Total Syntheses of *R*-(-)-Argentilactone, *S*-(+)-Argentilactone, *R*-(-)-Massoilactone, (5*S*,6*R*)-*O*-Acetylosmundalactone *as*-Triazin-, Trithiocarbonate- and 4-(4-Substituted-1-piperazinyl) Derivatives from Sugar Templates

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Dedicated to

The moments of encouragements.

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Abbreviations

Ac	acetyl
AcONa	sodium acetate
aq.	Aqueous
as	asymmetric
Bn	benzyl
BuLi	butyl lithium
Bz	benzoyl
cat.	Catalytic
conc.	concentrated
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DIPT	diisopropyl tartrate
DMF	N,N´-dimethylformamide
DMSO	dimethyl sulfoxide
eq.	equation
equiv.	equivalent
EtOAc	ethyl acetate
EtOH	ethanol
GASPE	gated spin echo
h	hour
LDA	lithium diisopropylamide
M	molar
m.p.	melting point
m-CPBA	meta-chloroperbenzoic acid
MeOH	methanol
min	minute
Ms	mesyl
n	normal

NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
p	para
PPL	porcine pancreatic lipase
ppm	parts per million
Py	pyridine
rt	room temperature
s	singlet
t	triplet
TBDPS	tertiary butyl diphenyl silyl
TBHP	tertiary butyl hydroperoxide
TEA	triethylamine
tert	tertiary
THF	tetrahydrofuran
TLC	thin-layer chromatography
TsOH	*p*-toluenesulfonic acid

A. Introduction

Recent efforts, directed towards the syntheses of complex natural products have pointed out the need for a variety of versatile chiral synthetic intermediates, so-called “chiral building blocks” [1]. Easy available ones are prepared from chiral materials produced in nature including carbohydrates, amino acids, hydroxy acids, terpenes etc. Among them, carbohydrates are ideally suited as synthons for natural products as the combination of the natural chirality and inherent topology of a cyclic sugar derivative provides a high degree of regio- and stereocontrol for the systematic functionalization of predetermined sites in the molecules. Such carbohydrate-derived ‘chiral templates’ can be further modified and eventually integrated into the structural framework of the synthetic target [2].

6-Substituted 5,6-dihydro-α-pyrones, so-called α,β-unsaturated δ-lactones (Fig. 1) are widely distributed in, both, plants and fungi and have been isolated from thirteen families of plants and twenty fungal species. They possess a diverse range of biological activities and have been reported as plant growth inhibitors, insect antifeedants, antifungal and antitumour agents [3]. In some instances they have been used as intermediates for the synthesis of other natural products [4], since they accept conjugate addition with high stereoselectivity [5].

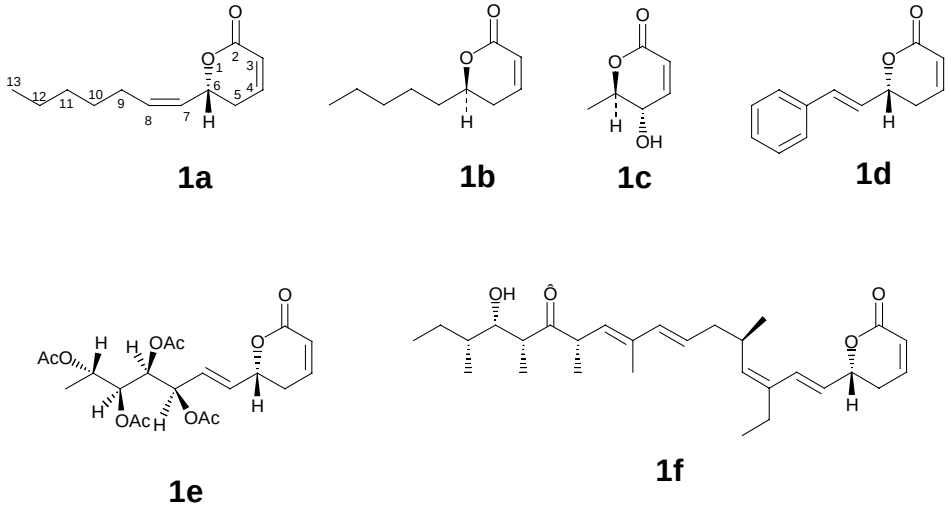
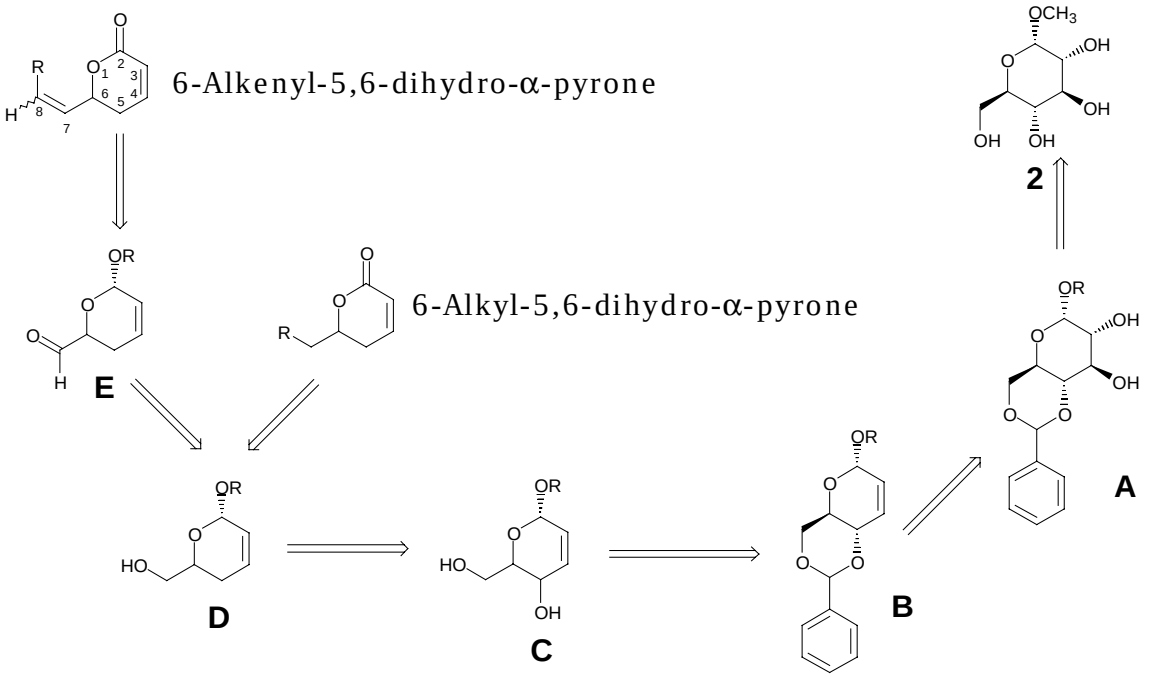


Fig. 1. Representative examples of some 6-substituted 5,6-dihydro-α-pyrones; (-)-argentilactone (**1a**), (-)-massoilactone (**1b**), (+)-osmundalactone (**1c**), (+)-goniothalamine (**1d**), (+)-anamarine (**1e**) and callystatin A (**1f**).

Inspite of their rather simple structure, these lactones possess a complete diverse nature. The side chain at C-6 (pyran nomenclature is followed in numbering) may be saturated (e.g. **1b**) , unsaturated (e.g. **1a**, **1d**) or highly functionalized (e.g. **1e**, **1f**), containing additional chiral centers. C-5 can also be substituted (e.g. **1c**) and thus presenting a challenge to the chemist with respect to their asymmetric syntheses.

Retrosynthetically it can be envisioned (Scheme 1) that the intermediate, alcohol **D**, can be a common precursor for the synthesis of all types of such α,β-unsaturated δ-lactones. The lactones containing double bond between C_7-C_8 can be constructed *via* a Wittig reaction between aldehyde **E** and a suitable

phosphonium salt. The saturated side chain on the other hand can be introduced through the nucleophilic displacement of some leaving group (e.g. halide, mesyl, or tosyl group) prepared from the alcohol **D** which itself can be constructed *via* a ring opening reaction on the benzylidene acetal **B**. As it becomes obvious from Scheme 1, methyl-α-D-glucopyranoside (**2**) can be selected as the starting material for their total synthesis.



Scheme 1. Retrosynthetic analysis for the synthesis of 6-alkyl and 6-alkenyl 5,6-dihydro-α-pyrones.

Another important feature of these α,β-unsaturated δ-lactones is the presence of an asymmetric centre at C-6 which can be either *S* or *R*, as natural products with either configurations exist in nature. Application of carbohydrate

templates in the total synthesis of natural products suffers, if L-sugars are demanding.

This thesis demonstrates the asymmetric total syntheses of some representative examples from this class of natural product such as *S*-(+)-argentilactone (**11**), *R*-(-)-massoilactone (**1b**), (+)-osmundalactone (**1c**), and *R*-(-)-argentilactone (**1a**), starting from carbohydrate templates. Both, *S*- and *R*-configurations were achieved from the same starting material i.e. D-glucose.

On the other hand, a variety of examples for regio- and stereoselective transformations of 2,3-anhydropentoses (and in some cases 3,4-anhydropentoses), delivering a series of chiral heterocyclic systems and a selected set of 4-substituted 2,3-anhydrosugar derivatives for bioassays have been synthesized (Fig. 2).

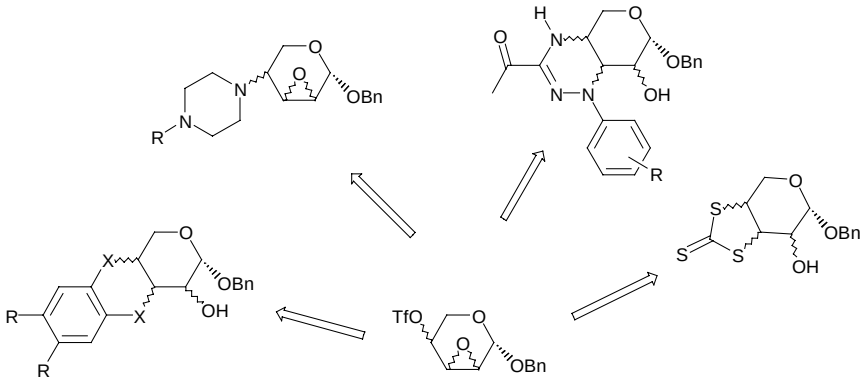


Fig. 2. Some new targets from 2,3-anhydropentoses.

B. Results and Discussion

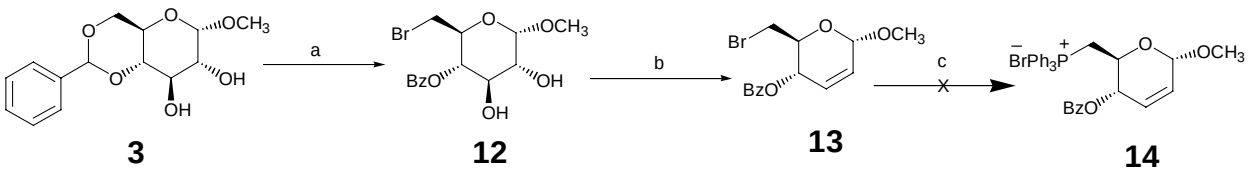
I. Total Synthesis of *S*-(+)-Argentilactone (11), the Non-natural Enantiomer of Argentilactone (1a)

Argentilactone **(1a)**, an α,β-unsaturated δ-lactone, was originally isolated in 1977 from the rhizomes of *Aristolochia argentina* Gris [6]. This compound is the major constituent of the essential oil and hexane extract of *Annona haematantha* [7] and also present in the methanolic extract of the leaves of *Chorisia crispiflora* [8]. The biological studies on **1a** have revealed high antileishmanial [7] and cytotoxic activity against P-388 mouse leukemia cells [8]. Moreover, it can also be used as starting material for the synthesis of interesting pheromones [9]. These features prompted some research groups to undertake the total synthesis of argentilactone [10-13].

As carbohydrates and their derivatives possess several attributes which make them ideal precursors for enantiopure syntheses [2a], this was one of the purposes of this thesis to design an efficient strategy to synthesize α,β-unsaturated δ-lactones in an enantioselective way and in good yield which can be applied to the majority of the natural products belonging to this class of compounds. According to the retroanalysis (Scheme 1), methyl-α-D-glucopyranoside (**2**) can be a potential starting material for the synthesis of argentilactone and other δ-lactones. Unfortunately, the stereochemistry at C-6

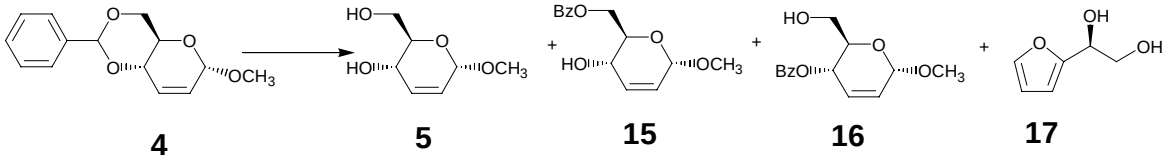
(pyran numbering) of **1a** is *R* which requires a sugar from the L-series. Nevertheless, to confirm the absolute stereochemistry of **1a**, and to test any biological activity, we describe here an asymmetric total synthesis of *S*-(+)-argentilactone **11**.

Thus, under the modifications suggested by Holder and Fraser-Reid [14] for Evan's reaction, **2** was efficiently converted into methyl-4,6-di-*O*-benzylidene-α-D-glucopyranoside (**3**) in 90 % yield. The spectroscopic data ware found to be exactly identical with those, already reported. The vicinal diol in **3** was now ready to undergo 2,3-dideoxygenation and we applied, firstly, the conditions described by Garegg and Samualsson [15a]. The reaction was not, however, clean and an impure product with a low yield was obtained. As a second choice, we found that iodoform/imidazole/triphenylphosphine in toluene [15b] is an excellent reagent to produce **4** (87% yield) as nice crystals (m.p. 122 ^{o}C (ethanol)). At this stage, we wanted to open the benzylidene ring in a regio- and stereoselective manner. Surprisingly the known oxidative[16] and reductive [17] ring opening methods gave a mixture of products in low yield. Alternatively, it was decided to open the acetal **3** under Hanessian's conditions (NBS, $BaCO_3$ in refluxing CCl_4) to produce methyl 6-bromo-6-deoxy-4-*O*-benzoyl-α-D-glucopyranoside (**12**) [18] followed by the 2,3-dideoxygenation with the above mentioned system (CHI_3/PPh_3/imidazol). The bromo-olefine **13**, so obtained, was reacted with triphenylphosphine [19] to prepare the phosphonium salt **14**, but only decomposed material was obtained.



Scheme 2. Opening of benzylidene ring according to reference [18]. *Reagents and conditions*: a) NBS, $BaCO_3$, reflux for 1 h in CCl_4, b) PPh_3, imidazole, CHI_3, toluene, reflux for 1 h, c) PPh_3, toluene, 90 ^oC for 6 days.

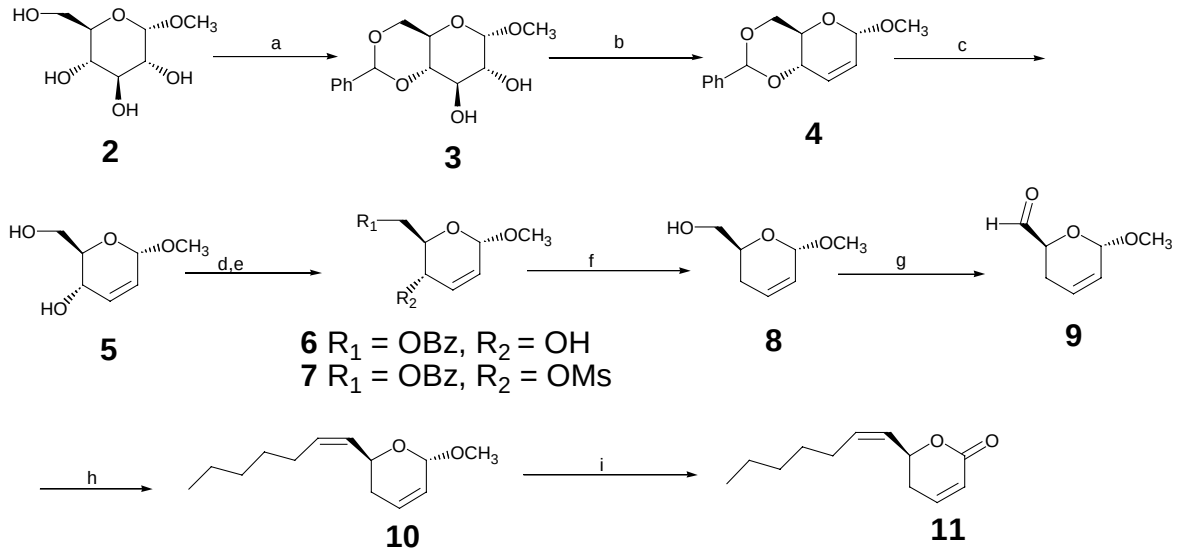
Table 1. Benzylidene ring opening of **4**, using different reagents.



Entry	Reagent	Solvent	**5** (%)	**15** (%)	**16** (%)	**17** (%)	Yield (%)	Other conditions
1	$AlCl_3/{}^tBuOOH$	CH_2Cl_2	100	-	-	-	80	Under N_2 at –40^oC
2	$Pd(OAc)_2/{}^tBuOOH$	Benzene	-	66	33	-	50	Stirring at rt for 6 days
3	$CuCl_2/{}^tBuOOH$	Benzene	-	60	40	-	65	Stirring at rt for 6 days
4	I_2	MeOH	90	-	-	10	45	Refluxing for 5 hr
5	p-TsOH.H_2O	MeOH	90	-	-	10	65	-10^oC
6	p-TsOH.H_2O	MeOH	-	-	-	100	70	Refluxing
7	$AlCl_3/LiAlH_4$	THF	-	50	50	-	30	Under N_2 at 0^oC

In a further attempt, we hydrolysed the benzylidene ring by the I_2/MeOH [20] to get the diol **5**, but the desired product was formed in about 10% yield only.

Stirring the olefin acetal **4** in methanol containing catalytic amounts of *p*-toluenesulfonic acid monohydrate [21] gave, at –10 ^{o}C, the hydrolysed product **5** in good yield. It was, however, observed that at higher temperature (even at room temperature) a considerable amount of furandiol **17** was also formed. Various attempts to open the benzylidene ring are summarised in Table 1 and it was shown that $AlCl_3$/^{t}BuOOH in CH_2Cl_2 at –40 ^{0}C was the best method for the hydrolysis of **4.**



Scheme 3. Total synthesis of *S*-(+) argentilactone **(11)** starting from methyl-α-D-glucopyranoside **(2)**. *Reagents and conditions*: a) α,α–dimethoxytoluene, *p*-toluenesulfonic acid, DMF, reflux under reduced pressure, 1h, 97%; b) PPh_3, imidazole, CHI_3, toluene, reflux, 2h, 87%; c) $AlCl_3$, t-BuOOH, CH_2Cl_2, -40 ^{o}C, 30 min, 80%; d) benzoyl chloride, pyridine, 0 ^{o}C, 8h, 90%; e) MsCl, pyridine, 5 ^{o}C, 4h, 95%; f) lithium triethylborohydride, THF, 12h, 70%; g) oxalyl chloride, DMSO, -40 ^{o}C, Et_3N, 1h, 90%; h) $C_6H_{13}PPh_3Br$, *n*-BuLi, 80%; i) aq H_2O_2, MoO_3 and then Ac_2O, pyridine, 70%.

Selective protection of the diol **5** at primary position with benzoyl chloride at 0 ^{o}C and mesylation of the secondary alcohol was carried out easily to produce **7** in 90 % yield over two steps. The mesyl group was displaced with Superhydride® (lithium triethylborohydride, 1 M solution in THF). Presence of a CH_2 signal at δ = 26 ppm in the ^{13}C NMR (GASPE) and a multiplet around δ = 2 ppm in ^{1}H NMR spectrum confirmed the deoxygenation at C-4 of the alcohol **8**. Swern oxidation of **8** generated the aldehyde **9**. Wittig reaction of hexyltriphenylphosphonium bromide with the aldehyde **9** produced the double bond between C-7 and C-8 in compound **10**. The *cis* stereochemistry of the double bond was indicated by the low coupling constant (J = 10.3 Hz). Finally, **10** was oxidized at the anomeric position with aqueous H_2O_2 in the presence of a catalytic amount of MoO_3 [22] to generate the target argentilactone **11** in ~30% overall yield from **2.** All spectroscopic data correlated with the reported natural product **1a** except the optical rotation ($[\alpha]_D$ = +21, c =1, EtOH) which was reverse compared to that reported ($[\alpha]_D$ = -21.1, c = 2.25, EtOH) for **1a** [6].

II. Total Synthesis of *R*-(-)-Massoilactone (1b) and 5*S*,6*R*-(+)-*O*-Acetylosmundalactone (1c)

II.1. Massoilactone (1b)

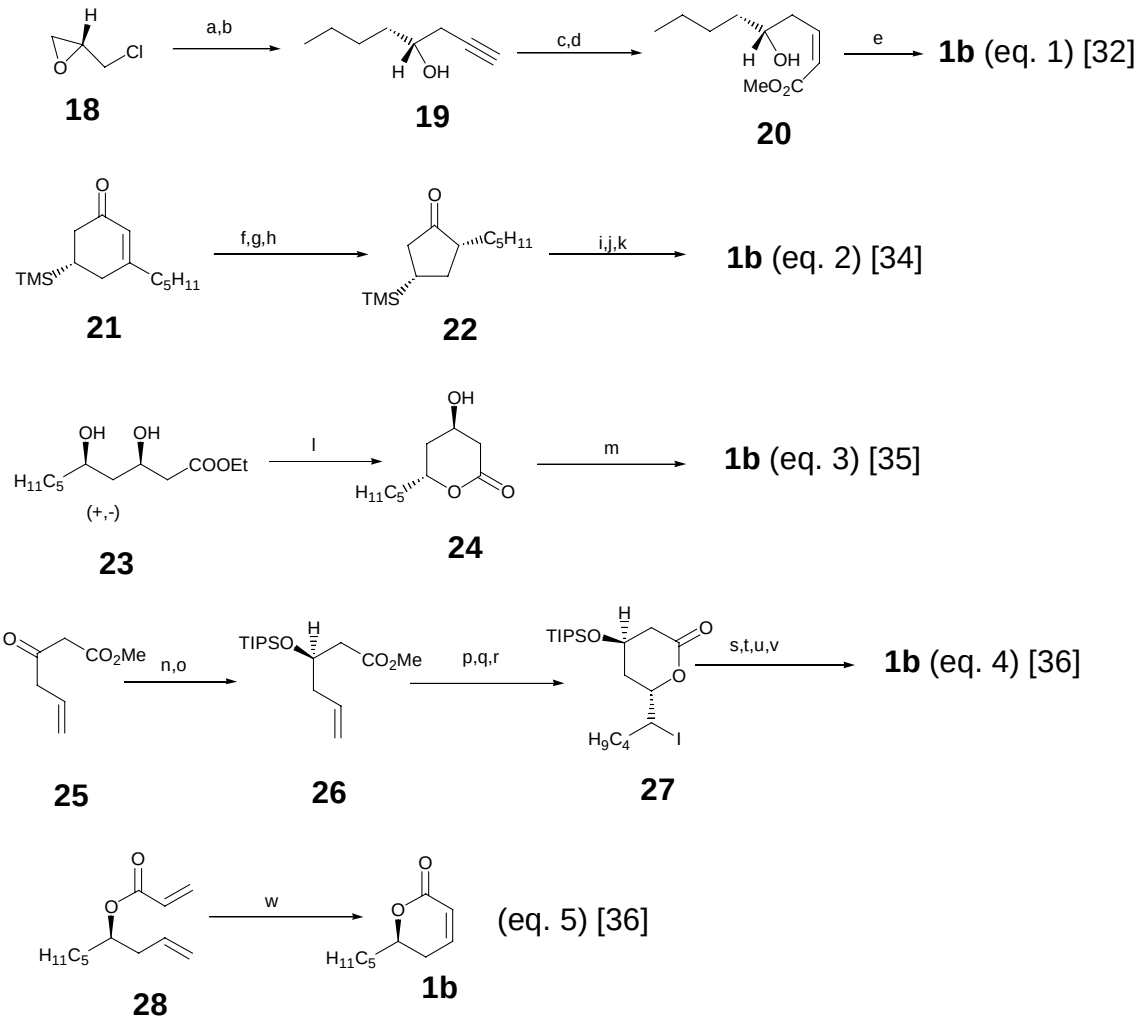
Pheromones, allomones and kairomones are chemical substances that control the inter- and intraspecific behavior of a variety of bioorganisms e.g. flies, moths, cockroaches, beetles, weevils, rootworms, ants and bees, etc [23]. (-)-Massoilactone (**1b**) is the allomone of the two species of formicine ants of the genus *camponotus*, collected in Western Australia [24]. In 1937, Abe isolated (-)-massoilactone (**1b**) for the first time from the bark oil of *Cryptocarya massoia*, used for many centuries as a constituent of native medicine [25]. It has also been isolated from jasmine flowers [26] as well as from cane molasses (in which it is a flavor component) [27]. Its gross structure was confirmed by the synthesis of its racemic material [28] and the assignment of the absolute stereochemistry, as *R*, was confirmed by comparative ORD studies [29] and syntheses of the non-natural (6*S*) enantiomer [30]. In addition to various methods [28,30,31] for the synthesis of **1b**, a number of asymmetric syntheses have been reported in the literature, based on the chiral pool as starting material [32-34], chiral induction [35-37,39] or chromatographic resolution of diastereomeric derivatives of the lactone precursor [38].

An efficient strategy involving the use of *R*-epichlorohydrin (**18**) as chiral pool material was reported, where **18** undergoes successive alkylations to generate **19**. Methoxy carbonylation of the acetylenic end followed by reduction with Lindlar

catalyst and lactonization produced **1b** [32] (Scheme 4, eq. 1). A similar approach was adopted by Kjær [33] who reacted the *tert*-butyl propiolate ion with a chiral epoxide, obtained from D-glutamic acid through a series of steps. In another approach chiral starting material was used for the asymmetric synthesis of **1b** using a Baeyer-Villiger oxidation of cyclopentanone **22**, obtained by epoxidation and rearrangement of the enone **21** [34] (Scheme 4, eq. 2).

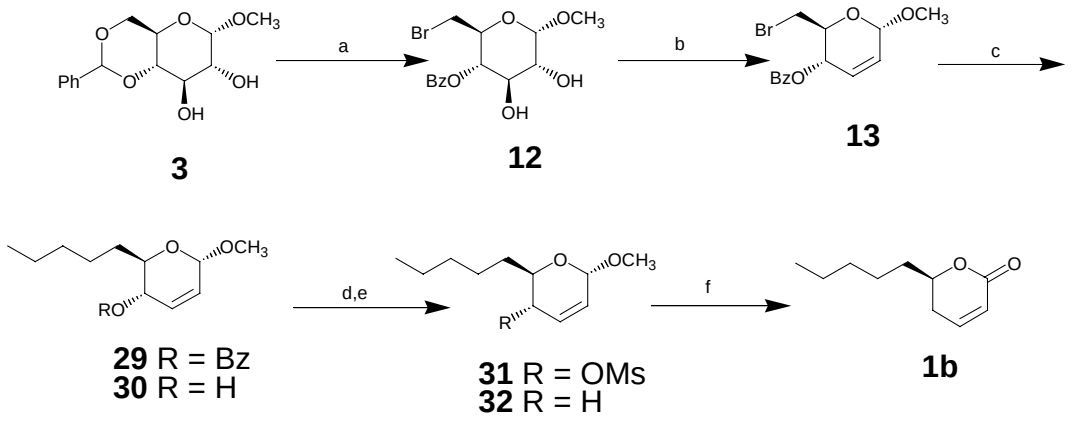
Enzymatic resolution (porcine pancreatic lipase, PPL) of racemic open chain 3,5-*syn* dihydroxy ester **23** resulted in the lactone **24** [35] which was transformed to **1b** *via* dehydration by $POCl_3$ in CH_2Cl_2 (Scheme 4, eq. 3). Use of Baker's yeast to reduce keto esters has been studied extensively. F. Bannett et al. [36] reduced β-ketoester **25** to enantiopure β-hydroxyester **26** by using baker's yeast. The hydroxyester **26** underwent a series of reactions to generate lactone **27** which can be finally dehydrated to **1b** by using $POCl_3$ in pyridine (Scheme 4, eq. 4). Recently, P. V. Ramachandram et al. [37] have reported an asymmetric synthesis of **1b** *via* an asymmetric allylboration-esterification-cyclization strategy. The key reaction is a ring-closing metathesis reaction on the di-olefine **28** in the presence of Grubbs' catayst (Scheme 4, eq. 5).

Asymmetric synthesis of **1b** still requires a method that involves the use of cheap and easily available chiral starting materials such as carbohydrates. Thus, following the lines drawn in the retrosynthetic Scheme 1, we use methyl-α-D-glucopyranoside (**2**) as a starting material for the synthesis of **1b.**



Scheme 4. Aymmetric total syntheses of **1b**. *Reagents and conditions*: a) *n*-BuLi, CuI, THF, -30 ^{o}C; b) lithium acetylide ethylenediamine (4 eq), DMSO, rt; c) CO, $PdCL_2$, $CuCl_2$, AcONa, MeOH, rt; d) H_2, Lindlar catalyst, quinoline, AcOEt, rt; e) conc. HCl-MeOH (1:3), rt; f) H_2O_2, cat. base; g) $BF_3.Et_2O$; h) NaOH; i) m-CPBA; j) LDA, Br_2; k) Bu_4NF; l) porcine pancreatic lipase (PPL), Et_2O; m) $POCl_3$, CH_2Cl_2, rt; n) baker's yiest; o) triisopropylsilyl chloride, DMF, imidazole; p) ozone, CH_2Cl_2, -70 ^{o}C and then dimethyl sulfide; q) BuLi, pentyl (triphenyl)-phosphonium bromide, THF, 20 ^{o}C; r) KOH, MeOH 16 h; s) sodium hydrogen carbonate, CH_3CN, I_2, 0^{o}C, 3h; t) Bu_3SnH, THF, reflux, 3h; u) aq HF, CH_3CN, 7h; v) $POCl_3$, pyridine, 0^{o}C→ 65^{o}C, 5h; w) bis (tricyclohexylphosphine)-benzylidene ruthenium (IV) dichloride, CH_2Cl_2, reflux, 6h.

Benzylidene acetal **3** was regioselectively opened prior to the 2,3-dideoxygenation, under the conditions developed by Hanessian [18]. The 6-bromodiol **12**, so prepared, was transformed to the 6-bromoolefine **13** by using 2,4,5-triimidazole, as described in ref. [15a] or by using iodoform/imidazole/triphenylphophine in toluene [15b].



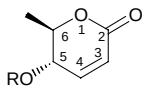
Scheme 5. Asymmetric synthesis of *R*-(-)-massoilactone (**1b**) on carbohydrate scaffold. *Reagents and conditions*: a) NBS, CCl_4, reflux; b)CHI_3, imidazole, PPh_3, toluene, reflux; c) *n*-BuLi, CuCN, THF, -30^oC ; d) MsCl, pyridine, 5 ^oC; e) Superhydride®, THF, reflux; f) MoO_3, H_2O_2, and them Et_3N and Ac_2O.

We envisioned at this point that nucleophilic attack by lithium dibutylcuprate would generate the intermediate **29**. However, it was observed that nucleophilic displacement of bromine in **13** with lithium dibutyl cuprate, $(n\text{-}Bu)_2Cu(CN)Li_2$, obtained from *n*-butyl lithium and CuCN in the same flask [40], afforded **30** in good yield. It seems that under highly basic conditions deprotection of the benzoyl group also take place. Mesylation of the resulting secondary alcohol was achieved almost quantitatively under standard methods. Hydride displacement of

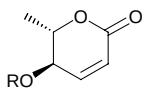
the mesylate **31** with Superhydride® was carried out successfully to yield **32**. Anomeric oxidation with aqueous H_2O_2 in the presence of catalytic amounts of MoO_3 [22] was conducted to produce *R*-(-)-massoilactone (**1b**) in 40% overall yield from **2**. All the physical data (mass, NMR, optical rotation) corresponded to the natural massoilactone (**1b**).

II.2. Osmundalactone (1c)

(5*S*,6*R*)-Osmundalactone (**1c**) (pyran nomenclature is followed for numbering) was isolated by Buchanan from *Paxillus atrotomentosus*, a lignicolous mushroom [41]. Its absolute stereochemistry was determined as 5*S*,6*R*, when spectroscopic and optical rotation data were compared with the 5*R*,6*S*-enantiomer **34**, which was isolated earlier from *Osmunda japonica* Thunb [42].



1c R = H
33 R = Ac

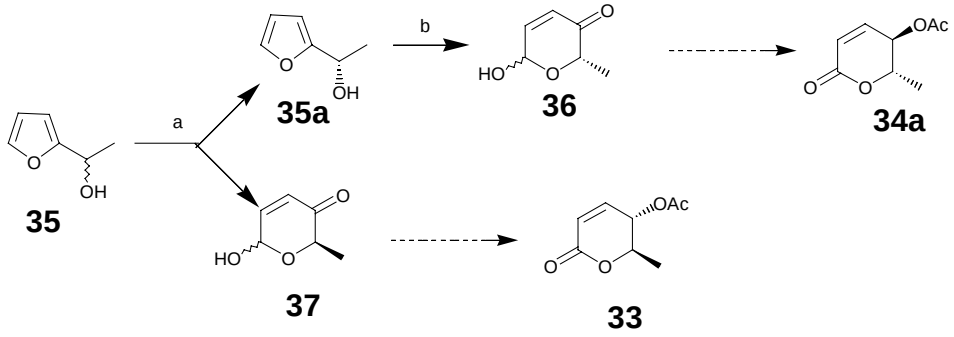


34 R = H
34a R = Ac

Fig. 3. 5S,6R-Osmundalactone **(1c)**, its enantiomer **34** and their 5-O-acetylated derivatives **33** and **34a**.

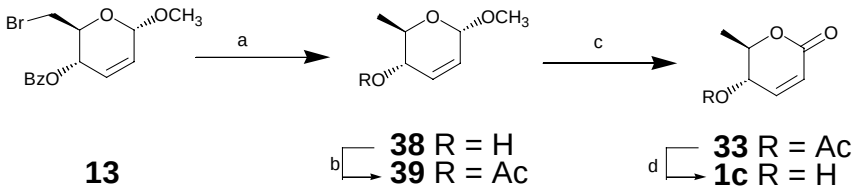
Owing to some interesting biological activity [43], a number of syntheses on **34** were reported [44-46]. However, to the best of our knowledge, only one synthesis for **1c** has been achieved so far, based upon the resolution of the furyl methyl alcohol **35** [47] (Scheme 6). The enones **36** and **37** were further transformed to

the acetylated natural products **33** and **34a**, respectively, in less than 20% overall yield from the starting furfural.



Scheme 6. Syntheses of both enantiomers of 5-*O*-acetylosmundalactone **33** and **34a** [47]. *Reagents and conditions*: a) $Ti(OPr^i)_4$, D-(-)-DIPT, TBHP, CH_2Cl_2, b) NBS, THF:H_2O (4:1)

In order to extend our strategy for α,β–unsaturated δ–lactones from carbohydrates, we started to synthesize **1c**. Methyl 6-bromo-4-benzoyl-2,3,4-trideoxy-α-D-2-hex-enopyranoside (**13**), which failed to produce the triphenyl-phonium salt **14** (see the total synthesis of *S*-argentilactone **(11)**), was chosen as a candidate for the formation of the allylic alcohol **38** by treating it with an excess of lithium triethylborohydride (Superhydride®, 1 M in THF). The alcohol **38** was protected with acetic anhydride and finally oxidized at anomeric position to produce the target 5-*O*-acetylosmundalactone in excellent yield. The acetate **33** can be exposed to enzymatic hydrolysis using the lipase „Amano P“ from *Pseudomonas* sp [48] for the total synthesis of natural **1c**.



Scheme 7. Asymmetric synthesis of acetylosmundalactone **32**. *Reagents and conditions*: a) $LiBHEt_3$, THF, rt and then heat at 40 °C for 30 min. b) Ac_2O, Py, 5 °C, c) aq H_2O_2, MoO_3 and then Ac_2O, pyridine, d) Lipase „Amano P“, phosphate buffer.

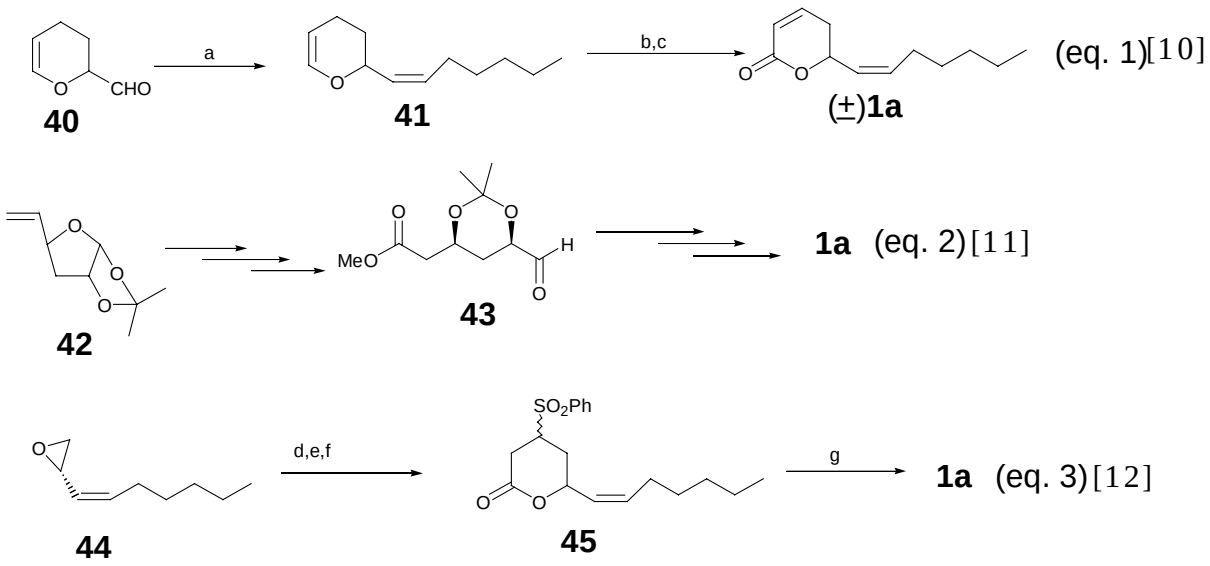
III. Total Synthesis of *R*-(-)-Argentilactone (1a)

Argentilactone (**1a**), an α,β-unsaturated δ-lactone, was originally isolated in 1977 from the rhizomes of *Aristolochia argentina* Gris [6]. This compound is the major constituent of the essential oil and hexane extract of *Annona haematantha* [7] and also present in the methanolic extract of the leaves of *Chorisia crispiflora* [8]. The biological studies on **1a** have revealed high antileishmanial [7] and cytotoxic activity against P-388 mouse leukaemia cells [8]. Moreover, it can also be used as starting material for the synthesis of interesting pheromones [9]. These features prompted some research groups to undertake the total synthesis of this compound.

In 1981, Fehr C. et al [10] reported the first synthesis of racemic argentilactone (**1a**), based on the dye-sensitised photooxigenation of dihydropyrane **41** and dehydration of the intermediate allylic hydroperoxide (Scheme 8, eq. 1). S. Chandrasekaran et al later on improved the method by using PDC/t-BuOOH as an oxiding reagent for dihydropyrans [13].

B. O'Connor and G. Just [11], later on, reported on the total synthesis of **1a** on carbohydrate scaffold (Scheme 8 eq. 2). Starting from the olefin **42**, the aldehyde **43** was obtained in about 49% yield over six steps. Finally, they obtained the target argentilactone over a series of reaction on **43** in around 10% overall yield from **42** [11]. L. Ghosez [12] employed an efficient strategy, by reacting the epoxide **44** with the anion generated from methyl 3-phenylsulphonylortho-

propionate which subsequently underwent lactonization and elimination to produced α,β-unsaturated δ–lactone **1a** (Scheme 8, eq. 3).



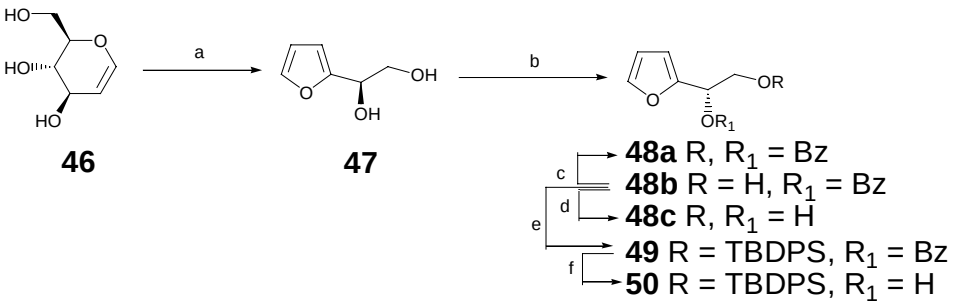
Scheme 8. Earlier syntheses of **1a.** *Reagents and conditions*: a) $Ph_3P(CH_2)_5CH_3Br$, $NaN(SiMe_3)_2$, THF; b) $^1O_2$, meso-tetraphenylporphine, toluene, irradiated with high pressure mercury lamp; c) Et_3N, Ac_2O, rt, overnight, d) *n*-BuLi, methyl 3-phenylsulphonylorthopropionate; e) H_3O^+; f) p-TsOH; g) Et_3N or DBU.

In the first chapter of this thesis, the total synthesis of the non-natural enantiomer of argentilactone **11** from glucose has been described. As the stereochemistry of the natural argentilactone (**1a**) at C-6 (pyran nomenclature) is *R*, one needs a sugar from the L-series. If L-glucose would have been easily available, the strategy given in Scheme 3 would have been successful for the syntheses of *R*-(-)-argentilactone (**1a**) and other α,β–unsaturated δ-lactones having similar stereochemistry at C-6. In order to solve this stereochemical problem, we have applied the efficient method of F. M. Hauser [47] to convert commercially available D-glucal (**46**) into the optically active furan glycol **47**, followed by inversion of the configuration at the asymmetric centre at C-2 by the

Mitsunobu reaction [48]. Although the authors used 2 equivalents of the reagent PPh_3, DEAD and benzoic acid to produce the crystalline dibenzoate **48a** in 92 % yield, we found that the use of one equivalent of reagent gave the monobenzoate **48b** with the free primary hydroxyl group in more than 80% yield containing dibenzoate **48a** in less than 5% yield. Verification that the inversion was stereospecific was obtained from the fact that the optical rotation of **48c** was identical in magnitude, but opposite in sign to that of the furandiol **47**. **48c** was prepared by hydrolysis of **48b** and **48a**.

Thus, the commercially available D-glucal (**46**) was converted into the furandiol **47** under the conditions ($HgSO_4$, 0.002 M H_2SO_4) defined by Gonzalez and co-workers [49] in 90% yield. The appearance of characteristic signals at δ 153.6, 110.3 and 106.9 ppm in the ^{13}C NMR spectrum of **47** indicated the furan moiety to be substituted at C-5. Inversion of the configuration of the secondary alcohol in **47** was carried out by the Mitsunobu reaction, using, 2.1 equivalents of PPh_3, DEAD, and benzoic acid, each in dry THF, to produce the dibenzoate **48a** (mp 82-84 ^oC, $[\alpha]_D^{25}$ –72.2, in CH_2Cl_2). The reaction was then repeated using the same conditions but a 1:1 equivalent amount of the reagents to yield the monobenzoate **48b**. A down-field absorption of the methane proton at δ 6.19 ppm of H-2 in the ^1H-NMR spectrum of **48b** indicated the benzoylation of the secondary hydroxyl group. Furthermore, benzoylation (PhCOCl, Py, Et_2O) of **48b** yielded **48a** with identical physical data, including the optical rotation. On the other hand, removal of the benzoyl group ($MeOH/Et_3N/H_2O$ (5:1:4)) in **48b** gave the furan glycol **48c**, having the optical rotation, same in magnitude, but opposite in the sign ($[\alpha]_D^{25}$ –36, in CH_2Cl_2) to **47**, hence confirming the inversion of the configuration at C-2.

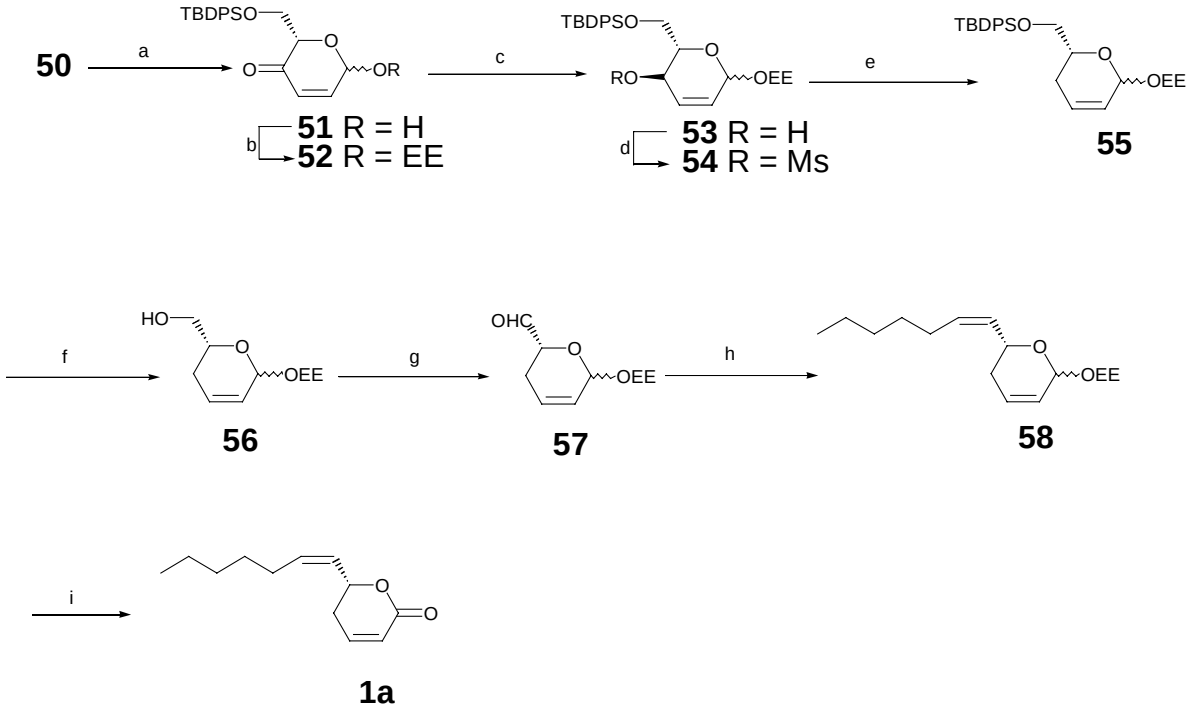
The free hydroxyl group was protected as *tert*-butyldiphenylsilyl ether (TBDPSCl, DMF, imidazole) [50] in quantitative yield to afford **49**. Removal of the benzoyl group was tested by reacting **49** with $MeOH/H_2O/Et_3N$, however the yield was low and most of the starting material was recovered back even after stirring at reflux for more than 36 h. Use of lithium aluminium hydride was also not successful because it removed the TBDPS group [51] to yield **48c**. Finally, sodium in methanol was tried giving optimum result. Thus, catalytic sodium in methanol was used to afford the monohydroxyfuran derivative **50**, protected at its primary position with TBDPS group (Scheme 9).



Scheme 9: Conversion of D-glucal (**46**) into furan-alcohol **50**. *Reagents and condititons*: a) H_2O/H^+, $HgSO_4$, rt, 3h, b) PPh_3, DEAD, benzoic acid, THF, 2h, c) BzCl, Py, ether, d) MeOH, Et_3N, H_2O (5:1:4), overnight at rt, e) TBDPSCl, DMF, imidazole, 0 ^oC to rt, 2h, f) $NaOCH_3$, MeOH.

Having a successful preparation of the furan alcohol **50** from D-glucal (**46**) in hand, as next step the transformation of **50** into the L-hexenulose **51** was approached. This was accomplished smoothly when **50** was oxidized with NBS [54]. The hemiacetal **51**, having the required stereochemistry at C-6 in the target argentilactone (**1a**), was obtained as a diastereometrically enriched (1:1) mixture

of anomers in deuterated chloroform. Because of its instability, **51** had to be protected as glycoside **52** recovered as a 2:3 (β:α) anomeric mixture.



Scheme 10. Total synthesis of *R*-(-)-argentilactone **1a**. *Reagents and conditions*: a) NBS, $NaHCO_3$, $NaOAC.3H_2O$, $THF:H_2O(4:1)$, 0 °C, 30 min., b) ethyl vinyl ether, PPTS, CH_2Cl_2, rt, 2h, c) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, -40 °C, 30 min., d) MsCl, Py, 5 °C, e) $LiBHEt_3$, THF, 40 °C, 3 h, f) tetrabutylammonium fluoride, THF, under nitrogen, 1 h, g) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 °C, 30 min., h) hexyltriphenylphosphonium bromide, *n*-BuLi, THF, -50 °C, i) H_2O_2, MoO_3 (catalytic), and then Et_3N, Ac_2O.

The ketone **52** was reduced with $NaBH_4$ in methanol at –40 °C in the presence of $CeCl_3.7H_2O$ to give the trans product **53**, which was mesylated (MsCl, Py, 5 °C) in excellent yield to produce the mesylate **54**. The rest of the strategy was similar as was adopted for the synthesis of the non-natural enantiomer **11**, i.e. the mesylate **54** was treated with superhydride® to produce the C-5 deoxygenated product **55**. The TBDPS group was removed with tetra-*n*-butylammonium fluoride in

quantitative yield and the generated primary alcohol **56** was subjected to Swern oxidation (oxalyl chloride, DMSO, Et_3N, -78 ^oC) to produce the aldehyde **57** in 90% yield. Wittig reaction of **57** with hexyltriphenylphosphonium bromide gave the olefin **58** in the desired *cis* configuration in 78% yield as was indicated by the coupling constant $J_{7,8}$ = 10.2 Hz in the ^1H NMR spectra of the final compound. Compound **58**, an anomeric mixture, produced a very complex ^1H NMR spectrum and the assignments were not carried out. Finally, **58** was oxidized by H_2O_2 in the presence of catalytic amounts of MoO_3 to generate the target argentilactone (**1a**). All physical data (MS, ^1H and ^{13}C NMR, optical rotation etc) were found to be identical with those reported for the natural argentilactone [6]. Biological studies, carried out on the argentilactone are discussed in the next chapter.

IV. Leishmaniasis and Antileishmanial Activity of *R*-(-)-Argentilactone (1a)

IV.1 Introduction

Leishmaniasis, also known as „Kala Azar“, „black fever“ or „black sickness“ is caused by Protozoan parasites of the genus *Leishmania*. Although the infection is endemic in tropical and subtropical countries, it is spreading to Spain, southern France and Italy, reaching 88 countries world-wide. It has affected 12 million people and more than 350 million people are currently living in endangered areas [55]. According to the estimates of WHO, about 2 million people are infected every year, and 500,000 suffer from visceral leishmania [56], a particular serious and, without treatment, always fatal form of the disease.

Leishmania parasites exist in two forms: an amastigote in the mammalian host and a flagellated promastigote in the insect vector. The natural vectors of all leishmania are almost 30 species of sandflies (Phlebotominae). After a sandfly bites a Leishmania-infected mammal, amastigotes, present in the ingested blood, undergo a number of morphological changes in the insect's abdominal midgut. This leads to the formation of haptomonad promastigotes, either free-swimming or attached to the cutile by flagella and free-swimming, highly motile, non-dividing metacyclic promastigotes, present mainly in the insect's foregut [57]. This latter stage is transmitted into the skin of a mammalian host during the bite of an infected sandfly and

exhibits several preadaptations for this radical change of their environment [58]. In the mammalian skin, the metacyclic promastigotes bind to receptors on the surface of macrophages and are subsequently taken up by phagocytosis. Inside the host cell, the promastigotes rapidly transform within 12-24 h to amastigotes, while the initial phagosome matures to a phagolysosome by acidification and acquisition of lysosomal hydrolases. Within this hostile environment the amastigotes multiply, and eventually, the host cell lyses by an unknown mechanism. The released amastigotes spread by invasion and colonization of other macrophages.

IV.2. Forms of leishmaniasis

There are various forms of leishmaniasis. A particularly dangerous and often fatal form is visceral leishmaniasis (Kala Azar) which is caused by the pathogen *Leishmania donovani.* The parasites live in the liver, spleen and marrow and reproduce rapidly. Typical symptoms of visceral leishmaniasis are fever, tiredness and rheumatism along with general weakness which ends in a gradual but complete destruction of the liver and spleen. Without treatment, the infection results in death [59]. More recently, visceral Leishmaniasis has emerged as an opportunistic disease in AIDS patients [60). In addition to the visceral form, there are other forms of cutaneous leishmaniasis (oriental sores or oriental buttons) which cause skin ulcers and sometimes lead to a total disfigurement of the face. However these forms usually heal by themselves and are not lethal.

IV.3. Treatment

IV.3.1. Physical methods

Leishmania parasites are thermosensitive. In an *in vitro* study, *L. tropica* multiplied best at 35 ^{o}C and was completely eliminated at 37 ^{o}C [61] In view of this feature, treatment of the local skin ulcers has been carried out by exposure to heat [62], irradiation with ultraviolet light and infrared therapy [63] , cryosurgery with a CO_2 cryomachine [64]. Surgical excision such as scraping the lesions with a sharp spoon or cauterisation has also been employed. Currie treated 78 patients with cutaneous leishmaniasis in Pakistan by curettage under local anesthetics. He noticed that small sores responded especially well and heal within three weeks with good cosmetic results [65]. Treatment of lesions with skin flaps or free grafting in Saudi Arabia presented with good results [66], however, surgical curettage is not recommended in view of the risk of dissemination along lymphatics [67].

IV.3.2. Drug therapy

Since the earliest report of Kikuth and Schmidt [68], the pentavalent antimony compounds, sodium stibogluconate (Pentostam®, Wellcome Foundation, UK), and N-methylglucamine antimonate (Glucantime®, Specia, France) are still the drugs of choice for the treatment of visceral leishmaniasis [69,70] and cutaneous leishmaniasis [71,72]. However, they are extremely toxic and show a number of side effects like cardiotoxicity,

reversible renal insufficience, pancreatitis, anemia, leukopenia, rash, headache, myagia etc [73]. In addition, treatment failure has been frequently observed [74-76]. More recently, strains of leishmania resistant to pentavalent antimonials have emerged and this has reached alarming proportions in some contries [77]. Other drugs in use involve pentamidine [78], ketoconazole, clotrimazole, miconazole, fluconazole and itraconazole [79,80].

IV.3.2.1. Miltefosine

In 1999, Barbara Herwaldt introduced Miltefosine as a new drug for the treatment of leishmaniasis, showing good results against *leishmania donovani* in the cell culture [81a]. In animal experiments, some problems were encountered in the initial trials by injecting miltefosine intravenously as this resulted in homolysis and significant changes in the tissue. Injecting it directly underneath the skin did not help as well because of extensive and intolerable ulcers and changes in the skin around the puncture point. Surprisingly, the oral intake of the substance *via* the alimentary canal worked well. The results were exciting and very revealing: the typical symptoms of the disease- enlargement of the liver and the spleen- did actually disappear rapidly. In comparison with the conventional pentostam therapy, the effect of miltefosine was at least 600 times better- a result which no one had ever dared to dream of after the negative experience with the intravenous or subcutaneous administration method.

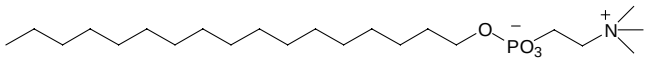


Fig. 4a. Structure of hexadecylphosphocholine (Miltefosine).

Chemically, miltefosine is hexadecylphosphocholine, having a simple molecular structure (Fig. 4a). It was discovered by Hansjörg Eibl and Clemens Unger by studying the effect of structural modification in alkyllysolecithins on the antineoplastic activity of these compounds [81b]. Surprisingly, some of compounds like hexadecylphosphocholine were highly effective in animal models after oral applications and were, therefore, prepared for clinical studies. In many years of work, Eibel's and Unger's research groups developed the world-wide first drug that is based on the structure of the phospholipid molecule. They also tested miltefosine, as a drug useful against skin metastases in breast cancer, its effects against leishmaniasis and malaria in cell culture experiments and in animal tests.

IV.3.2.2. Argentilactone

Twenty years after its isolation, argentilactone (**1a**) [6-8] was evaluated as an antileishmanial natural product [7]. The *in vivo* studies carried out on BALB/c mice, infected with *Leishmania amazonensis*, showed a decrease of the lesions size in treated mice, especially in the mice which have received argentilactone by the subcutaneous route; in this case, the decline of lesion

size was up to 50%. These results were comparable with those that were obtained with the reference drug, N-methylglucamine antimonate.

These results prompted us to undertake the total synthesis of the natural compound. Chapter III of this thesis describes the synthetic pathway of argentilactone (**1a**). The impact of the synthetic argentilactone on the growth on *Leishmania mexicana* was then assessed. *Leishmania* (L) *mexicana* LV4 (MNYC/BZ/62/M379, LEM280) promastigotes were grown in semi-defined medium 79 [82], supplemented with 4% heat-inactivated fatal calf serum at 26-27 ^{o}C. To preserve their virulence, *L. mexicana* promastigotes were isolated from mouse lesion amastigotes at 8-12 week intervals. For toxicity studies, cultures were seeded at 10^5/ml promastigotes with the addition of either 5 g/ml or 10 μg/ml argentilactone (dissolved in 5 mg/ml in dimethylsulphoxide) or equivalent volume solvent. After the initial lag phase (~90h), the promastigotes density was determined at 24 h intervals by triplicate counting of the cell numbers.

In the present study the impact of the synthetic argentilactone on the growth of *L. mexicana* is assessed to investigate whether this substance is indeed the active principle of the above preparations. Fig. 4b shows the results of this assessment. At 5μg/ml concentration, synthetic argentilactone leads to marked growth retardation in promastigote cultures, while at 10μg/ml, the parasites are unable to proliferate and die within 2-3 days. These results unequivocally indicate the pharmacological activity of argentilactone. The efficiency of argentilactone against *in vitro*-cultured *Leishmania* promastigotes is comparable to that of the main clinical anti-*Leishmania* drug,

sodium stiboglucanate [83]. This indicates the promising future for argentilactone to be used as a lead compound for the development of new anti-*Leishmania* drugs by a combination of chemical modifications of its basic structure and *in vivo* drug efficacy studies in the *Leishmania*/mouse model.

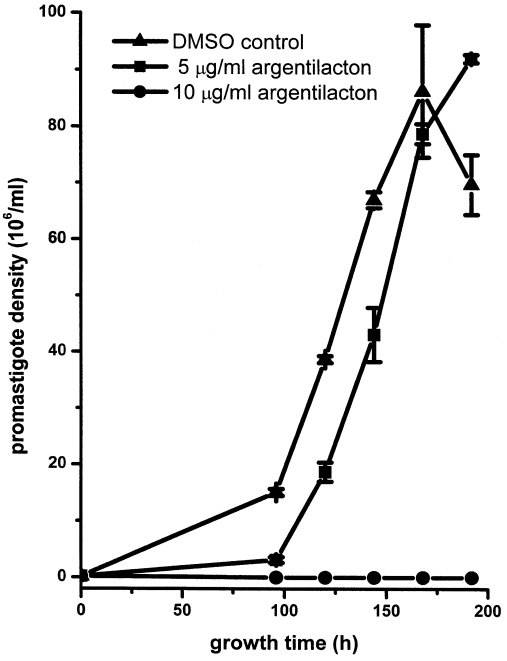


Fig. 4b. The effect of argentilactone concentration on the growth of *L. mexicana*.

V. 2,3-Anhydropentoses: Preparation of Starting Materials

This part of the thesis demonstrates a veriety of examples for regio- and stereoselective transformations of 2,3-anhydropentoses delivering a series of chiral targets (Fig. 2)

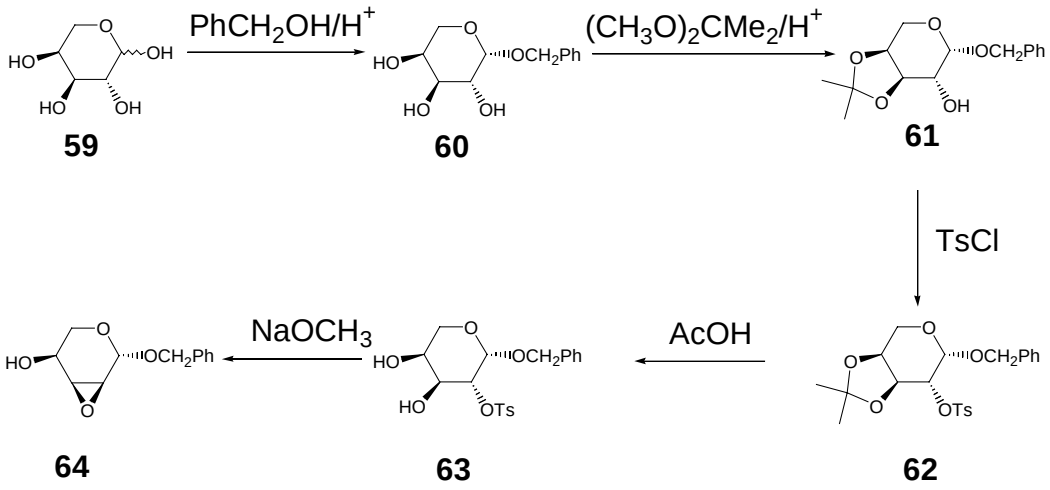
V.1. Synthesis of benzyl 2,3-anhydro-β-L-ribopyranoside (64) [84a]

The synthesis of the compound **64** was successfully performed in 6 steps, starting from the commercially available L-arabinose (**59**). Benzylation of L-arabinose in the presence of hydrogen chloride leads to the anomerically protected benzyl β-L-arabinopyranoside (**60**) [85]. The *cis*-oriented hydroxyl groups at C-3 and C-4 were protected *via* 2,2-dimethoxypropane and *p*-toluene sulfonic acid (as a catalyst) in acetone, performing benzyl 3,4-di-O-isopropylidene-β-L-arabinopyranoside (**61**). The free hydroxyl group at C-2 was directly tosylated with *p*-toluene sulfonyl chloride in pyridine, affording compound **62**. The isopropylidene protecting group was selectively removed from **62** with 90% acetic acid to yield **63** [86]. The target compound **64** was finally obtained by the action of sodium methoxide in methanol on compound **63**, followed by the neutralization with dilute hydrochloric acid (Scheme11).

V.2. Synthesis of benzyl 2,3-anhydro-α-D-ribopyranoside (73) [84a]

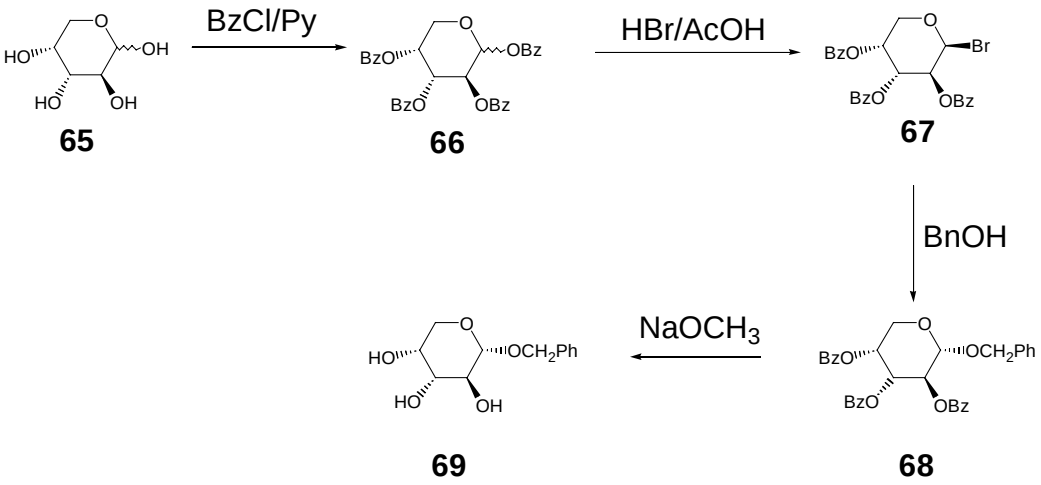
The synthesis of compound **73** was achieved from D-arabinose (**65**), whereby it is known that direct benzylation does not yield the α-anomer in high quantity due the anomeric effect. In order to overcome this problem, one has to follow an

alternative procedure (Scheme 12) [87], in which **65** is converted to the tetrabenzoyl derivative **66** by the action of benzoyl chloride in pyridine. The anomeric mixture of compound **66** was treated with hydrogen bromide in 30% acetic acid to furnish **67** which, *via* an SN_2 reaction with benzyl alcohol, affords the α-D-benzyl glycoside. The benzoyl groups in **68** were removed by sodium methoxide in methanol, to give benzyl α-D-arabinopyranoside (**69**).

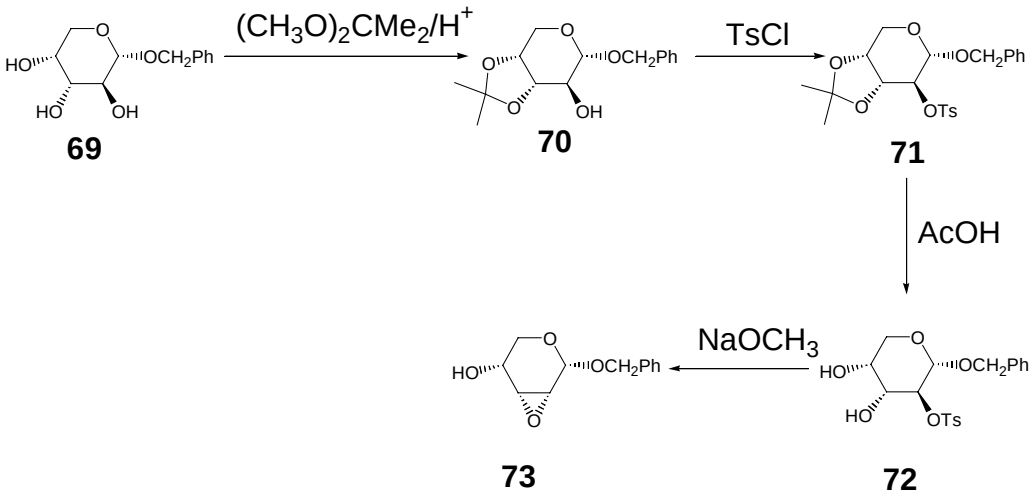


Scheme 11. Synthesis of benzyl 2,3-anhydro-β-L-ribopyranoside (**64**) from L-arabinose (**59**) *via* benzyl β–L-arabinopyranoside (**60**), benzyl 3,4-O-isopropylidene-β-L-arabinopyranoside (**61**), benzyl 3,4-O-isopropylidene-2-O-*p*-tolylsulphonyl-β-L-arabinopyranoside (**62**) and benzyl 2-O-*p*-tolylsulphonyl-β-L-arabinopyranoside (**63**).

The target compound **73** was obtained following an analogous reaction sequence as described for the synthesis of compound **64** (Scheme 13) [84a].



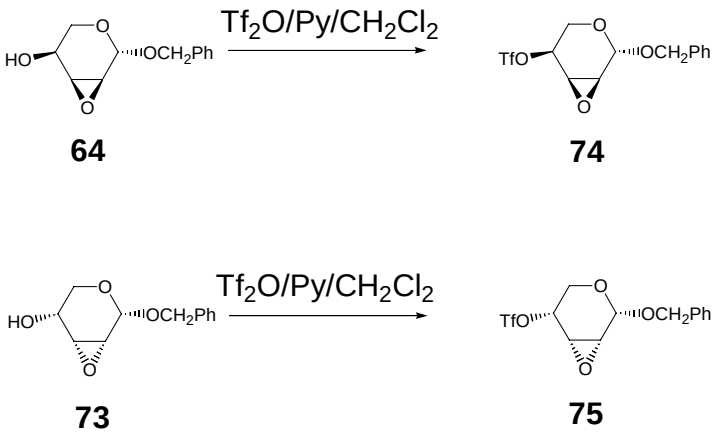
Scheme 12. Synthesis of benzyl α-D-arabinopyranoside (**69**) from D-arabinose (**65**) *via* the tetrabenzoate of arabinose (**66**), 2,3,4.tri-O-benzoyl-β-D-arabinopyranosyl bromide (**67**) and benzyl 2,3,4-tri-O-benzoyl-α-D-arabinopyranoside (**68**).



Scheme 13. Synthesis of benzyl 3,4-anhydro-α-D-ribopyranoside (**73**) *via* benzyl α-D-arabinopyranoside (**69**), benzyl 3,4-O-isopropylidene-α-D-arabinopyranoside (**70**), benzyl 3,4-*O*-isopropylidene-2-*O*-*p*-tolylsulphonyl-α-D-arabinopyranoside (**71**) and benzyl 2-*O*-*p*-tolylsulphonyl-α-D-arabinopyranoside (**72**).

V.3. Syntheses of benzyl 2,3-anhyro-4-O-triflyl-ribopyranosides [84a]

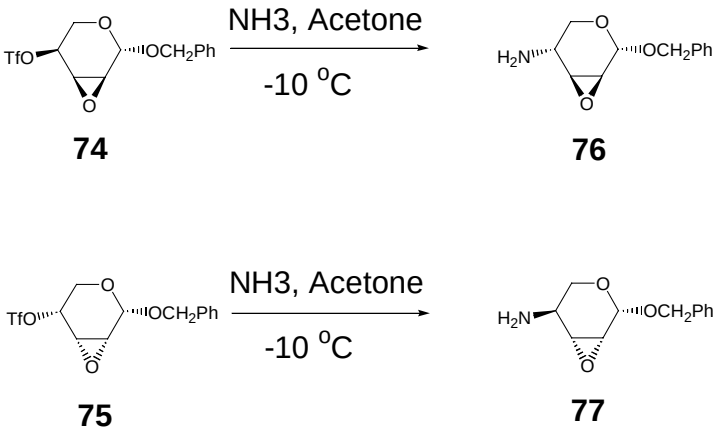
The triflation of the free hydroxyl groups in **64** and **73** were successfully achieved at low temperature (-20 °C) *via* treatment with trifluoromethane-sulfonic anhydride in dichloromethane. The triflates **74** and **75** were obtained in high yield upon basic work up at 0 °C (Scheme 14).



Scheme 14. Synthesis of benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside (**74**) and benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (**75**) from benzyl 2,3-anhydro-β-L-ribopyranoside (**64**) and benzyl 2,3-anhydro-α-D-ribopyranoside (**73**), respectively.

V.4. Syntheses of benzyl 4-amino-2,3-anhydro-4-deoxy-lyxopyranosides [88]

The reaction of epoxy triflates **74** and **75** with ammonia gas were carried out in acetone at –10 °C to afford benzyl 2,3-anhydro-4-amino-4-deoxy-α-D-lyxopyranoside (**76**) and benzyl 2,3-anhydro-4-amino-4-deoxy-β-L-lyxopyranoside (**77**), respectively, in excellent yield (scheme 15) [88].



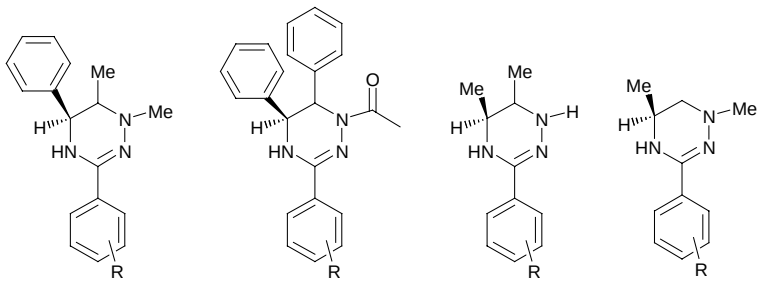
Scheme 15. Synthesis of benzyl 2,3-anhydro-4-amino-4-deoxy-α-D-lyxopyranoside (**76**) and its β-L-isomer **77** from epoxy triflates **74** and **75**, respectively.

VI. Expeditious Syntheses of Optically Pure 1,4,5,6-Tetrahydro-*as*-triazines, Fused to the Carbohydrate Skeleton

Carbohydrates provide an important source for the synthesis of optically pure targets in organic and medicinal chemistry. The defined topology and stereochemistry of the carbohydrate framework permits an array of new strategies with unique synthetic properties to design artificial as well as natural materials [89,90]. Quite some time ago, we became interested in developing new methodologies for the synthesis of sugar-fused heterocycles [91]. Despite the achievements in the earlier described areas, we intended to expand the versatility and specificity of our strategies to other important targets.

Substituted 1,4,5,6-tetrahydro-*as*-triazines like **78-81a-g** (Fig 5) have been reported in literature [92-97)] showing insecticidal, herbicidal and fungicidal activities [92]. They can also prolong the hypnotic effects of barbiturates [93], act as analgesics [94,95], and also possess anticonvulsant properties [95]. However their syntheses suffer from the formation of a mixture of products [96,97] or involve hard reaction conditions [93,94]. Recently, one coworker of Voelter's group has demonstrated that benzyl 4-amino-2,3-anhydro-4-deoxy-α-D-lyxopyranoside (**76**) and benzyl 4-amino-2,3-anhydro-4-deoxy-β-L-lyxopyranoside (**77**), containing an amino group adjacent to an oxirane ring, displayed electrophilic and nucleophilic reactivity which upon reaction with *p*-

substituted phenylisothiocyanate afforded the corresponding thiazoline ring in one step [98].



78 **79** **80** **81**

	a	**b**	**c**	**d**	**e**	**f**	**g**
R	*o*-Cl	*m*-Cl	*p*-Cl	*p*-F	*p*-NO_2	*m*-Me	*p*-MeO

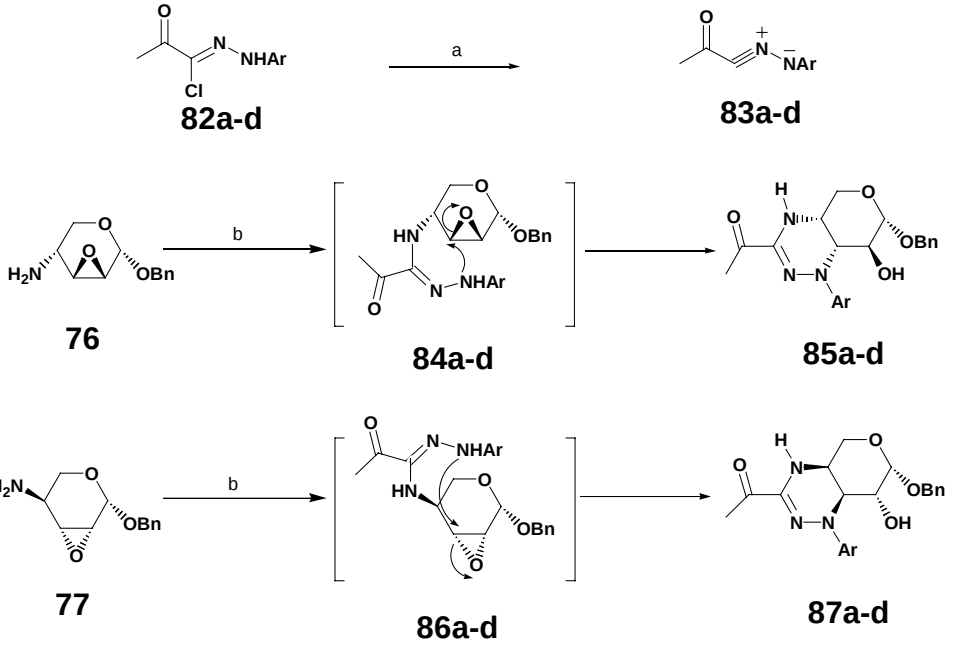
Fig. 5. Substituted 1,4,5,6-tetrahydro-*as*-triazines.

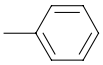
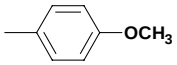
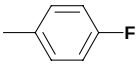
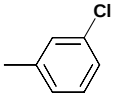
In continuation of our interest in the synthesis of carbohydrate-fused heterocycles, we synthesized some representative examples of such *as*-triazines, fused to the carbohydrate skeleton, which are, to the best of our knowledge, unknown so far.

The potentials of the novel aminodeoxy sugars **76** and **77** were exploited further by reacting them with a 1,3-dipole such as nitrile imine **83**, generated *in situ* from the reaction of triethyl amine onto the hydrazonoyl chlorides **82** [99]. The primary amine of **76** added readily on to the nitrile imine **83a-d** to yield the intermediate (*Z*)-amidrazone adducts **84a-d** [100] as the kinetically-controlled

product. The latter transient acyclic adduct underwent cyclization by opening the epoxide ring to yield pyrano[4,3-e][1,2,4]triazines **85a-d** in good to excellent yields in a one step reaction. In the similar fashion, **77** reacted with **83a-d** to produce the respective 1,2,4-triazines **87a-d** *via* the intermediate amidrazones **86a-d** (Scheme 16). The general procedure involved adding hydrazonoyl chloride **82a-d** (2 equiv.) to a stirred solution of **76** or **77** (200 mg) in methanol (10 ml) at 0 ^{o}C. Et_3N (2 ml) was added dropwise within 10 min and the temperature was allowed to raise slowly to room temperature and further stirred for 4-6 h. Normal work up and purification on silica gel column at 5% ethyl acetate in dichloromethane gave the desired triazines.

^{1}H and ^{13}C NMR, mass spectrometry and elemental analysis techniques were used to establish the structure of these compounds and unequivocally confirmed by X-Ray analysis. All compounds showed a prominent molecular ion peak in their FAB-MS spectra. The ^{13}C NMR spectra showed a quaternary carbon resonance at about δ =150 ppm indicative of imine bond (C = N). C-3 and C-4 appeared at δ = 54-56 and 46-48 ppm, respectively. Extensive ^{1}H NMR studies enabled to diagnose the predominant conformation of the pyranose ring in the final compounds.



	c	b	d	d
Ar				

Scheme 16. Synthesis 1,4,5,6-tetrahydro-*as*-triazines on pyranose templates. *Reagents and conditions*: a) Et_3N, MeOH, 0°C, b) **83a-d**, MeOH; 0 °C and then at rt, 4-6 h.

A salient feature of the ^1H NMR spectra of the series **85a-d** are the chemical shifts and the coupling constants of H-1 (δ = 4.33-4.42 ppm; *J* ~7.9 Hz), indicating an axial-axial relationship between H-1 and H-2. The coupling interaction between H-2 and H-3 were found to be large in the range of 9-10 Hz, and thus showing that $^1C_4$ is the predominant conformation in these compounds. For the other series **87a-d**, small $J_{1,2}$ coupling constants were

determined (3.36 Hz), indicating a quasi equatorial-axial relationship between the respective protons. In addition large $J_{2,3}$ (around 10 Hz), confirmed $^4C_1$ as the predominant conformation in this series.

Figure 6 shows the ORTEP diagram of compound **85a** with selected bond lengths and angles. C(4)-N(19) and C(3)-N(16) are found to have bond length values of 1.439(3) and 1.461(3) Å, respectively. A shorter bond length of the bond N(17)-C(18) is found with the value 1.303(3) Å indicating C=N bond.

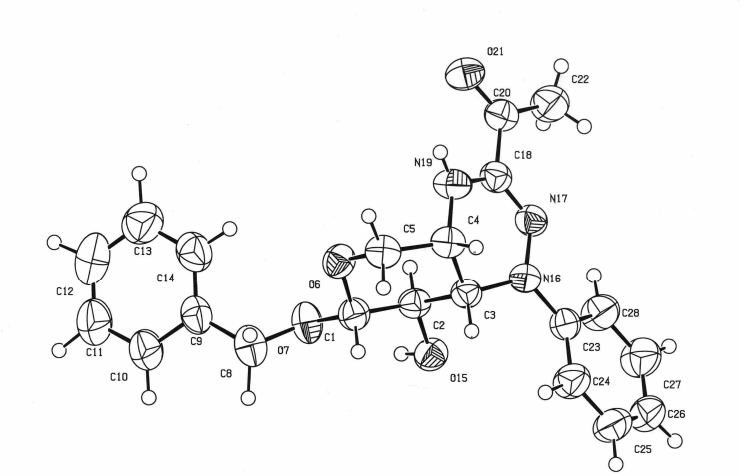


Fig. 6. The molecular structure of **85a**. Selected bond lengths (Å) and bond angles (º): C(4)-N(19) 1.439(3); N (19)-C(18) 1.352(3); C(18)-N(17) 1.303(3); N(17)-N(16) 1.369 (3); N(16)-C(3) 1.461 (3); C(3)-C(4) 1.527 (3); C(5)-C(4)-N(19) 111.1 (2); C(4)-N(19)-C(18) 120.2(2); N(19)-C(18)-N(17) 126.1 (2); C(18)-N(17)-N(16) 116.03 (19); N(17)-N(16)-C(3)118.12 (18); N(16)-C(3)-C(4) 109.34 (19); C(3)-C(4)-N(19)107.1 (2).

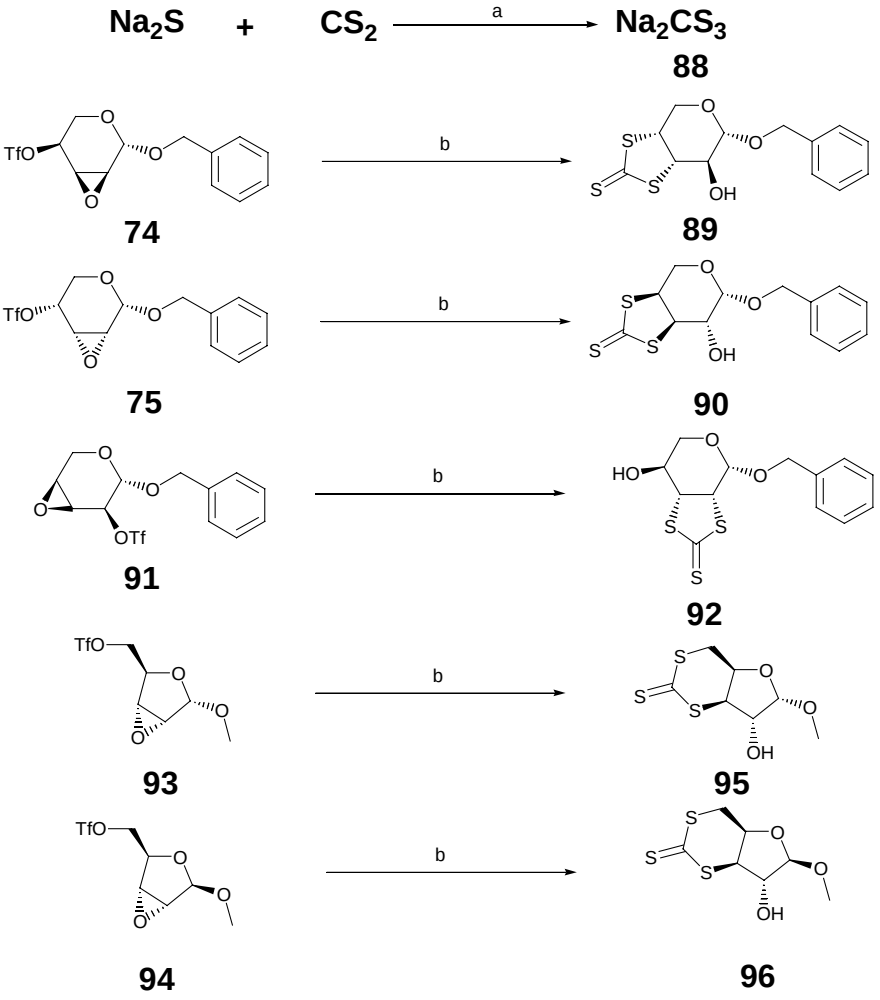
VII. A Convenient Method for the Synthesis of Cyclic Trithiocarbonates on Carbohydrate Scaffold

The preparation of monosaccharides in which one or more oxygen atoms have been replaced by a sulfur atom has received considerable attention, primarily due to the fact that these compounds provide a route to the synthesis of deoxy sugars (101). Trithiocarbonate derivatives of carbohydrates are versatile intermediates for the synthesis of dithiosugars [102] and dideoxy sugars [103]. Many non-carbohydrate organic compounds containing trithiocarbonate moiety have been reported to possess interesting biological activities [104-107], but, to the best of our knowledge, no sugar-embedded trithiocarbonate has been reported for its biological activity. Moreover only a few methods are available for the synthesis of such carbohydrate derivatives, such as the reaction of potassium methyl xanthate on epoxides [108] and episulphides [109] or in some cases the use of toxic thiophosgene gas [110].

The reaction of organic halides with sodium trithiocarbonate has been widely used for the preparation of disubstituted trithiocarbonates [111]. Moreover, alkyl mono- and dihalides, upon treatment with sodium trithiocarbonate, could easily be converted into the corresponding mono- or dimercaptan [112]. Recent efforts towards the preparation of dialkyl trithiocarbonates [113] prompted us to investigate the epoxy triflates **74** and **75** for possible candidates of sugar-based trithiocarbonates.

In the past, the triflates of the 2,3-anhydro-ribopyranosides **74** and **75** have been used by W. Voelter's research group as starting materials towards the synthesis of either new useful chiral building blocks or biologically active natural products [114-116]. The strategy banks upon the difference in the reactivity between the *cis*-oriented triflate at C-4 as a powerful leaving group and the epoxide. This strategy enables us to control the regioselective nucleophilic displacement of the triflate group forming *trans*-oriented systems which can be further modified by chemical transformations. In this chapter, a simple and efficient route for the synthesis of cyclic trithiocarbonates **89** and **90** from the anhydrotriflates **74** and **75** is described (Scheme 17). The simple one pot reaction involves the addition of a red-colored aqueous solution of Na_2CS_3 to a stirred solution of benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside (**74**) (354 mg, 1 mmol) in ethanol (5 ml) at room temperature over a period of 10 min. Na_2CS_3 can be produced by reacting Na_2S (2,44 gm, 10 mmol) in water (5 ml) with CS_2 (0.608 ml, 10 mmol) with or without a phase transfer catalyst e.g. trioctylmethyl-ammonium chloride (aliquat 336®) (22.5 µl) [117]. The nucleophilic displacement of the triflyl group at C-4 by sulfur was followed by the simultaneous intramolecular ring opening of the epoxide to afford benzyl 3,4-dideoxy-3,4-S-thiocabonyl-α-D-arabinopyranoside (**89**) in 95% yield. Similarly benzyl 2,3-anhydro-4-O-triflyl-α-L-ribopyranoside (**75**) yielded benzyl 3,4-dideoxy-3,4-S-thiocarbonyl-β-L-arabinopyranoside (**90**) in 90% yield. The reaction was then tested for triflates of other anhydrosugars. Benzyl 3,4-anhydro-2-*O*-triflyl-β-L-ribopyranoside (**91**) was prepared from **64**

by a two step reaction [118]. After treatment with the solution of Na_2CS_3, **91** is converted into trithiocarbonate **92** in a good yield (75%). However, the anhydrofuranoside **93** and **94** [119] gave a sluggish reaction to yield the trithiocarbonates **95** and **96** in less than 50% yields containing other impurities (Scheme17).



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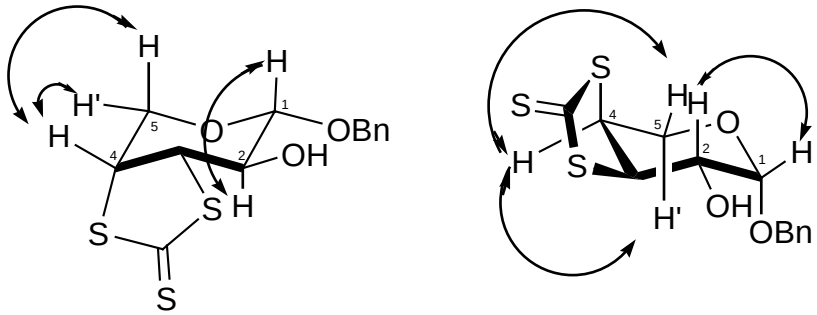
Scheme 17. Synthesis of sugar trithiocarbonates (**89**), **90**, **92**, **95** and **96** from epoxytriflates **74**, **75**, **91**, **93** and **94** respectively: *Reagents and conditions*: a) H_2O, aliquat 336®, 40 °C, 90 min [117], b) **88**, ethanol, rt, 0.5 h.

The structures of all products were established through MS, elemental analysis, ^{1}H and ^{13}C NMR spectroscopy. The conformations adopted by the pyranoside rings in the products **89** and **90** were determined by vicinal coupling constants and chemical shifts of their ^{1}H NMR spectra. 5-H and 5′-H were recognized easily from their large geminal coupling constant (~13 Hz) at δ = 4.30 and 3.87 ppm, respectively in **89**, and at δ = 4.15 and 3.88 ppm, respectively in **90**. A symmetrical ddd pattern appeared for H-4 of **89** with $J_{4,5}$ = 3.05, $J_{4,5'}$ = 3.05 and $J_{3,4}$ = 4.27 Hz. This indicates a quasi equatorial-quasi equatorial relation between 4-H and 5'-H and a quasi equatorial-axial relationship between 4-H and 5-H; conformation of pyranoside ring in **89** is, therefore, predominately $^{1}C_{4}$. This is further supported by large axial-axial coupling ($J_{1,2}$ = 6.41 Hz) for H-1 and H-2.



$^{1}C_{4}$ **89** $^{4}C_{1}$ **90**

Fig. 7. Preferred conformations of the pyranose rings in **89** and **90** as determined from the coupling interactions in ^{1}H NMR spectroscopy.

On the other hand in **90** 4-H appeared as a multiplet at δ = 4.81 ppm buried under the signal of the benzylidene protons. Although the direct calculation

of the coupling constant is not possible in this case, the coupling interactions of 4-H with 5-H and 5′-H were calculated from dd patterns observed for the latter protons, revealing a 1.83 Hz value for $J_{4,5}$ and a 3.06 Hz value for $J_{4,5'}$. From these assignments we assumed a quasi equatorial position for 4-H; hence the pyranoside ring in **90** occurred predominately in the $^4C_1$ conformation (Fig. 7).

Fig 8 shows the ORTEP diagram of compound **90** with selected bond lengths and bond angles.

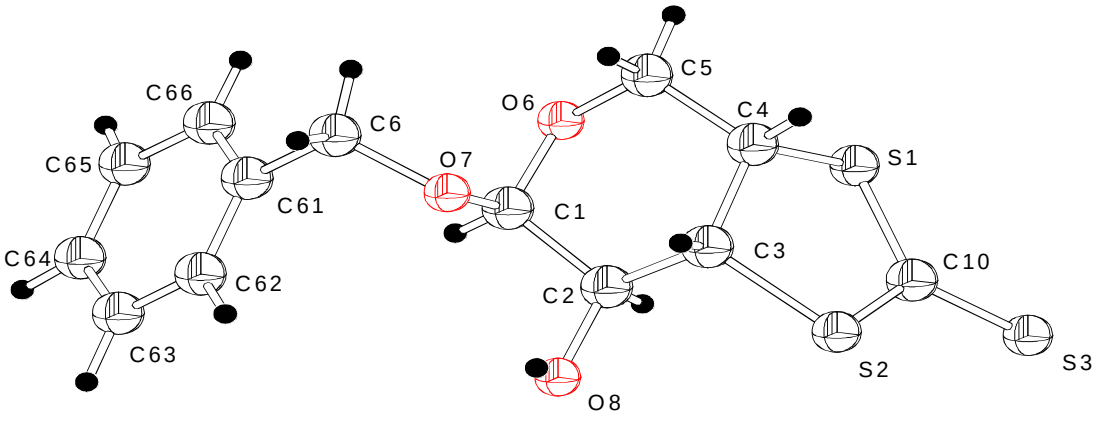


Fig 8. Molecular structure of **90**. Selected bond length (Å) and angles (º): C(2)-O(8) 1.421 (3), C(3)-S(2) 1.817(3), S(2)-C(10) 1.734(3), C(10)-S(3) 1.640(3), S(1)-C(10) 1.742(2), S(1)-C(4) 1.825(3); O(8)-C(2)-C(3) 111.3(2), C(2)-C(3)-S(2) 110.3(2), S(2)-C(10)-S(1) 114.8(2), S(1)-C(10)-S(3) 122.9 (2), C(10)-S(1)-C(4) 96.84 (12), S(1)-C(4)-C(5) 113.3(2).

In summary, our new template **89**, **90**, **92**, **95** and **96** would allow further elaboration to other targets through chemical modifications on the trithiocarbonate part of the molecules.

VIII. Synthesis and Properties of Selected 4-Substituted Anhydro Sugars

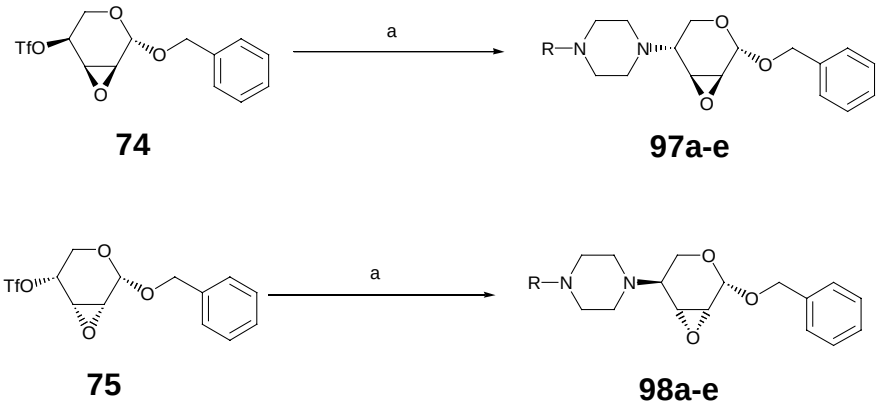
Piperazine and its derivatives have earned a repute as medicinal and pharmaceutical interesting compounds, showing a broad spectrum of biological activities [120-123]. Some of 1,4-disubstituted piperazine derivatives show anticonvulsant [124], bronchospasmolytic [125], antipsychotic [126], and H_1-antagonist activity [127]. On the other hand, carbohydrate derivatives containing on oxirane rings are of current interest due to their enzyme inhibiting effect [128-131]. It is considered to be of high interest to extend the ongoing research and introduce some 4-substituted piperazines, morpholines and thiomorpholines into the 4-position of the *cis*-oriented epoxy triflates **74** and **75** in order to obtain new compounds to be tested for the biological activities.

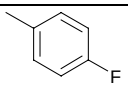
Recently, Voelter's group has reported a new methodology for the construction of the chiral piperazines on carbohydrate templates [132] and in continuation of this research, an easy access to 4-desoxy-4-[4-substituted-1-piperazinyl]-pyranosides (**97a-e** and **98a-e**; Scheme 18) is developed.

Thus, the reaction of the epoxy triflate derivatives **74** and **75** with three equivalents of the 4-substituted piperazine derivatives in THF at room temperature affords after conventional work up the corresponding benzyl 4-(4-

substituted-1-piperazinyl)-4-deoxy-2,3-anhydro-α-D-lyxopyranoside derivatives **97a-e** and their β-L-isomers **98a-e**,respectively, Scheme 18.

The facile nucleophlic substitution is due to the powerful triflyl leaving group and the strong nucleophilicity of the substituted piperazine derivatives. The reaction leads to the formation of lyxo products according to the inversion of configuration at C-4.



	a	**b**	**c**	**d**	**e**
R	CH_3	CH_2CH_3			

Scheme 18. Synthesis of 4-substituted piperazinyl-4-deoxy-2,3-anhydro-pentopyranoside derivatives. *Reagents and conditions*: a)  , THF, rt

Vicinal coupling constants in the ^1H NMR spectra are of great value in determining the predominant conformation of pyranoside rings, and in the

series **97a-e**, $J_{4,5}$ or $J_{4,5'}$ is the important feature in determining their configuration. For compounds **98a-e**, the protons at C-5 appear as broad triplets (accidentally $J_{4,5}$ is equal to the geminal coupling constant $J_{5,5'}$) with coupling constants in the range of 10-11 Hz, indicating a diaxial relationship for 4-H and 5-H and the conformation is therefore predominantly $^{O}H_5$. In the other series, **98a-e**, $J_{4,5}$ or $J_{4,5'}$ are small (0-4 Hz and 0 respectively), indicating axial-equatorial, equatorial-equatorial relationships and the adopted conformation is therefore again predominantly $^{O}H_5$. In a preliminary report from our group [133], the displacement of the triflate group with a variety of amino acids is described leading to products with conformations in full agreement with the structure presented here.

All the newly synthesized compounds **97a-e**and **98a-e**, were tested *in vitro*, in the form of their hydrochloride salts in aqueous solutions, against *E. coli* ATCC11229, *S. aureus* ATCC6538 and *C. albicans* SATCC10231. The *in vitro*-antibacterial activity was evaluated by the minimal inhibitory method [134]. For the positive control, the commercial antibiotic Ciprofloxacine was used. However, none of the above compounds showed any significant activity at concentration ≤ 500 μg/ml.

In conclusion, introduction of the 2,3-anhydropyranoside at the position 4 of the piperazine moiety decrease the biological activity against selected types of bacteria and fungi, compared to piperazine derivatives containing alkyl or aryl substituents, therefore, it is worth to test these new compounds after hydrogenation of the benzyl group not only against bacteria or fungi, but also

their CNS depressant activity, since a large number of piperazine derivatives are CNS-depressant compounds.

C. Experimental Part

All chemicals and reagents were obtained from commercial suppliers and used as such without further purification. Solvents were dried and distilled according to standard procedures. The reactions were monitored by thin layer chromatography, carried out on 0.25 mm silica gel plates (60 F-254, Merck, Darmstadt, Germany). Plates were visualized under UV light (where appropriate), sprayed with an orcinol/H_2SO_4/$FeCl_3$ solution and heated to develop. Column chromatography was performed on silica gel 60 (0.063-0.200 mm, Merck, Darmstadt, Germany) using the indicated solvent system. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker AC 250 (^1H NMR: 250 MHz, ^{13}C NMR: 63 MHz) or a Bruker WM 400-spectrometer (^1H NMR: 400 MHz, ^{13}C NMR: 100 MHz). The chemical shifts are reported in parts per million (ppm) on a δ scale from TMS as internal standard. The EI, FAB and FD mass spectra were recorded on a Finnigan MAT 312 mass spectrometer connected to a PDO 11/34 (DEC) computer system. Optical rotations were obtained with an LEP AZ polarimeter (Zeiss, Jena) at 546 nm. All melting points are uncorrected.

C.1. Total synthesis of *S*-(+)-argentilactone (11)

C.I.1. Methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (3)

To a stirred suspension of methyl α-D-glucopyranoside (**2**) (60 g, 0.31mol) in dry DMF (247 ml) was added α,α-dimethoxytoluene (47 ml, 0.31 mol) and *p*-toluenesulfonic acid (6.18 g, 0.03 mol). The mixture was then refluxed on a steam bath under vacuum, produced by water aspirator, for 1 h. The solvent

was evaporated at reduced pressure and the solid material was suspended in hot aqueous $NaHCO_3$. After cooling to room temperature, crystals of almost pure compound were obtained which were recrystallized in hot ethanol and dried in a desiccator under vacuum at 70 °C overnight to afford **3** as colourless crystals. Yield 78.4 g (90%), m.p. 162-164 °C (ethanol); $[\alpha]_D^{20}$ +110 (c = 0.5, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.48 (s, 1 H, OH), 3.02 (s, 1 H, OH), 3.44 (s, 3 H, OMe), 3.47 (dd, *J* = 9.3 and 9.1 Hz, 1 H, H-4), 3.61 (dd, *J* = 3.9 and 9.5 Hz, 1 H, H-2), 3.72 (m, 2 H, 5-H, H-6'), 3.88 (dd, *J* = 9.5 and 9.3 Hz, 1 H, H-3), 4.26 (dd, *J* =10.3 and 9.7 Hz, 1 H, H-6), 4.76 (d, *J* = 3.9 Hz, 1 H, H-1), 5.5 (s, 1 H, PhC*H*), 7.33-7.87 (m, 5 H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 55.4 (OMe), 62.3 (C-5), 68.8 (C-6), 71.6 (C-3), 72.8 (C-2), 80.9 (C-4), 99.7 (C-1), 101.8 (PhCH), 126.2-129.7 (PhH). FAB-MS: m/z = 283 (M+1, 100%).

$C_{14}H_{18}O_6$ (282.11)

Calculated C 59.57 H 6.43%,

Found C 59.63 H 6.57%.

C.I.2. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (4)

To a stirred solution of benzylidene acetal **3** (30 g, 0.11 mol) in toluene (300 ml) was added triphenylphosphine (115 g, 0.44 mol), iodoform (86.6 g, 0.22 mol), and imidazole (15.0 g, 0.22 mol). With vigorous stirring the mixture was refluxed for 1 h. The solution was cooled and washed with saturated aqueous sodium bicarbonate. The organic layer was separated, dried over

$MgSO_4$ and evaporated to dryness to yield a brown residue that was extracted with hot hexane. The solid material was filtered and the filtrate evaporated. Purification on a column of silica gel and eluting with dichloro-methane/petroleum ether (80:20) gave **4** as a white solid. Yield 23.6 g (87%), m.p. 122 ^oC (ethanol); $[\alpha]_D^{25}$ +115.2 (c = 0.7, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ = 3.46 (s, 3 H, OMe), 3.74-3.88 (m, 2 H, H-6 and H-6'), 4.12-4.17 (m, 1 H, H-5), 4.31 (m, 1H, H-4), 4.90 (brs, 1 H, H-1), 5.58 (s, 1 H, PhC*H*), 5.73 (dt, *J* = 10.37 and 2.45 Hz, 1 H, H-3), 6.14 (d, *J* = 10.37 Hz, 1 H, H-2), 7.35-752 (m, 5H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 56.0, 64.0, 69.5, 75.3, 96.2, 102.3, 126.3, 126.7, 128.4, 129.2, 130.9. FD-MS: m/z = 248.2 (M^+, 100%).

$C_{14}H_{16}O_4$ (248.10)

Calculated C 67.73 H 6.50%,

Found C 67.54 H 6.35%.

C.I.3. Methyl 2,3-didehydro-2,3-dideoxy-α-D-*erythro*-hexoside (5)

To a stirred solution of **4** (20 g, 0.08 mol) in absolute CH_2Cl_2 (100 ml) was added anhydrous ^{t}BuOOH (14.5 ml, 5.5 M sol. in decane) under nitrogen. After 10 min $AlCl_3$ (10.7 g, 0.08 mol) was added and stirring was continued at the same temperature till TLC analysis showed no starting material. The reaction was quenched with slow addition of water and extracted with CH_2Cl_2 (2 x 100 ml). The combined organic layers were dried over anhydrous sodium sulfate and evaporated under low pressure to yield almost pure **5** as

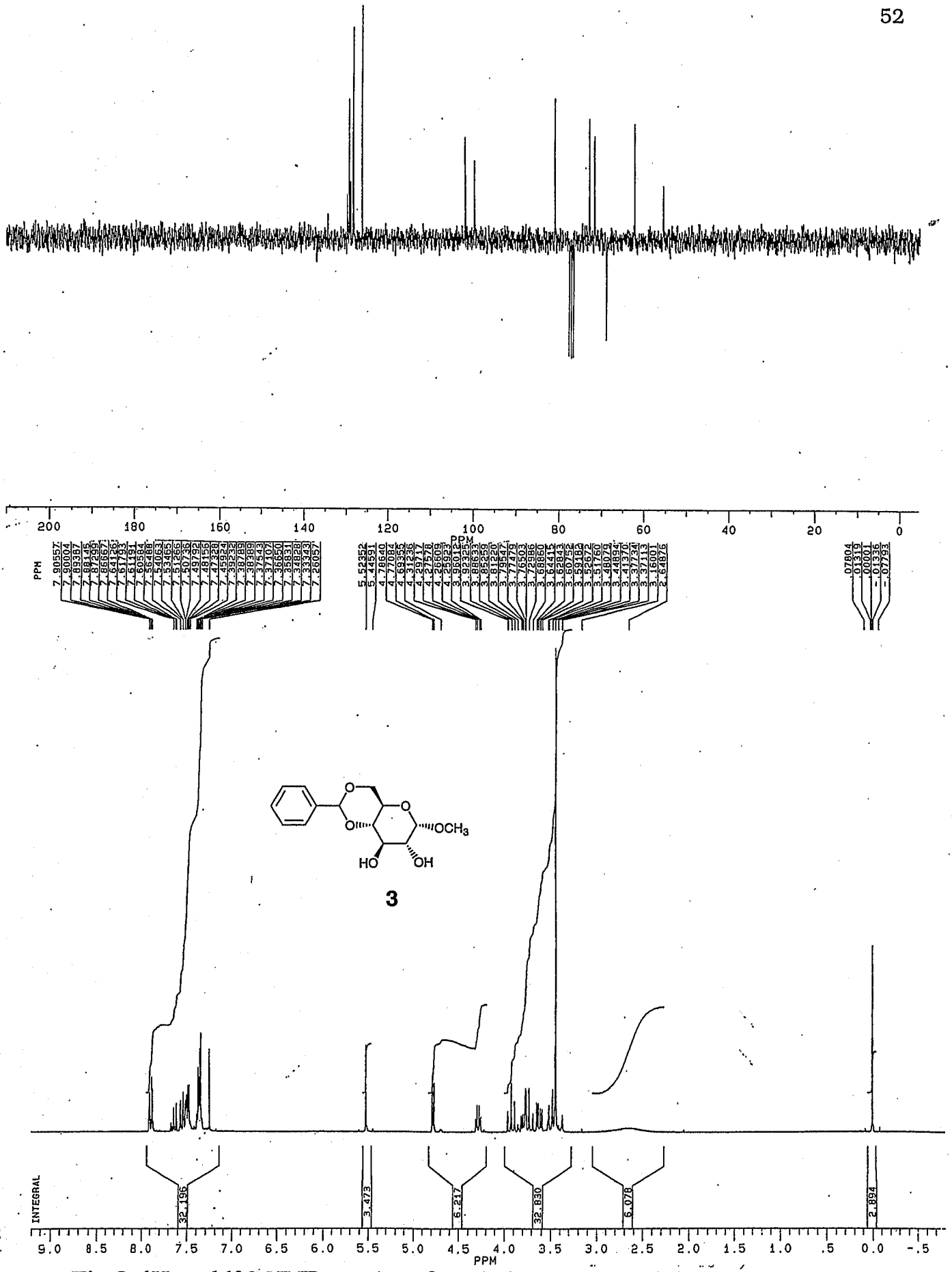


Fig 9. ^{1}H and ^{13}C NMR spectra of methyl 4,6-O-benzylidene-α-D-glucopyranoside (**3**).

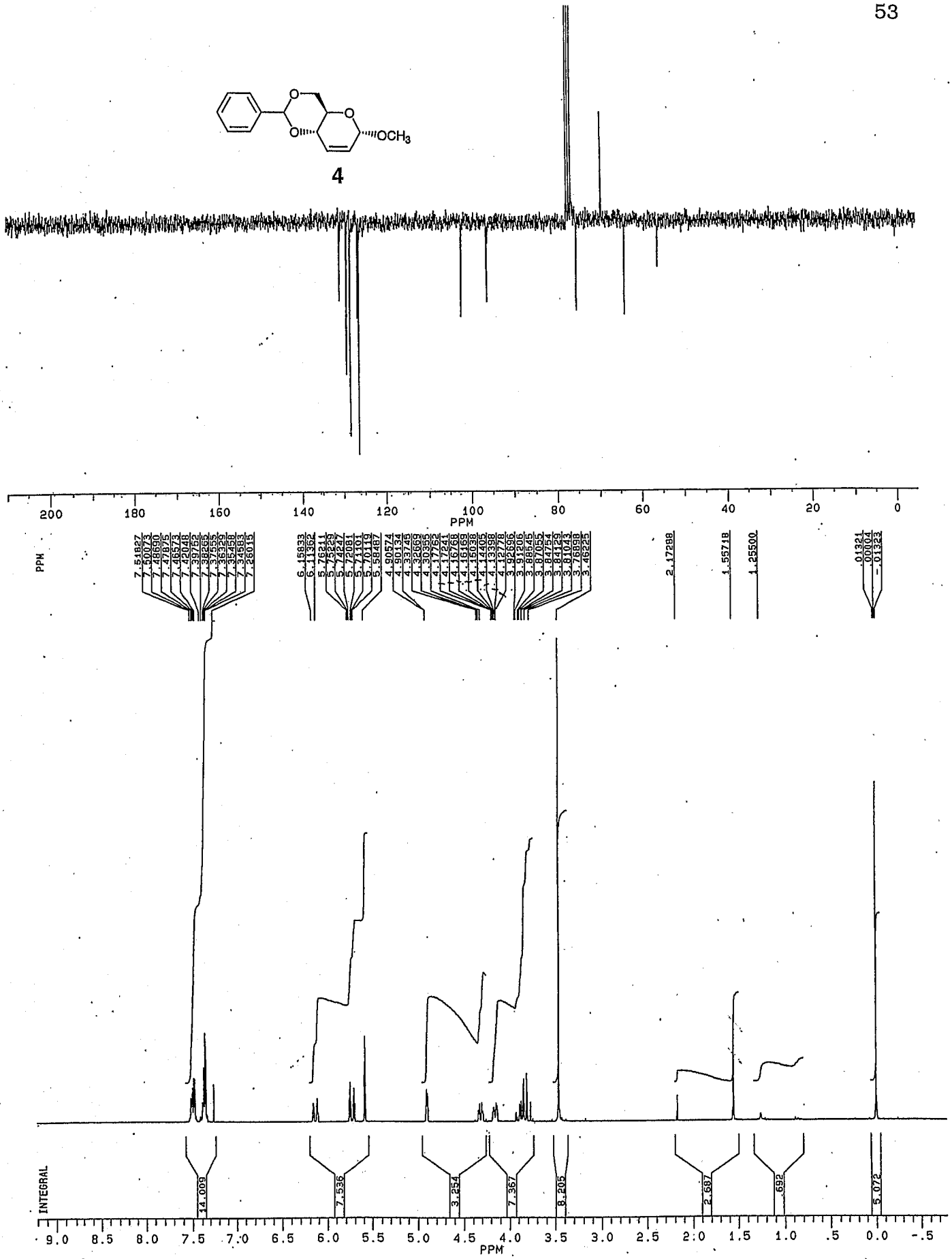


Fig. 10. ^{1}H and ^{13}C NMR spectra of methyl 4,6-O-benzylidene-2,3-dideoxy-α-D-eryrthro-hex-2-enopyranoside (**4**).

a colourless oil. Yield 10.3 g (75%); $[\alpha]_D^{24}$ +104.3 (c = 1, methanol); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.0 (br s, 1 H, OH), 3.44 (s, 3 H, OMe), 3.64-3.72 (m, 1 H, H-5), 3.86 (br s, 2 H, H-6, H-6'), 4.18 (m, 1 H, H-4), 4.87 (br s, 1 H, H-1), 5.74 (dt, *J* = 2.46 and 10.2 Hz, 1 H, H-3), 5.96 (d, *J* = 10.2 Hz, 1 H, H-2); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 55.9 (OMe), 64.2 (C-6), 62.7, 71.5 (C-4, C-5), 95.4 (C-1), 126.0, 133.7 (C-2, C-3). FAB-MS: m/z = 159.0 (M^+-1).

$C_7H_{12}O_4$ (160.07)

Calculated C 52.49 H 7.55%,

Found C 52.15 H 7.45%.

C.I.4. Methyl 6-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (6)

To a stirred solution of **5** (10.3 g, 0.06 mol) in absolute pyridine (25 ml) was dropped a solution of benzoyl chloride (12.4 gm, 0.09 mol) in CH_2Cl_2 (15 ml) in such a rate that temperature did not rise above -5 ^{o}C. The reaction was stirred at the same temperature for 5 hr. The normal work up and purification of the crude material on a silica gel column with pure dichloromethane yielded **6** as a colourless oil. Yield 15.1 g (90%) $[\alpha]_D^{25}$ –12 ^{o} (c = 0.5, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.39 (s, 3 H, OMe), 3.83-3.88 (m, 1 H, H-5), 4.07 (d, *J* = 8.85 Hz, 1 H, H-4), 4.45 (dd, *J* = 2.14 and 12.21 Hz,1 H, H-6'), 4.73 (dd, *J* = 4.88 and 12,21 Hz, 1 H, H-6), 4.85 (br s, 1 H, H-1), 5.70 (dt, *J* = 2.44 and 10.37 Hz, 1 H, H-3), 5.92 (br d, *J* 10.37,1 H, H-2), 7.35-8.03 (m, 5 H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 55.9, 64.0,

64.3, 70.6, 95.6, 126.4, 128.4, 129.8, 133.1, 133.3. FAB-MS: m/z = 233.1 (M^+-OMe).

$C_{14}H_{16}O_6$ (264.10)

Calculated C 63.63 H 6.10%,

Found C 62.99 H 6.03%.

C.I.5. 2(*S*)-Methoxy-6(*S*)-hydroxymethyl-5,6-dihydro-2*H*-pyran (8)

To a stirred solution of **6** (15 g, 0.057 mol) in pyridine (25 ml) at 0 °C was added mesyl chloride (5 ml). Stirring was continued at the same temperature for 4 hr. On completion of the reaction (TLC control), the mixture was plunged into a beaker containing crushed ice. The aqueous solution was extracted with ether (2 x 50 ml) and the combined organic layers were washed successively with a cooled 2 N HCl and saturated aqueous $NaHCO_3$ solution, and finally with water. After drying over anhydrous Na_2SO_4, the solvent was removed at low pressure, the crude material was dissolved in dry THF and under nitrogen atmosphere and gentle stirring Superhydride® (5 ml, 1M solution in THF) was added at 0 °C. The temperature was slowly raised to 40 °C. After 3 h the TLC showed no starting material. Excess hydride was destroyed with slow addition of water, then a 3N NaOH solution (10 ml) was added, followed by the addition of a 30% aqueous H_2O_2 solution (10 ml). The mixture was than brought into a separatory funnel and the THF layer was collected. The aqueous layer was further extracted with ether, the combined organic layers were dried over

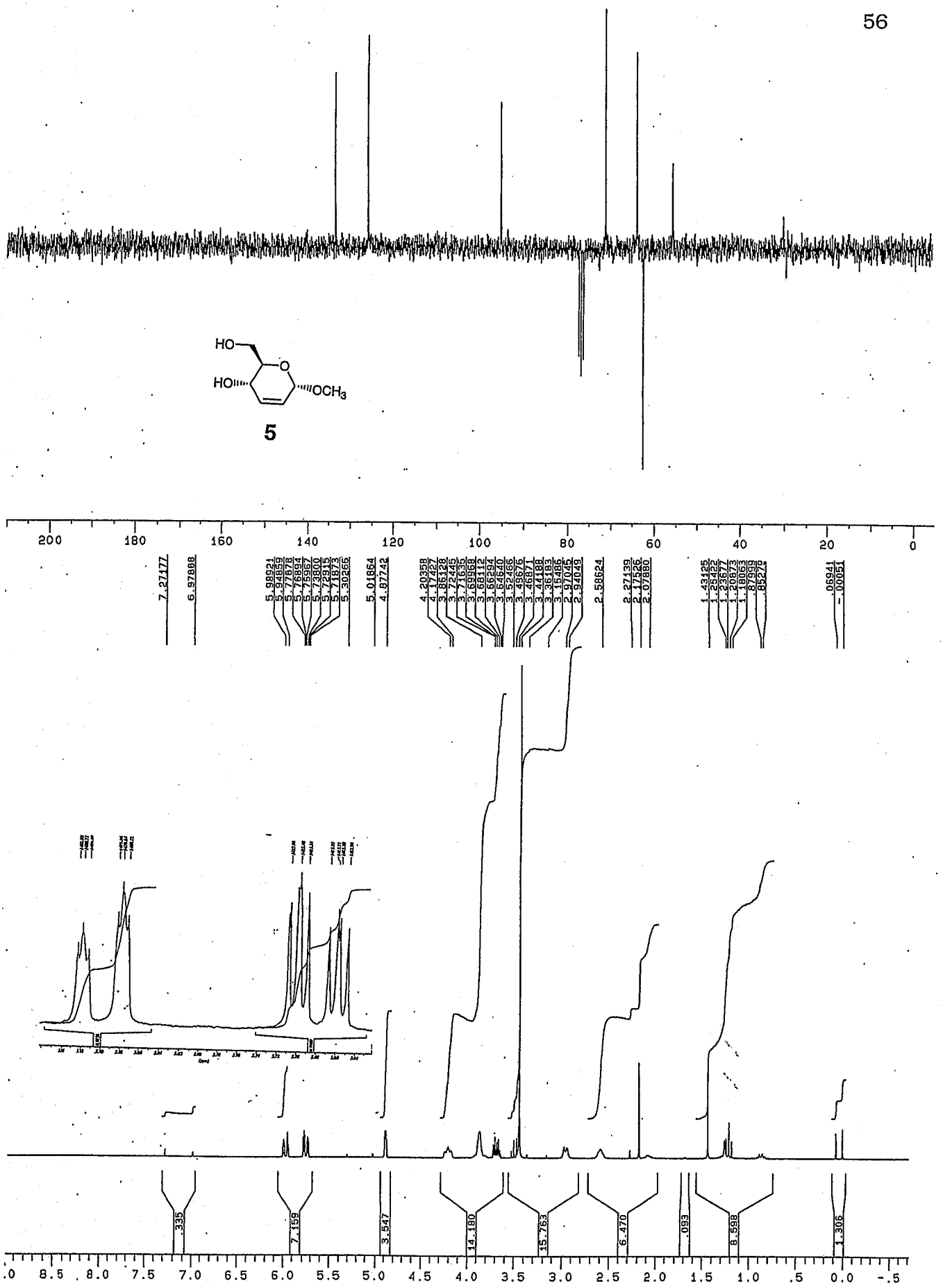


Fig 11. ^{1}H and ^{13}C NMR spectra of methyl 2,3-didehydro-2,3-dideoxy-α-D-*erythro*-hexoside (**5**).

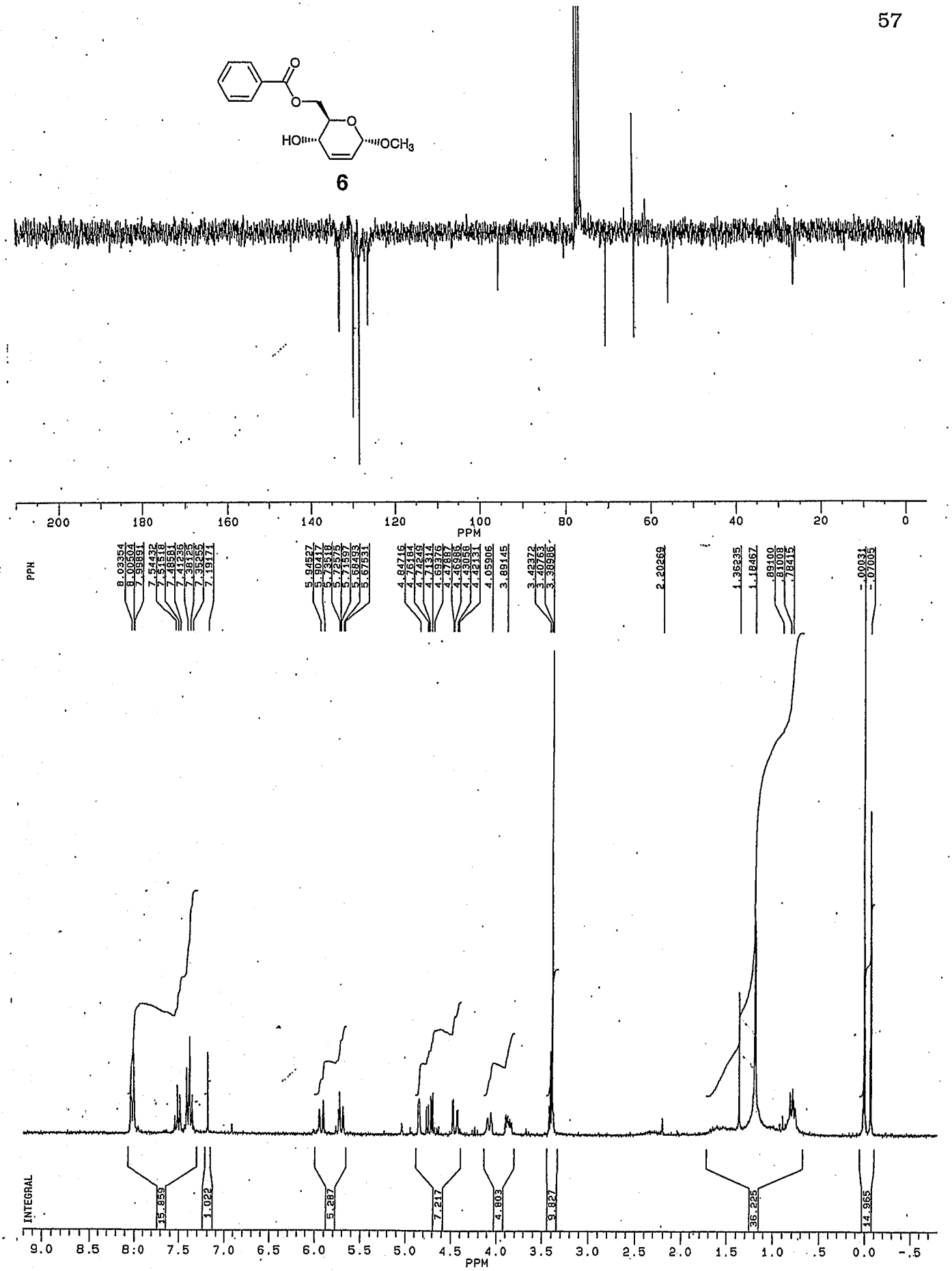


Fig. 12. ^{1}H and ^{13}C NMR spectra of methyl 6-O-benzoyl-2,3-dideoxy-α-D-*eryrthro*-hex-2-enopyranoside (**6**).

anhydrous sodium sulfate and the solvent was removed. After flash chromatography on a silica gel column by eluting with 5% ethyl acetate in CH_2Cl_2 **8** was obtained as colorless oil. Yield 5.76 g (70%) $[\alpha]_D^{25}$ –75.3 ^{o} (c = 0.74, C_6H_6); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.99-1.81 (m, 1 H, H-4'), 2.25-2.04 (m, 1 H, H-4), 2.29 (brs, 1 H, OH), 3.44 (s, 3 H, OMe), 3.82-3.54 (m, 2 H, H-6', H-5), 4.01 (m, 1 H, H-6), 4.90 (d, *J* = 2.0 Hz, 1 H, H-1), 5.81-5.70 (m, 1 H, H-3), 6.09-5.98 (m, 1 H, H-2); ^{13}C NMR (63 MHz, $CDCl_3$): δ= 26.0, 55.3, 65.2, 67.0, 95.7, 125.3, 128.6; EI-MS: m/z = 113 (M^+-OMe).

$C_7H_{12}O_3$ (144.08)

Calculated C58.32 H 8.39%,

Found C 58.29 H 8.25%.

C. I.6. 2(*S*)-Methoxy-5,6-dihydro-2H-pyran-6(*S*)-carbaldehyde (9)

A solution of oxalyl chloride (4 ml) in of CH_2Cl_2 (75 ml) was brought in a 250 ml three neck flask, equipped with two dropping funnels, containing DMSO (6.8 ml) in CH_2Cl_2 (20 ml) and alcohol **8** (5.76 gm, 40 mmol) in CH_2Cl_2 (40 ml). At -78 ^{o}C DMSO was slowly dropped. The mixture was stirred for 2 min, then the alcohol was added within 5 min and stirring continued for 15 min. Triethylamine (30 ml) was added, the reaction mixture stirred for 5 min and then allowed to warm to room temperature. Water was added and the organic phase removed. The aqueous layer was further extracted with CH_2Cl_2 (50 ml), the organic layers were combined, dried and evaporated. The compound was finally purified by flash chromatography using pure CH_2Cl_2 as an eluent to afford **9** as a colorless oil. Yield 5.11 g (90%); ^{1}H NMR (250

MHz, $CDCl_3$): δ = 2.10-2.22 (m, 2 H, H-4), 3.75 (s, 3 H, OMe), 4.40 (dd, *J* = 4.8 and 10.1 Hz, 1 H, H-5), 5.19 (d, *J* = 2.6 Hz, 1 H, H-1), 5.79-5.68 (m, 1 H, H-3), 5.91-6.08 (m, 1 H, H-2), 9.71 (s, 1 H, H-6); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 26.1, 62.3, 70.7, 92.8, 126.3, 126.4, 200.6. FAB-MS: m/z = 141.1 (M^+-1).

$C_7H_{10}O_3$ (142.06)

Calculated C 59.14 H 7.09%,

Found C 58.92 H 6.99%.

C. I.7. 6(*S*)-Hept-1'-enyl-2(*S*)-methoxy-5,6-dihydro-2*H*-pyran (10)

A solution of hexyltriphenylphsphonium bromide (15.34 g, 40 mmol) in a mixture of THF-HMPA (2:1, 150 ml) was cooled to -50 ^oC and *n*-BuLi (25 ml, 1.6 M in hexane) was added *via* a syringe. After stirring for several min at the same temperature, a solution of aldehyde **9** (5.0 gm, 35.2 mmol) in THF (25 ml) was added to the reaction mixture *via* a syringe. The solution was allowed to warm to -10 ^oC over 45 min, petroleum ether was added, followed by extraction with water, aqueous $NaHCO_3$ and finally with water. The organic layer was separated, dried and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with CH_2Cl_2: hexane (80:20) as an eluent to afford pure **10** as colorless oil**.** Yield 6.09 g (80%); $[\alpha]_D^{20}$ -50 ^{o} (c = 0.74, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.89 Hz, 3 H, CH_3), 1.34 (m, 6 H, 3 x CH_2), 2.01-2.30 (m, 4 H, 2 x CH_2), 3.38 (s, 3 H, OCH_3), 3.75 (m, 1 H, H-6), 4.88 (br s, 1H, H-2), 5.48 (m, 1 H, H-10), 5.76 (m, 2 H, H-3, H-9), 6.08 (m, 1 H, H-4); ^{13}C NMR (63 MHz,

$CDCl_3$): δ = 14.0, 22.5, 23.1, 30.2, 32.0, 34.4, 55.5, 68.9, 96.2, 124.7, 127.4, 130.7. FAB-MS: m/z = 210 (M+).

$C_{13}H_{22}O_2$ (210.16)

Calculated C 74.24 H 10.54%,

Found C 74.16 H 10.35%.

C.I.8. (*S*)-(+)-argentilactone (11)

To a suspension of **10** (6 gm, 22 mmol) in aqueous 30% H_2O_2 (250 ml) was added MoO_3 (0.6 gm). The mixture was stirred at room temperature till completion of reaction (TLC control). After disappearance of the substrate, water (250 ml) was added and the mixture extracted with CH_2Cl_2 (4x 50 ml). The combined extracts were washed with water, dried, and concentrated to dryness, to afford an anomeric mixture of peroxide which was dissolved in CH_2Cl_2 (25 ml) and added dropwise to a cooled and stirred mixture (1:1) of acetic anhydride and pyridine (50 ml) at <30 °C. The mixture was stored at room temperature for 2 hr, then poured to crushed ice and extracted with CH_2Cl_2 (3x30 ml). The combined extracts were washed with saturated aqueous $NaHCO_3$ and water, and dried and concentrated to dryness, to afford **11** as a yellow oil. Yield 2.99 g (70% over two steps); $[\alpha]_D^{23}$ + 19.1 (c = 0.5, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, Me), 1.3 (m, 6 H, 3 x CH_2), 2.10 (m, 2 H, CH_2), 2.38 (m, 2 H, CH_2), 5.0-5.8 (m, 3 H, H-5, H-6, H-7), 6.04 (ddd, *J* = 10.3 and1.8 Hz, 1 H, H-2), 6.91 (ddd, *J* =10.3 and 4.2 Hz,1 H, H-3); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.0, 22.5, 27.8, 29.0, 29.9, 31.4, 73.9, 121.7, 126.4, 135.7, 144.8. EI-MS: m/z =194 (M+).

$C_{12}H_{18}O_2$ (194.13)

Calculated C 74.19 H 9.34%,

Found C 73.92 H 9.28%.

C.II. Total Synthesis of massoilactone (1b) and osmundalactone(1c)

C.II.1. Massoialactone (1b)

C.II.1.1. Methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (12)

To a suspension of **3** (2.78 g, 10 mmol), 100 ml of carbon tetrachloride and 7ml of 1,1,2,2-tetrachloroethane were added 1.95 g of NBS and 1.2 g of barium carbonate. The suspension was heated at reflux with efficient stirring for 2.5 h and filtered while hot. The cake was washed with hot carbon tetrachloride and the filtrate and washing were evaporated to dryness. The resulting syrup was dissolved in ether (100 ml) and the solution was washed with water and dried (sodium sulfate). The evaporation of solvent afforded colorless syrup, which was purified by column chromatography using dichloromethane/ethyl acetate (50:50) as an eluting solvent. Yield 2.52 g (70%); white crystals, m.p. 124-125°C; $[\alpha]_D^{25}$ = 116 ° (*c* =1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.36 (m, 3 H, H-2, H-3, H-5), 3.46 (s, 3 H, OMe), 3.67 (bs, 1 H, OH), 3.82 (bs, 1 H, OH), 3.94-4.11 (m, 2 H, H-6, H-6'), 4.79 (d, *J* = 3.66 Hz, 1 H, H-1), 5.01 (t, *J* = 9.46 Hz, 1 H, H-4), 7.42 (t, *J* = 7.32 Hz, 2 H, Ph), 7.57 (t, *J* = 7.32 Hz, 1 H, Ph), 8.02 (d, *J* = 7.33 Hz, 2 H, Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 31.7 (C-6), 55.5 (OMe), 69.2, 72,2, 72.4, 73.5 (C-2, C-3, C-4, C-5), 99.0 (C-1), 128.4, 129.0, 129.8, 133.4 (C_6H_5), 165.9 (CO). FAB-MS: m/z = 361.0 [M^++1].

$C_{14}H_{17}BrO_6$ (360.02)

Calculated	C 46.56	H 4.74	Br 22.12%,
Found	C 46.30	H 4.65	Br 22.05%.

C.II.1.2. Preparation of 2,4,5-triiodoimidazole

Iodine (76.1 g, 0.3 mol) is stirred in hexane (1.5 l) at room temperature for 0.5 h. Water (1.5 l) and imidazole (6.81 g, 0.1 mol) are added and then sodium hydroxide (32 g) in water ((400 ml), gradually in small portions whenever precipitation occurred (200-300 ml is generally required). After being stirred at room temperature for 24 h, the mixture is filtered. Most of the hexane layer is removed by decantation and discarded. The pH of the water layer is brought to about 5 by the gradual addition of conc. hydrochloric acid to the stirred solution. The precipitate is filtered off, washed thoroughly with water, and recrysrallized from ethanol/water to form large prisms. Yield 35.3 g (76%); m.p. 192-194^{o}C.

C. II.1.3. Methyl 4-*O*-benzoyl-6-bromo-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranoside (13)

A mixture of methyl 4-*O*-benzyl-6-bromo-6-deoxy-α-D-glucopyranoside (**12**) (2.0 g, 5.6 mmol), triphenylphosphine (6.28 g, 24.0 mmol), 2,4,5-triiodoimidazole (5.71 g, 12.8 mmol), and imidazole (1.09 g, 16.01 mmol) in dry toluene (100 ml) was boiled under reflux for 2.5 h, after which time slow moving **12** was replaced with fast moving **13** (R_f ~0.8, PE/EtOAc (3:1)). After cooling the mixture to room temperature the solution was decanted from the

gummy residue into a conical flask containing a stirred saturated aqueous $NaHCO_3$. The gummy residue was washed with several portions of ether and added to the sodium bicarbonate solution. The mixture was stirred for 15 min and then transferred to a separatory funnel. The organic phase is washed once with saturated, aqueous sodium hydrogencarbonate, twice with saturated sodium thiosulfate and once with water. The organic layer separated, dried ($MgSO_4$) and evaporated *in vaccuo* to give a brownish mixture of products from which some crystalline triphenylphosphonium oxide was separated by trituration with ether. The residual syrup was chromatographed on a column of silica gel by eluting with PE/EtOAc (20:80) to obtain pure **13** as colorless syrup. Yield 1.37 g (75%); ^{1}H NMR (250 MHz, $CDCl_3$): δ =3.18 (dd, *J* = 8.54 and 10. 7 Hz, 1 H, H-6'), 3.36-3.59 (m, 4 H, H-6, OMe), 4.00 (dt, J = 2.44 and 8.85 Hz) , 4.21 (ddd, J = 2.44, 7.63 and 9.77 Hz, 1 H, H-5), 4.94 (br s, 1H, H-1), 5.36, 5.46 (m, 1 H, H-4), 5.84 (m, 2 H, H-2, H-3), 7.39, 7.54 and 7.96 (3 x m, 5 H, C_6H_5); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 5.5 (C-6), 32.4 (C-6), 56.4, 56.6 (OMe), 68.4, 68.8 (C-4), 70.0 (C-5), 95.8 (C-1), 128.0 (C-2), 129.0 (C-3), 128.5-129.8, 133.6 (C_6H_5), 165.8 (CO).

$C_{14}H_{15}BrO_4$ (326.02)

Calculated C 51.40 H 4.62 Br 24.42%,

Found C 51.25 H 4.55 Br 24.40%.

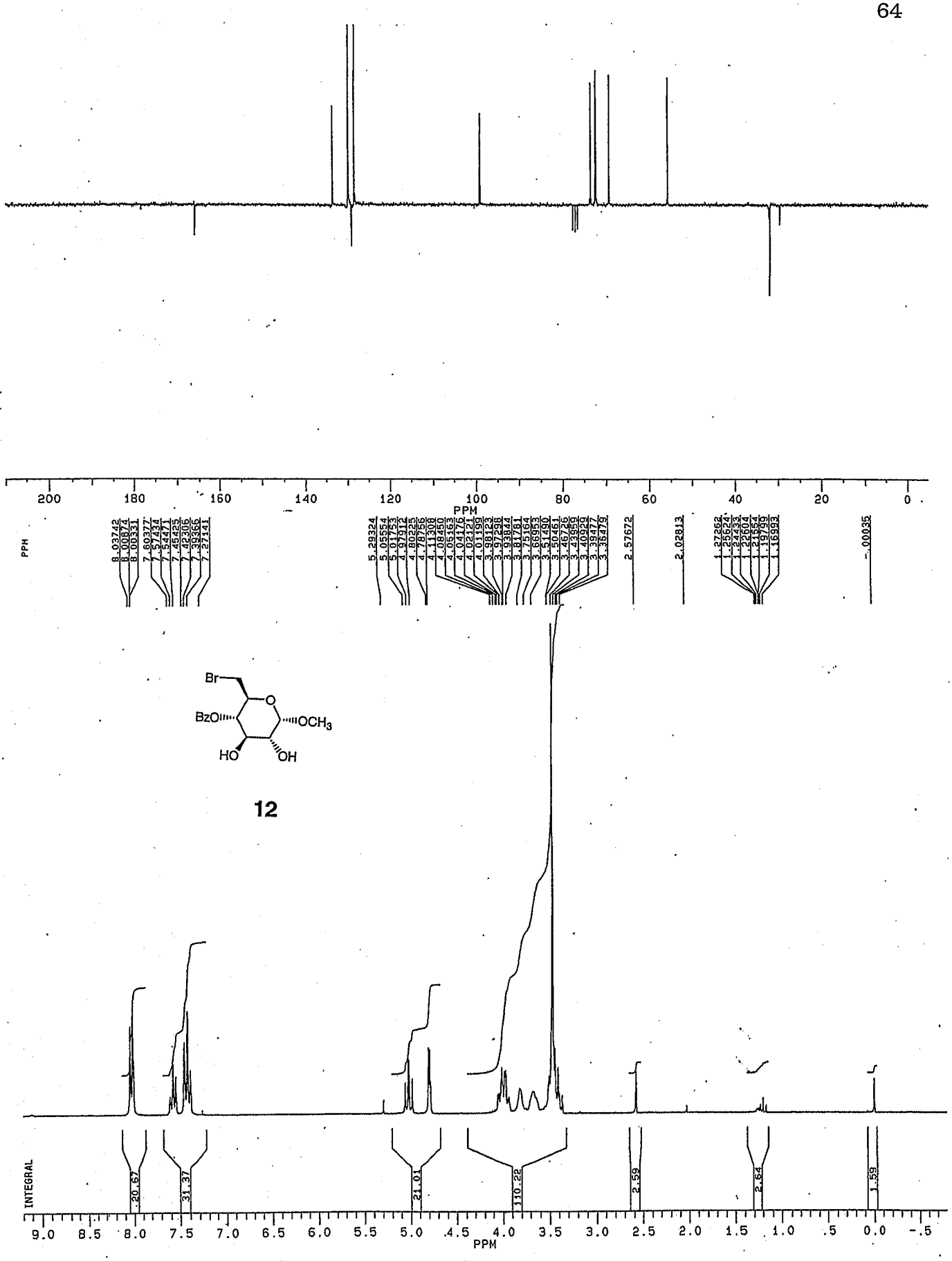


Fig 13. ^{1}H and ^{13}C NMR spectra of methyl 4-O-benzyl-6-bromo-6-deoxy-α-D-glucopyranosode **(12).**

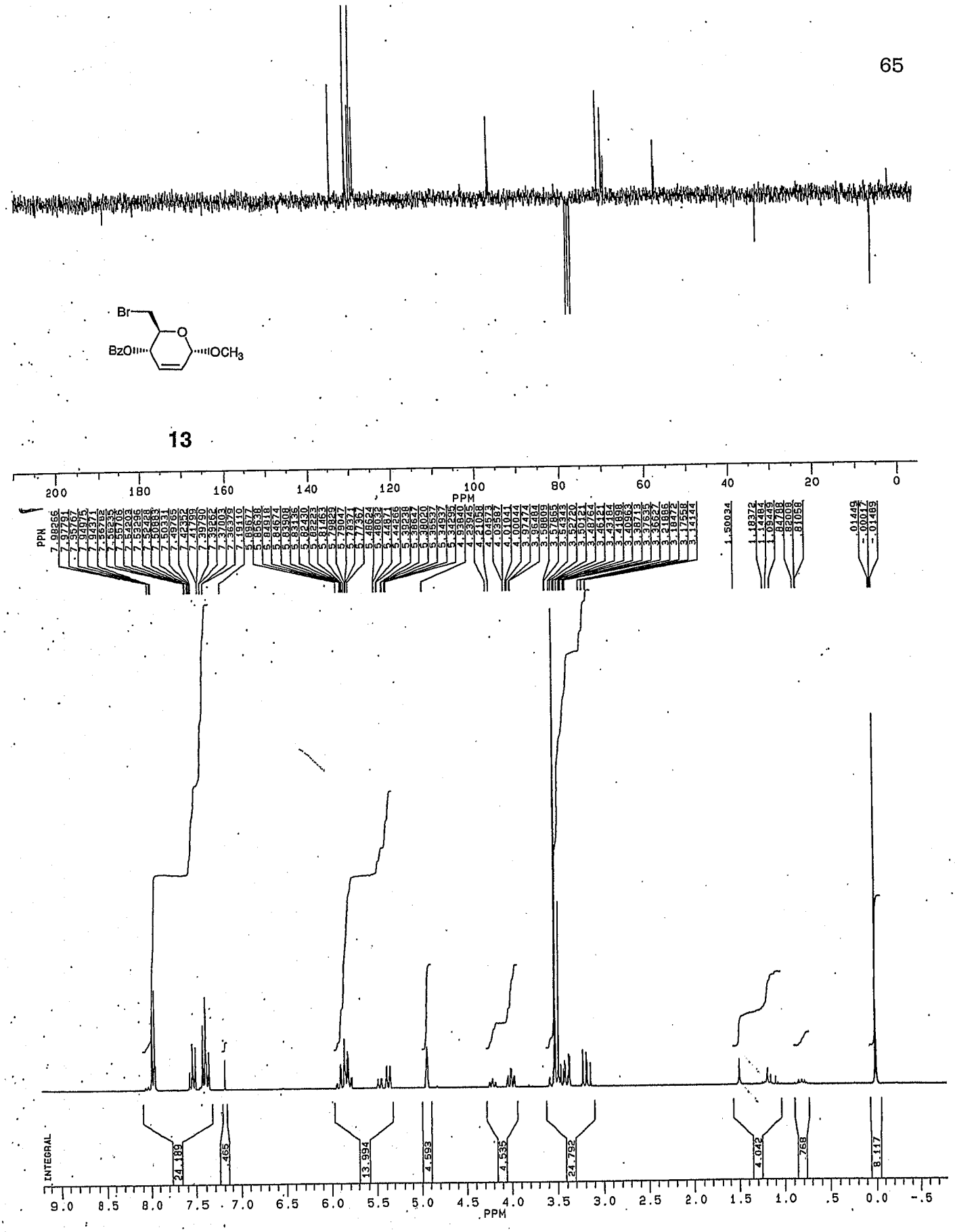


Fig. 14. ^{1}H and ^{13}C NMR spectra of methyl 4-*O*-benzyl-6-bromo-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranoside **(13).**

C.II.1.4. 2(*S*)-Methoxy-6(*R*)-pentyl-5,6-dihydro-2*H*-pyran (31)

In a dry two-neck flask was placed CuCN (184 mg, 2.04 mmol). Under the supply of argon dry THF (2.2 ml) was introduced *via* a syringe and the slurry was cooled to –78 °C. To this slowly stirring suspension was added *n*-BuLi (3.9 mmol) dropwise. The heterogeneous mixture was allowed to warm gradually until complete dissolution (near 0 °C) and is then cooled again to –78 °C. The bromo-sugar **13** (326 mg,1 mmol) was introduced at –78 °C, the solution was warmed to room temperature for 6 h and then quenched with a mixture of 10% conc. NH_4OH/saturated aqueous NH_4Cl solution and allowed to stir for 1 h. The extraction with ether (3 times), drying and evaporation of the solvent at low pressure yielded **28** as thick oil which was dissolved in pyridine (2 ml). At 0 °C was dropped a solution of mesyl chloride (120 µl) in CH_2Cl_2 (1 ml). In 5 h the mesylate **29** was received as yellow oil. Under a stream of nitrogen gas **29** was dissolved in freshly distilled THF and treated with lithium triethylborohydride (Superhydride®, 1 M solution in THF, 2 ml) *via* a syringe. The stirring at room temperature for 3 h showed the completion of reaction (TLC control). The standard work up and evaporation of the solvent yielded an oil. The purification on a short column of silica gel with dichloromethane as an eluent afforded **30** as a colorless oil. Yield 83 mg (45% form **13**); ^1H NMR (250 MHz, $CDCl_3$): δ = 0.95 (t, 3 H, CH_3), 1.1-2.2 (m, 10 H, 4 x CH_2, H-5, H-5'), 3.45 (s, 3 H, OMe), 3.95 (m, 1 H, H-6), 4.92 (br s, 1 H, H-2), 6.2-5.6 (m, 2 H, C-3, C-4). FAB-MS: m/z = 185.1 [M^++1]

$C_{11}H_{20}O_2$ (184.28)

Calculated C 71.70 H 10.94%,

Found C71.56 H 10.58%.

C.II.1.5. *R* (-)-Massoilactone (1b)

Pyran **31** (80 mg, 0.43 mmol), H_2O_2 (5 ml), MoO_3 (12 mg) and a 1:1 mixture of acetic anhydride and pyridine was treated as was described for the synthesis of *S* (+)-argentilactone **11** (see page 48). Colorless liquid, Yield 42 mg (56 %); $[\alpha]_D^{20}$ = -102 ^{o} (*c* = 0.2, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (br t, 3 H, CH_3), 1.07-1.92 (m, 8 H, 4 x CH_2), 2.16-2.45 (m, 2 H, H-5, H-5'), 4.12-4.53 (m, 1 H, H-6), 5.77-6.03 (m, 1 H, H-3), 6.67-6.92 (m, 1 H, H-4); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.4, 24.5, 29.4, 31.4, 34.9 (5 x CH_2), 78.1(C-6), 121.5 (C-3), 145.0 (C-4), 165.1 (CO). FAB-MS; m/z = 169.1 [M^++1].

$C_{10}H_{16}O_2$ (168.23)

Calculated C 71.39 H 9.59%,

Found C 71.35 H 9.45%.

C.II.2. Osmundalctone (1c)

C. II.2.1. Methyl 2,3,6-trideoxy-α-D-erythro-hex-2-enopyranoside (37)

To a solution of bromo sugar **13** (326 mg, 1 mmol) in THF (10 ml, dried over Na) was added dropwise, at room temperature, 3 ml of an M solution of lithium triethylbirohydride (Superhydride®)in THF. The mixture was kept over night in a refrigerator, whereupon **13** was seen to be absent. The mixture was cooled to 0 ^{o}C, stirred for 30 min with added methanol, in order to decompose the excess of hydride. The solvent was evaporated and the

residue was placed on a short column of silica gel by mean of a little ethyl acetate. The elution with PE/EtOAc (3:1) gave pure **37** as colorless syrup. Yield 130 mg (90%); $[\alpha]_D^{25}$ = +109 °(*c* = 1.2 , CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 6.02 Hz, 3 H, Me-6), 2.9 (brs, 1 H, OH), 3.42 (s, 3 H, OMe), 3.5-3.9 (m, 2 H, H-4, H-5), 4.80 (brs, 1 H, H-1), 5.71 (dt, *J*= 10.3 Hz, 1 H, H-2), 5.90 (dt, *J* = 10.02 Hz, 1 H, H-3); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 18.0 (Me-6), 55.5 (OMe), 68.0 (C-4), 69.5 (C-5), 95.4 (C-1), 126.2 (C-2), 133.4 (C-3). EI-MS: m/z = 113 (M+-OMe).

$C_7H_{12}O_3$ (144.08)

Calculated C 58.32 H 8.39%,

Found C 58.25 H 8.32%.

C.II.2.2. Methyl 4-O-acetyl-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranoside (38)

To a stirred solution of the alcohol **37** (130 mg, 0.9 mmol) in dichloromethane (5 ml) containing triethylamine (1 ml) at 0 °C was added acetic anhydride (0.44 ml). On the completion of reaction, the solvent was evaporated and the residue was chromatographed on a short column of silica gel. The elution with ethyl acetate removed the triethylammonium salt and the effluent was evaporated to give the acetate **38** in a quantitative yield as a colorless liquid that was used as such for the next step.

C.II.2.3. (+)-*O*-Acetylosmundalactone (32)

The acetate **38** was oxidized at the anomeric position as described in the synthesis of *S*-(+)-argentilactone (**11**). Yield 110 mg (72%); $[\alpha]_D^{25}$ = +158 ^oC (*c* = 0.7, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.6 Hz, 3 H, C-6), 1.97 (s, 3 H, CH_3CO), 4.44 (m, 1 H, H-5), 5.12 (dd, *J* = 3.3 and 1.3 Hz, 1 H, H-4), 5.93 (d, *J* = 10.1 Hz, 1 H, H-2), 6.66 (dd, J = 10.1 and 3.3 Hz, 1 H, H-3). EI-MS: m/z = 126 (M^+-44).

$C_8H_{10}O_4$ (170.06)

Calculated C 56.47 H 5.92%,

Found C 56.50 H 6.01%.

C.III. Total Synthesis of *R*-(-)-argentilactone (1a)

C. III.1. 1*R*-(2'-Furyl)-ethane-1,2-diol (47)

A solution of D-glucal (**46**) (5.0 g, 0.034 mol) in 5mM sulfuric acid (118 ml) containing mercuric sulfate (0.197 g) was stirred for 2 h at room temperature. TLC examination, then, showed the completion of reaction. The acid was neutralized with barium carbonate, the suspension was filtered and the filtrate was evaporated *in vacuo* to afford a light yellow residue. The purification on a column of silica gel after eluting with ether/petrol ether (7:3) yielded **47** as a thick oil. Yield 3.7 (85%); $[\alpha]_D^{25}$ = + 38.0 (*c* = 0.3, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ = 3.59 (br s, 1 H, OH), 3.80 (d, *J* = 5.49 Hz, 2 H, H-2), 3.99 (br s, 1 H, OH), 4.75 (t, *J* = 5.49 Hz, 1 H, H-1), 6.27-6.32 (m, 2 H, H-3', H-4'), 7.35 (dd, *J* = 1.83 and 0.92 Hz, 1 H, H-5'); ^{13}C NMR

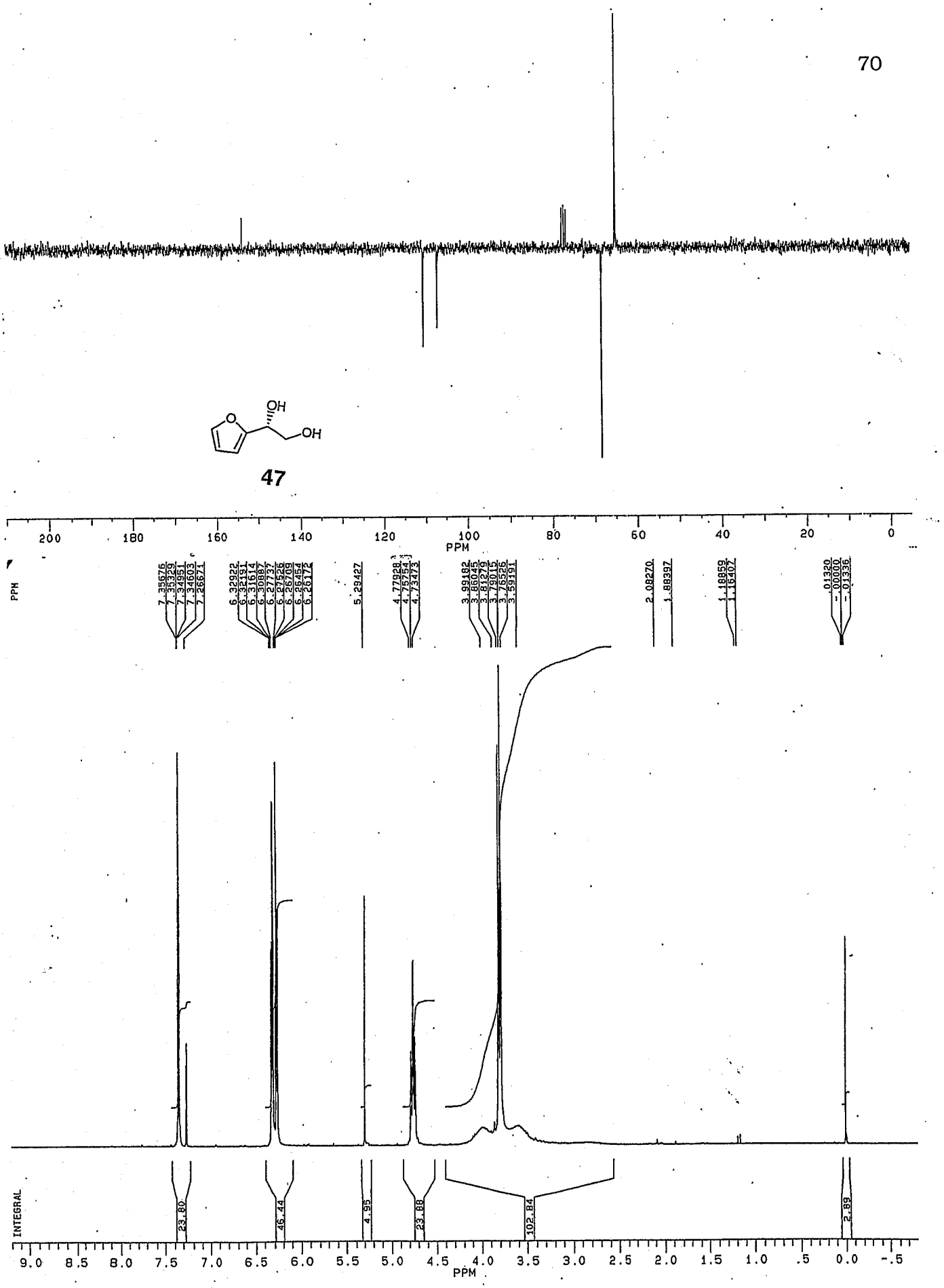


Fig 15. ^{1}H and ^{13}C NMR spectra of 1*R*-(2'-furyl)-ethane-1,2-diol **(47)**.

(63 MHz, $CDCl_3$): δ = 65.0 (C-2), 68.4 (C-1), 106.9, 110.3 (C-3', C-4'), 153.6 (C-5'), 153.6 (C-2'). EI-MS: m/z = 128 [M^+]

$C_6H_8O_3$ (128.13)

Calculated C 56.24 H 6.29%,

Found C 55.84 H 5.99%.

C.III.2. Benzoic acid 1*S*-(2'-furyl)-2-hydroxyethyl ester (48 b)

In a two-neck flask, furandiol **47** (1.28 g, 10 mmol) was dissolved in 100 ml of freshly distilled and dried THF. Triphenylphophine (3.94 g, 15 mmol), and benzoic acid (1.22 g, 10 mmol) were added into it. A dropping funnel, containing a solution of diethyl azodicarboxylate (DEAD, 2.36 ml), in 25 ml of THF was attached in one neck and a condenser in the second one. The solution of the funnel was let to drop slowly into the stirred contents of the flask over a period of 2 h. The stirring was continued a further period of 1 h after the final drop and TLC showed the completion of the reaction. The solvent was evaporated and the residual oil was triturated to crystallize triphenylphosphine. The filtration removed the crystals and evaporation of the filtrate left a thick oil which was placed on a column of silica gel with the help of a little dichloromethane. The elution with 15% ethyl acetate in petroleum ether removed most of the low polar impurities. The polarity was increase slowly to 20% ethyl acetate/pet. ether to afford **48b** as a colorless oil. Yield 1.86 g (80%); $[\alpha]_D^{20}$ = -17.6 ^{o} (*c* = 1.4, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.09 (dd, *J* = 4.88 and 12.21 Hz, 1 H, H-2), 4.18 (dd, *J* = 7.02 and 12.21 Hz, 1 H, *H*-2), 6.19 (dd, *J* = 4.88 and 7.02 Hz, 1 H, H-1), 6.37 (dd,

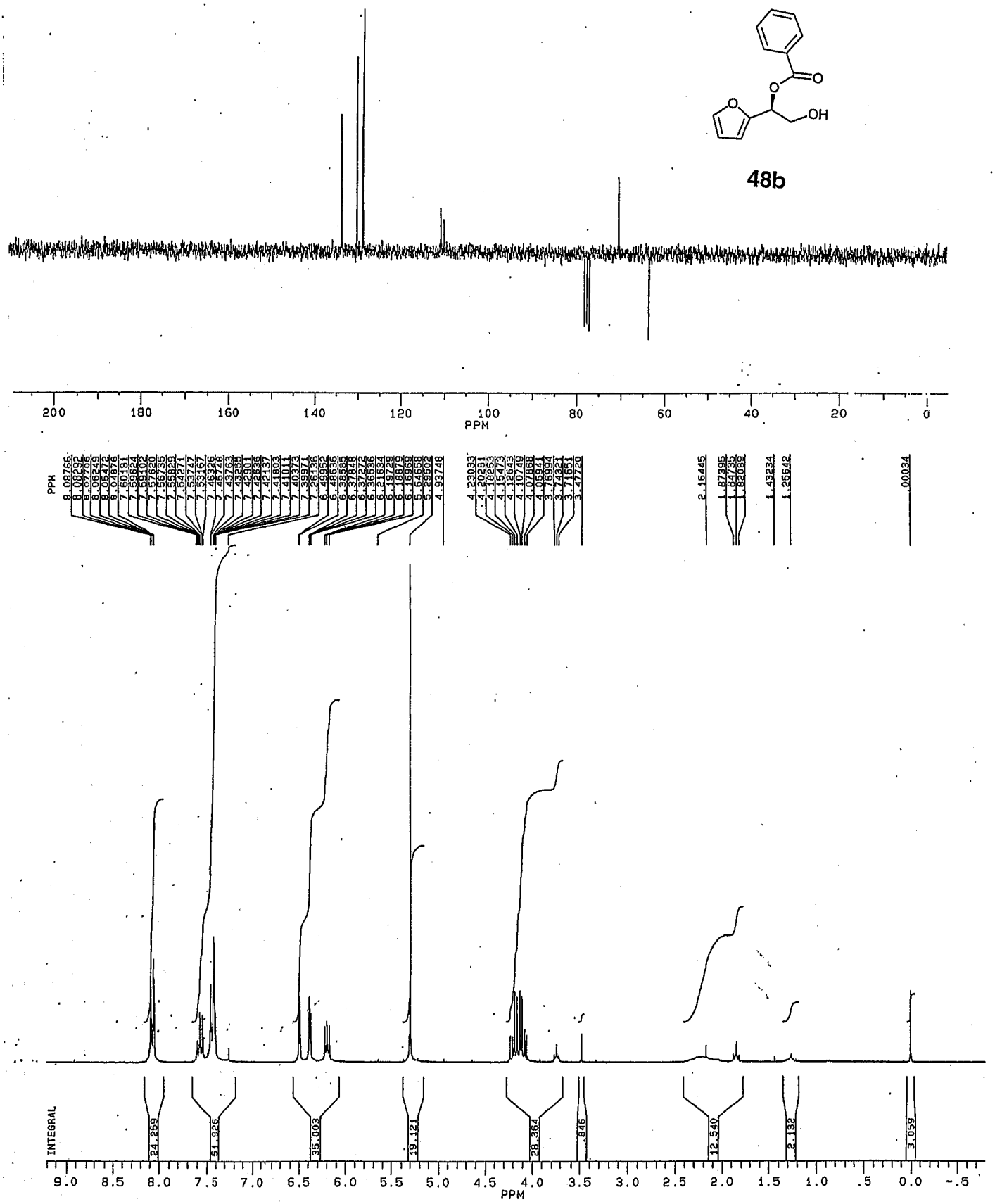


Fig 16. ^{1}H and ^{13}C NMR spectra of benzoic acid 1S-(2'-furyl)-2-hydroxyethyl ester (**48 b**).

J = 1.83 and 3.35 Hz, 1 H, H-2'), 6.49 (d, *J* = 3.36 Hz, 1 H, H-4'), 7.43 (m, 3 H, H-5', 2 x H-2''), 7.56 (tt, *J* = 1.53 and 7.05 Hz, 1 H, H-3''), 8.06 (dd, *J* = 1.23 and 8.24 Hz, 2 H, H-1''); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 63.23 (C-2), 70.21 (C-1), 109 (C-3'), 110.5 (C-4'), 128.46, 129.88, 133.3 (aromatic).

$C_{13}H_{12}O_4$ (232.23)

Calculated C 67.23 H 5.21%,

Found C 67.30 H 4.96%.

C. III.3. Benzoic acid 2-benzoyloxy-1*S*-(2'-furyl)-ethyl ester (48a)

The above experiment was carried out with furandiol **47** (256 mg, 2mmol), DEAD (0.63 ml), PPh_3 (1.048 g) and benzoic acsid (0.5 g) in 25 ml THF to get the dibenzoate **48a** as a solid. The removal of triphenylphosphine oxide was accomplished by flash column chromatography by using 5% ethyl acetate/petroleum ether as an eluent. Yield 403 mg (60%), m.p. = 71-73 ^{o}C; $[\alpha]_D^{20}$ = -18.7 ^{o} (*c* = 0.2, CH_2Cl_2). Alternatively, to a stirred solution of **48b** (232 mg, 1 mmol) in pyridine (5 ml) at 0^{o}C, benzoyl chloride (1 ml) in CH_2Cl_2 (2 ml) was dropped slowly. The reaction was monitored by TLC. After completion of the reaction the aqueous work up was performed to yield **48a**.

$C_{20}H_{16}O_5$ (336.34)

Calculated C 71.42 H 4.79%,

Found C 71.75 H 4.65%.

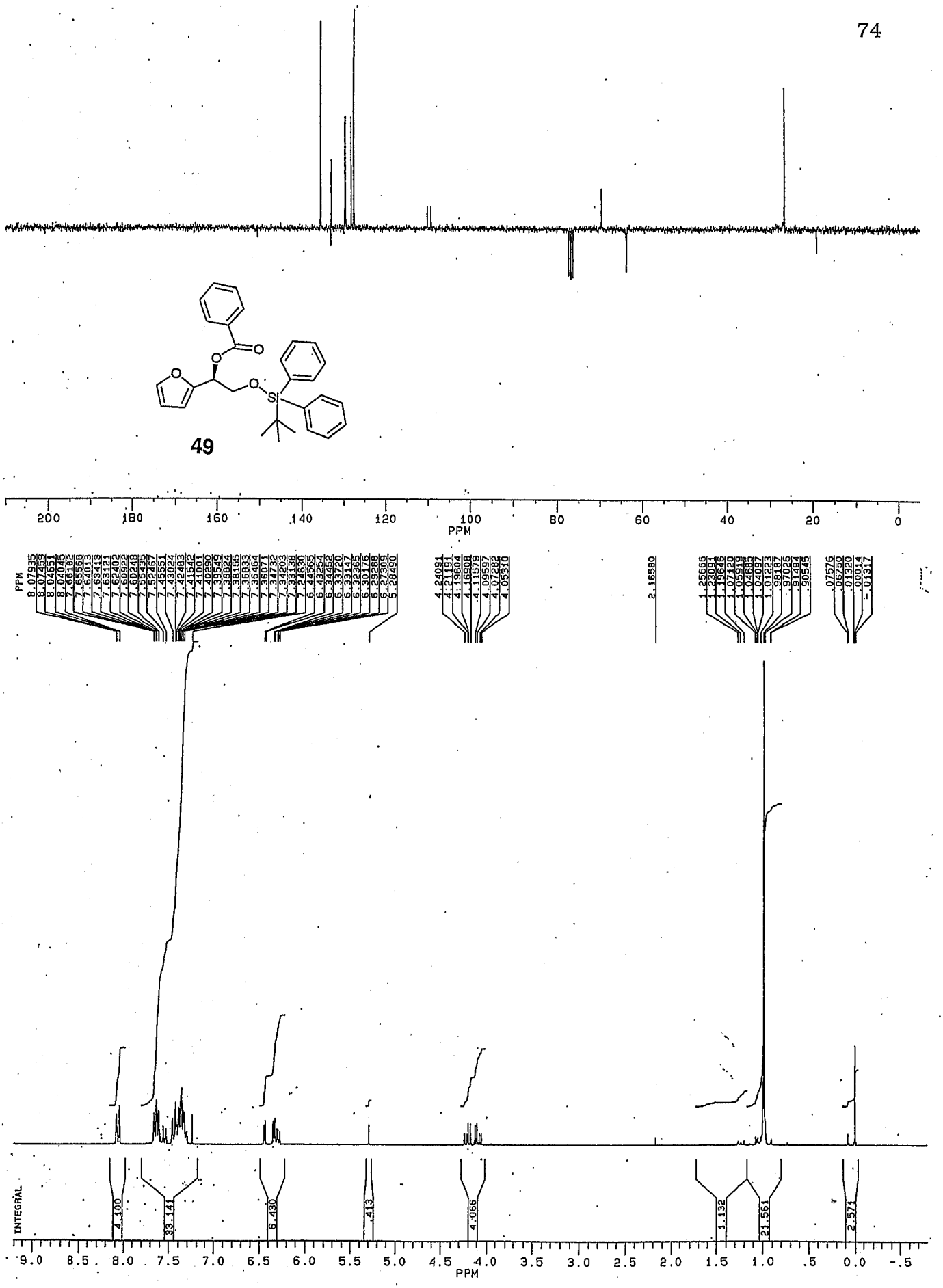


Fig 17. ^{1}H and ^{13}C NMR spectra of benzoic acid 1S-(2'-furyl)-2-*tert*-butyldiphenylsilyloxyethyl ester **(49)**.

C.III.4. Benzoic acid 1*S*-(2'-furyl)-2-*tert*-butyldiphenylsilyloxyethyl ester (49)

To a stirred solution of furan-monalcohol **47b** (1.5 g, 6.5 mmol) in dry DMF (10 ml), containing 2.2 equiv. of imidazole (0.97 g) was added slowly *tert*-butyldiphenylsilyl chloride (1.96 g, 7.15 mmol) at 0 ^{o}C. The ice bath is removed and the temperature is allowed to rise slowly to room temperature. Stirring the reaction mixture for a period of 4 h at room temperature showed the completion of reaction (TLC analysis). The solvent was removed at high vacuum, the residual oil was dissolved in 10 ml dichloromethane and extracted with water (5 ml, 3 times). The organic layer was separated, dried (Na_2SO_4), and evaporated *in vacuo* to yield sufficiently pure **49** as an oil in almost quantitative yield. The reaction was also carried out in pyridine to afford an excellent yield of **49**. Thus **47b** (143 mg, 0.62 mmol) was dissolved in 2 ml pyridine and under continued stirring was added TBDPSCl (1.1 equiv.) at 0 ^{o}C. The ice bath was removed and the reaction was stirred at rt for 2 h, after which the reaction was almost completed. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.0 (s, 9 H, 3 x CH_3), 4.09 (dd, *J* = 5.18 and 10.98 Hz, 1 H, H-2´), 4.19 (dd, *J* = 7.32 and 10.68 Hz, 1 H, H-2), 6.30 (dd, *J* = 5.5 and 7.63 Hz, 1 H, H-1), 6.33 (dd, *J* = 1.83 and 3.05 Hz, 1 H, H-4'), 6.44 (br d, *J* = 3.35 Hz, 1 H, H-3'), 7.24-7.71 (m, 14 H, H-5', aromatic protons), 8.05 (dd, *J* = 8.05 and 1.2 Hz, 2 H, Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.2 (C-Me_3), 26.7 (3 x CH_3), 64.0 (C-2), 69.8 (C-1), 109.4, 110.4 (C-3', C-4'), 127.7, 128.3, 129.8, 129.9, 133.1, 133.2, 135.7 (aromatic). FAB-MS: m/z = 413.1 $[M- C_4H_9]^+$

$C_{29}H_{30}O_4Si$ (470.63)

Calculated C 74.01 H 6.43 Si 5.97%,

Found C 73.78 H 6.29 Si 5.95%.

C. III.5. 2-*tert*-Butyldiphenylsilyloxy-1*S*-(2'-furyl)-1*S*-ethanol (50)

To a stirred solution of **49** (3.0 g, 6.4 mmol) in 25 ml of absolute methanol at 0 ^oC was added dropwise a freshly prepared solution of sodium methoxide (prepared by dissolving 30 mg sodium in 15 ml methanol). The stirring was continued till the completion of reaction (TLC control), after which the solution was neutralized with 1 N HCl. The solution is filtered (if there is precipitation due to the salt formation) and the filtrate is evaporated to dryness. The oily residue is purified on a column of silica gel by eluting with CH_2Cl_2/petroleum ether (1:1) to afford **50** as colorless oil. Yield 2.0 g (85%) $[\alpha]_D^{20}$ = - 8.36 (*c* = 0.7, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ = 1.06 (br s, 9 H, 3 x CH_3), 3.92 (m, 2 H, H-2, *H*-2), 4.82 (br t, *J* = 5.15 Hz, 1 H, H-1), 6.27-6.32 (m, 2 H, H-3', H-4'), 7.33-7.43 (m, 6 H, H-5', Ph), 7.59-7.72 (m, 5 H, Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.3 (C-Me_3), 26.9 (3 x CH_3), 66.4 (C-2), 68.5 (C-1), 107.2, 110.3 (C-3', C-4'), 127.8, 127.9, 129.7, 129.9, 132.9, 134.9, 135.6 (aromatic), 153.6 (H-2'). FAB-MS: m/z = 413.1 $[M- C_4H_9]^+$

$C_{22}H_{26}O_3Si$ (366.53)

Calculated C 72.09 H 7.15 Si 7.66%,

Found C 72.21 H 6.99 Si 7.45%.

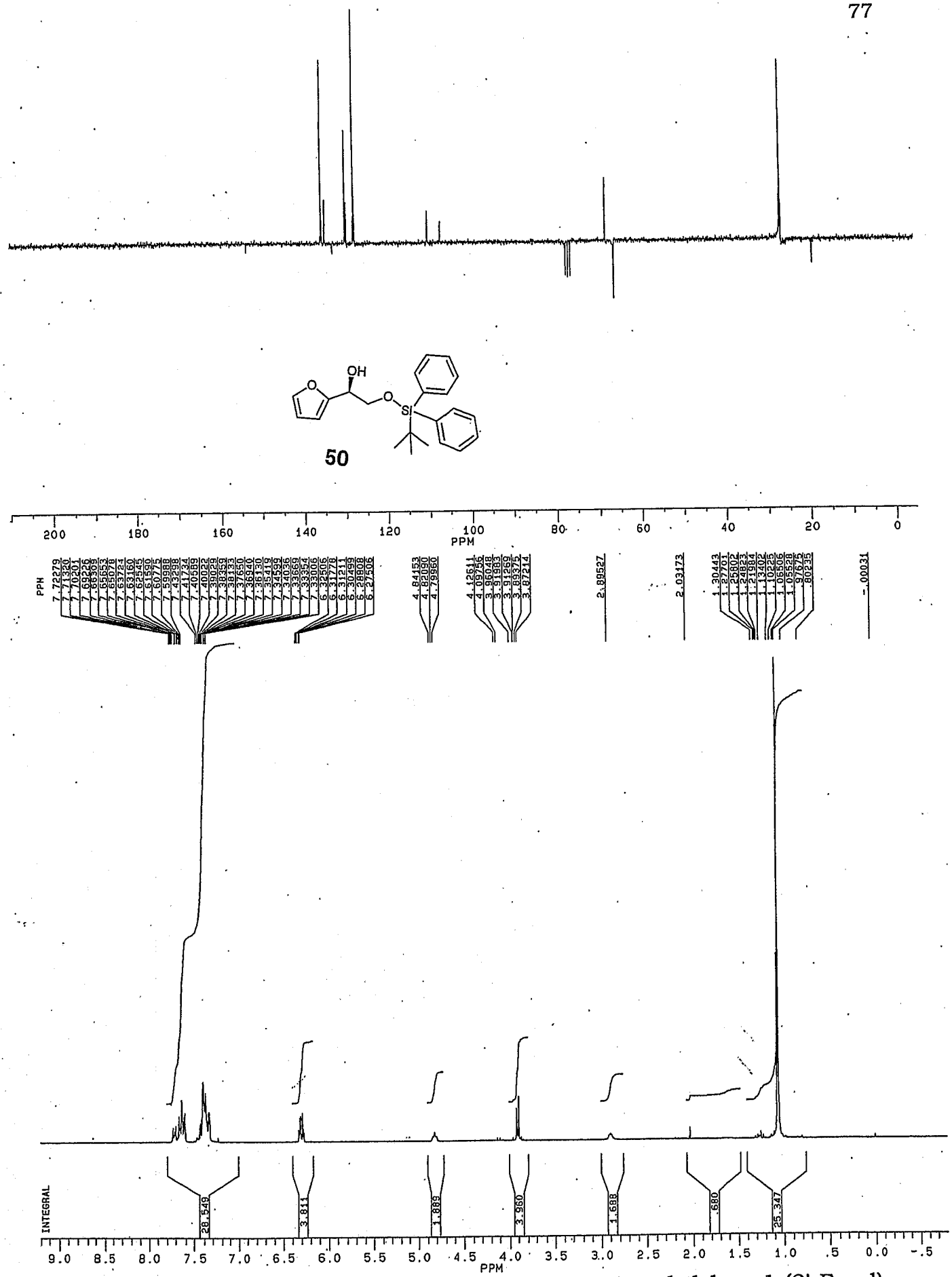


Fig 18. ^{1}H and ^{13}C NMR spectra of 2-*tert*-butyldiphenylsilyloxy-1-(2'-Furyl)-1S-ethanol **(50).**

C.III.6. 6-hydroxy-(2*S*)-2-*tert*-butyldiphenylsilyloxymethyl-2H-pyran-3(6H)-one (51)

Compound **50** (1.5 g, 4.1 mmol), 7 ml of THF and 1.75 ml of water were added to a round bottom flask and cooled to 0 ^{o}C. $NaHCO_3$ (0.68 g), $NaOAc.3H_20$ (556 mg) and NBS (0.73 g, 4.1 mmol) were added to the solution and the mixture was stirred for 1 hour at 0 ^{o}C. The reaction was quenched with saturated $NaHCO_3$ (10 ml), extracted with ether (3 x 15 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give 1.33 g (85%) of **51** as a colorless solid, m.p. 124-127 ^{o}C; Yield 1.4 g (91%); ^{1}H NMR of the anomeric mixture (250 MHz, $CDCl_3$): δ = 1.0 (s, 9H, 3 x CH_3), 4.05 (m, 2 H, -CH_2-OTBDPS), 4.33 (dd, *J* = 3.05 and 2.14 Hz, H-2β), 5.59 (dd, *J* = 4.27 and 2.44 Hz, H-2α), 5.53 (br s, H-6α), 5.76 (d, *J* = 3.05 Hz, H-6β), 6.16 (d, *J* = 10.38 Hz, H-4β), 6.26 (d, *J* = 10.38 Hz, H-4 α), 6.92 (dd, *J* = 10.38 and 3.05 Hz, H-5β), 7.02 (d, *J* = 10.38 Hz, H-5α), 7.40 and 7.66 (m, 10 H, Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.3 (C-Me_3), 26.6 and 26.8 (3 x CH_3), 66.05, 64.04 (CH_2), 79.6 (C-2), 88.0, 87.4 (C-6), 127.7-147.1 (Ph), 135.5, 135.7, 135.9 (C-4, C-5),194.7, 194.4 (CO).

$C_{22}H_{26}O_4Si$ (382.52)

Calculated C 69.08 H 6.85 Si 7.34%,

Found C 68.85 H 6.79 Si 7.32%.

C. III.7. 6-(1'-Ethoxyethyl)-2*S*-2-tert-butyldimethylsilyloxymethyl-2H-pyran-3(6H)-one (52)

To a solution of enone **51** (1.3 g, 3.4 mmol) in dichloromethane (20 ml) was added ethyl vinyl ether (2.44 g, 3.24 ml) and pyridinium *p*-toluenesulfonate (PPTS, 60 mg). The mixture was stirred for 1.5 h, and then H_2O (5 ml) was added, extracted by dichloromethane (15 ml x 3) and dried over Na_2SO_4. After the removal of the solvent the residue was purified through column chromatography using 5% ethyl acetate/petroleum ether, as an eluent, to afford **52** as an oil. Yield 1.47 (95 %); $[\alpha]_D^{20}$ = +10.21 0 (*c* = 0.5, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01, 1.02 (2 x s, 9 H, 3 x CH_3), 1.19, 1.24 (2 x t, *J* = 7.02 Hz, 3 H, CH_3), 1.40, 1.44 (2 x d, *J* = 5.19 Hz, 3 H, CH_3), 3.74-3.40 (m, 2H), 4.02-3.98 (m, 2H), 4.53, 4.60 (2 x dd, *J* = 2.74 and 5.18 Hz, 1 H), 4.97, 5.08 (2 x q, *J* = 5.19 Hz, 1 H), 5.58 (d, *J* = 3.36 Hz), 6.07 (d, *J* = 10.07 Hz, H-3), 6.85-6.75 (m, 1 H, H-2), 7.38-7.27 8m, 6 H, Ph*H*), 7.63 (m, 4 H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 15.2, 15.4, 19.3, 20.9, 21.1, 26.7, 61.8, 63.3, 63.6, 88.0, 88.2, 89.8, 98.7, 100.0, 127.7-135.7, 144.02, 144.7, 194.5, 194.7.

$C_{26}H_{34}O_5Si$ (454.63)

Calculated C 68.69 H 7.54 Si 6.18%,

Found C 68.65 H 7.51 Si 6.10%.

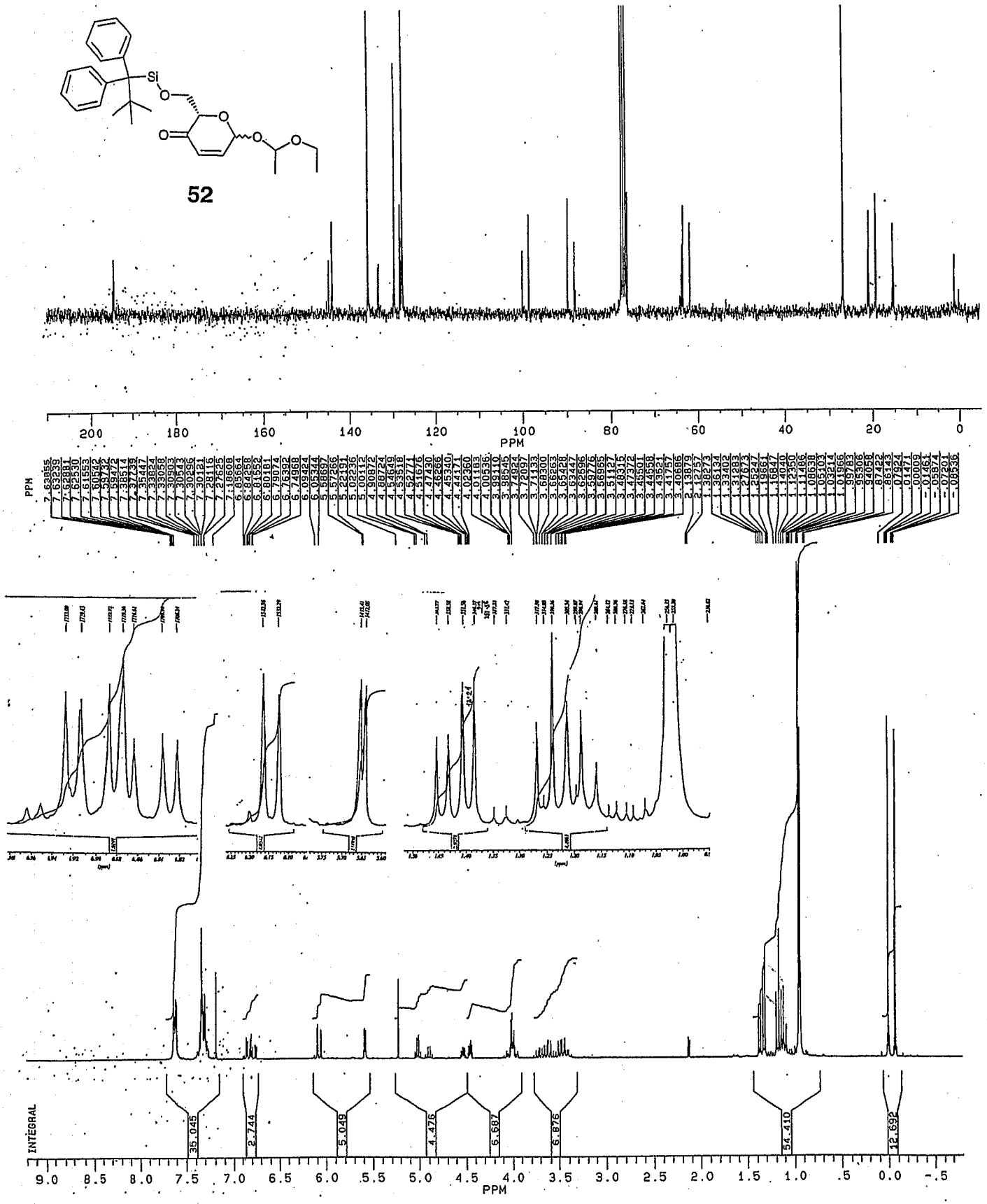


Fig 19. ^{1}H and ^{13}C NMR spectra of 6-(1'-ethoxyethyl)-2*S*-2-*tert*-butyldimethylsilyloxymethyl-2*H*-pyran-3(6H)-one **(52)**.

C. III.8. 6-(1'-Ethoxyethyl)-3 *R* -hydroxy-2 *S* -*tert*-butyldiphenylsilyloxy-methyl-3,6-dihydro-2H-pyran (53)

At –40 °C, $NaBH_4$ (0.58 g) was added portionwise to a solution of **52** (1.4 g, 3.08 mmol) in methanol (20 ml) containing $CeCl_3.7H_2O$ (1.15 g, 3.08 mmol). The reaction was monitored by TLC. The reaction was quenched with water (15 ml) and extracted with ether (30 ml x 3), the ether layer was washed with brine and dried over Na_2SO_4. The allylic alcohol **53** was obtained quantitatively as colorless oil. Yield 1.22 g (87%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, 3 x CH_3), 1.09-1.21 (m, 3 H, CH_3), 1.26-1.35 (m, 3 H, CH_3), 3.32-3.92 (m, 6H), 4.82, 4.92 (2 x m, 1H), 5.15, 5.24 (2 x m, 1 H), 5.66-5.79 (m, 1 H), 5.97 (brd, *J* = 10.38 Hz, 1 H, H-2), 7.35-7.46, 7.66-7.72 (2 x m, 10 H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 15.1, 15.4(CH_3), 19.2 (C), 21.0, 21.3 (CH_3), 26.9 (3 x CH_3), 61.6, 62.8, 65.7, 65.9, 66.4, 66.5, 70.7, 70.9 (C-4, C-5, C-6, CH_2) 89.7, 91.0, 98.1, 99.4, 125.9-135.6.

$C_{26}H_{36}O_5Si$ (456.65)

Calculated C 68.39 H 7.95 Si 6.15%,

Found C 68.32 H 7.93 Si 6.14%.

C. III.9. 6-(1'-Ethoxyethyl)-2*S*-*tert*-butyldiphenylsilyloxymethyl-3,6-dihydro-2H-pyran (55)

To a stirred solution of the allylic alcohol **53** (1.20 g, 2.63 mmol) in pyridine (10 ml) was dropped slowly mesyl chloride at 0 °C. The stirring was continued at the same temperature till the completion of reaction (TLC control). After completion, the contents of the reaction flask were poured on

ice, extracted with dichloromethane, dried (Na_2SO_4) and evaporated to afford **54** as colorless oil which was dissolved in THF (5 ml). Under nitrogen atmosphere was added lithium triethylborohydride (Superhydride®, 1 M solution in THF, 1 ml). The reaction was monitored by TLC. After completion, methanol was added to destroy the excess hydride. The solvent was evaporated and the residue was placed on a column of silica gel with the help of little dichloromethane. Elution with 80% dichloromethane/petroleum ether yielded **55** as a colorless oil. Yield 1.1 g (95%).

$C_{26}H_{36}O_4Si$ (440.65)

Calculated C 70.87 H 8.23 Si 6.37%,

Found C 70.73 H 8.16 Si 6.35%.

C. III.10. 6-(1'-Ethoxyethyl)-2*S*-*hydr*oxymethyl-3,6-dihydro-2H-pyran (56)

To a stirred solution of **55** (1.1 g, 2.5 mmol) in THF was added tetra-*n*-butylammonium fluoride (1 M solution in THF, 5 ml). Stirring was continued at room temperature for a period of 3h, which showed completion of the reaction. Water (10 ml) was added, extracted with dichloromethane (10 ml, 3 times), dried (Na_2SO_4) and evaporated to yield **56** as colorless oil. Yield 500 mg (99%).

$C_{10}H_{18}O_4$ (202.25)

Calculated C 59.39 H 8.97%,

Found C 59.35 H 8.96%.

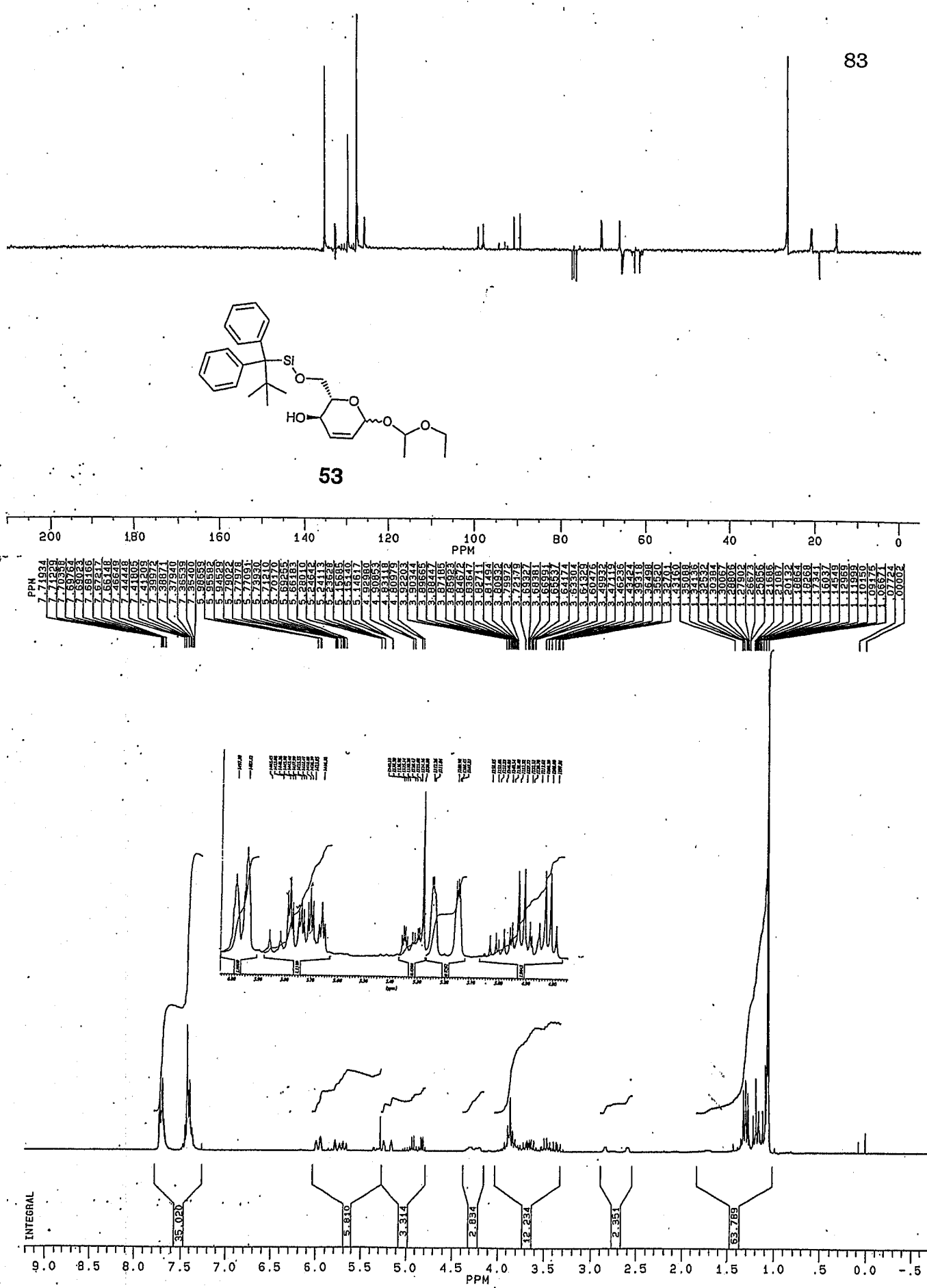


Fig 20. ^{1}H and ^{13}C NMR spectra of 6-(1'-ethoxyethyl)-3 *R*-hydroxy-2 *S* -*tert*-butyldiphenylsilyloxy-methyl-3,6-dihydro-2H-pyran **(53).**

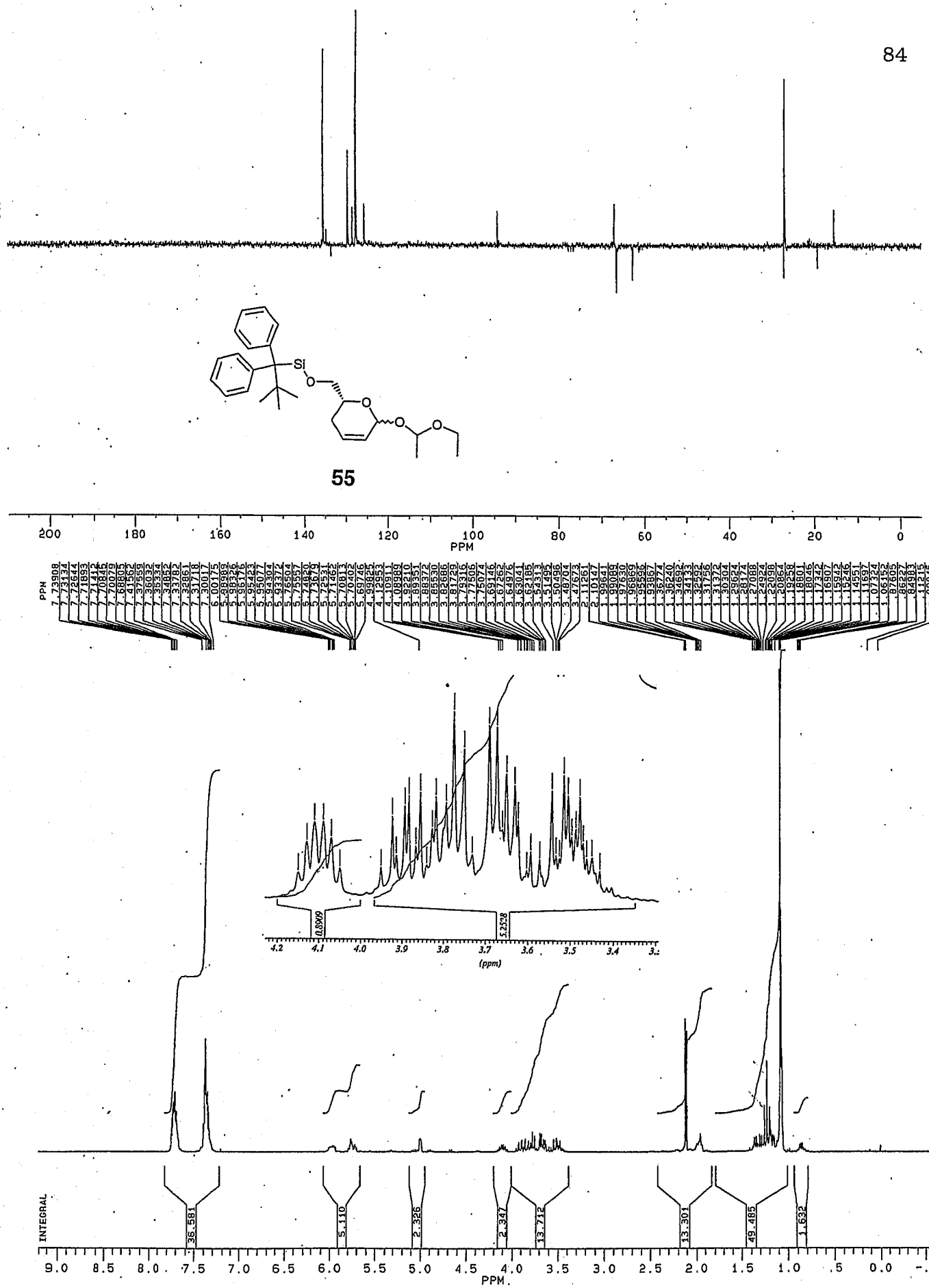


Fig 21. ^{1}H and ^{13}C NMR spectra of 6-(1'-ethoxyethyl)-2*S*-*tert*-butyldiphenylsilyloxymethyl-3,6-dihydro-2H-pyran (**55**).

C.III.11. 6-(1'-Ethoxyethyl)-3,6-dihydro-2H-pyran-2*R* -carbaldehyde (57)

The alcohol **56** (500 mg, 2.47 mmol)), oxalyl chloride (247 µl), DMSO (420 µl) and triethylamine (1.85 ml) were treated as described for the synthesis of **9** (see page 51). Yield 419 mg (85%).

$C_{19}H_{16}O_4$ (200.23)

Calculated C 59.98 H 8.05%,

Found C 59.67 H 7.98%.

C. III.12. 2*R*-Hept-1-enyl-6-(1'-ethoxyethyl)-3,6-dihydro-2H-pyran (58)

The aldehyde **57** (400 mg, 2 mmol), n-hexyltriphenylphosphonium bromide (871 mg), n-BuLi (1.42 ml) were treated as described for the synthesis of **10**(see page 52). Yield 375 mg 870%).

$C_{16}H_{28}O_3$ (268.39)

Calculated C 71.60 H 10.52%,

Found C 71.45 H 10.49%.

C. III.13. R-(-)-argentilactone (1a)

Pyran **56** (80 mg, 0.43 mmol), H_2O_2 (5 ml), MoO_3 (12 mg) and a 1:1 mixture of acetic anhydride and pyridine was treated as was described for the synthesis of *R* (+)-argentilactone **11** (see page 48). Yellow oil, yield 2.99 g (70% over two steps); $[\alpha]_D^{23}$ - 19.9 (c = 0.5, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, Me), 1.3 (m, 6 H, 3 x CH_2), 2.10 (m, 2 H, CH_2), 2.38 (m, 2 H, CH_2), 5.0-5.8 (m, 3 H, H-5, H-6, H-7), 6.04 (ddd, *J* = 10.3 and1.8

Hz, 1 H, H-2), 6.91 (ddd, *J* =10.3 and 4.2 Hz,1 H, H-3); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.0, 22.5, 27.8, 29.0, 29.9, 31.4, 73.9, 121.7, 126.4, 135.7, 144.8. EI-MS: m/z =194 (M+).

$C_{12}H_{18}O_2$ (194.13)

Calculated C 74.19% H 9.34%,

Found C 73.92 H 9.28%.

C.V. Syntheses of starting 2,3-anhydro-pentopyranosides

C. V. 1. Benzyl 2,3-anhydro-β-L-ribopyranoside (62)

C. V.1.1. Benzyl β-L-arabinopyranoside (58)

58 was prepared from 50 gm (0.33 mol) L. arabinose (**57**) and 250 ml freshly distilled benzyl alcohol and 1000 ml abs. Ether as described in reference [84b]. Yield: 73 g (91%); m.p. 171-173 ^{o}C (ethanol/H_2O), ref [84b]: 168-171 ^{o}C (ethanol); $[\alpha]_D$ = +210^{o} (c = 1, H_2O), ref. [84b]: +206 ^{o} (c = 0.3, H_2O).

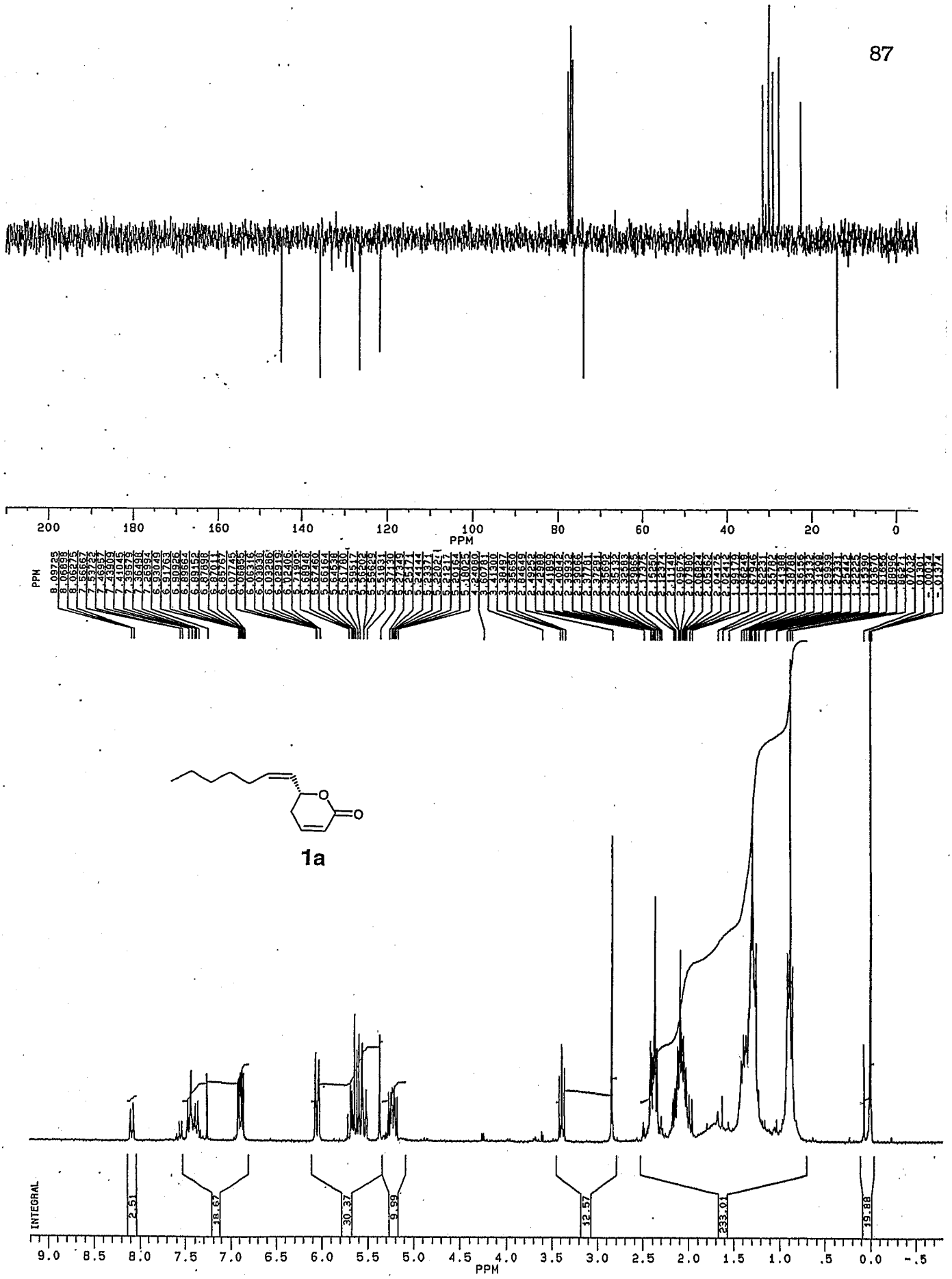
$C_{12}H_{16}O_5$ (240.23)

Calculated C 59.99 H 6.70%,

Found C 59.55 H 6.50%.

C.V.1.2. Benzyl 3,4-O-isopropylidene-β-L-arabinopyranoside (59)

59 was prepared from 72 gm of 2 (0.3 mol), 500 ml 2,2-dimethoxypropane and 1 g *p*-toluensulphonic acid in 500 ml acetone. The resultant syrup **59** was used as such for the next step without further purification. Yield: 53 g (89%).



1a

Fig 22. ^{1}H and ^{13}C NMR spectra of argentilactone **(1a).**

C. V.1.3 Benzyl 3,4-O-isopropylidene-2-*O*-*p*-tolylsulphonyl-β-L-arabino-pyranoside (60)

60 was prepared from 75 g (0.27 mol) of **59**, dissolved in 500 ml pyridine and 199 g *p*-toluensulphonyl chloride as described in ref. [84a]: Yield: 107.3 g (92%); m.p. 93-95 ^{o}C (ethanol/H_2O), ref [84a]: 93-94 ^{o}C (ethanol/H_2O); $[\alpha]_D$ = +183^{o} (c = 1, $CHCl_3$), ref. [84a]: +183 ^{o} (c = 1, $CHCl_3$).

$C_{22}H_{26}O_7S$ (434.47)

Calculated	C 60.81	H 6.02	S 7.37%,
Found	C 60.61	H 6.06	S 7.15%.

C. V.1.4. Benzyl 2-O-p-tolylsulphonyl-β-L-arabinopyranoside (61)

61 was prepared from 107 g (0.24 mol) of **60** and 100 ml 90% acetic acid as described in ref. [84a]. Yield: 88.7 g (91%); m.p. 119-120 ^{o}C (methanol/H_2O), ref [84a]: 118-120 ^{o}C (methanol/H_2O); $[\alpha]_D$ = +128^{o} (c = 1, $CHCl_3$), ref. [84a]: +134 ^{o} (c = 1, $CHCl_3$).

$C_{19}H_{22}O_7S$ (394.41)

Calculated	C 51.81	H 4.61	S 8.12%,
Found	C 57.71	H 5.50	S 8.05%.

C. V.1. Benzyl 2,3-anhydro-β-L-ribopyranoside (62)

62 was prepared from 88 g (0.224 mol) of **61**, 950 ml methanol and 7.1 g (0.3 mol) sodium. Yield: 28.7 g (92.6%); m.p. 76-77 ^{o}C (EE), ref [84a]: 76-77 ^{o}C (EE); $[\alpha]_D$ = - 13 ^{o} (c = 1, EE), ref. [84a]: -11 ^{o} (c = 1, EE).

$C_{12}H_{14}O_4$ (222.22)

Calculated C 64.86 H 6.34%

Found C 64.32 H 6.32%.

C.V.2. Benzyl 2,3-anhydro-α-D-ribopyranoside (71)

C.V.2.1. Tetrabenzoate of β-D-arabinopyranoside (64)

64 was prepared from 50 g (0.33 mol) D-arabinose **63**, 300 ml CH_2Cl_2, 100 ml pyridine and 250 ml benzoyl chloride as described in ref. [55a]. Yield: 170 g (90%); m.p. 172-173 °C (ethanol), ref. [84a] 175 °C (ethanol); $[\alpha]_D$ = -321 ° (c = 1, $CHCl_3$), ref. [84a]: -322 ° (c = 1, ethanol).

$C_{33}H_{26}O_9$ (566.56)

Calculated C 69.96 H 4.63%,

Found C 70.35 H 4.52%.

C.V.2.2. 2,3,4-Tri-O-benzoyl-β-D-arabinopyranosyl bromide (65)

65 was prepared from 170 g **64**, 200 ml CH_2Cl_2 and 320 ml HBr/acetic acid (33%) as described in the ref. [84a]. Yield: 125 g (79%); m.p. 144-146 °C (CH_2Cl_2/EE), ref. [84a]: 146-148 °C (EE); $[\alpha]_D$ = -358 ° (c = 1, $CHCl_3$), ref. [87a]: -353.3 (c = 1.4, $CHCl_3$).

C26H21BrO9 (524.05)

Calculated C 59.44 H 4.03 Br 15.21%,

Found C 59.68 H 4.00 Br 15.09%.

C.V.2.3. Benzyl 2,3,4-tri-*O*-benzoyl-α-D-arabinopyranoside (66)

66 was prepared from 125 g **65**, 1000 ml benzyl alcohol, as described in ref. [84a]. Yield 112 g (85%); m.p. 143-144 °C (ethanol), ref. [87a]: 143-144 °C (ethanol); $[\alpha]_D$ = -153 ° (c = 1, $CHCl_3$), ref. [87a]: -146.7 [*c* = 2.11, $CHCl_3$).

$C_{32}H_{28}O_8$ (552.55)

Calculated C 71.73 H 5.11%,

Found C 72.26 H 5.07%.

C.V.2.4. Benzyl α-D-arabinopyranoside (67)

67 was prepared from 112 g **66**, 365 ml CH_2Cl_2 and 250 ml MeOH and 2.5 g sodium as described in ref. [84a]. Yield: 47 g (96%); m.p. 138.139 °C (ethanol), ref. [87a]: 140-141 °C (ethanol); $[\alpha]_D$ = +12 ° (c = 1, H_2O), ref. [87a]: +12.3 ° (c = 1, H_2O).

$C_{12}H_{16}O_5$ (240.23)

Calculated C 59.99 H 6.71%,

Found C 59.80 H 6.50%.

C.V.2.5. Benzyl 3,4-*O*-isopropylidene-α-D-arabinopyranoside (68)

68 was prepared from 47 g **67**, 500 ml acetone, 300 ml 2,2-dimethoxypropane and 1 g *p*-toluenesulfonic acid as described in ref. [84a]. the product was not characterized, and was used as such for the next step. Yield: 48.9 g (89%).

$C_{15}H_{20}O_5$ (280.31).

C.V.2.6. Benzyl 3,4-*O*-isopropylidene-2-*O*-tolylsuphonyl-α-D-arabinopyranoside (69)

69 was prepared from 48.9 g **68**, 600 ml pyridine and 199 g *p*-toluenesulfonyl chloride as describe in ref. [84a]. Yield: 62.5 g (82.5%); m.p. 82-83 °C (ethanol/H_2O),ref. [84a]: 80-82 °C (ethanol/H_2O); $[\alpha]_D$ = -10 ° (c = 1, $CHCl_3$), ref. [84a]: -7 °(c = 1, $CHCl_3$).

$C_{22}H_{26}O_7S$ (434.47)

Calculated C 60.81 H 6.02 S 7.37%,

Found C 61.02 H 6.00 S 7.20%.

C.V.2.7. Benzyl 2-*O*-tolylsulphonyl-α-D-arabinopyranoside (70)

70 was prepared from 62.5 g **69**, 100 ml 90% acetic acid as described in ref. [84a]. Yield: 51.4 (90%); m.p. 110-112 °C (ethanol/H_2O) ref. [84a]: 116-117 °C (methanol/H_2O); $[\alpha]_D$ = +22 °(*c* = 1, $CHCl_3$), ref. [84a]: + 25 ° (*c* = 1, $CHCl_3$).

$C_{19}H_{22}O_7S$ (394.41)

Calculated C 57.81 H 5.61 S 8.12%,

Found C 57.64 H 5.60 S 8.02%.

C.V.2. Benzyl 2,3-anhydro-α-D-ribopyranoside (71)

71 was prepared from 51.9 g **70**, 950 ml methanol and 3.6 g sodium as describe in ref. [84a]. Yield: 20.88 g (72%); m.p. 96-97 °C (EE/PE), ref. [84a]: 97-98 °C (PE); $[\alpha]_D$ = +190 °(*c* = 1, EE), ref. [84a]: +188 °(*c* = 1, EE)

$C_{12}H_{14}O_4$ (222.22)

Calculated C 64.86 H 6.34%,

Found C 64.56 H 6.22%.

C.V.3. Benzyl 2,3-anhydro-4-O-triflyl-β-L-ribopyranoside (72) and -α-D-ribopyranoside (73)

72 and **73** were prepared from 2.22 g (10 mmol) **62** and **71** respectively, 75 ml CH_2Cl_2, 2 ml pyridine and 1.8 ml (10.97 mmol) trifluoromethanesulfonic anhydride (Tf_2O), synthesized as described in ref. [84a].

C.V.3.1. Benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside (72)

Yield: 3.13 g (90%); m.p. 83-84 °C (ethanol), ref. [84a]: 82-83 °C (ethanol); $[\alpha]_D$ = +16 ° (*c* = 1, $CHCl_3$),ref. [84a]: +16 °(*c* =1, $CHCl_3$)

$C_{13}H_{13}F_3O_6S$ (354.29)

Calculated C 44.07 H 3.69 S 9.04%,

Found C 43.85 H 3.60 S 9.25%.

C.V.3.2. Benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (73)

Yield: 3.3 g (94.3%); m.p. 67-68 °C (ethanol), ref. [84a]: 66-68 °C (ethanol); $[\alpha]_D$ = +126 ° (*c* = 1, $CHCl_3$),ref. [84a]: +128 °(*c* =1, $CHCl_3$)

$C_{13}H_{13}F_3O_6S$ (354.29)

Calculated C 44.07 H 3.69 S 9.04%,

Found C 43.85 H 3.60 S 9.25%.

C.V.4 Standard procedure for the syntheses of the amino sugars 74 and 75

The amino deoxy sugar **74** and **75** were prepared following the published procedure [88] by passing ammonia gas through a solution of epoxy triflates **72** and **73** in acetone at -10 ^{o}C for 1 h, followed by the aqueous work up in the conventional manner.

C.V.4.1 Benzyl 4-Amino-4-deoxy-2,3-anhydro-α-D-lyxopyranoside (74)

Yield: 73%; m.p. 46-48 ^{o}C; $[\alpha]_D^{20}$ = +93 ^{o} (*c* = 0.20, CH_2Cl_2).

$C_{12}H_{15}NO_3$ (221.11)

Calculated C 65.14 H 6.83 N 6.33%,

Found C 64.99 H 6.81 N 6.30%.

C.V.4.2. Benzyl 4-Amino-4-deoxy-2,3-anhydro-β-L-lyxopyranoside (75)

Yield: 73%; m.p. 35-37 ^{o}C; $[\alpha]_D^{20}$ = +102 ^{o} (*c* = 0.25, CH_2Cl_2).

$C_{12}H_{15}NO_3$ (221.11)

Calculated C 65.14 H 6.83 N 6.33%,

Found C 64.99 H 6.81 N 6.30%.

C.VI. Synthesis of chiral *as*-triazines

C.VI.1. General procedure for the preparation of hydrazonoyl chloride

(i) The particular arylamine (0.1 mol) was dissolved in cold aqueous hydrochloric acid (80 ml, 5N). To this solution was added dropwise a solution of sodium nitrite (7.6 g, 0.11 mol) in water (25 ml) with efficient stirring at 0-

5 °C. Stirring was continued for 20-30 min and the resulting fresh cold arenediazonium chloride solution was used immediately as such for the following coupling step.

(ii) A cold (-5 °C), freshly prepared solution of the particular arenediazonium chloride (0.1 mol) was poured onto a cooled solution (-8 °C, ice-salt bath) of α-chloroacetylacetone (13.5 g, 0.1 mol) in pyridine/water (140 ml, 1:1 v/v) with vigorous stirring. Stirring of the resulting yellow mixture was continued until a cold precipitate was formed (5-10 min). The reaction mixture was then diluted with cold water, dried, and recrystallized from the appropriate solvent.

C.VI.2. General procedure for the preparation of *as*-triazines

To a solution of the appropriate hydrazonoyl chloride (1 mmol) in a mixture of dichloromethane and methanol (10 ml, 1:1) was added a solution of the aminosugar **75** or **76** (1 mmol) in methanol (2 ml). Triethylamine (1 ml) in methanol was then dropwise added to the stirred mixture at 0 °C. Stirring was continued at 0 °C for 2-4 h, and then at ambient temperature for 5-12 h till TLC showed no starting aminosugar. The solvent was then removed *in vacuo* and the residue was washed with water. The resulting crude solid was then collected and recrystalized or purified on a column of silica gel.

C.VI.2.1. 1-Phenyl-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-α-D-arabinopyranoso)-[4,3-e]-1,2,4-triazine (85a)

Yellow crystals; yield 324 mg (85%); $[\alpha]_D^{25}$ = +606.4 °(*c* = 0.04, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ = 2.5 (s, 3 H, CH_3), 3.43 (br s, 1H, H-4), 3.55 (dd, *J* = 7.9 and 9.7 Hz, 1 H, H-2), 3.76 (dd, *J* = 1.5 and 13.13 hz, 1 H, H-5'), 4.07 (dd, *J* = 1.5 and 13.13 Hz, 1 H, H-5), 3.84 (dd, *J* = 3.35 and 9.7 Hz, 1 H, H-3), 4.42 (d, *J* = 7.77 Hz, 1 H, H-I), 4.59 (d, *J* = 11.5 Hz, 1 H, PhC*H*H), 4.88 (d, *J* = 11.5 Hz, 1 H, PhCH*H*), 5.54 (s, 1 H, NH), 6.90 (m, 1 H, Ph*H*), 7.26-7.32 (m, 7 H, Ph*H*), 7.40-7.44 (m, 2 H, Ph*H*); ^{13}C NMR (63 MHz, CDCl3): δ = 23.5 (CH_3), 46.9, 54.7 (C-3, C-4), 65.5 (C-5), 68.5 (C-2), 71.1 (PhCH2), 103.4 (C-1), 114.9, 120.5, 128.1, 128.3, 128.6, 128.9 (Ph) FAB-MS: m/z = 381.1 (M^+).

$C_{21}H_{23}N_3O_4$ (381.43)

Calculated C 66.13 H 6.03 N 11.02%,

Found C 66.11 H 6.04 N 10.98%.

C.VI.2.2. 1-(4-Methoxyphenyl)-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-α-D-arabinopyranoso)-[4,3-e]-1,2,4-triazine (85b)

Yellow crystals; yield 350 mg (85%); $[\alpha]_D^{25}$ = +690.6 o (*c* = 0.13, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ = 2.5 (s, 3 H, CH_3), 3.77 (m, 3 H, H-2, H-3, H-5'), 4.08 (d, *J* = 12.8 Hz, 1 H, H-5), 4.41 (d, *J* = 7.97 Hz, 1 H, H-I), 4.62 (d, *J* = 11.6 Hz, 1 H, PhC*H*H), 4.90 (d, J = 11.6 Hz, 1 H, PhCH*H*), 5.29 (s, 3H, OMe), 6.86 (m, 2 H, Ph*H*), 7.33 (m, 7 H, Ph*H*); FAB-MS: m/z = 411.3 (M^+).

$C_{22}H_{25}N_3O_5$ (411.45)

Calculated C 64.22 H 6.12 N 10.21%,

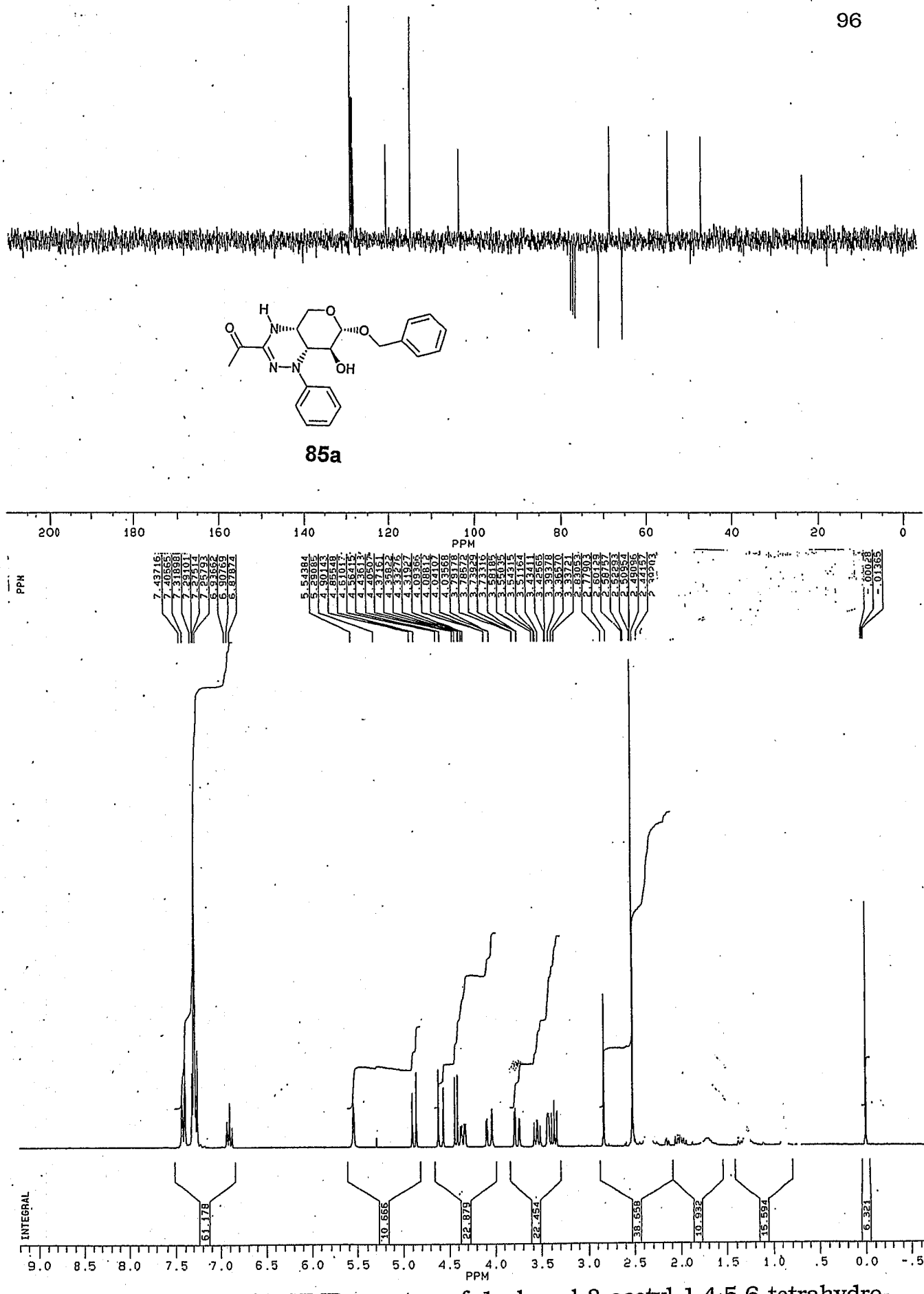


Fig 23. ^{1}H and ^{13}C NMR spectra of 1-phenyl-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-α-D-arabinopyranoso)-[4,3-e]-1,2,4-triazine **(85a).**

Found C 64.14 H 6.06 N 10.25%.

C.VI.2.3. 1-(4-Fluorophenyl)-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-α-D-arabinopyranoso)-[4,3-e]-1,2,4-triazine (85c)

Yellow crystals, m.p. 111-113 °C; yield 312 mg (78%); $[\alpha]_D^{25}$ = +617.0 °(*c* = 0.1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.5 (s, 3 H, CH_3), 3.42 (m, 1 H, H-4), 3.52 (dd, *J* = 7.63 and 9.76 Hz, 1 H, H-2), 3.75 (dd, *J* =1.53 and 13.4 Hz, 1 H, H-5'), 4.06 (dd, *J* = 1.53 and 13.12 Hz, 1 H, H-5), 4.22 (dd, *J* = 3.36 and 9.76 Hz, 1 H, H-3), 4.40 (d, J = 7.63 Hz, 1 H, H-1), 4.57 (d, *J* = 11.6 Hz, 1 H, PhC*H*H), 4.87 (d, J = 11.6 Hz, 1 H, PhCH*H*), 5.55 (s, 1H, OMe), 6.98 (m, 2 H, Ph*H*), 7.29 (m, 5 H, Ph*H*), 7.25-7.37 (m, 2 H, Ph*H*); ^{13}C NMR (63 MHz, CDCl3): δ = 23.5 (CH3), 46.9, 55.3 (C-3, C-4), 65.4 (C-5), 68.5 (C-2), 71.1 (PhCH2), 103.4 (C-1), 115.1, 115.4, 116.3, 116.4, 128.2, 128.3, 128.6 (Ph) FAB-MS: m/z = 399.1 (M^+).

$C_{21}H_{22}FN_3O_4$ (399.42)

Calculated C 63.15 H 5.55 N 10.52 F 4.76%,

Found C 63.12 H 5.50 N 10.25 F 4.75%.

C.VI.2.4. 1-(3-Chlorophenyl)-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-α-D-arabinopyranoso)-[4,3-e]-1,2,4-triazine (85d)

Yellow oil; yield 300 mg (72%); $[\alpha]_D^{25}$ = +457.4 °(*c* = 0.1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.5 (s, 3 H, CH_3), 3.54 (m, 3 H, H-2, H-3, H-4), 3.69 (d, *J* =13.12 Hz, 1 H, H-5'), 4.02 (d, *J* = 13.12 Hz, 1 H, H-5), 4.24 (dd, *J* = 2.74

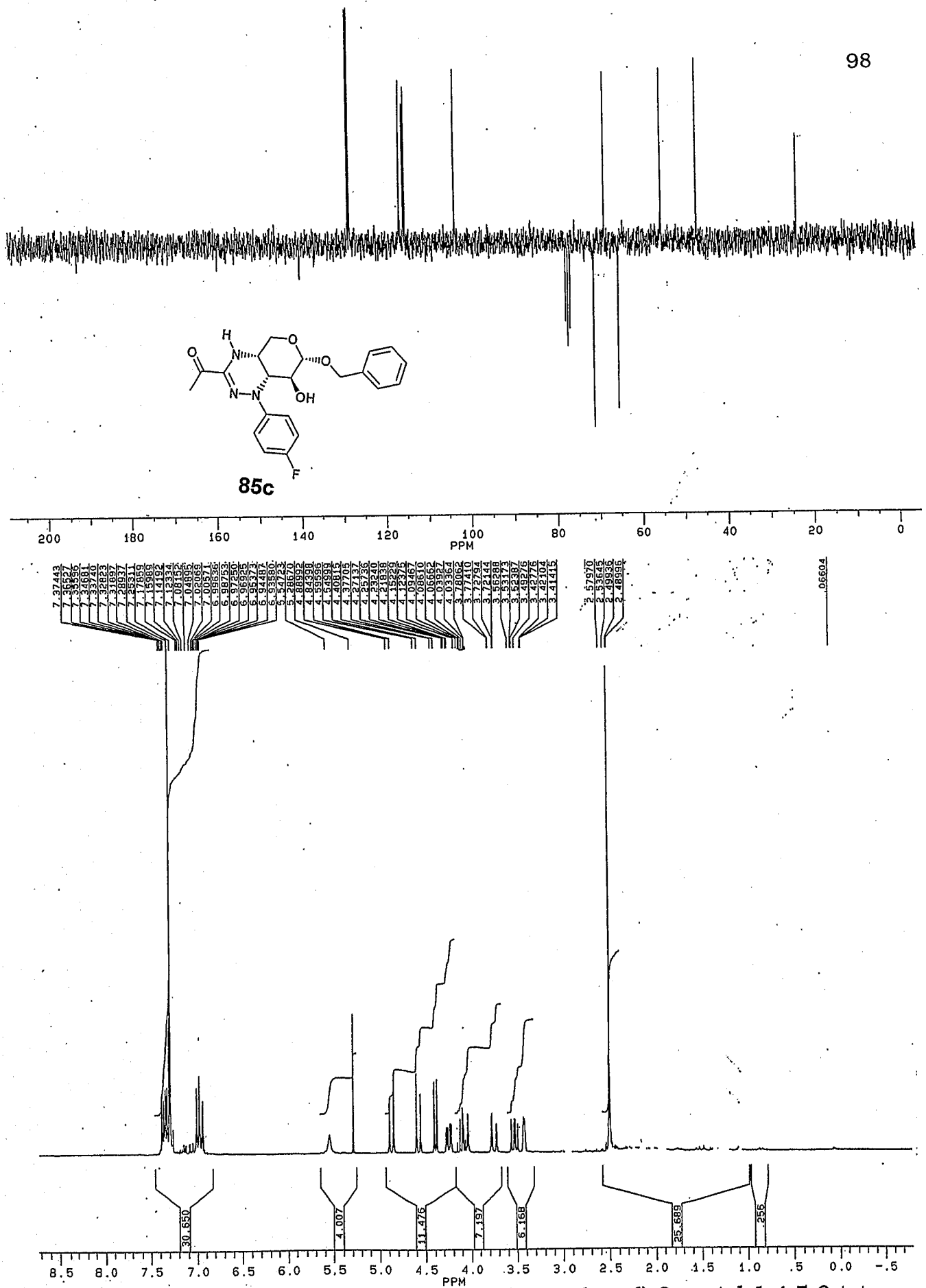


Fig 24. ^{1}H and ^{13}C NMR spectra of 1-(4-fluorophenyl)-3-acetyl-1,4,5,6-tetra-hydro-(benzyl 3,4-dideoxy-α-D-arabinopyranoso)-[4,3-e]-1,2,4-triazine **(85c).**

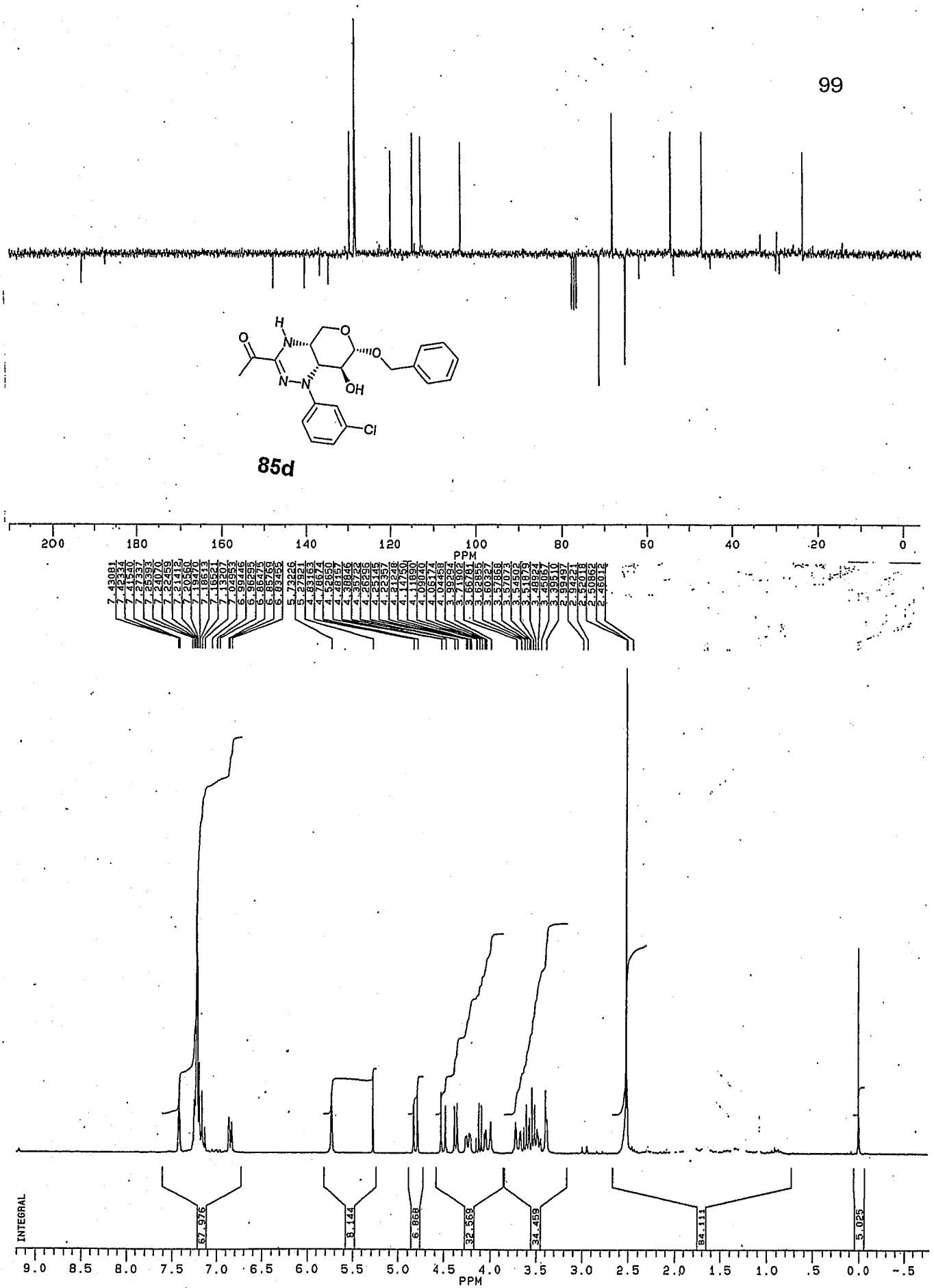


Fig 25. ^{1}H and ^{13}C NMR spectra of 1-(3-chlorophenyl)-3-acetyl-1,4,5,6-tetra-hydro-(benzyl 3,4-dideoxy-α-D-arabinopyranoso)-[4,3-e]-1,2,4-triazine **(85d).**

and 9.76 Hz, 1 H), 4.37 (d, *J* = 7.94 Hz, 1 H, H-1), 4.50 (d, *J* = 11.3 Hz, 1 H, PhC*H*H), 4.81 (d, *J* = 11.3 Hz, 1 H, PhCH*H*), 5.73 (s, 1H, NH), 6.83-6.86 (m, 2 H, Ph*H*), 7.13-7.42 (m, 5 H, Ph*H*), 7.42-7.43 (m, 2 H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.6 (CH_3), 47.0, 54.4 (C-3, C-4), 65.1 (C-5), 68.2 (C-2), 71.3 (Ph*C*H_2), 103.6 (C-1), 112.8, 114.8, 119.9, 128.2, 128.3, 128.5, 129.7, 134.7, 140.3, 147.8 (Ph), 193.3 (CO). FAB-MS: m/z = 415.0 (M^+).

$C_{21}H_{22}ClN_3O_4$ (415.87)

Calculated C 60.65 H 5.33 N 10.10 Cl 8.52%,

Found C 60.56 H 5.31 N 10.06 Cl 8.45%.

C.VI.2.5. 1-Phenyl-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-β-L-arabinopyranoso)-[4,3-e]-1,2,4-triazine (86a)

Yellow crystals; yield 300 mg (79%); $[\alpha]_D^{25}$ = -476.6 °(*c* = 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 3.52 (br s, 1H, H-3), 3.68 (dd, *J* = 0.8 and 12.00 Hz, 1 H, H-5'), 3.70 (m, 1 H, H-4),4.11 (dd, *J* = 0.8 and 12.00 Hz, 1 H, H-5), 4.60 (d, *J* = 11.9 Hz, 1 H, PhC*H*H), 4.64 (m, 1 H, H-4), 4.81 (d, *J* = 11.9 Hz, 1 H, PhCH*H*), 4.97 (d, J = 3.36 Hz, 1 H, H-1), 5.43 (s, 1 H, NH), 6.82-7.42 (m, 10 H, Ph*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (CH_3), 46.9 (C-3), 52.0 (C-4), 61.5 (C-5), 66.3 (C-2), 69.8 (Ph*C*H_2), 98.3 (C-1), 114.4, 120.5, 128.1, 128.3, 128.6, 128.9, 146.8 (Ph), 1982.3 (CO). FAB-MS: m/z = 381.1 (M^+).

$C_{21}H_{23}N_3O_4$ (381.43)

Calculated C 66.13 H 6.03 N 11.02%,

Found C 66.11 H 6.04 N 10.98%.

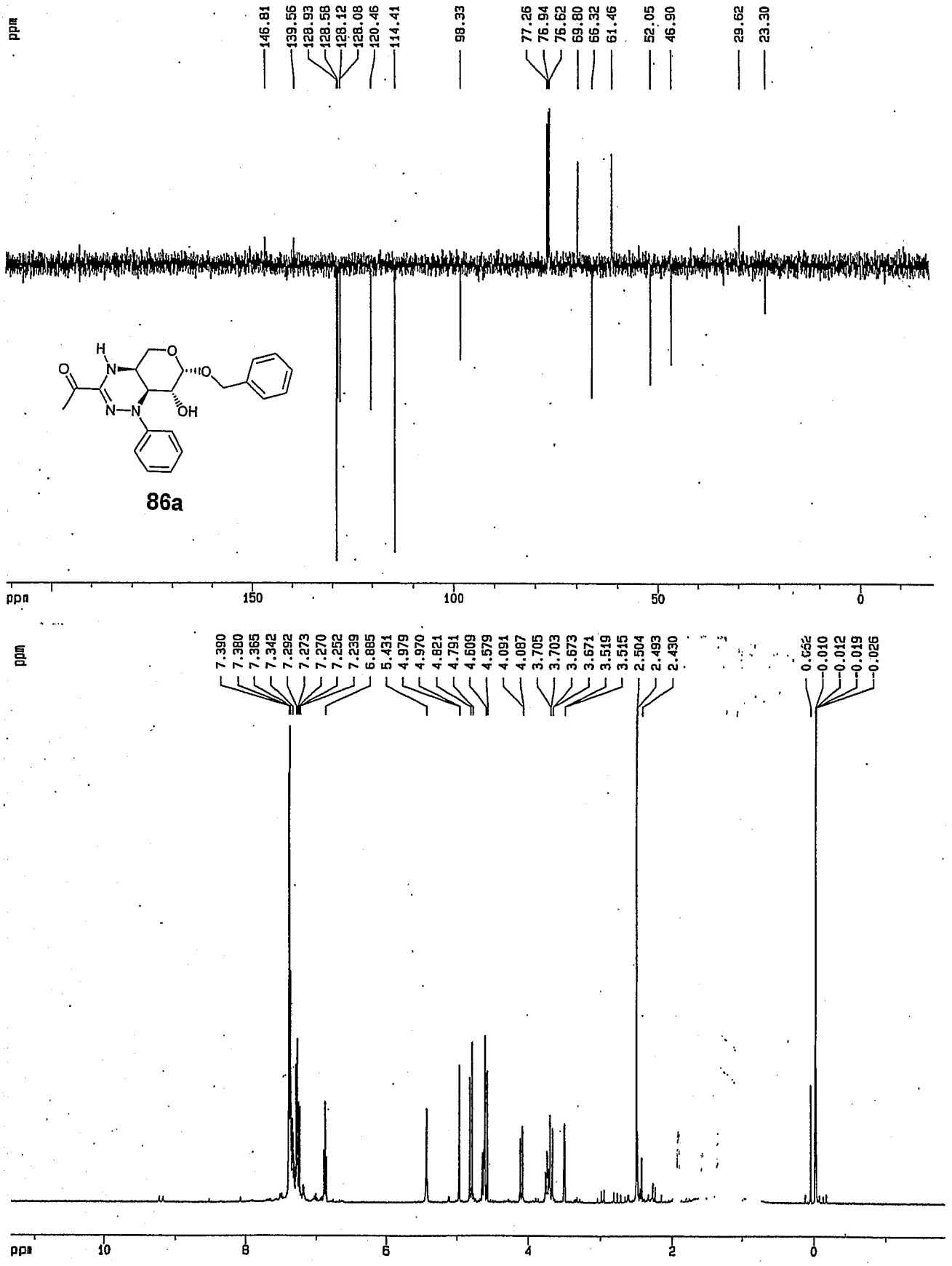
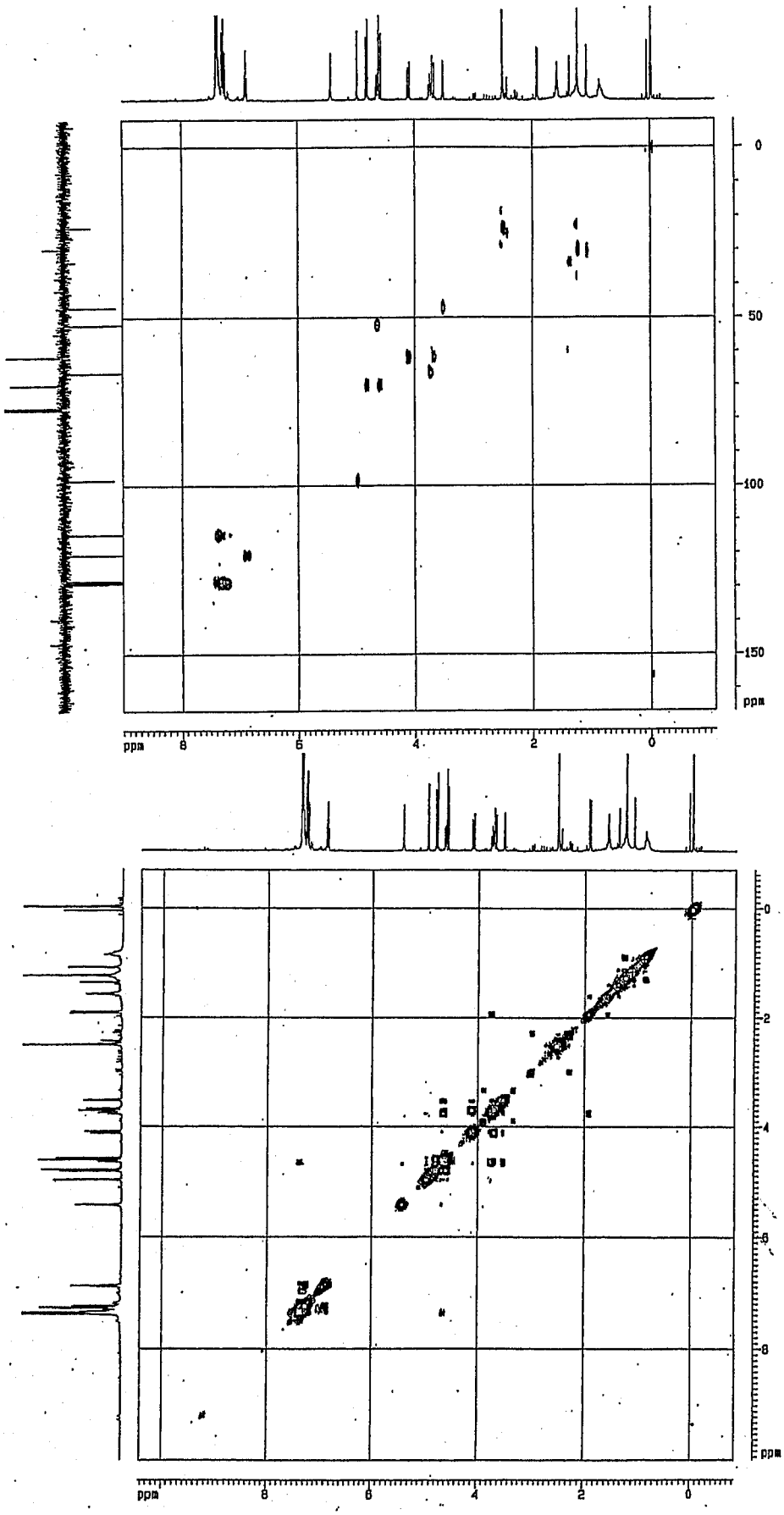
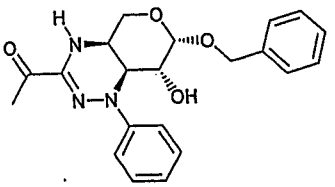


Fig 26. ^{1}H and ^{13}C NMR spectra of 1-Phenyl-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-β-L-arabinopyranoso)-[4,3-e]-1,2,4-triazine **(86a).**





86a

Fig 27. HMQC and ^{1}H-^{1}H COSY spectra of 1-Phenyl-3-acetyl-1,4,5,6-tetra-hydro-(benzyl 3,4-dideoxy-β-L-arabinopyranoso)-[4,3-e]-1,2,4-triazine **(86a).**

C.VI.2.6. 1-(4-Methoxyphenyl)-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-β-L-arabinopyranoso)-[4,3-e]-1,2,4-triazine (86b)

Yellow solid, m.p. 170 °C (decomp.); yield 350 mg (85%); $[\alpha]_D^{25}$ = -442.5 ° (*c* = 0.1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.5 (s, 3 H, CH_3), 3.70 (dd, J = 1.5 and 12.80 Hz, 1 H, H-5'), 3.77 (s, 3 H, OMe), 3.80 (m, 1 H, H-2), 4.11 (dd, *J* = 1.5 and 12.8 Hz, 1 H, H-5), 4.52 (m, 1 H, H-4), 4.59 (d, *J* = 11.8 Hz, 1 H, PhC*H*H), 4.81 (d, *J* = 11.8 Hz, 1 H, PhCH*H*), 4.98 (d, *J* = 3.6 Hz, 1 H, H-1),5.38 (s, 1H, NH), 6.83-6.92 and 7.16-7.40 (m, 9 H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.3 (CH_3), 46.8, 53,4 (C-3, C-4), 61.6 (C-5), 66.5 (C-2), 69.9 (CH_2Ph), 98.5 (C-1), 114.4, 116.4, 128.2, 128.7 (Ph), 193.0 (CO). FAB-MS: m/z = 411.3 (M^+).

$C_{22}H_{25}N_3O_5$ (411.45)

Calculated C 64.22 H 6.12 N 10.21%,

Found C 64.14 H 6.06 N 10.25%.

C.VI.2.7. 1-(4-Fluorophenyl)-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-β-L-arabinopyranoso)-[4,3-e]-1,2,4-triazine (86c)

Yellow oil; yield 312 mg (78%); $[\alpha]_D^{25}$ = -295.2 °(*c* = 0.16, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 3.54 (brs, 1 H, H-3), 3.68-3.79 (m, 2 H, H-2, H-5'), 4.12 (dd, *J* = 1.8 and 12.81 Hz, 1 H, H-5), 4.54 (m, 1 H, H-4), 4.60 (d, *J* = 11.6 Hz, 1 H, PhC*H*H), 4.82 (d, *J* = 11.6 Hz, 1 H, PhCH*H*), 4.98 (d, *J* = 3.6 Hz, 1 H, H-1), 5.45 (s, 1 H, NH), 6.95-7.01, 7.16-7.41 (m, 9 H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.4 (CH3), 47.0, 52.9 (C-3, C-4), 61.5

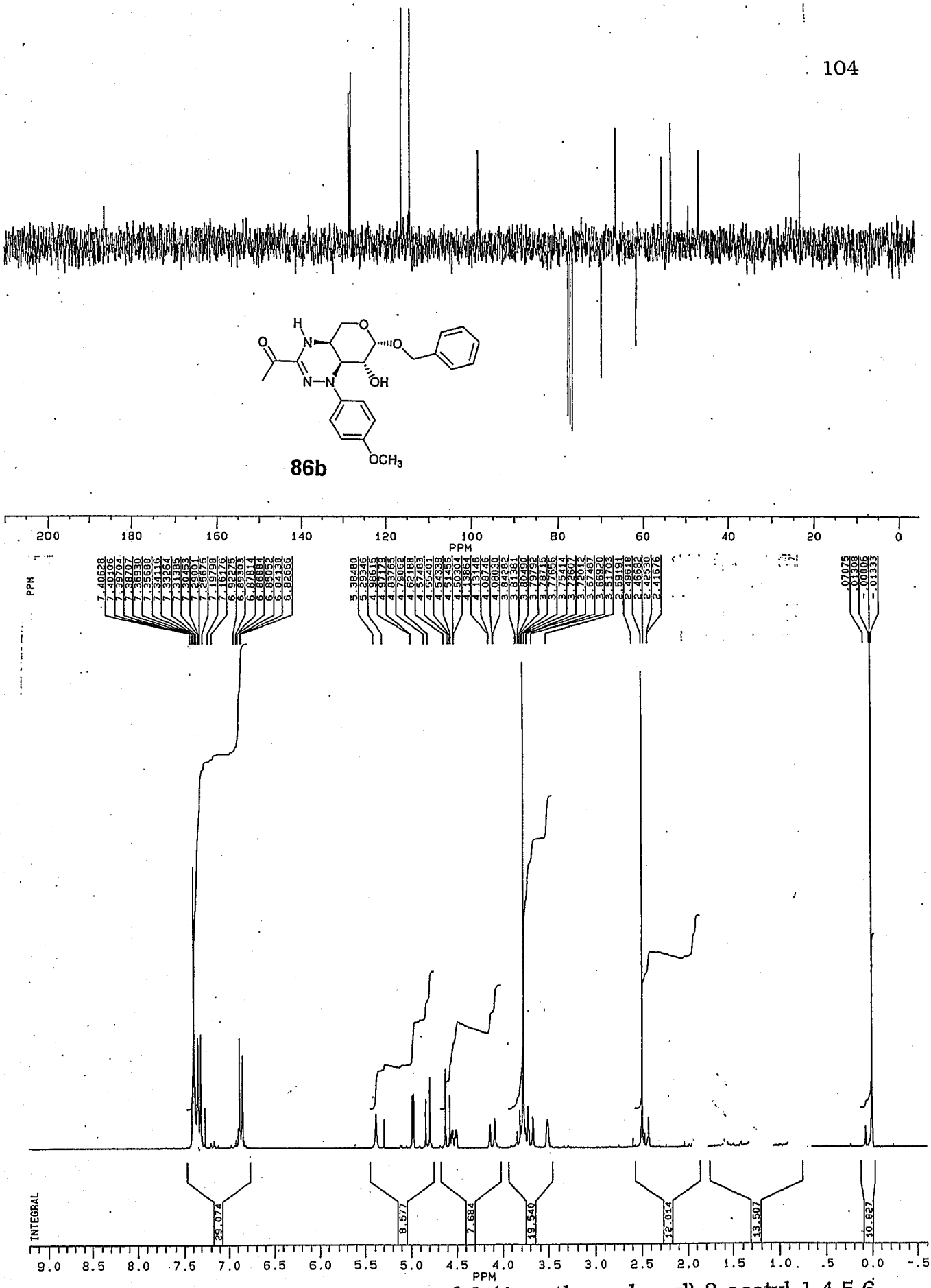


Fig 28. ^{1}H and ^{13}C NMR spectra of 1-(4-methoxyphenyl)-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-β-L-arabinopyranoso)-[4,3-e]-1,2,4-triazine (**86b**).

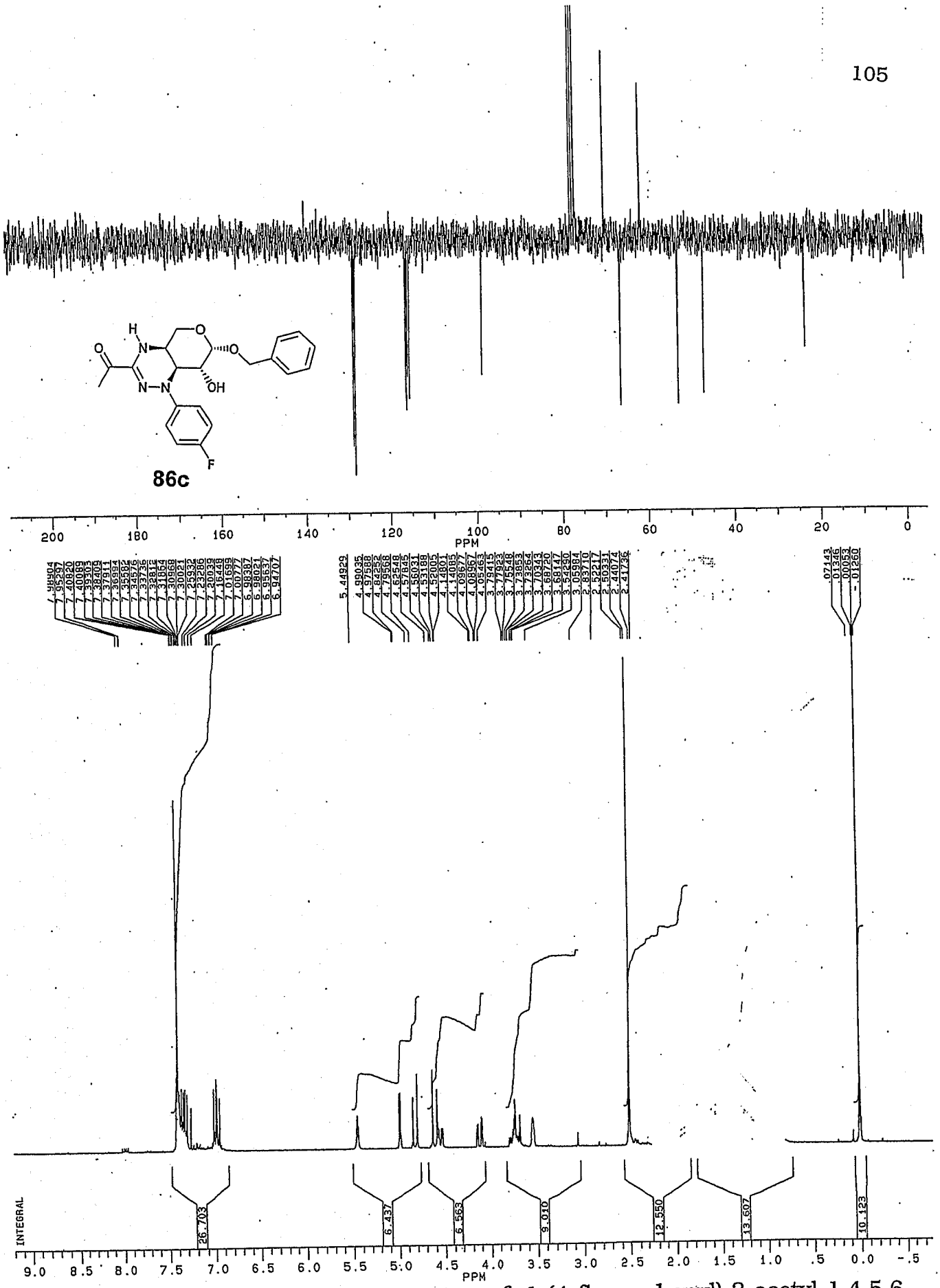


Fig 29. ^{1}H and ^{13}C NMR spectra of 1-(4-fluorophenyl)-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-β-L-arabinopyranoso)-[4,3-e]-1,2,4-triazine **(86c)**.

$C_{21}H_{22}FN_3O_4$ (399.42)

Calculated	C 63.15	H 5.55	N 10.52	F 4.76%,
Found	C 63.12	H 5.50	N 10.25	F 4.75%.

C.VI.2.8. 1-(3-Chlorophenyl)-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-β-L-arabinopyranoso)-[4,3-e]-1,2,4-triazine (86d)

Yellow oil; yield 300 mg (72%); $[\alpha]_D^{25}$ = -303.2 °(*c* = 0.16, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.55 (brs, 1 H, H-3), 3.71 (m, 2 H, H-2, H-5'), 4.12 (dd, *J* = 1.5 and 12.8 Hz, 1 H, H-5), 4.59 (m, 2 H, H-4, PhC*H*H), 4.83 (d, *J* = 11.7 Hz, 1 H, PhCH*H*), 4.98 (d, *J* = 3.6 Hz, 1 H, H-1), 5.52 (s, 1H, NH), 6.82-6.87 (m, 2 H, Ph*H*), 7.14-7.42 (m, 5 H, Ph*H*), 7.42-7.43 (m, 2 H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.5 (CH_3), 47.2, 52.0 (C-3, C-4), 61.4 (C-5), 66.3 (C-2), 70.0 (Ph*C*H_2), 98.3 (C-1), 112.3, 114.6, 120.2, 128.2, 128.3, 128.5, 129.7, 134.7, 140.3, 147.8 (Ph), 193.3 (CO). FAB-MS: m/z = 415.0 (M^+).

$C_{21}H_{22}ClN_3O_4$ (415.87)

Calculated	C 60.65	H 5.33	N 10.10	Cl 8.52%,
Found	C 60.56	H 5.31	N 10.06	Cl 8.45%.

C.VII. General procedure for the preparation of trithiocarbonates

Sodium sulfide (479 mg, 2 mmol) was dissolved in 100 ml water at 30 °C. To this solution was added 189 mg (2.5 mmol) carbon disulfide. The reaction mixture was warmed to 40 °C and allowed to stir for 6 h. The excess carbon disulfide was removed by evaporation at reduced pressure. To the

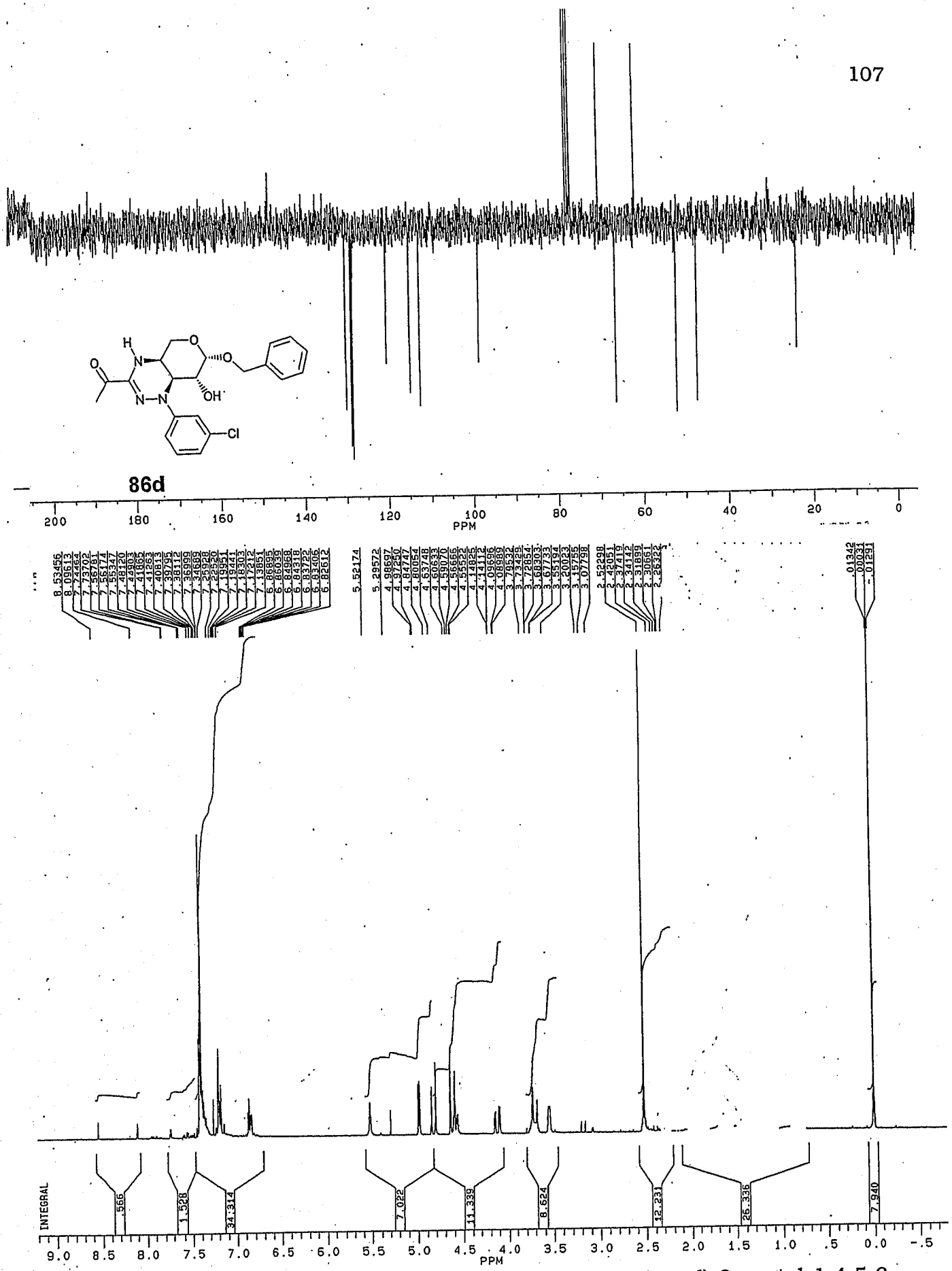


Fig 30. ^{1}H and ^{13}C NMR spectra of 1-(3-chlorophenyl)-3-acetyl-1,4,5,6-tetrahydro-(benzyl 3,4-dideoxy-β-L-arabinopyranoso)-[4,3-e]-1,2,4-triazine **(86d).**

resulting deep red-colored solution was dropped slowly a solution of 354 mg (1 mmol) triflate **75** and **76**, respectively in little amount of ethanol. Stirring at room temperature for 10 min produced the trithiocarbonates as yellow colored precipitates.

C.VII.1. Benzyl 3,4-dideoxy-3,4-S-thiocabonyl-α-D-arabinopyranoside (**89**)

Yellow crystals, m.p. 131-133 ^{o}C, ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.87 (dd, *J* = 3.35 and 13.42 Hz, 1H, H-5'), 4.07 (m, 2H, H-3, H-2), 4.30 (dd, *J* = 3.05 and 13.42 Hz, 1H, H-5), 4.46 (d, *J* = 6.41 Hz, 1H, H-1), 4.62 (d, *J* = 11.9 Hz, 1 H, PhC*H*H), 4.76 (ddd, *J* = 4.27 and 3.05 Hz, 1 H, H-4), 4.95 (d, *J* = 11.9 Hz, 1 H, PhCH*H*), 7.36-7.38 (m, 5 H, Ph*H*); ^{13}C NMR (63MHz, $CDCl_3$): δ = 58.7, 61.4 (C-3, C-4), 61.6 (C-5), 69.9 (C-2), 70.8 (*C*HHPh), 102.3 (C-1), 128.1, 128.3, 128.7 (Ph), 162.1 (C=S). FAB-MS: m/z = 384.1 (M^+)

$C_{13}H_{14}O_3S_3$ (314.45)

Calculated C 49.66 H 4.49 S 30.59%,

Found C 49.58 H 4.45 S 30.56%.

C.VII.2. Benzyl 3,4-dideoxy-3,4-S-thiocabonyl-β-L-arabinopyranoside (**90**)

Yellow crystals, m.p. 162.3 ^{o}C, ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.88 (dd, *J* = 1.83 and 13.42 Hz, 1H, H-5'), 4.17 (m, 3H, H-5, H-3, H-2), 4.61 (d, *J* = 11.6 Hz, 1 H, PhC*H*H), 4.81 (m, 2 H, H-4, PhCH*H*), 5.07 (brs, 1H, H-1), 7.34-7.42 (m, 5 H, Ph*H*); ^{13}C NMR (63 MHz, $CDCl_3$):δ = 56.8 (C-5), 60.09, 60.38 (C-3,

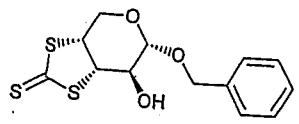


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Fig 31. ^{1}H and ^{13}C NMR spectra of benzyl 3,4-dideoxy-3,4-S-thiocabonyl-α-D-arabinopyranoside (**89**).

C-4), 68.3 (C-2), 70.4 (*C*HHPh), 97.05 (C-1), 128.3, 128.5, 128.8 (Ph). FAB-MS: m/z = 384.1 (M^+)

$C_{13}H_{14}O_3S_3$ (314.45)

Calculated C 49.66 H 4.49 S 30.59%,

Found C 49.58 H 4.45 S 30.56%.

C.VII.3. Methyl 3,5-dideoxy-3,5-S-thiocarbonyl-α-D-xylofuranoside (94)

Yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.35 (s, 3H, OCH_3), 3.52 (m, 2H), 3.66 (m, 2 H), 4.29 (t, *J* = 7.3 Hz, 1 H, H-4), 5.23 (s, 1 H, H-1); ^{13}C NMR (63 MHz, $CDCl_3$):δ = 38.6 (C-5), 55.7 (C-3), 56.1 (OCH_3), 75.7 (C-2), 102.7 (C-1). FAB-MS: m/z = 207.1 (M^+-OCH_3)

$C_7H_{10}O_3S_3$ (238.35)

Calculated C 35.27 H 4.23 S 40.36%,

Found C 35.15 H 4.16 S 40.34%.

C.VIII. General procedure for the preparation of compounds 97a-e and 98a-e

To a stirred solution of the epoxy triflate **62** or **71** (354 mg, 1 mmol) in 10 ml dry THF, 3 mmol of the corresponding substituted piperazine was added. The reaction mixture was then stirred until TLC analysis showed no more starting material. The aqueous work up yielded the 4-substituted lyxopyranoside derivatives.

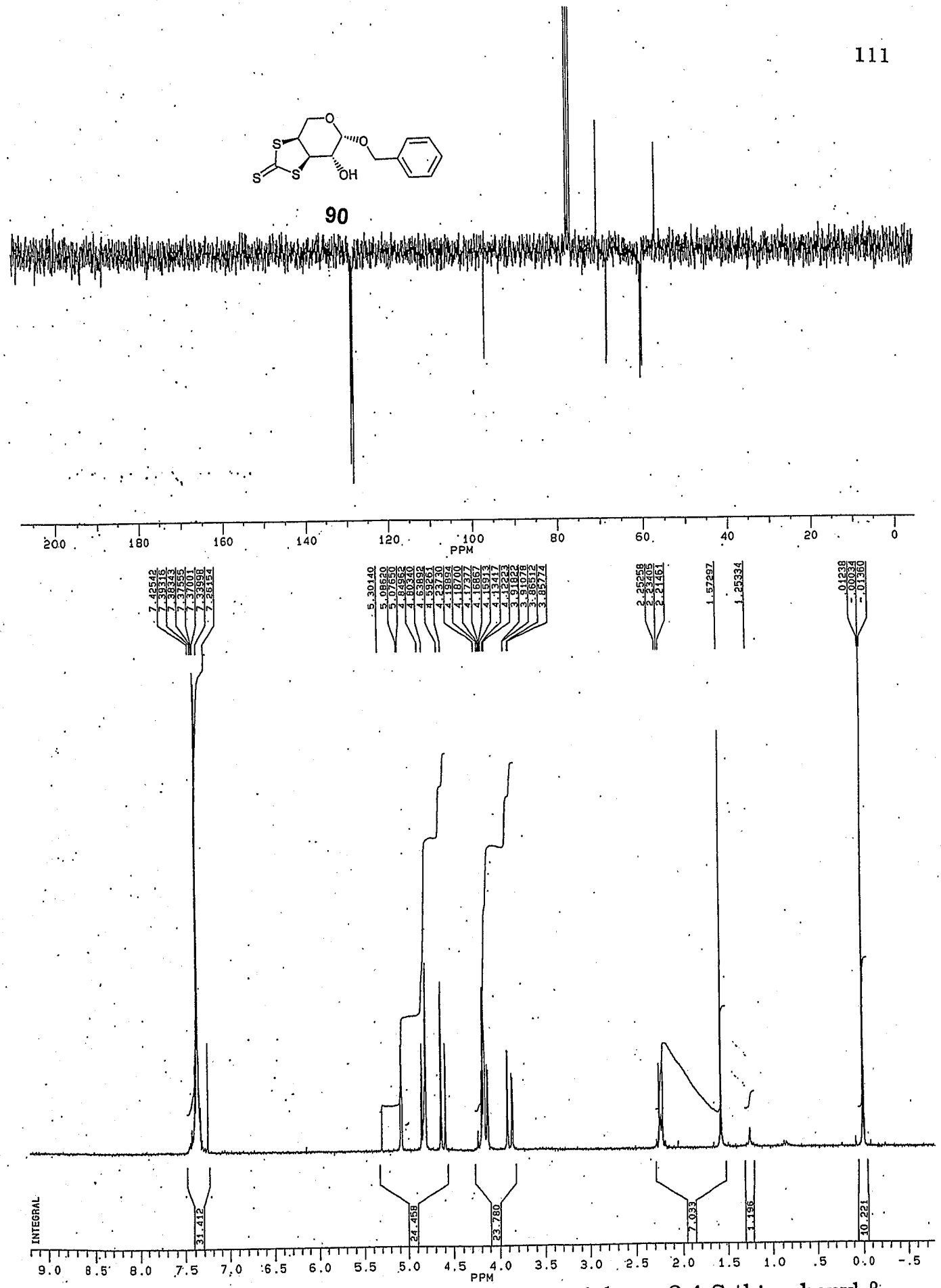

Fig 32. ^{1}H and ^{13}C NMR spectra of benzyl 3,4-dideoxy-3,4-S-thiocabonyl-β-L-arabinopyranoside (**90**).

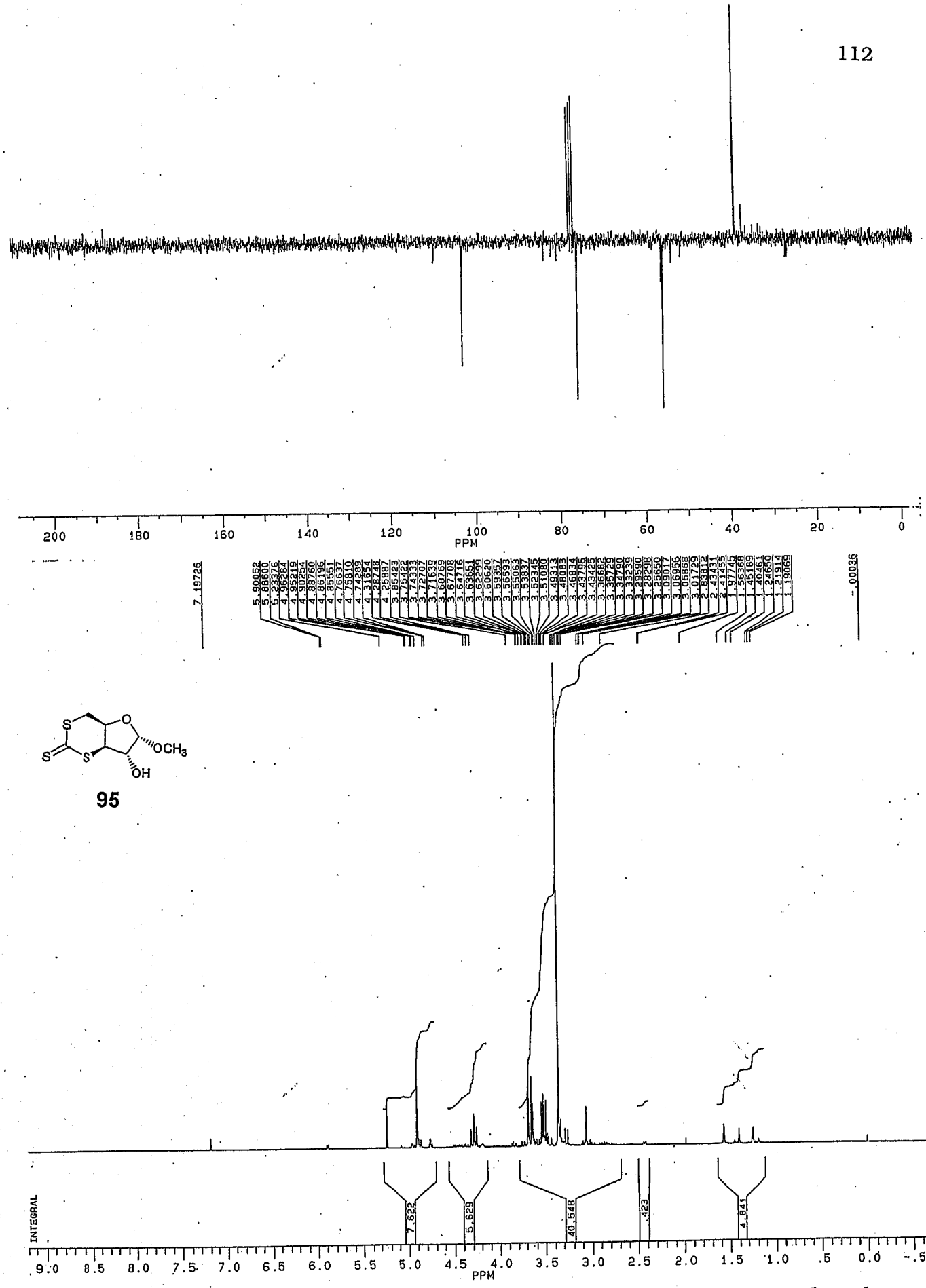

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Fig 33. ^{1}H and ^{13}C NMR spectra of methyl 3,5-dideoxy-3,5-S-thiocarbonyl-α-D-xylofuranoside **(95)**.

C.VIII.1. Benzyl 2,3-anhydro-4-deoxy-4-(4-methyl-1-piperazinyl)-α-D-lyxo-pyranoside (97a)

Yellow oil; Yield 0.258 g (85%); $[\alpha]_D^{20}$ = +77.3 ^{o} (*c* = 0.35, CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, N-CH_3), 2.61-2.85 (m, 8 H, H-2', H-3', H-5', H-6'), 2.91 (dd, *J* = 6.4 and 10.7 Hz, 1 H, H-4), 3.09 (d, *J* = 4.0 Hz, 1 H, H-3), 3.35 (d, *J* = 3.7 Hz, 1 H, H-2), 3.52 (ddd, *J* = 0.9, 6.4 and 11 Hz, 1 H, H-5′), 3.74 (dd, *J* = 10.7 and 11.0 Hz, 1 H, H-5), 4.56 (d, *J* = 11.6 Hz, 1 H, OC*H*HPh), 4.80 (d, *J* = 11.6 Hz, 1 H, OCH*H*Ph), 4.99 (s, 1 H, H-1), 7.28-7.38 (m, 5 H, C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 44.5 (N-CH_3), 47.9, 53.8 (C2', C3', C5', C6'), 48.6, 51.1 (C-2, C-3),54.1 (C-5), 54.4 (C-4), 68.3 (O*C*HHPh), 92.5 (C-1), 126.4-127.0, 137.0 (C_6H_5). FAB-MS: m/z = 305.1 [M^++1].

$C_{17}H_{24}N_2O_3$ (304.39)

Calculated C 67.08 H 7.95 N 9.20%,

Found C 66.95 H 7.82 N 9.15%.

C.VIII.2. Benzyl 2,3-anhydro-4-deoxy-4-(4-ethyl-1-piperazinyl)-α-D-lyxo-pyranoside (97b)

Yellow oil; Yield 0.257 g (81%); $[\alpha]_D^{20}$ = +71.1 ^{o} (*c* = 0.44, CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.2 Hz, 3 H, N-$CH_2C\underline{H}_3$), 2.39-2.86 (m, 10 H, H-2', H-3', H-5', H-6', N-$C\underline{H}_2CH_3$), 2.91 (dd, *J* = 6.1 and 10.4 Hz, 1 H, H-4), 3.10 (d, *J* = 4.0 Hz, 1 H, H-3), 3.36 (d, *J* = 3.7 Hz, 1 H, H-2), 3.50 (ddd, *J* = 0.9, 6.4 and 11.0 Hz, 1 H, H-5′), 3.75 (dd, *J* = 10.7 and11.0 Hz, 1 H, H-5), 4.56 (d, *J* = 11.9 Hz, 1 H, OC*H*HPh), 4.79 (d, *J* = 11.6 Hz, 1 H, OCH*H*Ph),

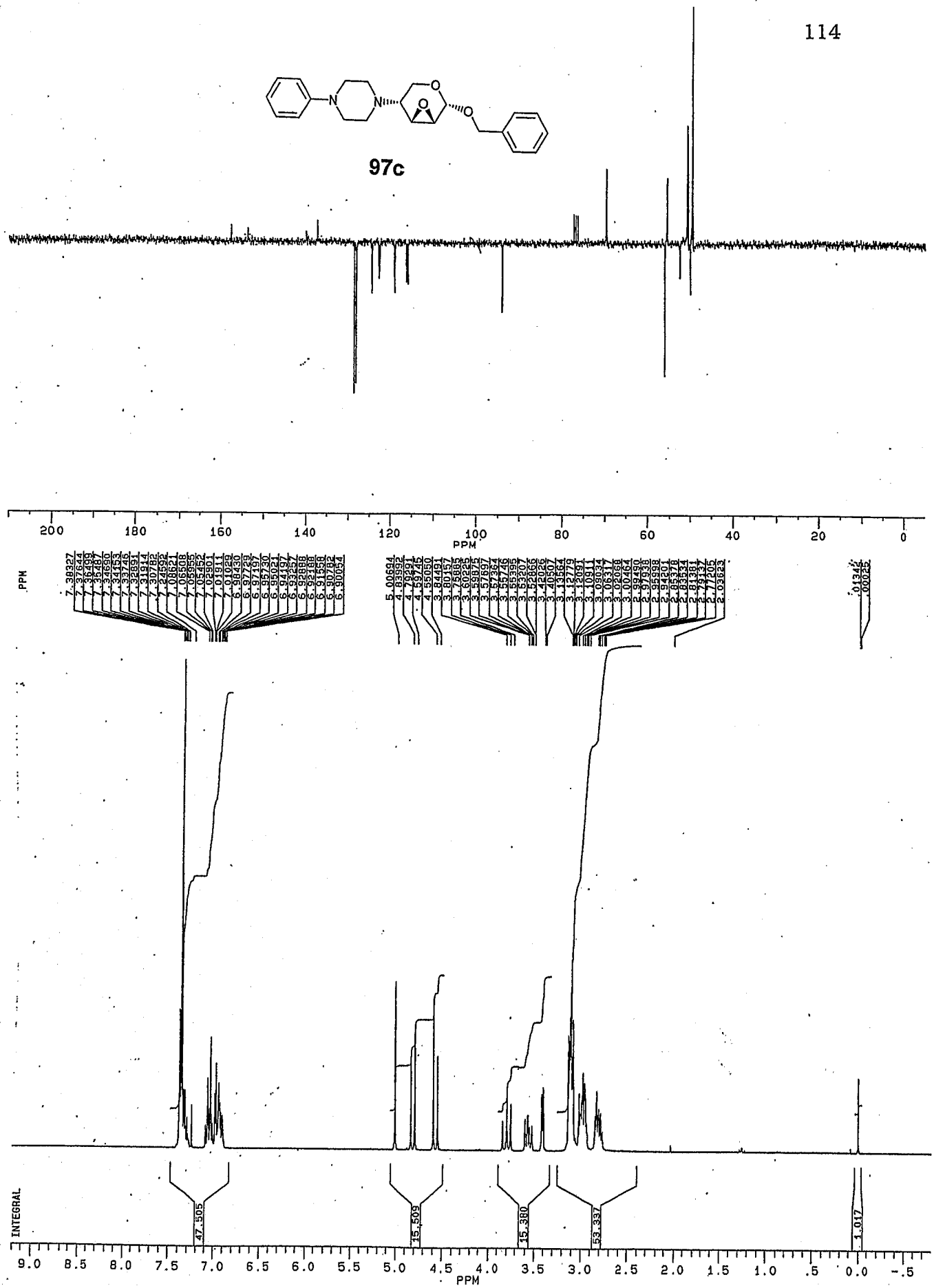

Fig 34. ^{1}H and ^{13}C NMR spectra of benzyl 2,3-anhydro-4-deoxy-4-(4-phenyl-1-piperzinyl)-α-D-lyxopyranoside (**97c**).

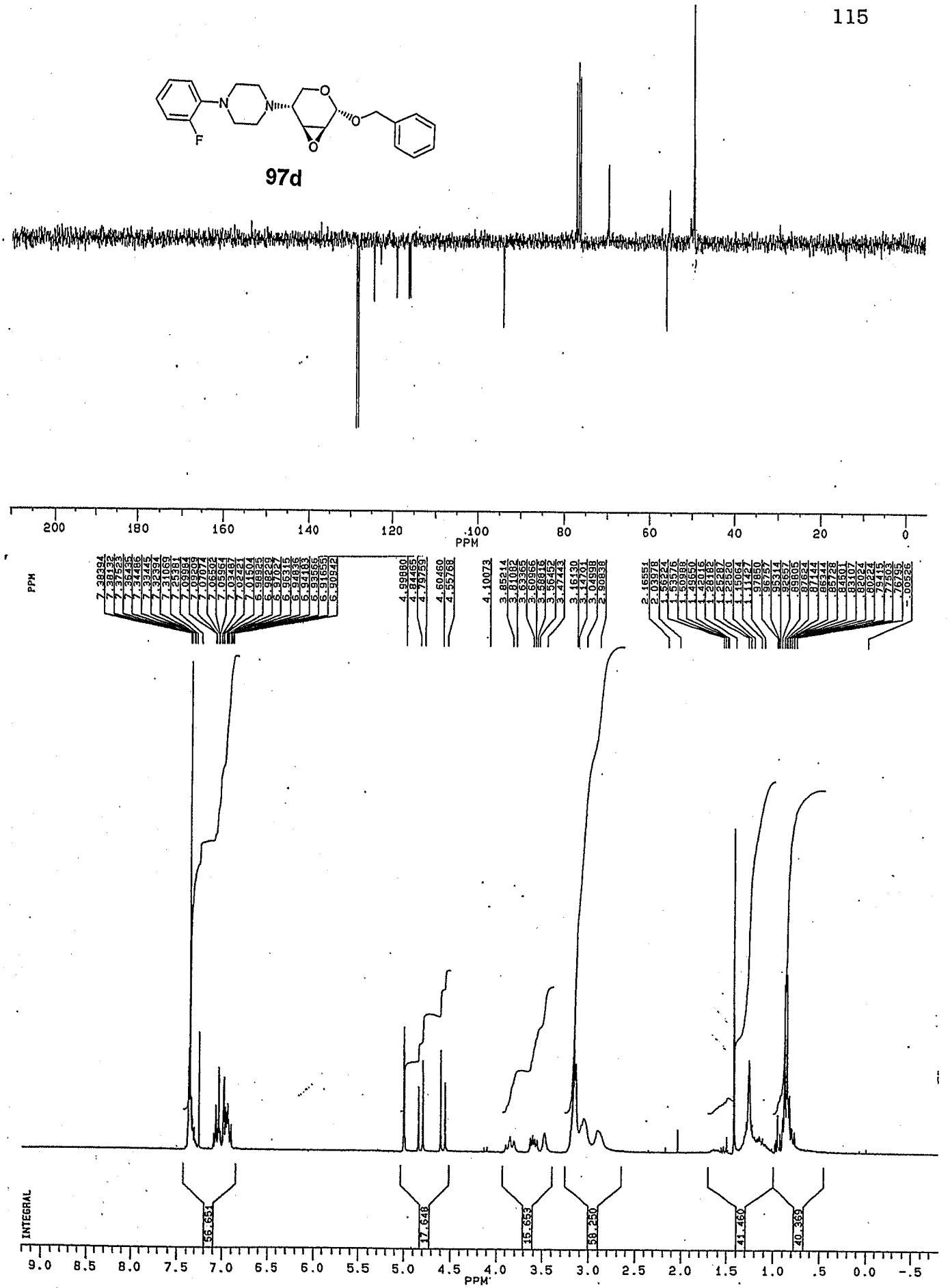

Fig 35. ^{1}H and ^{13}C NMR spectra of benzyl 2,3-anhydro-4-deoxy-4-[4-(2-fluorophenyl)-1-piperzinyl]-α-D-lyxopyranoside (**97d**).

4.99 (s, 1 H, H-1), 7.27-7.70 (m, 5 H, C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 11.9 (N-$CH_2\underline{C}H_3$), 52.7 (N-$\underline{C}H_2CH_3$), 49.4, 53.0 (C2', C3', C5', C6'), 50.1,52.3 (C-2, C-3), 55.7 (C-5), 56.0 (C-4), 69.8 (O*C*HHPh), 94.0 (C-1), 128.0-128.5, 137.3 (C_6H_5). FAB-MS: m/z = 319.1 [M^++1].

$C_{18}H_{26}N_2O_3$ (318.42)

Calculated C 67.908 H 8.23 N 8.80%,

Found C 67.75 H 8.12 N 8.65%.

C.VIII.3. Benzyl 2,3-anhydro-4-deoxy-4-(4-phenyl-1-piperazinyl)-α-D-lyxo-pyranoside (97c)

White solid, m.p. 118-110 °C; Yield 0.315 g (86%); $[\alpha]_D^{20}$ = +67.6 ° (*c* = 0.11, CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.07-3.30 (m, 5 H, H-4, H-2', H-6'), , 3.41 (d, *J* = 4.0 Hz, 1 H, H-3), 3.50 (bt, *J* = 4.6 Hz, 4 H, H-3', H-5'), 3.70 (bd, *J* = 3.4 Hz, 1 H, H-2), 3.85 (dd, *J* = 6.1 and 11.0 Hz, 1 H, H-5′), 4.09 (dd, *J* = 10.6 and10.7 Hz, 1 H, H-5), 4.58 (d, *J* = 11.7 Hz, 1 H, OC*H*HPh), 5.10 (d, *J* = 11.6 Hz, 1 H, OCH*H*Ph), 5.28 (s, 1 H, H-1), 6.85-7.39 (m, 10 H, 2 X C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 49.5, 49.7 (C2', C3', C5', C6'), 50.3, 52.1 (C-2, C-3),55.7 (C-5), 56.1 (C-4), 70.0 (O*C*HHPh), 94.1 (C-1), 116.3, 120.1, 128.1, 129.2, 137.1, 158.2 (2 X C_6H_5). FAB-MS: m/z = 367.1 [M^++1].

$C_{22}H_{26}N_2O_3$ (366.46)

Calculated C 72.11 H 7.15 N 7.64%,

Found C 72.06 H 7.12 N 7.51%.

C.VIII.4. Benzyl 2,3-anhydro-4-deoxy-4-[4-(2-fluorophenyl)-1-piperazinyl]-α-D-lyxopyranoside (97d)

Yellow oil; Yield 0.318 g (83%); $[\alpha]_D^{20}$ = +58.5 ^{o} (*c* = 0.19, CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.92-3.17 (m, 10 H, H-3, H-4, H-2', H-3', H-5', H-6'), 3.47 (bs, 1 H, H-2), 3.60 (dd, *J* = 5.6 and 11.3 Hz, 1 H, H-5′), 3.86 (dd, *J* = 10.1 and10.7 Hz, 1 H, H-5), 4.59 (d, *J* = 11.9 Hz, 1 H, OC*H*HPh), 4.83 (d, *J* = 11.9 Hz, 1 H, OCH*H*Ph), 5.00 (s, 1 H, H-1), 6.91-7.07 (m, 4 H, C_6H_5), 7.25-7.38 (m, 5 H, C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 49.8, 50.6 (C2', C3', C5', C6'), 50.3, 52.1 (C-2, C-3),55.5 (C-5), 56.2 (C-4), 70.0 (O*C*HHPh), 94.1 (C-1), 116.0, 116.3, 119.2, 123.0, 124.5, 128.1-128.6, 137.1, 155.2 (2 X C_6H_5). FAB-MS: m/z = 385.1 [M^++1].

$C_{22}H_{25}FN_2O_3$ (384.45)

Calculated C 68.73 H 6.55 N 7.29%,

Found C 68.69 H 6.50 N 7.17%.

C.VIII.5. Benzyl 2,3-anhydro-4-deoxy-4-[4-(4-fluorophenyl)-1-piperazinyl]-α-D-lyxopyranoside (97e)

Yellow solid, m.p. 94-95 ^{o}C; Yield 0.301 g (78%); $[\alpha]_D^{20}$ = +67.3 ^{o} (*c* = 0.11, CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.74-3.13 (m, 10 H, H-3, H-4, H-2', H-3', H-5', H-6'), 3.41 (d, *J* = 3.7 Hz, 1 H, H-2), 3.57 (ddd, *J* = 0.91, 6.4 and 11.3 Hz, 1 H, H-5′), 3.80 (dd, *J* = 10.5 and10.7 Hz, 1 H, H-5), 4.57 (d, *J* = 11.9 Hz, 1 H, OC*H*HPh), 4.82 (d, *J* = 11.9 Hz, 1 H, OCH*H*Ph), 5.03 (s, 1 H, H-1), 6.90-7.00 (m, 4 H, C_6H_5), 7.31-7.39 (m, 5 H, C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 49.8, 50.9 (C2', C3', C5', C6'), 50.3, 52.7 (C-2, C-3),55.7 (C-5),

56.1 (C-4), 69.9 (O*C*HHPh), 94.1 (C-1), 116.0, 116.4, 119.2, 122.5, 122.8, 124.5, , 124.6, 128.0-128.5, 137.3, 153.2, 157.7 (2 X C_6H_5). FAB-MS: m/z = 385.1 [M^++1].

$C_{22}H_{25}FN_2O_3$ (384.45)

Calculated C 68.73 H 6.55 N 7.29%,

Found C 68.64 H 6.53 N 7.24%.

C.VIII.6. Benzyl 2,3-anhydro-4-deoxy-4-(4-methyl-1-piperazinyl)-β-L-lyxo-pyranoside (98a)

Yellow oil; Yield 0.301 g (78%); $[\alpha]_D^{20}$ = +46.9 ^{o} (*c* = 0.06, CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, N-CH_3), 2.46-2.82 (m, 8 H, H-2', H-3', H-5', H-6'), 2.92 (brs, 1 H, H-4), 3.34 (m, 2 H, H-2, H-3), 3.66 (d, *J* = 12.8 Hz, 1 H, H-5′), 3.86 (dd, *J* = 3.4 and 12.5 Hz, 1 H, H-5), 4.60 (d, *J* = 12.6 Hz, 1 H, OC*H*HPh), 4.79 (d, *J* = 12.2 Hz, 1 H, OCH*H*Ph), 5.01 (d, J = 2.4 Hz, 1 H, H-1), 7.29-7.40 (m, 5 H, C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 46.1 (N-CH_3), 50.3, 55.5 (C2', C3', C5', C6'), 51.1, 51.8 (C-2, C-3),57.0 (C-5), 56.95 (C-4), 69.1 (O*C*HHPh), 92.4 (C-1), 127.8-128.5, 137.6 (C_6H_5). FAB-MS: m/z = 305.1 [M^++1].

$C_{17}H_{24}N_2O_3$ (304.39)

Calculated C 67.08 H 7.95 N 9.20%,

Found C 67.01 H 7.86 N 9.12%.

C.VIII.7. Benzyl 2,3-anhydro-4-deoxy-4-(4-ethyl-1-piperazinyl)-β-L-lyxo-pyranoside (98b)

Yellow oil; Yield 0.257 g (81%); $[\alpha]_D^{20}$ = +49.0 ^{o} (*c* = 0.24, CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.2 Hz, 3 H, N-$CH_2C\underline{H}_3$), 2.34-2.78 (m, 10 H, H-2', H-3', H-5', H-6', N-$C\underline{H}_2CH_3$), 2.84 (dd, *J* = 1.5 and 2.2 Hz, 1 H, H-4), 3.27 (m, 2 H, H-2, H-3), 3.59 (bd, *J* = 12.5 Hz, 1 H, H-5′), 3.79 (dd, *J* = 3.4 and12.5 Hz, 1 H, H-5), 4.53 (d, *J* = 12.5 Hz, 1 H, OC*H*HPh), 4.73 (d, *J* = 12.5 Hz, 1 H, OCH*H*Ph), 4.93 (d, *J* = 3.1 Hz, 1 H, H-1), 7.19-7.33 (m, 5 H, C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 11.8 (N-$CH_2\underline{C}H_3$), 52.3 (N-$\underline{C}H_2CH_3$), 50.2, 53.2 (C2', C3', C5', C6'), 51.0, 51.8 (C-2, C-3), 57.0 (C-4), 57.5 (C-5), 69.1 (O*C*HHPh), 92.4 (C-1), 127.8-128.5, 137.6 (C_6H_5). FAB-MS: m/z = 319.1 [M^++1].

$C_{18}H_{26}N_2O_3$ (318.42)

Calculated C 67.90 H 8.23 N 8.80%,

Found C 67.83 H 8.11 N 8.72%.

C.VIII.8. Benzyl 2,3-anhydro-4-deoxy-4-(4-phenyl-1-piperazinyl)-β-L-lyxo-pyranoside (98c)

Yellow oil; Yield 0.315 g (86%); $[\alpha]_D^{20}$ = +22.1 ^{o} (*c* = 0.12, CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.92 (m, 5 H, H-4, H-2', H-6'), , 3.34 (m, 2 H, H-2, H-3), 3.34 (br s, 4 H, H-3', H-5'), 3.67 (d, *J* = 12.5 Hz, 1 H, H-5′), 3.84 (dd, *J* = 3.4 and 12.6 Hz, 1 H, H-5), 4.54 (d, *J* = 12.2 Hz, 1 H, OC*H*HPh), 4.74 (d, *J* = 12.2 Hz, 1 H, OCH*H*Ph), 4.98 (d, *J* = 2.7 Hz, 1 H, H-1), 6.84-7.41 (m, 10 H, 2 X C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 49.6, 50.6 (C2', C3', C5', C6'),

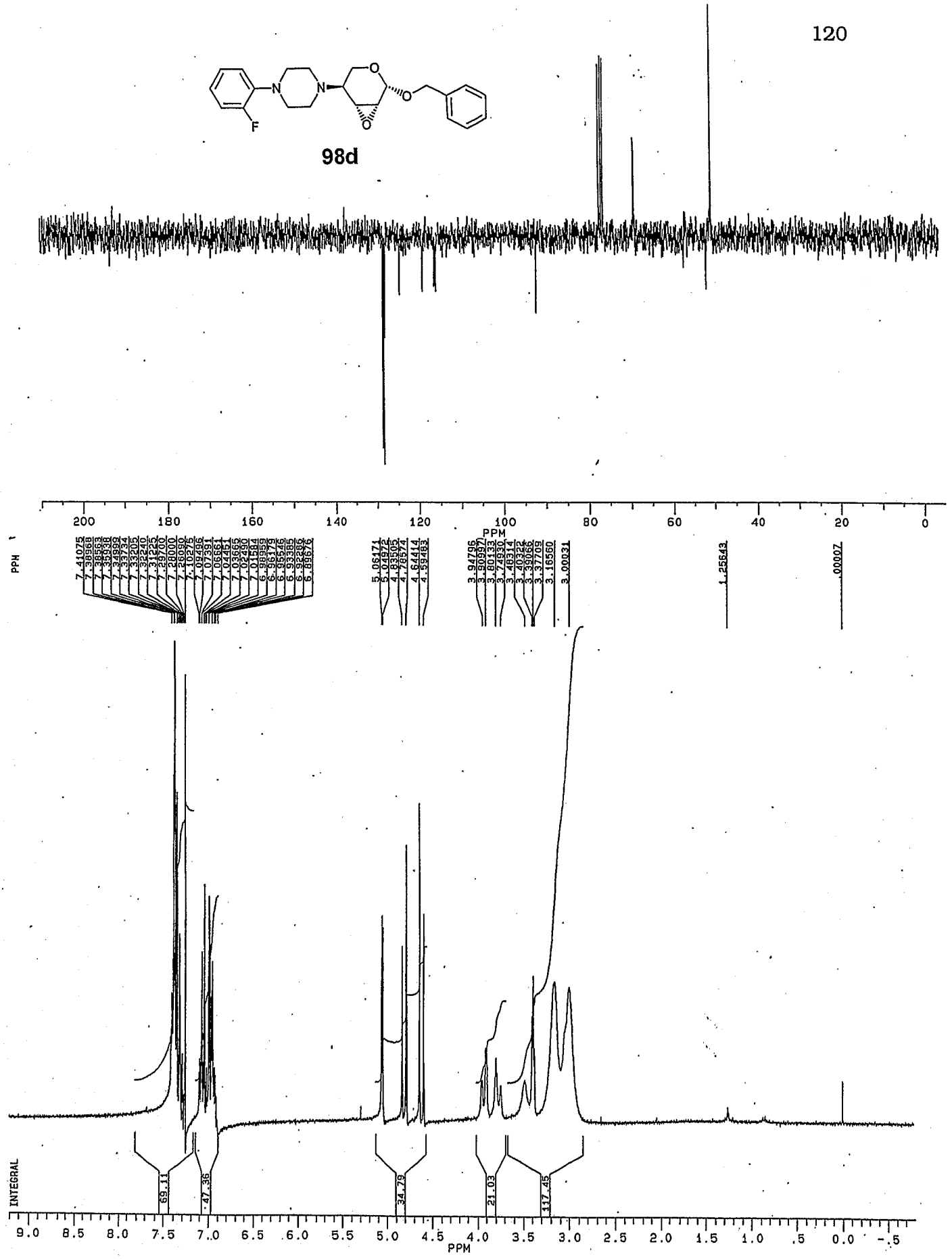

Fig 36. ^{1}H and ^{13}C NMR spectra of benzyl 2,3-anhydro-4-deoxy-4-[4-(2-fluorophenyl)-1-piperzinyl]-β-L-lyxopyranoside (**98d**).

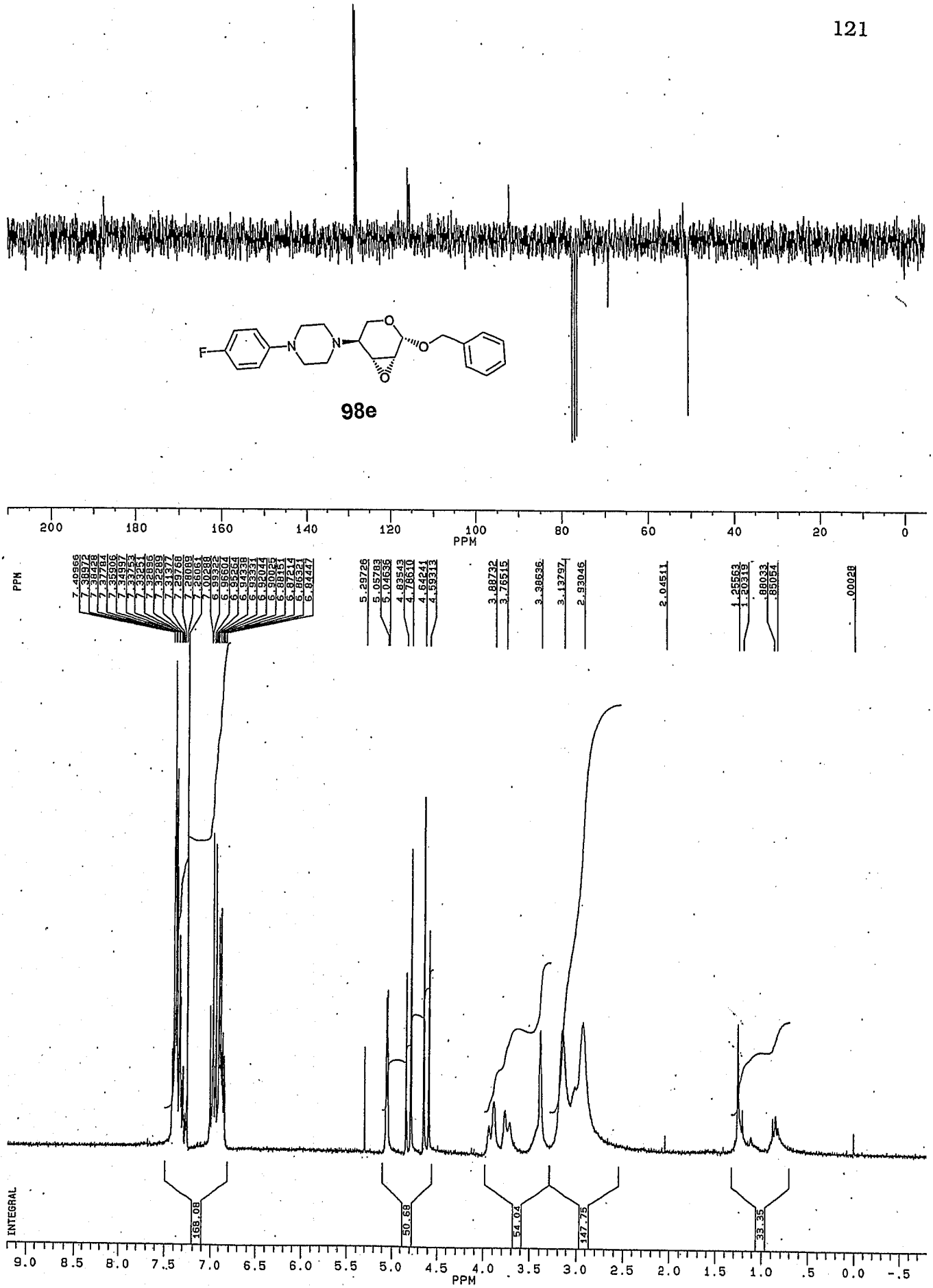

Fig 37. ^{1}H and ^{13}C NMR spectra of benzyl 2,3-anhydro-4-deoxy-4-[4-(4-fluorophenyl)-1-piperzinyl]-β-L-lyxopyranoside (**98e**).

51.8 (C-2, C-3), 56.7 (C-5), 57.3 (C-4), 69.2 (O*C*HHPh), 92.3 (C-1), 116.3, 120.0, 127.0-129.2, 137.2 (2 X C_6H_5). FAB-MS: m/z = 367.1 [M^++1].

$C_{22}H_{26}N_2O_3$ (366.46)

Calculated C 72.11 H 7.15 N 7.64%,

Found C 72.00 H 7.02 N 7.55%.

C.VIII.9 Benzyl 2,3-anhydro-4-deoxy-4-[4-(2-fluorophenyl)-1-piperazinyl]-β-L-lyxopyranoside (98d)

Yellow solid, m.p. 94-95 ^oC; Yield 0.318 g (83%); $[\alpha]_D^{20}$ = +36.9 ^{o} (*c* = 0.10, CH_2Cl_2): ^1H NMR (250 MHz, $CDCl_3$): δ = 3.00-3.17 (m, 9 H, H-4, H-2', H-3', H-5', H-6'), 3.39 (dd, *J* = 2.9 and 3.1 Hz, 1 H, H-2), 3.48 (bs, 1 H, H-3), 3.77 (d, *J* = 13.1 Hz, 1 H, H-5′), 3.92 (dd, *J* = 3.1 and 12.5 Hz, 1 H, H-5), 4.62 (d, *J* = 12.2 Hz, 1 H, OC*H*HPh), 4.81 (d, *J* = 12.2 Hz, 1 H, OCH*H*Ph), 5.05 (d, *J* = 2.7 Hz, 1 H, H-1), 6.99-7.10 (m, 4 H, C_6H_5), 7.28-7.41 (m, 5 H, C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 50.7 (C2', C3', C5', C6'), 51.9, 55.1 (C-2, C-3),56.2 (C-5), 57.1 (C-4), 69.9 (O*C*HHPh), 92.3 (C-1), 116.0, 119.2, 124.5, 127.9-128.5, 137.1 (2 X C_6H_5). FAB-MS: m/z = 385.1 [M^++1].

$C_{22}H_{25}FN_2O_3$ (384.45)

Calculated C 68.73 H 6.55 N 7.29%,

Found C 68.64 H 6.48 N 7.21%.

C.VIII.10. Benzyl 2,3-anhydro-4-deoxy-4-[4-(4-fluorophenyl)-1-piperazinyl]-β-L-lyxopyranoside (98e)

Yellow solid, m.p. 111-112 ^{o}C; Yield 0.301 g (78%); $[\alpha]_D^{20}$ = +34.0 ^{o} (*c* = 0.36, CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.94-3.15 (m, 9 H, H-4, H-2', H-3', H-5', H-6'), 3.38 (m, 2 H, H-2, H-3), 3.74 (bd, *J* = 11.3 Hz, 1 H, H-5′), 3.92 (bd, *J* = 11.3 Hz, 1 H, H-5), 4.61 (d, *J* = 12.2 Hz, 1 H, OC*H*HPh), 4.81 (d, *J* = 12.2 Hz, 1 H, OCH*H*Ph), 5.05 (d, *J* = 3.1 Hz, 1 H, H-1), 6.84-7.00 (m, 4 H, C_6H_5), 7.28-7.41 (m, 5 H, C_6H_5); GASPE NMR (63 MHz, $CDCl_3$): δ = 50.6 (C2', C3', C5', C6'), 54.5 (C-2, C-3), 55.7 (C-5), 56.1 (C-4), 69.2 (O*C*HHPh), 92.1 (C-1), 116.0-128.5, 137.3, 155.1 157.7 (2 X C_6H_5). FAB-MS: m/z = 385.1 [M^++1].

$C_{22}H_{25}FN_2O_3$ (384.45)

Calculated C 68.73 H 6.55 N 7.29%,

Found C 68.60 H 6.51 N 7.25%.

D. Abstract

This thesis describes the application of carbohydrates as “chiral synthons” for the stereoselective syntheses of, both, natural products and new synthetic classes of compounds. Combination of the natural chirality and inherent topology of cyclic sugar derivatives allowed to design a strategy for the enantio-selective total synthesis of α, β–unsaturated δ-lactones.

In chapter I, a facile total synthesis of the non-natural *S*-(+)-argentilactone has been achieved, starting from methyl α-D-glucopyranoside. 2,3-Dideoxy-genation of the benzylidene acetal was followed by the deprotection of the benzylidene group and selective protection of the resulting diol at primary position. The secondary alcohol was mesylated and reductively displaced with Supehydride®. Swern oxidation and then Wittig reaction introduced the desired side chain. Finally, the anomeric position was oxidized with catalytic amounts of MoO_3 to furnish the target argentilactone.

Chapter II involved the total syntheses of massoilactone and *O*-acetyl osmundalctone, both naturally occurring α, β–unsaturated δ-lactones. The benzylidene acetal, produced from methyl α-D-glucopyranoside, was stereo-selectively opened under the conditions developed by Hanessian. The resulting 6-bromodiol was subjected to 2,3-dideoxygenation with 2,4,5-triiodoimidazole. Nucleophilic displacement with lithium dibutyl cuprate (for massoilactone) and Superhydride® (for osmundalactone) generated the inter-mediates that were further manipulated for the total syntheses of the respective natural products.

In chapter III, the total synthesis of naturally occurring argentilactone is presented, following a different approach. The furanglycol, prepared from D-

glucal, was subjected to the Mitsunobu reaction for the inversion of the configuration. The benzoyl group was removed from the secondary position of the furan derivative after protection of the free primary alcohol, and the resulting monoalcohol underwent oxidative rearrangement with NBS to furnish the L-hexenulose. The anomeric position was blocked and the keto group reduced to produce the partially protected allylic alcohol. After mesylation, a similar sequence of reactions was followed as is described in chapter I for *S*-(+)-argentilactone. The synthetic argentilactone was tested *in vitro* against *Leishmania mexicana*. Chapter IV describes preliminary results of a biological study.

In chapter VI, an efficient and one pot reaction for the synthesis of 1,4,5,6-tetrahydro-[1,2,4]triazine is described. The *in situ*-generated nitrilimines from the corresponding hydrazonoyl chlorides reacted readily with benzyl 4-amino-4-deoxy-2,3-anhydro-lyxopyranosides to furnish chiral triazines in good to excellent yields.

Chapter VII presents examples for the syntheses of chiral cyclic trithiocarbonates from the triflates of 2,3- and 3,4-anhydropentopyranosides. Sodium trithiocarbonate, prepared from Na_2S and CS_2, undergoes a nucleophilic displacement of the triflyl group, followed by a simultaneous ring opening reaction of the epoxide to produce 5- and 6-membered cyclic trithiocarbonates in good yield.

In chapter VIII, a selected set of 4-(4-substituted-1-piperazinyl)-anhydro-lyxopyranosides were prepared for biological testing. In the present form they did not show any activity against bacteria or fungi, however, they could have CNS-depressant activity.

E. Zusammenfassung

Im Rahmen der hier vorliegenden Arbeit wurden Kohlehydrate als “chirale Synthone” für die stereoselektive Synthese von Naturstoffen sowie neuen synthetischen Substanzklassen verwendet. Die Kombination von natürlicher Chiralität mit der Topologie eines cyclischen Zuckerderivats erlaubte eine Strategie zur enantioselectiven Totalsynthese von α, β–ungesättigten δ-Lactonen zu entwickeln.

In Kapital I dieser Arbeit wird eine Totalsynthese des nicht natürlichen *S*-(+)-Argentilactons, ausgehend von Methyl-α-D-glucopyranosid, vorgestellt. Nach der 2,3-Didesoxyenierung vom Benzylidenacetal und Abspaltung der Benzylidenschutzgruppe wird das resultierende Diol an der 1-Position selektiv geschützt. Der sekundäre Alkohol wird mesyliert und anschließend durch “Superhydrid” entfernt. Eine Swern-Oxidation mit anschließender Wittig-Reaktion führt die Seitenkette ein. Anschließend wird die anomere Funktion mit katalytischen Mengen MoO_3 oxidiert, um schließlich das Zielmoleküle Argentilacton zu erhalten.

Kapital II beschreibt die Totalsynthese von Massoilacton und O-Acetyl-Osmundalacton, beides sind natürlicher vorkommende α, β-ungesättigte δ–Lactone. Das Benzylidenacetal, aus Methyl-α-D-glucopyranosid synthetiziert, wird stereoselektiv unter Hanessian-Bedingungen geöffnet. Das resultierende 6-Bromdiol wird mit 2.4.5-Triiodoimidazol didesoxigeniert. Nukleophile Verdrängung mit Lithiumdibutylcuprat (für Massoilacton) bzw. Superhydrid (für Osmundalacton) generieren die Zwischenprodukte, die für die Totalsynthese dieser Naturstoffe benötigt werden.

In Kapitel III wird die Totalsynthese von natürlich vorkommenden Argentilacton präsentiert. Das Furanglykol, aus D-Glucal synthesiert, wird einer Mitsunobu-Reaktion unterzogen, um eine Umkehr der Konfiguration zu erzielen. Die Benzoylgruppe an der sekundären Position des Furanderivates wird entfernt, nachdem die freie primäre Alkoholfunktion geschützt wurde. Der resultierende Monoalkohol wird einer oxidativen Umlagerung mit N-Bromsuccinimid unterzogen, um schließlich zur L-Hexenulose zu gelangen. Die anomere Position wird blockiert, die Ketogruppe reduziert, um so einen partialgeschützten allylischen Alkohol zu erhalten. Nach erfolgter Mesylierung folgt eine ähnliche Sequenz von Reaktionen wie in Kapitel I für das (+)-Argentilaction beschrieben. Das synthetische (-)-Argentilacton wurde *in vitro* gegen *Leishmania mexicana* getestet. Kapitel IV beschreibt die vorläufigen Ergebnisse dieser biologischen Studie.

In Kapitel VI wird eine effiziente 1-Stufenreaktion für die Synthese von 1.4.5.6-Tetrahydro-[1.2.4]triazinen beschrieben. Das *in situ* generierte Nitrilimin reagiert direkt mit Benzyl-4-amino-4-desoxy-2,3-anydro-lyxopyranosid, um so das chirale Triazin in guten Ausbauter zu ergeben.

Kapital VII präsentiert die Synthese chiraler cyclischer Trithiocarbonate aus den Triflaten der 2,3- bzw. 3,4-Anhydropentopyranoside. Natrium-trithiocarbonat, aus Na_2S und CS_2 dargestellt, substituiert die Triflatgruppe unter gleichzeitiger simultaner Ringöffnung des Epoxids, um 5- bzw. 6-gliedrige cyclische Trithiocarbonate zu bilden.

In Kapitel VIII werden eine Reihe von 4-(4-substituierte-1-piperazinyl)-anhydrolyxcopyranoside synthetisiert, um deren biologische Aktivitat zu

testen. Obwohl keines dieser neuen Derivate eine signifikante Aktivität gegen Bakterien und Pilze zeigte, sollte die CNS-Wirkung noch untersucht werden.

F. References

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