) for 3h. The reaction mixture was cooled to room temperature. The DEA was removed under vacuum (B.p. = 68°C). The residue was extracted with ethyl acetate (three times, 50mL each). The ethyl acetate extracts were combined and washed with HCl (10% sol., three times, 30mL each), with water (30mL), dried over $MgSO_4$ and concentrated. The residue was chromatographed (silica gel, chloroform) to yield a 2.4/1.6 mixture of chloro-2-methyl benzofurans **27**, **28** (0.8g, 40%) with traces of the chlorochromenes **35**, **37**.

Mixture of chlorochromenes 35, 37: (C_9H_7OCl), Method A: 48.5% (2/1), Method B: traces detected by ^1H NMR. ^1H NMR (300 MHz): δ 6.65-7.22 (overlapping 4H from 35, H-4, 6, 7, 8, 3H from 37, H-5, 6, 8), 6.32-6.36 (d, 1H from 37, H-4, J_{4-3} = 9.7Hz), 5.81-5.88 (dt, 1H from 35, H-3, J_{3-2} = 3.7Hz, J_{3-4} = 10.0Hz), 5.69-5.74 (dt, 1H from 37, H-3, J_{3-2} = 3.6Hz, J_{3-4} = 9.9Hz), 4.77-4.79 (dd, 2H from 37, H-2, J_{2-3} = 3.5Hz, J_{2-4} = 1.9Hz), 4.75-4.77 (dd, 2H from 35, H-2, J_{2-3} = 3.5Hz, J_{2-4} = 1.8Hz).

MS(ei): m/z 166(M^+), 168($M+2^+$).

Mixture of bromochromenes 36, 38: (C_9H_7OBr), Method A 48.6% (2/1*), Method B (traces),^{1}H NMR (300 MHz): δ 6.70-7.16 (overlapping, 4H from 36, H-4, 6, 7, 8, 3H from 38, H-5, 6, 8), 6.33-6.36 (d, 1H from 38, H-4, J_{4-3} = 9.8Hz), 5.83-5.89 (dt, 1H from 36, H-3, J_{3-2} = 3.7Hz, J_{3-4} = 10.1Hz), 5.72-5.78(dt, 1H from 38, H-3, J_{3-2} = 3.5Hz, J_{3-4} = 9.8Hz), 4.78-4.81 (dd, 2H from 38, H-2, J_{2-3} = 3.4Hz, J_{2-4} = 2.1Hz), 4.75-4.77 (dd, 2H from 36, H-2, J_{2-3} = 3.6Hz, J_{2-4} = 1.8Hz).

MS(ei): m/z 210(M^+), 212($M+2^+$).

Mixture of chloro-2-methylbenzofurans 27, 28: (C_9H_7OCl), Method B 40% (2.4/1.6), ^{1}H NMR (300 MHz): δ 6.8-7.38 (overlapping 3H from 27, H-5, 6, 7, 3H from 28, H-4, 5, 7), 6.44 (s, 1H from 27, H-3), 6.30 (s, 1H from 28, H-3), 2.43 (s, 3H from 27, 2-Me), 2.41(s, 3H from 28, 2-Me).

MS(ei): m/z 166(M^+), 168($M+2^+$).

Mixture of bromo-2-methylbenzofurans 29, 30: (C_9H_7OBr), Method B, 50% (9.0/4.7), ^{1}H NMR (300 MHz): δ 7.00-7.32 (overlapping 3H from 29, H-5,, 6, 7, 3H from 30, H-4, 5, 7), 6.39 (s, 1H from 29, H-3), 6.29 (s, 1H from 30, H-3), 2.42 (s, 3H from 29, 2-Me), 2.39 (s, 3H from 30, 2-Me).

MS(ei): m/z 210(M^+), 212($M+2^+$).

4-Nitro-2-methylbenzofuran 39: ($C_9H_7NO_3$), Method B 30%, yellow crystalls, mp 82-82.5°C, ^{1}H NMR (300 MHz): δ 8.047-8.07 (d, 1H, H-5, J_{5-4} = 8.2Hz), 7.61-7.63 (d, 1H, H-7, J_{7-6} = 8.1Hz), 7.22-7.27 (t, 1H, H-6, $J_{6-5,7}$ = 8.1Hz), 7.04 (s, 1H, H-3), 2.50 (s, 3H, 2-Me).

IR (Nujol mull): 1365(s), 1375(s), 1530(s), 1580(m), 1595(s), 1623(w).

MS(ei): m/z 177(M^+).

6-Nitro-2-methylbenzofuran 40: ($C_9H_7NO_3$), Method B 2%, pale yellow crystalls, mp 102-103°C, ^{1}H NMR (300 MHz): δ 8.28 (s, 1H, H-7), 8.10-8.13 (d, 1H, H-5, J_{5-4} = 8.3Hz), 7.51-7.54 (d, 1H, H-4, J_{4-5} = 8.6Hz), 6.50 (s, 1H, H-3), 2.53 (s, 3H, 2-Me).

IR (Nujol mull): 1340(s), 1355(s), 1535(s), 1600(s).

MS(ei): m/z 177(M^+), 178(M+1$^+$).

4-Chloro-2-methyl-methylbenzofuroate-7 50: ($C_{11}H_9O_3Cl$), Method B 87.9%, ^{1}H NMR (300 MHz): δ 7.76-7.79 (d, 1H, H-6, J_{6-5} = 8.2Hz), 7.19-7.22 (d, 1H, H-5, J_{5-6} = 8.2Hz), 6.52 (s, 1H, H-3), 3.99 (s, 3H, H(CO_2Me)), 2.54 (s, 3H, H-2Me).

4-Bromo-2,7-dimethylbenzofuran 59: ($C_{10}H_9OBr$), Method B 23.7%, ^{1}H NMR (300 MHz): δ 7.15-7.18 (d, 1H, H-5, J_{5-6} = 7.9Hz), 6.79-6.81 (dd, 1H, H-6, J_{5-6} = 7.9Hz), 6.34 (d, 1H, H-3, J_{3-2} = 1Hz), 2.37 (s, 6H, H-2Me, 7Me, J_{2Me-3} = 1Hz).

IR: 1600(s),1710(w), 2880(w), 2910(m), 2950(w).

MS(ei): m/z 224(M^+), 226(M+2$^+$).

5-Bromo-8-methylchromene 60: Method B 8.6%, ^{1}H NMR (300 MHz): δ 6.95-6.99 (d, 1H, H-6, J_{6-7} = 8.1Hz), 6.79-6.82 (d, 1H, H-7, J_{7-6} = 8.1Hz), 6.69-6.74 (dt, 1H, H-4, J_{4-3} = 10.0Hz, J_{4-2} = 1.8Hz), 5.81-5.87 (dt, 1H, H-3, J_{3-4} = 10..0Hz, J_{3-2} = 3.7Hz), 4.75-4.78 (dd, 2H, H-2, J_{2-3} = 3.6Hz, J_{2-4} = 1.8Hz).

IR : 1590(s), 1635(m), 1730(m), 1850(w), 2850(m), 2915(s), 2950(s), 3050(w), 3425(w).

MS(ci): m/z 224(M^+), 226(M+2$^+$).

The [3,3] Claisen rearrangement of the 4-chloro-2-propargyloxy-methyl benzoate 49 and the subsequent hydrolysis of the ester 50 to the acid 51: A 100mL round bottom flask equipped with refluxed condenser was charged with a solution of 4-chloro-2-propargyloxy-methyl benzoate **49** (6.8g, 30.3mmol) in DEA (35mL). K_2CO_3 (4.6g, 33.3mmol) was added and the mixture was refluxed under N_2 for 4 hours. The mixture was cooled to room temperature and the DEA was removed under vacuum (B.p = 68°C). The residue was dissolved in ethanol (50mL 95%) and NaOH (2.0g, 50.0mmol) was added. The mixture was refluxed for 3 hours (monitoring with TLC showed consumption of the benzofuroate ester). A white solid precipitated. The solution was cooled with an ice bath and made acidic to lithmus with 10% aqueous HCl. After standing for 30min, it was filtered under reduced pressure to obtain a white solid which

was washed with water, and ice-cold 95% ethanol. After air-drying 5.6g (87.9%) of 4-chloro-2-methyl-benzofuran-7- carboxylic acid **51** was obtained.

4-Chloro-2-methylbenzofuran-7-carboxylic acid 51: ($C_{10}H_7O_3Cl$), 87.9%, white amorphous solid, mp 230-232°C, ^1H NMR (300 MHz) ($(CD_3)_2CO$, D_2O impurity): δ 7.83-7.86 (d, 1H, H-6, J_{6-5} = 8.3Hz), 7.32-7.35 (d, 1H, H-5, J_{5-6} = 8.3Hz), 6.66 (s, 1H, H-3), 2.54 (s, 3H, H-2Me).

IR (Nujol mull): 1585(m), 1595(s), 1610(s), 1690(s), 3000(m. broad)

Preparation of the (4-chloro-2-hydroxy)-methyl benzoate 48: 4-Chlorosalicylic acid **47** (5.3g 95%, 29.2mmol) was dissolved in methanol (25mL reagent grade), conc. H_2SO_4 (6mL) was added and the solution was refluxed overnight (12 hours). The reaction mixture was cooled to room temperature, and poured over ice-water. The resulted aqueous suspension was extracted with ether 3 times (50mL each). The combined ether extracts were washed with water (30mL), aqueous $NaHCO_3$ (10%, 30mL) and water (30mL), dried over $MgSO_4$ and concentrated to yield the liquid ester **48** (4.7g, 86.4%). Acidification of the basic aqueous solution and extraction with ether (50mL), followed by washing with water (30 mL), drying and concetration yielded 0.5g of the acid **47** 10%.

Decarboxylation of the 2-methyl-4-chloro-benzofuran-7-carboxylic acid 51: A 100mL round bottom flask was charged with 2-methyl-4-chloro-benzofuran-7-carboxylic acid **51** (1.0g, 4.75 mmol), isoquinoline (10mL) and Cu_2O (0.4g, 2.7mmol). The flask was equipped with a reflux condenser and the mixture was heated under N_2 to reflux (240°C) for 20-30min. The reaction was cooled to room temperature and diluted with ether (150mL). The solid precipitate was filtered under reduced pressure and the filtrate was washed with HCl (10% sol., 3 times, 30mL each). The organic phase was washed with water (30mL), NaOH (10% sol., 30mL), water (30mL), dried over $MgSO_4$, and

concentrated. The residue was chromatographed (silica-gel, chloroform) to yield 4-chloro-2-methyl-benzofuran **52** (0.5g ,63.3%). The basic extract was acidified with HCl (10% sol., to lithmus), and extracted with 50mL ether. The ether phase was washed with water (20mL), dried over $MgSO_4$ and concentrated to yield 0.06g of the acid **51** (6%).

4-Chloro-2-methylbenzofuran 52: (C_9H_7OCl), 63.3%, ^1H NMR (300 MHz): δ 7.23-7.27 (d, 1H, H-5, J_{5-6} = 8.1Hz), 7.03-7.15 (overlapping, d, 1H, H-7, J_{7-6} = 8.0Hz, dd,1H, H-6, J_{6-7} = 7.8Hz, J_{6-5} = 8.0Hz), 6.42 (s, 1H, H-3), 2.40 (s, 3H, H-2Me).

IR : 1585(s), 1605(s), 2890(w), 2910(w), 2950(w), 3100(w).

MS(ei): m/z 167($M+1^+$), 168($M+2^+$).

Reduction of 2,4-dinitrotoluene 53 to 2-nitrotoluidine-4 54: 500mL round bottom flask was charged with 2,4-dinitrotoluene **53** (34g, 0.187mmol). The 2,4-dinitrotoluene was gently heated with ethanol (95%, 40mL) until it was dissolved. A solution of $(NH_4)_2S_x$ (23.5%, 172mL) was added dropwise over a period of 30-45min under vigorous stirring. The resulting solution was refluxed for two hours and then poured over ice (300g). The nitrotoluidine **54** was cystallized as a yellow solid, after reaching room temperature. The yellow solid was filtered (suction filtration) and washed with cold water. After drying, 28.2g (99,2%) of crystals were obtained. The crude crystals were pure enough to be used for the next reaction. Analytically pure sample was obtained by recrystallization from ethanol.

4-Amino-2-nitrotoluene 54: ($C_7H_8O_2N_2$), 99.2%, yellow crystalls, mp 75.5-76.5°C, ^1H NMR (300 MHz): δ 7.27-7.28 (d, 1h, H-3, J_{3-5} = 2.6Hz), 7.06-7.09 (d, 1H, H-6, J_{6-5} = 8.2Hz), 6.78-6.82 (dd, 1H, H-5, J_{5-3} = 2.5Hz, J_{5-6} = 8.2Hz), 3.65 (s, 2H, H(NH_2), 2.45 (2, 3H, H-2Me).

IR (Nujol mull): 1520(s), 1620(s), 3350(m), 3450(m).

MS(ci): m/z 170(MNH_4^+).

Preparation of 4-bromo-2-nitrotoluene 55 from 2-nitro-4-toluidine 54: 2-Nitro toluidine **54** (15.2g, 0.1mol) was dissolved in a solution of H_2SO_4 (15mL conc. H_2SO_4 diluted with 150mL H_2O). The resulting suspension was cooled to 0°C by an ice-bath. A cold aqueous solution of $NaNO_2$ (6.9g, 0.1mol in 18mL H_2O, 0°C) was added dropwise under vigorous stirring maintaining the temperature at 0-5°C. The solution was left to stand for 10min. and then it was added dropwise under vigorous stirring in an 800mL erlenmeyer flask containing a freshly* made solution of Cu_2Br_2 (15g, 0.11mol) in HBr (100mL 48%) and water (50mL), at room temperature. After the evolution of N_2 was ceased the solution was stirred overnight and extracted with ether (3 times, 150mL each). The ether extracts were combined and washed with HCl (6N, 50mL), aqueous NaOH (10%, twice, 50mL each), and water (50mL). The organic phase was dried over $MgSO_4$, decolorized with NORIT A and concentrated to yield an oil which was crystallized upon standing to yield 17.2g (79.6%) of 4-bromo-2-nitrotoluene **55**. The crude crystalls obtained were pure enough for the next reaction, but analytically pure crystalls were obtained by column chromatography ($CHCl_3$).

***Preparation of the solution of Cu_2Br_2**: $CuSO_4.5H_2O$ (29.9g, 0.12mol) was dissolved in water (100mL). NaBr (19.36g, 0.19mol) was added. The solution was heated to 56°C. A solution of $Na_2S_2O_5$ (5.0g, 0.026 mol) in H_2O (15mL) was added at once under stirring. The white precipitate, formed almost intstantly, was filtered (15.0g) and dissolved in HBr (100mL 48%, 0..59mol) and H_2O (50mL) to give a deep purple solution. Upon prolonged exposure to the atmosphere, the white solid was darkened due to oxidation to the Cu^{2+}.

4-Bromo-2-nitrotoluene 55: ($C_7H_6O_2NBr$), 79.6%, pale yellow crystalls, mp 38-40°C, ^1H NMR (300 MHz): δ 8.11-8.12 (d, 1H, H-3, J_{3-5} = 1.8Hz), 7.60-7.64 (dd, 1H, H-5, J_{5-3} = 1.9Hz, J_{5-6} = 8.2Hz), 7.22-7.25 (d, 1H, H-6, J_{6-5} = 8.2Hz), 2.56 (s, 3H, H-Me).

IR (Nujol mull): 1525(s), 1600(m), 1660(w), 1755(w), 1940(w).

MS(ci): m/z 233($MNH4^+$), 235($(M+2)NH4^+$).

Reduction of the 4-bromo-2-nitrotoluene 55 to the 2-amino-4-bromotoluene 56: 4-Bromo-2-nitrotoluene **55** (17.2g, 79.63mmol) was dissolved in ethanol (95%, 80mL). A solution of $SnCl_2.2H_2O$ (57.1g, 0.253mol) in conc. HCl (85mL) was added dropwise under stirring at room temperature within 10min. The resulting solution was stirred for an extra hour, it was cooled to 0°C with an ice bath and diluted with aqueous NaOH (30%, 500mL). The resulting suspension was extracted with ether (four times, 200mL each). The ether extracts were combined and washed twice aqueous NaOH (10%, 50mL each), dried and concentrated to yield 13.7g of 4-bromo-2-aminotoluene **56** (dark oily liquid, 92.5%). The product was pure enough for the next reaction.

4-Bromo-2-aminotoluene 56: (C_7H_8NBr), 92.5%, ^1H NMR (300 MHz): δ 6.62-6.86 (d, 1H, H-6, J_{6-5} = 7.9Hz), 6.74-6.78 (dd, 1H, H-5, J_{5-3} = 1.8Hz, J_{5-6} = 7.9Hz), 6.72-6.73 (d, 1H, H-3, J_{3-5} = 1.7Hz), 3.54 (s, 2H, H-NH_2), 2.03(s, 3H, H-Me).

IR: 1570(s), 1595(s), 1620(s), 2850(m), 2890(m), 2925(m),2970(m), 3015(w), 3100(w), 3380(s), 3470(s).

MS(ci): m/z 203(MNH_4^+), 205($(M+2)NH_4^+$).

Preparation of 3-bromo-6-methylphenol 57 from 4-bromo-2-aminotoluene 56: 3-Bromo-6-methylaniline **56** (13.7g, 73.66mmol) was dissolved under stirring in a solution of conc. H_2SO_4 (13mL) and H_2O (160mL). The resulted suspension was cooled to 0°C by an ice bath. An aqueous cold solution of $NaNO_2$ (5.1g, 73.91mmol dissolved in 16mL H_2O, 0°C) was added dropwise under stirring at such a rate that the temperature of the solution was maintained at 0-5°C. The reaction was left to stand for 15min. and was poured portionwise under vigorous stirring to a boiling solution of H_2SO_4 (50%, 105mL), at such a rate that the evolution of N_2, that made the surface of the solution rise was controlled and contained within the vessel. After the addition was completed, the reaction was boiled for extra 15min and the solution was poured over ice (500g).

The resulting mixture was extracted with ether 3 times (200mL each). The combined ether extracts were washed with water (50mL), dried over $MgSO_4$ and concentrated to yield 11.6g (84.2%) of the phenol **57**, pure enough to be carried to the next reaction. Analytical sample was obtained by column chromatography ($CHCl_3$).

4-Bromo-2-hydroxytoluene 57: (C_7H_7OBr), 84.2%, pale pink crystalls, mp 76.5-77°C, ^1H NMR (300 MHz): δ 6.91-6.96 (overlapping 3H, H-3, H-5, H-6, $J_{6-5} = J_{5-6}$ = 14.2Hz), 5.10 (s, 1H, H-OH), 2.18 (s, 3H, H-Me).

IR (Nujol mull): 1590(s), 1690(w), 1895(w), 3300(s).

MS: m/z 204(MNH_4^+), 206($(M+2)NH_4^+$).

General procedure for the bromination of 3-halo-phenols: The 3-chlorophenol **13** (1.0g, 7.8mmol) was dissolved in CCl_4 (50mL), K_2CO_3 (1.2g, 8.5mmol) was added, followed by liquid bromine (1.37g, 0.44mL 98%, 8.5mmol). The solution was stirred for half hour. The reaction was exothermic and the bromine color was discharged. The solids were removed by suction filtration. The filtrate was concentrated and the residue was chromatographed with benzene on silica-gel. Two products were isolated. The 4-bromo-3-chlorophenol **61** (0.5g, 31.1%) and the 2-bromo-5-chlorophenol **63** (0.5g, 31.1%).

4-bromo-3-chlorophenol 61: (C_6H_4OClBr), 31.1%, white crystalls, mp 69-70°C, ^1H NMR (300 MHz): δ 7.34-7.37 (d, 1H, H-5, J_{5-6} = 8.5Hz), 7.02-7.03 (d, 1H, H-2, J_{2-6} = 2.4Hz), 6.78-6.81 (dd, 1H, H-6, J_{6-5} = 8.4Hz, J_{6-2} = 2.5Hz), 5.6 (s, 1H, H-OH).

IR (Nujol mull): 1575(s), 1590(s), 1600(m), 1695(w), 1720(w), 1880(w), 3350(s),

MS(ei): m/z 206(M^+), 208($M+2^+$).

2-bromo-5-chlorophenol 63: (C_6H_4OClBr), 31.1%, white crystalls, mp 66-66.5°C, ^1H NMR (300 MHz): δ 7.42-7.45 (d, 1H, H-3, J_{3-4} = 8.7Hz), 6.98-6.99 (d, 1H, H-6, J_{6-4} = 2.9Hz), 6.63-6.67 (dd, 1H, H-4, J_{4-3} = 8.7Hz, J_{4-6} = 2.8Hz), 5.93 (s, 1H, H-OH).

IR (Nujol mull): 1590(s), 1710(w), 1880(w), 2540(w), 2640(w), 2740(w), 3275(s), 3560(m).

MS(ei): m/z 205.6(M^+), 207.6($M+2^+$).

3,4-dibromophenol 62: ($C_6H_4OBr_2$), 27.4%, white crystalls, mp 63-65°C, ^{1}H NMR (300 MHz): δ 7.27-7.30 (d, 1H, H-5, J_{5-6} = 8.6Hz), 7.16-7.17 (d, 1H, H-2, J_{2-6} = 2.3Hz), 6.91-6.94 (dd, 1H, H-6, J_{6-5} = 8.5Hz, J_{6-2} = 2.2Hz), 5.7 (s, 1H, H-OH).

IR (Nujol mull): 1580(m), 1590(m), 3400(m), 3520(m).

MS(ei): m/z 250(M^+), 252($M+2^+$), 254($M+4^+$).

2,5-dibromophenol 64: ($C_6H_4OBr_2$) 37.3%, white crystalls, 74.8-75°C, ^{1}H NMR (300 MHz): δ 7.41-7.44 (d, 1H, H-5, J_{5-4} = 8.7Hz), 7.12-7.13 (d, 1H, H-2, J_{2-4} = 2.8Hz), 6.65-6.69 (dd, 1H, H-4, J_{4-2} = 2.8Hz, J_{4-5} = 8.7Hz), 5.39 (s, 1H, H-OH).

IR (Nujol mull): 1580(s), 1875(w), 3050(s).

MS(ei): m/z 250(M^+), 252($M+2^+$), 254($M+4^+$).

General procedure for the nitration of 3-halophenols: The 3-chlorophenol **13** (2.0g, 15.6mmol) was dissolved in glacial acetic acid (10mL), conc. HNO_3 (2.7g, 17.2mmol, 1.1mL) was added and the solution was stirred at room temperature for 30 min. Then the solution was diluted with ice water and extracted with ether three times (50mL at a time). The ether extracts were combined and dried over $MgSO_4$. They were concentrated and the residue was chromatographed with $CHCl_3$, (silica-gel was the stationary phase) to yield 4-nitro-3-chlorophenol **65** (1.11g, 40.7%), 6-nitro-3-chlorophenol **67** (0.50g, 18.5%), 2-nitro-3-chlorophenol **69** (0.31g, 11.1%)

4-Nitro-3-chlorophenol 65: ($C_6H_4O_3NCl$), 40.7%,yellow crystalls, mp 117.5-118.5°C, ^{1}H NMR (300 MHz): δ 7.96-7.99 (d, 1H, H-5, J_{5-6} = 8.9Hz), 7.00-7.01 (d, 1H, H-2, J_{2-6} = 2.6Hz), 6.81-6.85 (dd, 1H, H-6, J_{6-2} = 2.6Hz, J_{6-5} = 8.9Hz), 6.1 (s, 1H, H-OH).

IR (Nujol mull): 1515(s), 1570(s), 1585(s), 1605(s), 1620(m). 3350(s).

MS(ci): m/z 174(MH^+).

2-Nitro-5-chlorophenol 67: ($C_6H_4O_3NCl$), 18.5%, yellow crystalls, mp 39-40°C, ^1H NMR (300 MHz): δ 10.64 (s, 1H, H-OH), 8.03-8.06 (d, 1H, H-5, J_{5-4} = 9.0Hz), 7.15-7.16 (d, 1H, H-2, J_{2-4} = 2.1Hz), 6.95-6.99 (dd, 1H, H-4, J_{4-2} = 2.1Hz, J_{4-5} = 9.0Hz).

IR (Nujol mull): 1535(s), 1590(s), 1620(s), 1665(w), 1770(w), 3200(s).

MS(ei): m/z 173(M^+), 175($M+2^+$).

2-Nitro-3-chlorophenol 69: ($C_6H_4O_3NCl$), 11.1%, yellow crystalls, mp 34.5-35°C, ^1H NMR (300 MHz): δ 9.41 (s, 1H, H-OH), 7.36-7.42 (t, 1H, H-5, $J_{5-4,6}$ = 8.2Hz), 7.05-7.10 (dd, 2H, H-4,6, J_{4-6}=1,3Hz, J_{4-5} = 8.1Hz, J_{6-5} = 8.4Hz).

IR (Nujol mull): 1540(s), 1580(s), 1605(s),m 3450(s).

MS(ei): m/z 173(M^+), 175($M+2^+$).

4-Nitro-3-bromophenol 66: ($C_6H_4O_3NBr$), 32.9%, yellow crystalls, mp 128.5-129°C, ^1H NMR (300 MHz): δ 6.15 (s, 1H, H-OH), 7.94-7.97 (d, 1H, H-5, J_{5-6} = 8.9Hz), 7.21-7.22 (d, 1H, H-2, J_{2-6} = 2.6Hz), 6.85-6.89 (dd, 1H, H-6, J_{6-2} = 2.6Hz, J_{6-5} = 8.9Hz).

IR (Nujol mull): 1510(s), 1580(s), 1610(s), 3400(s).

MS(ci): m/z 218(MH^+), 220($(M+2)H^+$), 235(MNH_4^+), 237($(M+2)NH_4^+$).

2-Nitro-5-bromophenol 68: ($C_6H_4O_3NBr$), 19.6%, yellow crystalls, mp 42-43°C, ^1H NMR (300 MHz): δ 10.6 (s, 1H, H-OH), 7.95-7.98 (d, 1H, H-5, J_{5-4} = 9.0Hz), 7.35-7.36 (d, 1H, H-2, J_{2-4} = 2.0Hz), 7.11-7.15 (dd, 1H, H-4, J_{4-2} = 2.0Hz, J_{4-5} =9.0Hz).

IR (Nujol mull): 1530(s), 1580(s), 1615(s), 3200(m).

MS(ci): m/z 218(MH^+), 235(MNH_4^+).

2-Nitro-3-bromophenol 70: ($C_6H_4O_3NBr$), 11.9%, yellow crystalls, mp 65-65.5°C, ^1H NMR (300 MHz): δ 9.28 (s, 1H, H-OH), 7.30-7.31 (dd, 1H, H-5, $J_{5-6,4}$ = 8.3Hz), 7.06-7.12 (dd, 2H, H-4, H-6, J_{4-5} = 6.8Hz, J_{6-5} = 12.7Hz).

IR (Nujol mull): 1520(s), 1575(s), 1600(s), 3200(m).

MS(ci): m/z 218(MH^+), 235(MNH_4^+).

Formylation of 3-bromophenol: A 100mL three neck flask equipped with a reflux condenser a thermometer and a pressure equilibrating addition funnel, was charged with a 50% aqueous NaOH (9.0g, 0.225 mol diluted with H_2O, 9mL). A suspension of 3-bromo phenol **14** (5.0g, 28.9mmol) in H_2O (5mL) was added. The apparatus was flushed with N_2, and a positive pressure of N_2 was maintained throughout the reaction. The resulting yellow colored suspension of phenoxide was heated in a water bath to 65-70°C until it was completely dissolved. Chloroform (7.0g, 58.6mmol, 4.75mL) was then added dropwise during a 15min period and the temperature was raised to 80-90°C for one and a half hour. The reaction mixture was cooled in an ice bath and acidified to pH = 3 (pH indicator), with 20% acetic acid solution. The acidified solution was extracted three times with ethyl acetate (50mL each time). The ethyl acetate extracts were combined and washed with aqueous $NaHCO_3$ (5%, 30mL), and water (30mL). The organic solution was dried over $MgSO_4$ and concentrated to yield 2.91g of residue, a mixture of four compounds. Column chromatography to the residue (silica-gel, tol./EtOAc=13/1 or $CHCl_3$ /EtOAc=13/1), yielded 6-bromosalicylaldehyde **73** (1.345g, 23.15%), 4-bromo salicylaldehyde **71** (0.847g, 14.58%), 2-bromo-4-hydroxy benzaldehyde **72** (0.717g, 12.34%).

4-Bromosalicylaldehyde 71: ($C_7H_5O_2Br$), 14.6%, white crystalls, mp 51-52°C, ^1H NMR (300 MHz): δ 11.13 (s, 1H, H-OH), 9.8 (s, 1H, H-CHO), 7.37-7.40 (d, 1H, H-6, J_{6-5} = 7.8Hz), 7.11-7.14 (overlapping, 1H, H-3, d, 1H, H-5, J_{5-6} = 7.6Hz).

IR (Nujol mull): 1600(s), 1615(s), 1665(s), 3100(s).

MS(ci): m/z 200(M^+), 202($M+2^+$).

2-Bromo-4-hydroxybenzaldehyde 72: ($C_7H_5O_2Br$), 12.3%, white crystalls, mp 162-163°C, ^1H NMR (300 MHz) [$(CD_3)_2O$]: δ 10.15 (s, 1H, H-OH), 9.76 (s, 1H, H-CHO), 7.78-7.81 (d, 1H, H-6, J_{6-5} = 8.7Hz), 7.16-7.17 (d, 1H, H-3, J_{3-5} = 2.3Hz), 6.95-6.98 (dd, 1H, H-5, J_{5-3} = 2.3Hz, J_{5-6} = 8.7Hz).

IR (Nujol mull): 1590(s), 1650(m), 1690(s), 2850(w), 2975(w), 3050(w), 3100(w).

MS(ci): m/z 218(MN_4^+), 220((M+2)NH_4^+).

6-Bromosalicylaldehyde 73: ($C_7H_5O_2Br$), 23.2%, white crystalls, mp 125-127°C, ^1H NMR (300 MHz): δ 11.95 (s, 1H, H-OH), 10.28 (s, 1H, H-CHO), 7.28-7.32 (t, 1H, H-4, $J_{4-3,6}$ = 8.2Hz), 7.1-7.3 (d, 1H, H-5, J_{5-4} = 8.2Hz), 6.88-6.92 (d, 1H, H-3, J_{3-4} = 8.2Hz).

IR (Nujol mull): 1650(s), 1690(s), 3000(m).

MS(ci): m/z 200(M^+), 202($M+2^+$).

Chapter 4

General procedure for the preparation of 2-acyl-benzofurans: A 20% w/v solution of ortho-vanillin (15.2g, 0.1mol) in methanol (75mL, reagent grade) was stirred overnight with α-chloro-acetone (12.5g, 0.13mol, 12mL 90% sol.) and K_2CO_3 (17.0g, 0.12mol). The reaction mixture was diluted with water and left to stand for 30min. The precipitated solid was filtered (suction filtration), washed with cold water and dried. Usually the crude 2-acetyl-7-methoxybenzofuran **10** (17.0g, 89.5%) was pure enough for the next reaction. Analytically pure samples were obtained by recrystallization from ethanol.

2-Benzoyl benzofuran 7: ($C_{15}H_{10}O_2$), 66.3%, white crystals, mp 88-88.5°C, ^{1}H NMR (300MHz): δ 8.00-8.03 (d, 2H, H-2', 6', $J_{2',6'-3',5'}$ = 7.4Hz), 7.68-7.71 (d, 1H, H-4, J_{4-5} = 7.8Hz), 7.58-7.63 (t, 2H, H-4', 5, $J_{4'-3',5'}$ =$J_{5-4,6}$ = 7.6Hz), 7.44-7.53 (overlapping 4H, H-3, 7, 3', 5'), 7.26-7.32 (t, 1H, H-6, $J_{6-5,7}$ = 7.1Hz).

IR(Nujol mull): 1600(s), 1615(s), 1640(s).

MS(ci): m/z 223(MH^+), 240(MNH_4^+).

4-Bromo-2-benzoyl benzofuran 8: ($C_{15}H_9O_2Br$), 74.3%, white crystals, mp 108-109°C, ^{1}H NMR (300MHz): δ 8.02-8.05 (d, 2H, H-2',6', $J_{2',6'-3',5'}$ = 7.1Hz), 7.63-7.68 (t, 1H, H-4', $J_{4'-5',3'}$ = 7.4Hz), 7.47-7.60 (overlapping 5H, H-3,5,7,3',5'), 7.32-7.38 (t, 1H, H-6, $J_{6-7,5}$ = 8.1Hz).

IR(Nujol mull): 1580(s), 1595(s), 1605(s), 1645(s).

MS(ci): m/z 318(MNH_4^+), 320((M+2)NH_4^+).

2-Benzoyl-7-methoxy benzofuran 9: ($C_{16}H_{12}O_3$), 79.4%, ^{1}H NMR (300MHz): δ 8.01-8.04 (d, 2H, H-2',6', $J_{2',6'-3',5'}$ = 7.8Hz), 7.53-7.57 (t, 1H, H-4', $J_{4'-3',5'}$ = 7.2Hz), 7.43-7.48 (overlapping 3H, H-3,3',5'), 7.16-7.23 (overlapping 2H, H-4,5, J_{4-5} = 7.1Hz, J_{5-4} = 7.0Hz, J_{5-6} = 7.6Hz), 6.87-6.90 (d, 1H, H6, J_{6-5} = 7.5Hz).

2-Acetyl-7-methoxy benzofuran 10: ($C_{11}H_{10}O_3$), 89.5%, white crystalls, mp 93°C, ^{1}H NMR (300MHz): δ 7.47 (s, 1H, H-3), 7.18-7.28 (overlapping 2H, d, 1H, H-4, J_{4-5} =

8.1Hz, J_{4-6} = 1.5Hz, dd, 1H, H-5, J_{5-4} = 8.1Hz, J_{5-6} = 7.5Hz), 6.92-6.95 (dd, 1H, H-6, J_{6-5} = 7.5Hz, J_{6-4} = 1.4Hz), 4.02 (s, 3H, H-7MeO), 2.62 (s, 3H, H-2Ac).

IR(Nujol mull): 1590(s), 1605(w), 1620(m), 1685(s).

MS(ci): m/z 190(MH^+), 208(MNH_4^+).

Bromination of 2-acetyl-7-methoxy benzofuran 10, method A: A 250mL flask was charged with a solution of 2-acetyl-7-methoxy benzofuran **10** (5.0g, 26.3mmol) in CCl_4 (100mL) and K_2CO_3 (4.36g, 31.5mmol). Br_2 (10.1g, 63.12mmol, 3.25mL) was added dropwise within 15min. The mixture was stirred at room temperature for four hours, washed with aqueous $Na_2S_2O_7$ (5%, 30mL), water (30mL), dried over $MgSO_4$ and concentrated to yield a crude solid product, consisting mainly of 2-[2, 2-dibromo]-acetyl 4-bromo-7-methoxy-benzofuran **12**, 9.74g (86.7%).

2-[(2',2'-dibromo)-acetyl]-4-bromo-7-methoxy benzofuran 12: 86.7%, ^1H NMR (300 MHz): δ 7.77 (s, 1H, H-3), 7.36-7.39 (d, 1H, H-5, J_{5-6} = 8.6Hz), 6.84-6.88 (d, 1H, H-6, J_{6-5} = 8.5Hz), 6.77 (s, 1H, H-2'), 44.02 (s, 3H, H-7MeO).

Reduction of 2-((2',2'-dibromo)-acetyl)-4-bromo-7-methoxy benzofuran 12: A solution of (2',2'-dibromo)-acetyl-4-bromo-7-methoxy-benzufuran **12** (5.0g, 11.71mmol) in acetic acid (50mL) was stirred vigorously under reflux with Zn powder (4.0g, 61.2mmol). HBr vapors were detected escaping the condenser. The solution was refluxed for an extra 30min, after the HBr vapors ceased to escape. The reaction mixture was diluted with water (300mL) and extracted with ether (3 x 100mL). The ether extracts were combined and washed with water (50mL), aqueous $NaHCO_3$ (sat. sol., 50mL), and water (30mL), dried over $MgSO_4$, and concentrated, to yield an oily mixture (2.8g) consisting of a number of reduction products 39 . After column chromatography ($CHCl_3$) 3 partial mixtures of 2,3 dihydro-benzofurans were obtained.

2-Acetyl-2,3-dihydro-4-bromo-7-methoxy benzofuran 14a: ^{1}H NMR (300MHz): δ 6.94- 6.97 (d, 1H, H-5, J_{5-6} = 8.7Hz), 6.65-6.68 (d, 1H, H-6, J_{6-5} = 8.7Hz), 5.09-5.12 (dd, 1H, H-2, J_{2-3a} = 10.6Hz, J_{2-3b} = 7.0Hz), 3.87 (s, 3H, H-7MeO), 3.41-3.50 (dd, 1H, H-3a, J_{3a-2} = 10.7Hz, J_{3a-3b} = 16.4Hz), 3.27-3.35 (dd, 1H, H-3b, J_{3b-2} = 7.0Hz, J_{3b-3a} = 16.4Hz), 2.33 (s, 3H, H-2Ac).

2-((1',2'-diacetoxy-ethyl)-4-bromo-7-methoxy-2,3-dihydro benzofuran 14b: ^{1}H NMR (300MHz) : δ 7.23-7.26 (d, 1H, H-5, J_{5-6} = 8.6Hz), 6.8 (s, 1H, H-3), 6.65-6.68 (d, 1H, H-6, J_{6-5} = 8.5Hz), 6.20-6.24 (dd, 1H, H-1', $J_{1'-2'a}$ = 7.0Hz, $J_{1'-2'b}$ = 4.6Hz), 4.57-4.64 (dd, 1H, H-2'b, $J_{2'b-1'}$ = 4.6Hz, $J_{2'b-2'a}$ = 11.8Hz), 4.49-4.56 (dd, 1H, H-2'a, $J_{2'a-1'}$ = 7.0Hz, $J_{2'a-2'b}$ = 11.8Hz), 3.95 (s, 3H, H-7MeO), 2.14 (s, 3H, H-1OAc), 2.07 (s, 3H, H-2OAc).

General procedure for the bromination of the 2-acyl-7-methoxy benzofurans, method B: Br_2 (17.1g, 104.6mmol, 5.5mL 98%) was added dropwise at room temperature within 15min to a suspension of 2-acetyl-7-methoxy-benzofuran **10** (17.0g, 89.5mmol) in t-butanol (95%, 5% H_2O, 175mL) and K_2CO_3 (16.4g, 118.7mmol) under stirring. The reaction mixture warmed up during the addition of Br_2. After it returned to room temperature it was stirred for an extra 2 hours. It was then diluted with water and left to stand for 30min. The precipitated solid was filtered under reduced pressure and dried. The white solid obtained (20.8g, 86.3%) was pure enough for the next reaction. An analytically pure sample **13** was either obtained by recrystallization (ethanol) or column chromatography ($CHCl_3$).

2-Benzoyl-4-bromo-7-methoxy benzofuran 11: ($C_{16}H_{11}O_3Br$), 91.4%, white crystalls, mp 115-117°C, ^{1}H NMR (300MHz): δ 8.04-8.07 (d, 2H, H-2',6', $J_{2',6'-3',5'}$ = 7.2Hz), 7.59-7.66 (dd, 1H, H-4', $J_{4'-3',5'}$ = 7.4Hz), 7.51-7.56 (t, 2H, H-3',5', $J_{3',5'-4',2',6'}$ = 7.7Hz), 7.47 (s, 1H, H-3), 7.31-7.34 (d, 1H, H-5, J_{5-6} = 8.4Hz), 6.79-6.82 (d, 1H, H-6, J_{6-5} = 8.4Hz), 3.99 (s, 3H, H-7MeO).

IR(Nujol mull): 1580(m), 1590(s), 1600(m), 1650(s).

MS(ci): m/z 348(MNH_4^+), 350($(M+2)NH_4^+$).

2-Acetyl-4-bromo-7-methoxy benzofuran 13: ($C_{11}H_9O_3Br$), 86.3%, white crystalls, mp 142-143°C, ^1H NMR (300MHz): δ 7.46 (s, 1H, H-3), 7.32-7.35 (d, 1H, H-5, J_{5-6} = 8.3Hz), 6.79-6.82 (d, 1H, H-6, J_{6-5} = 8.3Hz), 4.00 (s, 3H, H-(7-MeO)), 2.63 (s, 3H, H-2Ac).

IR(Nujol mull): 1560(s), 1580(s), 1610(w), 1680(s), 1850(w).

MS(ci): m/z 286(MNH_4^+).

General procedure for the reduction of the 2-acyl benzofurans: Solid $NaBH_4$ (0.7g, 99%, 18.5mmol) was added with stirring into a suspension of the 4-bromo-2-acetyl-7-methoxybenzofuran **13** (5.0g, 18.6mmol in ethanol (50mL). The mixture warmed up after an incubation time of a few minutes and the solid was dissolved. The reaction was stirred for an extra hour after reaching room temperature, or until TLC analysis ($CHCl_3$) showed that the ketone had completely reacted. The mixture was diluted with aqueous NaCl (10%, 200mL) and extracted with methylene chloride (4 times, 50mL each). The combined extracts of methylene chloride were washed once with water, dried over MgSO4 and concentrated to an oily residue (4.5g, 90.1%) which solidified upon standing for a few days. The residue was pure enough for the next reaction. Analytically pure alcohol **19** was obtained by column chromatography ($CHCl_3$) which crystallized to white or colorless crystals.

2(1'-Hydroxy-ethyl)-7-methoxy benzofuran 18: 97%, ^1H NMR (300MHz): δ 7.08-7.11 (overlapping 2H, H-6,4), 6.70-6.75 (dd, 1H, H-5, J_{5-4} = 5.4Hz, J_{5-6} = 3.2Hz), 6.55 (s, 1H, H-3), 4.95-5.02 (q, 1H, H-1', $J_{1'-2'}$ = 6.5Hz), 3.94 (s, 3H, H-7MeO), 3.03 (s, 1H, H-OH), 1.57-1.60 (d, 3H, H-2', $J_{2'-1'}$ = 6.5Hz).

2-(1'-Hydroxy)-ethyl)-7-methoxy-4-bromo benzofuran 19: ($C_{11}H_{11}O_3Br$), 90.1%, white crystalls, mp 63-64°C, ^1H NMR (300MHz): δ 7.19-7.23 (d, 1H, H-5, J_{5-6} = 8.5Hz), 6.60-6.63 (overlapping 2H, H-3(s), H-6(d)), 4.90-5.01 (q, 1H, H-1', $J_{1'-2'}$ = 6.5Hz), 3.94 (s, 3H, H-7MeO), 3.1 (s, 1H, H-OH), 1.59-1.62 (d, 3H, H-2', $J_{2'-1'}$ = 6.6Hz).

IR(Nujol mull): 1580(s), 1595(s), 1617(s), 1820(w), 3300(s).

MS(ci): m/z 288(MNH_4^+).

2(1'-Hydroxy-1'-phenyl)methyl-4-bromo-7-methoxy benzofuran 20: ($C_{16}H_{13}O_3Br$), 86.7%, white crystalls, mp 110-111°C, ^1H NMR (300MHz): δ 7.30-7.51 (overlapping 5H, H-Ph), 7.23-7.26 (d, 1H, H-5, J_{5-6} = 8.3Hz), 6.64-6.67 (d, 1H, H-6, J_{6-5} = 8.6Hz), 6.53 (s, 1H, H-3), 5.95-5.96 (d, 1H, H-1', $J_{1'-OH}$ = 3.2Hz), 3.95 (s, 3H, H-7MeO), 2.69-2.70 (d, 1H, H-OH, $J_{OH-1'}$ = 3.9Hz).

IR(Nujol mull): 1580(m), 1590(m), 1600(w), 1615(m), 1820(w), 3200(s).

MS(ci): m/z 350(MNH_4^+), 352((M+2)NH_4^+).

2-(1'-Hydroxy-1'-phenyl)methyl benzofuran 16: ($C_{15}H_{12}O_2$), white crystalls, mp 70-72°C.

IR(Nujol mull): 1585(s), 1595(s), 1660(w), 1760(w), 1800(w), 1885(w), 3100(s).

MS(ci): m/z 242(MNH_4^+).

2-(1'-Hydroxy-1'-phenyl)methyl-4-bromo benzofuran 17: ($C_{15}H_{11}O_2Br$).

IR: 1580(w), 1600(m), 1690(w), 2900(m), 2960(m), 3025(m), 3060(m), 3400(s).

MS(ci): m/z 320(MNH_4^+).

General procedure for the methylation of the benzofuranyl alcohols: A solution of the 2-(1-hydroxy-ethyl)-7-methoxy-4-bromobenzofuran **19** (6.6g, 24.4mmol), in benzene (70mL) was added in a flask charged with aqueous NaOH (4.0g, 100mmol, 10mL H_2O) and tetra butyl ammonium iodide (TBAI, 0.9g, 2.4mmol). The two phase system was stirred for 15min. to reach an equilibrium, then dimethyl sulfate (8.0g, 63.5mmol, 6.0mL) was added dropwise. The reaction was stirred overnight at room temperature and monitored with TLC ($CHCl_3$). When the alcohol had completely reacted, the reaction mixture was diluted with ether (100mL) and washed with water (75mL), aqueous NaOH (10%, 50mL) , and water (50mL). It was dried over $MgSO_4$ and concentrated to yield the oily product 2-(1'-methoxy-ethyl)-4-bromo-7-methoxy

benzofuran **24** (6.1g, 87.8%). The product was further purified by passing it through a small column ($CHCl_3$).

2-(1-methoxy-1-phenylmethyl)-benzofuran 21: ($C_{16}H_{14}O_2$), 84.7%, ^1H NMR (300MHz): δ 7.0-7.8 (overlapping 9H, 5H-Ph, H-4,5,6,7), 6.4-6.6 (2s, 1H, H-3), 5.3 (s, 1H, H-1'), 3.41 (s, 3H, H-MeOH).

IR: 1575(m), 1605(m), 1655(m), 1720(w), 1800(w), 2820(m), 2900(m), 2930(m), 2980(m), 3040(m), 3060(m).

MS(ci): m/z 256(MNH_4^+).

2-(1-methoxy-1-phenylmethyl)-4-bromo benzofuran 22: ($C_{16}H_{13}O_2Br$), 87.8%, ^1H NMR (300MHz): δ 6.97-7.46 (overlapping 8H, 5H-Ph, H-5,6,7), 6.59 (s, 1H, H-3), 5.34 (s, 1H, H-1'), 3.97 (s, 3H, H-MeO).

IR: 1580(s), 1610(s), 1655(w), 1720(w), 1760(w), 1820(w), 1900(w), 1950(w), 2820(s), 2900(s), 2930(s), 2990(s), 3030(s), 3060(s).

MS(ci): m/z 334(MNH_4^+), 336((M+2)NH_4^+).

2-(1'-methoxy-ethyl)-7-methoxy benzofuran 23: ($C_{12}H_{14}O_3$), 84.8%, ^1H NMR (300MHz): δ 7.12-7.15 (overlapping, 2H, H-4,6, J_{4-5} = 3.6Hz, J_{6-5} = 5.3Hz), 6.76-6.79 (dd, 1H, H-6, J_{5-6} = 5.2Hz, J_{5-4} = 3.7Hz) 6.63 (s, 1H, H-3), 4.45-4.53 (q, 1H, H-1', $J_{1'-2'}$ = 6.6Hz), 3.99 (s, 3H, H-7MeO), 3.36 (s, 3H, H-1'MeO), 1.57-1.59 (d, 3H, H-Me, $J_{2'-1'}$ = 6.6Hz).

2-(1'-methoxy-ethyl)-4-bromo-7-methoxy benzofuran 24: ($C_{12}H_{13}O_3Br$), 87.8%, ^1H NMR (300MHz): δ 7.21-7.24 (d, 1H, H-5, J_{5-6} = 8.3Hz), 6.67 (s, 1H, H-3), 6.61-6.64 (d, 1H, H-6, J_{6-5} = 8.4Hz), 4.45-4.53 (q, 1H, H-1', $J_{1'-2'}$ = 6.5Hz), 3.95 (s, 3H, H-7MeO), 3.36 (s, 3H, H-1'MeO), 1.56-1.59 (d, 3H, H-Me, $J_{2'-1'}$ = 6.5Hz).

IR: 1585(s), 15955(s), 1620(s), 1685(w), 1720(w), 2825(s), 2900(s), 2940(s), 2990(s).

MS(ci): m/z 285(MH^+), 287((M+2)H^+).

2-(1-Methoxy-1-phenylmethyl)-4-bromo-7-methoxy benzofuran 25: ($C_{17}H_{15}O_3Br$), 91.7%, ^1H NMR (300MHz): δ 7.3-7.5 (5H, H-Ph), 7.21-7.24 (d, 1H, H-5, J_{5-6} = 8.5Hz),

6.60-6.64 (d, 1H, H-6, J_{6-5} = 8.6Hz), 6.55 (s, 1H, H-3), 3.40 (s, 1H, H-1'), 3.93 (s, 3H, H-7MeO), 3.44 (s, 3H, H-1'MeO).

General procedure for the deoxygenation of the benzofuranyl methyl ethers: A 250mL round bottom flask was charged with a solution of 2-(1'-methoxy-ethyl)-4-bromo-7-methoxybenzofuran **24** (9.03g, 31.7mmol) in acetonitrile (50mL, dried overnight over CaH_2 and distilled from it). Solid $NaBH_3CN$ (12.6g, 98%, 201mmol) and molecular sieves 3Å (2.0g) were added. The solution was cooled with an ice bath to 0°C and trimethylsilylchloride (TMSCl, 24mL, 210mmol) was added dropwise. The solution was stirred under N_2 until the originally viscous suspension that was formed upon the addition of TMSCl could be separated into a solid and a liquid phase (10days). At that point TLC analysis showed that the reaction had been completed; if not, the stirring was continued until the reaction was completed. The reaction mixture was diluted with ether and filtered (suction filtration) through celite and silica gel. The filtrate was stirred with aqueous Na_2CO_3 (10%, 100mL) for 1 hour. The organic phase was separated and washed with aqueous NaCl (sat. sol., 100mL), aqueous Na_2CO_3 (10%, 100mL), aqueous NaCl (sat. sol., 100mL), dried over $MgSO_4$ and concentrated to yield an oily residue. The residue underwent column chromatography ($CHCl_3$) to yield the 4-bromo-2-ethyl-7-methoxybenzofuran **28** (6.84g, 84.8%) as white solid.

4-Bromo-2-ethyl-7-methoxy benzofuran 28: ($C_{11}H_{11}O_2Br$), 77.3%, white crystalls, mp 68-70°C, ^{1}H NMR (300MHz): δ 7.21-7.24 (d, 1H, H-5, J_{5-6} = 8.4Hz), 6.60-6.63 (d, 1H, H-6, J_{6-5} = 8.6Hz), 6.41 (s, 1H, H-3), 3.98 (s, 3H, H-MeO), 2.78-2.86 (q, 2H, H-1', $J_{1'-2'}$ = 7.6Hz), 1.31-1.37 (t, 3H, H-2', $J_{2'-1'}$ = 7.6Hz).

IR(Nujol mull): 1575(s), 1595(s), 1615(s), 1820(m).

MS(ci): m/z 255(MH^+), 257($(M+2)H^+$).

2-Ethyl-7-methoxy benzofuran 29: ($C_{11}H_{12}O_2$), 80.3%, ^{1}H NMR (300MHz): δ 7.08-7.10 (overlapping, 2H, H-4,6, J_{4-5} = 3.0Hz, J_{6-5} = 5.9Hz), 6.70-6.73 (dd, 1H, H-6, J_{5-6} =

5.9Hz, $J_{5\text{-}4}$ = 3.0Hz), 6.36 (t, 1H, H-3, $J_{3\text{-}1'}$ = 1.0Hz), 3.99 (s, 3H, H-7MeO), 2.78-2.84 (q, 2H, H-1', $J_{1'\text{-}2'}$ = 7.5Hz, $J_{1'\text{-}3}$ = 1.0Hz, 1.30-1.35 (t, 3H, H-2', $J_{2'\text{-}1'}$ = 7.5Hz).

IR: 1575(m), 1585(s), 16o00(s), 1620(s), 2840(s), 2900(s), 2940(s), 2975(s), 3060(m), 3110(w).

MS(ci): m/z 177(MH^+), 194(MNH_4^+).

4-Bromo-2-benzyl-7-methoxy benzofuran 30: ($C_{16}H_{13}O_2Br$), 77.2%, white crystals, mp 84-86°C, ^1H NMR (300MHz): δ 7.26 (s, 5H, H-Ph), 7.15-7.18 (d, 1H, H-5, $J_{5\text{-}6}$ = 8.6Hz), 6.50-6.54 (d, 1H, H-6, $J_{6\text{-}5}$ = 8.6Hz), 6.33(s, 1H, H-3), 4.06(s, 2H, H-CH_2), 3.87 (s, 3H, H-MeO).

IR(Nujol mull): 1585(s), 1595(s), 1605(s), 1620(s).

MS(ci): m/z 334(MNH_4^+), 338((M+2)NH_4^+).

Acidic cleavage of the 2-(1'-methoxy-ethyl)-4-bromo-7-methoxy benzofuran 24: A solution of 2-(1-methoxy-ethyl)-4-bromo-7-methoxybenzofuran **24** (2.0g, 7.02mmol) in AcOH (20mL, 80%) was refluxed for 5 hours. The solution was diluted with water, 150mL and extracted with ether (3x50mL). The ether extracts were washed with water (30mL), aqueous $NaHCO_3$ (sat. sol., 50mL), water (30mL), dried over $MgSO_4$, and concentrated to yield a residue which was separated by column chromatography to its components, the starting compound **24** (1.1g, 55.0%), the corresponding alcohol **19** (0.37g, 19.4%), and the corresponding acetate **27** (0.43g, 19.5%).

2-(1'-O-acetyl)ethyl-4-bromo-7-methoxy benzofuran 27: ($C_{13}H_{13}O_4Br$), 19.5%, ^1H NMR (300MHz): δ 7.19-7.22 (d, 1H, H-5, $J_{5\text{-}6}$ = 8.4Hz), 6.71 (s, 1H, H-3), 6.60-6.63 (d, 1H, H-6, $J_{6\text{-}5}$ = 8.4Hz), 6.0-6.1 (q, 1H, H-1', $J_{1'\text{-}2'}$ = 6.6Hz), 3.93 (s, 3H, H-MeO), 2.09 (s, 3H, H-OAc), 1.66-1.68 (d, 3H, H-2', $J_{2'\text{-}1'}$ = 6.7Hz).

IR: 1585(s), 1600(s), 1620(s), 1740(s), 2830(m), 2900(m), 2940(s), 2970(s), 3110(w).

MS(ci): m/z 330(MNH_4^+), 332((M+2)NH_4^+).

Deoxygenation of the acetate 27: In a solution of the acetate **27** (1.57g, 5.02mmol) in CH_3CN (20mL), at 0°C, under N_2, $NaBH_3CN$ (1.9g, 98%, 27.5mmol), trimethylsilyl chloride (3.8mL, 29.3mmol) and molecular sieves 3Å (0.3g) were added. The reaction was stirred under N_2, overnight (24 hours), at room temperature. It was diluted with 100mL ether and filtered (suction filtration) through celite. The filtrate was washed wtih aqueous Na_2CO_3 (sat.sol., 2x30mL each), aqueous NaCl (sat. sol., 30mL), dried over $MgSO_4$ and concentrated to yield 1.6g of the original acetate. ^{1}H-NMR (300MHz) of the crude product showed traces of the parent alcohol **19** as well as traces of the 2-ethyl-4-bromo-7-methoxy benzofuran **28**.

Deoxygenation of the 2-benzoyl-4-bromo-7-methoxy benzofuran 11: In a solution of 2-benzoyl-4-bromo-7-methoxybenzofuran **11** (1.5g, 4.53mmol), in acetonitrile (20mL), at 0°C under N_2, $NaBH_3CN$ (1.8g, 95%, 27.2mmol), TMSCl (3.5mL, 98%, 29.3mmol) and molecular sieves 3Å (0.3g) were added. The reaction was stirred overnight (24hrs), at room temperature, under N_2. Then it was diluted with ether (100mL), filtered (suction filtration) through celite, washed with aqueous K_2CO_3 (sat. sol., 2x30mL), aqueous NaCl (sat. sol., 30mL), dried over $MgSO_4$, and concentrated to yield 1.64g of residue. Column chromatography yielded the corresponding alcohol **20** (0.73g, 48.6%) and the 2-benzyl-4-bromo-7-methoxy benzofuran **30** (0.70g, 48.6%).

General procedure for the acetylation of the 7-methoxy benzofurans:In a solution of Ac_2O (0.3mL, 2.9mmol) in CH_2Cl_2 (5mL), $BF_3.OEt_2$ (0.4mL, 3.2mmol) was injected under N_2, the solution was stirred for 30min at room temperature and 2-ethyl-7-methoxybenzofuran **29** (0.45g, 2.6mmol) was added. The reaction was stirred overnight under N_2. It was diluted with CH_2Cl_2 (50mL), washed with water (30mL), dried over $MgSO_4$ and concentrated.The acetylated compound **36** (0.2g, 40%) was obtained after column chromatography ($CHCl_3$) on the residue.

2,4-Diacetyl-7-methoxy benzofuran 35: ($C_{13}H_{12}O_4$), 32.8%, yellow crystalls, mp 146-147°C, ^{1}H NMR (300MHz): δ 8.23 (s, 1H, H-3), 7.83-7.86 (d, 1H, H-5, J_{5-6} = 8.4Hz), 6.91-6.94 (d, 1H, H-6, J_{6-5} = 8.4Hz), 4.06 (s, 3H, H-7MeO), 2.64 (s, 6H, H-2Ac).

IR: 1585(s), 1615(m), 1685(s), 3020(s).

MS(ci): m/z 233(MH^+), 250(MNH_4^+).

2-Ethyl-4-acetyl-7-methoxy benzofuran 36: ($C_{13}H_{14}O_3$), 40.1%, ^{1}H NMR (300MHz) δ 7.76-7.72 (d, 1H, H-5, J_{5-6} = 8.4Hz), 7.19 (s, 1H, H-3), 6.71-6.74 (d, 1H, H-6, J_{6-5} = 8.4Hz), 4.06 (s, 3H, H-MeO), 2.83-2.87 (q, 2H, H-1', $J_{1'-2'}$ = 7.6Hz), 2.62 (s, 3H, H-Ac), 1.33-1.39 (t, 3H, H-2', $J_{2'-1'}$ = 7.6Hz).

IR: 1595(s), 1623(s), 1663(s), 2845(m), 2880(m), 2940(m), 2970(s), 3020(m).

MS(ci): m/z 219(MH^+), 236(MNH_4^+).

Chapter 5

Preparation of the 1,2-O,O-benzylidene-6,3-glucuronolactone 3: Method A: A 100ml flask equipped with a magnectic stirring bar, a reflux condenser and a $CaCl_2$ guard drying tube was charged with THF (50ml), 6,3-glucuronolactone (5.0g, 28.4mmol), dimethyl benzaldehyde acetal (5.2g 99%, 5.5ml, 33.0mmol) and PTSA (0.480g, 2.5mmol). The solution was refluxed under stirring until the lactone was completely dissolved (6h). It was left to reach room temperature and anhydrous K_2CO_3 (3.5g, 25.3mmol) was added, and stirred for 15min. The solid was filtered and the filtrate was concentrated to a viscous pale yellow gum. The residue was purified by column chromatography ($CHCl_3$/EtOAc = 10/3) to yield the exo-phenyl **3** (2.5g, 33.3%) and the endo-phenyl **3** (0.8g, 10.7%) product.

Method B: A 100ml flask equipped with a magnetic stirring bar and a drying $CaCl_2$, guard tube was charged with 6,3-glucuronolactone (5.0g, 28.4mmol), DMF (50ml), PTSA (0.480g, 2.5mmol) and dimethyl benzaldehyde acetal (5.2g 99%, 5.5ml, 33.0mmol). The solution was stirred overnight at room temperature. K_2CO_3 (3.5g, 25.3mmol) was added. It was stirred for 15min, and filtered. The filtrate was concentrated to yield a viscous oil. The oil was chromatographed ($CHCl_3$/EtOAc = 10/3) to yield the endo-phenyl **3** (2.4g, 32.0%) and the exo-phenyl **3** (2.7g, 36%) product.

Method C: A mixture of D-glucurono-6,3-lactone (17.6g, 0.1mol), $ZnCl_2$ (20.0g, 0.15mol) and benzaldehyde 150ml, was stirred at room temperature for 2 days. The mixture was diluted with ether (250ml) and washed with water (500ml total), repeatedly, then concentrated under reduced pressure. Trituration with water yielded a solid which was filtered, dried and crystallized from ethyl acetate-petroleum ether to yield the exo-phenyl benzylidene **3** (10.6g, 40%). The filtrate was concentrated to yield a 1/1 mixture of endo/exo-phenyl **3** (8.4g, 32%) product.

1,2-O,O-benzylidene-D-glucofuranurono-6,3-lactone 3 (endo-phenyl):

^{1}H NMR 300MHz: δ 7.39-7.48 (5H, Ph), 6.13-6.15 (d, 1H, H-1, J_{1-2} = 3.9Hz), 6.05 (s, 1H, benzylidene), 4.90-4.92 (d, 1H, H-2, J_{2-1} = 3.9Hz), 4.84-4.85 (d, 1H, H-3, J_{3-4} = 2.9Hz), 4.69-4.72 (dd, 1H, H-4, J_{4-3} = 2.9Hz, J4-5=4.4Hz), 4.47-4.48 (d, 1H, H-5, J_{5-4} = 4.4Hz).

IR (nujol mull): 1780(vs), 3400(s).

1,2-O,O-benzylidene-D-glucofuranurono-6,3-lactone 3 (exo-phenyl):

^{1}H NMR 300MHz: δ 7.41-7.43 (5H, Ph), 6.16-6.17 (d, 1H, H-1, J_{1-2} = 3.6Hz), 6.05 (s, 1H, benzylidene), 4.97-5.02 (overlapping 3H, H-2,3,5), 4.57(s, 1H, H-4).

IR (nujol mull): 1770(vs), 3400(s).

Preparation of the 1,2-O,O-isopropylidene-D-glucofuranurono-6,3-lactone 4:

A 500ml R.B. flask equipped with magnetic stirring barr and a $CaCl_2$ drying guard tube was charged with a solution of 6,3-Glucuronolactone (17.6g, 0.1mol) in acetone (175ml) and conc. H_2SO_4 (4ml). The solutiion was stirred overnight (12-16h). $Ba(OH)_2$ (15.0g, 0.09mol) was added. The dark red solution was stirred for 15 min. and filtered. The filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (300ml), cooled in an ice bath and washed twice with ice-cold aqueous $NaHCO_3$ (30ml each), once with ice-cold water (30ml), dried over $MgSO_4$ and concentrated to yield the acetonide **4** (15.1g, 70.0%).

1,2-O,O-isopropylidene-D-6,3-glucofuranuronolactone 4: 70%, ^{1}H NMR 300MHz: δ 6.00-6.01 (d, 1H, H-1, J_{1-2}=3.6Hz), 4.94-4.97 (dd, 1H, H-4, J_{4-3} = 2.9Hz, J_{4-5} = 4.3Hz), 4.85-4.86 (d, 1H, H-3, J_{3-2} = 2.8Hz), 4.82-4.84 (d, 1H, H-2, J_{2-1} = 3.6Hz), 4-58-4.62 (dd, 1H, H-5, J_{5-4} = 4.4Hz, J_{5-OH} = 7.1Hz), 1.52, 1.35 (2s, 3H each, 2 Me from isopropylidene).

IR (nujol mull): 1780(vs), 3440(s).

General procedure for the preparation of the 5-O-t-butyl-dimethyl-silyl ethers: A R.B. flask equipped with magnetic stirring bar, $CaCl_2$ guard-drying tube was charged with a solution of the 1,2-O,O-isopropylidene-D-6,3-glucofuranuronolactone **4** (13.5g, 62.5mmol), in DMF (75ml), t-butyldimethylsilylchloride (TBDMSiCl, 11.6g, 77.1mmol) and imidazole (10.64g, 156.5mmol) were added. The reaction was stirred at room temperature and monitored with TLC until the carbohydrate completely reacted (5 days). Then the solution was diluted with aqueous NaCl (sat. sol., 250ml) and extracted with methylene chloride (4 times 75ml each). The combined organic extracts were washed repeatedly with water (4 times, 50ml each), dried over $MgSO_4$, and concentrated to yield a colorless viscous oil **6** (17.3g, 84.0%) which solidified on standing. The product placed under vacuum over P_2O_5 was usually pure enough for further reactions. Analytically pure was obtained with column chromatography ($CHCl_3$).

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-D-glucofuranurono-6,3-lactone 5:

80.3%, ^1H NMR 300MHz: δ 7.45(5H, Ph), 6.18-6.19 (d, 1H, H-1, J_{1-2} = 3.7Hz), 6.05 (s,1H, benzylidene), 4.93-4.95 (overlapping d, 2H, H-2, H-3, J_{2-1} = 3.4Hz, J_{3-4} = 2.5Hz), 4.85-4.87 dd, 1H, H-4, J_{4-3} = 3.1Hz, J_{4-3} = 4.2Hz), 4.56-4.5 7 (d, 1H, H-5, J_{5-4} = 4.4Hz), 0.98 (s, 9H, t-Bu), 0.24(s, 3H, Me), 0.21 (s, 3H, Me).

IR: 1800(vs), 2850(s), 2895(s), 2920(s), 2945(s).

1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-D-glucofuranurono-6,3-lactone 6:

84%, ^1H NMR 300MHz: δ 6.02-6.03(d, 1H, H-1, J_{1-2} = 3.7Hz), 4.80-4.83 (dd, 1H, H-4, J_{4-3} = 2.9Hz, J_{4-5} = 4.2Hz), 4.77-4.79 (d, 1H, H-2, J_{2-1} = 3.8Hz), 4.73-4.75 (d, 1H, H-3, J_{3-4} = 2.8Hz), 4.52-4.54 (d, 1H, H-5, J_{5-4} = 4.3Hz), 1,52, 1.34 (2s, 2Me -isopropylidene), 0.95 (s, 9H, t-Bu), 0.22, 0.18 (2s, 2Me of TBDMS).

IR: 1805(vs), 2850(s), 2895(s), 2920(s), 2945(s), 3010(s).

1,2-isopropylidene-5-O-t-butyldimethylsilyl-L-idofuranurono-6,3-lactone 25:

80.9%, ^1H NMR 300MHz: δ 5.89-5.90 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.00-5.02 (d, 1H, H-4, J_{4-3} = 2.9Hz), 4.80-4.82 (d, 1H, H-2, J_{2-1} = 3.6Hz), 4.59-4.61 (d, 1H, H-3, J_{3-4} = 2.9Hz),

4.22 (s, 1H, H-5), 1.53, 1.35 (2s, 3H each, 2-Me from isopropylidene), 0.90 (s, 9H, t-butyl), 0.18, 0.16 (2s, 3H each, 2-Me from TBDMS).
IR: 1790(vs), 2395(w), 2855(s), 2875(s), 2940(s), 3020(s).

Preparation of the 1,2-O,O-benzylidene-5-trityl-D-6,3-glucuronolactone 7: A solution of exo-1,2-O,O-benzylidene-6,3-glucuronolactone **3** (6.9g, 26.1 mmol) in THF (15ml) and pyridine (15ml) was stirred refluxing under N_2 with triphenylmethylbromide (10.1g, 31.4mmol) overnight (16h). The solution was diluted with Et_2O (100ml). A white solid precipitated which was collected by filtration. The white solid was dissolved in 100ml CH_2Cl_2, washed with water 30ml, dried over $MgSO_4$, concentrated to yield a viscous oil which crystallized on standing to yield colorless to pale yellow crystalls 6.0g. The ether phase was washed with aqueous $NaHCO_3$ (sat. sol., 30ml) and water (30ml). Dried over $MgSO_4$ and concentrated. The residue was chromatographed ($CHCl_3$/EtOAC = 13/1) to yield 4.6g product and 1.0g of the parent lactone (recovered). Totally 10.6g 80.3% of product **7** was obtained and 1.0g of parent lactone was recovered.
1,2-O,O-benzylidene-5-O-trityl-D-glucofuranurono-6,3-lactone 7: ($C_{32}O_5H_{26}$), 80.3%, ^{1}H NMR 300MHz: δ 7.10-7.70 (20H, 15H-Trityl, 5H benzylidene), 5.96-5.97 (d, 1H, H-1, $J_{1\text{-}2}$ = 3.9Hz), 5.74 (s, 1H, benzylidene), 4.68-4.69 (d, 1H, H-2, $J_{2\text{-}1}$ = 3.9Hz), 4.36-4.39 (2d, H-3, H-5, $J_{3\text{-}4}$ = 3.0Hz, $J_{5\text{-}4}$ = 4.1Hz), 2.95-2.97 (dd, 1H, H-4, $J_{4\text{-}3}$ = 3.0Hz, $J_{4\text{-}5}$ = 3.8Hz).
IR: 1590(w), 1800(vs), 2395(m), 2875(m), 2975(m), 3010(s), 3055(s).
MS: m/z 507(MH^+), 524($MNH4^+$).

Preparation of the 1,2-O,O-benzylidene-5-O-t-butoxydimethylsilyl-glucurono-6,3-lactone 9: A 100ml R.B. flask equiped with a magnetic stirring barr and a reflux condenser was charged with exo-1,2-O,O-benzylidene-6,3-glucuronolactone **3** (4.6g, 17.4mmol) in 20ml DMF, dichlorodimethylsilane (2.5g, 19.4mmol) and pyridine (1.5ml,

18.9mmol). The mixture was stirred at room temperature and monitored with TLC ($CHCl_3$/ETOAc = 13/1) until the reaction was completed, then t-butanol (2.0ml, 27.0mmol) and pyridine (1.5ml, 18.9 mmol) were added and the temperature was raised to 60-65°C. The reaction was monitored with TLC until it was completed (5h). The solution after cooling to room temperature was diluted with aqueous NaCl (sat. sol., 100ml) and extracted with ether (3x50ml) The combined ether extracts were washed with water (3x30ml), dried over $MgSO_4$ and concentrated. The residue was chromatographed ($CHCl_3$/EtOAC = 13/1) to yield the product **9** (4.8g, 72.2%, white solid).

1,2-O,O-benzylidene-5-O-t-butoxydimethylsilyl-6,3-glucofuranurono-6,3-lactone 9: ($C_{19}O_7H_{27}Si$).

IR: 1720(w), 1800(vs), 2395(m), 2925(w), 2955(s), 3005(s).

MS: m/z 396(MH^+).

Preparation of the 1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-gluco-hexodialdodi furanose (1,4: 6,3) 10: A 100ml R.B. three neck flask equipped with magnetic stirring bar and rubber septum was charged with a solution of exo-1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6,3-glucuronolactone **3** in ether (20ml). The solution was cooled with dry ice-acetone bath. The solution of diisobutylaluminum hydride (DIBAH, 6ml, 1.0M) was injected maintaining a positive pressure under N_2. The reaction was monitored with TLC ($CHCl_3$) and poured over a mixture of ice (25g) and acetic acid (6ml) when the lactone was consumed (1.5h). The organic phase was separated, washed with aqueous $NaHCO_3$ (sat. sol., 10ml), water (10ml). Dried over $MgSO_4$, and concentrated. The residue was chromatographed (silica-gel, $CHCl_3$/EtOAc = 10/1) to yield the product **10** as white solid (1.32g, 80%) consisting of two isomers (endo/exo = 3/1).

Exo/endo 6-OH mixture of 1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-D-gluco hexodialdofuranose (1,4: 6,3) 10: 80% (1/3), ^1H NMR 300MHz: **endo 6-OH**: δ 7.38-7.5

(5H, Ph), 6.16-6.17 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.95 (s, 1H, Benzylidene), 5.11-5.13(d, 1H, H-6, J_{6-5} = 4.4Hz), 4.94-4.96 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.70-4.73 (t, 1H, H-4, J_{4-3} = 4.2Hz, J_{4-5} = 4.3Hz), 4.63-4.65 (d, 1H, H-3, J_{3-4} = 4.1Hz), 4.15-4.18 (t, 1H, H-5, J_{5-4} = 4.6Hz, J_{5-6} = 4.6Hz) 0.97 (s, 9H, t-Bu), 0.20, 0.18 (2s, 3H each 2Me).

exo 6-OH: δ 7.38-7.50(5H, Ph), 6.12-6.13 (d, 1H, J_{1-2} = 3.7Hz), 5.96 (s, 1H, benzylidene), 5.23-5.24 (d, 1H, H-6, J_{6-5} = 1.9Hz), 4.96-4.98 (d, 1H, H-4), 4.78-4.80 (d, 1H, H-2, J_{2-1} = 5.3Hz), 4.77-4.78 (d, 1H, H-3, J_{4-3} = 3.5Hz), 4.04-4.07 (dd, 1H, H-5, J_{5-6} = 1.7Hz, J_{5-4} = 4.3Hz), 3.87 (1H, OH), 0.94 (s, 9H, t-Bu), 0.17, 0.15(2s, 3H each, 2Me).

IR: 2820(w), 2850(s), 2860(s), 2880(s), 2920(s), 2950(s), 3020(s), 3350(s).

Preparation of the 1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-exo-acetoxy-D-gluco-hexodialdodifuranose (1,4: 6,3) 11: The lactol 10 (0.15g, 4.07mmol) was dissolved in a 1/1 v/v mixture of Ac_2O/pyridine (2ml/2ml). The solution was stirred overnight protected by a $CaCl_2$ drying guard tube. The Ac_2O and pyridine were evaporated under reduced pressure and the residue was dissolved in ether (20ml), washed with aqueous $NaHCO_3$ (sat. sol., 10ml) and water (10ml). Dried over $MgSO_4$ and concentrated to yield the acetate **11** (0.16g, 95.8%) .

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-exo-O-acetate-gluco-hexodialdodi furanose(1,4: 6,3) 11: ($C_{21}O_7H_{30}Si$), 95.8%: ^1H NMR 300MHz: δ 7.3-7.5 (5H, Ph), 6.13-6.15 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.96-5.97 (d, 1H, H-6, J_{6-5} = 1.9Hz), 5.94 (s, 1H, H-benzylidene), 4.92-4.96 (t, 1H, H-4, J_{4-3} = 4.9Hz, J_{4-5} = 5.1Hz), 4.79-4.83 (overlapping 2d, 2H, H-2,3, J_{2-1} = 4.0Hz, J_{4-3}= 6.2Hz), 4.17-4.20 (dd, 1H, H-5, J_{5-6} = 1.9Hz, J_{5-4} = 4.7Hz), 2.06 (s, 3H, 6-OAc), 0.93(s, 9H, t-Butyl), 0.16, 0.15 (2s, 3H each, 2Me).

IR: 1740(vs), 2850(s), 2895(s), 2925(s), 2950(s).

MS: m/z 423(MH^+), 440(MNH_4^+).

General procedure for the preparation of the sulfonate esters 12, 13: A solution of 1,2-O,O-isopropylidene-6,3-glucuronolactone **4** (8.7g, 40.3mmol) in pyridine (45ml) was cooled to 0°C. Methylsulfonyl chloride (3.6ml, 48.4mmol) was added and the solution was stirred at 0°C overnight. The solution was diluted with water and extracted with CH_2Cl_2 (3 times, 100ml each). The combined organic extracts were washed once with aqueous $NaHCO_3$ (5% sol., 50ml) and once with water, dried over $MgSO_4$ and concentrated to yield **12** (11.8g, 72%).

1,2-O,O-isopropylidene-5-methylsulfonate-D-glucofuranurono-6,3-lactone 12: 72%, ^{1}H NMR 300MHz: δ 6.02-6.03 (d, 1H, H-1, $J_{1,2}$ = 3.6Hz), 5.39-5.41 (d, 1H, H-5, $J_{5,4}$ = 4.3Hz), 5.07-5.09 (dd, 1H, H-4, $J_{4,3}$ = 2.8Hz, $J_{4,5}$ = 4.2Hz), 4.91-4.92 (d, 1H, H-3, $J_{3,4}$ = 2.7Hz), 4.83-4.84 (d, 1H, H-2, $J_{2,1}$ = 3.6Hz), 3.30 (s, 3H, H-Mes), 1.52, 1.35 (2s, 3H each, 2Me from isopropylidene).

IR (nujol mull): 1810(vs).

1,2-O,O-isopropylidene-5-toluenesulfonate-D-glucofuranurono-6,3-lactone 13: 81.2 %, ^{1}H NMR 300MHz: δ 7.87-7.91(d, 2H, H-2', 6', $J_{2',6'-3',5'}$ = 8.4Hz), 7.35-7.38 (d, 2H, H-3', 5', $J_{3',5'-2',6'}$ = 8.6Hz), 5.96-5.97 (d, 1H, H-1, $J_{1,2}$ = 3.6Hz), 5.23-5.25 (d, 1H, H-5, $J_{5,4}$ = 4.2Hz), 4.94-4.97 (dd, 1H, H-4, $J_{4,3}$ = 2.8Hz, $J_{4,5}$ = 4.1Hz), 4.82-4.85 (d, 1H, H-3, $J_{3,4}$ = 2.8Hz), 4.77-4.79 (d, 1H, H-2, $J_{2,1}$ = 3.6Hz), 2.45 (s, 3H, Me from Tos), 1.48, 1.33 (2s, 3H each, 2Me from isopropylidene).

IR (nujol mull): 1595(w), 1810(vs).

Preparation of the hydrazide 14: A solution of 1,2-O,O-isopropylidene-5-methylsulfonate-6,3-glucuronolactone **12** (8.7g, 29.6mmol) in dioxane (200ml) was cooled by an ice bath to 0°C (the solution was solidified). Hydrazine (4.9g, 0.15mol, 4.8 ml) was added and the solution was stirred under N_2 until it reached room temperature (overnight).The dioxane was removed by reduced pressure and the residue was diluted with ethanol (100ml). The precipitated solid methylsulfonate hydrazinium was filtered

and the ethanol solution was concentrated to a viscous oil (7.0g) of the crude product **14** (contaminated with hydrazine). The crude product was used without any further purification.

Preparation of the 5-deoxy-1,2-O,O-isopropylidene-glucofuranurono-6,3-lactone 15: **Method A**: Hydrazide **14** (1.0g, 4.3mmol, crude product) was dissolved in methanol (5 ml). A suspension of NBS (1.5g, 8.6mmol) in water (25ml) was added. When no more gases were produced, the reaction was extracted with CH_2Cl_2 (3X25ml). The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated. Column chromatography on the residue ($CHCl_3$ solvent) yielded the 5-deoxy-lactone **15** (0.09g, 10%). The aqueous phase from the extraction was concentrated and the residue was acetylated with pyridine/Ac_2O. The excess of pyridine and Ac_2O was removed under reduced pressure and the residue was chromatographed ($CHCl_3$) to yield the 1-β-1,2-diacetoxy-5-deoxy-glucofuranurono-6,3-lactone **17** (0.2g, 20%).

Method B: Hydrazide **14** (1.0g, 4.3mmol, crude product) was dissolved in 30ml acetonitrile. Powdered ceric ammonium nitrate (CAN, 4.95g, 12.9 mmol) was added in one portion. After the N_2 efferverscence stopped, the solution was diluted with water (50ml) and extracted with CH_2Cl_2 (3x25ml). The organic extracts were combined, washed with water (25ml), dried over $MgSO_4$, and concentrated. The residue was chromatographed to yield the 5-deoxylactone **15** (0.12g, 14%).

Method C: A solution of $Cu_2Cl_2.2H_2O$ (1.84g, 10.75mmol) in ethanol (100ml) was added in a solution of the hydrazide **14** (1.0g, 4.3mmol) in ethanol (50ml). The reaction was stirred for 24h. Excess ethanol was evaporated, the residue was extracted with ether (100ml). The organic phase was washed with aqueous NaOH (10% solution, 3x25ml), and water (30ml), then dried over $MgSO_4$. The solution was concentrated and the residue was chromatographed to yield the 5-deoxy-6, 3-lactone **15** (0.1g, 12%).

5-Deoxy-1,2-O,O-isopropylidene-glucofuranurono-6,3-lactone 15: ^{1}H NMR 300MHz: δ 5.96-5.98 (d, 1H, H-1, J_{1-2}=3.8Hz), 4.98-5.0 (Multiplet, 1H, H-4), 4.84-4.85 (d, 1H, H-2, J_{2-1} = 3.8Hz), 4.82-4.83 (d, 1H, H-3, J_{3-4} = 3.5Hz), 2.72-2.73 (overlapping, 2H, H-5), 1.51, 1.35 (2s, 3H each, 2Me from isopropylidene).

IR: 1635(m), 1735(m), 1800(vs), 2850(s), 2900(w), 2930(s), 2980(s), 3020(s).

1-β-2-Diacetoxy-5-deoxy-glucofuranurono-6,3-lactone 17: ($C_{10}O_7H_{12}$), ^{1}H NMR 300MHz: δ 6.24 (s, 1H, H-1), 5.35 (s, 1H, H-2), 5.16-5.20 (t, 1H, H-4, J_{4-5} = 6.6Hz, J_{4-3} = 5.7Hz), 4.98-5.00 (d, 1H, H-3, J_{3-4} = 5.3Hz), 2.83-2.92 (dd, 1H, H-5a, J_{5a-4}=7.2Hz, J_{5a-5b} = 19.0Hz), 2.69-2.76 (d, 1H, H-5b, J_{5b-5a} = 18.9Hz), 2.14, 2.07 (2s, 3H each, 2-OAc).

IR: 1750(vs), 1790(vs), 2975(w), 3010(s).

MS: m/z 262(MNH_4^+).

Deoxygenation of the 5-tosylate-6,3-glucuronolactone 13: A 200ml R.B. flask equipped with a reflux condenser and magnetic stirring bar was charged with a solution of 1,2-O,O-isopropylidene-5-toluenesulfonate-6,3-glucuronolactone **13** (2.0g, 5.4mmol) in glyme (50ml) and NaI (1.4g, 9.34mmol). The solution was brought to reflux under N_2, AIBN (0.1g, 0.61mmol) and Bu_3SnH (1.73g, 5.77mmol, 1.6ml) were added. The solution was reflux for 1.5 hrs and more Bu_3SnH (1.6ml) was added. The refluxing continued for 2 more hours and the solution was cooled to room temperature. Aqueous KF (sat. sol., 10ml) was added and it was stirred overnight at room temperature. The solvent was evaporated at reduced pressure . The residue was extracted with ethyl acetate (4x20ml). The organic extracts were combined and washed with water (20ml), dried over $MgSO_4$ and concentrated. The residue underwent column chromatography ($CHCl_3$) to yield the deoxygenated product **15** (0.42g, 38.9%).

Preparation of the 5-O-triflate-1,2-O,O-isopropylidene-glucofuranurono-6,3-lactone 23: A 500ml three neck R.B. flask equipped with a thermometer, two pressure

equilibrium addition funnels and a magnetic stirring bar was flushed with N_2 and charged with a solution of triflic anhydride (16.77g, 59.4mmol, 10ml) in 200ml CH_2Cl_2. The solution was cooled to -10°C (ice-acetone bath) under N_2. One of the pressure eq. addition funnels was charged with a solution of pyridine (4.89g, 61.8mmol, 5.0ml) in CH_2Cl_2 (5ml) and the other with a solution of 1,2-O,O-isopropylidene-6,3-glucurono lactone **4** (12.0g, 55.6mmol) in CH_2Cl_2 (30ml). The pyridine solution was added first under stirring to the triflic anhydride solution, under N_2, at temperatures below -5°C. The resulted white suspension was left to reach the -10°C temperature, again, and the lactone solution was added dropwise at temperatures below -5°C. After the addition was completed the solution was stirred for an extra 30min at (-5)-(-10)°C. It was washed with ice-cold water three times (100ml each). Dried over $MgSO_4$ and concentrated to yield the product **23** (white solid, 17.5g, 90.4%).

Preparation of the 1,2-O,O-isopropylidene-idofuranurono-6,3-lactone 22: A solution of 1,2-O,O-isopropylidene-5-trifluoromethylsulfonate-6,3-glucuronolactone **23** (10.0g, 28.7 mmol) in DMF (100ml) was stirred with sodium trifluoroacetate (8.0g, 58.8mmol) for 1h at room temperature. The DMF was removed at reduced pressure, the residue was dissolved in methanol (100ml) and stirred overnight. It was filtered through celite and concentrated. The residue was purified by column chromatography ($CHCl_3$/ETOAc 10/3) to yield the product **22** (white solid, 5.5g, 88.7%).

1,2-O,O-isopropylidene-idofuranurono-6,3-lactone 22: 88.7%, ^{1}H NMR 300MHz: δ 5.92-5.94 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.06-5.07 (d, 1H, H-4,J_{4-3} = 3.2Hz), 4.83-4.84 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.79-4.80 (d, 1H, H-3, J_{3-4} = 3.2Hz), 4.34 (s, 1H, H-5), 3.36(s, 1H, H-OH), 1.52, 1.35 (2s, 3H each2-Me from isopropylidene).

IR (nujol mull): 1765(vs), 3380(s).

1,2-O,O-isopropylidene-5-O-acetate-idofuranurono-6,3-lactone 22a: ^{1}H NMR 300 MHz: δ 5.97-5.99 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.09-5.11 (d, 1H, H-4, J_{4-3} = 3.7Hz), 4.95 (s,

1H, H-5), 4.86-4.87 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.81-4.83 (d, 1H, H-3, J_{3-4} =3 .7Hz), 2.2 (s, 3H, 5-OAc), 1.50, 1.4 (2s, 3H each, 2-Me from isopropylidene).
IR: 1750(vs), 1795(vs), 2950(m), 2995(s).

Acetylation of the 6,3-glucuronolactone: A 100ml R.B. flask equipped with a magnetic stirring bar was charged with 6,3-glucuronolactone (8.8g, 50.0mmol) and acetic anhydride (20ml). $BF_3.Et_2O$ (2.0ml, 16.3mmol) was added and the suspension was stirred for 5 min. at room temperature. The solid was dissolved to a pale-yellow reddish solution. The solution was left to stand for one hour and poured over ice-cold water (150ml). After 15min standing the precipitated white solid was filtered (suction filtration) and recrystallized from ethanol/acetic acid to yield needle white crystalls **26** (11.9g, 78.8%).

1-β-2,5-triacetoxy-D-glucofuranurono-6,3-lactone 26: 78.8%, ^1H NMR 300MHz: δ 6.17 (d, 1H, H-1, J_{1-2} = 0.7Hz), 5.29 (s, 1H, H-2), 5.25-5.26 (overlapping, 2H, H-3, H-5, J_{5-4} = 2.0Hz), 5.10-5.12 (t, 1H, H-4, J_{4-5} = 2.1Hz), 2.16, 2.15, 2.07 (3s, 3H each, 3-OAc).
IR: 1750(vs),1800(s), 2940(m), 3030(s).

Preparation of the 1,2-(exo-allyl-methyldioxolane)-5-acetoxy-glucofuranurono-6.3-lactone 27: A 50ml R. B. flask was charged with a solution of 1,2,5-triacetate-6,3-glucuronolactone **26** (1.0g 3.3mmol) in acetonitrile (10ml). The solution was cooled to 0°C by an ice-bath under N_2. $BF_3.Et_2O$ (0.5ml, 4.1mmol) was injected and after 5min. the allyltrimethylsilane (1.15g, 10.1mmol, 1.6ml). The solution was stirred at 0°C under N_2 and left to reach room temperature over a 3hour period. It was then diluted with aqueous $NaHCO_3$ (10% sol., 30ml) and extracted with CH_2Cl_2 (three times, 50ml each). The combined organic extracts were washed once with water (30ml), dried over $MgSO_4$ and concentrated. The residue was chromatographed to yield **27** (0.7g, 88.0%).
1,2-(exo-allyl-methyldioxolane)-5-acetoxy-glucofuranurono-6.3-lactone 27:

($C_{13}O_7H_{16}$), 88.0%, 6.02-6.03 (d, 1H,H-1,J_{1-2} = 3.6Hz), 5.70-5.80 (m, 1H, H-2'), 5.50-5.52 (d, H-5, J_{5-4} = 4.3Hz), 5.18 (s, 1H, H-1'trans), 5.13-5.14 (d, 1H, H-1'cis, $J_{1'-2'}$ = 4.4Hz), 5.05-5.07 (dd, 1H, H-4, J_{4-3} = 2.9Hz, J_{4-5} = 4.1Hz), 4.87-4.88 (d, 1H, H-3, J_{3-4} = 2.7Hz), 4.83-4.85 (d, 1H, H-2, J_{2-1} = 3.6Hz), 2.33-2.35 (d, 2H, H-3', $J_{3'-2'}$ = 7.2Hz), 2.23(s, 3H, H-2OAc), 1.47 (s, 3H, Me).

^{1}H COSY: H-1(6.02) coupled with H-2(4.83), H-2'(5.70) coupled with H-1'cis(5.13), H-3' (2.33), H-5(5.50) coupled with H-4(5.05), H-4(5.05), coupled with H-5(5.50), H-3(4.88).

IR: 1630(w), 1755(vs), 1815(vs), 2395(m), 2910(m), 2975(s), 3010(s), 3075(m).

MS: m/z 302(MNH_4^+).

IR: 1635(m), 1760(vs), 1800(vs), 1815(vs), 2915(m), 2975(m), 3015(m).

Preparation of 4,2-diacetyl-7-methoxy-benzofuran 29: A 50ml R. B. flask was charged with a solution of 1,2,5-triacetoxy-6,3-glucuronolactone **26** (1.0g 3.3mmol) in acetonitrile (10ml) and 2-acetyl-7-methoxy-benzofuran (0.7g, 3.7mmol). $BF_3.OEt_2$ (1.35ml, 11.0mmol) was injected and the solution was stirred at room temperature under N_2 for 24h monitored with TLC and no change was observed. Then it was refluxed for 6h, diluted with water (50ml) and extracted with CH_2Cl_2 (three times, 20ml each). The combined extracts were washed with water (20ml), dried over $MgSO_4$, concentrated and chromatographed ($CHCl_3$) to recover unchange benzofuran and traces of 4, 2-diacetyl-7-methoxy benzofuran **29**.

^{1}H NMR 300MHz: **ch. 4: 35**.

Preparation of 4-acetyl-2-ethyl-7-methoxybenzofuran 28: 1,2,5-triacetoxy-6,3-glucuronolactone (0.5g, 1.66mmol), 2-ethyl-7-methoxybenzofuran (0.32g, 1.82mmol), and $BF_3.Et_2O$ (0.7ml, 5.7mmol) were dissolved in acetonitrile (5ml). The solution was stirred overnight at room temperature under N_2, diluted with 50ml water and extracted with CH_2Cl_2 (3x20ml). The extracts were combined and washed with water, dried over

$MgSO_4$ and concentrated. The residue underwent column chromatography to yield a very small amount of 2-ethyl-4-acetyl-7-methoxy-benzofuran **28** the majority was degradation products from the carbohydrate.

^1H NMR 300MHz: **ch. 4: 36**.

Chapter 6

General procedure for the Grignard reaction: A two-neck flask equipped with a magnetic stirring bar, a pressure equilibrium addition funnel, sealed with a rubber septum, was flushed with N_2. The addition funnel was charged with a solution of 1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6,3-glucuronolactone **12f** (5.0g, 15.2mmol) dissolved in THF (25mL). The flask was charged with a solution of 2-ethyl-4-bromo-7-mehtoxy-benzofuran **10** (3.85g, 15.1mmol) in THF (50mL). The solution in the flask was cooled to -78°C with a dry-ice acetone bath. t-BuLi solution (0.9M in pentane, 19mL, 17.1mmol) was injected through the rubber septum during 10min. into the benzofuran solution. The resulting solution was stirred for 3h at -78°C and the lactone solution was released in it dropwise. The reaction solution was stirred until it reached room temperature (3 hours) and continued being stirred for an extra 30min.. The solution was diluted with water and extracted with ether (4 times, 50mL each). The combined ether extracts were washed with water (50mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography ($CHCl_3$/EtOAc = 10/1) to yield the product **13f** (5.1g, 65.8%).

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-keto-6-phenylglucofuranose (1,4) 13a: 83.5%.

1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-keto-6-phenylglucofuranose (1,4) 13b: 80.9%, ^{1}H NMR 300MHz: δ 8.10-8.17 (dd, 2H, H-2',6'), 7.51-7.59 (m, 1H, H-4'), 7.42-7.49 (dd, 2H, H-3',5'), 5.91-5.92 (d, 1H, H-1, J_{1-2} = 3.4Hz) 5.62-5.63 (d, H-3, J_{3-4} = 2.4Hz), 5.15-5.18 (d, 1H, H-5, J_{5-4} = 9.0Hz), 4.73-4.77 (dd, 1H, H-4, J_{4-3} = 2.5Hz, J_{4-5} = 9.2Hz), 4.60-4.62 (d, 1H, H-2, J_{2-1} = 3.5Hz), 1.43, 1.26 (2s, 3H each, 2-Me from isopropylidene), 0.77 (s, 9H, t-Butyl), -0.18, -0.20 (2s, 3H, 2-Me from OTBDMS).

1,2-O,O-benzylidene-5-O-trityl-6-keto-6-phenylglucofuranose (1,4) 13c: ($C_{38}O_6H_{32}$), 88.1%, ^{1}H NMR 300MHz: 7.10-7.50 (20H, Aromatic benzylidene Trityl), 6.18-6.19 (d,

1H, H-1, J_{1-2} = 3.9Hz), 5.83 (s, 1H benzylidene). 4.98(s, 1H, H(3-OH)), 4.79-4.80 (d, 1H, H-2, J_{2-1} = 3.9Hz), 4.44-4.45 (d, 1H, H-5, J_{2-1} = 3.5Hz), 3.97-3.98 (d, 1H, H-3, J_{3-4} = 3.5Hz), 3.25-3.28 (t, 1H, H-4, $J_{4-3,5}$ = 3.5Hz).

IR: 1595(m), 1685(w), 1805(w), 1940(w), 2930(m), 3025(s), 3060(s), 3530(s).

MS: m/z 602(MNH_4^+).

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-keto-6-4'-(2',7'-dimethyl)benzofuran glucofuranose (1,4) 13d: 77.7%.

1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-keto-6-(4'-(2'(1''-methoxy)-ethyl)-7'-methoxy)benzofuranglucofuranose (1,4) 13e: 67.5%,

1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-keto-6-4'-(2'-ethyl-7'-methoxy)) benzofuranglucofuranose (1,4) 13f: 65.8%,

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-keto-6-4'-(2'-ethyl-7'methoxy)) benzofuranglucofuranose (1,4) 13g: 74.4%,

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-keto-6-4'-(2'-1''-methoxy-ethyl-7'-methoxy)benzofuranglucofuranose (1,4) 13h: 70.5%,

1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-keto-6-4'-(2'-ethyl-7'-methoxy) benzofuranidofuranose (1,4) 13i: 91.2%.

IR: 1605(s), 1630(s),2850(s), 2875(s), 2900(s), 2925(s), 2950(s), 3010(s), 3500(s).

General procedure for the acetylation of the ketoalcohols 13: A solution of 1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-keto-6-(4'-(2'-ethyl-7'-methoxy))benzofuran glucofuranose (1,4) **13f** (4.6g, 9.0mmol) in a 50/50 v/v mixture of pyridine (10mL) and acetic anhydride (10mL) was stirred overnight at room temperature, protected with a $CaCl_2$-drying guard tube. The mixture of pyridine/Ac_2O was evaporated under reduced pressure. The residue was dissolved in ether (100mL). The ether solution was washed with aqueous $NaHCO_3$ (10% sol., 30mL) and twice with water (30mL each). Dried over $MgSO_4$ and concentrated to yield pure acetate **14f** as viscous oil (4.2g, 86.5%).

1,2-O,O-benzylidene-3-acetoxy-5-O-t-butylmethylsilyl-6-keto-6-phenylgluco furanose (1,4) 14a: ($C_{27}O_7H_{34}Si$) 90.65%, ^1H NMR 300MHz: δ 8.10-8.13 (d, 2H, H-2',6', $J_{2'-3'}$ = 8.2Hz), 7.25-7.60 (8H, aromatic, H-3', 4', 5' from 6-Ph, 5H-Ph from benzylidene), 5.97-5.98 (d, 1H, H-1, J_{1-2} = 3.8Hz), 5.84 (s, 1H, H-benzylidene), 5.40-5.41 (d, 1H, H-3, J_{3-4} = 2.2Hz), 4.98-4.95 (d, 1H, H-5, J_{5-4} = 9.3Hz), 4.69-4.73 (dd, 1H, H-4, J_{4-3} = 2.4Hz, J_{4-5} = 9.3Hz), 4.54-4.56 (d, 1H, H-2, J_{2-1} = 3.6Hz), 2.16 (s, 3H, 3-OAc), 0.81 (s, 9H, t-Butyl), 0.00, -0.11(2s, 3H each 2-Me from OTBDMS).

IR: 1580(w), 1595(m), 1685(vs), 1750(vs), 2855(s), 2875(m), 2925(s), 2950(s), 3010(m).

MS: m/z 499(MH^+), 516(MNH_4^+).

1,2-O,O-isopropylidene-3-acetoxy-5-O-t-butylmethylsilyl-6-keto-6-phenylgluco furanose (1,4) 14b: 90.65%, ^1H NMR 300MHz: δ 8.09-8.12 (d, 2H, H-2',6', $J_{2'-3'}$ = 7.2Hz), 7.54-7.59 (t, 1H, H-4', $J_{4'-3'}$ = 7.3Hz, $J_{4'-2'}$ = 2.0Hz), 7.42-7.48 (d, 2H, H-3',5', $J_{3'-4'}$ = 7.2Hz = $J_{3'-2'}$), 5.82-5.84 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.30-5.31 (d, 1H, H-3, J_{3-4} = 2.8Hz), 5.03-5.07 (d, 1H, H-5, J_{5-4} = 9.1Hz), 4.56-4.61 (dd, 1H, H-4, J_{4-3} = 2.8Hz, J_{4-5} = 9.1Hz), 4.48-4.50 (d, 1H, H-2, J_{2-1} = 3.6Hz), 2.17 (s, 3H, 3(OAc)), 1.41, 1.25 (2s, 3H each, 2-Me from isopropylidene), 0.84 (s, 9H, t-Bu), 0.01, -0.10(2s, 3H each 2-Me from OTBDMS).

1,2-O,O-benzylidene-3-acetoxy-5-O-t-butyldimethylsilyl-6-keto-6-4'-(2',7'-dimethyl) benzofuranglucofuranose (1,4) 14d: 90.7%, ^1H NMR 300MHz: δ 7.96-7.98 (d, 1H, H-5', $J_{5'-6'}$ = 7.8Hz), 7.23-7.30 (6H, 5H-benzylidene, 1H, H-3'), 7.00-7.04 (d, 1H, H-6', $J_{6'-5'}$ = 7.9Hz), 5.96-5.98 (d, 1H, H-1, J_{1-2} = 3.8Hz), 5.83 (s, 1H, H-benzylidene), 5.39-5.41 (d, 1H, H-3, J_{3-4} = 2.7Hz), 5.01-5.05 (d, 1H, H-5, J_{5-4} = 9.2Hz), 4.75-4.79 (dd, 1H, H-4, J_{4-3} = 2.8Hz, J_{4-5} = 9.2Hz), 4.55-4.56 (d, 1H, H-2, J_{2-1} = 3.8Hz), 2.51, 2.59 (2s, 3H each, 2-Me of benzofuran), 2.19 (s, 3H, 3(OAc)), 0.82 (s, 9H, H-t-butyl), 0.01, -0.12 (2s, 3H each, 2Me of OTBDMS).

^1H NOE: Irradiation at 4.55 (H-2) enhancement at 5.39 (H-3), 5.83 (H-Bn), 5.98 (H-1),

irradiation at 5.98 (H-1) enhancement at 4.55 (H-2), irradiation at 7.98 (H-5') enhancement at 7.0 (H-6'), 5.01 (H-5), 4.78 (H-4), irratiation at 5.01 (H-5), enhancement at 7.98 (H-5'), 4.78 (H-4).

^{1}H COSY: H-5'(7.9) coupled with H-6'(7.00), H-1(5.96), coupled with H-2(4.54), H-3 (5.39), coupled with H-4(4.74), H-5(5.01), coupled with H-4(4.74).

1,2-O,O-isopropylidene-3-acetoxy-5-O-t-butyldimethylsilyl-6-keto-6-4'-(7'-methoxy-2'-1"-methoxyethyl)benzofuranglucofuranose (1,4) 14e: ($C_{29}O_{10}H_{42}Si$), 91.5% ^{1}H NMR 300MHz: δ 8.11-8.15 (dd, 1H, H-5', $J_{5'-6'}$ = 8.5Hz, $J_{5'-3'}$ = 2.1Hz), 7.52 (s, 1H, H-3'), 6.78-6.81 (d, 1H, H-6', $J_{6'-5'}$ = 8.6Hz),5.83-5.84 (d, 1H, H-1, J_{1-2} = 33.6Hz), 5.31-5.32 (d, 1H, H-3, J_{3-4} = 2.6Hz), 5.06-5.11 (dd, H5, J_{5-4} = 9.2Hz), 4.61-4.66 (dt, 1H, H-4, J_{4-5} = 9.1Hz, J_{4-3} = 2.4Hz), 4.52-4.59 (q, 1H, H-1", $J_{1"-2"}$ = 6.6Hz), 4.49-4.51 (d, 1H, H-2, J_{2-1} = 3.6Hz), 4.08 (s, 3H, 7'-MeO), 3.37 (s, 3H, 1" MeO), 3.37 (s, 3H, 1"MeO), 2.19 (s, 3H, 3OAc), 1.60-1.62 (d, 3H, 2"-Me, $J_{2"-1"}$ = 6.6Hz), 0.85 (s, 9H, t-butyl), 1.43, 1.25 (2s, 3H each, 2 Me from isopropylidene), 0.00, -0.10 (2s, 3H each, 2 Me from TBDMS).

IR: 1570(s), 1615(s), 1660(s), 1740(vs), 2855(s), 2875(s), 2925(s), 2950(s), 3010(m).

MS: m/z 579(MH^+), 596(MNH_4^+).

1,2-O,O-isopropylidene-3-acetoxy-5-O-t-butyldimethylsilyl-6-keto-6-4'(7'-methoxy-2'-ethyl)benzofuranglucofuranose (1,4) 14f: ($C_{28}O_9H_{40}Si$) 86.5%, ^{1}H NMR 300MHz: δ 8.07-8.10(d, 1H, H-5', $J_{5'-6'}$ = 8.4Hz), 7.27 (s, 1H, H-3'), 6.73-6.76 (d, 1H, H-6', $J_{6'-5'}$ = 8.4Hz), 5.82-5.84 (d, 1H, H-1, J_{1-2} = 3.4Hz), 5.31-5.32 (d, 1H, H-3, J_{3-4} = 2.0Hz), 5.08-5.11 (d, 1H, H-5, J_{5-4} = 9.2Hz), 4.62-4.66 (dd, 1H, H-4, J_{4-3} = 2.3Hz, J_{4-5} = 9.0Hz), 4.48-4.50 (d, 1H, H-2, J_{2-1} = 3.4Hz), 4.07 (s, 3H, 7'MeO), 2.80-2.90 (q, 2H, H-2", $J_{2"-3"}$ = 7.7Hz), 2.18 (s, 3H, 3(OAc)), 1.42, 1.25 (2s, 3H each, 2-Me from isopropylidne), 1.33-1.37 (t,3H, H-2', $J_{2-1'}$ = 7.7Hz), 0.85 (s, 9H, H-t-butyl), 0.00-0.10 (2s, 3H each, 2-Me from TBDMS).

1,2-O,O-benzylidene-3-acetoxy-5-O-t-butyldimethylsilyl-6-keto-6-4'-(7'-methoxy-2'-

ethyl)benzofuranglucofuranose (1,4) 14g: ($C_{32}O_9H_{40}Si$), 95.6%, ^1H NMR 300MHz: δ 8.06-8.09 (d, 1H, H-5', $J_{5'-6'}$ = 8.6Hz), 7.29-7.40 (6H, 5H-benzylidene, H-3'), 6.76-6.79 (d, 1H, H-6', $J_{6'-5'}$ = 8.6Hz), 6.08 (s, 1H, H-benzylidene), 5.99-6.01 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.51-5.52 (d, 1H, H-3, J_{3-4} = 3.1Hz), 5.15-5.18 (d, 1H, H-5, J_{5-4} = 8.7Hz), 4.66-4.70 (dd, 1H, H-4, J_{4-3} = 3.1Hz, J4-5=8.7Hz), 4.63-4.65 (d, 1H, H-2, J_{2-1} = 3.6Hz), 4.05 (s, 3H, 7'-OMe), 2.82-2.90 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.20 (s, 3H, 3(OAc)), 1.34-1.40 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

IR: 1570(s), 1590(s), 1620(s), 1660(s), 1740(s), 2855(s), 2880(s), 2930(s), 3020(s).
MS: m/z 597(MH^+), 614(MNH_4^+).

1,2-O,O-isopropylidene-3-acetoxy-5-O-t-butyldimethylsilyl-6-keto-6-4'-(7'-methoxy-2'-ethyl)benzofuranidofuranose (1,4) 14i: ($C_{28}O_9H_{40}Si$), 92.6%, ^1H NMR 300 MHz: δ 7.93-7.97 (d, 1H, H-5', $J_{5'-6'}$ = 8.6Hz), 7.16 (s, 1H, H-3'), 6.73-6.77 (d, 1H, H-6', $J_{6'-5'}$ = 8.6Hz), 5.97-5.98 (d, 1H, H-1, J_{1-2} = 3.9Hz), 5.13-5.14(d, 1H, H-3, J_{3-4} = 3.5Hz), 5.11-5.14 (d, 1H, H-5, J_{5-4} = 7.1Hz), 4.71-4.76 (dd, 1H, H-4, J_{4-3} = 3.6Hz, J_{4-5} = 7.1Hz), 4.48-4.50 (d, 1H, H-2, J_{2-1} = 3.9Hz), 4.07 (s, 3H, 7'-OMe), 2.80-2.88 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.81 (s, 3H, 3(OAc)), 1.52, 1.31 (2s, 3H each, 2-Me from isopropylidene), 0.84 (s, 9H, H-t-butyl), 0.15, 0.12 (2s, 3H each, 2-Me TBDMS).

IR: 1570(s), 1595(s), 1620(s), 1660(s), 1740(s), 2855(s), 2890(s), 2930(s), 3020(s).
MS: m/z 549(MH^+), 566(MNH_4^+).

General procedure for the reduction of the ketoalcohols 13 and the ketoacetates 14: Solid $NaBH_4$ (0.11g 99%, 2.9mmol) was added in a solution of 1,2-O,O-isopropylidene-3-acetoxy-5-O-t-butyldimethylsilyl-6-keto-6-4'-(7'-methoxy-2'-ethyl)-benzofuranglucofuranose (1,4) **14f** (1.5g, 2.7mmol) in ethanol (15mL). The solution was stirred at room temperature and was monitored by TLC. The reaction was completed within 3 hours. The solution was diluted with aqueous NaCl (sat. sol., 50mL) and extracted with CH_2Cl_2 (four times, 25mL each). The organic extracts were combined,

washed with water (twice, 30mL each) dried over $MgSO_4$ and concentrated to yield an oily residue **18e** (1.35g, 97.1%) which solidified on standing. The crude diol was pure enough for the next reaction. Better purification was obtained by column chromatography ($CHCl_3$).

1,2-O,O-benzylidene-3,6-diol-5-O-t-butyl-dimethylsilyl-6-phenylglucofuranose (1,4) 18a: ($C_{25}O_6H_{34}Si$), 96.5% from14a, ^1H NMR 300MHz: δ 7.33-7.40 (10H, 6-Ph, benzylidene), 6.09-6.11 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.99 (s, 1H, benzylidene), 5.00-5.01 (d, 1H, H-6, J_{6-5} = 2.0Hz), 4.63-4.64 (d, 1H, H-2, J_{2-1} = 3.6Hz), 4.43-4.44 (d, 1H, H-3, J_{3-4} = 3.0Hz), 4.10-4.13 (dd, 1H, H-4, J_{4-3} = 3.0Hz, J_{4-5} = 8.2Hz), 3.76-3.80 (dd, 1H, H-5, J_{5-6} = 2.0Hz, J_{5-4} = 8.2Hz), 0.96 (s, 9H, t-butyl), 0.12, -0.08 (2s, 3H,each, 2-Me from TBDMS).

IR: 2855(s), 2880(s), 2930(s), 2950(s), 3020(s), 3425(s).

MS: m/z 459(MH^+), 476(MNH_4^+).

1,2-O,O-benzylidene-3,6-diol-5-O-t-butyldimethylsilyl-6-4'-(2',7'-dimethyl)benzofuranglucofuranose (1,4) 18b: 96.8% from 14b, 99.6% from 13b, ^1H NMR 300 MHz: δ 7.3 (5H, benzylidene), 7.01-7.04 (d, 1H, H-5', $J_{5'-6'}$ = 7.5Hz), 6.88-6.91 (7d, 1H, H-6', $J_{6'-5'}$ = 7.6Hz), 6.41 (s, 1H, H-3'), 6.07-6.09 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.9 (s, 1H, benzylidene), 5.15-5.17 (d, 1H, H-6, J_{6-5} = 2.7Hz), 4.60-4.61 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.42-4.43 (d, 1H, H-3, J3-4 = 3.0Hz), 4.04-4.09 (dd, 1H, H-4, J4-3 = 3.0Hz, J_{4-5} = 7.7Hz) 3.85-3.89 (dd, 1H, H-5, J_{5-4} = 7.7Hz, J_{5-6} = 2.7Hz), 2.38, 2.40 (2s, 3H each, 2',7'methyl), 0.88 (s, 9H, t-butyl), 0.39, -0.19 (2s, 3H each, 2Me from TBDMS).

1,2-O,O-isopropylidene-3,6-diol-6-4'-(7'-methoxy-2'-1"-methoxyethyl)benzofuran-5-t-butyldimethylsilylglucofuranose (1,4) 18c: ($C_{27}O_9H_{42}Si$), 92.2% from 14c, ^1H NMR 300MHz: δ 7.10-7.14 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.76 (s, 1H, H-3'), 6.72-6.75 (d, 1H, H-6', $J_{6'-5'}$ = 8.3Hz), 5.98-5.99 (dd, 1H, H-1, J_{1-2} = 3.6Hz), 5.10-5.13 (dd, 1H, H-6, J_{6-5} = 3.4Hz), 4.52-4.54 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.48-4.54 (dt, 1H, H-4), 4.34-4.36 (d, 1H, H-3, J_{3-4} = 2.6Hz), 3.98-4.07 (overlapping 5H, H-5, H-1", 7' MeO), 3.35, 3.36 (3H, 2s, 1"

MeO), 1.58-1.60 (d, 3H, 2" Me, J2"-1" = 6.6Hz), 1.40-1.41 (2s, 3H, 1 Me from isopropylidene), 1.30 (s, 3H, 1 Me from isopropylidene), 0.92, 0.93 (2s, 9H, t-butyl), (-0.16)-(-0.2) (2s, 3H each, 2Me from TBDMS).

IR: 1580(m), 1600(m), 1620(m), 1660(s), 2390(m), 2850(s), 2880(s), 2920(s), 2950(s), 3010(s), 3425(s).

MS: m/z 539(MH^+), 556(MNH_4^+).

1,2-O,O-benzylidene-3,6-diol-5-O-t-butyldimethylsilyl-6-4'-(2'-ethyl-7'-methoxy) benzofuranglucofuranose (1,4) 18d: ($C_{30}O_8H_{40}Si$), 82.9% from 14d, ^1H NMR 300MHz: δ 7.39 (s, 5H, benzylidene), 7.10-7.13 (d, 1H, H-5', $J_{5'-6'}$ = 8.1Hz), 6.70-6.72 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.49 (s, 1H, H-3'), 6.17-6.18 (d, 1H, H-1, J_{1-2} = 3.5Hz), 5.96 (s, 1H, benzylidene), 5.18-5.19 (d, 1H, H-6, J_{6-5} = 3.1Hz), 4.70-4.72 (d, 1H, H-2, J_{2-1} = 3.6Hz), 4.54 (s, 1H, H-3), 4.11-4.14 (dd, 1H, H-4, J_{4-5} = 7.0Hz, J_{4-3} = 2.5Hz), 3.99 (s, 4H, 3H from 7'MeO, 1H, H-5(overlapping)), 3.27 (s, 1H, H-6(OH)), 2.89-2.91 (d, 1H, H-3(OH), J_{OH-3} = 6.0Hz), 2.78-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.31-1.36 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz), 0.96 (s, 9H, t-butyl), 0.12, -0.13 (2s, 3H each, 2 Me from TBDMS).

IR: 1600(s), 1625(s), 2150(w), 2850(s), 2875(s), 2925(s), 2955(s), 3010(s), 3425(s).

MS: m/z 557(MH^+), 574(MNH_4^+).

1,2-O,O-isopropylidene-3,6-diol-5-O-t-butyldimethylsilyl-6-4'-(2'-ethyl-7'-methoxy)-benzofuranglucofuranose (1,4) 18e: ($C_{26}O_8H_{40}Si$), 97.1% from 14e, ^1H NMR 300 MHz: δ 7.07-7.10 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.67-6.70 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.48 (s, 1H, H-3'), 5.96-5.98 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.09-5.10 (d, 1H, H-6, J_{6-5} = 3.3Hz), 4.50-4.52 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.33-4.35 (t, 1H, H-3, J_{3-4} = 2.8Hz), 4.04-4.07 (dd,1H, H-4, J_{4-3} = 2.7Hz, J_{4-5} = 7.1Hz), 3.95-4.01 (4H, s(3H, 7' MeO), dd, 1H, H-5, overlapping), 3.31-3.33 (d, 1H, H-6(OH) J_{OH-6} = 3.0Hz), 2.95-2.98 (d, 1H, H-3(OH), J_{OH-3} = 6.6Hz), 2.77-2.85 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.40, 1.29 (2s, 3H each, 2 Me of isopropylidene), 1.31-1.36 (t, 3H, H-2", $J_{2"-1"}$ = 7.6Hz), 0.93 (9H, H-t-butyl), 0.09, -0.16 (2s, 3H each, 2Me of TBDMS).

IR: 1585(s), 1605(s), 1630(s), 2855(s), 2880(s), 2925(s), 3425(s).

MS: m/z 509(MH^+), 526(MNH_4^+).

1,2-O,O-isopropylidene-3,6-diol-5-O-t-butyldimethylsilyl-6-4'-(2'-ethyl-7'-methoxy)-benzofuranidofuranose (1,4) 18f: ($C_{26}O_8H_{40}Si$), 86.7% from [5(11)], ^1H NMR 300MHz: δ 7.11-7.14 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.66-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.61 (s, 1H, H-3'), 5.99-6.00 (d,1H, H-1, J_{1-2} = 3.6Hz), 5.00-5.03 (d, 1H, H-6, J_{6-5} = 8.8Hz), 4.63 (s, 1H, H-3), 4.40-4.42 (d, 1H, H-2, J_{2-1} = 3.6Hz), 4.16-4.19 (d, 1H, H-5, J_{5-6} = 8.7Hz), 4.05 (s, 1H, H-4), 3.98 (s, 3H, H-7'MeO), 3.61 (s, 1H, H-6(OH)), 3.47 (s, 1H, H-3(OH)), 2.77-2.85 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.32-1.38 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz), 1.24, 1.11 (2s, 3H each, 2 Me from isopropylidene), 0.89 (s, 9H, t-butyl), 0.05, -0.28 (2s, 3H each, 2 Me from TBDMS).

IR: 1585(m), 1600(s), 1630(s), 2395(w), 2850(s), 2925(s), 3010(s), 3450(s).

MS: m/z 509(MH^+), 526(MNH_4^+).

1,2-Isopropylidene-3,6-diol-5-deoxy-6-4'-(7'-methoxy-2'-ethyl)benzofurangluco furanose (1,4) 18g: 31.8%, ^1H NMR 300MHz: δ 7.04-7.07 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.65-6.68 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.49 (s, 1H, H-3'), 5.88-5.90 (d, 1H, H-1, J_{1-2} = 3.8Hz), 5.00-5.05 (dd, 1H, H-6, J_{6-5b} = 2.1Hz, J_{6-5a} = 10.1Hz), 4.54-4.56 (d, 1H, H-2, J_{2-1} = 3.8Hz), 4.36-4.42 (ddd, 1H, H-4, J_{4-3} = 2.6Hz, J_{4-5b} = 6.2Hz, J_{4-5a} = 9.1Hz), 4.23-4.25 (d, 1H, H-3, J_{3-4} = 2.5Hz), 3.97 (s, 3H, 7'MeO), 2.76-2.81 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.22-2.33 (dt, 1H, H-5a, $J_{5a-4,6}$ = 9.2Hz, J_{5a-5b} = 14.4Hz), 2.10-2.19 (ddd, 1H, H-5b, J_{5b-6} = 2.2Hz, J_{5b-4} = 6.2Hz, J_{5b-5a} = 14.0Hz), 1.49, 1.30 (2s, 3H each, 2-Me-isopropylidene), 1.30-1.35 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz),

1,2-O,O-isopropylidene-3,6-diol-5-deoxy-6-4'-(7'-methoxy-2'-ethyl)benzofurangluco furanose (1,4) 18g: 19.1%, ^1H NMR 300MHz: δ 7.10-7.13 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.67-6.70 (d, 1H, H-6', $J_{6'-5'}$ = 8.1Hz), 6.55 (s, 1H, H-3'), 5.91-5.93(d, 1H, J_{1-2} = 3.7Hz), 5.21-5.25 (dd, 1H, H-6, J_{6-5a} = 7.2Hz, J_{6-5b} = 4.4Hz), 4.49-4.51 (d, 1H, H-2, J_{2-1} = 3.8Hz), 4.14-4.18 (ddd, H-4, J_{4-3} = 2.2Hz, J_{4-5a} = 6.3Hz, J_{4-5b} = 6.3Hz), 4.06-4.07 (d, 1H, H-3, J_{3-}

$_4$ = 2.3Hz), 3.98 (s, 3H, H-7'(OMe)), 2.77-2.83 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.27-2.38 (dt, 1H, H-5a, J_{5a-4} = 6.3Hz, J_{5a-6} = 6.3Hz, J_{5a-5b} = 13.8Hz), 2.12-2.24 (dt, 1H, H-5b, J_{5b-4} = 5.0Hz, J_{5b-6} = 5.0Hz, J_{5b-5a} = 13.8Hz), 1.40, 1.29 (2s, 3H each, 2Me of isopropylidene), 1.31 1.37 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

Identical mixture of the18g was obtained from 13g (90.4%).

General procedure for the dehydration of the 3,6-diols 18: A solution of 1,2-O,O-isopropylidene-3,6-diol-5-O-t-butyldimethylsilyl-6-4'-(2'-ethyl-7'-methoxy)benzofuranglucofuranose (1,4) **18e** (2.63g, 5.2mmol) in pyridine was cooled to 0°C by an ice-bath, under N_2. Thionyl chloride (0.98g, 8.2mmol, 0.60mL,) was added and the solution was stirred at room temperature, under N_2, until TLC ($CHCl_3$) showed that the diol had completely reacted (3 days). Pyridine was evaporated under reduced pressure and the residue was diluted with ether (150mL). The ether solution was washed twice with aqueous $NaHCO_3$ (sat. sol., 50mL each) and twice with water (50mL each), dried over $MgSO_4$ and concentrated. The residue was chromatographed ($CHCl_3$) to yield the cyclized glycosides the exo **19** (1.06g, 41.8%) and endo **20** (0.79g, 31.2%) .

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-endo-phenylglucodifuranose (1,4: 3, 6) 20a: 32.2%, ^{1}H NMR 300MHz: δ 7.24-7.40 (10H, 2-Ph), 6.02-6.04 (d, 1H, H-1, J_{1-2} = 3.9Hz), 5.88 (s, 1H, benzylidene), 5.02-5.05 (d, 1H, H-6, J_{6-5} = 6.2Hz), 4.99-5.00 (d, 1H, H-3, J_{3-4} = 2.9Hz), 4.71-4.73 (d, 1H, H-2, J_{2-1} = 3.8Hz), 4.36-4.39 (dd, 1H, H-4, J_{4-3} = 3.3Hz, J_{4-5} = 4.6Hz), 4.14-4.18 (dd, 1H, H-5, J_{5-6} = 5.6Hz), 0.86 (s, 9H, t-butyl), 0.05, -0.17 (2s, 3H each, 2 Me from TBDMS).

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-exo-phenylglucodifuranose (1,4: 3,6) 19a: 64.3%, ^{1}H NMR 300MHz: δ 7.41, 7.30 (2s, 5H each, 2 Ph), 6.14-6.16 (d, 1H, H-1, J_{1-2} = 3.9Hz), 5.95 (s, 1H, benzylidene), 4.90-4.92 (d, 1H, H-6, J_{6-5} = 3.7Hz), 4.74-4.76 (d, 1H, H-2, J_{2-1} = 3.9Hz), 4.54-4.62 (overlapping 2(dd), 2H, H-4, H-5), 4.46-4.48

(d, 1H, H-3, J_{3-4} = 3.0Hz), 0.88 (s, 9H, t-butyl), 0.03, -0.15 (2s, 3H each, 2 Me from TBDMS).

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-exo-4'-(2',7'-dimethyl)benzofuran glucodifuranose (1,4:3,6) 19b: 57.5%, ^{1}H NMR 300MHz: δ 7.37-7.40 (5H, Ph), 7.08-7.10 (d, 1H, H-5', $J_{5'-6'}$ = 7.6Hz), 6.95-6.98 (d, 1H, H-6', $J_{6'-5'}$ =7.6Hz), 6.53 (s, 1H, H-3', $J_{3'-1'}$ = 1.0Hz), 6.15-6.17 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.86 (s, 1H, H-benzylidene), 5.21-5.23 (d, 1H, H-6, J_{6-5} = 3.8Hz), 4.85-4.87 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.73-4.77 (dd, 1H, H-5, J_{5-6} = 3.8Hz, J_{5-4} = 6.5Hz), 4.61-4.64 (dd, 1H, H-4, J_{4-3} = 3.8Hz, J_{4-5} = 6.5Hz), 4.59-4.61 (d, 1H, H-3, J_{3-4} = 3.9Hz), 2.46-2.49 (2s, 3H each, 2',7' Me), 0.93 (s, 9H, t-butyl), 0.08, 0.00 (2s, 3H each, 2 Me from TBDMS).

1,2-O,O-benzylidene-5-O-t-butyldimethylsilyl-6-endo-4'-(2,7'-dimethyl)benzofuran glucodifuranose (1,4:3,6) 20b: 28,7%, ^{1}H NMR 300MHz: δ 7.37-7.40 (5H, Ph), 7.07-7.10 (d, 1H, H-5', $J_{5'-6'}$ = 7.6Hz), 6.96-6.99 (d, 1H, H-6', $J_{6'-5'}$ =7.6Hz), 6.54 (s, 1H, H-3', $J_{3'-1'}$ = 1.0Hz), 6.05-6.07 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.76 (s, 1H, H-benzylide ne), 5.26-5.28 (d, 1H, H-6, J_{6-5} = 5.5Hz), 5.14-5.15 (d, 1H, H-3, J_{3-4} = 3.5Hz), 4.83-4.84 (d, 1H, H-2, J_{2-1} = 3.8Hz), 4.55-4.59 (dd, 1H, H-4, J_{4-3} = 3.5Hz, J_{4-5} = 5.7Hz), 4.12-4.16 (t, 1H, H-5, $J_{5-4,6}$ = 5.6Hz), 2.46-2.49 (2s, 3H each, 2', 7' Me), 0.90 (s, 9H, H t-butyl), -0.13, -0.18 (2s, 2Me from TBDMS).

1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-endo-4'-(7'-methoxy-2'-1"-methoxy-ethyl)benzofuranglucodifuranose (1,4:3,6) 20c: ($C_{27}O_8H_{40}Si$), 33.3%, ^{1}HNMR 300 MHz: δ 7.08-7.12 (2d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.83, 6.84 (2s, 1H, H-3'), 6.72-6.76 (d, 1H, H-6',$J_{6'-5'}$ = 8.2Hz), 5.89-5.91 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.29-5.32 (d, 1H, H-6, J_{6-5} =6.4Hz), 4.97-4.98 (d, 1H, H-3, J_{3-4} = 2.9Hz), 4.64-4.66 (d, 1H, H-2, J_{2-1} = 3.7Hz) 4.48-4.55 (2q overlapping 1H, H-1", $J_{1"-2"}$ = 6.2Hz), 4.36-4.40 (dd, 1H, H-5, J_{5-4} = 4.2Hz, J_{5-6} = 7.5Hz), 4.22-4.27 (dd, 1H, H-4, J_{4-3} = 2.7Hz, J_{4-5} = 4.5Hz), 3.99 (s, 3H, 7'-MeO), 3.34-3.36 (2s, 3H, 1"-MeO), 1.58-1.61 (2d, 3H, H-2"), 1.27 (s, 6H, 2 Me from iso-propylidene), 0.86, 0.87 (2s, 9H, t-butyl), 0.08 (s, 3H, Me from TBDMS), -0.21, -0.22

(2s, 3H, Me from TBDMS).

^{1}H NOE: Irradiation at 3.36 (1" MeO) enhancement at 4.5 (H-1"), irradiation at 5.90 (H-1) enhancement at 4.64 (H-2), irradiation at 6.72 (H-6') enhancement at 7.10 (H-5'), 3.99 (7' MeO), irradiation at 7.10 (H-5') enhancement at 6.80 (H-3'), 5.90 (H-1), 5.30 (H-6)

IR: 1600(m), 1625(m), 1720(w), 2850(s), 2900(s), 2925(s), 3020(s)..

MS: m/z 521(MH^+), 538(MNH_4^+).

1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-exo-4'-(7'-methoxy-2'-1"-methoxyethyl)benzofuranglucodifuranose (1,4:3,6) 19c: ($C_{27}O_8H_{40}Si$) 53.2%, ^{1}H NMR 300 MHz: δ 7.09-7.13 (2d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.80, 6.82 (2s, 1H, H-3'), 6.72-6.75 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.00-6.02 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.15-5.18 (2d, 1H, H-6, J_{6-5} = 3.5Hz), 4.69-4.72 (dd, 1H, H-4, J_{4-3} = 3.1, J_{4-5} = 5.9Hz), 4.66-4.67 (d, 1H, H-2, J_{1-2} = 3.6Hz), 4.61-4.65 (2q, 1H, H-1", $J_{1"-2"}$ = 6.6Hz), 4.49-4.51 (d, 1H, H-3, J_{3-4} = 3.2Hz), 4.48-4.53 (2dd, 1H, H-5),3.99 (s, 3H, H-7'MeO), 3.34, 3.36 (2s, 3H, H-1"MeO), 1.57-1.60 (d, 3H, H-2", $J_{2"-1"}$ = 6.6Hz), 1.44, 1.31 (2s, 3H each, 2 Me from isopropylidene), 0.90, 0.91 (2s, 9H, t-butyl), 0.06 (s, 3H, Me from TBDMS), -0.18, -0.19 (2s, 3H, Me from TBDMS).

^{1}H NOE: Irradiation at 5.15 (H-6) enhancement at 7.10 (H-5'), at 6.80 (H-3'), at 4.50 (H-5) irradiation at 1.55 (H-2") enhancement at 4.49 (H-5'), irradiation at 6.7 (H-6') enhancement at 7.10 (H-5'), 3.93 (7' MeO), irradiation at 7.10 (H-5'), enhancement at 6.70 (H-6'), 5.10 (H-6), irradiation at 5.96 (H-1) enhancement at 4.61 (H-2).

IR: 1600(s), 1628(s), 1725(w), 2825(s), 2850(s), 2875(s), 2900(s), 2925(s), 2960(s), 2990(s), 3050(m).

MS: m/z 521(MH^+), 538(MNH_4^+).

1,2-O-Isopropylidene-5-O-t-butyldimethylsilyl-6-endo-4'-(7'-methoxy-2'-ethyl) benzofuranglucodifuranose (1,4:3,6) 20e: ($C_{26}O_7H_{38}Si$), 31.2%, ^{1}H NMR 300 MHz: δ 7.07-7.10 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.68-6.71 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.53 (s, 1H,

H-3'), 5.88-5.89 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.28-5.30 (d, 1H, H-6, J_{6-5} = 6.6Hz), 4.95-4.97 (d, 1H, H-3, J_{3-4} = 2.8Hz), 4.63-4.64 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.33-4.36 (dd, 1H, H-4, J_{4-3} = 2.9Hz, J_{4-5} = 4.3Hz), 4.21-4.25 (dd, 1H, H-5, J_{5-6} = 6.5Hz, J_{5-4} = 4.4Hz), 3.99 (s, 3H, 7'MeO), 2.77-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.6Hz), 1.31-1.36 (t, 3H, H-2", $J_{2"-1"}$ = 7.6Hz), 1.24, 1.27 (2s, 3H each, 2Me from isopropylidene), 0.87 (s, 9H, t-butyl), 0.07, -0.21 (2s, 3H each, 2 Me from TBDMS).

^{1}H NOE: Irradiation at 7.10 (H-5') enhancement at 6.70 (H-6'), at 5.3 (H-6), irradiation at 6.53 (H-3') enhancement at 5.30 (H-6), irradiation at 5.90 (H-1) enhancement at 4.63 (H-2).

^{1}H COSY: H-1(d, 5.90) coupled with H-2(d, 4.65), H-6(d, 5.30) coupled with H-5(dd, 4.25), H-3(d, 4.95) coupled with H-4(dd, 4.35), H-2(d, 4.65) coupled with H-1(d, 5.90), H-4(dd, 4.35) coupled with H-5(dd, 4.25), H-3(d, 4.95), H-5(dd, 4.25) coupled with H-4(dd, 4.35), H-6(d, 5.30).

IR: 1605(s), 1630(s), 2855(s), 2880(s), 2930(s), 2955(s), 3025(s).

MS: m/z 491(MH^+), 508(MNH_4^+).

1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-exo-4'-(7'-methoxy-2'-ethyl) benzofuranglucodifuranose (1,4:3,6) 19e: ($C_{26}O_7H_{38}Si$) 41.8%, ^{1}H NMR 300 MHz: δ 7.07-7.10 (d, 1H, H-5', $J_{5-6'}$ = 8.2Hz), 6.67-6.71 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.52 (s,1H, H-3'), 6.00-6.02 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.15-5.16 (d, 1H, H-6, J_{6-5} = 3.6Hz), 4.68-4.71 (dd, 1H, H-5, J_{5-6} = 3.2Hz, J_{5-4} = 5.9Hz), 4.65-4.67 (d, 1H, H-2, J_{2-1} = 3.4Hz), 4.62-4.66 (dd, 1H, H-4, J_{4-3} = 3.6Hz, J_{4-5} = 5.9Hz), 4.48-4.50 (d, 1H, H-3, J_{3-4} = 3.1Hz), 3.99 (s,3H, 7'-MeO), 2.80(q, 2H, H-2", $J_{2"-3"}$ = 7.5Hz), 1.44, 1.31 (2s, 3H each, 2 Me of isopropylidene), 1.31-1.36 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz), 0.89 (s, 9H, H-t-butyl), 0.06, -0.17 (2s, 3H each 2 Me from TBDMS).

^{1}H NOE: Irradiation at 7.10 (H-5') enhancement at 6.70 (H-6'), at 5.2 (H-6), at 4.65 (H-5) irradiation at 6.53 (H-3') enhancement at 5.20 (H-6), at 4.65 (H-5), at 2.80 (H-1"), irradiation at 6.0 (H-1) enhancement at 4.65 (H-2).

^{1}H COSY: H-1(d, 6.00) coupled with H-2(d, 4.65), H-6(d, 5.15) coupled with H-5(dd, 4.65), H-5(dd, 4.65) coupled with H-6(d, 5.15), H-4(dd, 4.60), H-4(dd, 4.60) coupled with H-5(dd, 4.65), H-3(d, 4.50), H-3(d, 4.50) coupled with H-4(dd, 4.60).

IR: 1605(s), 1628(s), 1730(w), 2855(s), 2880(s), 2900(s), 2930(s), 2950(s), 2975(s), 3050(m).

MS: m/z 491(MH^+), 508(MNH_4^+).

1,2-O,O-isopropylidene-O-t-butyldimethylsilyl-6-endo-4'-(7'-methoxy-2'-ethyl) benzofuranidodifuranose (1,4:6,3) 20f: ($C_{26}O_7H_{38}Si$) 43.3%: ^{1}H NMR 300MHz: δ 7.17-7.20 (d, 1H, H-5', $J_{5'-6'}$ = 7.9Hz), 6.70 (s, 1H, H-3'), 6.65-6.70 (d, 1H, H-6', $J_{6'-5'}$ = 7.9Hz), 5.97-5.98 (d, 1H, H-1, J_{1-2} = 3.5Hz), 5.11-5.14 (d, 1H, H-6, J_{6-5} = 9.0Hz), 4.98-5.02 (d, 1H, H-5, J_{5-6} = 7.7Hz), 4.71-4.72 (d, 1H, H-3, J_{3-4} = 1.9Hz), 4.46-4.47 (d,1H, H-2, J_{2-1} = 3.5Hz), 3.97 (s, 3H, H-7'MeO, 3.36 (1H, H-4), 2.78-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.4Hz), 1.33-1.38 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz), 1.24, 1.03 (2s, 3H each, 2Me of isopropylidene), 0.83 (s, 9H, t-butyl), 0.06, -0.14 (2s, 3H each, 2 Me from TBDMS).

IR: 1605(m), 1630(s), 2400(w), 2860(s), 2930(s), 3020(s).

MS: m/z 491(MH^+), 508(MNH_4^+).

1,2-O,O-isopropylidene-O-t-butyldimethylsilyl-6-exo-4'-(7'-methoxy-2'-ethyl) benzofuranidodifuranose (1,4:3,6) 19f: ($C_{26}O_7H_{38}Si$) 36.1%: ^{1}H NMR 300MHz: δ 7.19-7.22 (d, 1H, H-6', $J_{6'-5'}$ = 7.3Hz), 6.67-6.69 (d, 1H, H-5', overlapping with H-3'), 6.69 (s, 1H, H-3') , 6.05-6.06 (d, 1H, H-1, J_{1-2} = 3.4Hz), 5,18-5.21 (d, 1H, H-6, J_{6-5} = 8.5Hz), 4.63-4.64 (d, 1H, H-3, J_{3-4} = 2.3Hz), 4.60-4.64 (1H, H-5, overlapping with H-3), 4.55-4.57 (d, 1-H, H-2, J_{2-1} = 3.4Hz), 3.98 (s, 3H, H-7' MeO), 3.41 (1H, H-4), 2.78-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.33-1.38 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz), 1.25, 1.06 (2s, 3H each, 2 Me from isopropylidene), 0.83 (s, 9H, H-t-butyl), 0.09, -0.09 (2s, 3H each, 2 Me from TBDMS).

1,2-O,O-isopropylidene-5-deoxy-6-exo-4'(2'-ethyl-7'-methoxy)-benzofurangluco

difuranose (1,4:3,6) 19g: ($C_{20}O_6H_{24}$) 60.3%, ^{1}H NMR 300MHz: δ 7.04–7.07 (d, 1H, H-5', $J_{5'-6'}$ = 8.1Hz), 6.66-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.1Hz), 6.39 (s, 1H, H-3'), 6.02-6.04 (d, 1H, H-1, J_{1-2} = 3.8Hz), 5.22-5.27 (dd, 1H, H-6, J_{6-5a} = 5.1Hz, J_{6-5b} = 10.7Hz), 5.10-5.12 (t, 1H, H-4, J_{4-5} = 3.4Hz, J_{4-3} = 3.2Hz), 4.77-4.78 (d, 1H, H-3, J_{3-4} = 3.2Hz), 4.73-4.74 (d, 1H, H-2, J_{1-2} = 3.7Hz), 3.97 (s, 3H, H-7' MeO), 2.78-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.48-2.54 (dd, 1H, H-5a, J_{5a-6} = 5.1Hz, J_{5a-5b} = 13.6Hz), 1.97-2.07 (ddd, 1H, H-5b, J_{5b-4} = 3.6Hz, J_{5b-6} = 10.2Hz, J_{5b-5a} = 14Hz), 1.53, 1.36 (2s, 3H each, 2 Me from isopropylidene), 1.34-1.36 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

^{1}H NOE: Irradiation at 7.07 (H-5') enhancement at 6.67 (H-6'), irradiation at 6.40 (H-3'), enhancement at 4.78 (H-3), irradiation at 2.5 (H-5exo) enhancement at 2.00 (H-5endo), at 5.23 (H-6), irradiation at 2.00 (H-5endo) enhancement at 2.50 (H-5exo), at 5.22 (H-6), at 5.10 (H-4), at 4.73 (H-2).

1,2-O,O-isopropylidene-5-deoxy-6-endo-4'-(2'-ethyl-7'-methoxy)-benzofuranglucodi furanose (1,4:3,6) 20g: ($C_{20}O_6H_{24}$), 30.1%, ^{1}H NMR 300MHz: δ 7.07–7.10 (d, 1H, H-5', $J_{5'-6'}$ = 8.1Hz), 6.66-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.1Hz), 6.57 (s, 1H, H-3'), 6.00-6.02 (d, 1H, H-1, J_{1-2} = 3.8Hz), 5.10-5.12 (dd, 1H, H-6,overlapping with H-4 of α), 5.02-5.06 (dd, 1H, H-4, J_{4-5} = 5.6Hz, J_{4-3} = 3.6Hz), 4.79-4.80 (d, 1H, H-2, J_{2-1} = 3.8Hz), 4.45-4.46 (d, 1H, H-3, J_{3-4} = 3.2Hz), 3.97 (s, 3H, H-7' MeO), 2.78-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.33-2.40 (dd, 1H, H-5a, J_{5a-6} = 7.3Hz, J_{5a-5b} = 14.2Hz), 1.97-2.07 (ddd, 1H, H-5b, J_{5b-4} = 3.6Hz, J_{5b-6} = 10.2Hz, J_{5b-5a} = 14Hz), 1.53, 1.36 (2s, 3H each, 2 Me from isopropylidene), 1.34-1.36 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

^{1}H NOE: Irradiation at 7.10 (H-5') enhancement at 6.67(H-6').

IR (mixture of19 and 20): 1600(s), 1625(s), 2925(s), 2975(s), 3010(s).

MS: m/z 361(MH^+), 378(MNH_4^+).

General procedure for the desilylation of the furanosides: In a solution of 1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-endo-4'-(7'-methoxy-2'-ethyl)benzofurangluco

difuranose (1,4:3,6) **20e** (0.77g, 1.6mmol) in THF (10mL), tetrabutylammonium fluoride (TBAF, 0.5g, 1.9mmol) was added. The solution was stirred at room temperature under N_2. It was monitored by TLC ($CHCl_3$/EtOAc). The reaction was completed within 2hours. The solution was diluted with ether (50mL), washed with water (25mL), aqueous $NaHCO_3$ (sat. sol., 25 mL) and water (25mL). Dried over $MgSO_4$ and concentrated. The product **25b** (0.52g, 88%) was isolated by column chromatography ($CHCl_3$/EtOAc) on the residue. (Acetylation of the residue under standard conditions led to the corresponding acetate **25b*** 91.5%)

Mixture of the 24a, 25a: 78.7%.

1,2-O,O-isopropylidene-6-exo-4'-(7'-methoxy-2'-ethyl)benzofuranglucodifuranose (1,4:3,6) 24b: 87.9%, ^{1}H NMR 300MHz: δ 7.08-7.11 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.72-6.75 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.45 (s, 1H, H-3'). 5.95-5.96 (d, 1H, H-1, J_{1-2} = 3.8Hz), 5.20-5.25 (dd, 1H, H-4, J_{4-3} = 5.1Hz, J_{4-5} = 8.7Hz), 5.04-5.06 (d, 1H, H-6, J_{6-5} = 2.0Hz), 4.78-4.80 (d, 1H, H-3, J_{3-4} = 4.8Hz), 4.67-4.68 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.42 (s, 1H, H-OH), 4.12-4.15 (d, 1H, H-5, J_{5-4} = 8.9Hz), 3.99 (s, 3H, 7'-MeO), 2.8 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.32-1.37 (t, 3H, H-2", $J_{2"-1"}$ = 7.6Hz), 1.33, 1.25 (2s, 3H each, 2 Me from isopropylidene).

1,2-O,O-isopropylidene-6-endo-4'-(7'-methoxy-2'-ethyl)benzofuranglucodifuranose (1,4:3,6) 25b: ($C_{20}O_7H_{24}$), 88.0%, ^{1}H NMR 300MHz: δ 7.09-7.12 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.67-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.51 (s, 1H, H-3'), 5.93-5.95 (d, 1H, H-1, J_{1-2} = 3.7Hz)5.05-5.07 (d, 1H, H-6, J_{6-5} = 5.2Hz), 4.48-4.49 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.35-4.36 (d, 1H, H-3, J_{3-4} = 2.6Hz), 4.27-4.31 (t, 1H, H-5, $J_{5-4,6}$ = 5.3Hz), 3.97-4.00 (4H overlapping, 3H, 7'-MeO, 1H, H-4, J_{4-3} = 2.6Hz), 2.79-2.82 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.30-1.35 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz), 1.33, 1.26 (s, 3H each, 2 Me from isopropylidene).

IR: 1605(s), 1630(s), 2400(w), 2845(m), 2890(s), 2915(s), 2945(s), 2995(s), 3025(s), 3450(s).

MS: m/z 377(MH^+), 394(MNH_4^+).

1,2-O,O-isopropylidene-5-acetoxy-6-exo-4'(-7'-methoxy-2-ethyl) benzofuranglucodi furanose (1,4:3,6) 25*: 91.5%, ^1H NMR 300MHz: δ 7.04-7.07 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.66-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.59 (s, 1H, H-3'), 6.18-6.19 (d, 1H, H-6, J_{6-5} = 2.6Hz), 5.95-5.96 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.37-5.42 (dd, 1H, H-5, J_{5-6} = 2.6Hz,J_{5-4} = 9.5Hz), 5.32-5.33 (d, 1H, H-3, J_{3-4} = 2.8Hz), 4.54-4.59 (dd, 1H, H-4, J_{4-3} = 2.8Hz,J_{4-5} = 9.5Hz), 4.47-4.48 (d, 1H, H-2, J_{2-1} = 3.6Hz), 3.95 (s, 3H, H-7'MeO), 2.78-2.85 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.13 (s, 3H, 5(OAc)), 1.51, 1.31 (2s, 3H each, 2 Me of isopropylidene).

IR: 1605(m), 1630(s), 1750(vs), 2945(s), 2980(s), 3020(s).

General procedure for the oxidation with Ac_2O/DMSO: A solution of Ac_2O (4.1mL) in DMSO (6.2mL) was left to stand at room temperature for 1 hour. Then it was transferred into a R.B. flask containing the 1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-keto-6-4'-(2'-ethyl-7'-methoxy)benzofuranglucofuranose (1,4) **13f** (0.97g, 1.9mmol). The resulted solution was stirred overnight (16h). It was diluted with water (100mL). The solution was extracted with CH_2Cl_2 (4 times, 25mL each). The combined organic extracts were washed with water. The organic phase was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography ($CHCl_3$) to yield the diketone **34** (0.42g, 43.4%) and the acetate **14f** (.28g, 26.8%).

General procedure for the oxidation with $(COCl)_2$, DMSO:A 100mL R.B. flask equipped with a magnetic stirring bar, two pressure equilibrium addition funnels and a drying guard $CaCl_2$ tube was charged with a solution of $(COCl)_2$ (0.24g, 1.9mmol, 0.164mL), in CH_2Cl_2 (5mL). The addition funnels were charged, the first with a solution of 1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-keto-6-4'-(2'-ethyl-7'-methoxy)-

benzofuranglucofuranose (1,4) **13f** (0.83g, 1.64mmol) in CH_2Cl_2 (5mL) and the second with a solution of DMSO (0.33g, 4.2mmol, 0.3mL)) in CH_2Cl_2 (2mL). The oxallyl chloride solution was cooled to -78°C (dry ice-acetone), and the DMSO solution was added to it. The solution was stirred for 5min.. Then the alcohol was added. After the solution was stirred for 20min triethylamine (0.87g, 8.6mmol, 1.2mL) was added. The solution was stirred for 5min and allowed to reach room temperature The reaction was quenched with water (20mL). The aqueous phase was extracted with CH_2Cl_2 (30mL). The organic phases were combined, washed with aqueous NaCl (sat. solution, 20mL) dried over $MgSO_4$ and concentrated. The residue was chromatographed ($CHCl_3$) to yield the parent alcohol **13f** (0.17g, 20.2%) and the diketone **34** (0.44g, 53%).

1,2-O,O-isopropylidene-3,6-diketo-5-O-t-butyldimethylsilyl-6-4'-(7'-methoxy-2'-ethyl)benzofuran-glucofuranose 34: ($C_{26}O_8H_{36}Si$), ^1H NMR 300MHz: δ 7.80-7.84 (d, 1H, H-5', $J_{5'-6'}$ = 8.4Hz), 7.03 (s, 1H, H-3'), 6.66-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.6Hz), 6.07-6.09 (d, 1H, H-1, J_{1-2} = 4.6Hz), 5.27-5.28 (d, 1H, H-5, J_{5-4} = 2.4Hz), 4.66-4.67 (d, 1H, H-4, J_{4-5} = 1.9Hz), 4.53-4.55 (d, 1H, H-2, J_{2-1} = 4.6Hz), 4.01 (s, 3H, H-7'MeO), 2.75-2.83 (q, 2H, H-1", $J_{1"-2"}$ = 7.7Hz), 1.39, 1.37 (2s, 3H each, 2-Me isopropylidene), 1.28, -1.35 (t, 3H, H-2", $J_{2"-1"}$ = 7.6Hz).

MS: m/z 505(MH^+), 522(MNH_4^+).

2-Ethyl-7-methoxy-benzofuranyl-4-aldehyde 33: ($C_{12}O_3H_{12}$), white solid, mp 65-66.5°C, ^1H NMR 300MHz: δ 10.02 (s, 1H, (HO)), 7.82-7.84 (d, 1H, H-5, J_{5-6} = 8.3Hz), 7.16 (t, 1H, H-3, $J_{3-1"}$ = 1.0Hz), 6.83-6.85 (d, 1H, H-6, J_{6-5} = 8.3Hz), 4.09 (s, 3H, H-7'MeO), 2.84-2.88 (q, 2H, H-1',$J_{1'-2'}$ = 7.4Hz, $J_{1'-3}$ = 1.0Hz), 1.34-1.40 (t, 3H, H-2', $J_{2'-1'}$ = 7.5Hz).

IR: 1595(s), 1625(s), 1680(vs), 2725(m), 2815(w), 2845(m), 2900(w), 2945(m), 2970(s), 3020(s).

MS: m/z 205(MH^+), 222(MNH_4^+).

Chapter 7

General procedure for the xanthate esters preparation: A 100mL R.B. 3 neck flask equipped with a magnetic stirring bar, reflux condenser and an addition pressure equilibrium funnel was charged with a suspension of NaH (0.13g 80%, 4.3mmol, washed with petroleum ether three times), in THF (5mL). Imidazole (0.013g, .19mmol) was added, under N_2. The addition funnel was charged with a solution of the 1,2-O,O-isopropylidene-6-exo-4'-(2'-ethyl-7'-methoxy)benzofuranglucodifuranose (1,4:3,6) **1b** (0.7g, 1.9mmol) in THF (5mL). The apparatus was flushed with N_2 and the reaction was carried through under N_2. The alcohol solution was released dropwise in the NaH suspenion. After the initial gas evolution ceased the solution was refluxed for 30min. It was cooled to room temperature and excess of CS_2 (1.27g, 16.6mmol, 1mL) was injected. After stirring for 15 min at room temperature, excess of MeI (2.28g, 16.1mmol, 1mL) was injected and the solution was stirred for another hour. The reaction was quenched with water (50mL). The aqueous phase was extracted with ether 3-4 times. The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude xanthate ester **2b**. Purification with column chromatography ($CHCl_3$) yielded 0.845g (97.5%) of **2b**.

1,2-O,O-benzylidene-5-O-xanthate-6-exo-4'-(7'-methoxy-2'-ethyl)benzofurangluco difuranose (1,4:3,6) 2a: ^{1}H NMR 300MHz: δ 7.38-7.55 (5H, Ph), 7.12-7.15 (d, 1H, H-5', $J_{5'-6'}$ = 8.3Hz), 6.69-6.72 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.50 (s, 1H, H-3'), 6.29-6.30 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.98 (s, 1H, benzylidene), 5.73-5.77 (dd, 1H, H-5, J_{5-4} = 3.8Hz, J_{5-6} = 8.9Hz), 5.38-5.41 (t, 1H, H-4, $J_{4-3,5}$ = 3.9Hz), 5.28-5.32 (d, 1H, H-6, J_{6-5} = 8.9Hz), 5.04-5.06 (d, 1H, H-3, J_{3-4} = 3.7Hz), 4.94-4.96 (d, 1H, H-2, J_{2-1} = 3.6Hz), 3.97 (s, 3H, H-7'MeO),2.81 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.74 (s, 3H, H-MeSCS), 1.35 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

1,2-O,O-isopropylidene-5-O-xanthate-6-exo-4'-(7'-methoxy-2'-ethyl)benzofuran glucodifuranose (1,4:3,6) 2b: ^{1}H NMR 300MHz: δ 7.09-7.12 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.68-6.71 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.47 (t, 1H, H-3', $J_{3'-1''}$ = 1.0Hz), 6.13-6.15 (d, 1H, H-1, J_{1-2} = 3.6Hz), 5.73-5.77 (dd, 1H, H-5, J_{5-4} = 3.8Hz, J_{5-6} = 8.9Hz), 5.33-5.36 (t, 1H, H-4, $J_{4-3,5}$ = 3.6Hz), 5.27-5.31 (d, 1H, H-6, J_{6-5} = 8.9Hz), 4.92-4.93 (d, 1H, H-3, J_{3-4} = 3.5Hz), 4.76-4.77 (d, 1H, H-2, J_{2-1} = 3.7Hz), 3.98 (s, 3H, H-7'MeO),2.78-2.87 (q, 2H, H-1", $J_{1''-2''}$ = 7.5Hz, $J_{1''-3'}$ = 1.0Hz), 2.51 (s, 3H, H-MeSCS), 1.51, 1.37 (2s, 3H each, 2Me from isopropylidene),1.32-1.37 (t, 3H, H-2", $J_{2''-1''}$ = 7.5Hz).

IR: 1605(m), 1628(s), 1700(w), 2250(w), 2850(m), 2905(m), 2940(s), 2990(s).

General procedure for the xanthate 2 deoxygenation: A 100mL R.B. flask equipped with a magnetic stirring bar and a reflux condenser was charged with a solution of the crude xanthate ester **2b** (0.85, 1.8mmol) in toluene (20mL) and catalytic amount of AIBN (0.1g, 0.61mmol). Bu_3SnH (1.08g, 3.6mmol, 1mL) was injected and the solution was refluxed overnight under N_2. It was diluted with ether (100mL), washed twice with aqueous KF (10% sol., 35mL each) and water (35mL). Dried over $MgSO_4$ and concentrated. Column chromatography ($CHCl_3/C_6H_{12}$) on the residue yielded the deoxygenated product **3b** (0.36g, 53.7%) along with the parent alcohol **1b** (0.12g, 17.1%).

1,2-O,O-benzylidene-5-deoxy-6-exo-4'-(7'-methoxy-2'-ethyl)benzofuranglucodi furanose (1,4:3,6) 3a: 34.7%, ^{1}H NMR 300MHz: δ 7.39-7.55(5H, Ph), 7.04-7.07 (d, 1H, H-5', $J_{5'-6'}$ = 8.5Hz), 6.66-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.38 (s, 1H, H-1, J_{1-2} = 4.1Hz), 6.00 (s, 1H, benzylidene), 5.26-5.31 (dd, 1H, H-6, J_{6-5a} = 5.1Hz, J_{6-5b} = 10.7Hz), 4.97-4.99 (t, 1H, H-4, J_{4-3} = 3.2Hz), 4.82-4.84 (2d overlapping H-3, H-2, J_{3-4} = 3.2Hz), 3.98 (s, 3H, H-7'MeOH), 2.80 (q, 2H, H-1", $J_{1''-2''}$ = 7.5Hz), 2.49-2.58 (dd, 1H, H-5a, J_{5a-6} = 5.2Hz, J_{5a-5b} = 13.4Hz), 1.95-2.07 (ddd, 1H, H-5b, J_{5b-4} = 3.7Hz, J_{5b-6} = 10.34Hz, J_{5b-5a} = 13.4Hz), 1.33 (t, 3H, H-2", $J_{2''-1''}$ = 7.5Hz).

1,2-O,O-isopropylidene-5-deoxy-6-exo-4'-(2'-ethyl-7'-methoxy)benzofuranglucodi furanose (1,4:3,6) 3b: 53.7%, ^{1}H NMR 300MHz: δ 7.04–7.07 (d, 1H, H-5', $J_{5'-6'}$ = 8.1Hz), 6.66-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.1Hz), 6.39 (s, 1H, H-3'), 6.02-6.04 (D, 1H, H-1, J_{1-2} = 3.8Hz), 5.22-5.27 (dd, 1H, H-6, J_{6-5a} = 5.1Hz, J_{6-5b} = 10.7Hz), 5.10-5.12 (t, 1H, H-4, J_{4-5} = 3.4Hz, J_{4-3} = 3.2Hz), 4.77-4.78 (d, 1H, H-3, J_{3-4} = 3.2Hz), 4.73-4.74 (d, 1H, H-2, J_{1-2} = 3.7Hz), 3.97 (s, 3H, H-7' MeO), 2.78-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.48-2.54 (dd, 1H, H-5a, J_{5a-6} = 5.1Hz, J_{5a-5b} = 13.6Hz), 1.97-2.07 (ddd, 1H, H-5b, J_{5b-4} = 3.6Hz, J_{5b-6} = 10.2Hz, J_{5b-5a} = 14Hz), 1.53, 1.36 (2s, 3H each, 2 Me from isopropylidene), 1.34-1.36 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

General procedure for the benzoylation of carbohydrates: Benzoyl chloride (0.49g, 3.5mmol, 0.41mL) was added to a solution of the 1,2-O,O-isopropylidene-5-O-t-butyldi methylsilyl-6-keto-6-4'-(2'-ethyl-7'-methoxy)benzofuranglycofuranose (1,4) **7** (1.6g, 3.2 mmol) in pyridine (8mL). The solution was stirred at room temperature until TLC monitoring showed the reaction was completed (overnight). The solvent was evaporated under reduced pressure. The residue was dissolved in ether (100mL) and washed with water (50mL). Dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography ($CHCl_3$) to yield the benzoate **8** (1.5g, 77.8%).

1,2-O,O-isopropylidene-3-O-benzoate-5-O-t-butyldimethylsilyl-6-keto-6-4'-(7'-methoxy-2'-ethyl)benzofuranglucofuranose (1,4) 8: 77.8%, ^{1}H NMR 300MHz: δ 8.12-8.16 (d, 2H, H-2, 6 (Bz), J_{2-6} = 7.2Hz), 7.60-7.67 (t, 1H, H-4(Bz), $J_{4-5,3}$ = 7.2Hz), 7.30-7.52 (t, 2H, H-3,5(Bz), $J_{3,5-4,2,6}$ = 7.2Hz), 8.17-8.20 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 7.30 (s, 1H, H-3'), 6.78-6.82 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 5.90(d, 1H, H-1), 5.55 (d, 1H, H-3), 5.20 (dd, 1H, H-5), 4.82 (dd, 1H, H-4), 4.60 (d, 1H, H-2), 4.05 (s, 3H, H-7'MeO), 2.82 (q, 2H, H-1", $J_{1"-2"}$ = 7.8Hz), 1.46, 1.26 (2s, 3H each, 2 Me from isopropylidene), 1.32-1.37 (t, 3H, H-2", $J_{2"-1"}$ = 7.8Hz), 0.77 (s, 9H, t-butyl), -0.17, -0.20 (2s, 3H each, 2-Me of TBDMS).

Preparation of the dibenzoate 10: 1,2-O,O-isopropylidene-3-O-benzoate-6-keto-6-4'-(7' -methoxy-2'-ethyl)benzofuranglucofuranose (1,4) **9** (1.5g, 2.46mmol) was dissolved in THF (15mL). Tetrabutylammonium fluoride (3mL, 1M solution in THF, 3mmol) was added and the solution was stirred at room temperature under N_2 for 2 hours. Then it was diluted with ether (100mL), washed with water twice (25mL each), dried over $MgSO_4$ and concentrated to yield 1.25g crude product **9**. The solid was dissolved immediately in pyridine (6mL) and benzoyl chloride (0.387g, 99%, 2.7mmol, 0.32mL) was added. The solution was stirred at room temperature (overnight, TLC showed completion of the reaction). The solvent was removed under reduced pressure and the residue was dissolved in ether (100mL). The organic phase was washed with water (twice, 35mL each), dried with $MgSO_4$ and concentrated. The product was purified by column chromatography ($CHCl_3$) to yield the dibenzoate **10** (1.42g, 96.3%) as a pale yellow crystalline solid.

1,2-O,O-isopropylidene-3-O-benzoate-6-keto-6-4'-(7'-methoxy-2'-ethyl)benzofuran glucofuranose (1,4) 9: ^{1}H NMR 300MHz: δ 8.00-8.08 (2d, 3H, 2H-2,6(Bz), $J_{2,6\text{-}3,5}$ = 7.2Hz, 1H-5', $J_{5'\text{-}6'}$ = 8.7Hz), 7-6 (dd, 1H, H-4(Bz), $J_{4\text{-}5,3}$ = 7.2Hz), 7.38-7.43 (dd, 2H, H-3, 5(Bz), $J_{3,5\text{-}4,2,6}$ = 7.5Hz), 7.24 (s, 1H, H-3'), 6.73-6.76 (d, 1H, H-6',$J_{6'\text{-}5'}$ = 8.5Hz), 6.54-6.57 (d, 1H, H-5, $J_{5\text{-}4}$ = 7.9Hz), 5.93-5.94 (d, 1H, H-1, $J_{1\text{-}2}$ = 3.5Hz), 4.61-4.65 (dd, H-4, $J_{4\text{-}3}$ = 2.4Hz, $J_{4\text{-}5}$ = 7.9Hz), 4.54-4.56 (d, 1H, H-2, $J_{2\text{-}1}$ = 3.5Hz), 4.36-4.37 (d, 1H, H-3, $J_{3\text{-}4}$ = 2.4Hz), 4.03 (s, 3H, H-7'MeO), 2.79-2.87 (q, 2H, H-1", $J_{1\text{"-}2\text{"}}$ = 7.5Hz), 1.46, 1.26 (2s, 3H each, 2Me of isopropylidene), 1.33-1.36 (t, 3H, H-2", $J_{2\text{"-}1\text{"}}$ = 7.4Hz)

1,2-O,O-isopropylidene-3,5-dibenzoate-6-keto-6-4'-(7'-methoxy)-2'-ethyl)benzo-furanglucofuranose (1,4) 10: ($C_{34}O_{10}H_{32}$), 96.3%, ^{1}H NMR 300MHz: δ 7.30-8.20 (11H, Aromatic, 10h from 2Bz, 1H, H-5'), 7.25 (s, 1H, H-3'), 6.80-6.83 (d, 1H, H-6',$J_{6'\text{-}5'}$ = 8.6Hz), 6.44-6.48 (d, 1H, H-5, $J_{5\text{-}4}$ = 9.4Hz), 6.00-6.01 (d, 1H, H-1, $J_{1\text{-}2}$ = 3.7Hz), 5.78-5.79 (d, 1H, H-3, $J_{3\text{-}4}$ = 3.0Hz), 4.99-5.04 (dd, 1H, H-4, $J_{4\text{-}3}$ = 3.0Hz, $J_{4\text{-}5}$ = 9.4Hz), 4.70-

4.72 (d, 1H, H-2, $J_{2\text{-}1}$ = 3.7Hz), 4.07 (s, 3H, H-7'MeO), 2.81-2.85 (q, 2H, H-1",$J_{1"\text{-}2"}$ = 7.6Hz), 1.56, 1.31 (2s, 3H each, 2Me of isopropylidene), 1.31-1.36 (t, 3H, H-2", $J_{2"\text{-}1"}$ = 7.6Hz).

IR: 1585(s), 1605(s), 1625(s), 1690(vs), 2400(w), 2545(w), 2660(w)3020(s).

MS: m/z 601(MH^+), 618(MNH_4^+).

Deoxygenation of the dibenzoate 10: A 100mL R.B. flask equipped with a reflux condenser was charged with a solution of 1,2-O,O-isopropylidene-3,5-dibenzoate-6-keto -6-4'-(7'-methoxy-2'-ethyl)benzofuranglucofuranose (1,4) **10** (1.66g, 2.77mmol) in toluene (35mL). Bu_3SnH (8.64g, 28.85mmol, 8mL) and AIBN (0.4g, 2.44mmol) were added. The reaction solution was stirred refluxing under N_2 for 4h. After reaching room temperature, it was diluted with ether and stirred overnight with aqueous KF (10% sol, 20mL). The organic phase was washed with water (20mL), aqueous $NaHCO_3$ (sat. sol., twice, 20mL each), water (20mL), dried over $MgSO_4$ and concentrated. The residue was chromatographed ($CHCl_3$) to yield **11** (0.52g, 39.2%) and **12** (0.55g, 41.4%).

1,2-O,O-isopropylidene-3-benzoate-5-deoxy-6-keto-6-4'-(7'-methoxy-2'-ethyl) benzofuranglucofuranose (1,4) 11: ($C_{27}O_8H_{28}$), 39.2%, ^1H NMR 300MHz: δ 7.96-7.99 (d, 2H, H-2, 6(Bz), $J_{2,6\text{-}3,5}$ = 7.8Hz), 7.70-7.73 (d, 1H, H-5', $J_{5'\text{-}6'}$ = 8.5Hz), 7.52-7.58 (t, 1H, H-4(Bz), $J_{4\text{-}5,3}$ = 7.4Hz), 7.37-7.43 (dd, 2H, H-3, 5Bz, $J_{3,5\text{-}2,6}$ = 7.8Hz, $J_{3,5\text{-}4}$ = 7.4Hz), 7.16 (t, 1H, H-3', $J_{3'\text{-}1'}$ = 1.0Hz), 6.64-6.67 (d, 1H, H-6', $J_{6'\text{-}5'}$ = 8.5Hz), 5.99-6.00 (d, 1H, H-1, $J_{1\text{-}2}$ = 3.8Hz), 5.64-5.65 (d, 1H, H-3, $J_{3\text{-}4}$ = 2.9Hz), 5.04-5.10 (ddd, 1H, H-4, $J_{4\text{-}3}$ = 2.9Hz, $J_{4\text{-}5a}$ = 7.4Hz, $J_{4\text{-}5b}$ = 8.9Hz), 4.70-4.71 (d, 1H, H-2, $J_{2\text{-}1}$ = 3.8Hz), 4.02 (s, 3H, H-7'MeO), 3.52-3.60 (dd, 1H, H-5a, $J_{5a\text{-}4}$ = 6.0Hz, $J_{5a\text{-}5b}$ = 17.0Hz), 3.39-3.48 (dd, 1H, H-5b, $J_{5b\text{-}4}$ = 7.5Hz, $J_{5b\text{-}5a}$ = 17.0Hz), 2.77-2.85 (dq, 2H, H-1", $J_{1"\text{-}2"}$ = 7.5Hz, $J_{3'\text{-}1"}$ = 0.9Hz), 1.60, 1.35 (2s, 3H each, 2 Me of isopropylidene), 1.29-1.35 (t, 3H, H-2", $J_{2"\text{-}1"}$ = 7.5Hz).

IR: 1590(s), 1615(s), 1660(s), 1720(s), 2850(s), 2925(s), 2950(s).

MS: m/z 481(MH^+).

1,2-O,O-isopropylidene-3-benzoate-5-deoxy-6-4'-(7'-methoxy-2'-ethyi)benzofuran) glucofuranose (1,4) 12: 41.4%: ^{1}H NMR 300MHz: δ mixture: 8.00-8.10 (2d, 2H from each isomer, H-2,6 of Bz), 7.49-7.60 (2t, 1H from each isomer, H-4 of Bz), 7.30-7.42(t, 2H from each isomer, H-3, 5(Bz)), 7.05-7.11 (2d, 1H, H-5' of each isomer), 6.60-6.66 (2d, 1H, H-6' from each isomer), 6.50 (2s, 1H, H-3' from each isomer), 6.00 (2d, 1H, H-1 of each isomer), 5.40 (d, 1H, H-3 of major isomer), 5.30 (d, 1H, H-3 of minor isomer), 5.15 (dd, 1H, H-6 of major isomer), 5.10 (dd, 1H, H-6 of minor isomer), 4.65 (dd, 1H, H-4 of major isomer), 4.65 (d, 1H, H-2 of major isomer), 4.60 (d, 1H, H-2 of minor isomer), 4.40 (ddd, 1H, H-4 of minor isomer), 3.94 (s, 3H, 7'-MeO of both isomers), 3.50 (6(OH) of major isomer), 2.00-2.90 (4H from each isomer, 2H (H-1",q), H-5a,5b from each (ddd)), 1.20-1.60 (9H from each, 6H from isopropylidene (2s), and 3H(H-2", t)). (Mixture 1.75/1).

General procedure for the basic hydrolysis of the benzoates 11, 12: NaOH (0.2g, 5.0mmol) was added in a solution of crude benzoate **12** (0.4g, 0.83 mmol) in methanol (20mL). The solution was stirred at room temperature for 1h. It was diluted with aqueous NaCl (sat. sol., 100mL) and extracted with CH_2Cl_2 (4x25mL). The combined organic extracts were washed with water (35mL), dried over $MgSO_4$ and concentrated. The residue was chromatographed ($CHCl_3$/EtOAc = 6/4) to yield the isomeric diols **16** (0.14g, 44.73% and 0.08g 25.56%, ^{1}H NMR 300MHz ch. 5 13g).

Chapter 8

General procedure for the acidic hydrolysis of benzylidene acetals: A 10% solution of 1,2-O,O-benzylidene-5-O-t-butyldimethysilyl-6–exo, endo-4'-2'-(1"-methoxy-ethyl-7'-methoxy)benzofuranglucodifuranose **5** (1.53g, 2.69mmol) in a mixture of AcOH (15mL), H_2O (3mL), was refluxed for 5 hours. TLC showed no remaining starting material. The solvent was evaporated under reduced pressure and the residue was acetylated (pyridine/Ac_2O, standard procedure). After column chromatography ($CHCl_3$/EtOAc = 9/1) the mixture of the tetraacetate products **3**, **4** was isolated (0.64g, 45.71%).

The BCl_3 reactions:

A solution of the 1,2-O,O-isopropylidene-5-acetate-6-exo-4'-(2'-ethyl-7'-methoxy)benzo-furanglucodifuranose (1,4:3,6) **7** (0.13g, 0.31mmol) in CH_2Cl_2 (5mL) was cooled to 0°C under N_2. BCl_3 (1mL, 1M sol. in CH_2Cl_2, 1mmol) was injected and the reaction was stirred at 0°C for 2min.

Procedure A: The solution was diluted with CH_2Cl_2 (50mL) and the reaction was quenched with water (10mL). The organic phase was washed with water (10mL), dried over $MgSO_4$ and concentrated. The residue was acetylated (standard procedure). The acetylated 8 products were isolated by column chromatography.

Procedure B: The solvent was evaporated under reduced pressure. Methanol (10mL) was introduced and after stirring for 30 min. it was also evaporated. The residue was separated by column chromatography to yield traces of the acetate **7**, the parent alcohol **6**, and a mixture of other hydrolyzed products diols and triols along with 1-methyl glycosides.

1,2,5-triacetoxy-6-(4'(2'-ethyl-7'-methoxy)benzofuran0glucodifuranose (1,4:3,6) 8: ($C_{23}O_{10}H_{26}$), MS: m/z 463(MH^+), 480(MNH_4^+).

1-β-2,5-triacetoxy-6-endo-4'-(2'-ethyl-7'-methoxy)benzofuranglucodifuranose (1,4:3,6) 8: ($C_{23}O_{10}H_{26}$), traces, ^{1}H NMR 300MHz: δ ^{1}H NMR 300MHz: δ 7.10-7.13 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.69-6.72 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.59-6.61 (d, 1H, H-1, J_{1-2} = 4.5Hz), 6.48 (s, 1H, H-3'), 5.28-5.31 (dd, 1H, H-4, J_{4-3} = 2.6Hz, J_{4-5} = 4.6Hz), 5.09-5.11 (d, 1H, H-6, J_{6-5} = 5.3Hz), 5.08 (2H overlapping H-2,3), 4.87-4.92 (dd, 1H, H-5, J_{5-4} = 4.5Hz, J_{5-6} = 6.6.Hz), 4.00 (s, 3H, H-7'MeO), 2.79-2.86(q, 2H, H-1", $J_{1"-2"}$ = 7.6Hz), 2.10, (s, 6H, 2, 5-OAc), 2.06 (s, 3H, 1-OAc), 1.32-1.37 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

^{1}H NOE: Irradiation at 7.10(H-5'), enhancement at 6.70(H-6'), 5.10(H-6).

IR: 1605(s), 1630(s), 1745(vs), 2840(m), 2940(s), 2975(s), 3025(s).

MS: m/z 463(MH^+), 480(MNH_4^+).

General procedure for the acetolysis of isopropylidene acetals: A solution of the 1, 2-O,O-isopropylidene-3,5-diacetate-6-keto-6-4'-(7'-methoxy-2'-ethyl)benzofurangluco furanose (1,4) **10** (0.86g, 1.81mmol) in a mixture of Ac_2O (1mL), AcOH (9mL), was cooled to 0°C. A drop of conc. H_2SO_4 was added and the solution was stirred at room temperature overnight (16h). The solution was diluted with ice/water (100mL) and the pH was adjusted to pH = 6-7 with solid NaOH. The slightly acidic solution was extracted repeatedly with $CHCl_3$ (5 times, 25mL each). The combined chloroform extracts were washed with aqueous $NaHCO_3$ (sat. sol., 30mL) and water (30mL). Dried over $MgSO_4$ and concentrated. The residue was chromatographed ($CHCl_3$/EtOAc = 9/1) to yield the products **11** (0.237g, 25.2%) and **12** (0.323g, 37.4%).

1,2-O,O-isopropylidene-3,5-O-diacetate-6-keto-6-4'-(7'-methoxy-2'-ethyl)benzofuran glucofuranose (1,4) 10: ($C_{24}O_{10}H_{28}$), ^{1}H NMR 300MHz: δ 7.97-8.00 (d, 1H, H-5', $J_{5'-6'}$ = 8.6Hz), 7.24 (s, 1H, H-3'), 6.77-6.80 (d, 1H, H-6', $J_{6'-5'}$ = 8.6Hz), 6.13-6.16 (d, 1H, H-5, J_{5-4} = 9.6Hz), 5.88-5.90 (d, 1H, H-1, J_{1-2} = 3.7Hz), 5.47-5.49 (d, 1H, H-3, J_{3-4} = 2.9Hz), 4.69-4.74 (dd, 1H, H-4, J_{4-3} = 2.9Hz, J_{4-5} = 9.6Hz), 4.51-4.53 (d, 1H, H-2, J_{2-1} = 3.7Hz), 4.07 (s, 3H, H-7'MeO), 2.80-2.89(q, 2H, H-1", $J_{1"-2"}$ = 7.6Hz), 2.16, 2.08 (2s, 3H each, 3,

5-OAc), 1.48, 1.27 (2s, 3H each, 2 Me of isopropylidene), 1.32-1.38 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

IR: 1595(s), 1625(s), 1675(s), 1750(vs), 2840(w), 2880(w), 2905(w), 2945(m), 2980(s), 3015(m).

MS: m/z 477(MH^+), 494(MNH_4^+).

1-α-2,3,5-tetraacetoxy-6-keto-6-4'-(7'-methoxy-2'-ethyl)benzofuranglucofuranose (1,4) 11: ($C_{23}O_{11}H_{26}$), 25.2%: ^1H NMR 300MHz: δ 7.88-7.91 (d, 1H, H-5', $J_{5'-6'}$ = 8.5Hz), 7.16 (s, 1H, H-3'), 6.77-6.80 (d, 1H, H-6', $J_{6'-5'}$ = 8.6Hz), 6.41-6.43 (d, 1H, H-1, J_{1-2} = 4.5Hz), 6.19-6.21 (d, 1H, H-5, J_{5-4} = 7.4Hz), 5.63-5.66 (dd, 1H, H-3, J_{3-4} = 5.5Hz), 5.32-5.35 (dd, 1H, H-2, J_{2-1} = 4.5Hz, J_{2-4} = 4.6Hz), 4.89-4.94 (dd, 1H, H-4, J_{4-3} = 5.8Hz, J_{4-5} = 7.4Hz), 4.08 (s, 3H, H-7'MeO), 2.81-2.89 (q, 2H, H-1", $J_{1"-2"}$ = 7.6Hz), 2.02, 2.10, 2.13, 2.17 (4s, 3H each (OAc)), 1.32-1.38 (t, 3H, H-2", $J_{2"-1"}$ = 7.6Hz).

IR: 1595(s), 1625(s), 1675(s), 1750(vs), 2850(w), 2947(m), 2985(m), 3030(s).

MS: m/z 521(MH^+), 538(MNH_4^+).

1-β-2,3,5-tetraacetoxy-6-keto-6-4'-(7'-methoxy-2'-ethyl)benzofuranglucofuranose (1,4) 12: ($C_{23}O_{11}H_{26}$), 37.4%: ^1H NMR 300MHz: δ 7.92-7.95 (d, 1H, H-5',$J_{5'-6'}$ = 8.6Hz), 7.20 (s, 1H, H-3'), 6.73-6.76 (d, 1H, H-6', $J_{6'-5'}$ = 8.6Hz), 6.25-6.29 (d, 1H,H-5, J_{5-4} = 9.0Hz), 6.06 (s, H-1), 5.53-5.55 (d, 1H, H-3, J_{3-4} = 4.9Hz), 5.21 (s, 1H, H-2), 4.89-4.94 (dd, 1H, H-4, J_{4-3} = 4.9Hz, J_{4-5} = 9.0Hz), 4.08 (s, 3H, H-7'MeO), 2.81-2.89 (q, 2H, H-1", $J_{1"-2"}$ = 7.6Hz), 2.17, 2.10, 2.09 (3s, 3H each, 3 (OAc)), 1.33-1.37 (t, 3H, H-2", $J_{2"-1"}$ = 7.6Hz).

IR: 1595(s), 1605(w), 1625(s), 1675(s), 1750(vs), 2850(w), 2910(w), 2940(m), 2980(m).

MS: m/z 521(MH^+), 538(MNH_4^+).

Isomerization of the 1-β-tetraacetate 12: A solution of the 1-β-2,3,5-tetraacetate **12** (0.12g, 2.5mmol) in CH_2Cl_2 (5mL) was stirred under N_2 with $BF_3.Et_2O$ (0.037mL, 0.3mmol). TLC ($CHCl_3$/EtOAc = 9/1) monitoring showed that a product was being formed. After the dissappearance of the starting substrate, the solution was diluted with

CH_2Cl_2 (30mL) and washed with aqueous NaCl (sat. sol., 30mL). The organic phase was dried over $MgSO_4$ and concentrated to yield a dark residue composing of two compounds, the starting 12 and the α-isomer **11**.

Acidic elimination and rearrangement of the diacetate 10: A solution of 1,2-O,O-isopropylidene-3,5-diacetoxy-6-keto-4'-(2'-ethyl-7'-methoxy)benzofuranglucofuranose (1,4) **10** (0.18g, 0.38mmol) in a mixture of MeOH (9mL), H_2O (1mL) and THF (4mL) was stirred with PTSA (0.9g 99%, 4.68mmol) at room temperature for 24h. The solution was diluted with water 50mL and extracted with CH_2Cl_2 (4x25mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (sat. sol., 30mL), water (30mL), dried over $MgSO_4$ and concentrated. Column chromatography on the residue yielded the starting diacetate **10** (0.096g, 53.3%) and the pyrone **15** (0.03g, 26.5%).

6-4'-(7'-methoxy-2'-ethyl)benzofuran-α-pyrone 15: ($C_{17}O_5H_{14}$), ^1H NMR 300MHz: δ 7.88-7.90 (d, 1H, H-3, $J_{2\text{-}3}$ = 5.9Hz), 7.27-7.69 (d, 1H, H-5', $J_{5'\text{-}6'}$ = 8.6Hz), 7.07 (t, 1H, H-3', $J_{3'\text{-}1}$ = 1.0Hz), 6.83-6.85 (d, 1H, H-5, $J_{5\text{-}4}$ = 2.5Hz), 6.77-6.80 (d, 1H, H-6', $J_{6'\text{-}5'}$ = 8.6Hz), 6.48-6.51 (dd, 1H, H-4, $J_{4\text{-}3}$ = 5.8Hz, $J_{4\text{-}5}$ = 2.6Hz), 4.11 (s, 3H, 7'MeO), 2.87 (q, 2H, H-1", $J_{1''\text{-}2''}$ = 7.5Hz), 1.35-1.40 (t, 3H, H-2", $J_{2''\text{-}1''}$ = 7.6Hz).

IR: 1615(s), 1650(vs), 2845(w), 2930(m), 2975(m), 3010(s).

MS: m/z 299(MH^+), 316(MNH_4^+).

Chapter 9

General procedure for the I_2/MeOH reaction:The 1,2-O,O-isopropylidene-5-O-t-butyldimethylsilyl-6-exo-4'-(2'-ethyl-7'-methoxy)benzofuranidodifuranose (1,4:3,6) **16** (0.96g, 1.96mmol), was dissolved in methanol (25mL). Iodine (0.25g) was added. The solution was refluxed for 4hours (until TLC monitoring ($CHCl_3$/EtOAc = 6/4) showed the reaction was completed). The reaction mixture after cooling to room temperature was diluted with aqueous $Na_2S_2O_7$ (5% solution, 100mL). The solution was extracted repeatedly with CH_2Cl_2 (4x25mL). The combined organic extracts were washed with water (30mL), dried over $MgSO_4$ and concentrated. The residue was chromatographed ($CHCl_3$/EtOAc) to yield the isomeric methyl glycosides **23** (0.07g, 10.2%), 1/2.65 mixture of **24** and **25** (0.28g, 40.8%), **26** (0.26g, 37.9%).

1-α-methoxy-6-exo-4'-(7'-methoxy-2'-ethyl)benzofuranglucodifuranose (1,4:3,6) 19: ($C_{18}O_7H_{22}$), ^{1}H NMR 300MHz: δ 7.09-7.12 (d, 1H, H-5', $J_{5'-6'}$ = 8.1Hz), 6.67-6.71 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.48 (s, 1H, H-3'), 5.10-5.12 (d, 1H, H-6, J_{6-5} = 4.4Hz), 4.67-4.70 (overlapping, 3H, H-2, H-3, H-1), 4.27-4.29 (d,d, 1H, H-4, J_{4-3} = 2.1Hz, J_{4-5} = 4.3Hz), 4.04-4.06 (dd, 1H, H-5 , $J_{5-4,6}$ = 4.8Hz), 3.97 (s, 3H, 7'-MeO), 2.77-2.84 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.30-1.35 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz), 3.51 (s, 3H, H-(1-MeO)).

IR: 1603(s), 1625(s), 2840(m), 2905(s), 2940(s), 2970(s), 3010(s), 3450(s).

MS: m/z 351(MH^+), 368(MNH_4^+).

1-α-methoxy-2,5-diacetoxy-6-exo-4'-(7'-methoxy-2'-etyl)benzofuranglucodifuranose (1,4:3,6) 19*: ($C_{22}O_9H_{26}$), 92.2%, ^{1}H NMR 300MHz: δ 7.10-7.14 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.69-6.72 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.50 (s, 1H, H-3'), 5.32-5.34 (d, 1H, H-1, J_{1-2} = 4.3Hz), 5.06-5.09 (2H, dd, H-5, 6, J_{5-6} = 3.2Hz, J_{5-4} = 8.4Hz), 4.99-5.02 (t(dd), 1H, H-2 , J_{2-1} = 4.1Hz, J_{2-3} = 3.8Hz), 4.86-4.95 (2H, overlapping dd, dd, H-1, 5, J = 4.6Hz, J = 5.8Hz, H- , J = 5.8Hz, J_{5-4} = 9.2Hz), 3.99 (s, 3H, H-7'MeO), 3.40 (s, 3H, H-1-OMe),

2.80-2.84 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.07, 2.14 (2s, 3H each, 2 (OAc)), 1.31-1.37 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

^{1}H COSY: H-1(d, 5.32) coupled with H-2(t, 5.02), H-5(dd, 5.08) coupled with H-4(dd, 4.95), H-6(d, 5.10), H-2(t, 5.05) coupled with H-1(d, 5.32), H-3(d, 4.95), H-3(d, 4.95) coupled with H-2(t, 5.02), H-4(dd, 4.90), H-4(dd, 4.90) coupled with H-3(d, 4.95), H-5(dd, 5.08).

^{1}H NOE: Irradiation at 6.5 (H-3'), enhancement at 5.05 (H-6), irradiation at 7.10 (H-5'), enhancement at 5.05 (H-6), 6.70 (H-6').

IR: 1603(m), 1625(s), 1735(vs), 2840(m), 2903(m). 2925(s), 2960(s), 3020(s).

MS: m/z 435(MH^+), 452(MNH_4^+).

Mixture of 1-β-methoxy-6-exo-4'-(7'-methoxy-2'ethyl)benzofuran 20 and 1-α-methoxy-6-endo-4'-(7'-methoxy-2'-ethyl)benzofuran 21 glucodifuranose (1,4:3,6): ($C_{18}O_7H_{22}$) (2/1), ^{1}H NMR 300MHz: δ 7.08-7.11 (d, 1H, H-5', $J_{5'-6'}$ = 8.3Hz), 6.67-6.70 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.47 (s, 1H, H-3'[20]), 6.37 (s, 1H, H-3'[21]), 5.20 (d, 1H, H-6[21], J_{6-5} = 7.8Hz), 5.13-5.15 , 1H, H-6 [20], J_{6-5} = 4.4Hz), 4.00-5.01(overlapping 5H from each (H-2,3,4,5,1)), 3.98 (s, 3H, H-7'MeO), 3.52 (s, 3H, 1MeO[20]), 3.51 (s, 3H, 1-MeO[21]), 2.80(q, 2H, H-1"), 1.30-1.35 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

IR: 1605(m), 1630(s), 2830(w), 2940(s), 2975(s), 3020(s), 3400(s).

MS: m/z 351(MH^+), 368(MNH_4^+).

1-β-methoxy-6-endo-4'-(7'-methoxy-2'-ethyl)benzofuranglucodifuranose (1,4:3,6) 22: ($C_{18}O_7H_{22}$), ^{1}H NMR 300MHz: δ 7.05-7.08 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.66-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.41 (s, 1H, H-3'), 4.98 (s, 1H, H-1), 4.92-4.95 (d, 1H, H-6, J_{6-5} = 8.3Hz), 4.84-4.88 (t, 1H, H-4, $J_{4-5,3}$ = 5.0Hz), 4.63-4.65 (d,1H, H-3, J_{3-4} = 4.8Hz), 4.26 (s, 1H, H-2), 4.07-4.11 (dd, 1H, H-5, J_{5-6} = 8.3Hz, J_{5-4} = 5.3Hz), 3.96 (s, 3H, 7'-MeO), 3.48 (s, 3H, 1-MeO), 2.76-2.83 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.29-1.34 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

^{1}H NOE: Irradiation at 7.05 (H-5'), enhancement at 6.65 (H-6'), 4.95 (H-6), irradiation at 6.40 (H-3'), enhancement at 4.95 (H-6), irradiation at 3.5 (H-1MeO), enhancement at , 4.95 (H-1).

IR: 1605(s), 1625(s), 2840(m), 2903(s), 2940(s), 2970(s), 3015(s), 3400(s).

MS: m/z 351(MH^+), 368(MNH_4^+).

1-β-methoxy-2,5-diacetoxy-6-endo-4'-(7'-methoxy-2'-ethyl)benzofuranglucodifuranose (1,4:3,6) 22*: ($C_{22}O_9H_{26}$), ^{1}H NMR 300MHz: δ 7.07-7.10 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.67-6.70 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.42 (t, 1H, H-3', $J_{3'-1''}$ = 0.9Hz), 5.34-5.38 (d, 1H, H-6, J_{6-5} = 9.3Hz), 5.22-5.26 (t, 1H, H-4, J_{4-3} = 5.3Hz), 5.19 (s, 1H, H-1), 5.03 (s, 1H, H-2), 4.87-4.88 (d, 1H, H-3, J_{3-4} = 5.2Hz), 4.84-4.89 (dd, 1H, H-5, J_{5-4} = 5.5Hz, J_{5-6} = 8.6Hz), 3.98 (s, 3H, 7'-MeO), 3.54 (s, 3H, 1-MeO), 2.78-2.83 (q, 2H, H-1", $J_{1''-2''}$ = 7.5Hz), 2.11, 2.09 (2s, 3H each, 2,5 OAc), 1.32-1.37 (t, 3H, H-2", $J_{2''-1''}$ = 7.5Hz).

^{1}H NOE: Irradiation at 7.10 (H-5'), enhancement at 6.65 (H-6'), 5.40 (H-6), 4.85 (H-5) irradiation at 6.42 (H-3'), enhancement at 5.40 (H-6), 4.85 (H-5), irradiation at 3.54 (H-1MeO), enhancement at , 5.05 (H-1).

^{1}H COSY: H-6(d, 5.35) coupled with H-5(dd, 4.85), H-4(t, 5.20) coupled with H-5(dd, 4.85),H-3(d, 4.88).).

IR:1610(m), 1630(s), 1750(vs), 2845(m), 2920(s), 2945(s).

MS: m/z 435(MH^+), 452(MNH_4^+).

1-α-methoxy-6-exo-4'-(7'methoxy-2'-ethyl)benzofuranidodifuranose (1,4:3,6) 23: ($C_{18}O_7H_{22}$): ^{1}H NMR 300MHz: δ 7.20-7.23 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.74-6.77 (d, 1H, H-6',$J_{6'-5'}$ = 8.2Hz), 6.46 (s, 1H, H-3'), 5.23-5.25 (d, 1H, H-1, J_{1-2} = 2.7Hz), 5.05-5.07 (d, 1H, H-6, J_{6-5} = 4.5Hz), 4.81-4.83 (dd, 1H, H-4, J_{4-5} = 2.3Hz, J_{4-3} = 4.7Hz), 4.72-4.73 (d, 1H, H-3, J_{3-4} = 4.7Hz), 4.30-4.31 (d, 1H, H-5, J_{5-6} = 2.7Hz), 4.26-4.28 (dd, H-5, J_{5-4} = 2.3Hz, J_{6-5} = 4.3Hz), 4.00 (s, 3H, H-7'MeO), 3.53 (s, 3H, H-OMe), 2.78-2.85 (q, 2H, H-1", $J_{1''-2''}$ = 7.5Hz, $J_{1''-3''}$ = 0.8Hz), 1.31-1.36 (t, 3H, H-2", $J_{2''-1''}$ = 7.5Hz).

^{1}H NOE:Irradiation at 7.23 (H-5'), enhancement at 6.80 (H-6'), 5.25 (H-1), irradiation at 6.50 (H-5'), enhancement at 6.80 (H-6'), 4.30 (H-5), 4.80 (H-4).

IR: 1605(s), 1630(s), 2395(w)< 2840(s), 2940(s), 3010(s), 3540(s).

MS: m/z 351(MH^+), 368(MNH_4^+).

Mixture of 1-β-methoxy-6-exo-4'-(7'-methoxy-2'-ethyl)benzofuran 24 and 1-α-methoxy-6-endo-4'-(7'-methoxy-2'-ethyl)benzofuran 25 idodifuranose (1,4:3,6):

($C_{18}O_7H_{22}$), (1/2.65), ^{1}H NMR 300MHz: δ 7.17-7.20 (d, H5'[25]), 7.10-7.13 (d, 1H, H-5'[24], $J_{5'-6'}$ = 8,2Hz), 6.73-6.76 (d, 1H, H-6'[25]), 6.68-6.71 (d, 1H, H-6'[24], $J_{6'-5'}$ = 8.2Hz), 6.51 (s, 1H, H-3'[24]), 6.40 (s, 1H, H-3'[25]), 5.60-5.61 (d, 1H, H-1[25], J_{1-2} = 2.9Hz), 5.15-5.17 (d, 1H, H-3[24], J_{3-4} = 4.5Hz), 4.97 (s, 1H, H-1[24]), 4.94-4.96 (d, 1H, H-6[25], J_{6-5} = 4.6Hz), 4.85-4.88 (d, 1H, H-6[24], J_{6-5} = 6.7Hz), 4.80-4.82 (d, 1H, H-3 [25], J_{3-4} = 4.5Hz), 4.70-4.73 (dd, 1H, H-4[24], J_{4-5} = 2.1Hz, J_{4-3} = 5.0Hz), 4.60-4.63 (dd, 1H, H-5[24], J_{5-4} = 1.8Hz, J_{6-5} = 4.9Hz), 4.33-4.39 (overlapping 3H[25],1H[24]), 4.00(s, 3H, H-7'MeO[25]), 3.99 (s, 3H, H-7'MeO[24]), 3.51 (s, 3H, H-1MeO[24]), 3.47 (s, 3H, H-1MeO[25]), 2.81-2.84(q, 2H from each H-1", $J_{1"-2"}$ = 7.5Hz), 1.31-1.36 (t, 3H from each, H-2", $J_{2"-1"}$ = 7.5Hz).

IR: 1605(s), 1630(s), 2840(m), 2930(s), 2975(s), 3015(s), 3415(s).

MS: m/z 351(MH^+), 368(MNH_4^+).

1-β-methoxy-6-endo-4'-(7'methoxy-2'-ethyl)benzofuranidodifuranose (1,4:3,6) 26:

($C_{18}O_7H_{22}$), ^{1}H NMR 300MHz: δ 7.05-7.08 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.85 (s, 1H, H-3'), 6.65-6.68 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 5.00 (s, 1H, H-1), 4.89-4.93 (dd, 1H, H-5, J_{5-4} = 3.5Hz, J_{5-6} = 6.2Hz), 4.58-4.61 (d, 1H, H-3, J_{3-4} = 8.6Hz), 4.49-4.51 (d, 1H, H-6, J_{6-5} = 6.3Hz), 4.40 (s, 1H, H-2), 4.21-4.26 (dd, 1H, H-4, J_{4-5} = 3.6Hz, J_{4-3} = 8.7Hz), 3.97 (s, 3H, H-7'MeO), 3.40 (s, 3H, H-MeO), 2.76-2.83 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.29-1.35 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

^{1}H NOE: Irradiation at 7.10(H-5'), enhancement at 6.85 (H-3'), 4.60 (H-3), irradiation at 6.85 (H-3'), enhancement at 4.60 (H-3), irradiation at 3.40 (H-1MeO), enhancement at 5.0 (H-1).

IR: 1605(m), 1630(s), 2830(m), 2940(s), 2970(s), 3020(s), 3400(s).

MS: m/z 351(MH^+), 368(MNH_4^+).

Mixture of the 1-methoxy-5-deoxy-6-4'-(7'methoxy-2'-ethyl)benzofuranglucodifuranose (1,4:3,6) 27, 28, 29, 30, the four isomers identified from the ^{1}H NMR 300MHz spectrum of the mixture: δ [6.37(H-3'), 3.45 (1-MeO) from 28], [6.44(H-3'), 3.49(1-MeO) from 27, 39% (28/27 = 2.2/1)], [6.53(H-3'), 3.45(1-MeO)from 29], [6.83(H-3'), 3.40(1MeO) from 30, 12% (29/30 = 1/3).

1-β-methoxy-2-acetoxy-6-exo-4'-(7'methoxy-2'-ethyl)benzofuran-5-deoxyglucodifuranose (1,4:3,6) 28*: ($C_{20}H_{24}O_7$) 91.8%: ^{1}H NMR 300MHz: δ 7.04-7.07 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.66-6.69 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.39 (s, 1H, H-3'), 5.45-5.51 (dd, 1H, H-6,J_{6-5a} = 5.4Hz, J_{6-5b} = 10.7Hz), 5.19 (s, 1H, H-1), 5.12-5.16 (t, 1H, H-4, $J_{4-3,5}$ = 5.2Hz), 4.97 (s, 1H, H-2), 4.75-4.76 (d, 1H, H-3, J_{3-4} = 4.8Hz), 3.98 (s, 3H, H-7'MeO), 3.49 (s, 3H, H-1MeO), 2.78-2.85 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.45-2.51 (dd, 1H, H-5a, J_{6-5a} = 5.4Hz, J_{5a-5b} = 13.7Hz), 2.05-2.12 (ddd, 1H, H-5b, J_{5b-4} = 5.4Hz, J_{5b-6} = 10.7Hz, J_{5b-5a}=13.9Hz), 2.12 (s, 3H, 2-OAc), 1.22-1.27 (t, 3H, H-2", $J_{1"-2"}$ = 7.5Hz).

MS: m/z 377(MH^+), 395(MNH_4^+).

1-β-methoxy-2-acetoxy-6-endo-4'-(7'methoxy-2'-ethyl)benzofuran-5-deoxyglucodifuranose (1,4:3,6) 30*: (minor in previous) identified by ^{1}H NMR 300MHz: δ such as 6.86(s, 1H, H-3'), (H-5',6' overlap with the H-5',6' of major), 5.40-5.46 (dd, 1H, H-6, J_{6-5} = 5.4Hz, J_{6-5} = 10.7Hz), 5.34 (s, 1H, H-1), 5.04-5.06(s, 1H, H-3, J_{3-4} = 4.1Hz), 4.99 (s, 1H, H-2), 4.88-4.94 (dd, 1H, H-4, J_{4-3} = 5.5Hz, J_{4-5} = 11.5hz), 3.98 (s, 3H overlap with major), 3.45 (s, 3H, 1-OMe), 2.78-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 2.50-2.62 (ddd, 1H, H-5a, J=5.4Hz, J=8.4Hz, J=13.8Hz), 2.10-2.27 (ddd, H-5b, J=5.4Hz, J=12Hz), 2.12 (s, 3H, H-2OAc overlap with major), 1.22-1.27 (t, 3H, H-2" overlap with major).

1-α-methoxy-2-acetoxy-6-exo-4'-(7'-methoxy-2'-ethyl)benzofuran-5-deoxyglucodifuranose (1,4:3,6) 27*: 91%: ^{1}H NMR 300MHz: δ 7.08-7.11 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.68-6.71 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.45 (s, 1H, H-3'), 5.24-5.26 (d, 1H, H-1, J_{1-2} = 4.3Hz), 5.14-5.20 (dd, 1H, H-6, J_{6-5} = 11.1Hz), 5.02-5.04 (dd, 1H, H-3, J_{3-2} = 3.5Hz, J_{3-4} = 5.2Hz), 4.94-4.97 (t, 1H, H-2, J_{2-1} = 4.1Hz, J_{2-3} = 3.9Hz), 4.89-4.91 (t, 1H, H-4, J=5.4Hz), 3.99 (s, 3H, 7'-MeO), 3.41(s, 3H, H-1MeO), 2.78-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.7Hz), 2.14 (s, 3H, H-2OAc), 1.32-1.37 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz), 2.38-2.44 (dd, 1H, H-5a, J_{5a-6} = 4.7Hz, J_{5-5} = 13.6Hz), 1.93-2.03 (ddd, 1H, H-5b, J_{5-6} = 5.4Hz, J_{5-5} = 13.7Hz).

IR (mix. of [8(29, 30)]: 1610(m), 1630(s), 1740(vs), 2840(w), 2930(s), 2980(s), 3020(s).

1-methoxy-2-pivaloyloxy-5-deoxy-6-4'-(7'-methoxy-2-ethyl)benzofuranglucodifuranose 40, 41, 42, 43: ($C_{23}H_{30}O_7$), 91.3%: Mixture of 4 diastereomers identified from the ^{1}H NMR spectrum of the mixture: [6.89(H-3') from 43), [6.54(H-3') from 42, 43/42 = 4/1], (β-Ar, 4/1), [6.46(H-3') from 41], [6.40(H-3') from 40 (41/40 = 1/2.34).

IR: 1605(m), 1630(s), 1735(s), 2870(m), 2930(s), 2980(s).

MS: m/z 419(MH^+), 437(MNH_4^+).

General procedure for the methylation of the idodifuranose diols 23, 24, 25, 26: A solution of the diol **23** (0.16g, .46mmol) in THF (5mL) was added dropwise using a pressure equilibrium addition funnel, into a suspension of NaH in THF (5mL) (made from 0.1g 80% NaH suspension, 3.3mmol, commercially available, after washing 3 times with petroleum ether). The solution after the initial gas release was refluxed for 30min under N_2. The reaction was cooled to room temperature and MeI (1.14g, 8.0mmol, 0.5mL) was added. It was stirred for an hour and quenched with water (35mL). The reaction solution was extracted with ether (3 times, 25mL each). The ether extracts were combined and washed with water (25mL), dried over $MgSO_4$ and

concentrated. After column chromatography the trimethylated product **44** (0.13g, 75.2%) was obtained.

1-α-2,5-trimethoxy-6-exo-4'-(7'-methoxy-2'-ethyl)benzofuranidodifuranose (1,4:3,6) 44: ($C_{20}H_{26}O_7$), 75.2%, ^{1}H NMR 300MHz: δ 7.21-7.25 (d, 1H, H-5', $J_{5'-6'}$ = 8.0Hz), 6.72-6.75 (d, 1H, H-6', $J_{6'-5'}$ = 8.3Hz), 6.49 (s, 1H, H-3'), 5.13(s, 1H, H-1), 5.08-5.09 (d, 1H, H-6, J = 4.0Hz), 4.90-4.93 (d, 1H, H-3, J = 4.8Hz), 4.73-4.75 (d, 1H, H-4, J = 5.2Hz), 4.00 (s, 3H, H-7'MeO), 3.87 (2H, overlapping H-5, H-2), 3.50, 3.52 (2s, 3H each, 1,2-MeO), 3.00 (s, 3H, 5-MeO), 2.80 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.38 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

IR: 1605(s), 1630(s), 2830(s), 2930(s).

MS: m/z 379(MH^+), 396(MNH_4^+).

1-β-2,5-trimethoxy-6-exo-4'-(7'-methoxy-2'-ethyl)benzofuranidodifuranose (1,4:3,6) 45: ($C_{20}H_{26}O_7$), 83.3%: ^{1}H NMR 300MHz: δ 7.16-7.19 (d, 1H, H-5', $J_{5'-6'}$ = 8.3Hz),6.69-6.72 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.43 (s, 1H, H-3'), 5.48-5.50 (d, 1H, H-6, J_{6-5} = 3.4Hz), 5.00 (s, 1H, H-1), 4.88-4.90 (d, 1H, H-4, J_{4-3} = 4.9Hz), 4.82-4.84 (d, 1H, H-3, J_{3-4} = 4.8Hz), 3.97 (s, 3H, 7'-MeO), 3.90-3.92 (d, 1H, H-5, J_{5-6} = 3.5Hz), 3.86 (s, 1H, H-2), 3.46, 3.48, 3.00 (s, 3H each, 1,2,5 MeO), 2.78-2.86 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.31-1.37 (t, 3H, H-2", $J_{1"-2"}$ = 7.5Hz).

^{1}H NOE: Irradiation at 7.18 (H-5'), enhancement at 6.70 (H-6'), 5.50 (H-6), irradiation at 6.43 (H-3'), enhancement at 5.5o (H-6), irradiation at 3.5 (H-1MeO), enhancement at , 5.50 (H-6), 5.0 (H-1).

MS: m/z 379(MH^+), 396(MNH_4^+).

1-α-2,5-trimethoxy-6-endo-4'-(7'-methoxy-2'-ethyl)benzofuranidodifuranose(1,4: 3,6) 46: ($C_{20}H_{26}O_7$), 83.3%: ^{1}H NMR 300MHz: δ 7.13-7.16 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.69-6.72 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 6.52 (s, 1H, H-3'), 5.24-5.26 (d, 1H, H-6, J_{6-5} = 4.5Hz), 4.90-4.93 (d, 1H, H-1, J_{1-2} = 7.4Hz), 4.70-4.73 (dd, 1H, H-3, J_{3-2} = 2.5Hz, J_{3-4} = 5.6Hz), 4.77-4.80 (dd, 1H, H-4, J_{4-3} = 2.1Hz, J_{4-5} = 5.7Hz), 4.00 (s, 3H, 7'-MeO), (4.0

overlapping 2H), 3.50 (s, 6H, 2 Me, 1,2,MeO), 3.34 (s, 3H, 5-MeO), 2.8 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz), 1.30-1.40 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

1-β-2,5-trimethoxy-6-endo-4'-(7'-methoxy-2'-ethyl)benzofuranidodifuranose (1,4: 3,6) 47: ($C_{20}H_{26}O_7$), 79.4%, ^{1}H NMR 300MHz: δ 7.10-7.13 (d, 1H, H-5', $J_{5'-6'}$ = 8.2Hz), 6.89 (t,1H, H-3', $J_{3'-1"}$ = 1.0Hz), 6.67-6.70 (d, 1H, H-6', $J_{6'-5'}$ = 8.2Hz), 5.10 (s, 1H, H-1), 4.89-4.92 (dd, 1H, H-4, J_{4-3} = 3.4Hz, J_{4-5} = 6.3Hz), 4.70-4.73 (d, 1H, H-6, J_{6-5} = 8.5Hz), 4.61-4.63 (d, 1H, H-3, J_{3-4} = 6.3Hz), 4.00 (s, 1H, H-2), 3.98 (s, 3H, H-7'MeO), 3.88-3.93 (dd, 1H, H-5, J_{5-4} = 3.4Hz, J_{5-6} = 8.5Hz), 3.34, 3.45, 3.49 (3s, 3H each 3-Me groups), 2.79-2.87 (q, 2H, H-1", $J_{1"-2"}$ = 7.5Hz, $J_{1"-3'}$ = 0.9Hz), 1.32-1.38 (t, 3H, H-2", $J_{2"-1"}$ = 7.5Hz).

^{1}H NOE: Irradiation at 7.12 (H-5'), enhancement at 6.70 (H-6'), 4.75 (H-6), 3.35 (H-5MeO) irradiation at 6.90 (H-3'), enhancement at 4.0 (H-7'MeO), irradiation at 3.5 (H-1MeO), enhancement at , 5.10 (H-1), irradiation at 3.45 (H-2MeO), enhancement at , 4.00 (H-2), irradiation at 3.35 (H-5MeO), enhancement at , 4.90 (H-4).

IR: 1605(s), 1630(s), 2395(w), 2840(s), 2940(s), 3020(s), 3125(w).

MS: m/z 379(MH^+), 396(MNH_4^+).

General procedure for the hydrolysis of the 1-methyl glycosides: A solution of the 1-methyl glycoside **44** (0.13g, 0.34mmol) in acetic acid (5mL, 80%) was heated under stirring at 80°C. The reaction was monitored with TLC ($CHCl_3$). After heating for 48 hrs the trimethylated substrate was completely consumed. The solvent was evaporated under reduced pressure. The residue was dissolved in ether (50mL). The ether solution was washed with water (25mL), aqueous $NaHCO_3$ (sat. sol., 20mL), and water (20mL), dried over $MgSO_4$ and concentrated. After column chromatography on the residue the mixture of hemiacetals **48** (0.08g, 64%) was obtained.

1-α-acetoxy-5-deoxy-6-4'-(2'-ethyl-7'-methoxy)benzofuran)glucodifuranose (1,4: 3,6) 38: ($C_{19}H_{22}O_7$), ^{1}H NMR 300MHz: two major isomers δ 2.16, 2.13 (1-Ac), (1.7/1.2).

MS: m/z 362(MH^+), 380(MNH_4^+).

6-4'-(2'-ethyl-7'-methoxy)benzofuran-5-deoxyglucodifuranose (1,4:3,6):

($C_{17}H_{20}O_6$), ^1H NMR 300MHz: three isomers.

MS: m/z 321(MH^+), 338(MNH_4^+).

IR: 1600(s), 1625(s), 1720(s), 2925(s), 3010(s), 3350(s).

2,5-dimethoxy-6-(exo, endo)-4'-(7'-methoxy-2'-ethyl)benzofuranidodifuranose (1,4: 3,6) 48: mixture of 4 isomers judged from the H-3' δ = 6.73, 6.50, 6.46, 6.45.

($C_{19}H_{24}O_7$), MS: m/z 365(MH^+), 382(MNH_4^+).

Oxidation of the idose-hemiacetal to the lactone: The hemiacetal **48** (0.060g, 0.17mmol) was dissolved in Ac_2O (1mL) and DMSO (1mL). The solution was stirred at room temperature overnight. It was diluted with water (25mL) and extracted with CH_2Cl_2 (four times, 15mL each). The CH_2Cl_2 extracts were combined and washed repeatedly with water (4x15mL), dried over $MgSO_4$ and concentrated. The product (0.030g, 50.2% mixture of the isomeric lactones **49/50** = 2.6/1) was isolated by column chromatography ($CHCl_3$).

Mixture of 2,5-dimethoxy-6-endo-4'-(7'-methoxy-2'-ethyl)benzofuranidodifurano-1-lactone 49 and 2,5-dimethoxy-6-exo-4'-(7'-methoxy-2'-ethyl)benzofuranidodifurano -1-lactone 50: ($C_{19}H_{22}O_7$), (49/50 = 2.65/1) 50.2%, ^1H NMR 300MHz: δ 7.14-7.17 (d, 1H, H-5'[50], $J_{5'-6'}$ = 8.3Hz), 7.06-7.09 (d, 1H, H-5'[49], $J_{5'-6'}$ = 8.2Hz), 6.71-6.75 (d, 1H, H-6'[50], $J_{6'-5'}$ = 8.2Hz), 6.69-6.71 (d, 1H, H-6'[49], $J_{6'-5'}$ = 8.2Hz), 6.41 (t, 1H, H-3'[50], $J_{3'-1'}$ = 1.0Hz), 6.36 (t, 1H, H-3'[49], $J_{3'-1'}$ = 1.0Hz), 5.23-5.24 (d, 1H, H-2[50], J_{2-3} = 3.2Hz), 5.16-5.18 (d, 1H, H-6[50], J_{6-5} = 3.9Hz), 5.09-5.10 (dd, 1H, H-6[49], $J_{6-3'}$ = 1.0Hz, J_{6-5} = 4.3Hz), 4.92-4.94 (d, 1H, H-2[49], J_{2-3} = 6.4Hz), 4.88-4.90 (d, 1H, H-5[50], J_{5-6} = 4.1Hz), 4.68-4.69 (d, 1H, H-5[49], J_{5-6} = 4.3Hz), 3.93-4.07 (overlapping 2H of each, H-3,4), 3.99 (s, 3H, 7'-MeO(b)), 4.00 (s, 3H, 7'-MeO)3.64 (s, 3H from [50], 3H from [49], 2-MeO), 3.40 (s, 3H from [49], 5-MeO), 3.00 (s, 3H from [50], 5-MeO), 2.78-

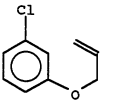
2.86 (q, 2H from each, H-1", $J_{1"-2"}$ = 7.5Hz, $J_{1"-3"}$ = 0.9Hz), 1.34 (t, 3H from each, H-2", $J_{1"-2"}$ = 7.5Hz).

^{1}H COSY: H-2[50](d, 5.23) coupled with H-3[50](dd, 4.05), H-6[50](d, 5.16) coupled with H-5[50](d, 4.90), H-6[49](dd, 5.10) coupled with H-5[49](d, 4.67), H-2[49](d, 4.92) coupled with H-3[49](dd, 4.05).

IR: 1600(m), 1625(s), 1790(vs), 2830(m), 2900(m), 2930(s), 3005(s).

MS: m/z 363(MH^+), 380(MNH_4^+).

Appendix



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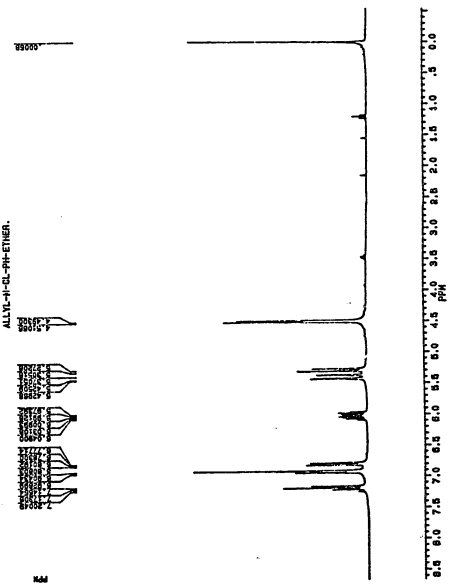

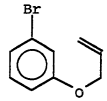

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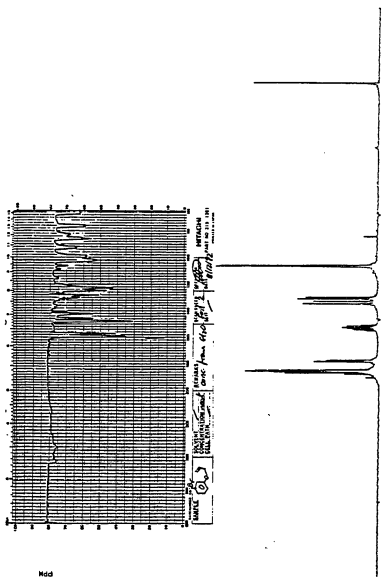

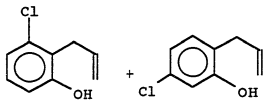

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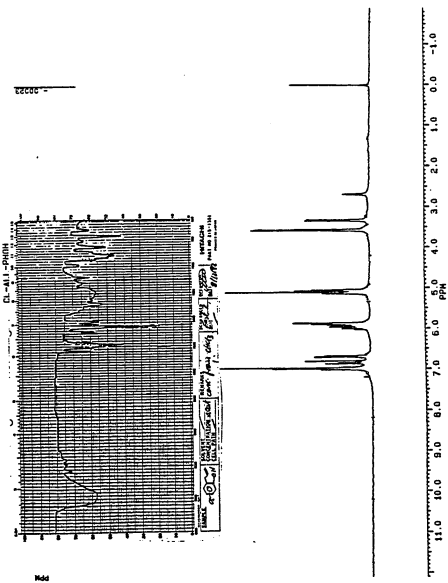

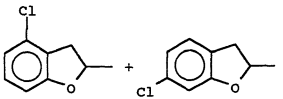

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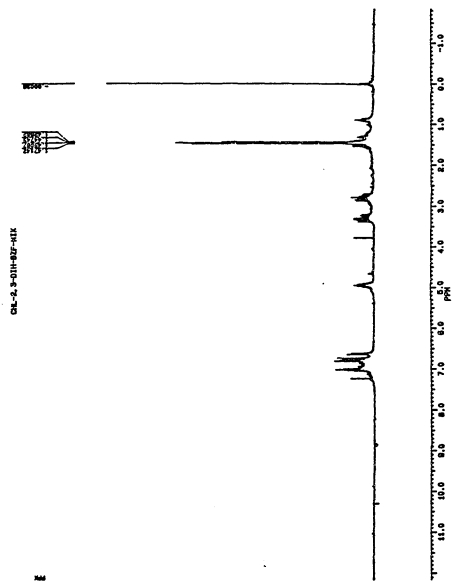

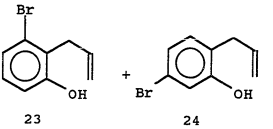

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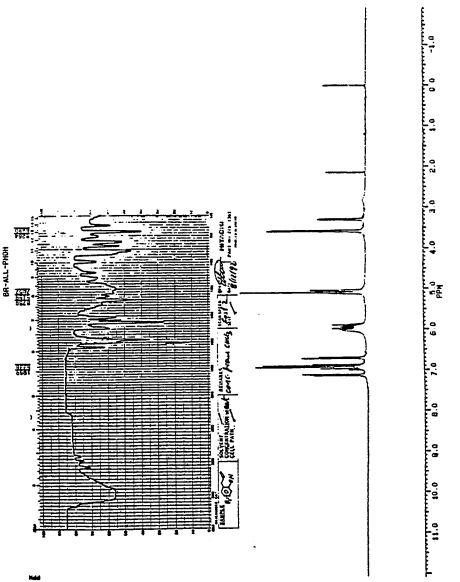

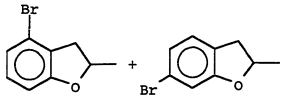

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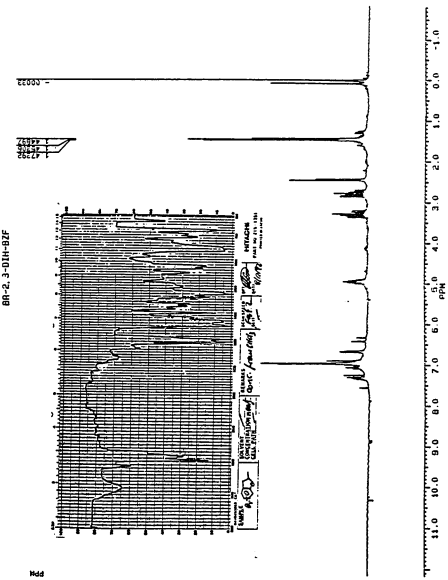

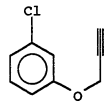

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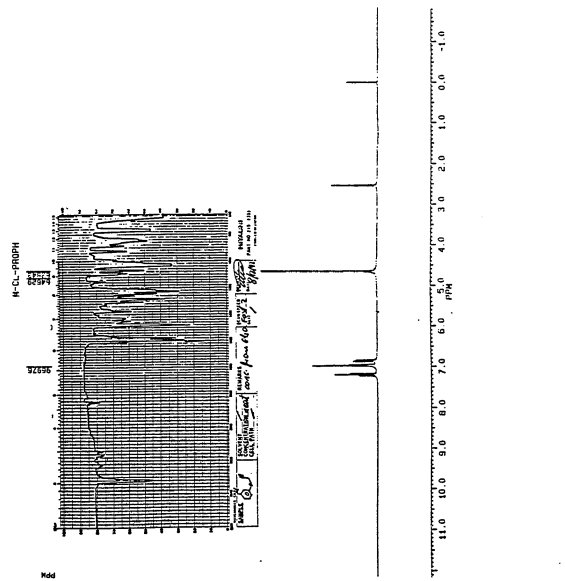

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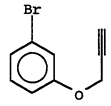

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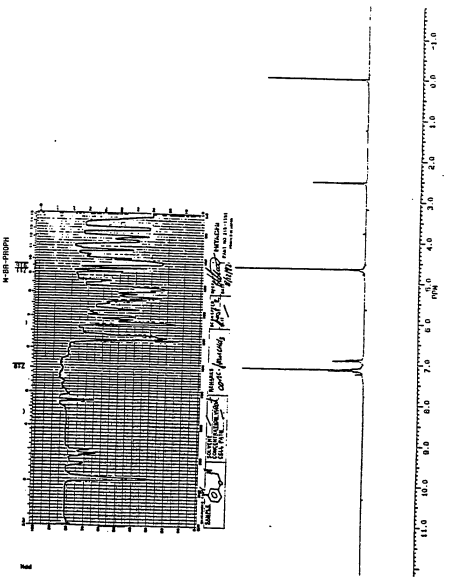

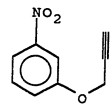

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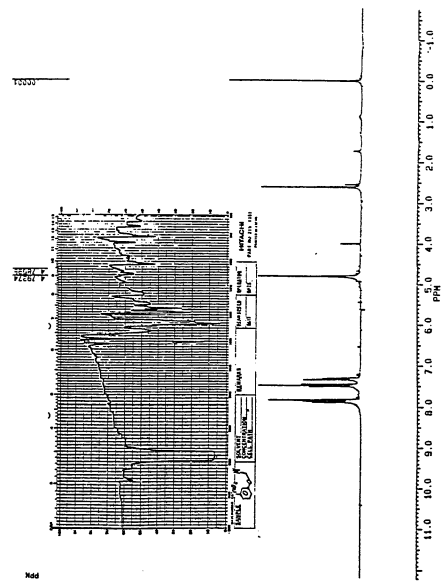

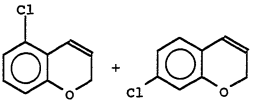

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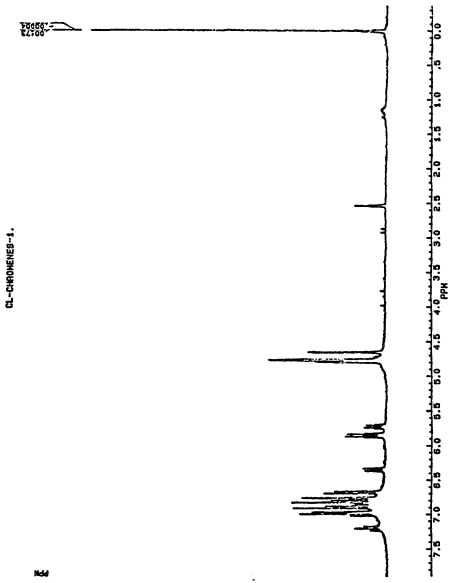

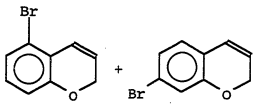

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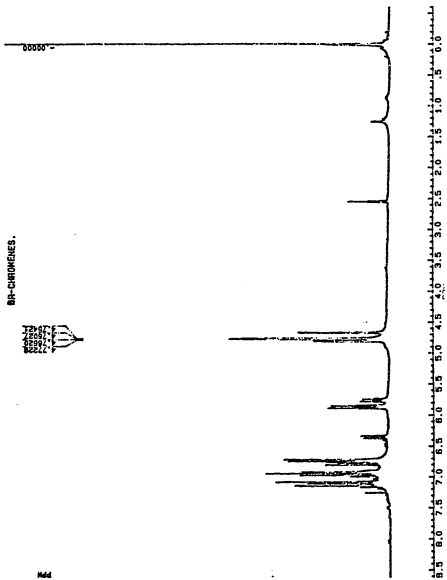

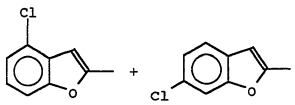

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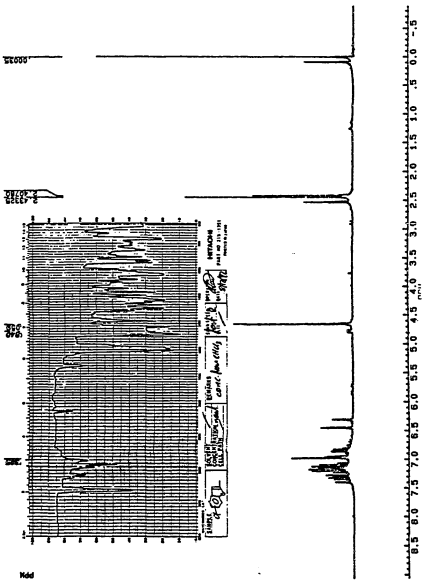

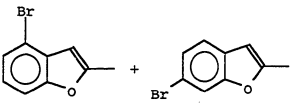

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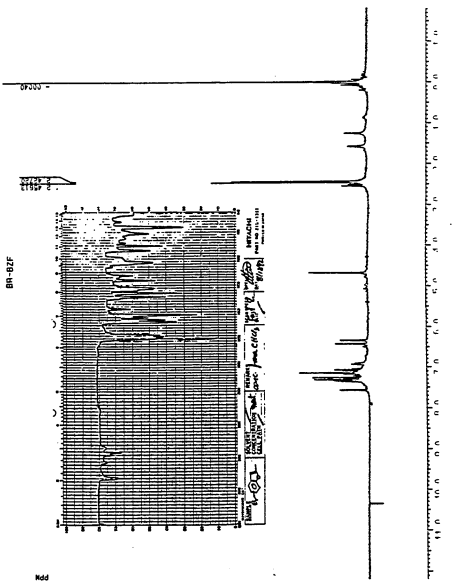

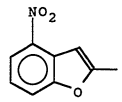

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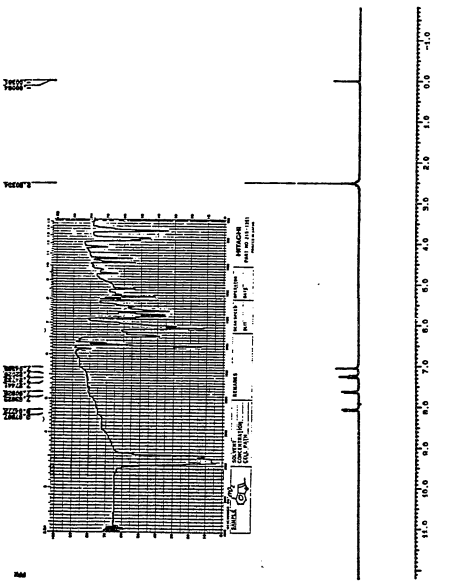

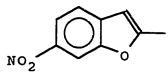

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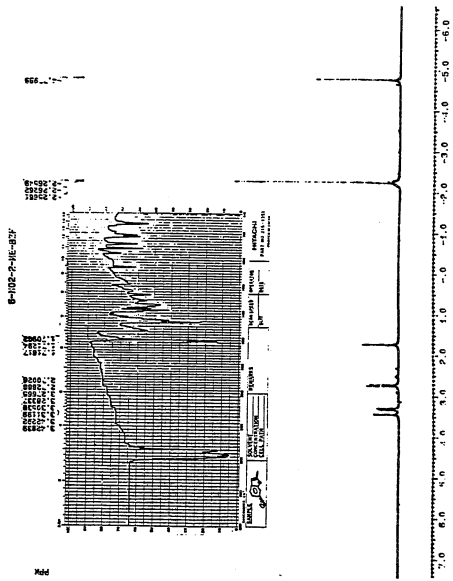

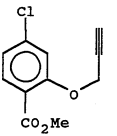

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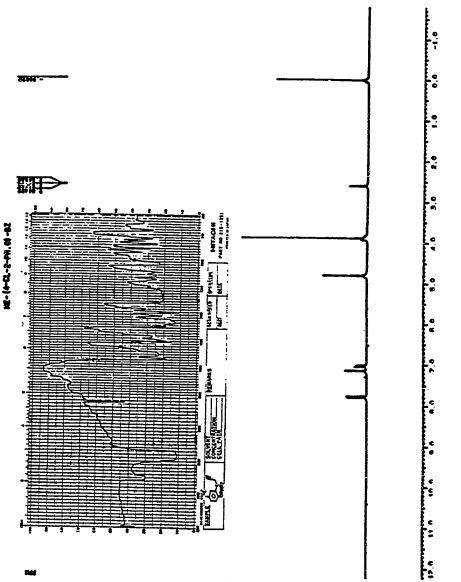

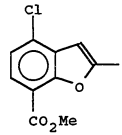

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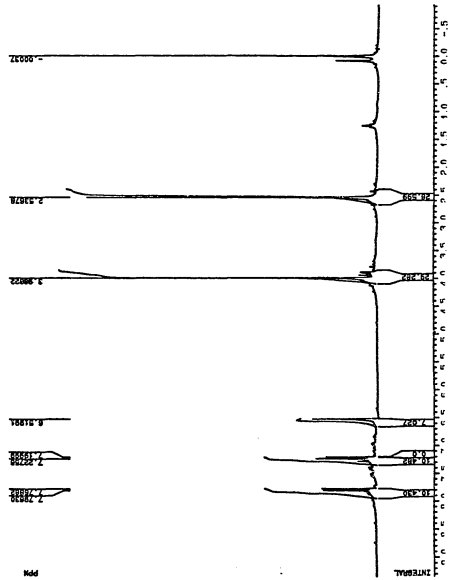

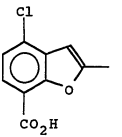

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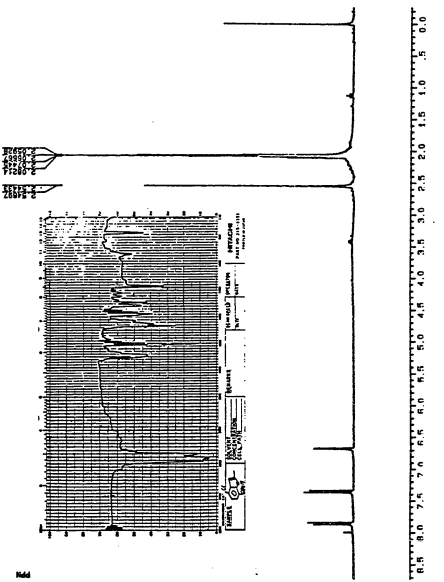

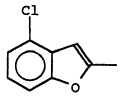

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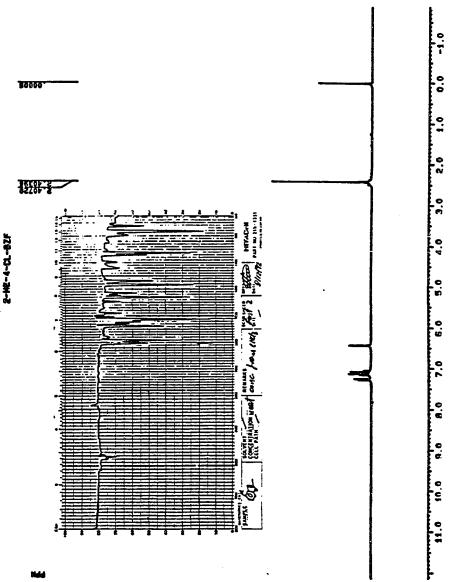

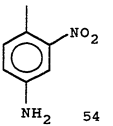

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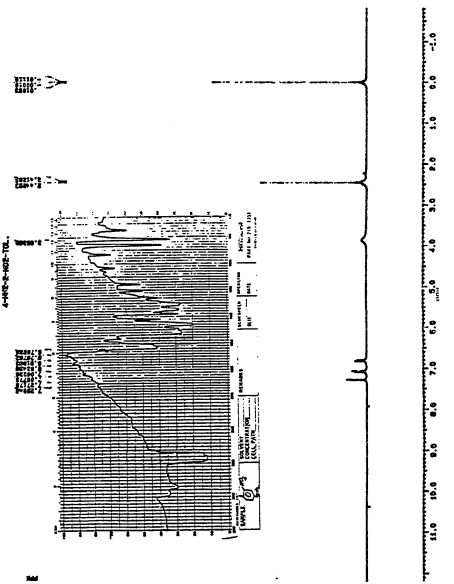

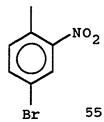

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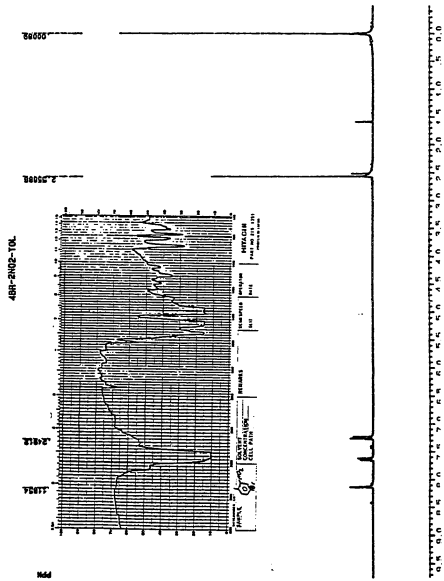

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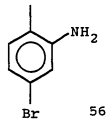

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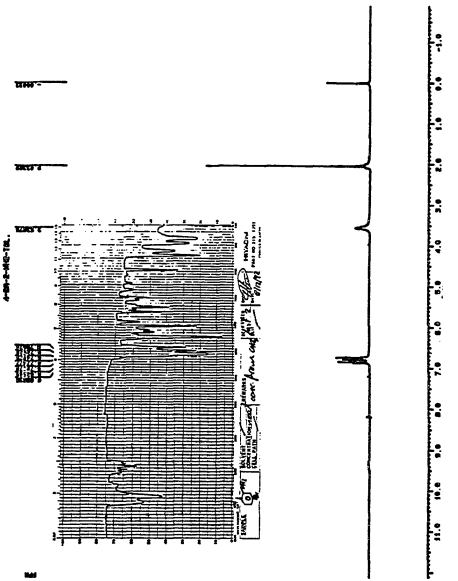

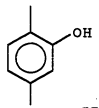

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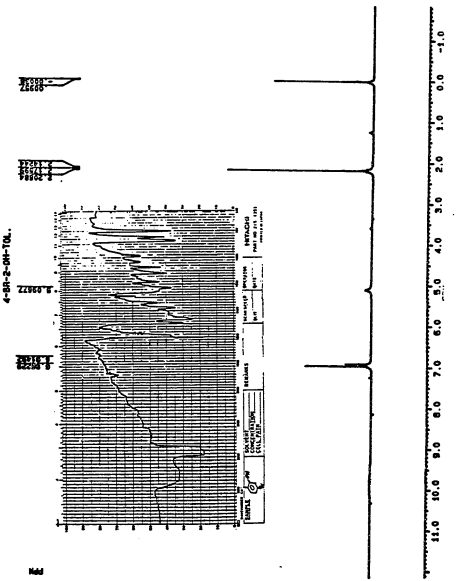

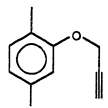

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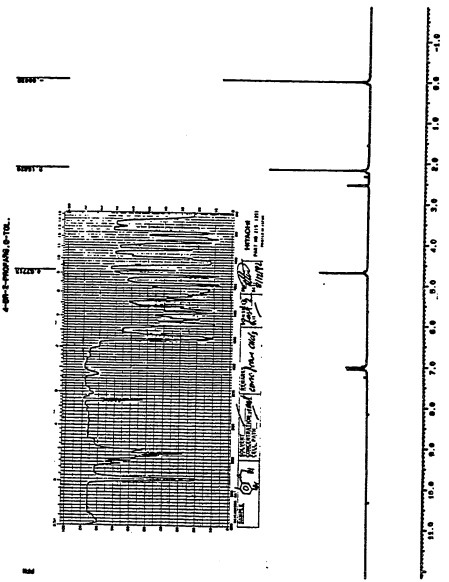

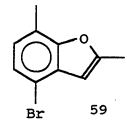

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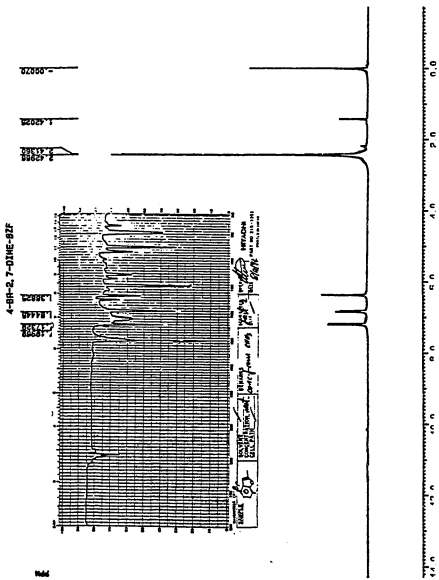

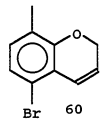

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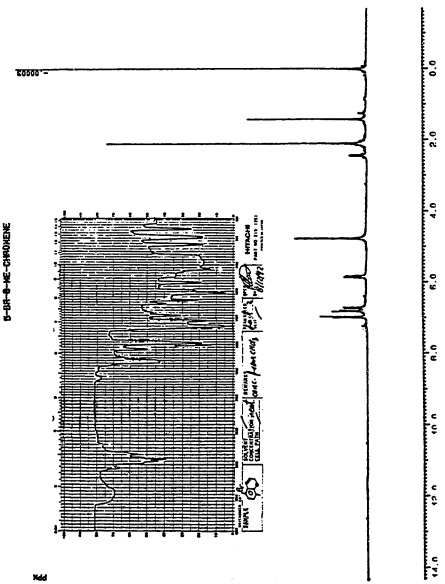

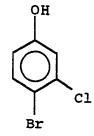

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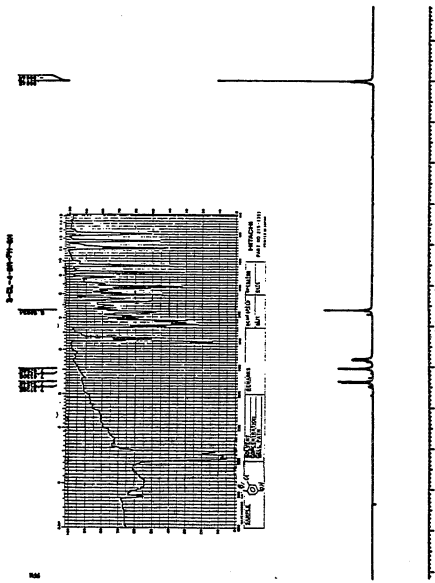

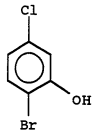

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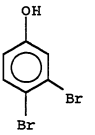

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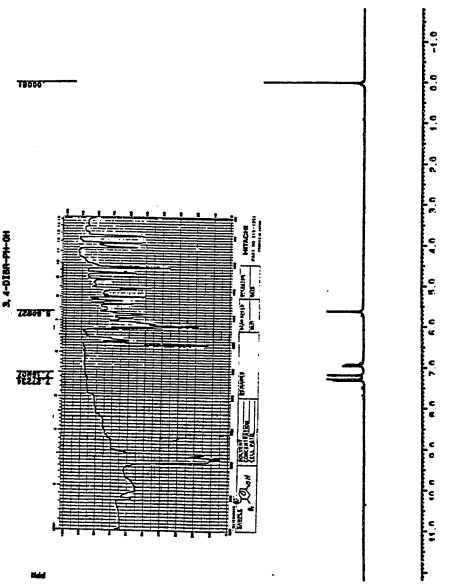

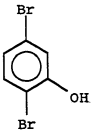

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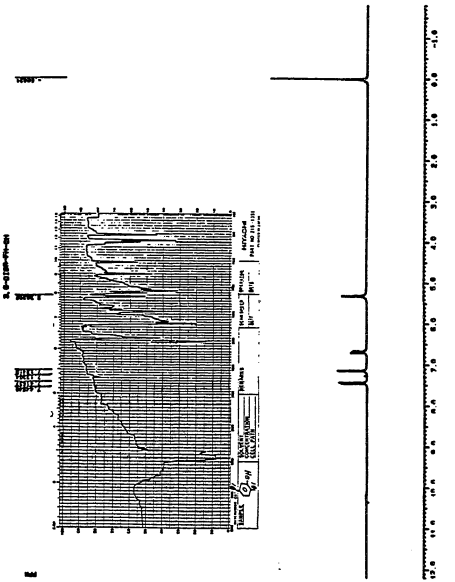

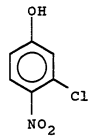

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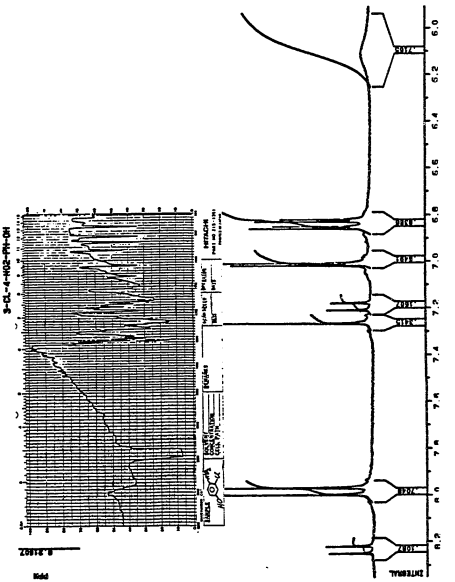

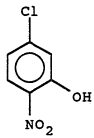

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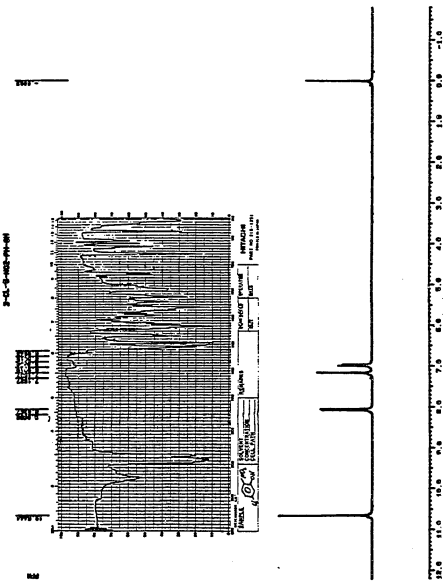

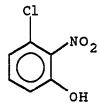

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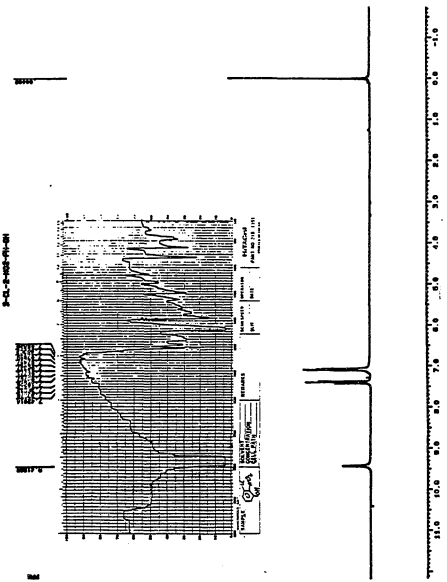

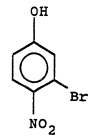

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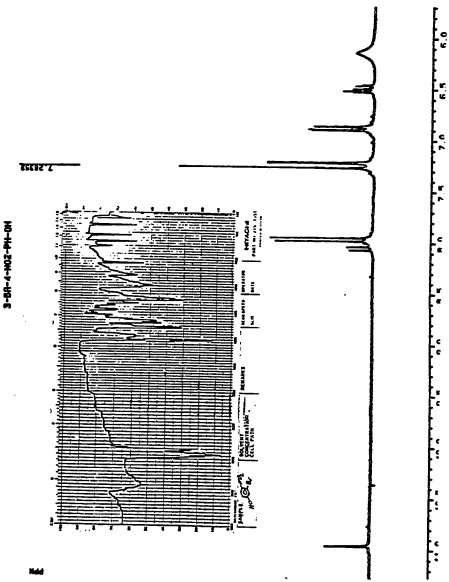

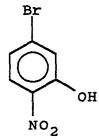

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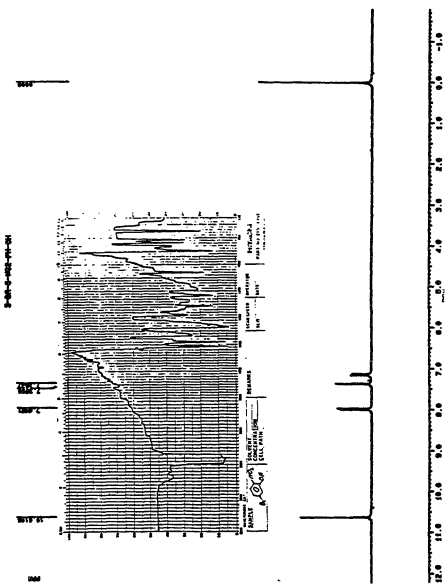

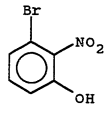

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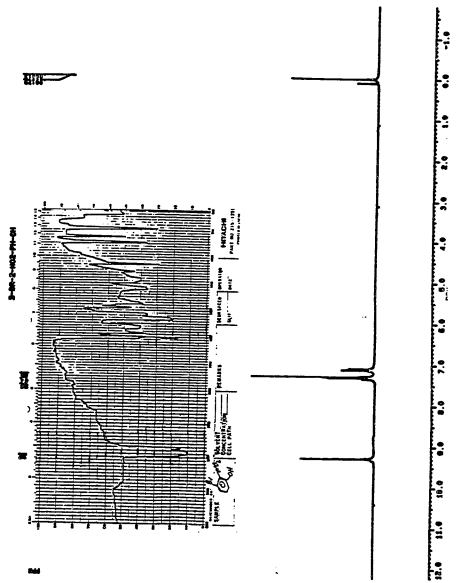

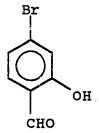

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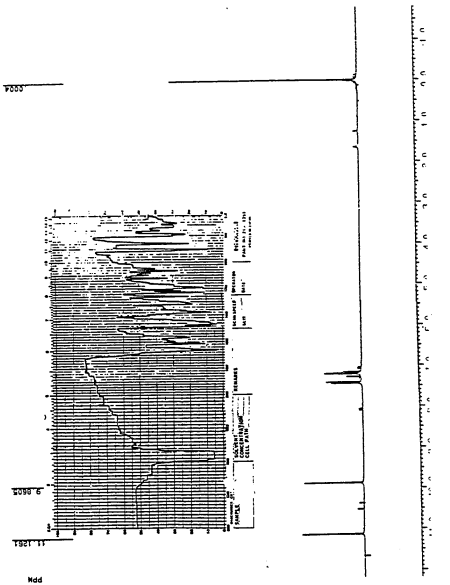

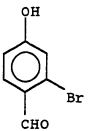

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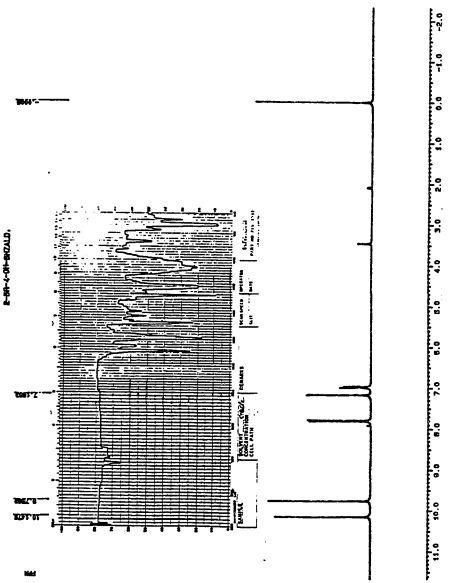

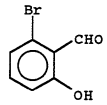

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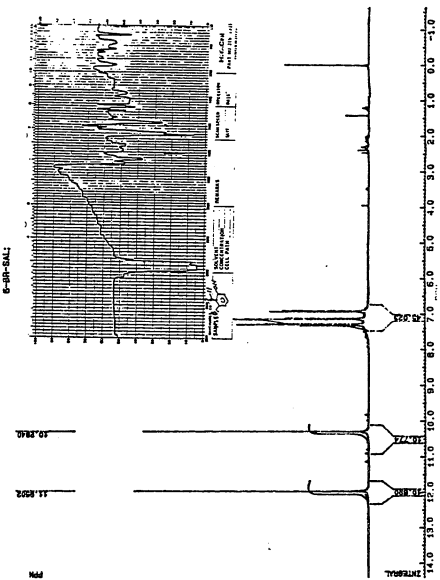

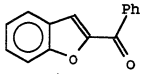

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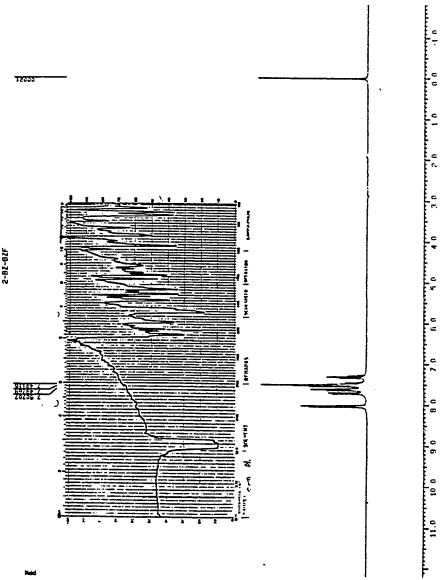

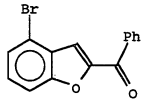

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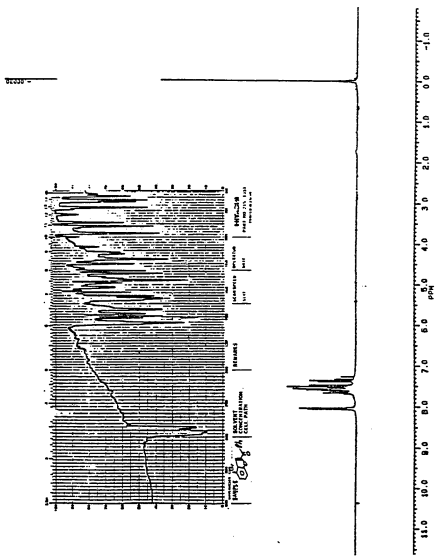

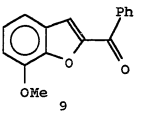

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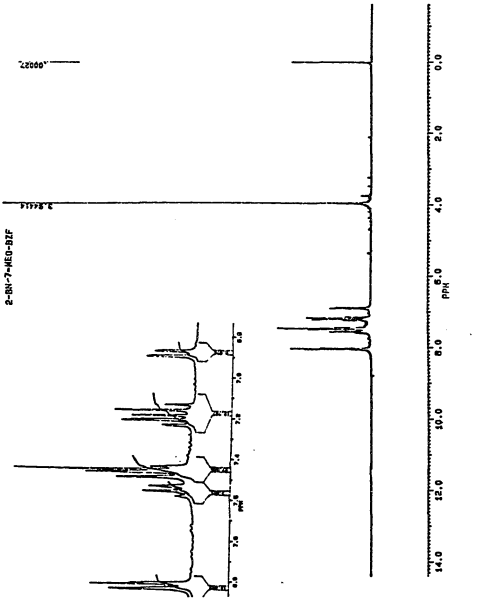

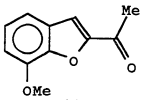

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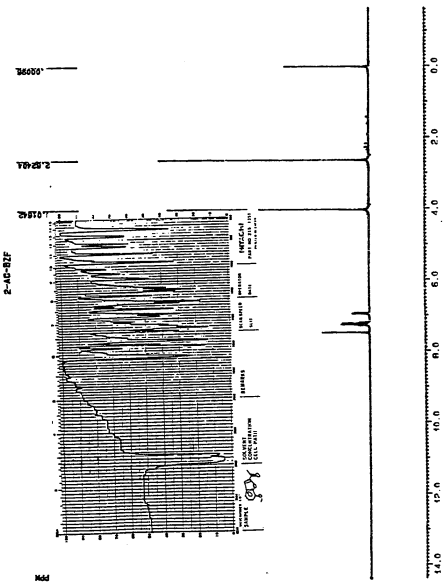

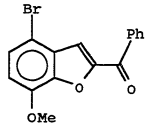

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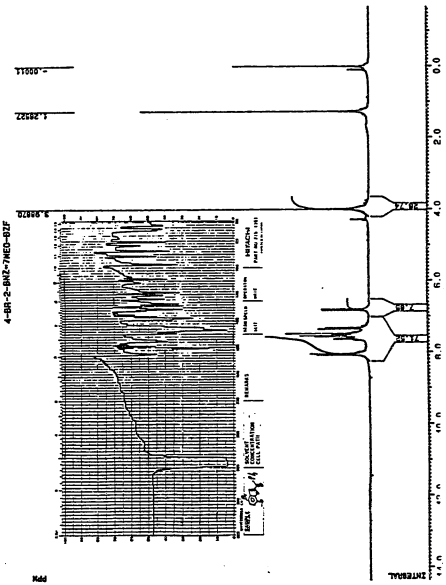

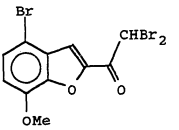

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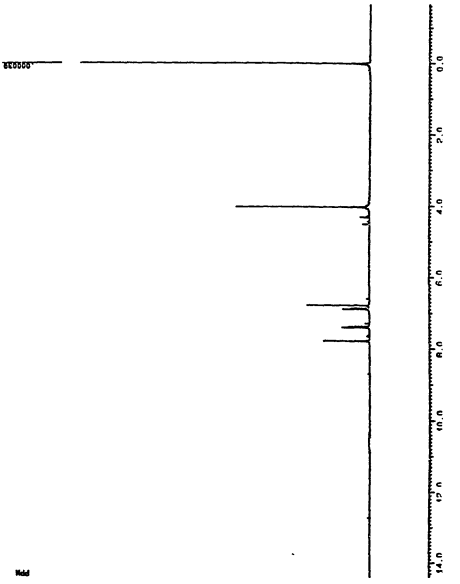

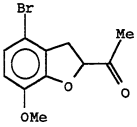

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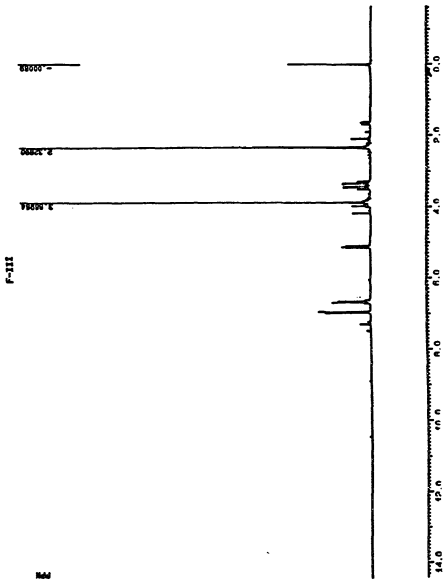

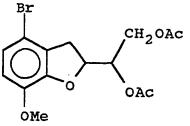

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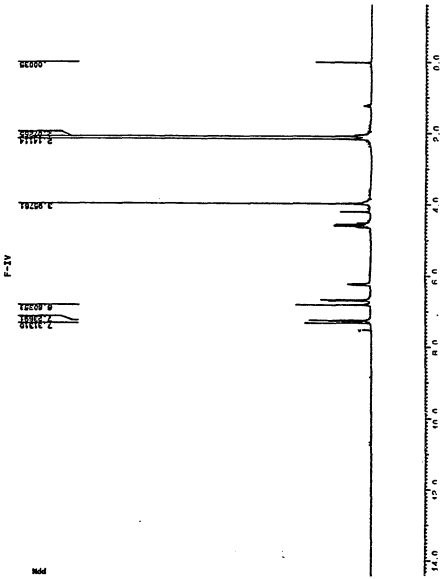

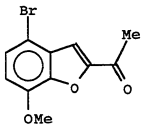

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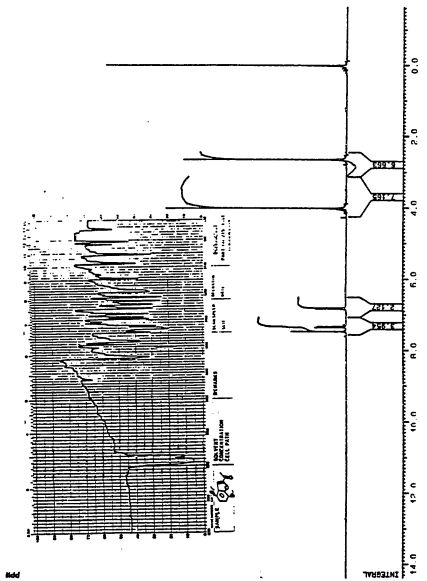

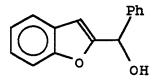

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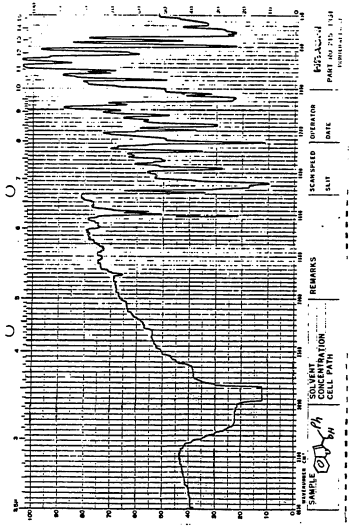

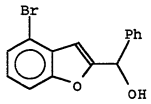

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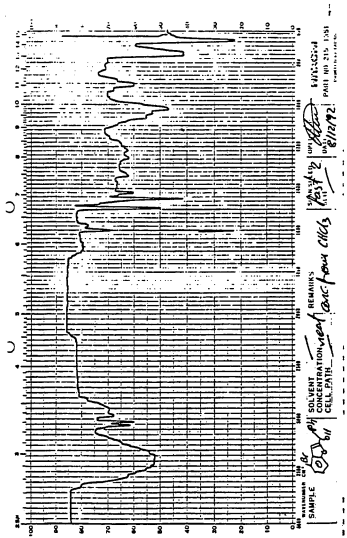

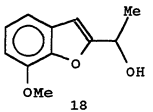

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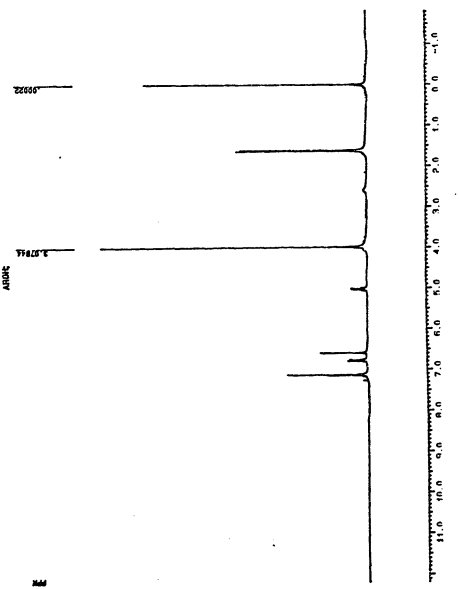

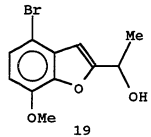

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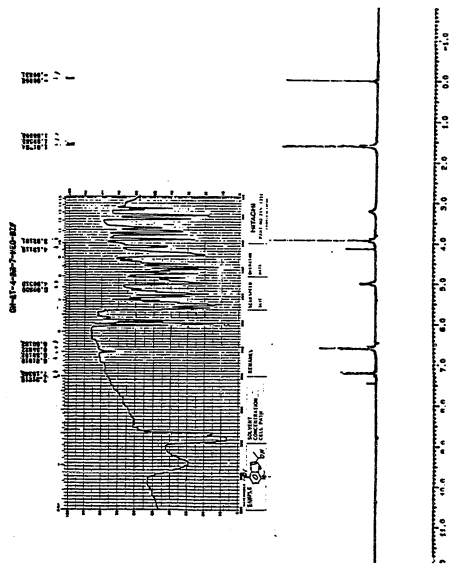

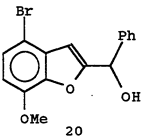

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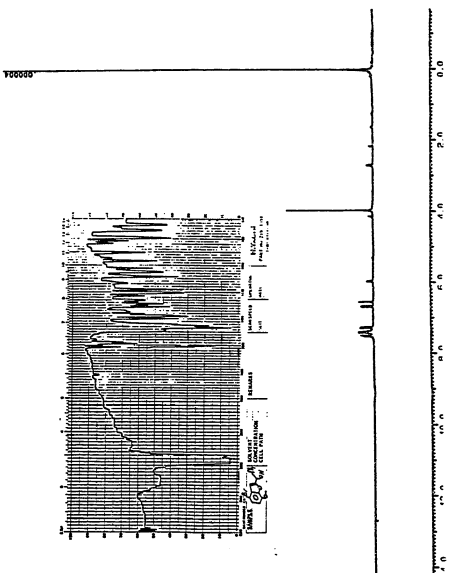

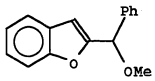

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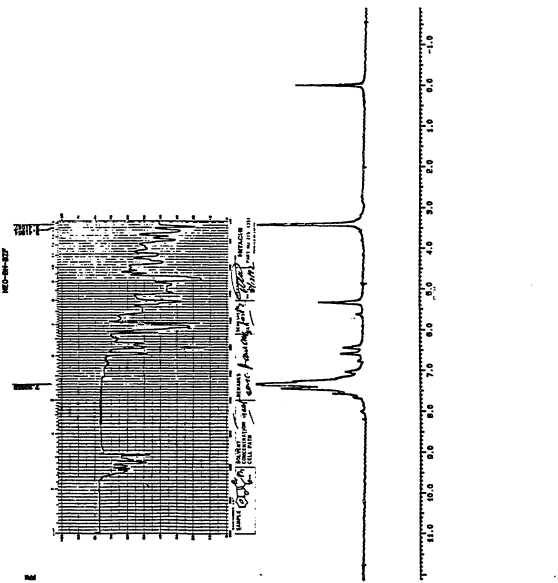

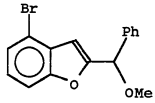

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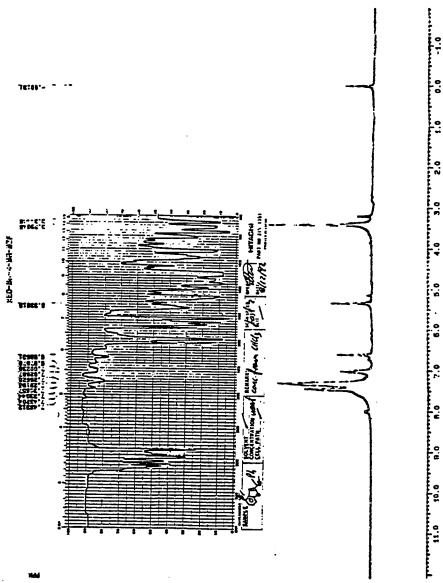

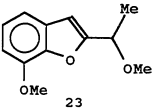

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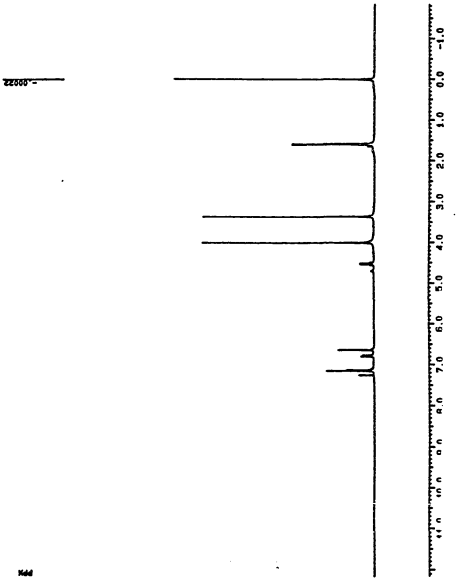

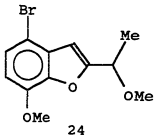

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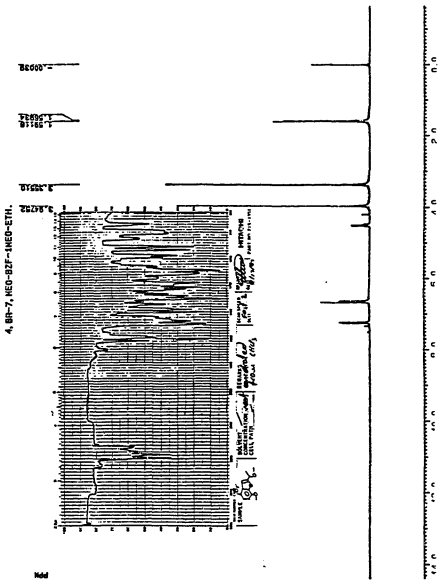

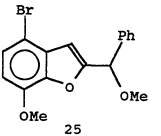

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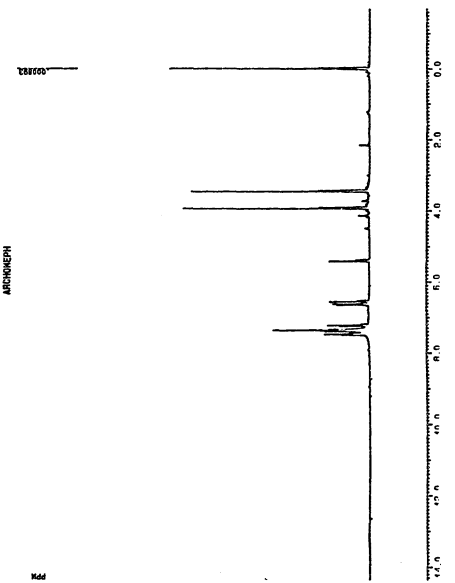

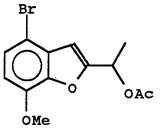

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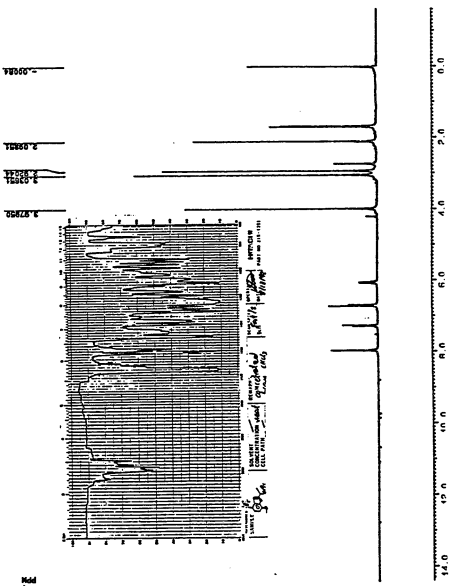

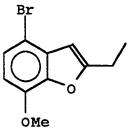

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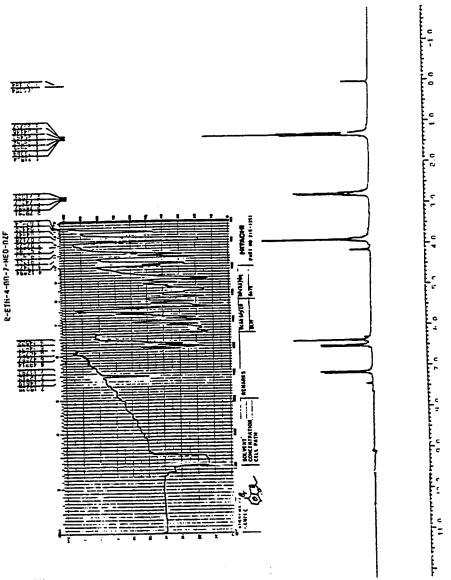

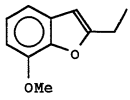

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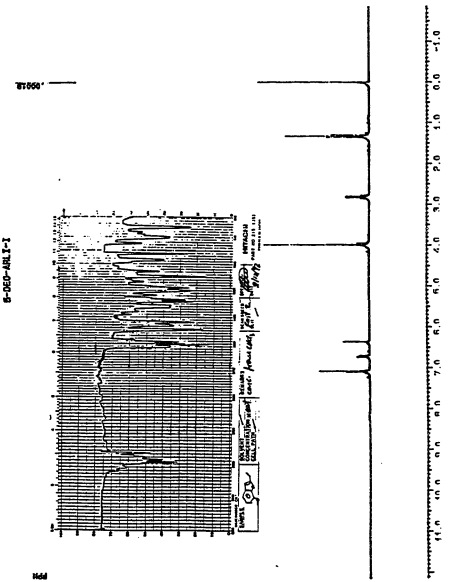

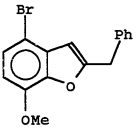

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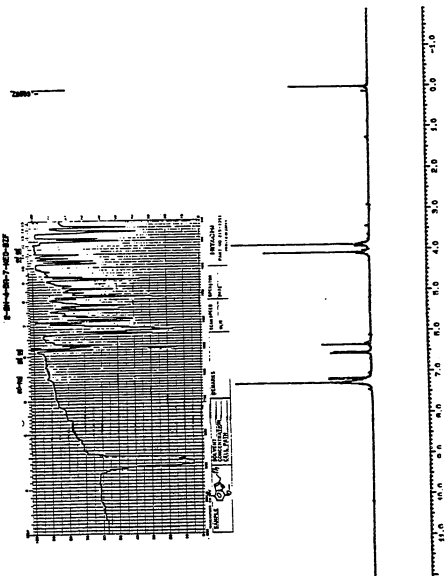

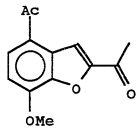

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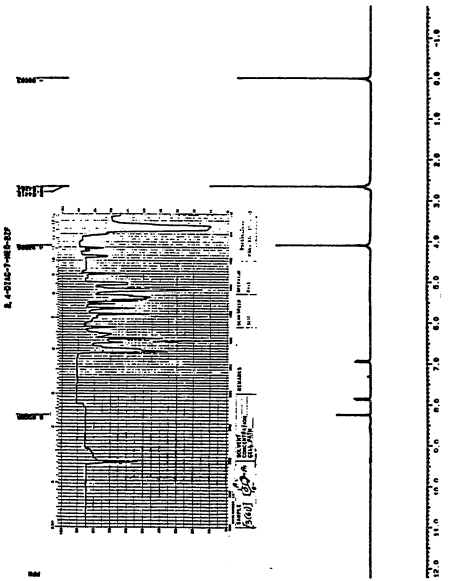

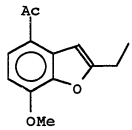

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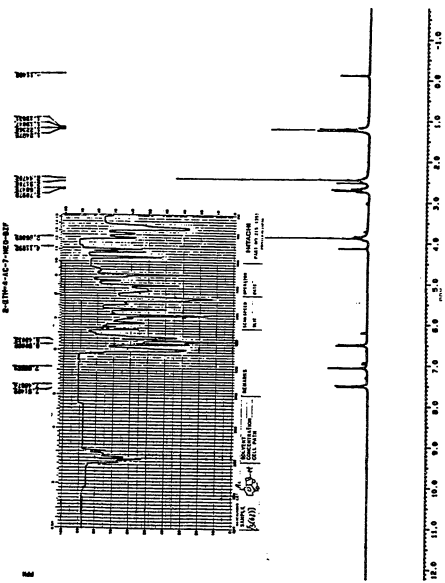

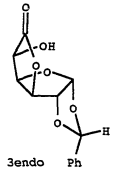

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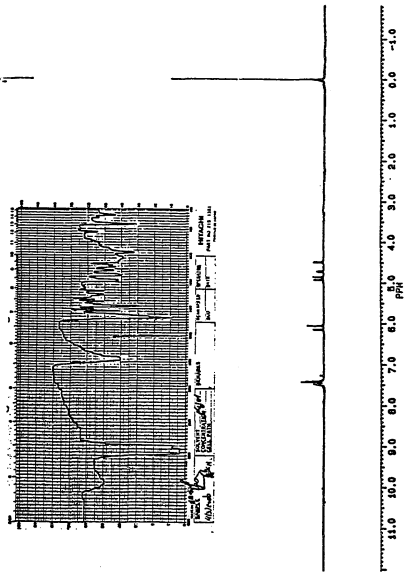

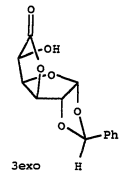

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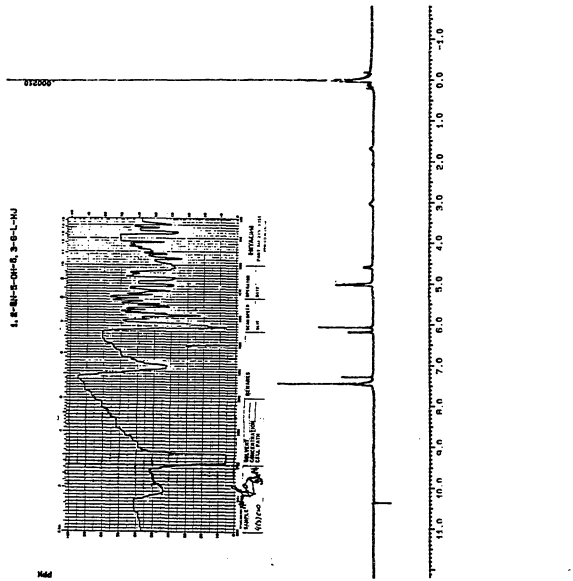

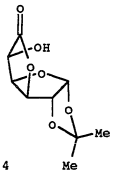

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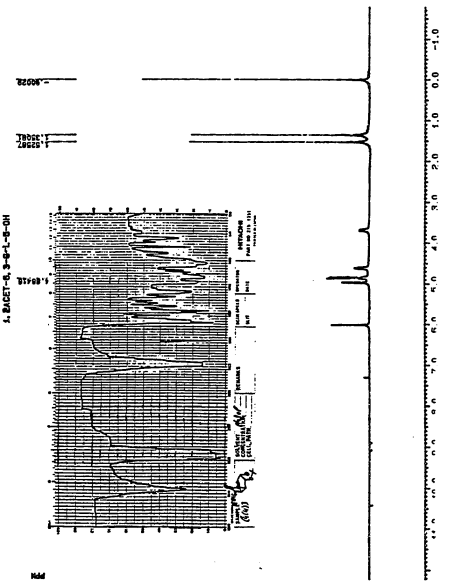

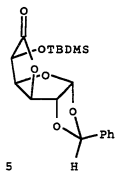

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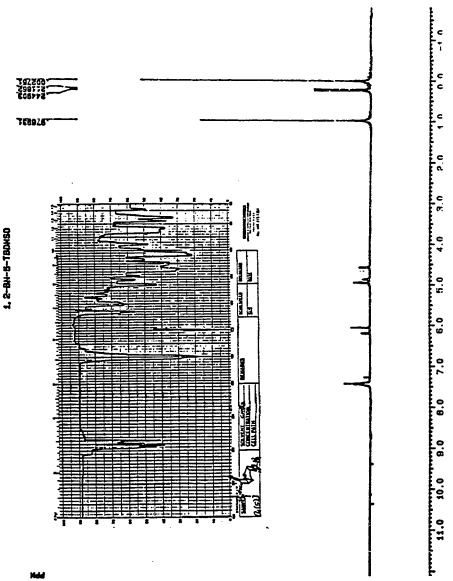

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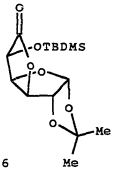

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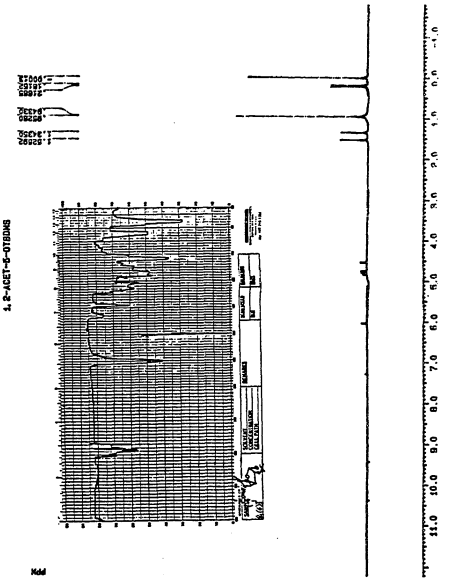

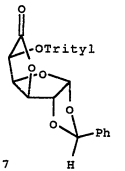

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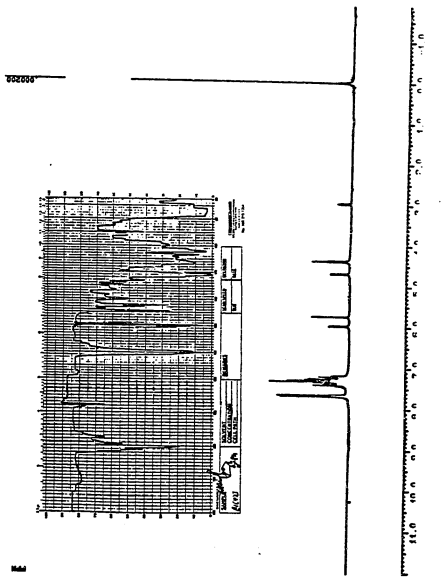

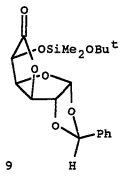

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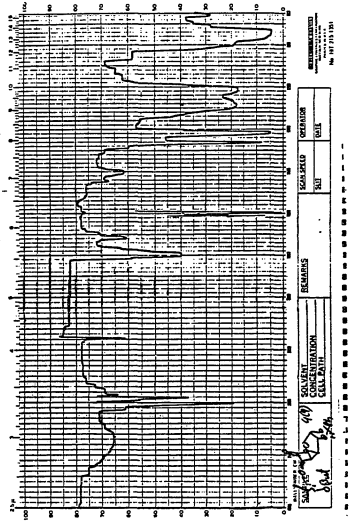

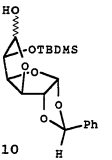

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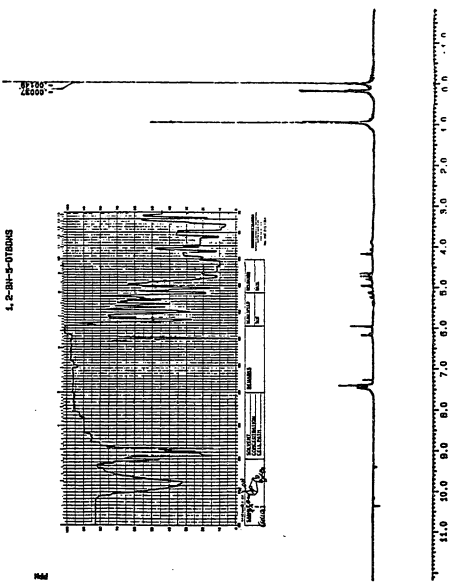

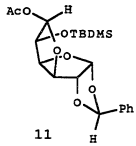

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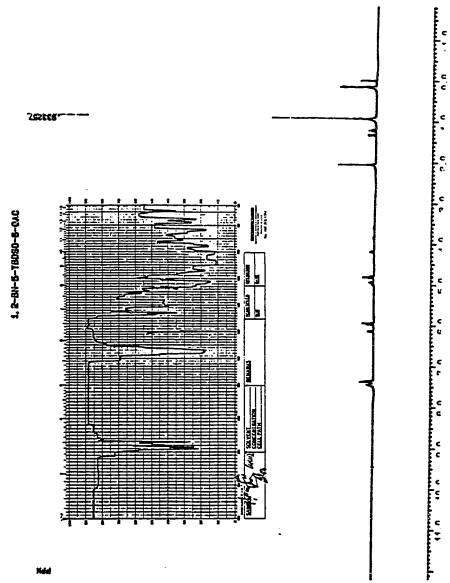

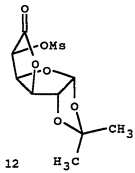

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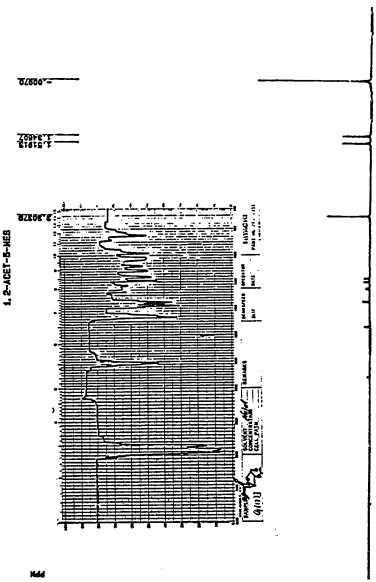

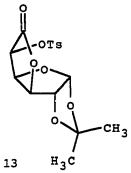

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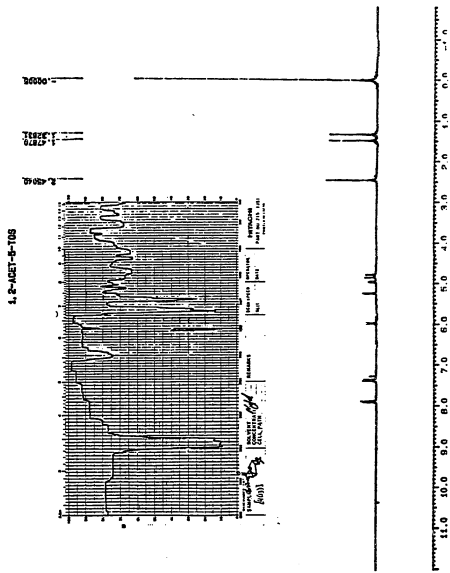

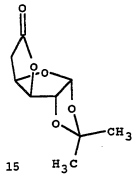

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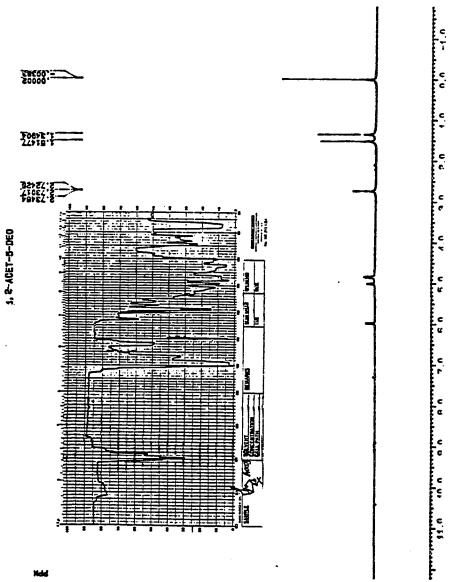

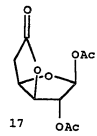

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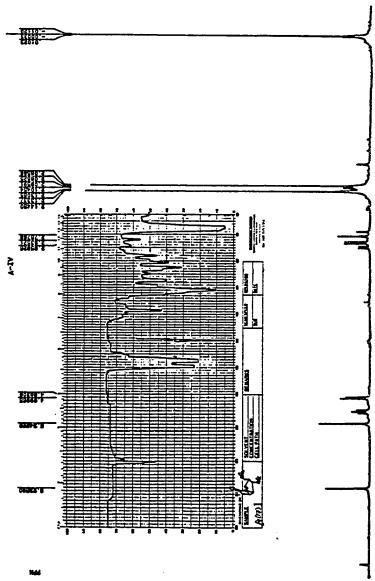

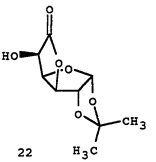

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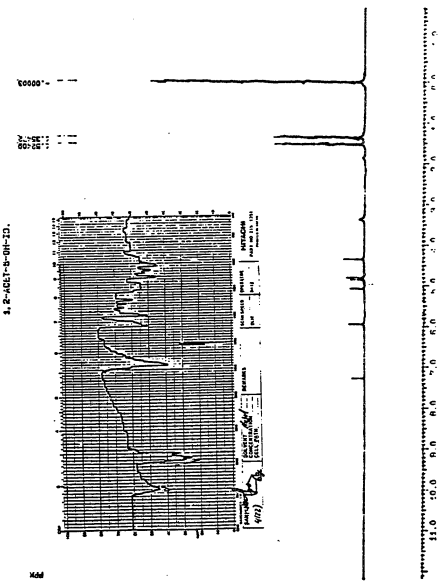

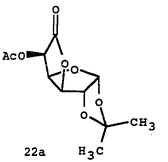

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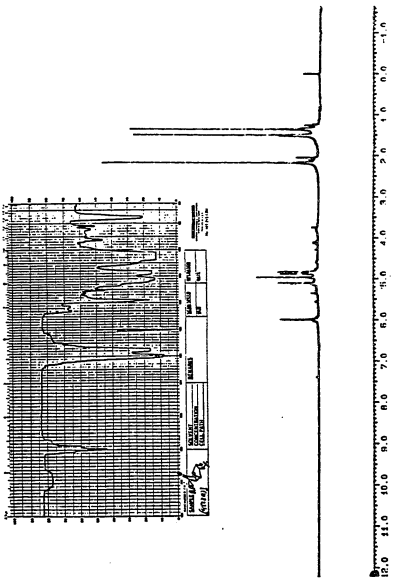

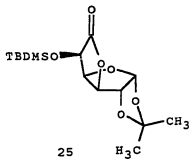

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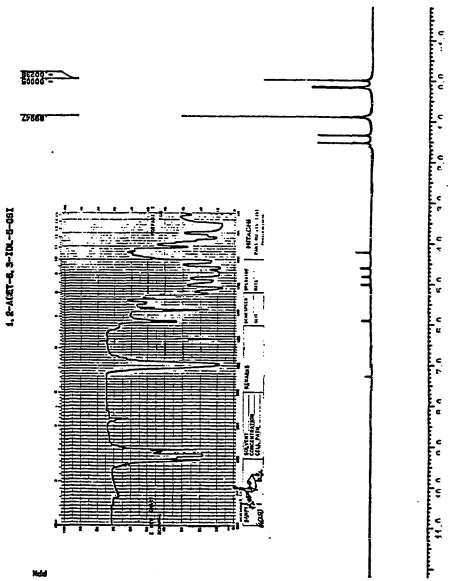

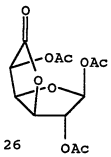

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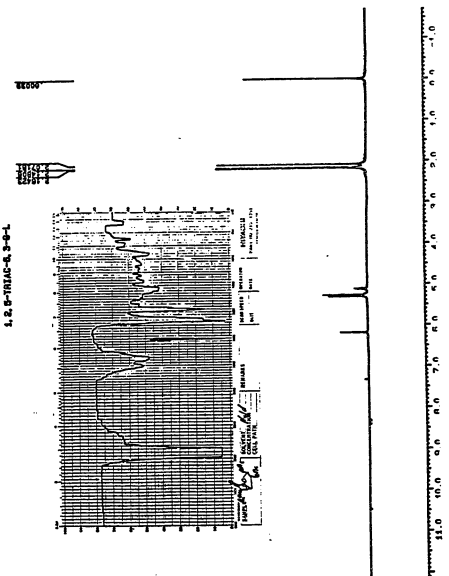

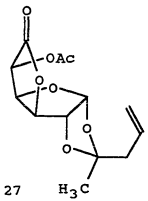

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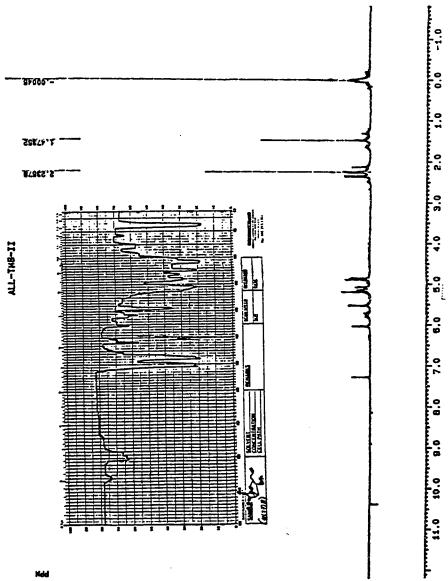

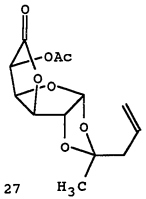

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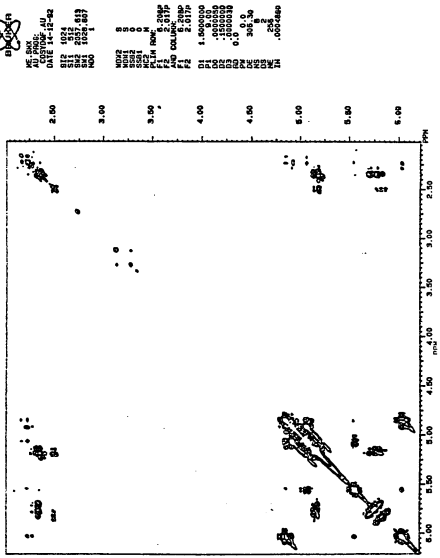

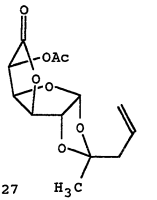

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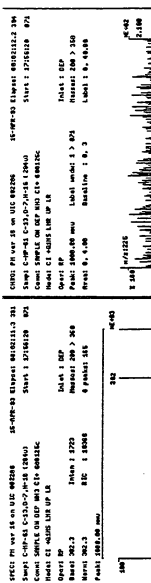
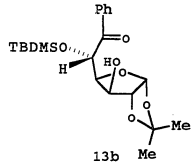
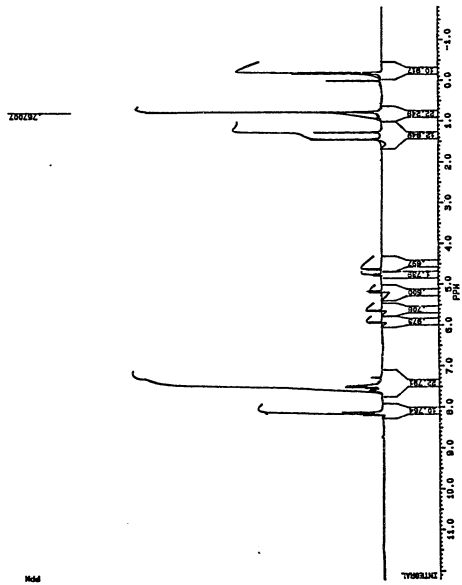
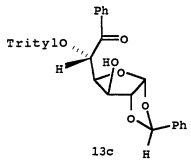


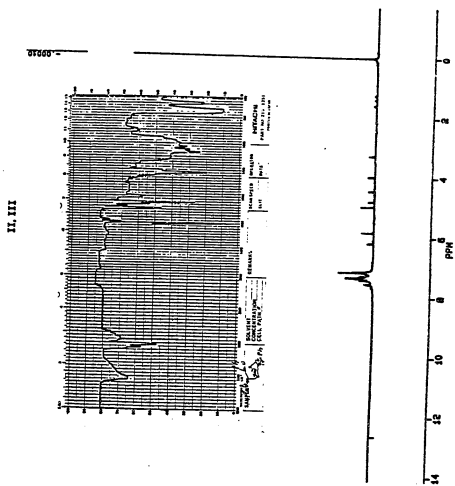


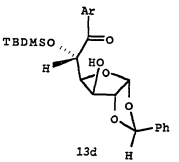
13b





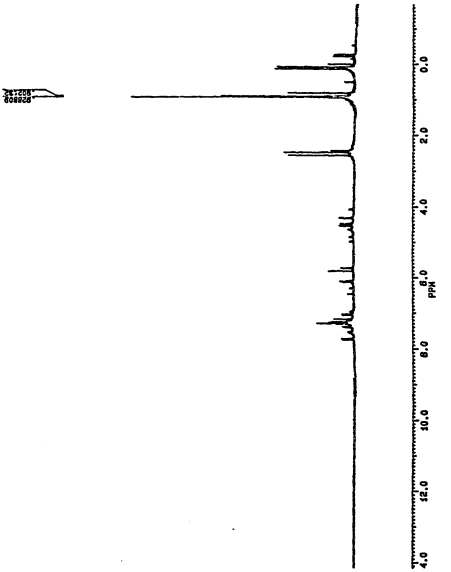
13c

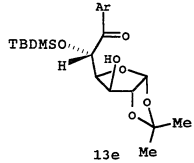




13d

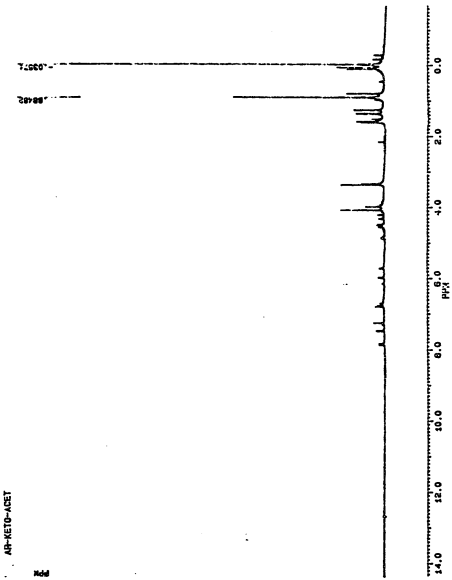
Ar: 2,7-diMe-Bz

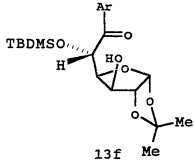




13e

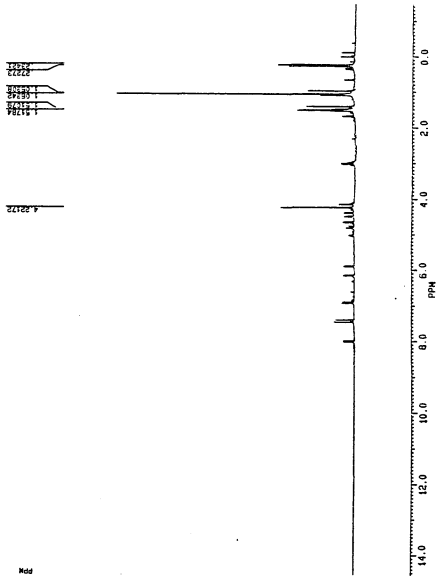
Ar: 2-(MeO)Et-7-MeO-Bz

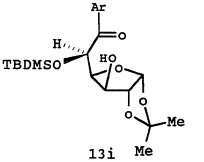




13f

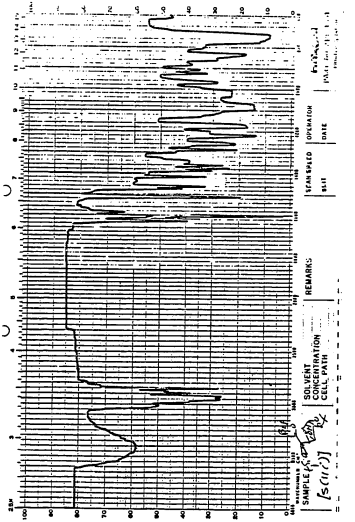
Ar: 2-Et-7-MeO-Bz

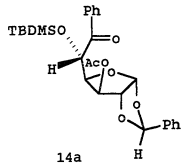




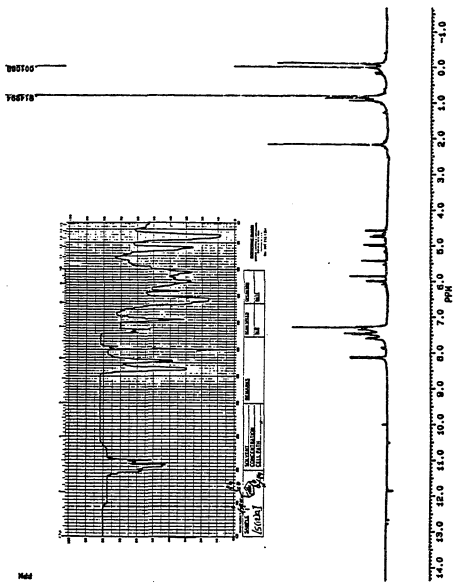
13i

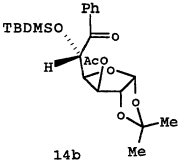
Ar: 2-Et-7-MeO-Bz



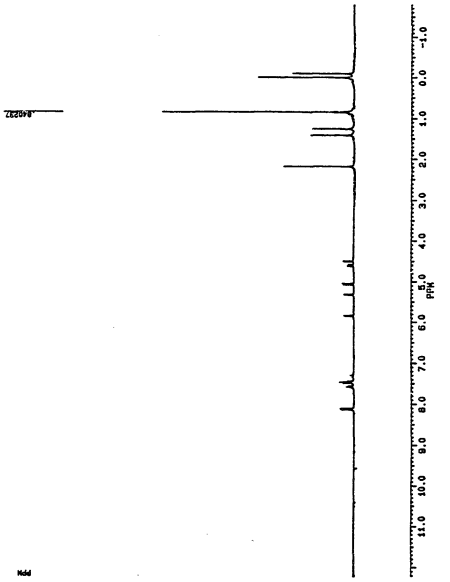


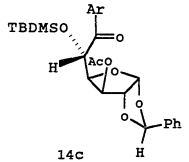
14a





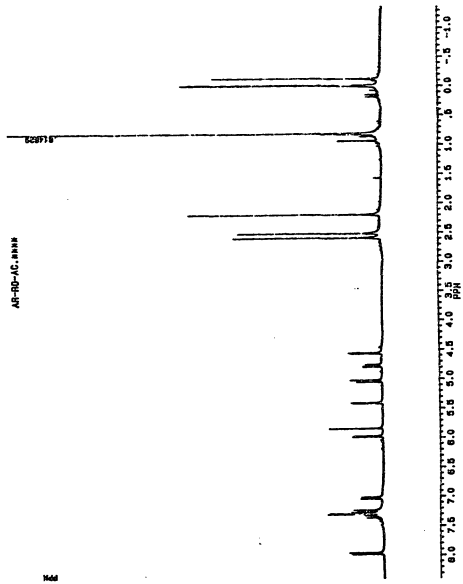
14b

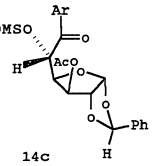




14c

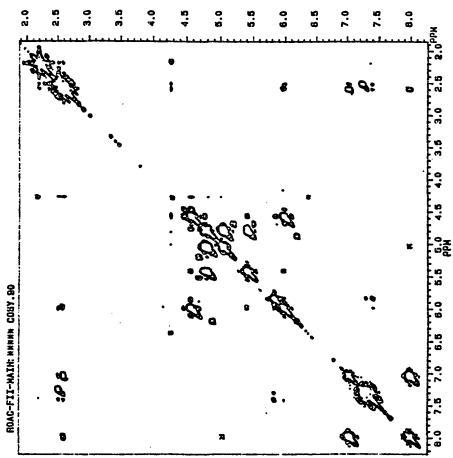
Ar: 2,7-diMe-Bz

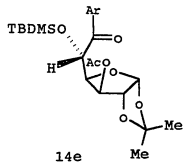




14c

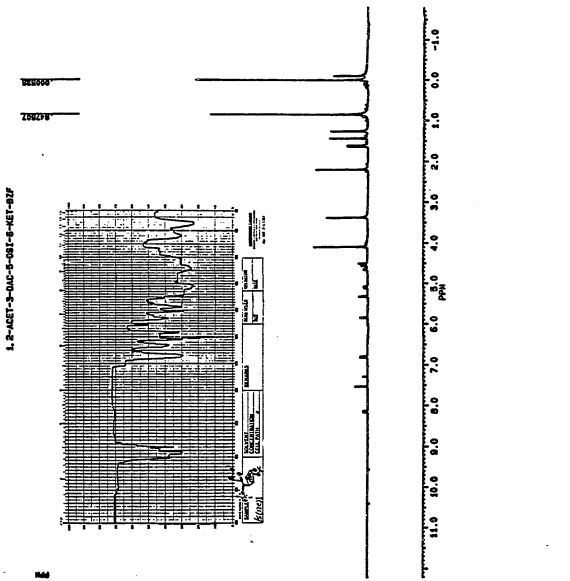
Ar: 2,7-diMe-Bz

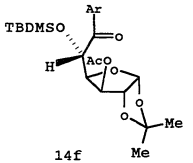




14e

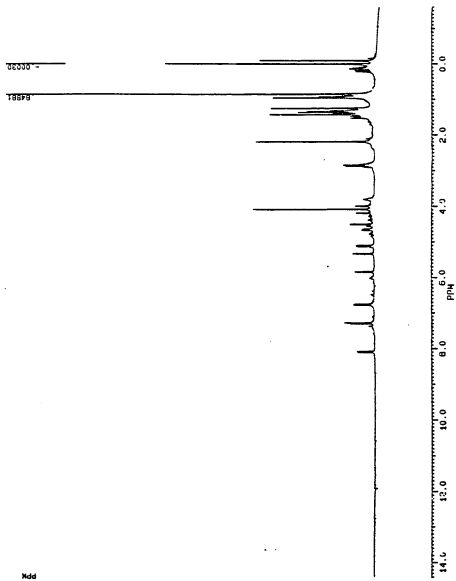
Ar: 2-(MeO)Et-7-MeO-Bz

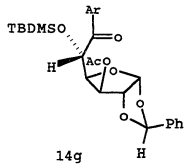




14f

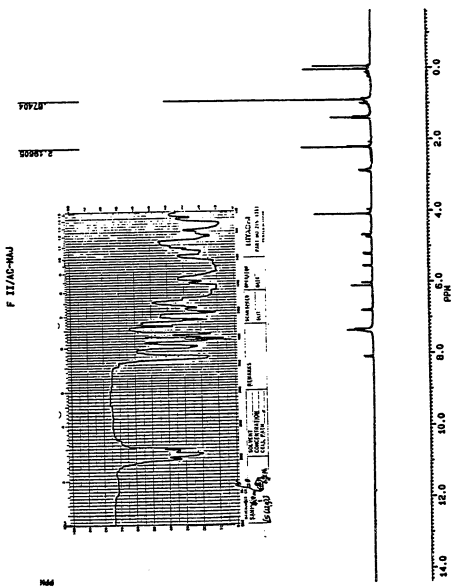
Ar: 2-Et-7-MeO-Bz

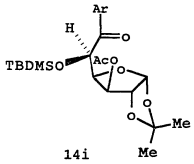




14g

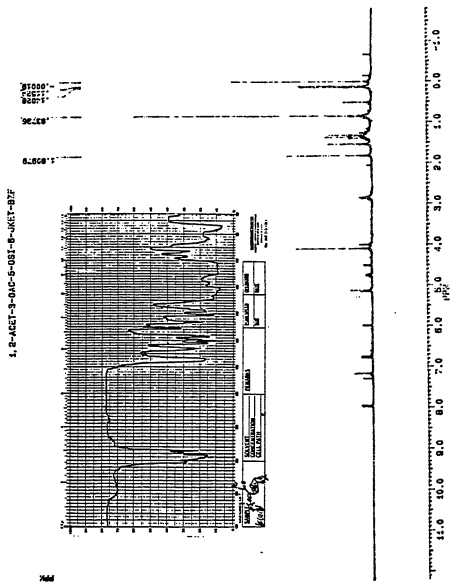
Ar: 2-Et-7-MeO-Bz

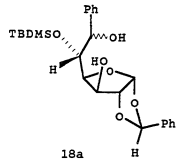




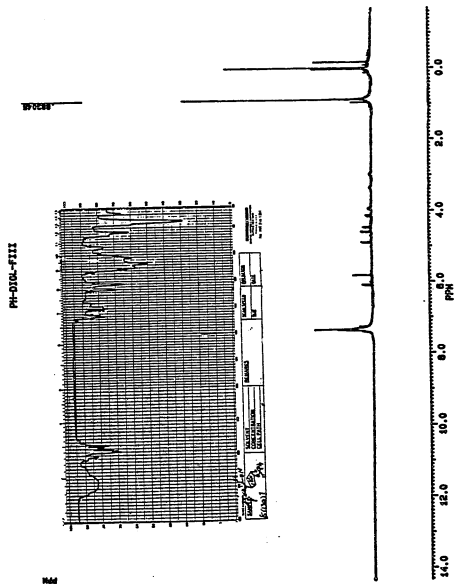
14i

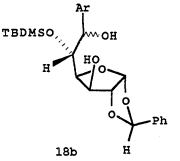
Ar: 2-Et-7-MeO-Bz





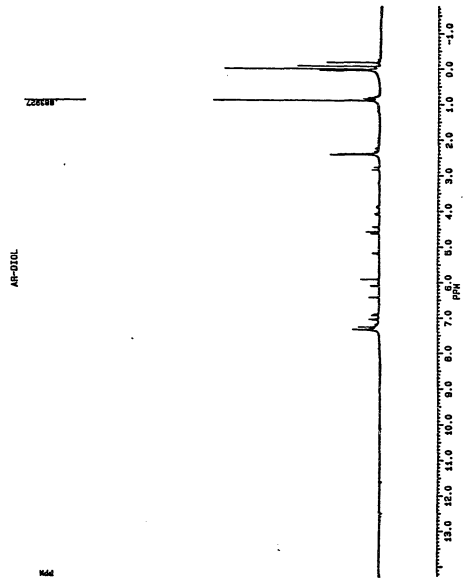
18a

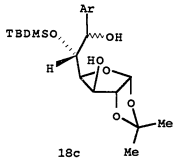




18b

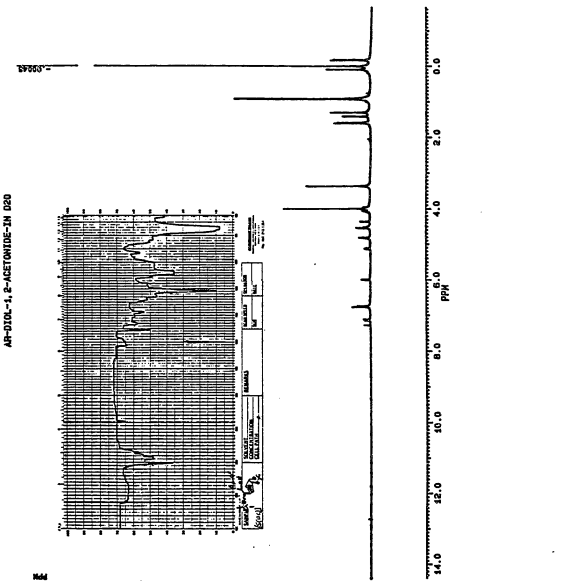
Ar: 2,7-diMe-Bz

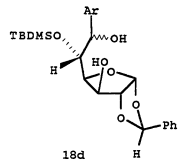




18c

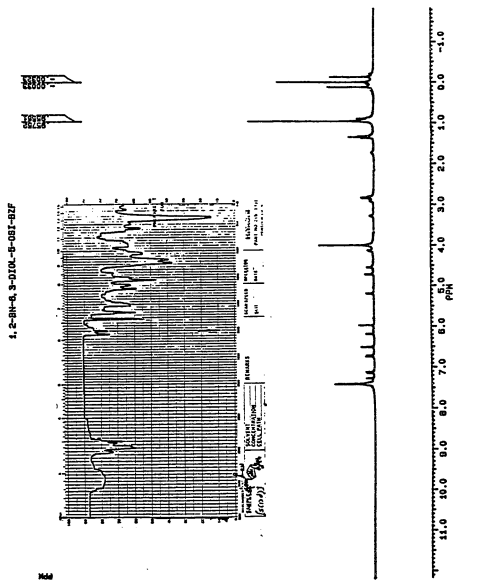
Ar: 2-(MeO)Et-7-MeO-Bz

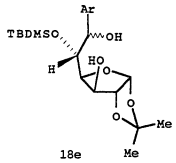




18d

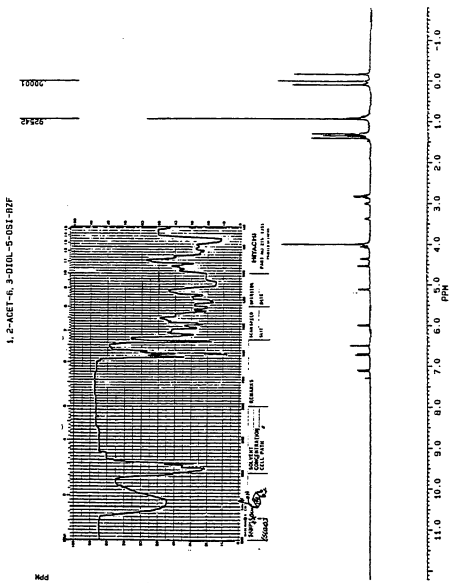
Ar: 2-Et-7-MeO-Bz

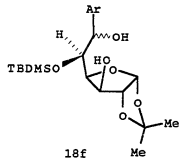




18e

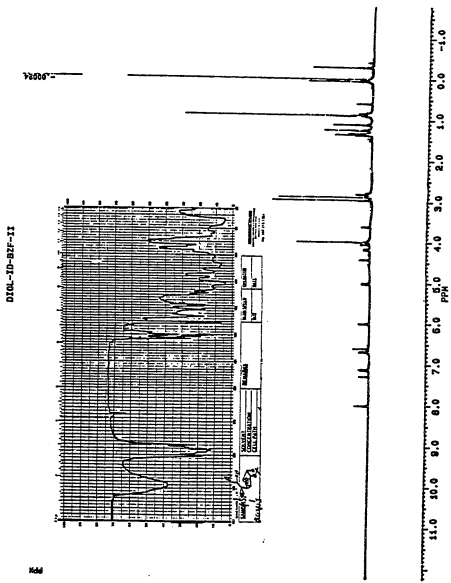
Ar: 2-Et-7-MeO-Bz

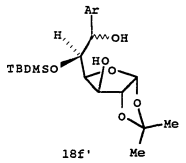




18f

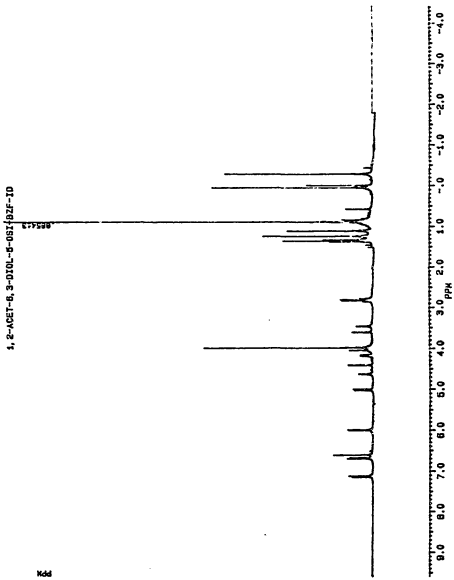
Ar: 2-Et-7-MeO-Bz

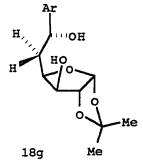




18f'

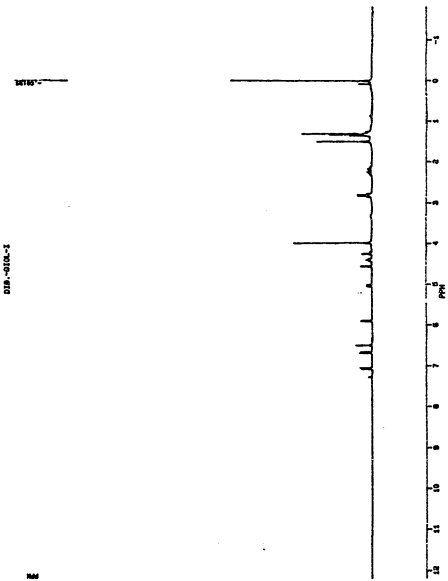
Ar: 2-Et-7-MeO-Bz

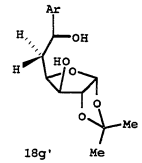




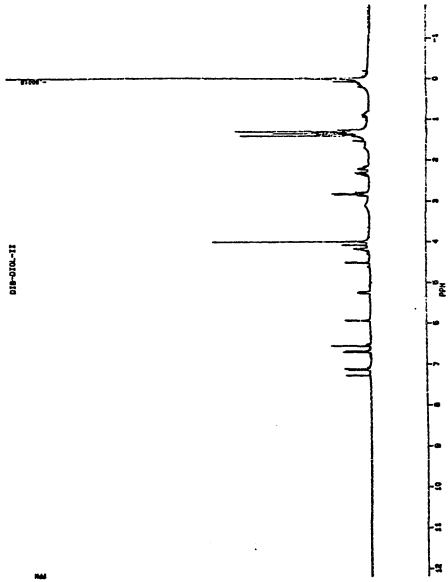
18g

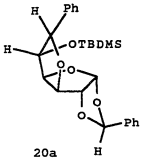
Ar: 2-Et-7-MeO-Bz



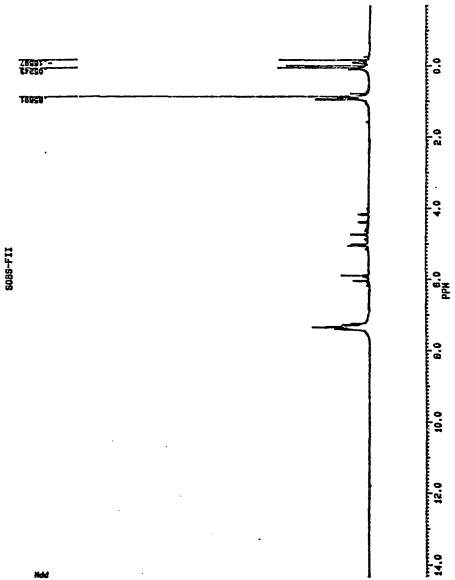


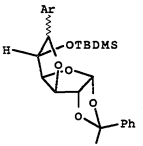
18g' Ar: 2-Et-7-MeO-Bz





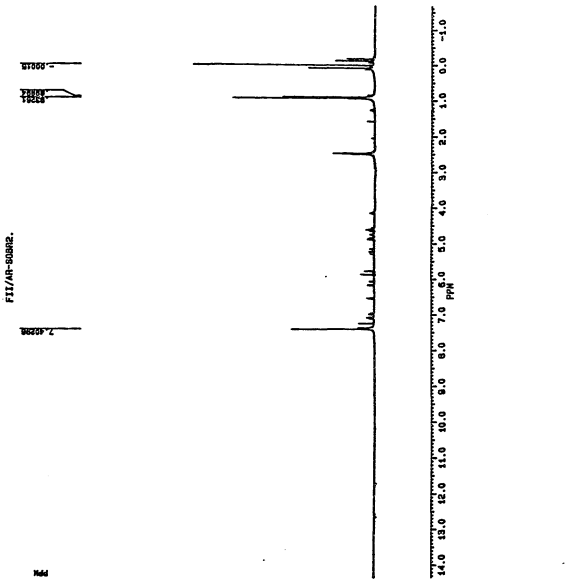
20a

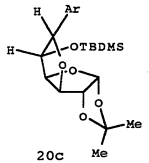




19b,20b H

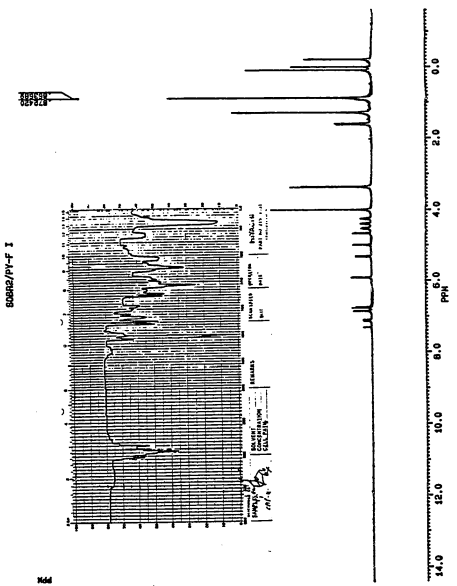
Ar: 2,7-diMe-Bz

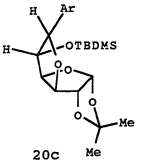




20c

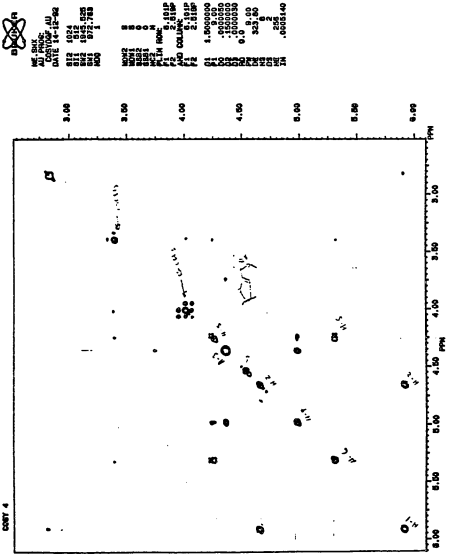
Ar: 2-(MeO)Et-7-MeO-BZ

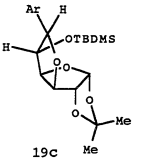




20c

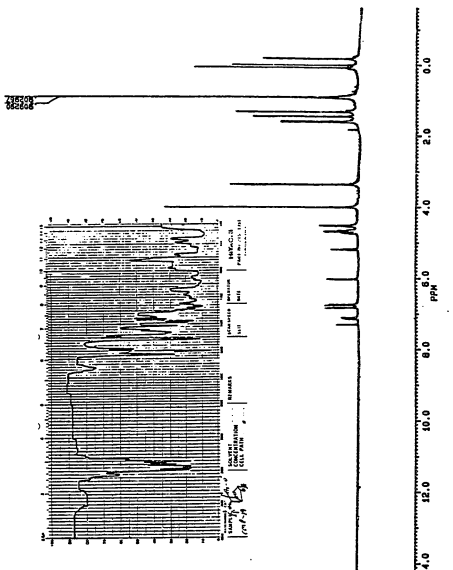
Ar: 2-(MeO)Et-7-MeO-Bz

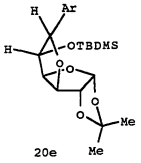




19c

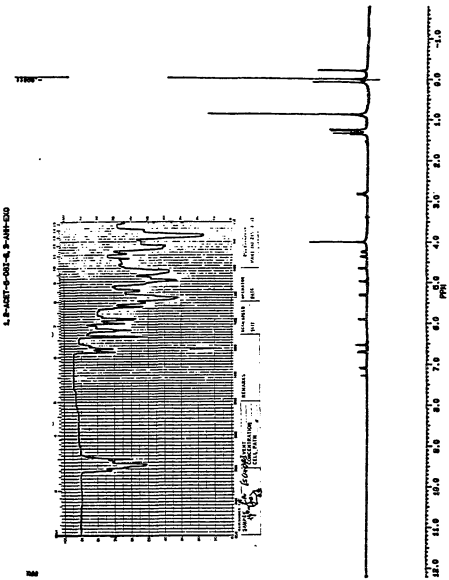
Ar: 2-(MeO)Et-7-MeO-Bz

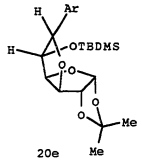




20e

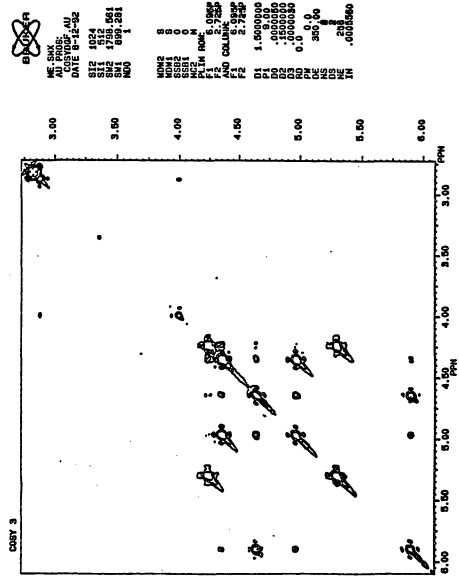
Ar: 2-Et-7-MeO-Bz

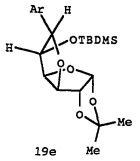




20e

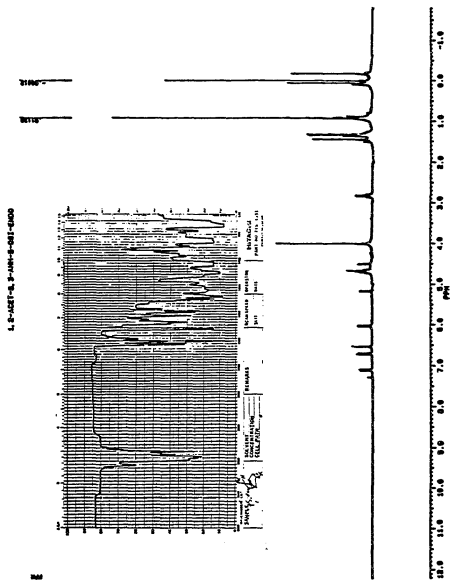
Ar: 2-Et-7-MeO-Bz

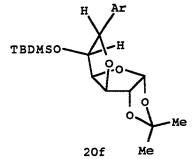




19e

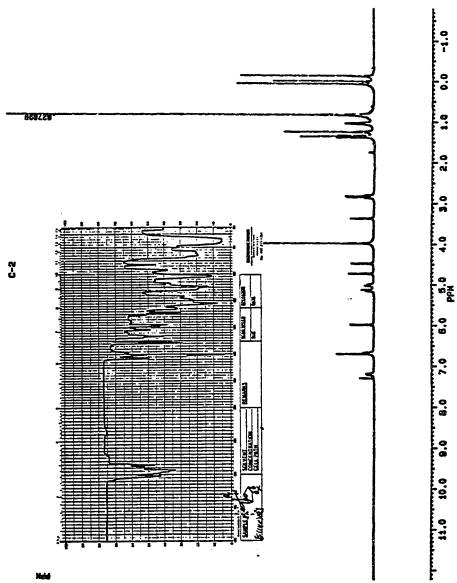
Ar: 2-Et-7-MeO-Bz

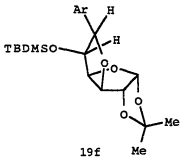




20f

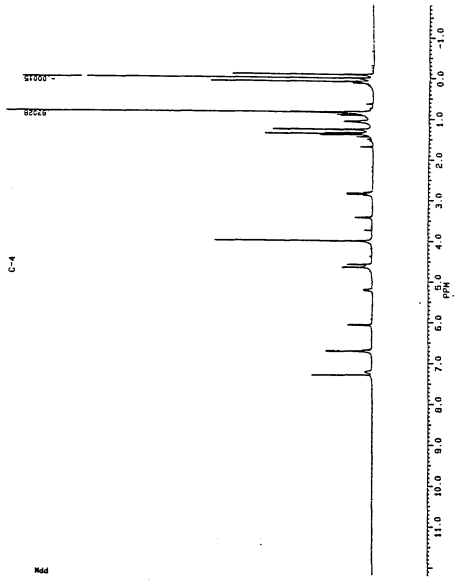
Ar: 2-Et-7-MeO-Bz

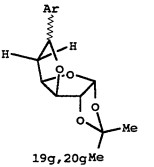




19f

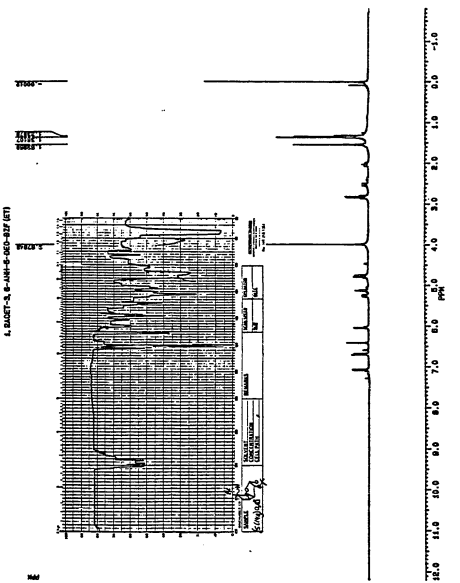
Ar: 2-Et-7-MeO-Bz

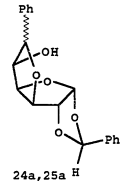




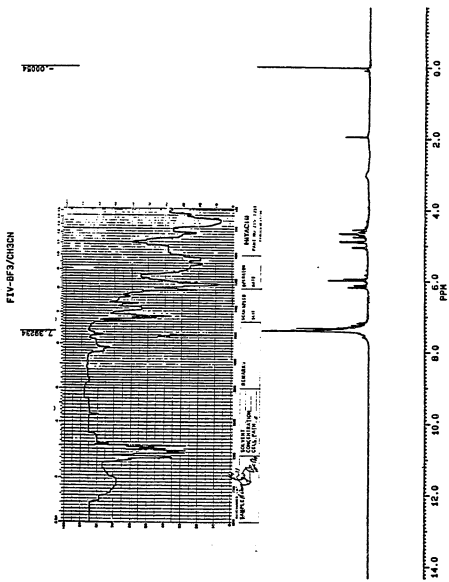
19g,20gMe

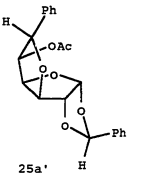
Ar: 2-Et-7-MeO-Bz



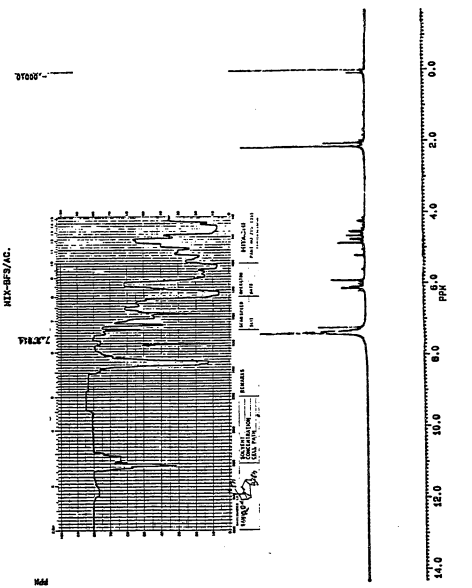


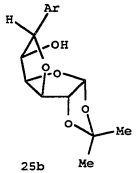
24a,25a





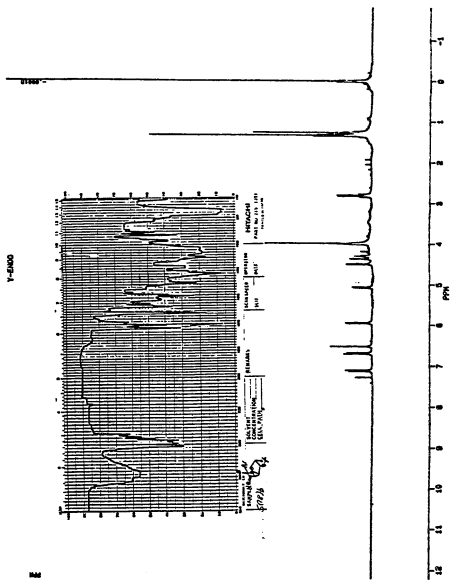
25a'

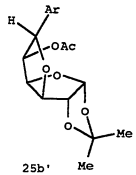




25b

Ar: 2-Et-7-MeO-Bz





25b'

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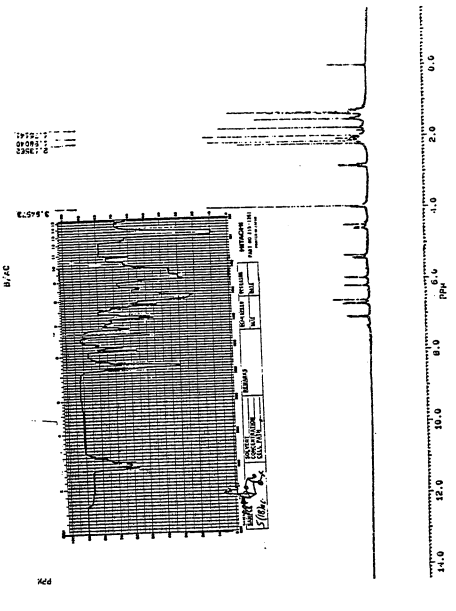
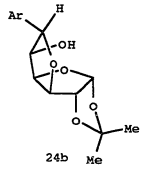
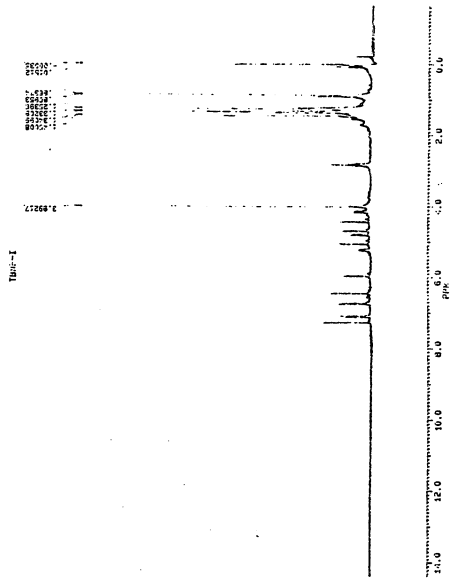
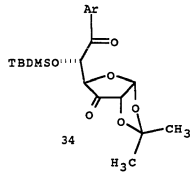




24b

Ar: 2-Et-7-MeO-Bz





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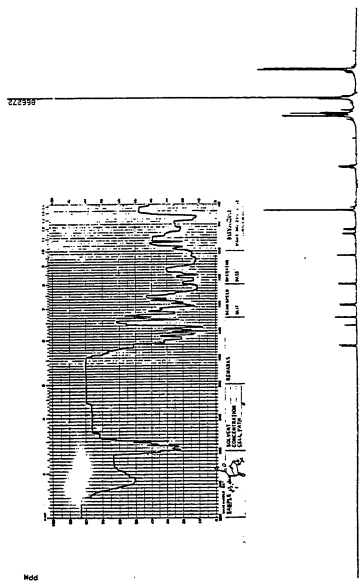
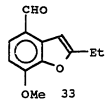
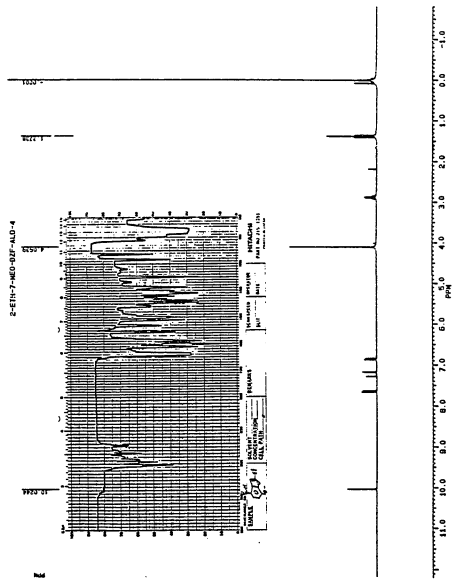
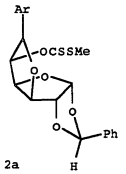




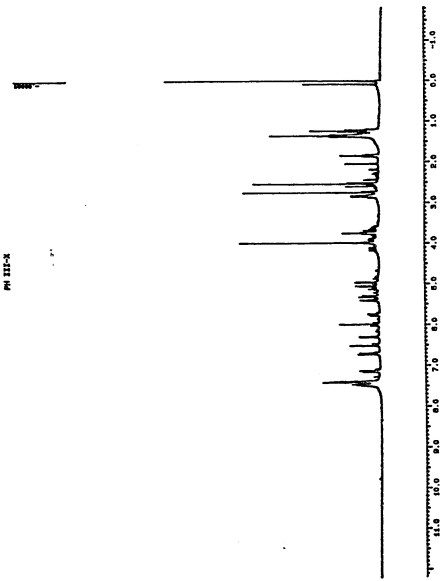
33

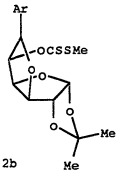




2a

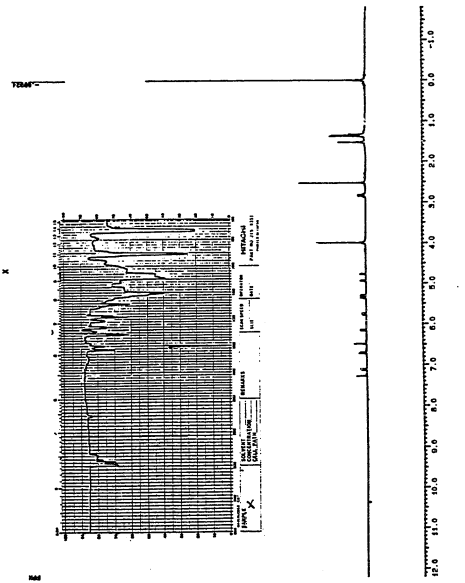
Ar: 2-Et-7-MeO-Bz

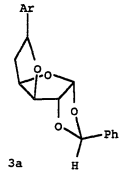




2b

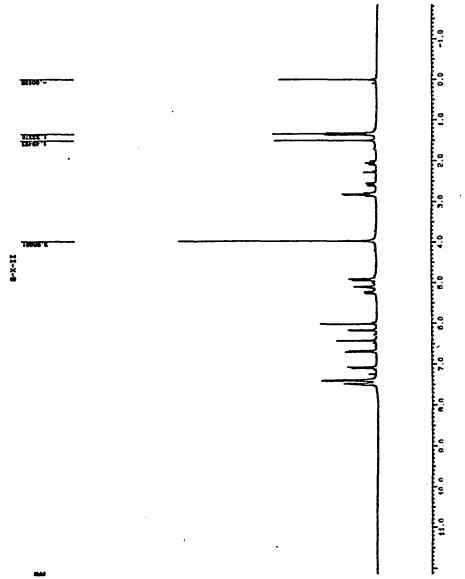
Ar: 2-Et-7-MeO-Bz

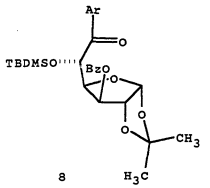




3a

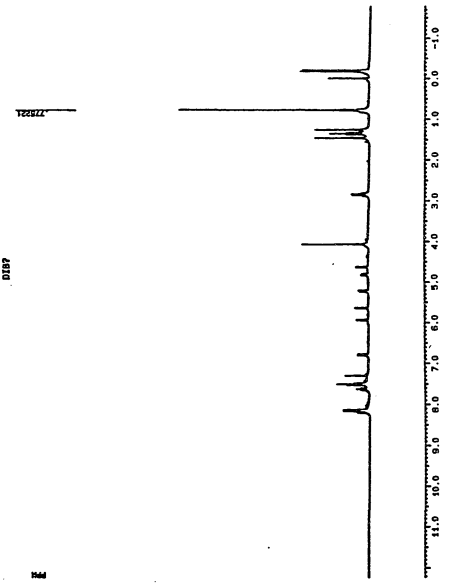
Ar: 2-Et-7-MeO-Bz

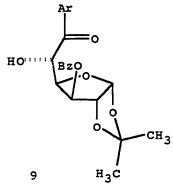




8

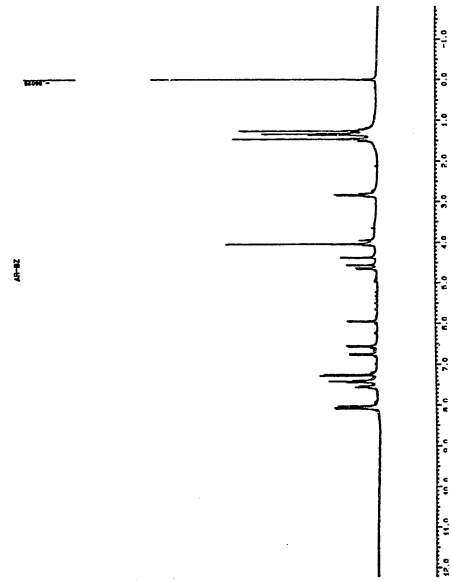
Ar: 2-Et-7-MeO-Bz

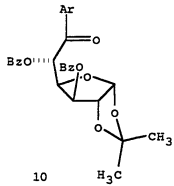




9

Ar: 2-Et-7-MeO-Bz





10

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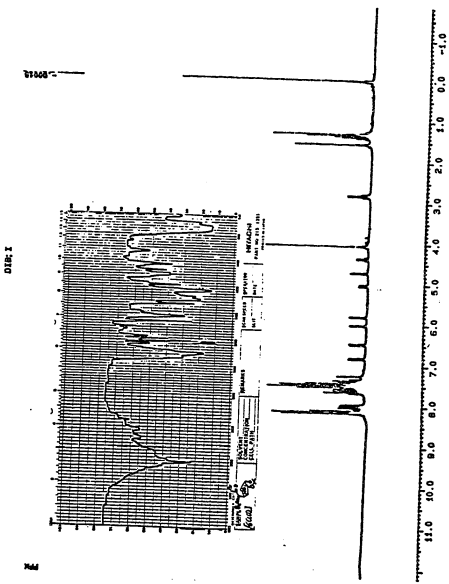
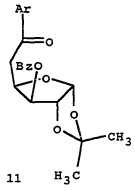
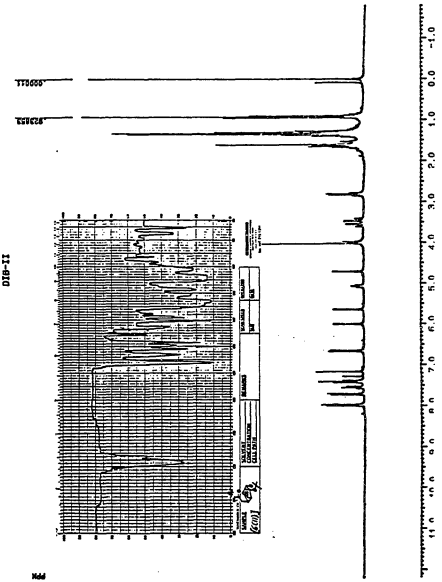
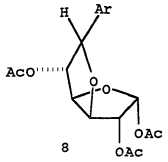




11

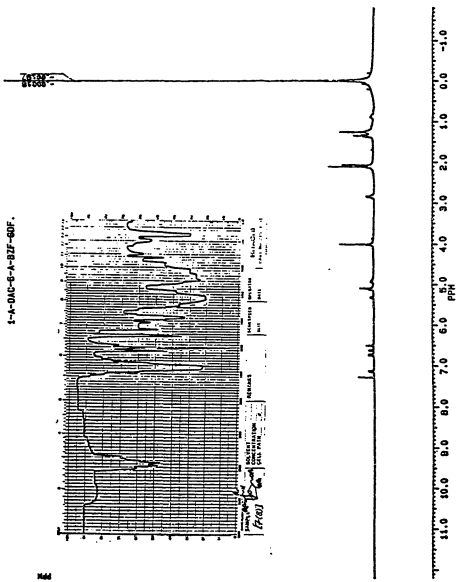
Ar: 2-Et-7-MeO-Bz

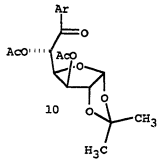




8

Ar: 2-Et-7-MeO-Bz





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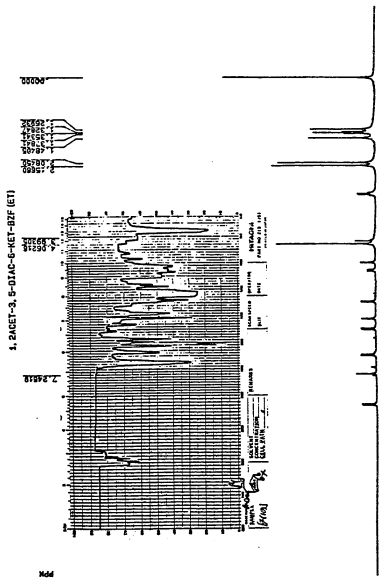
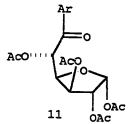
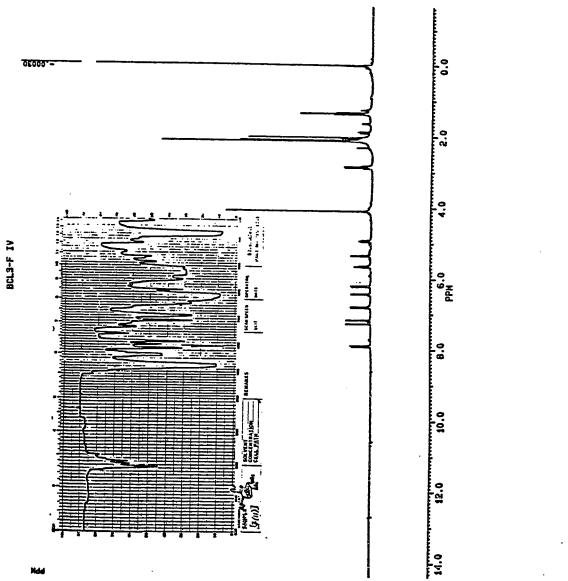
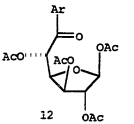




11

Ar: 2-Et-7-MeO-Bz





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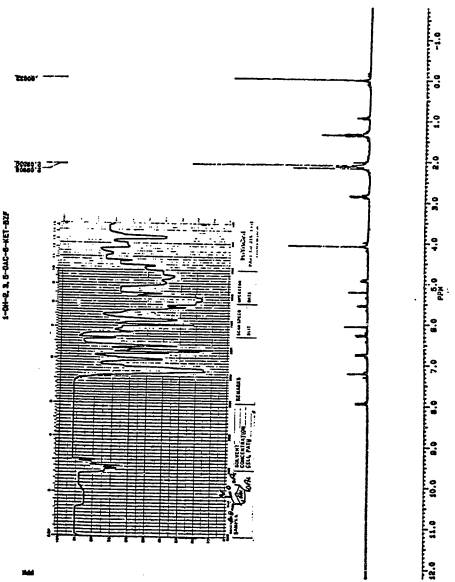
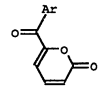
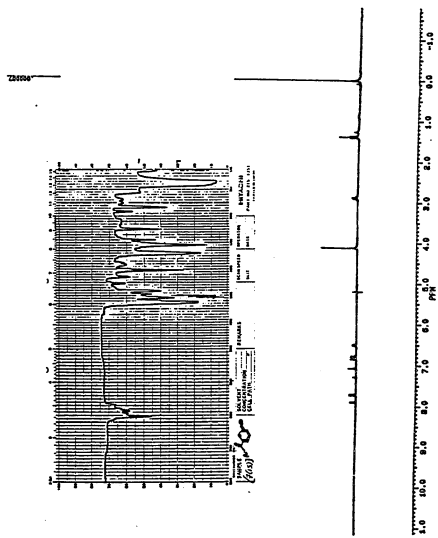
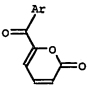




17

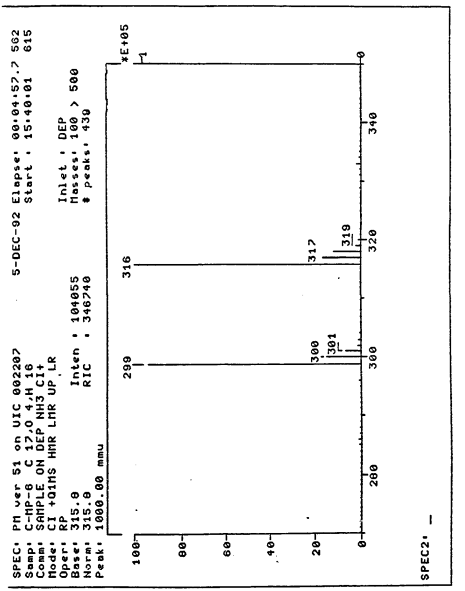
Ar: 2-Et-7-MeO-Bz

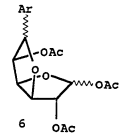




17

Ar: 2-Et-7-MeO-Bz





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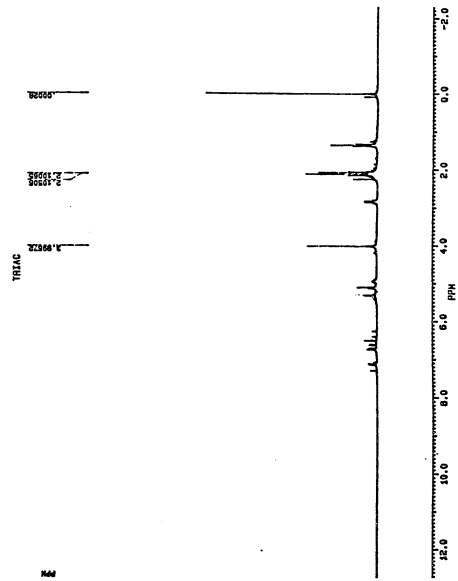

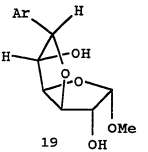

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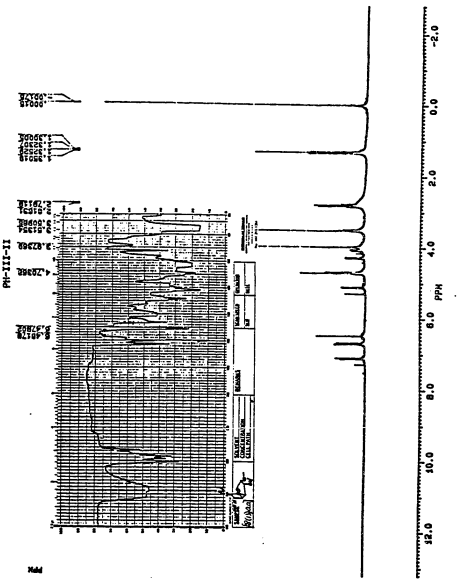
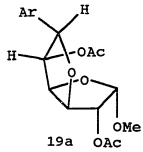
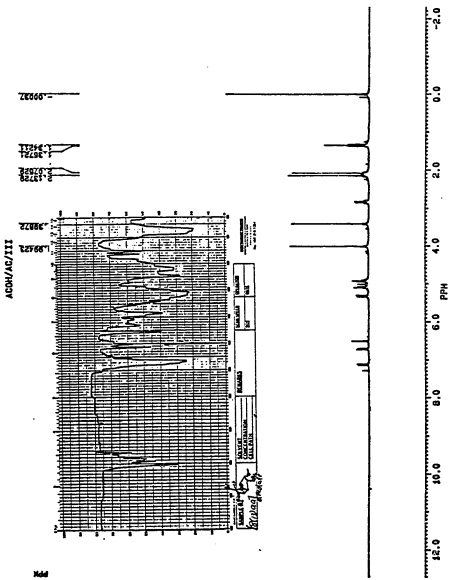
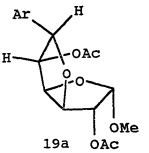




19a

Ar: 2-Et-7-MeO-Bz





19a

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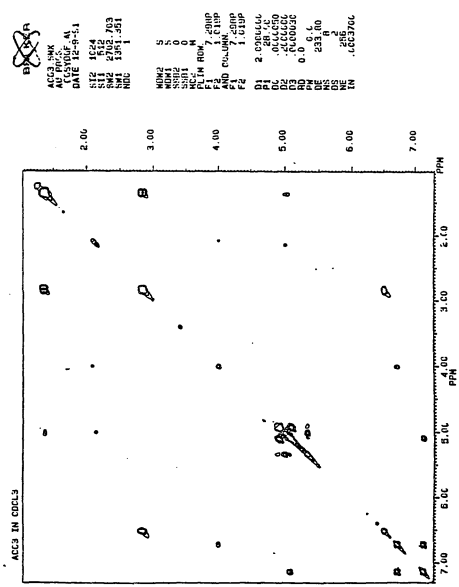

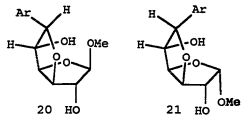

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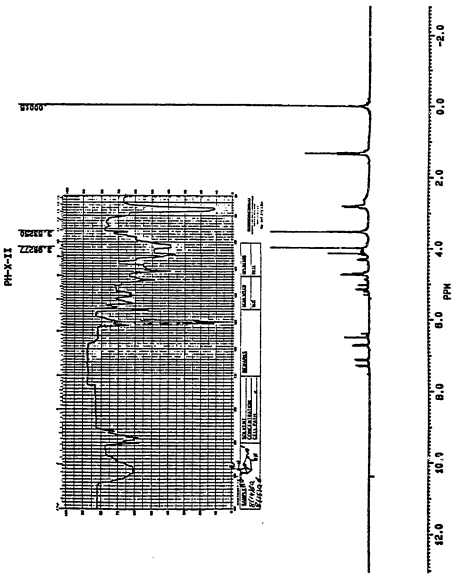

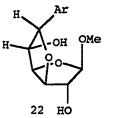

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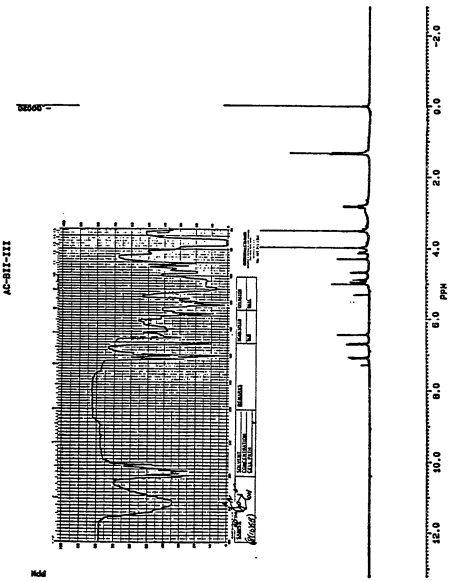

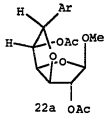

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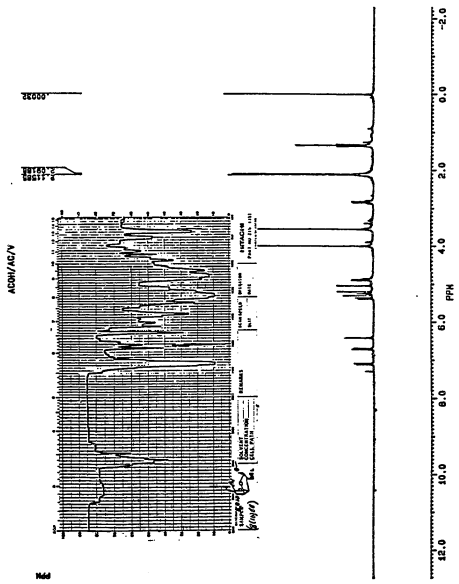

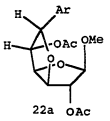

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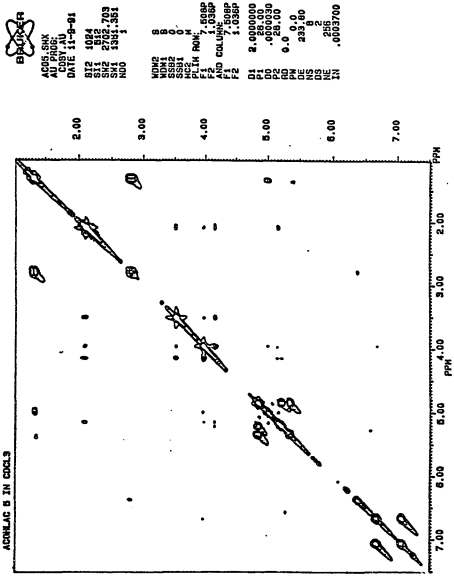

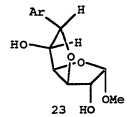

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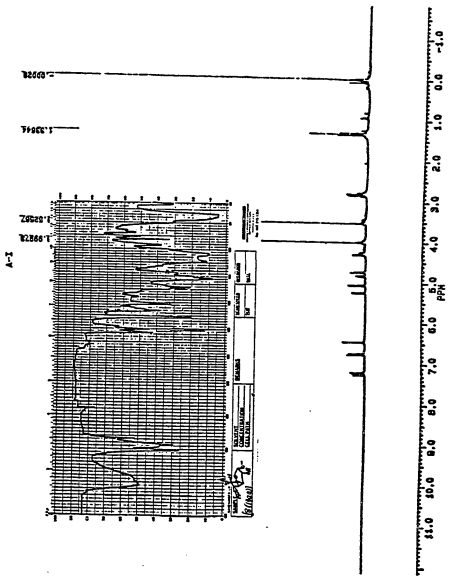

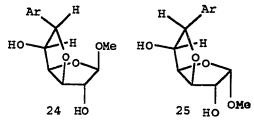

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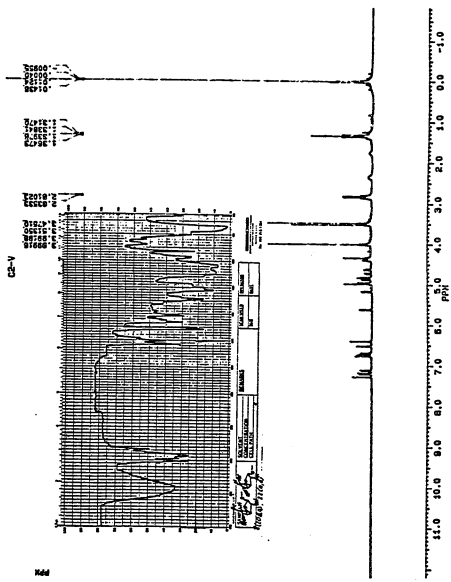

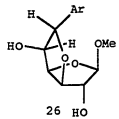

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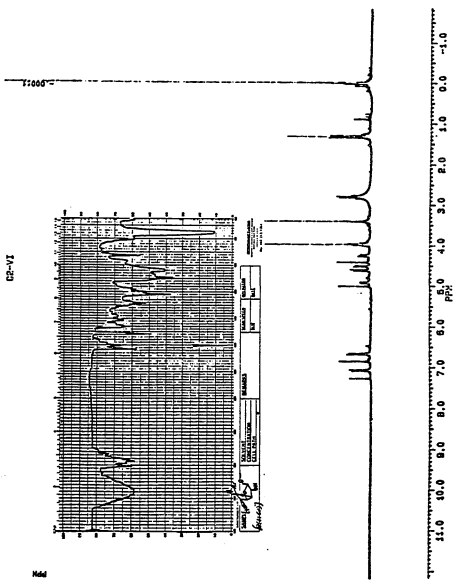

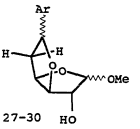

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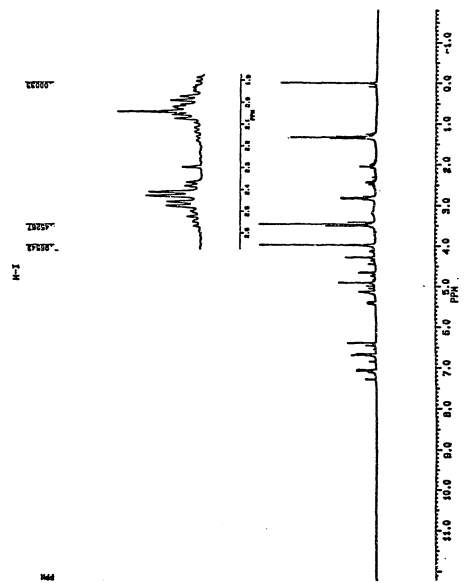

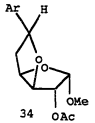

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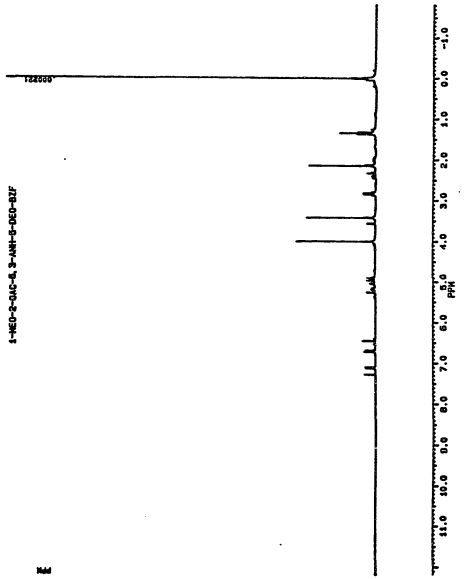

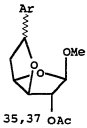

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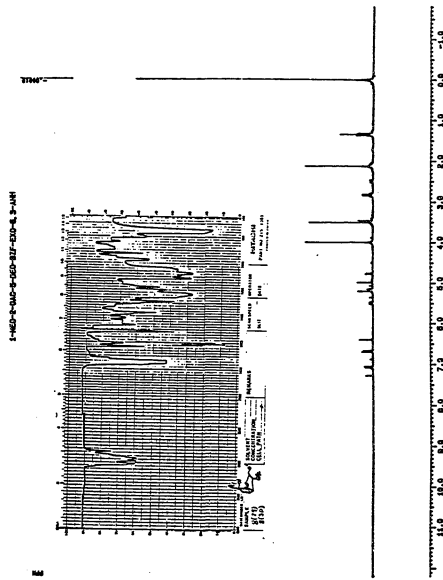

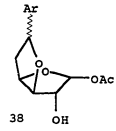

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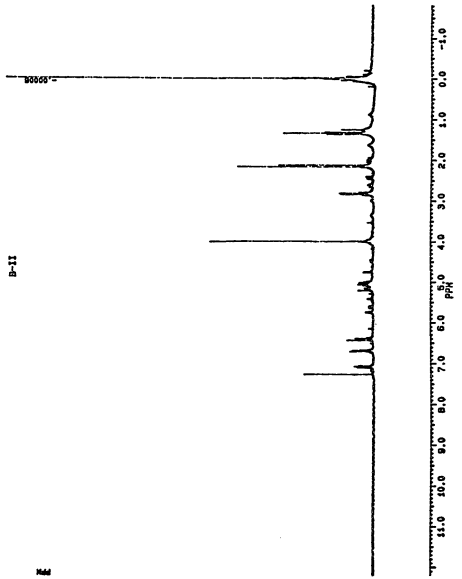

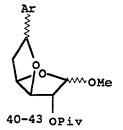

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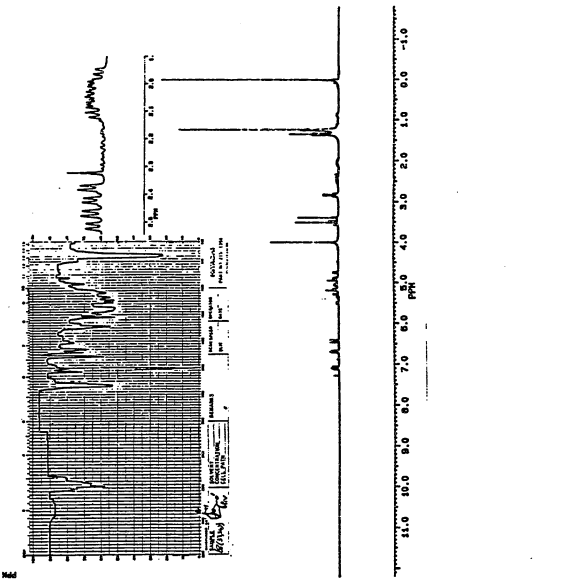

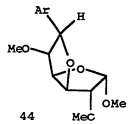

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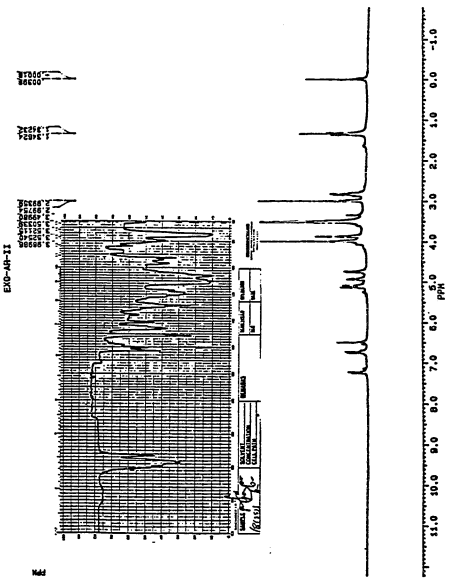

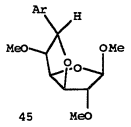

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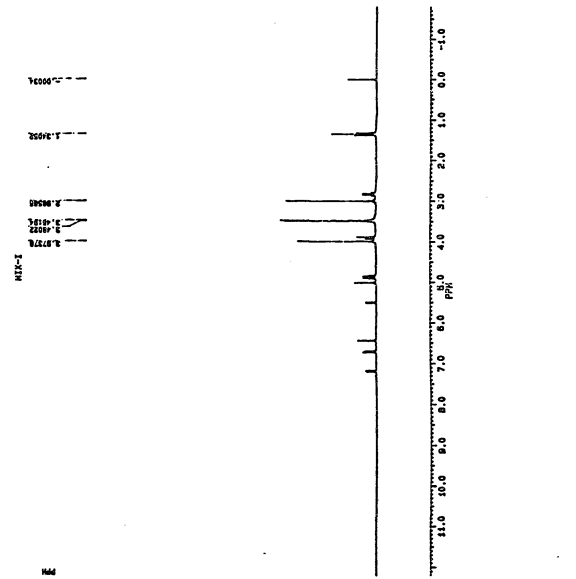

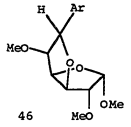

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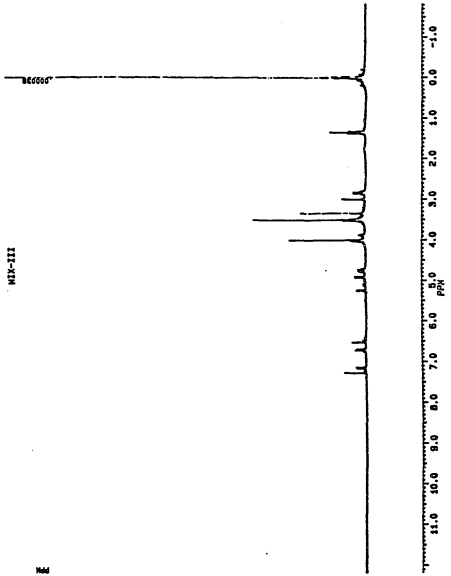

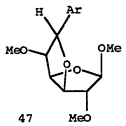

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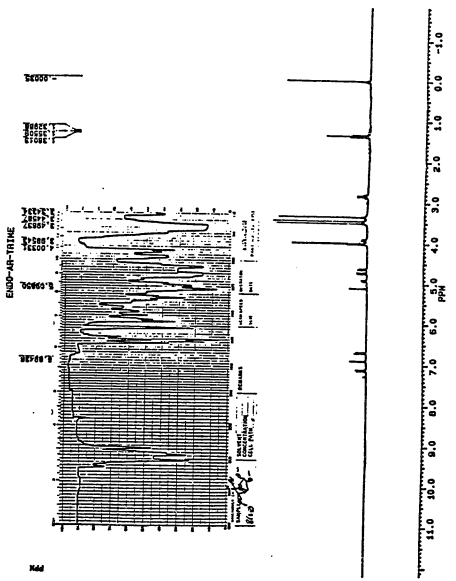

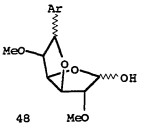

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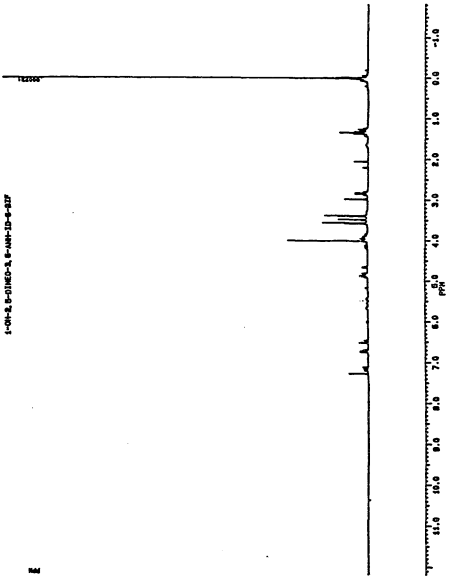

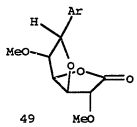

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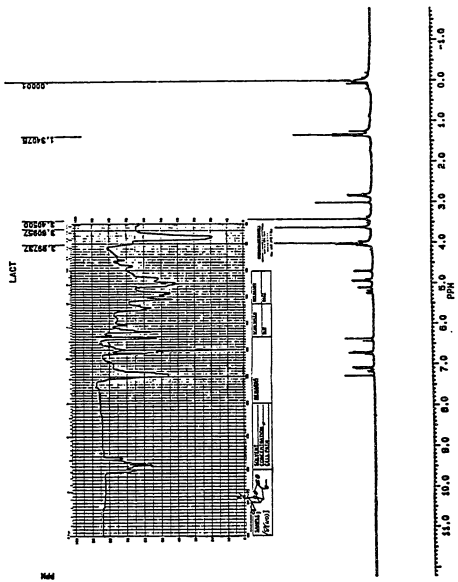

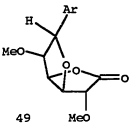

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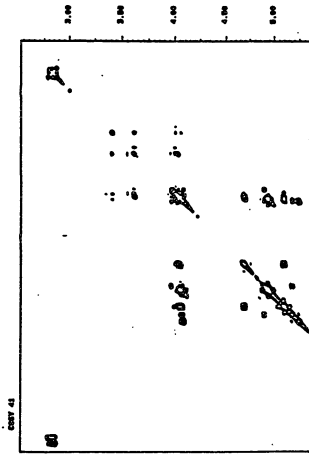

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