Synthetic Studies on the Spiroacetal Moiety of Stenocarpin, a Metabolite of *Diplodia maydis*

by

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SUMMARY

The fungus *Diplodia maydis*, (synonym *Stenocarpella maydis* (Berk)) is worldwide one of the most important cob rot pathogens of maize. The isolation of stenocarpin, a metabolite toxic to ducklings, from maize cultures of *D. maydis* as the 4,6-*O*-diacetate derivative and its structure elucidation has been reported in the literature. Detailed NMR studies established the structure as either (3*S*,4*R*,6*R*,7*R*)- or (3*R*,4*R*,6*R*,7*R*)-spiro[(4,6,7-trihydroxy-7-methyl-8-oxo-5,6,7,8-tetrahydroisochromane)-3,2′-tetrahydrofuran]. The absolute configuration of the C(3) spiroacetal stereogenic center remained unknown.

The aim of the synthetic studies described in this dissertation was to develop a synthetic methodology for the spiroacetal moiety present in stenocarpin in order to establish unambiguously the C(3) absolute configuration. Retrosynthetic analysis of stenocarpin identified two model compounds (5*S*,10*R*)- and (5*R*,10*R*)-1,6-dioxaspiro[4.5]dec-8-en-10-ol as the synthetic target. In turn the retrosynthetic analysis of these model compounds led to commercially available L-arabinose as starting material. Two strategies, which differ in the timing for the formation of the spiroacetal moiety as well as the initial type of protecting groups, were employed in the development of the synthetic route. In the first route the spirocyclisation reaction of a benzyl protected intermediate followed by the *syn* elimination of the *cis*-diol group resulted in the formation of only the (5*S*,10*R*) model compound. The use of the acetonide and TBDPS protecting groups from the outset of the synthetic route and once again a spirocyclisation reaction, led to the formation of two spiro compounds epimeric at the C(5) spiro stereogenic centre, which could be separated and transformed by a *syn* elimination of the *cis*-diol group to the two model compounds.

The configuration of the spiroacetal intermediates formed in the two synthetic routes and the changes in conformation that occurred in each of the steps were deduced from extensive NMR studies and especially the NOE technique.

The results established the 3*S* configuration for stenocarpin and provided a viable synthesis for the (5*S*,10*R*)-1,6-dioxaspiro[4.5]dec-8-en-10-ol model compound that is to be used in the total synthesis of stenocarpin. In the dissertation the results of the first steps in a total synthesis, a study on the epoxidation of the double bond, is presented.

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LIST OF ABBREVIATIONS

AcOH	Acetic acid
Ac_2O	Acetic anhydride
Ar	Argon
$BaCO_3$	Barium carbonate
BH_3	Borane
$BCl_3.\ SMe_2$	Boron trichloride dimethylsulfide complex
$BF_3.OEt_2$	Boron trifluoride diethyl etherate
$BH_3.SMe_2$	Borane dimethylsulfide complex
BnOH	Benzyl alcohol
BnCl	Benzyl chloride
BuLi	Butyllithium
$CaCO_3$	Calcium carbonate
CCl_4	Carbon tetrachloride
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
CSA	Camphor-10-sulfonic acid
CS_2	Carbon disulfide
$CH_2=CHMgBr$	Vinylmagnesium bromide
$CH_2=CHCH_2MgBr$	Allylmagnesium bromide
C_6H_{12}	Cyclohexene
DIB	(Diacetoxyiodo)benzene
DMAP	Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMP	Dimethoxypropane
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOH	Ethanol
HETCOR	Heteronuclear correlation
HMPA	Hexamethylphosphoric amide
Im	Imidazole
I_2	Iodine
HCl	Hydrochloric acid
HgO	Mercury(II) oxide
H_2O_2	Hydrogen peroxide
H_2SO_4	Sulfuric acid
KOH	Potassium hydroxide
MCPBA	*m*-Chloroperbenzoic acid
MeI	Methyl iodide
MeOH	Methanol
Me_2O	Acetone
$(MeO)_3P$	Trimethyl phosphite
$NaBH_4$	Sodium borohydride
NaH	Sodium hydride
$NaHCO_3$	Sodium hydrogencarbonate

NaOAc	Sodium acetate
NaOH	Sodium hydroxide
NBS	*N*-bromosuccinimide
Py	Pyridine
Pd	Palladium
$Pd(OH)_2$	Palladium hydroxide
$SOCl_2$	Thionyl chloride
TBAF	Tetrabutylammonium fluoride
TBSCl	*t*-Butyldimethylsilyl chloride
TBDPSCl	*t*-Butyldiphenylsilyl chloride
Bu_3SnH	Tributyltin hydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TsCl	Toluene-4-sulfonyl chloride
TsOH	Toluene-4-sulfonic acid
TLC	Thin-layer chromatography

CONTENTS

1 INTRODUCTION

1.1 General

Mycotoxins (from Greek, *mykes*: fungus) are toxic fungal secondary metabolites that have an adverse effect on man and his domestic animals. The diseases caused by the ingestion of foods and animal feeds contaminated by these toxic metabolites are commonly called mycotoxicoses and are characterized by their sporadic regional and seasonal occurrence.[1] Mycotoxins have been part of mankind's environment throughout the ages. Ergotism, which constituted one of the greatest recurring catastrophes of European history over a period of 2,000 years, is one of the earliest described mycotoxicoses. The ergotism epidemic for example of the year 944 in Aquitaine and Limoges in France killed an estimated 40,000 people.[2] Ergotism is caused by the parasitic fungus *Claviceps purpurea*, which readily infects rye and other grains and grasses and produces the physiologically-active ergot alkaloids related to lysergic acid.

Epidemic outbreaks of alimentary toxic aleukia occurred in Orenburg and other districts of Russia during World War 2.[3,4,5] The trichothecene T-2 toxin, a sesquiterpene mycotoxin produced by *Fusarium sporotrichioides*,[6] has been implicated in the etiology of the disease which was found to be associated with grain, wheat and barley that had been left on the fields during winter in the war years.

Although evidence for mycotoxicoses can be traced to ancient times the impetus for mycotoxin research was not provided until 1960. The current international awareness of mycotoxicoses and the interest in the structure, synthesis and also biosynthesis of mycotoxins is attributable to 'Turkey-X' disease that resulted in the death of 100,000 turkey

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[1] J.P.F. D'Mello and A.M.C. Macdonald, *Animal Feed Science Technology*, 1997, **69**, 155.
[2] A. Stoll, *Fortsch. Chem. Org. Naturstoffe*, 1952, **9**, 114.
[3] G.N. Wogan, *Mycotoxins in Foodstuffs*, MIT Press, Cambridge, Massachusetts, 1965, p. 77.
[4] A.W. Hayes, *Clinical Toxicol.*, 1980, **17**, 45.
[5] B.J. Wilson, *Nutritional Toxicol.*, 1982, 239.

poults that died from acute necrosis of the liver and hyperplasia of the bile duct after consuming feed containing Brazilian peanut meal contaminated with aflatoxins.[7,8] The four naturally occurring aflatoxins, B_1, B_2, G_1 and G_2,[9] are acutely toxic and carcinogenic metabolites produced by *Aspergillus flavus* and the closely related fungus *A. parasiticus*.[10] Other members of the group are derived from these four compounds as metabolic products of microbial or animal systems. Thus aflatoxin B_1 contaminated groundnut meal is converted by lactating dairy cows into aflatoxin M_1 and excreted in the milk[11] and thereby enters the human foodchain.

Maize is one of the major staple food and feed grains cultivated throughout both the developed and the developing world. However fungal contamination of maize remains a serious problem for farmers and can have grave consequences for both human and animal health.

The fungus *Diplodia maydis*, synonym *Stenocarpella maydis* (Berk.), is one of the most important cob rot pathogens of maize worldwide.[12,13] Diplodiosis is an endemic neurological disease of ruminants grazing on harvested maize fields in winter in southern Africa and is caused by the ingestion of maize infected by this common cob rot fungus *D. maydis*.[14,15] Outbreaks of diplodiosis have not been reported outside southern Africa. Diplodiosis is a nervous condition of cattle and sheep and is characterized by ataxia, paresis, and paralysis that can result in death.[16] The ability of culture material of *D.*

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6 R.J. Cole and R.H. Cox, *Handbook of Toxic Fungal Metabolites*, Academic Press, New York, 1981, Ch. 5.
7 W.P. Blount, *Turkeys*, 1961, **9**, 52.
8 F.D. Asplin and R.B.A Carnaghan, *Vet. Res.*, 1961, **13**, 1215.
9 R.J. Cole and R.H. Cox, *Handbook of Toxic Fungal Metabolites*, Academic Press, New York, 1981, Ch. 1.
10 L.A. Goldblatt, *Aflatoxin: Scientific Background, Control and Implications*, Academic Press, New York, 1969.
11 H.P. van Egmond, *Mycotoxins in Dairy Products*, Elsevier Applied Science, London, 1989, pp. 11-55.
12 W.F.O. Marasas in *Mycotoxic Fungi, Mycotoxins, Mycotoxicoses. An Encyclopedic Handbook* (T.D. Wylie and L.G. Morehouse, Eds.), Marcel Dekker, New York, 1977, Vol. I, pp.119-128.
13 T.S. Kellerman, J.A.W. Coetzer and T.W. Naude, *Plant Poisonings and Mycotoxicoses of Livestock in Southern Africa*, Oxford University Press, Cape Town, 1988.
14 D.T. Mitchell, *S. Afr. J. Sci.*, 1919, **16**, 446
15 A. Theiler, *Dstsch. Tieraerztl. Wochenschr.*, 1927, **35**, 395.
16 W.F.O. Marasas in *Mycotoxic Fungi, Mycotoxins, Mycotoxicoses. An Encyclopedic Handbook* (T.D. Wylie and L.G. Morehouse, Eds.), Marcel Dekker, New York, 1977, Vol. II, p. 163 and p. 218.

maydis to induce diplodiosis in cattle and sheep has been demonstrated.[17] The onset of diplodiosis is indicated by incoordination, paralysis and occasional tremors. In the event of continued ingestion of infected maize, these signs become more pronounced and eventually complete muscular paralysis sets in and death soon follows. If on the other hand feeding is discontinued a complete recovery of the animal is possible.

Recent investigations[18,19] indicate that the ingestion of maize contaminated with *D. maydis* by pregnant ewes has grave consequences: 66% of lambs born to ewes exposed to cultures of *D. maydis* in the second trimester were still-born or died soon afterwards. This figure increases to 87% for ewes exposed in the third trimester to cultures of *D. maydis*. Offspring of ewes exposed during the first trimester of pregnancy to cultures of *D. maydis* were unaffected and showed no signs of diplodiosis.

D. maydis contamination of maize affects not only ruminants but also poultry such as chickens and ducklings and leads to unacceptable losses and growth retardation.[20,21] The reported study[21] indicates that broilers fed with *D. maydis* culture material showed significantly lower weight gains compared to those on a control diet. A drastic drop in egg production and in egg weights of laying hens was also recorded. It is of interest to note that there was no correlation between the toxicity of *D. maydis* strains in ducklings and their ability to induce diplodiosis in cattle and sheep.[20] This result indicates that toxic metabolites other than the neurotoxin(s) responsible for diplodiosis are produced by cultures of *D. maydis*.

1.2 Structure Elucidation of Metabolites isolated from Diplodia sp.

1.2.1 Metabolites of *D. pinea*.

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[17] T.S. Kellerman, C.J. Rabie, G.C.A. van der Westhuizen, N.P.J. Kriek and L. Prozesky, *Onderstepoort J. Vet. Res.*, 1985, **52**, 35 and references cited.

[18] T.S. Kellerman, L. Prozesky, R.A. Schultz, C.J. Rabie, H. van Ark, B.P. Maartens and A. Lübben, *Onderstepoort J. Vet. Res.*, 1991, **58**, 297.

[19] L. Prozesky, T.S. Kellerman, D.P. Swart, B.P. Maartens and R.A. Schultz, *Onderstepoort J. Vet. Res.*, 1994, **61**, 247.

[20] C.J. Rabie, T.S. Kellerman, N.P.J. Kriek, G.C.A. van der Westhuizen and P.J. de Wet, *Food Chem. Toxicol.*, 1985, **23**, 349.

[21] C.J. Rabie, J.J. du Preez and J.P. Hayes, *Poultry Science*, 1987, **66**, 1123.

A number of toxic metabolites have been isolated from cultures of different *Diplodia* species and their structures have been elucidated using both spectroscopic and chemical methods. In the course of studies on steroid hydroxylase inhibitors produced by fungi, three polyketides, diplodialide A (**1**) as well as the related metabolites diplodialide B (**2**), C (**3**) and D (**4**) were isolated from the culture filtrates of *Diplodia pinea*.[22,23,24] The configuration of C(3) and C(9) of diplodialide (**4**) was not determined as insufficient material was available but was assumed to be the same as that for the other three metabolites.

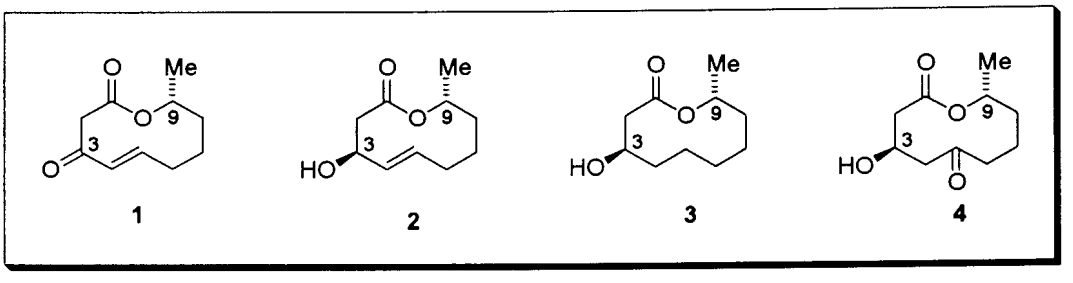

Figure 1.1: Metabolites of *Diplodia pinea*.

The structural elucidation and absolute configuration of the metabolites is based on the results obtained from NMR, UV, and IR spectroscopy and chemical degradation. The absolute configuration of diplodialide A (**1**), B (**2**) and C (**3**) was determined as follows.[23] Oxidation of diplodialide B (**2**) with activated MnO_2 gave a product identical to diplodialide A (**1**). $NaBH_4$ reduction of (**1**) gave diplodialide B (**2**) as the major stereoisomer. Diplodialide C (**3**) was identical with the dihydroderivative of diplodialide B (**2**) prepared by catalytic hydrogenation of diplodialide B (**2**) with 10% Pd/C. The absolute configuration at C(9) is therefore the same in all three compounds and was determined by degradation of diplodialide B (**2**) to (–)-hexane-1,5-diol that was converted to the di-(4-nitrobenzoate) ester. The specific rotation of these two compounds was similar in magnitude but opposite in sign to the values reported for *S*-(+)-hexane-1,5-diol and its di-4-nitrobenzoate ester thereby indicating the 9*R* configuration for the diplodialides.

The absolute configuration at C(3) of diplodialide B (**2**) was determined by ozonolysis of

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[22] T. Ishida and K. Wada, *J. Chem. Soc., Chem. Commun.*, 1975, 20
[23] T. Ishida and K. Wada, *J. Chem. Soc., Perkin Trans 1*, 1979, 1154.
[24] T. Ishida and K. Wada, *J. Chem. Soc., Chem. Commun.*, 1976, 340.

its acetate and oxidative work-up to give two acids that were converted to their methyl esters and isolated as their 4-nitrobenzoate esters. The products were identified as dimethyl (–)-p-nitrobenzoylmalate and the 4-nitrobenzoyl derivative of methyl 5-hydroxyhexanoate, with the former compound having the same specific rotation as the authentic *S*-(–)-compound prepared from *S*-(–)-malic acid. These results established the 3*S* configuration for diplodialide B (**2**) and the 3*R* configuration for diplodialide C (**3**). The change in stereochemical descriptors is due to the Cahn-Ingold-Prelog rules.

1.2.2 Metabolites of *D. macrospora*.

Diplodia macrospora causes leaf-blight and dry rot of stalks and cobs of maize. Diplosporin (**5**) was isolated from cultures of a toxigenic strain of *D. macrospora*, isolated from Zambian maize, which were acutely toxic to ducklings and rats.[25] It has an LD_{50} value of 88.4 mg/kg in ducklings.[26] The structure is based on data obtained by low-field ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. Although the relative configuration of the C(5) and C(6) stereogenic centres in (**5**) could not be deduced from the ^{1}H NMR data, the 5*S* absolute configuration was established by the partial resolution method of Horeau.[27,28] A subsequent single-crystal X-ray study of diplosporin established the *trans* relative configuration for the C(5) hydroxy and C(6) ethyl groups and thus the (5*S*,6*R*) absolute configuration.[29] Two related metabolites, 5-deoxydiplosporin (**6**)[30] and a diastereomer of diplosporin with the 5*R* configuration (**7**)[31], were isolated from liquid cultures of *D. macrospora* and their structures determined by high-field ^{1}H and ^{13}C NMR spectroscopy.

The biosynthesis of diplosporin (**5**) has been studied using ^{2}H-, ^{13}C- and ^{18}O-labelled precursors *viz.* [1-^{13}C]-, [2-^{13}C]-, [1,2-$^{13}C_2$]-, [2-$^{2}H_3$,1-^{13}C]- and [1-^{13}C,$^{18}O_2$]acetate, (2*S*)-

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[25] A.A. Chalmers, C.P. Gorst-Allman, P.S. Steyn, R. Vleggaar, W.F.O. Marasas and N.P.J. Kriek, *S. Afr. J. Chem.*, 1978, **31**, 111.

[26] H.G. Cutler, F.G. Crumley, R.H. Cox, R.J. Cole, J.W. Dorner, F.M. Latterell and A.E. Rossi, *J. Agric. Food Chem.*, 1980, **28**, 135.

[27] A. Horeau, *Tetrahedron Lett.*, 1961, 506.

[28] E.L. Eliel, S.H. Wilen and L. Mander, *Stereochemistry of Organic Compounds*, Wiley Interscience, New York, 1994, pp. 140-142 and references cited.

[29] J.L.M. Dillen, C.P. Gorst-Allman and P.H. van Rooyen, *S. Afr. J. Chem.*, 1983, **36**, 105.

[30] A.A. Chalmers, C.P. Gorst-Allman, P.S. Steyn, R. Vleggaar and D.B. Scott, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1481.

[31] C.P. Gorst-Allman and R. Vleggaar, *S. Afr. J. Chem.*, 1987, **40**, 116.

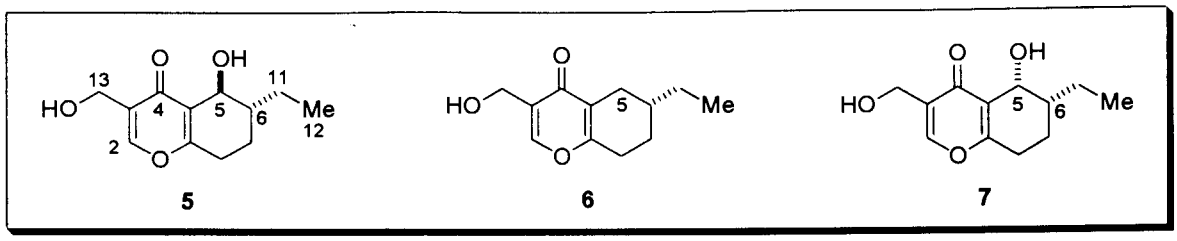

Figure 1.2: Metabolites of *Diplodia macrospora.*

[*methyl*-^{13}C]methionine and $^{18}O_2$ (see Figure 1.3).[30,31,32] The incorporation of methionine-derived carbon atoms into both a carbocyclic and a heterocyclic ring is a rare occurrence. The experiments indicated that the oxygen of the C(4) carbonyl group is derived from [^{18}O]acetate and that molecular oxygen contributes the oxygen atom of the C(5) hydroxy group.

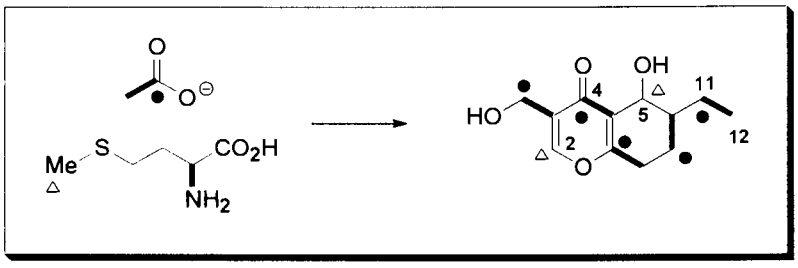

Figure 1.3: Incorporation of stable isotope labeled precursors in diplosporin.

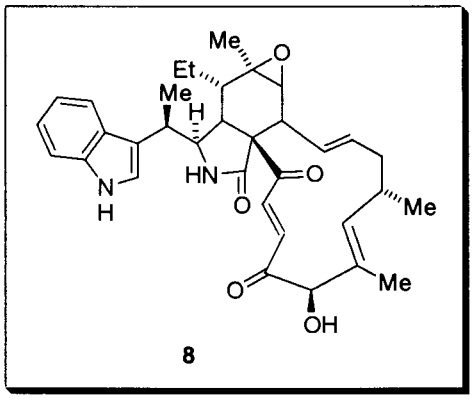

Figure 1.4: A plant growth inhibitor isolated from *D. macrospora.*

In the course of a survey of fungi for the production of plant growth inhibiting substances an isolate of *D. macrospora* isolated from maize in Costa Rica was found to produce a

[32] C.P. Gorst-Allman, P.S. Steyn and R. Vleggaar, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1357.

metabolite, identified as chaetoglobosin K (**8**) that was both toxic to day-old chicks with an LD_{50} between 25 and 62.5 mg/kg and a plant growth inhibitor.[33]

1.2.3 Metabolites of *D. maydis*.

Investigations by South African researchers on toxic extracts obtained from isolates of *D. maydis* responsible for diplodiosis in cattle and sheep, have led to the isolation of a number of metabolites toxic to ducklings and day-old chicks: diplodiatoxin (**9**)[34,35], 3-hydroxydiplodiatoxin (**10**),[35] carpellin (**11**), [35] and stenocarpin (**12**) as either the diacetate derivative (**13**) or the orsellinate ester (**14**).[35]

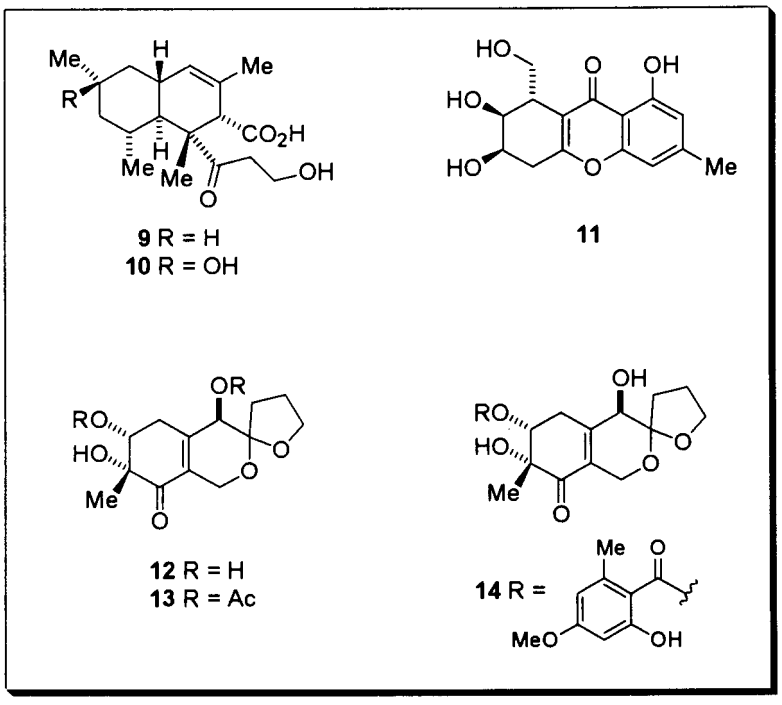

Figure 1.5: Metabolites of *D. maydis*.

Diplodiatoxin (**9**) is not the major toxin produced by cultures of *D. maydis* and accounts for only 10% of the total biological activity of the culture material.[34] The proposed structure by Steyn *et al.*,[34] based on chemical degradation reactions and ^{1}H and ^{13}C NMR

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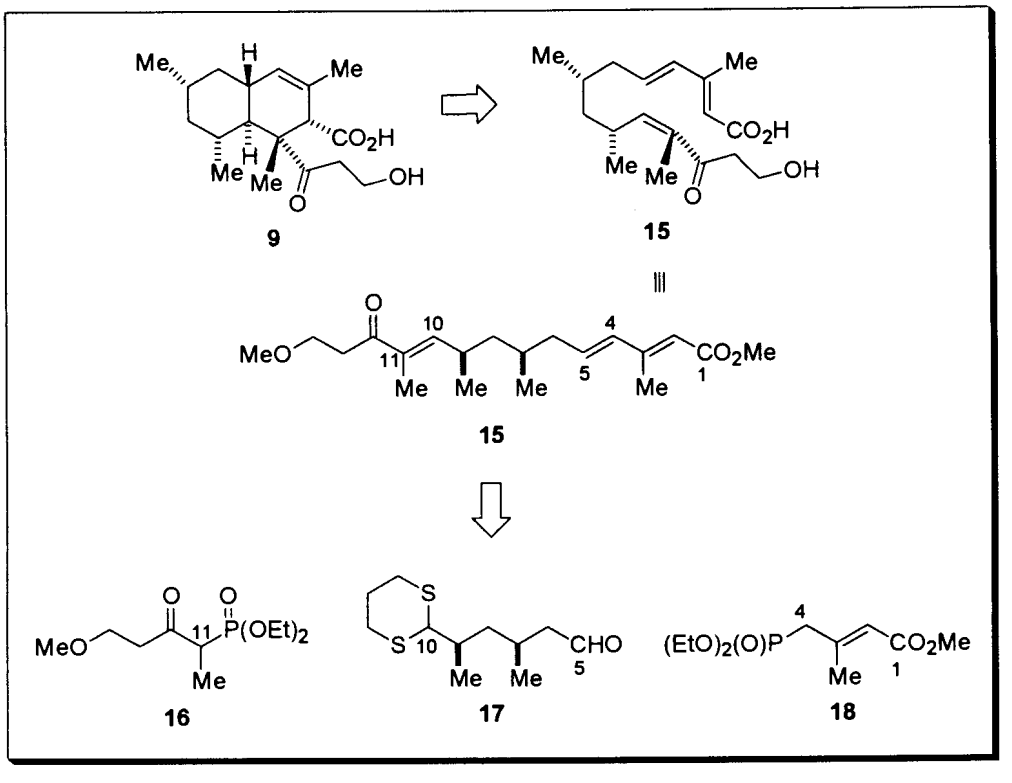
[33] H.G. Cutler, F.G. Crumley, R.H. Cox, R.J. Cole, J.W. Dorner, J.P. Springer, F.M. Latterell, J.E. Thean and A.E. Rossi, *J. Agric. Food Chem.*, 1980, **28**, 139.

[34] P.S. Steyn, P.L. Wessels, C.W. Holzapfel, D.J.J. Potgieter and W.K.A. Louw, *Tetrahedron*, 1972, **28**, 4775.

[35] S.F. Marais, *Isolation and Structure of the Metabolites from Diplodia maydis*, M.Sc. dissertation, University of Pretoria, 1990.

data, established the connectivity pattern for the metabolite. A novel feature of the structure is the β-ketol side-chain and a rare occurrence of a β,γ-unsaturated acid moiety. The relative configuration for the stereogenic centers and confirmation of the proposed structure was provided by X-ray crystallography.[36]

The absolute configuration of diplodiatoxin was established by the stereoselective synthesis of natural (+)-diplodiatoxin.[37] On the basis of the published data and by comparison with the ^{1}H NMR data for betaenone B,[38] but evidently unaware of the results of the X-ray study, the synthesis of the enantiomer as shown in (**9**) was undertaken. In the retrosynthetic analysis of diplodiatoxin the intramolecular Diels-Alder reaction of the (*E*,*E*,*E*)-trienone ester (**15**) (Scheme 1.1) is identified as the key step. Although this step may involve four possible transition states, the *endo* transition state leading to the *trans* decaline framework is most favourable as the three other transition states involve severe interaction between non-bonded atoms.



Scheme 1.1: Retrosynthetic analysis of diplodiatoxin (**9**).

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[36] G.J. Kruger, C.M. Weeks and J.P. Hazel, *Crystal Struct. Commun.*, 1977, 6, 193.
[37] A. Ichihara, H. Kawagishi, N. Tokugawa and S. Sakamura, *Tetrahedron Lett.*, 1986, **27**, 1347.
[38] A. Ichihara, H. Oikawa, K. Hayashi, S. Sakamura, A. Furasaki and T. Matsumoto, *J. Am. Chem. Soc.*, 1983, **105**, 2907.

Disconnection of the C(4)-C(5) and C(10)-C(11) bonds in the trienone ester **(15)** using the Wadsworth-Emmons transformation identifies the two readily available phosponates **(16)** and **(18)** and the half-masked dialdehyde **(17)** that was prepared from D-glucose in a 15-step synthetic route. In the synthetic direction the formation of the C(4)-C(5) and C(10)-C(11) bonds followed by an intramolecular Diels-Alder reaction produced (+)-diplodiatoxin. Comparison of the ^{1}H NMR and CD spectra of the synthetic diplodiatoxin with that of the natural compound established the absolute configuration as shown in **(9)**. In a subsequent publication by Potgieter *et al.*[39] on the products obtained by oxidative degradation of diplodiatoxin in the course of the original structural studies,[34] the enantiomer of diplodiatoxin is shown in error. The high-field ^{1}H and ^{13}C NMR assignments are reported in this paper[39] and two errors are corrected.

The biosynthetic pathway leading to diplodiatoxin was investigated using [1-^{13}C]-, [2-^{13}C]-, [1,2-$^{13}C_2$]-, [2-$^{2}H_3$,1-^{13}C]- and [1-^{13}C,$^{18}O_2$]acetate, and (2*S*)-[*methyl*-^{13}C]methionine.[35] The results indicate that diplodiatoxin is formed from a C_{14} acetate-derived polyketide precursor folded as shown in Figure 1.6 and that all the methyl groups present in the compound are derived from the methyl group of methionine. The methyl group of the acetate starter unit, C(7)-C(14), is oxidised to a carboxylic acid group in contrast to the carboxylate terminus of the polyketide chain [C(18)] which is reduced to a primary alcohol. The incorporation of ^{18}O from [1-^{13}C, $^{18}O_2$]acetate into the C(16) carbonyl group indicated that this carbon-oxygen bond had remained intact throughout the biosynthetic pathway.

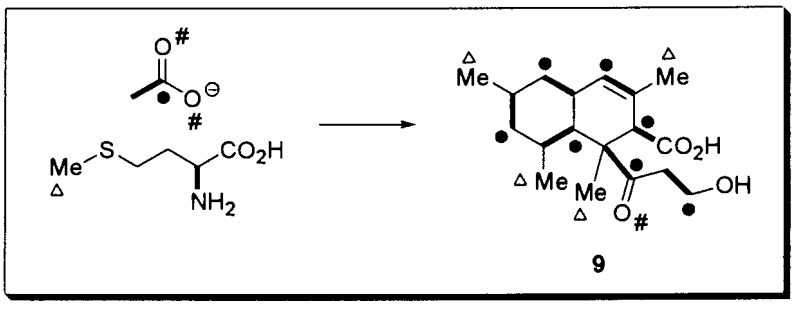
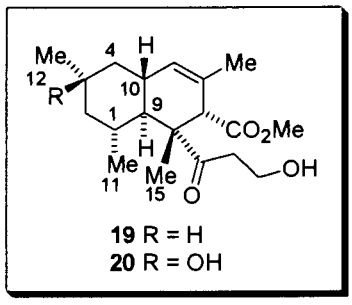


Figure 1.6: Incorporation of stable isotope labeled precursors in diplodiatoxin.

[39] M. Potgieter, P.S. Steyn and P.H. van Rooyen, *J. Chem. Research (S)*, 1989, 192.

The close structural similarity between diplodiatoxin (**9**) ($C_{18}H_{28}O_4$) and 3-hydroxy-diplodiatoxin (**10**) ($C_{18}H_{28}O_5$) was evident from their molecular formula and that of their methyl ester derivatives (**19**) and (**20**), as determined by elemental analysis and mass spectrometry.[35] The presence of an additional oxygen atom in 3-hydroxydiplodiatoxin (**10**) reduced the structure elucidation to locating this extra atom in the structure. Comparison of the ^1H and ^{13}C NMR data for the methyl ester derivatives (**19**) and (**20**)



19 R = H
20 R = OH

Figure 1.7: Diplodiatoxin methyl ester and its hydroxy derivative.

showed the close structural similarity between the two compounds. Thus one of the methyl groups in (**20**) appears as a singlet at δ_H 1.214 [H(12)] and the multiplets assigned to H(2) and H(4) are shifted downfield. In the ^{13}C NMR spectrum of (**20**) a signal of a quaternary carbon appeared at δ_C 70.09, characteristic of an oxygen-bearing carbon atom. The position of the hydroxy group was established by means of a two-dimensional (2D) long-range (^{13}C,^1H) chemical shift correlation experiment. The correlations observed between the signal at δ_H 1.214s [H(12)] and the ^{13}C resonances at δ_C 45.81T [(C(4)], 49.62T [(C(2)], and 70.09S [(C(3)] located the hydroxy group at C(3) in (**20**). The singlet nature of the H(12) signal in conjunction with the (C,H) connectivity pattern, implied that the two methylene carbon atoms must be three-bonds removed from H(12) and discounts any other location for the hydroxy group but C(3). The configura-tion of the C(3) stereogenic centre was established by proton-proton NOEs. The NOEs observed between H(11) and both H(12) and H(9) can only arise through a cis arrangement of the C(11) and C(12) methyl groups and the C(9) methane proton. With the knowledge of the relative and absolute configuration of diplodiatoxin (**9**)[36,37] to hand it follows that 3-hydroxydiplodiatoxin (**10**) has the same absolute configuration.

The strategy for the structure elucidation of carpellin (**11**) and stenocarpin (**12**), toxic metabolite isolated from maize cultures of *D. maydis*,[35] involved the collection of data on the constitution of these metabolites using spectroscopic techniques and chemical reactions. The molecular formulae were obtained from accurate mass determinations of the molecular ions observed in the mass spectra as well as elemental analysis. A detailed study of the ^{1}H NMR spectra provided both the ^{1}H chemical shift values and proton-proton spin couplings whereas the ^{13}C NMR spectra provided the chemical shift values and multiplicities of the carbon atoms. A number of different NMR techniques were then used for the assignment of specific structures and relative configurations to each of the two compounds. The signals of proton-bearing carbon atoms were correlated with specific proton resonances in two-dimensional (2D) (^{13}C,^{1}H) heteronuclear shift correlation experiments utilizing the one-bond (^{13}C,^{1}H) spin-spin couplings. Hetero-nuclear ^{13}C-{^{1}H} selective population inversion (SPI) experiments, a pulsed double resonance NMR technique, was used in the structure elucidation to determine the long-range (more than one-bond) (^{13}C,^{1}H) connectivity pattern, by using long-range (^{13}C,^{1}H) spin-spin couplings.[40,41,42,43] The location of the hydroxy groups in the two compounds was corroborated by the deuterium isotope shifts observed for the signals of the relevant carbon atoms in the ^{13}C NMR spectrum.[44,45]

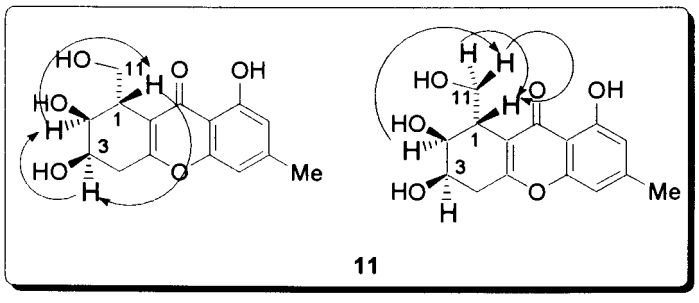


Figure 1.8: Proton-proton NOEs for carpellin.

The relative configuration of carpellin (**11**) was deduced from the magnitude of the proton-proton coupling constants and the observed NOEs.[35] The reported values of $J_{1,2}$

[40] K.G.R. Pachler and P.L. Wessels, *J. Magn. Reson.*, 1977, **28**, 53.
[41] T.G. Dekker, K.G.R. Pachler and P.L. Wessels, *Org. Magn. Reson.*, 1976, **8**, 530.
[42] K.G.R. Pachler and P.L. Wessels, *J. Magn. Reson.*, 1973, **12**, 33.
[43] A.E. Derome, *Modern NMR Techniques for Chemistry Research*, Pergamon Press, Oxford, 1987.
[44] R.A. Newmark and J.R. Hill, *Org. Magn. Reson.*, 1980, *13*, 40.
[45] P.E. Hansen, *Annu. Rep. NMR Spectrosc.*, 1983, *15*, 105.

3.1 and $J_{2,3}$ 2.3 Hz for the C(1), C(2) and C(3) protons indicated that there are no axial-axial interactions for these protons and that the A-ring has a half-chair confor-mation. Thus these protons must have either equatorial-equatorial or equatorial-axial relationships. The interpretation of the NOE difference was based on the assumption that the C(3) stereogenic centre has the *R* configuration (Figure 1.8). An NOE was observed between H(3) and one of the C(11) protons and pointed to a *trans* relationship between the C(3) hydroxy group and the C(1) hydroxymethyl substituent. The NOEs between the methine protons, H(2) and H(3) indicated a *cis*-diol arrangement for the C(2) and C(3) hydroxy groups. This finding was confirmed by the formation of a 2,3-O,O-acetonide derivative with $J_{2,3}$ 6.8 Hz, on treatment of carpellin with acetone and catalytic perchloric acid. The NOE connectivity observed between H(2) and H(1) is furthermore indicative of a *trans* diequatorial arrangement On the basis of these results the 1*S*,2*S*,3*R* configuration, or the enantiomer, was assigned to carpellin.

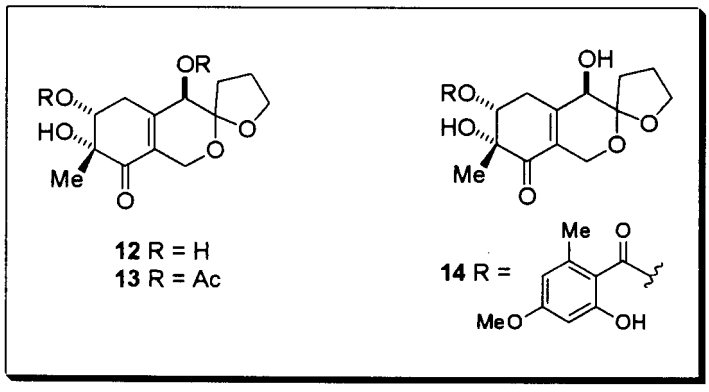


Figure 1.9: Stenocarpin and its derivatives.

Stenocarpin (**12**) was isolated from the first batch of culture material of *D. maydis* and purified as the diacetate derivative (**13**). In subsequent batches of culture material stenocarpin was completely replaced by the 6-*O*-(4-*O*-methylorsellinate) derivative (**14**). The constitution of both (**13**) and (**14**) was established following the strategy as outlined earlier with the extensive use of ^{1}H and ^{13}C NMR techniques.[35] The ^{1}H and ^{13}C NMR assignments obtained for stenocarpin 4,6-*O*,*O*-diacetate (**13**) are summarized in Table 1.1 as the spectra were re-analyzed for this dissertation and additional coupling constants were obtained. The data is also of importance for the synthetic work described in the following chapters of this dissertation.

Table 1.1: ^{13}C and ^{1}H NMR Data for Stenocarpin 4,6-*O*,*O*-Diacetate (13)[a,b]

Atom	δ_C	δ_H	J (Hz)
1	58.56T	a: 4.490 dddd b: 4.283 ddd	1.7, 3.0, 3.7, 16.6 0.8, 3.4, 16.6
3	105.24S	-	
4	69.20D	5.170 d	1.7
4a	142.89S	-	
5	32.56T	*Si*: 2.760 dddd *Re*: 2.515 dddd	3.4, 3.7, 3.8, 19.0 0.8, 3.0, 2.6, 19.0
6	74.88D	5.309 dd	2.7, 3.8
7	76.64S	-	
8	198.69S	-	
8a	130.96S	-	
9	23.11Q	1.365 s	
6-OAc	20.75Q 170.17S	2.011 s	
4-OAc	21.04Q 170.22S	2.126 s	
2′	69.40T	a: 4.009 ddd b: 3.981 ddd	5.2, 8.2, 8.2 7.3, 7.3, 8.3
3′	23.29T	a: 2.09 m b: 1.92 m	
4′	34.21T	a: 2.02 m b: 1.790 ddd	- 12.5, 9.3, 9.3

[a] The proton of the C(7) hydroxy group appears as a broad singlet at δ_H 3.36.
[b] Bruker WM500 spectrometer (11.7 T)

The relative configuration of stenocarpin 4,6-*O*,*O*-diacetate (**13**) was deduced from the magnitude of the proton-proton coupling constants (Table 1.1) and the NOE connectivity pattern (Figure 1.9). At the outset it was assumed that the C(4) stereogenic center had the *R* configuration. A strong NOE pattern was observed between H(4) and the C(5) prochiral methylene proton that resonates at δ_H 2.515. In contrast an NOE difference is observed between H(6) and both the C(5) protons. The NOEs observed between the protons of the C(7) methyl group (δ_H 1.365) and H(6)(δ_H 5.309) and the C(5) prochiral methylene proton that resonates at δ_H 2.760 established the *cis* relationship for the 6,7-diol moiety of stenocarpin and furthermore led to the assignment of the 5*Re* (δ_H 2.515) and 5*Si* (δ_H 2.760) protons. The configuration of the C(3) spiro carbon atom could not be established by NOE experiments as no unambiguous assignment of the C(4′) protons was available. The observed NOE between H(4) and the C(4′) prochiral methylene proton which resonates at δ_H 2.02 could therefore be rationalised by the deduction that it is the 4′*Si* proton that is affected when C(3) has the *S* configuration whereas in the case of the 3*R* configuration it is the 4′*Re* proton for which the NOE is observed.

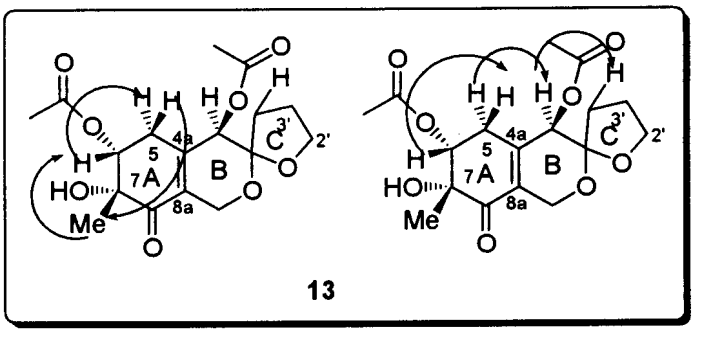


Figure 1.9: NOE connectivity pattern of stenocarpin 4,6-*O*,*O*-diacetate.

Application of the partial resolution method of Horeau[27,28] to the 6-*O*-(2,4-*O*,*O*-dimethyl-orsellinate derivative of stenocarpin (**12**) established the 4*R* absolute configuration and consequently the 4*R*,6*R*,7*R* and either the 3*R* or 3*S* absolute configuration.[35]

The main goal of this dissertation is the determination of the absolute configuration of the C(3) spiroacetal stereogenic centre using synthetic methods. The synthetic strategy involves the synthesis of a model compound for the B/C ring system of stenocarpin and to use NMR data and methodologies such as NOEs to determine the absolute configuration of the spiroacetal stereogenic centre. The model compound and the

synthetic route were identified by retrosynthetic analysis as described in Chapter 3 of this dissertation. The synthesis uses a carbohydrate as a chiral templet and a radical ring cyclisation as the key step for the formation of the spiroacetal ring system.

2 SPIRO COMPOUNDS

2.1 Nomenclature

Organic molecules in which one carbon atom is common to two rings are called spirocyclic compounds. The name spirane as well as the nomenclature for these compounds was initially proposed by von Bayer.[1,2] The modern nomenclature based on the von Bayer proposals has been reported as guidelines in the IUPAC 'Blue Book' on organic nomenclature.[3,4] Some of these rules that are relevant to the work described in this dissertation are listed below and examples are shown in Figure 2.1.

- Monospiro hydrocarbons with two monocyclic rings are named by the prefix spiro before a von Baeyer descriptor. This descriptor indicates the number of carbon atoms in each ring linked to the spiro atom in ascending order and separated by a full stop and is placed in square brackets. The name of the parent hydrocarbon indicating the total number of skeletal atoms follows after the descriptor e.g.(**21**).
- Numbering starts in the smaller ring at an atom adjacent to the spiro atom and proceeds around the smaller ring back to the spiro atom and then around the second ring *e.g.* (**21, 22–27**).
- Heteroatoms are indicated by replacement prefixes used in decreasing order of precedence *i.e.* oxa, thia, aza and the use of multipliers di-, tri-, ..when two or more identical heteroatoms are present (**22, 24–28**) .
- The presence of functional groups is indicated by the addition of the normal suffixes to the parent name (**23**).

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1 A. Baeyer, *Ber. Dtsch. Chem. Ges.*, 1900, **33**, 3775.
2 D. Radulescu, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 1023.
3 R. Panico, W.H. Powell and J-C. Richter, *A Guide to IUPAC Nomenclature of Organic Compounds*, Blackwell Science, Oxford, 1993.
4 IUPAC Commission on Nomenclature, *Pure Appl. Chem.*, 1999, **71**, 531.

Numbering in dispiro compounds begins with a ring atom next to the terminal spiro atom of the smaller terminal ring, proceeding around that terminal ring through its terminal spiro atom and, by the shortest path, through the other spiro atom, around the other terminal ring, and then back to the first terminal ring (**28**).

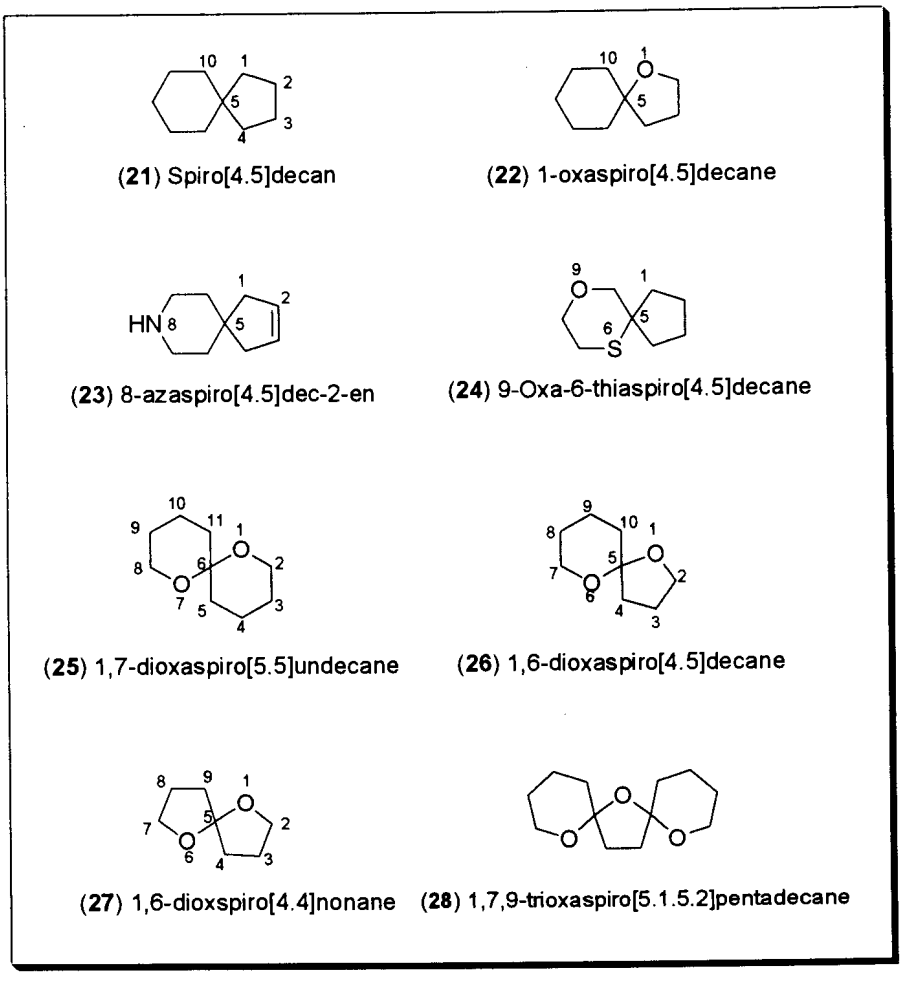


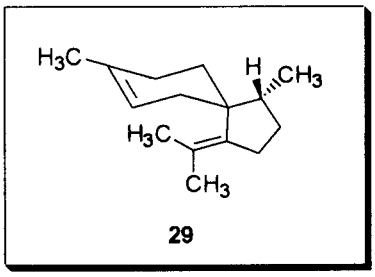
Figure 2.1: IUPAC Nomenclature for spiro-compounds.

2.2 Spiroacetal Natural Products

The simplest spirocyclic hydrocarbon is spiro[2.2]pentane, a product of laboratory synthesis. More complicated spirocyclic compounds have not only been synthesized but have also been isolated from natural sources. For example α-alaskene,[5] contains a

[5] F.A. Carey, *Organic Chemistry*, 4th Ed., 2000, p. 114.

spiro[4.5]dec-7-ene moiety and occurs in the fragrant oil given off by the needles of the Alaskan yellow cedar.



29

Figure 2.2: α-Alaskene

The majority of spiroacetal containing compounds isolated from natural sources are of the type illustrated by (**25**), (**26**) and (**27**) (Figure 2.1) and their chemistry has been extensively studied.[6,7,8] The dispiroacetal moiety is less common but does occur in a small number of polyether ionophores and marine natural products.[9] The formation of this system, in which two acetal carbons are linked in a spiro fashion, represents a synthetic challenge that has attracted the efforts of some of the leading synthetic research groups.[9]

The major sex pheromone of the olive fruit fly has been identified as 1,7-dioxaspiro[5.5]undecan-4-ol (**30**),[10] an assignment which was verified by synthesis.[11] Chalcogran is the principal aggregation pheromone of a species of beetles considered as a pest of Norway spruce. The natural product, 1,6-dioxaspiro[4.4]nonane derivative is a mixture of C(2) diastereomers (**31**) which have been synthesized.[12] The talaromycins *e.g.* talaromycin A (**32**), are avian toxins that contain a hydroxylated 1,7-dioxaspiro-[5.5]undecane ring system.[13,14]

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6 T.L.B. Boivin, *Tetrahedron*, 1987, **43**, 3309.
7 F. Perron and K.F. Albizati, *Chem. Rev.*, 1989, **89**, 1617
8 V. Vaillancourt, N.E. Praft, F. Perron and K.F. Albizati, in *The Total Synthesis of Natural Products*, (J. ApSimon, Ed.), Wiley, New York, 1992, Vol. 8, p. 533.
9 M.A. Brimble and F. A. Farès, *Tetrahedron*, 1999, **55**, 7661.
10 H. G. Davies and R.H. Green, *Chem. Soc. Rev.*, 1991, **20**, 211.
11 R. Baker, R. Herbert, P.E. Howse, O.T. Jones, W. Francke and W. Reith, *J. Chem. Soc. Chem. Commun.* 1980, 52.
12 H. Redlich and W. Francke, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 639.
13 D.G. Lynn, N.J. Phillips, W.C. Hutton, J. Shbanowitz, I. Fennell and R.J. Cole, *J. Am. Chem. Soc.*, 1982, **104**, 7319.
14 N.J. Phillips, R.J. Cole and D.G. Lynn, *Tetrahedron Lett.*, 1987, **28**, 1619.

Related spiro subunits occur in the structurally complex polyether antibiotics[15] of the monensin (**33**) type (Figure 2.3).

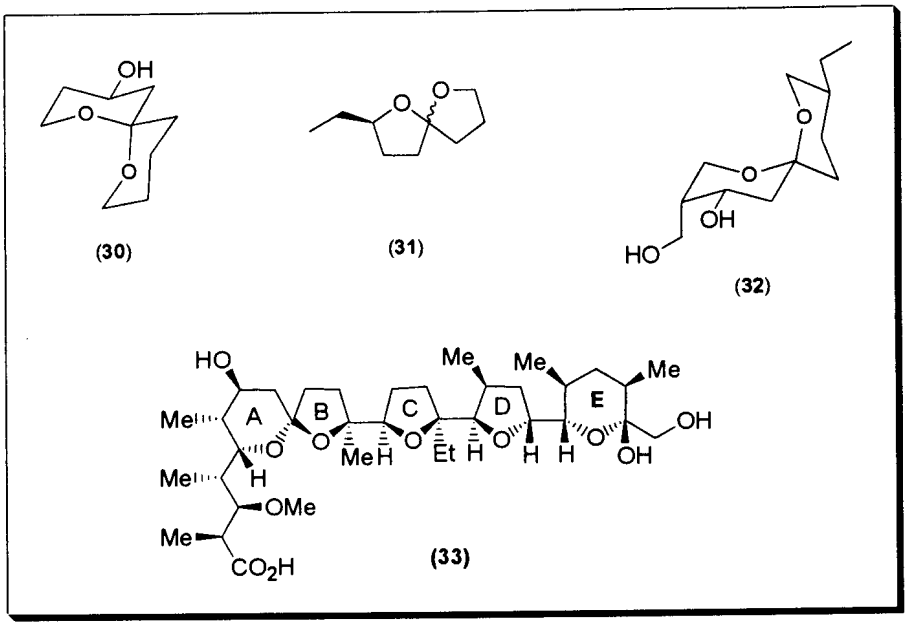

Figure 2.3: Simple spiroacetal compounds.

Salinomycin (**34**), a biologically active compound which contains a dispiroacetal unit was isolated from the culture broth of *Streptomyces albus* and was found to exhibit marked activity against mycobacteria and fungi in addition to antibacterial and anticoccidial properties. It is structurally one of the most complex coccidiostats in use and is available commercially. X-Ray crystallographic analysis of the *p*-iodophenacyl ester derivative of this polyether antibiotic by Kinashi *et al.*[16] revealed the presence of the 1,6,8-trioxa-spiro[4.1.5.3]pentadec-13-ene motif (Figure 2.4).

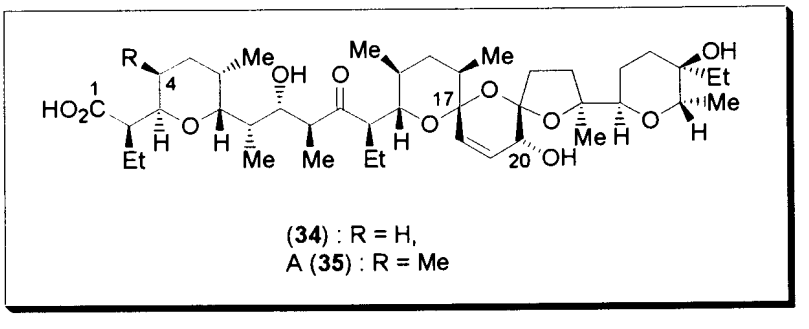

Figure 2.4: Polyether antibiotics containing a dispiroacetal ring system.

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[15] W. Wieringa in *The Total Synthesis of Natural Products*, (J. ApSimon, Ed.), Wiley, New York, 1992, Vol. 4, p.533.

[16] H. Kinashi, N. Otake, H. Yonehara, S. Sato and Y. Saito, *Tetrahedron Lett.*, 1973, **29**, 4955.

Narasin A (**35**) was isolated[17] from a culture of *S. aureofaciens* and the structure elucidated as the 4-methyl analogue of salinomycin after mass spectral comparison[18] with salinomycin (**34**) itself. The 4β configuration for this methyl group was established by ^{13}C NMR analysis.[19] The total syntheses of salinomycin and narasin A have been reported by Kishi,[20] by Yonemitsu *et al.*,[21,22,23,24] and by Brown and Kocienski.[25,26]

In 1995 Wright *et al.*[27] isolated two lipid-soluble macrocycles, spirolide B (**36**) and D (**37**) (Figure 2.5) from the digestive glands of both mussels (*Mytilus edulis*) and scallops (*Placopecten magellanicus*). These macrocycles contain a novel spiro-linked tricyclic dispiroacetal ring system as well as an unusual seven-membered spiro-linked imine moiety. The spirolides cause potent and characteristic symptoms in the mouse bioassay (LD_{100} 250 $\mu g.kg^{-1}$) and their toxicological properties are under investigation.

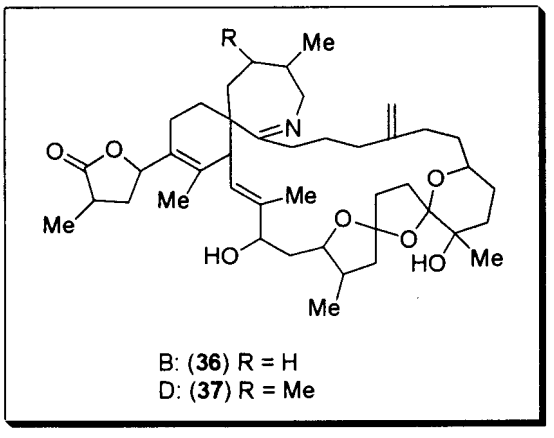

Figure2.5: Spirolide species

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[17] D.H. Berg and R.L.Hamill, *J. Antibiot.*, 1978, **38**, 1.
[18] J.L. Occolowitz, D.H. Berg, M. DeBuno and R.L. Hamill, *Biomedical Mass Spectrometry*, 1976, **3**, 272.
[19] H. Seto, T. Yahagi, Y. Miyazaki and N. Otake, *J. Antibiot.*, 1977, **30**, 530.
[20] Y. Kishi, S. Hatakeyama and M.D. Lewis, in *Frontiers of Chemistry*, K.J.Laidler, Ed., Oxford, 1982, 287.
[21] K. Horita, S. Nagato, Y. Oikawa and O. Yonemitsu, *Tetrahedron Lett.*, 1987, **28**, 3253.
[22] Y. Oikawa, K. Horita and O. Yonemitsu, *Tetrahedron Lett.*, 1985, **26**, 1541.
[23] K. Horita, Y. Oikawa, S. Nagato and O. Yonemitsu, *Tetrahedron Lett.*, 1988, **29**, 5143.
[24] K. Horita, Y. Oikawa and O. Yonemitsu, *Chem. Pharm. Bull.*, 1989, **37**, 1698.
[25] R.C.D. Brown and P.J. Kocienski, *Synlett.*, 1994, 415 and 417.
[26] P.J. Kocienski, R.C.D. Brown, A. Pommier, M. Procter and B. Schmidt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 9.
[27] T. Hu, J.M. Curtis, Y. Oshima, M.A. Quilliam , J.A. Walter, W.M. Watson-Wright and J.L. Wright, *C. J. Chem. Soc., Chem. Commun.* 1995, 2159

The avermectins and milbemycins are groups of closely related 16-membered macrocyclic lactones containing a 1,7-dioxaspiro[5.5]undecane moiety *e.g.* avermectin 1a (**38**) and milbemycin A3 (**39**).[28] These compounds are effective against parasitic helminths and arthropods in doses as low as 10 $\mu g.kg^{-1}$ and appear to act by interference with invertebrate neurotransmission and not by inhibition of protein synthesis. This potent and specific pesticidal activity of the milbemycin-avermectin family of antibiotics has stimulated widespread interest in their chemistry.[29]

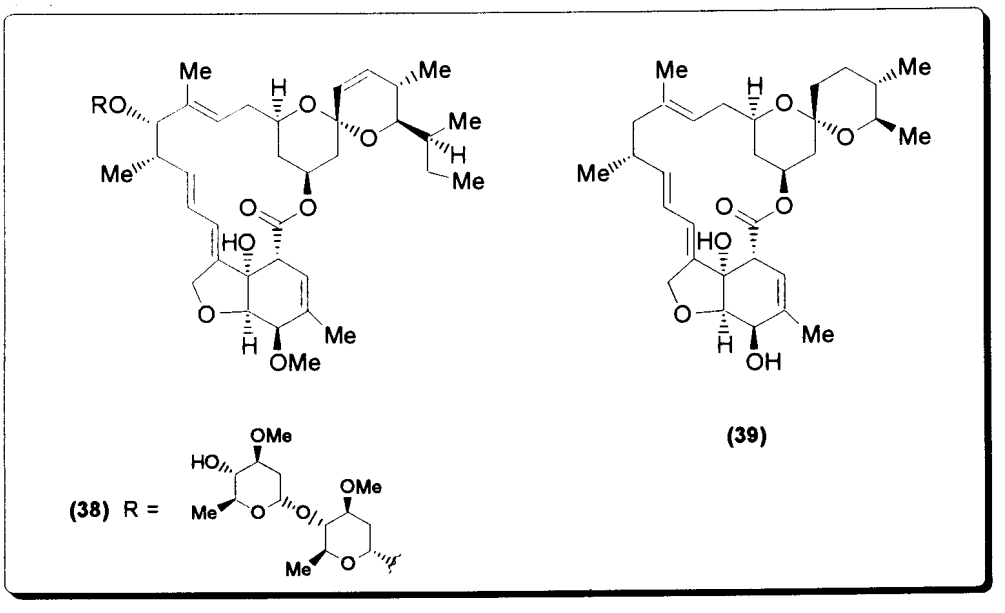


Figure 2.6: Complex spiroacetal compounds of avermectin and milbemycin

2.3 Synthesis of Spiroacetals from Carbohydrates.

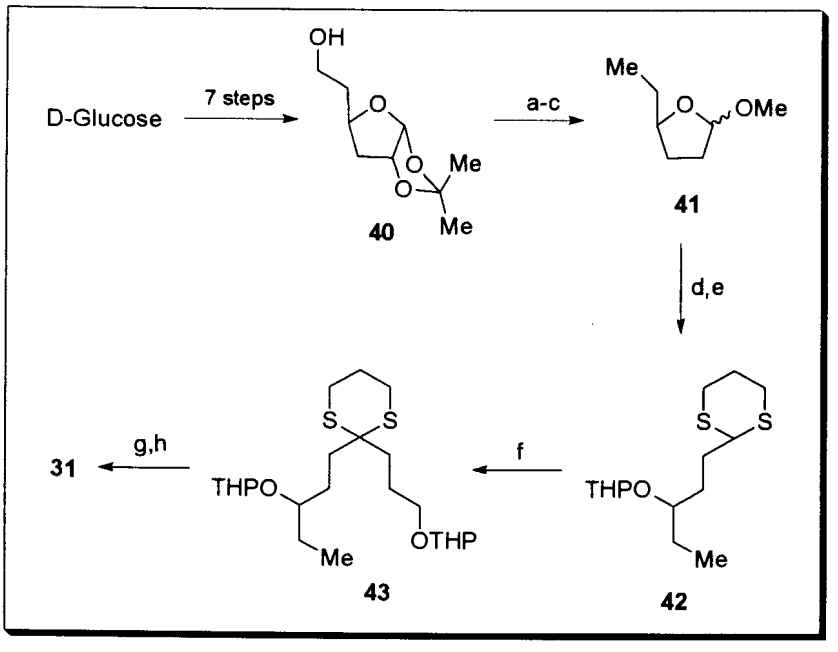
2.3.1 Acid-catalysed spirocyclisation.

The most common route to spiroacetals involves the acid-catalysed acetalisation of a dihydroxyketone progenitor under thermodynamic control, as this will result, by virtue of the anomeric stereoselection process, in the predominant formation of a spiroacetal unit with the axial orientation of the C–O bonds.[30] However, this well-explored method may not be compatible with acid-sensitive protecting groups in complex molecules. This

[28] T. Blizzard, M.H. Fisher, H. Mrozik and T.L. Shih, in *Recent Progress in the Chemical Synthesis of Antibiotics*, (G. Lukacs and M. Ohno, Eds.), Springer-Verlag, Berlin, 1990, 65.

[29] S.V. Ley and A. Armstrong, in *Strategies and Tactics in Organic Synthesis*, (T. Lindberg, Ed.), Academic Press, San Diego, 1991, Vol. 3, p. 237.

approach is illustrated by the synthesis of chalcogran (**31**) (Scheme 2.1). The starting material (**40**)[31] used in the synthesis was obtained from D-glucose in seven steps.[32,33] Treatment of (**40**) with methanolic HCl led to the formation of a methyl furanoside with two unprotected hydroxy groups. Removal of the oxygen functionalities using the Barton-McCombie procedure[32] gave (**41**). Reaction of (**41**) with propane-1,3-dithiol and $BF_3.OEt_2$ afforded the open-chain dithiane alcohol which was protected as the THP ether (**42**). Linkage of (**42**) with THP-protected 3-bromo-1-propanol by the Corey-Seebach method[34] gave the protected, masked open chain (**43**) corresponding to the chalcogran structure. Cleavage of the dithiane moiety using heavy metal catalysis led to a ketone intermediate[35] which on removal of the THP protecting groups in acid medium led *via* spontaneous cyclisation to the desired mixture of the diastereomers (2*R*,5*RS*) for chalcogran (**31**).



Scheme: 2.1: Synthesis of chalcogran (**31**).

Reagents: a) MeOH, HCl; b) NaH, CS_2, MeI; c) nBu_3SnH, azobisisobutyronitrile; d) propane-1,3-dithiol, $BF_3.Et_2O$, e) 3,4-Dihydro-2*H*-pyran, TsOH; f) BuLi, $Br(CH_2)_3$-OTHP; g) HgO, collidine; h) HCl.

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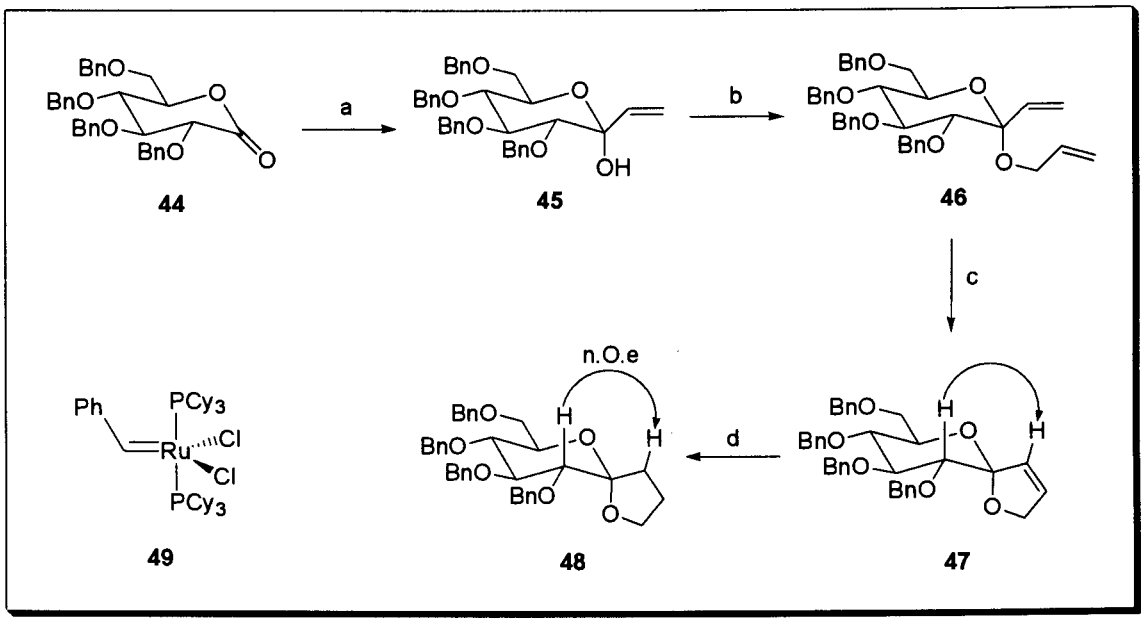
30 S. Hanessian and R. Roy, *J. Am. Chem. Soc.*, 1979, **101**, 5839.
31 H. Redlich and W. Francke, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 630.
32 D.H.R. Barton and S.W. McCombie, *J. Chem. Soc. Perkin Trans. I*, 1975, 1574.
33 A. Zobacova, V.Hermankova, Z. Kefurtova and J.Jary, *Coll. Czech. Chem Commun.* 1975, **40**, 3505,
34 D. Seebach, Synthesis, 1969, 17

2.3.2 Spiroacetals by ring-closing metathesis (RCM)

A three-step approach to chiral unsaturated [5.5], [5.6] and [5.7] spiroacetals by a ring-closing metathesis (RCM) reaction of a terminal alkene-*O*-alkene arrangement at the anomeric centre of sugars was reported by van Hooft *et al.*[36] and is illustrated in Scheme 2.2 using the perbenzylated D-glucono-1,5-lactone (**44**) as starting material. Addition of vinylmagnesium bromide to (**44**) gave exclusively the α-epimer (**45**) as was evident from a comparison of its ^{1}H NMR data with those of the same epimer prepared earlier by other workers from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose.[37] The conversion of the hydroxy group in (**45**) to the allyl ether (**46**) by treatment[38] of (**45**) with allyl alcohol in the presence of montmorillonite K-10 and 4Å molecular sieves proceeded with retention of configuration at C(1) in 75% yield.



Scheme 2.2: Ring-closing metathesis (RCM) in the synthesis of spiroacetals.

Reagents: a) CH_2=CHMgBr, THF (91%); b) H_2C=$CHCH_2OH$, montmorillonite K-10, molecular sieves (4Å) (75%); c) Grubbs catalyst (**49**) (95%); d) H_2, PtO_2 (85%).

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[35] H. Redlic, H.-J. Neumann and H. Paulsen, *Chem.Ber.* 1977, **110**, 2911

[36] P.A. van Hooft, M.A. Leeuwenburgh, H.S. Overkleeft, G.A. van der Marel, C.A.A. van Boeckel and J.H. van Boom, *Tetrahedron Lett.*, 1998, **39**, 6061.

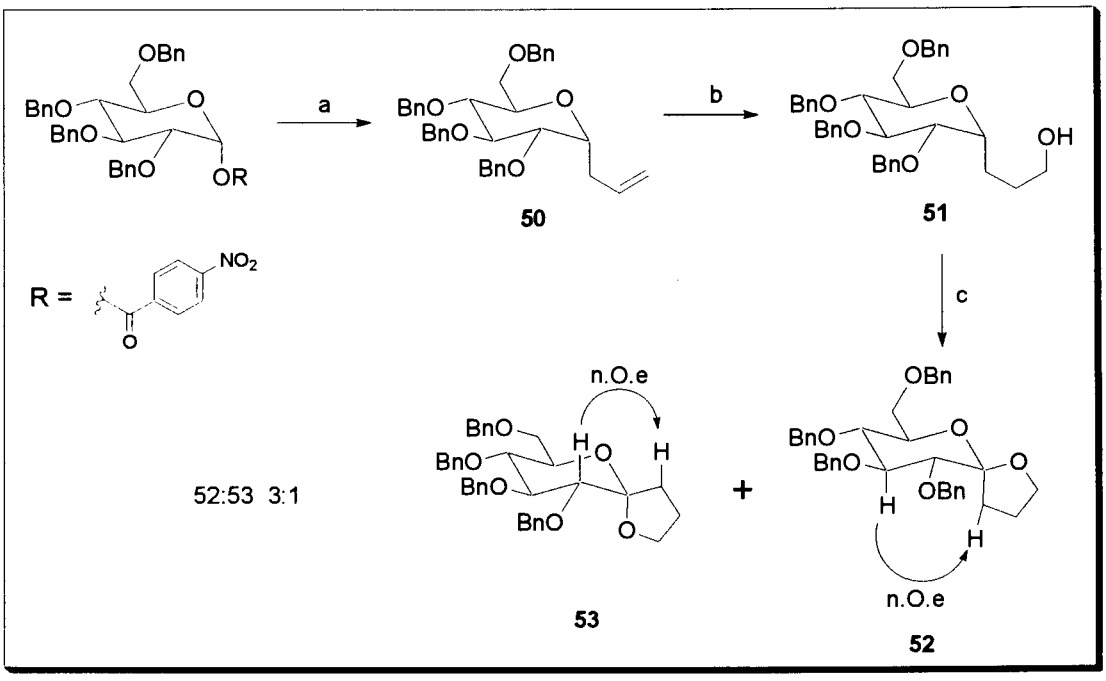
[37] K. Tomooka, Y. Nakamura and T. Nakai, *Synlett.*, 1995, 321.

[38] B.M. Trost and E.D. Edstrom, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 520.

The RCM reaction of (**46**) under the influence of Grubbs catalyst[39] (**49**) (6 mol%) in toluene 60°C for 16 h gave the (5*R*)-1,6-dioxaspiro[4,5]dec-3-ene derivative (**47**) in an excellent yield. The stereochemistry at the spiro center was firmly established by NOE difference experiments. In addition the structure of (**47**) was also corroborated independently by its nearly quantitative conversion to the known saturated spiroacetal (**48**)[40] via catalytic hydrogenation in the presence of platinum oxide.

2.3.3 Radical initiated spirocyclisation.

Martin *et al.*[40,41] reported an alternative synthetic route for chiral spiroacetals from carbohydrates in which the spirocyclisation is achieved by an intramolecular hydrogen abstraction reaction promoted by alkoxy radicals. In this way chiral 1,7-dioxaspiro[5.5]-undecane, 1,6-dioxaspiro[4.5]decane and 1,5-dioxaspro[4.4]nonane derivatives could be prepared in good yield.



Scheme 2.3: Synthesis of chiral spiroacetals: Radical initiated spirocyclisation at C(1).

Reagents: a) $H_2C{=}CHCH_2SiMe_3$, $BF_3.OEt_2$ (80%); b) i. BH_3, THF, 0°C, 5 h; ii. NaOH, H_2O_2, 40°C, 0.5 h (73%); (c) DIB, I_2, hv, 1 h, 40°C.

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[39] P. Schwab, R.H. Grubbs and J.W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100.
[40] A. Martin, J.A. Salazar and E. Suárez, *J. Org. Chem.*, 1996, **61**, 3999.
[41] A. Martin, J.A. Salazar and E. Sáurez, *Tetrahedron Lett.*, 1995, **36**, 4489.

The first step in the synthesis of the 1,6-dioxaspiro[4,5]decane type of spiroacetal was the formation of a *C*-glycopyranoside if the spiro center is to be generated at C(1) (see Scheme 2.3). The formation of the *C*-glycoside bond is based on the methodology reported by Kishi[42] and results in the preparation of either the α- or the β-anomer with a stereoselectivity of 10:1 in either case.

Treatment of 2,3,4,6-tetra-*O*-benzyl-α-(*p*-nitrobenzoyl)-D-glucopyranoside with allyltrimethylsilane and $BF_3.OEt_2$ gave a 9:1 α:β mixture of allylglucopyrans from which the α-isomer (**50**) was separated by chromatography. Kozikowski,[43] in the synthesis of methyl deoxypseudomonate B, developed a similar methodology to install an allyl group in the presence of functional groups sensitive to Lewis acids such as acetonides. Hydroboration/oxidation of the major stereoisomer (**50**) gave rise to the primary alcohol (**51**), The spirocyclisation of this alcohol (**51**) was accomplished by photolysis with visible light in the presence of (diacetoxyiodo)benzene and iodine to give two C(1) epimeric dioxaspiro-[4.5]decanyl derivatives, (**52**) and (**53**) in a ratio of 3:1 and 68% yield. The C(1) configuration was established by NMR methods using both HETCOR and ROESY experiments.[44,45,46,47,48] The most informative interactions are illustrated in Scheme 2.3. The minor compound (**53**) with the axial oriented C–O bond, is thermodynamically more stable (2.9 $kcal.mol^{-1}$) as indicated by the acid-catalyzed isomerization of (**52**) to (**53**). The equilibrium ratio (**52**):(**53**) of 1:4 was reached after 6 h at 50°C in AcOH containing a trace of aqueous HCl. The preferred conformation of this spirocenter is determined primarily by the anomeric effect[49,50,51] since all the sugar subsituents are in equatorial positions.

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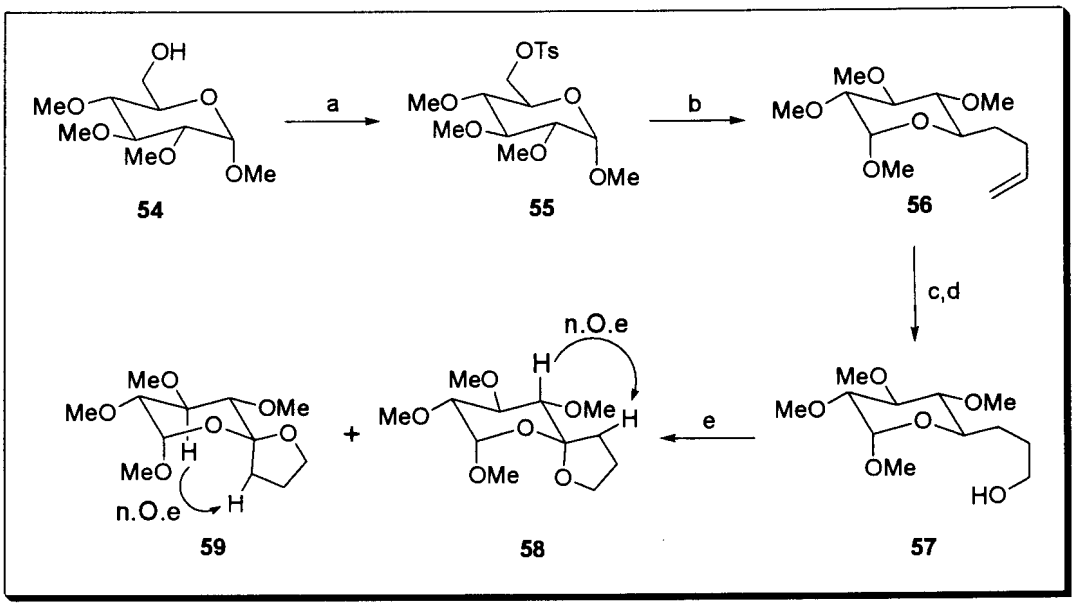
[42] M.D. Lewis, J.K. Cha and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 4976.
[43] A.P. Kozikowski and K.L. Sorgi, *Tetrahedron Lett.*, 1984, **25**, 2085.
[44] A.E. Derome, *Modern NMR Techniques for Chemistry Research*, Pergamon Press, Oxford, 1987.
[45] T.D.W. Claridge, *High-Resolution NMR Techniques in Organic Chemistry*, Pergamon Press, Oxford, 1999.
[46] A.A. Bothner-By, R.L. Stephens, J. Lee, C.D. Warren and R.W. Jeanloz, *J. Am. Chem. Soc.*, 1984, **106**, 811.
[47] H. Kessler, C. Griesinger, R. Kerssebaum, K. Wagner and R.R. Ernst, *J. Am. Chem. Soc.*, 1987, **109**, 607.
[48] A. Bax and D.G. David, *J. Magn. Reson.*, 1985, **63**, 207.
[49] P. Deslongchamps , D.D. Rowan, N. Pothier, T. Sauvé and J.K. Saunders, *J Am. Chem. Soc.*, 1981, **59**, 1105.
[50] N. Pothier, D.D. Rowan, P. Deslongchamps and J.K. Saunders, *Can J. Chem.*, 1981, **59**, 1132.
[51] A.J. Kirby, *The Anomeric Effect and Related Stereoelectronic Efects at Oxygen*, Springer-Verlag, Berlin, 1983.

Homologation of the carbohydrate C(5) side-chain is required if the spiro centre is to be constructed at C(5) (see Scheme 2.4). Martin *et al.*[40] prepared the required starting material (**54**) for this synthesis from methyl-α-D-glucopyranoside in a three step protocol[52,53] in 60% overall yield. The C(5) hydroxymethyl group was converted to the *O*-tosylate derivative (**55**). Treatment of (**55**) with allyl magnesium bromide in diethyl ether led to the formation of the C(5) but-3-en-1-yl side-chain in (**56**). Ozonolysis of the double bond and reductive work-up using $NaBH_4$ gave the 3-hydroxypropan-1-yl moiety of compound (**57**).



Scheme 2.4: Synthesis of chiral spiroacetals: Radical initiated spirocyclisation at C(1).

Reagents: (a) TsCl. Py, (98%); (b) CH_2=$CHCH_2MgBr$, Et_2O (88%); (c) i. O_3, $MeOH/CH_2Cl_2$, −78°C; ii. $NaBH_4$ (86%); (d) DIB, I_2, hν (75%).

Spirocyclisation of (**57**) by photolysis in the presence of (diacetoxyiodo)benzene and iodine involved intramolecular hydrogen abstraction to give the two spiroacetal epimers (**58**) and (**59**) in a ratio of 1:1.7 and 75% overall yield. Any possible 1,3-diaxial steric interaction by the 1α-methoxy group did not seem to influence the six-membered transition state necessary for the hydrogen abstraction. The assignment of the C(5) stereochemistry was once again established by the NOEs as shown in Scheme 2.4.

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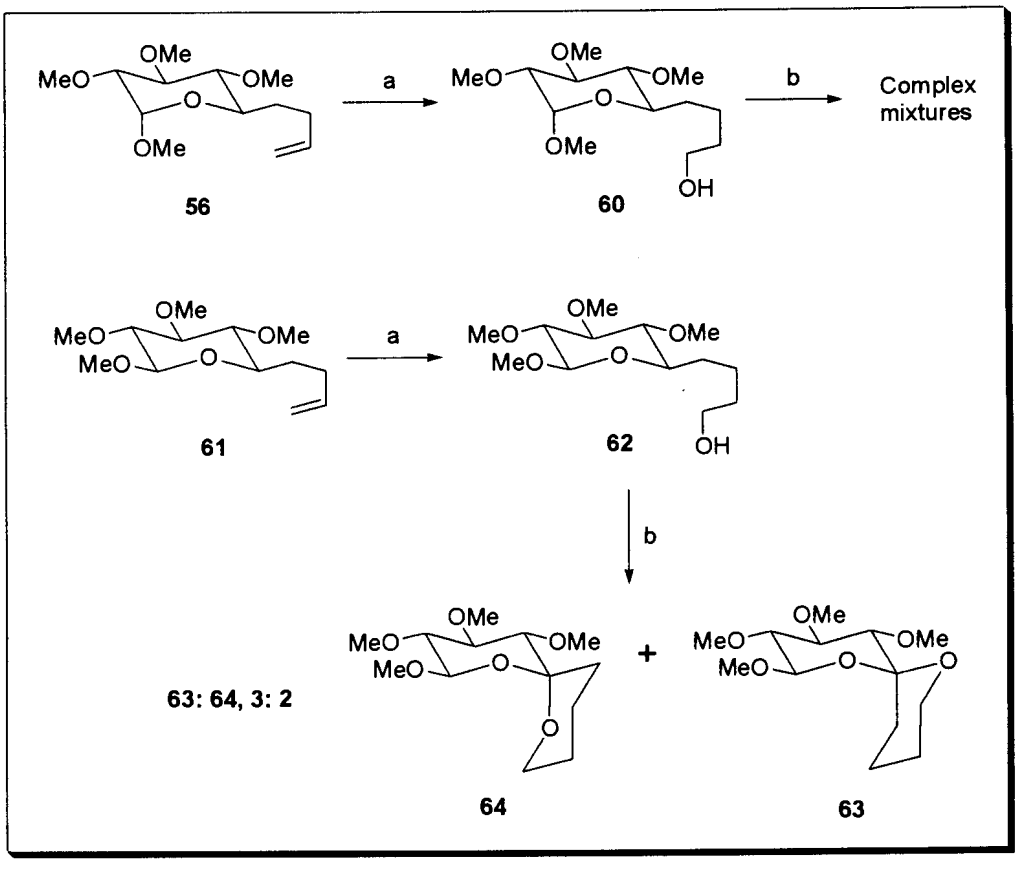
[52] B. Bernet and A. Vasella, *Helv. Chim. Acta.*, 1979, **62**, 1990.

[53] E.L. Hirst and E. Percival, *Methods in Carbohydrate Chemistry*, (R.L. Whistler and M. L. Wolfrom, Eds.), Academic Press, New York, 1963, Vol. 2, p. 147.

Reaction of the minor epimer (**58**), which has the axial orientation of the C–O bond, with *p*-toluenesulfonic acid in acetic acid gave after 7 h at room temperature an approximately 1:1 mixture of (**58**) and (**59**).

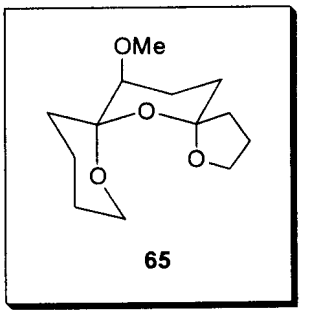
The formation of spiroacetals of the [5.5]undecane series was studied using compound (**56**) as starting material. Hydroboration/oxidation of this olefin gave the alcohol (**60**) in 90% yield. The spirocyclisation reaction of (**60**) with (diacetoxyiodo)benzene and iodine led to the formation of complex mixtures. Under the same conditions the methyl β-D-glycopyranoside derived alcohol (**62**) was transformed to the two spiroacetals (**63**) and (**64**) in a 3:2 and 88% yield. On the basis of these results it was deduced that 1,3-diaxial interactions play a critical role in the intramolecular hydrogen abstraction during spirocyclisation in the synthesis of dioxaspiro[5.5]undecane derivatives. In contrast these interactions appeared to have little effect on the synthesis of dioxaspiro[4.5]decanes.



Scheme 2.5: Synthesis of chiral dioxaspiro[5.5] spiroacetals.

Reagents: a) i. BH_3.THF, ii. H_2O_2, NaOH; b) DIB, I_2, hν, 1 h, 40°C.

The methodology outlined above has also been used for the spirocyclisation steps in the synthesis of chiral dispiroacetals such as 13-methoxy-1,6,8-trioxadispiro[4.1.5.3]pentadecane (**65**) from carbohydrate precursors.[54]



65

Figure 2.7: Bisspiroacetal

2.3.4 *Exo*-Glycals as intermediates in spiroacetal synthesis.

Endo-Glycals (1,2-unsaturated sugars) have been used as versatile building blocks in the synthesis of numerous natural products. However, the reactions of *exo*-glycals have not been investigated in any great detail, as a general facile synthesis for these compounds was not available. Lin *et al.* [55,56,57] recently reported a general synthetic method for the synthesis of *exo*-glycals *viz.* *C*-glycosyl conjugated dienes from fully protected sugar lactones as outlined in Scheme 2.6. Thus, tetra-*O*-*t*-butyldimethylsilyl-D-glucono-1,5-lactone (**66**)[58,59] for example, reacted with allylmagnesium chloride to give the addition product (**67**) as an anomeric mixture (7:1) in 92% yield. Dehydration of (**67**) was carried out by treatment with trifluoroacetic anhydride in the presence of pyridine to give the sugar diene (**68**) (75% yield) with exclusively the *Z* configuration. The method is applicable to the *gluco*-, *galacto*- and *manno*-1,5- and 1,4-lactones.

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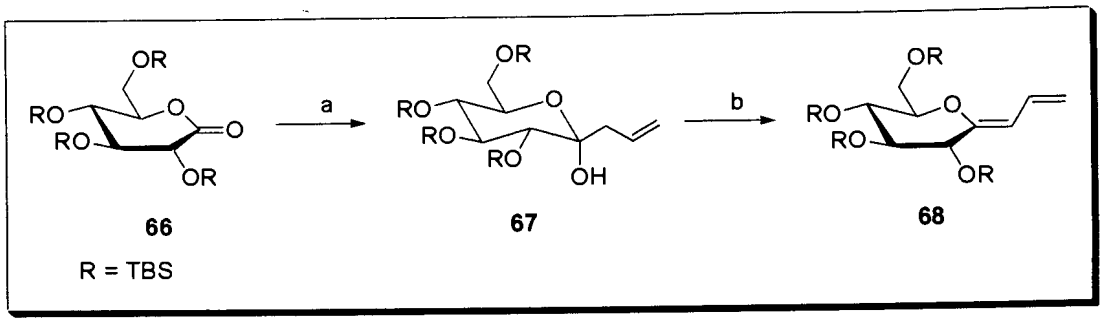
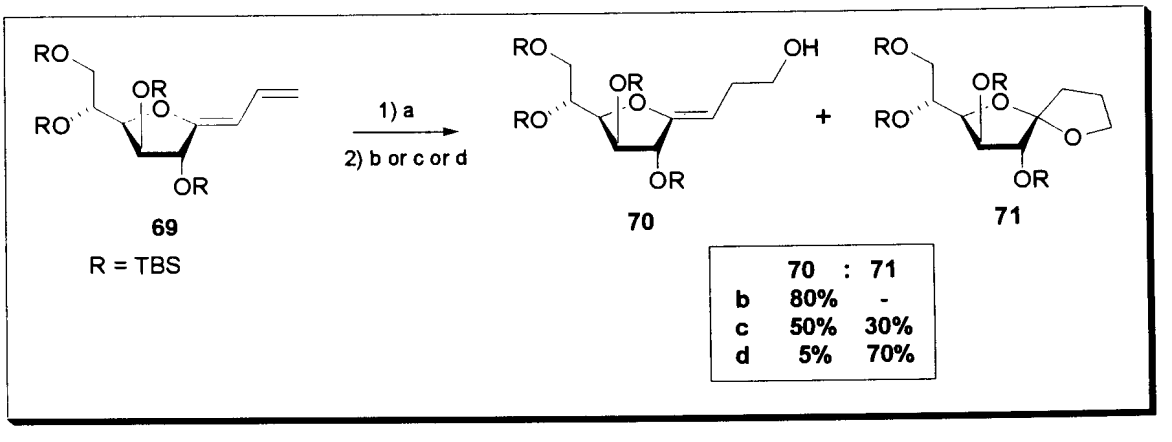
[54] L.D. Rosa, A. Martin, J.A. Salazar and E. Sáurez, *J. Org. Chem.*,1998, **63**, 2251.
[55] W.-B. Yang, C.-F. Chang, S.-H. Wang, C.-F. Teo and C.-H. Lin, *Tetrahedron Lett.*, 2001, **42**, 4657.
[56] W.-B. Yang, C.-Y. Wu, C.-C. Chang, S.-H. Wand, C.-F. Teo and C.-H. Lin, *Tetrahedron Lett.*, 2001, **42**, 6907
[57] W.-B. Yang, Y.-Y. Yang, Y.-F. Gu, S.-H. Wang, C.-C. Chang and C.-H. Lin, *J. Org. Chem.*, 2002, **67**, 3773.
[58] W.-B. Yang, C.-H. Tsai and C.-H. Lin, *Tetrahedron Lett.*, 2000, **41**, 2569.
[59] Y.-Y. Yang, W.-B. Yang and C.-H. Lin, *Synlett.*, 2000, 1634.



Scheme 2.6: Synthesis of exo-glycal intermediate.

Reagents: a) $H_2C{=}CHCH_2MgCl$ (92%); b) $(CF_3CO)_2O$, pyridine (75%).

The hydroboration of the C-glycosyl diene (**69**) followed by oxidation with alkaline H_2O_2 (condition b in Scheme 2.7) gave as only product the homoallylic alcohol (**70**) by selective oxidation of the terminal olefin. The use of H_2O_2 under acidic conditions resulted in the formation of the spiroacetal (**71**) in 70% yield (and later 90%)[60] when CSA was used. The homoallylic alcohol (**70**) could be converted quantitatively to (**71**) on treatment with CSA.[55]

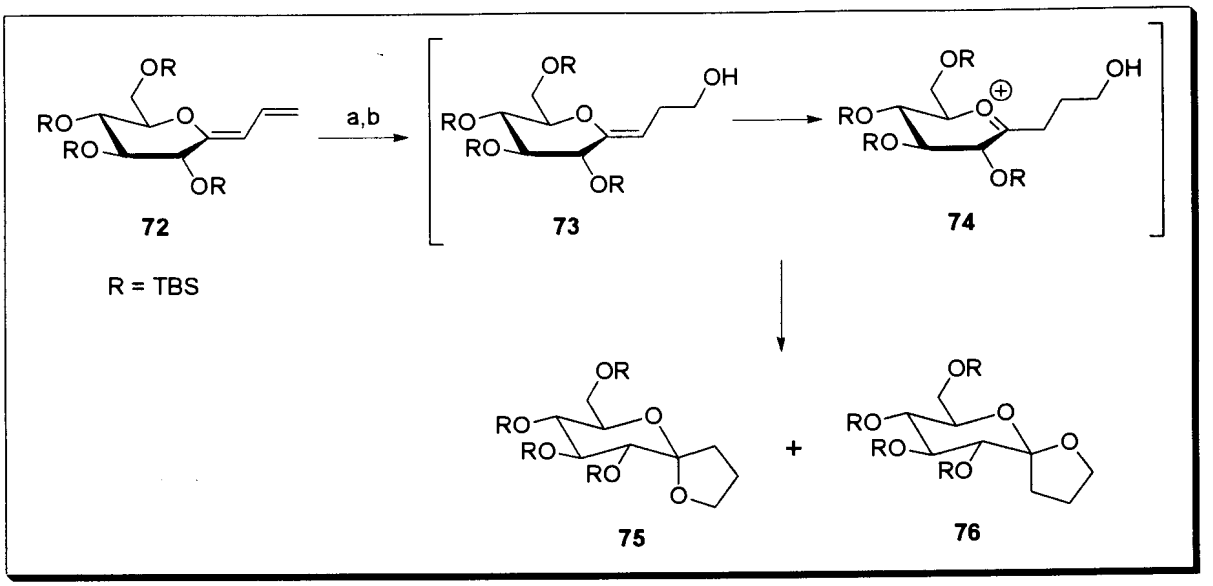


Scheme 2.7. Spirocyclisation of an *exo*-glycal under different conditions.

Reagents: a) $BH_3.HF$; b) H_2O_2, NaOH; c) H_2O_2, HOAc; d) H_2O_2, CSA.

This methodology was subsequently applied to the synthesis of a variety of 1,6-dioxaspiro[4.4] and 1,7-dioxaspiro[4.5] spiroacetals.[60] In the latter case hydroboration of the *C*-glycosyl diene (**72**) and quenching of the reaction with CSA gave the epimeric spiroacetals (**75**) and (**76**) in a 3:1 ratio. The homoallylic alcohol (**73**) has been postulated

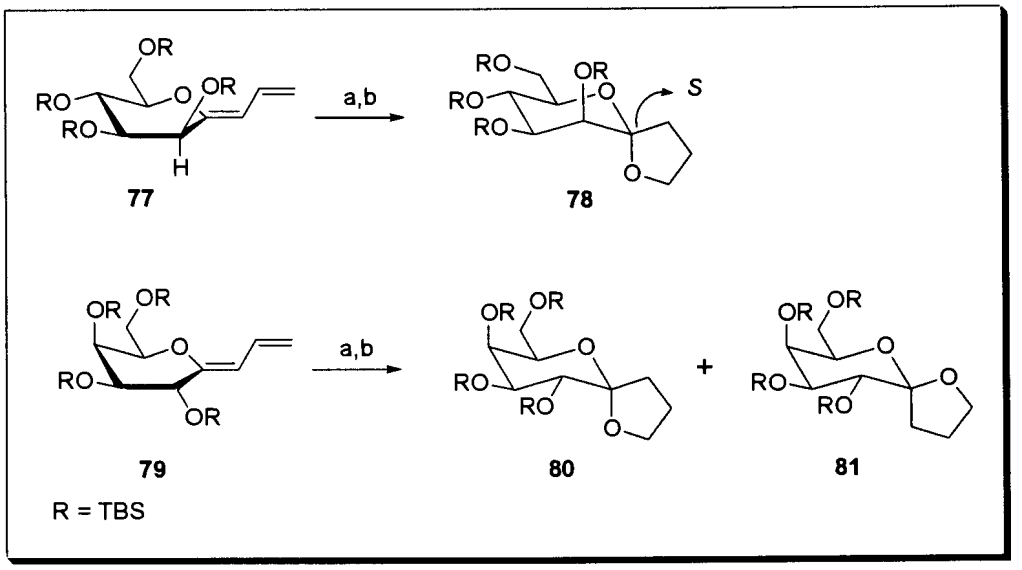
[60] C.-F. Chang, W.-B. Yang, C.-C. Chang and C.-H. Lin, *Tetrahedron Lett.*, 2002, **43**, 6515.



Scheme 2.8: Mechanism of the spirocyclisation of a C-glycosyl diene,

Reagents: a) BH_3.THF; b) H_2O_2, CSA.

as an intermediate that undergoes spirocyclisation. This ring closure would entail a 5-*endo*-trigonal annulation disfavoured in terms of the Baldwin rules.[61] The oxocarbenium ion (**74**) would be a more plausible intermediate, as ring closure would follow the favoured 5-*exo*-trigonal annulation pathway in accordance with the Baldwin rules.



Scheme 2.9: Spirocyclisation of the *manno*- and *galacto*-type dienes.

Reagents: a) BH_3.THF; b) H_2O_2, CSA.

[61] J.E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

Under the same conditions the *manno*-type diene (**77**) gave a single spiroacetal (**78**) and the *galacto*-type diene (**79**) gave the spiroacetals (**80**) and (**81**) as an 8:1 mixture. In each case the major or only spiroacetal had the axial C–O bond orientation (Scheme 2.9).

The outlined methods reported in the literature played a pivotal role in the retrosynthetic analysis of stenocarpin and the synthetic route leading to the model compounds, the 1,6-dioxaspiro[4.5]dec-8-en-10-ols, as reported in Chapter 3 of this dissertation.

3 SYNTHESIS OF SPIROACETAL MODEL COMPOUNDS

3.1 Retrosynthetic Analysis

3.1.1 Introduction

The ability to synthesize a particular compound from commercially available materials is of fundamental importance in organic chemistry. The appropriate selection of a suitable starting material for the synthesis of complex organic compounds can be a demanding and tedious exercise. In the early days of organic synthesis procedures were developed by selecting a suitable starting material (often by trial and error) and searching for a set of reactions, which in the end transformed it to the desired product (synthetic target). With an increasing need for the synthesis of more complex products, this approach with its frustrating and time-limited success rate was no longer viable. By the mid-1960s a different and more systematic approach started to become more popular with synthetic chemists. This approach depends on the structural features in the *reaction products* (as contrasted with starting materials) and the manipulation of structures in the reverse-synthetic sense. This method became known as *retrosynthetic* or *antithetic* analysis and its merits and power is evident from the way it has simplified and accelerated the planning process of synthetic routes and from the explosion in the number of natural products synthesised over the last few decades.[1]

Retrosynthetic analysis is a problem solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simpler structures along a pathway that ultimately leads to simple or commercially available starting materials. The application of a transform, the exact reverse of a synthetic reaction, to a target structure, accomplishes the transformation of a molecule to a synthetic precursor. Each structure derived antithetically from a target then itself becomes a target for further analysis. Repetition of this process eventually produces a tree of intermediates having chemical structures as nodes

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[1] Corey, E.J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, 1989.

and pathways from bottom to top corresponding to possible synthetic routes to the synthetic target.[1]

Simple homochiral starting materials, the so-called chiral building blocks obtainable from Nature, are often commercially available and have been used extensively in stereo-selective syntheses. Carbohydrates are a relatively cheap and replenishable source of homochiral compounds and are available in a variety of cyclic and acyclic forms, chain lengths and oxidation states. A possible disadvantage to their use is the sometimes excessive number of stereogenic centers. The use of carbohydrates as chiral building blocks or chirons in synthetic routes was developed by Hanessian[2] and involves the disconnection of strategic bonds in a target molecule with minimum perturbation of the stereogenic centres. A maximum overlap of functional groups, stereochemical elements and carbon framework between target (or substructure) and the chiron, is ideally sought. The basic premise of the chiron approach is to relate some aspects of functional group and stereochemistry present in the target molecule to those present in a suitable carbohydrate starting material which is to be used as a chiral template.

3.1.2 Retrosynthetic analysis of stenocarpin

The main goal of the project on stenocarpin (**12**) was to determine the absolute configuration of the spiroacetal stereogenic centre. At the outset of the project it was decided to use a model compound corresponding to rings B and C of stenocarpin (Figure 3.1) even though the subsequent conversion of this model compound to the stenocarpin structure by functional group transformation of the double bond and C-C bond formation, might not be a trivial matter. In retrosynthetic analysis this strategy would correspond to the disconnection of the C(4a)–C(5) and C(8)– C(8a) bonds to give two diastereomeric spiroacetal compounds (**82a**) and (**82b**) that are epimeric at the spiro stereogenic centre, as target molecules.

3.1.3 Retrosynthetic analysis of the 1,6-dioxaspiro[4.5]dec-8-en-10-ols.

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[2] S. Hanessian, in *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press, Oxford, 1983.

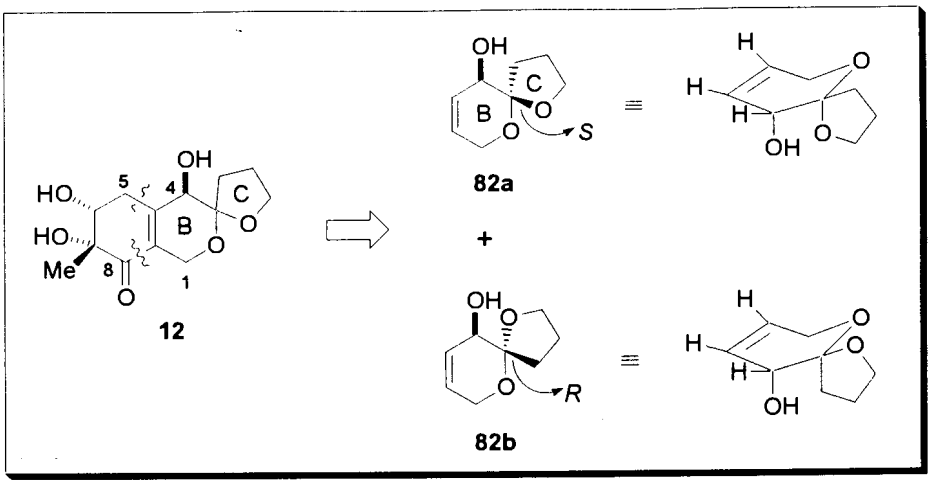

Figure 3.1: Bond disconnections in stenocarpin.

Two possible routes, which differ in the timing of the formation of the spiroacetal unit, are identified in the retrosynthetic analysis of the (5*S*,10*R*)- (**82a**) and (5*R*,10*R*)-1,6-dioxaspiro-[4.5]dec-8-en-10-ols (**82b**). The first route is outlined for the 5*S* diastereomer in Scheme 3.1. The free hydroxy group in (**82a**) is obtained from a suitably protected compound *e.g.* (**83a**) where P is a TBDPS group. It is envisaged that the double bond of (**83a**) can be formed by the Corey-Winter procedure[3] on a *cis*-diol such as (**84a**) which has the L-*arabino* configuration. Application of a protective group strategy for the exchange of protecting groups that will enable the selective protection of the *cis*-diol moiety leads to the acetonide (**85a**), which can be obtained from the tribenzyl derivative (**86**). A similar analysis can be formulated for the 5*R* series (**82b**-**86b**). Disconnection of the bond between C(5) and the oxygen in the five-membered ring of (**86**) gives the 3-hydroxypyran-1-yl derivative (**87**). The spirocyclisation reaction of the 3-hydroxypropan-1-yl side-chain in (**87**) by intramolecular hydrogen abstraction as outlined in Chapter 2, Scheme 2.3, would give an epimeric mixture of spiroacetals (**86a** and **86b**).[4] In the synthesis direction the 3-hydroxypropan-1-yl group of (**87**) is derived from the allyl group in (**88**) by a hydroboration-oxidation sequence. The disconnection of the *C*-glycoside bond in (**88**) leads to the *O*-acetyl compound (**89**) which is available from L-arabinose (**90**) following benzylation and functional group transformation at the anomeric centre.

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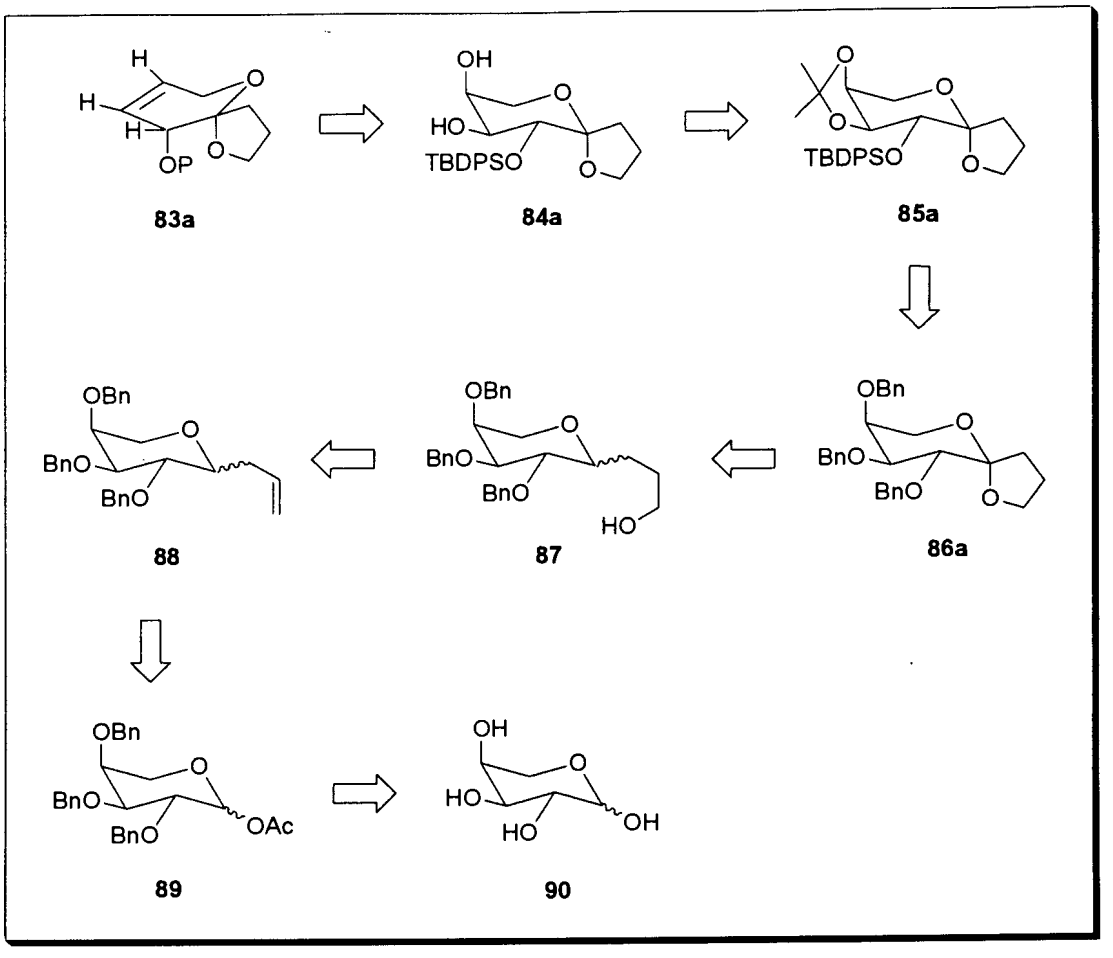
[3] E.J. Corey and R.A.E. Winter, *J. Am. Chem. Soc.*,1963, **85**, 2677.
[4] A. Martin, J.A. Salasar and E. Suarez, *J. Org. Chem.*, 1996, **61**, 3999.

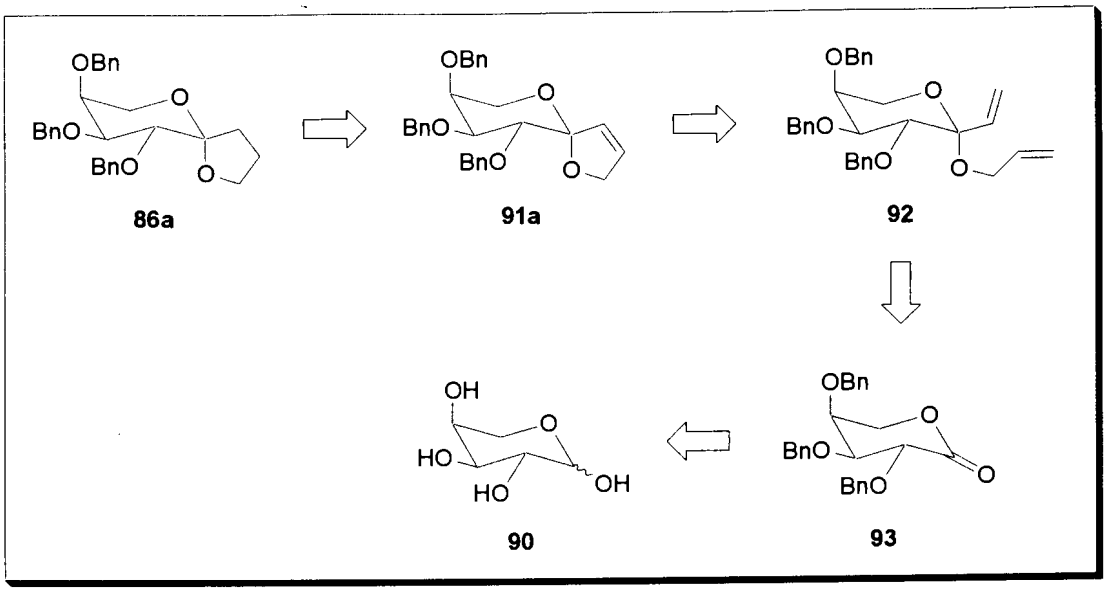


Scheme 3.1: Retrosynthetic analysis of 1,6-dioxaspiro[4.5]dec-8-en-10-ols: Route 1 (Use of *O*-benzyl groups)

An alternative retrosynthetic analysis for the spiro compound (**86**) using the ring-closing metathesis (RCM) reaction as described by van Hooft *et al.*[5] as the key methodology, is outlined in Scheme 3.2. Compound (**86a/b**) can be formed by catalytic hydrogenation of the corresponding olefin (**91a/b**). Disconnection of the double bond using the RCM transformation identifies the *C*-vinyl-*O*-allyl intermediate (**92**). The disconnection of first the *O*-glycoside and then the *C*-glycoside bond of (**92**) leads to the lactone (**93**) which in turn is obtained from L-arabinose (**90**) by introduction of the *O*-benzyl protecting groups and by oxidation at the anomeric carbon atom.

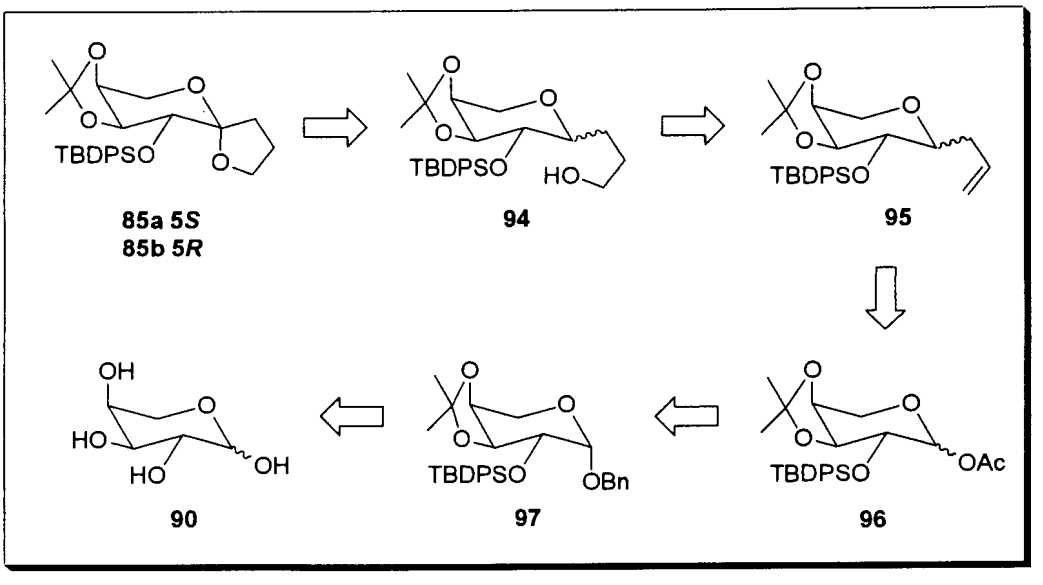
In the second route (Scheme 3.3) identified by retrosynthetic analysis, the formation of the spiroacetal moiety is seen as a late step in the synthesis and the TBDPS and acetonide

[5] P.A. van Hooft, M.A. Leeuwenburgh, H.S. Overkleeft, G.A. van der Marel, C.A.A. van Boeckel and J.H. van Boom, *Tetrahedron Lett.*, 1998, **39**, 6061.



Scheme 3.2: Alternative analysis of the spiroacetal (**86**): Use of ring-closure metathesis.

protecting groups are introduced as early as possible in the synthetic route. The two retrosynthetic analyses are identical until the common target molecule, the *O*-TBDPS O-acetonide protected spiroacetal (**85**) is obtained. The disconnection of the anomeric C–O bond in (**85**) leads to the *C*-glycoside with a 3-hydroxypyran-1-yl side-chain (**94**). In the synthetic direction the radical ring-closure reaction of (**94**) as outlined in Chapter 2.3.3 once again results in the formation of the two spiroacetal moieties (**85a**) and (**85b**). The 3-hydroxypyran-1-yl side-chain in (**94**) is obtained by a hydroboration/oxidation sequence



Scheme 3.3: Retrosynthetic analysis of the 1,6-dioxaspiro[4.5]dec-8-en-10-ols: Route 2.

from the *C*-allyl group in (**95**). Disconnection of the *C*-glycoside bond in (**95**) requires the 1-*O*-acetate (**96**) as starting material for the introduction of the *C*-allyl group by Lewis acid catalysis. Compound (**96**) is obtained by acetolysis from the protected benzyl glycoside (**97**). Sequential removal of first the TBDPS and then the acetonide protecting group leads to benzyl L-arabinopyranoside and thus to L-arabinose as starting material.

3.2 Conformational Analysis of Sugars

The two possible chair conformations of cyclohexane are indistinguishable, but the same doesn't apply for tetrahydropyran when the ring atoms are numbered since the two forms **A** and **C** are enantiomers (Figure 3.2). It is therefore necessary to adopt a nomenclature system that will distinguish between the different chair forms. A reference plane is selected which contains the maximum number of ring atoms, and superscript and subscript numbers describe the out-of-plane atoms, indicating whether these are above or below the reference plane. The convention when applied to the chair form takes the lowest-numbered carbon atom in the ring as an exoplanar atom. The reference plane, which contains four ring atoms, is thus defined, and **A** and **C**, when numbered according to the carbohydrate system for aldoses as shown, are said to have the $^{4}C_{1}$ and $^{1}C_{4}$ conformation, respectively. However, it is necessary to define which of the exoplanar atoms is to be superscript and which is to be subscript in order to accommodate the arrangement **B** obtained by rotation of **A** through 180°. The arbitrary choice is therefore made that the exoplanar atom that projects through the side of the plane of the ring from which the numbering appears clockwise is superscript.[6]

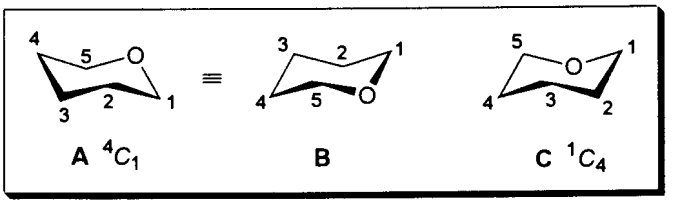


Figure 3.2: Chair conformations for the tetrahydropyran ring.

Aldopentoses *e.g.* arabinose, and aldohexoses *e.g.* glucose, possess a hemiacetal functional group at the C(1) anomeric centre, in the pyranose form. The two possible config-

[6] P. Collins and R. Ferrier, in *Monosccharides. Their Chemistry and their Roles in Natural Products*, John Wiley & Sons, New York, 1995.

urations at this stereogenic centre have been labelled as α and β. Freudenburg in 1932 developed a convention that is still used today, correlating the configuration at the anomeric centre with that of the highest numbered stereogenic centre of the sugar (marked as D or L in Figure 3.3). In the aldopentoses the α-anomer has the anomeric substituent on the same face of the ring as the C(4) hydroxy group whereas the β-anomer has these two groups on opposite faces. In the aldohexoses the α-anomer has the anomeric substituent on the opposite face of the ring to the C(5) hydroxymethyl group and the β-anomer has these two groups on the same face.[6]

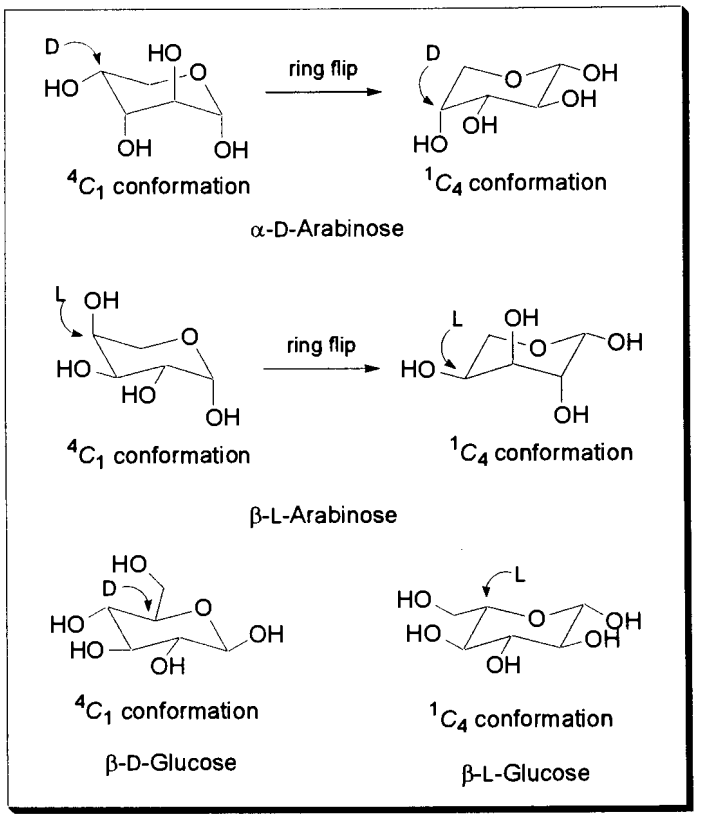


Figure 3.3: Conformational analysis of sugars.

The preferred conformation of the pyranose form of the aldopentoses and aldohexoses is dependent primarily on the substituents present in the ring, solvent and the operation of the anomeric effect (see Chapter 3.3). The conformation of a particular sugar can be deduced from the vicinal coupling constants, ^3J obtained by analysis of the proton-proton spin systems observed in the ^1H NMR spectrum: axial-axial ^3J couplings are in the range of 7-10 Hz, whereas axial-equatorial couplings are 3-5 Hz and equatorial-equatorial ones are 0-2 Hz.

3.3 The Anomeric Effect

An important feature of monosaccharide chemistry, which one has to be aware of when working in this field, is the anomeric effect.[6,7] This effect is of the greatest significance in carbohydrate chemistry, since it contributes significantly to the free energy of the sugar and hence to its preferred conformation, reactivity and also to the equilibrium mixtures of conformers. The effect is mainly caused by the interaction between the axial lone pairs of electrons on the ring oxygen atom and the antibonding σ*-orbital of the C–X bond. This leads to shortening of the bond connecting the ring oxygen atom to the anomeric center and lengthening of the C–X bond in the case of anomers with axial oxygen relative to the respective bond length in the equatorial oxygen anomer (Figure 3.4).

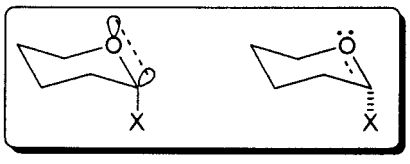


Figure 3.4: The anomeric effect

Another interpretation of the anomeric effect uses molecular orbital theory and is based on highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO-LUMO) interactions.[8] Thus, an overlap between the HOMO of the ring oxygen, the p orbital for a lone pair of electrons, and a suitably located LUMO (an antibonding σ*-orbital) of the anomeric C–X bond will increase the electron density at this carbon if the substituent group is located in an antiperiplanar position relative to the oxygen HOMO.

The result of the anomeric effect is seen in the ^{13}C chemical shift values for the anomeric carbon atom. Thus in any pair of anomeric sugars the chemical shift value of the anomeric carbon atom for the anomer with the C–X bond in an axial orientation is smaller (appears at higher field) compared to when this C–X bond is equatorial. For example, C(1) in α-D-glucose appears at δ_C 92.9 compared to δ_C 96.7 for β-D-glucose. This difference in the ^{13}C chemical shift values for the C(1) carbon atom of the two

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7 A.J. Kirby, in *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, 1983.

8 H.S. El Khadem, *Carbohydrate Chemistry. Monosaccharides and their Oligomers*, Academic Press, New York, 1988. p. 52.

anomers played a pivotal role in the conformational analysis of the intermediates obtained in the synthetic route leading to the two spiroacetal model compounds.

3.4 Synthesis of the 1,6-Dioxaspiro[4.5]dec-8-en-10-ols.

3.4.1. Route 1 (Benzyl protecting groups).

The proposed synthesis is outlined in Scheme 3.4 and uses L-arabinose (**90**) as starting material. Thus L-arabinose (**90**) was treated with benzyl alcohol in the presence of $SOCl_2$ to give a single diastereomer, benzyl β-L-arabinopyranoside (**98**) in 71% yield. The methylene protons of the benzyl group appeared as an AB-spin system at δ_H 4.663 and 3.484 with J 12.4 Hz. The C(1) proton appears at δ_H 4.777 as a doublet with J 1.5 Hz. The coupling constant is typical of an equatorial-axial arrangement between H(1) and H(2) and confirmed the β configuration at the anomeric carbon. In the ^{13}C NMR spectrum the signal for this carbon atom appeared at δ_C 98.94D.

Benzylation of the three hydroxy groups of the benzyl glycoside (**98**) to give the tetrabenzyl derivative (**99**) was achieved in 87% yield using benzyl chloride-KOH (powdered solid) in hot dioxane.[9] The ^{13}C NMR signals at δ_C 138.81S, 138.73S, 138.38S and 137.48S were assigned to the *ipso* aromatic carbon atoms of the four benzyl groups. The benzyl methylene groups appeared at δ_C 69.06T, 71.72T, 72.71T and 73.29T. The presence of four benzyl groups was also evident from an analysis of the ^1H NMR spectrum: one A_2 and three AB spin systems were found in the δ_H 4.79-4.58 region. The C(1) proton appears as a doublet ($J_{1,2}$ 3.4 Hz) at δ_H 4.943, H(2) as a double doublet ($J_{1,2}$ 3.4, $J_{2,3}$ 9.7 Hz) at δ_H 4.040 and H(3) as a double doublet ($J_{3,2}$ 9.7, $J_{3,4}$ 3.0 Hz) at δ_H 3.967. The observed *J* values are in agreement with the *trans* diaxial relationship between H(2)/H(3) and the axial-equatorial relationships between H(2)/H(1) and H(3)/H(4).

Hydrolysis of the *O*-benzyl glycoside bond in (**99**) using a 7:2 mixture of HOAc:1M HCl at 75 °C gave the tri-*O*-benzyl arabinose (**100**) as an anomeric mixture. The ratio of 1:1.3 for the α:β anomers was evident from the two signals at δ_C 94.33 and 91.93, respec-

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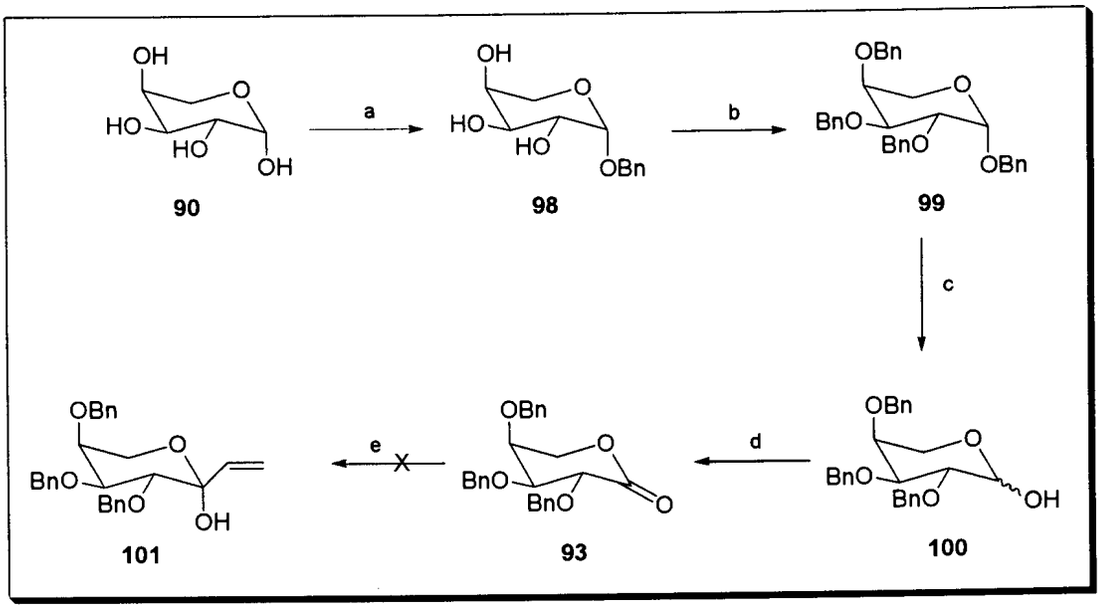
[9] C.M. McCloskey, *Advan. Carbohydrate Chem.*, 1957, **12**, 137.

tively in the ^{13}C NMR spectrum. The α- and β-anomers could not be separated by chromatography. The use of Lewis acids such as $BCl_3.SMe_2$[10] for the hydrolysis of the *O*-benzyl glycoside bond led to extensive decomposition.



Scheme 3.4: Synthesis of the spiroacetals using benzyl protecting groups (Part 1).

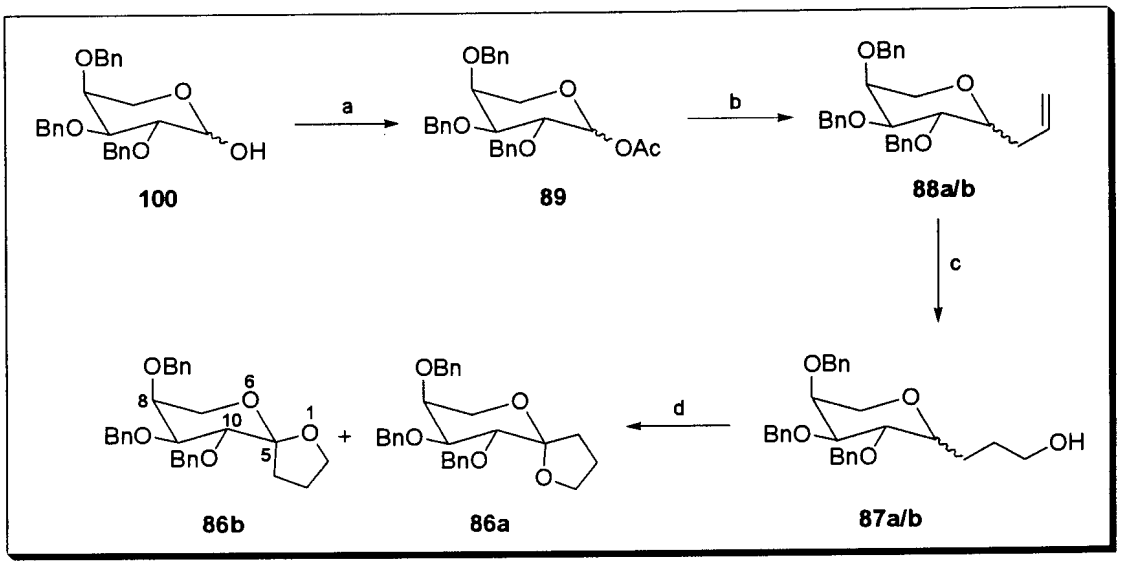
Reagents: a) $SOCl_2$, BnOH (71%); b) BnCl, dioxane, KOH (s), 70 °C, 2 h (87%); c) AcOH-1M HCl 7:2, 75 °C, 4 h (81%); d) PCC, 3Å molecular sieves, CH_2Cl_2(80%); e) $H_2C{=}CHMgBr$, THF.

The tri-*O*-benzyl arabinose (**100**) serves as the starting material for the synthetic route towards the model compounds based on ring-closing metathesis (RCM) methodology.[5] Oxidation of (**100**) using PCC in CH_2Cl_2 gave the lactone (**93**). The carbonyl carbon atom of the lactone appeared at δ_C 169.74S. The C(2) proton now appears as a doublet ($J_{2,3}$ 8.0 Hz) at δ_H 4.405 and confirmed the diaxial relationship for H(2) and H(3). The required 1*C*-vinyl–*O*-allyl moiety for the RCM methodology can be generated by reaction of a lactone with vinylmagnesium bromide to give the 1*C*-vinyl derivative which is then converted to the allyl 1*C*-vinylpyranoside. The reaction of the lactone (**93**) with vinylmagnesium bromide failed and only intractable mixtures were obtained. The reaction was unsuccessful with Grignard reagent freshly prepared from vinyl bromide and with commercial reagent. The failure of the reaction at this stage of the synthesis was disappointing and this approach had to be abandoned due to time constraints which did

[10] P.G. Williard and C.B. Fryhle, *Tetrahedron Lett.*, 1980, **21**, 3731.

not allow for a detailed investigation into the reasons for this failure. However, a viable alternative approach using once again the tribenzyl arabinose (**89**) as starting material was developed (Scheme 3.5).

In this approach the tribenzyl arabinose (**89**) was activated for a subsequent *C*-glycosidation reaction by conversion of the C(1) hydroxy group to an acetoxy group by reaction with acetic anhydride in pyridine to give (**89**). The ^{1}H and ^{13}C NMR spectra clearly showed the presence of both the α- and β-anomers in the ratio of 1.2:1.0 as expected. The ^{13}C signals for the anomeric carbon C(1) appeared at δ_C 93.92S (α) and 91.25S (β) whereas the C(1) protons of the α-anomer appeared at δ_H 5.634d ($J_{1,2}$ 6.3 Hz) and that of the β-anomer at δ_H 6.357d ($J_{1,2}$ 3.4 Hz).



Scheme 3.5: Synthesis of the spiroacetals using benzyl protecting groups (Part 2).

Reagents: a) Ac_2O, pyridine (75%); b) $H_2C{=}CHCH_2SiMe_3$, $BF_3.OEt_2$ (84%); c) i. $BH_3.SMe_2$, THF, ii. 3M NaOH, 30% H_2O_2 (69%); d) DIB/I_2, cyclohexane, hν (64%).

The *C*-allylation of the tri-*O*-benzyl-L-arabinopyranosyl acetate (**89**) followed the method described by Kishi[11] using allyltrimethylsilane and $BF_3.OEt_2$ to give compound (**88**) in 84% yield as a 1:7 diastereomeric mixture. Under the reaction conditions the pyranosyl acetate is converted to a tetrahydropyran oxonium ion which undergoes preferential (β)

[11] M.D. Lewis, J.K. Cha and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 4976.

axial nucleophilic attack due to the anomeric effect from the ring oxygen, to give the *C*-allyl product (**88a**) which is shown in the assumed $^1C_4$ conformation in figure 3.4. The correct assignment of the stereochemistry was done by analysis of the proton-proton connectivity pattern in the 500 MHz ^{1}H NMR spectrum. The observed spin-spin coupling constants for the ring protons established the preferred $^1C_4$ conformation for (**88a**) (Figure 3.4): $J_{1,2}$ 1.6, $J_{2,3}$ 3.9, $J_{3,4}$ 2.7, $J_{4,5ax}$ 10.6, $J_{4,5eq}$ 5.0 Hz. The $^4C_1$ conformer has a diaxial relationship for the C(2) and C(3) protons and only axial-equatorial relationships for H(4) and H(5ax) and H(5eq) and the expected *J* values for these relationships do not match the observed ones. In fact the spin-spin coupling constants observed for the minor product obtained from the reaction the α-*C*-allyl derivative (**88b**) are in complete agreement with a $^4C_1$ conformation: $J_{1,2}$ 9.3, $J_{2,3}$ 9.3, $J_{3,4}$ 3.4, $J_{4,5ax}$ 2.3, $J_{4,5eq}$ 1.3 Hz. It would appear that the steric strain between the axial 1-*C*-allyl group and the equatorial C(2) benzyloxy group in the initially-formed $^4C_1$ conformer of (**88a**) is relieved through a ring-flip to the $^1C_4$ conformation even though this conformer has two axial benzyloxy groups that participate in 1,3 diaxial interactions.

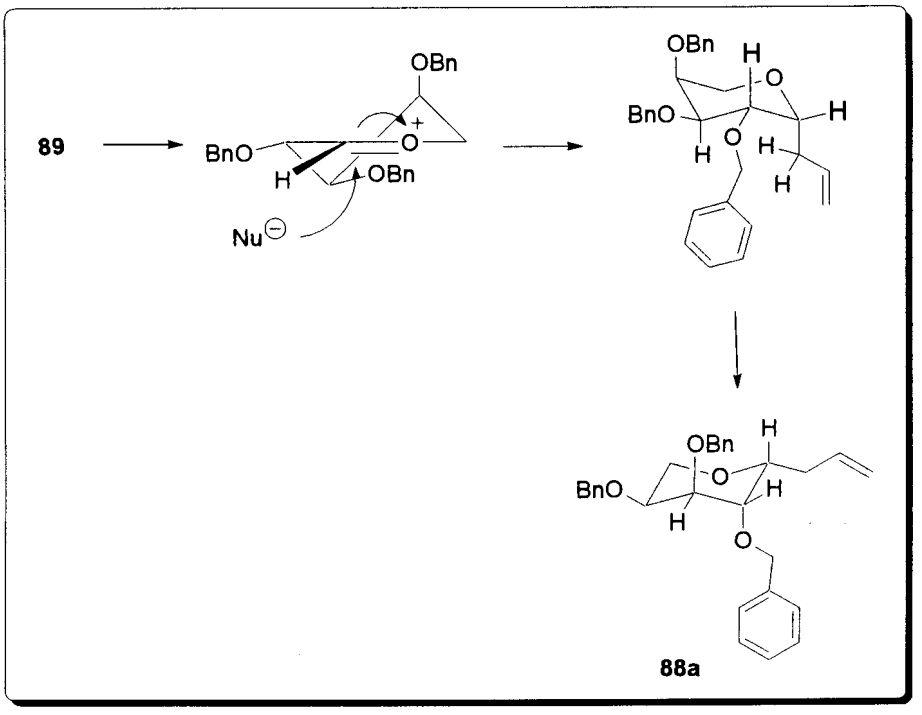


Figure 3.4: Conformational change observed in the *C*-glycoside formation.

In the normal course of the synthesis the 1-*C*-allyl diastereomeric mixture (**88**) was used as such in the hydroboration/oxidation step: thus treatment of (**88**) with $BH_3.SMe_2$

followed by addition of 3M NaOH and H_2O_2, a protocol described by Nicolaou *et al.*[12] gave the primary alcohol (**87**) without affecting the 1:7 α:β ratio. Once again a small sample of the diastereomeric mixture was separated by chromatography and each of the alcohols (**87a**) and (**87b**) analysed by NMR spectroscopy. Analysis of the proton-proton coupling constants established as expected the $^1C_4$ conformation for the β-anomer (**87a**) and the $^4C_1$ conformation for the α-anomer (**87b**).

The spirocyclisation reaction of the 3-hydroxypropan-1-yl side-chain in (**87**) is initiated by the formation of an alkoxy radical (**A**) (Figure 3.5) when (**87**) is irradiated with a 300W tungsten-filament lamp for 45 min in the presence of diacetoxyiodobenzene and iodine. The intramolecular hydrogen abstraction by this alkoxy radical proceeds through a six-membered transition state and places the radical at C(1) of the tetrahydropyran ring (**B**). The loss of an electron from (**B**) generates the oxonium intermediate (**C**) which then undergoes ring closure by attack of the hydroxy group at C(1) to give a mixture of the two C(5) epimeric dioxaspiro[4.5]decanyl derivatives (**86a**) and (**86b**) were formed in a 1.2:1.0 ratio and 62% yield.

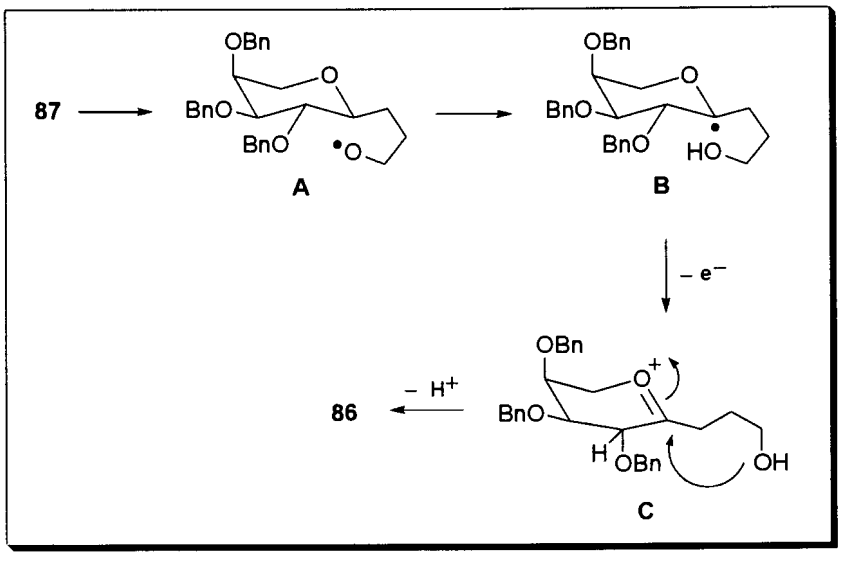


Figure 3.5: Mechanism of spirocylisation by intramolecular hydrogen abstraction.

The two C(5) epimers (**86a**) and (**86b**) could be separated by chromatography and their absolute configuration established by extensive ^1H and ^{13}C NMR experiments. Analysis

[12] K.C. Nicolaou, D.A Nugiel, E. Coulaourros and C.-K. Hwang, *Tetrahedron*, 1990, **46**, 4517,

of the proton-proton spin systems for (**86b**) provided the coupling constants that clearly illustrated that the compound exists in the $^4C_1$ conformation: $J_{9,10}$ 8.3, $J_{8,9}$ 3.4, $J_{7ax,8}$ 4.9, $J_{7eq,8}$ 2.3 Hz. A similar analysis of the epimer (**86a**) was complicated by the chemical equivalence of the C(7) protons in the ^{1}H NMR spectrum. However the values for the coupling constants for the C(10) and C(9) protons, $J_{9,10}$ 10.0 and $J_{8,9}$ 3.1 Hz are consistent with the proposed $^4C_1$ conformation. The NOE connectivity pattern for (**86a**) and (**86b**) established the absolute configuration as 5*S* and 5*R*, respectively and is in agreement with the proposed $^4C_1$ conformation for both these two compounds. The most informative interactions with the C(4) protons are illustrated in Figure 3.6. The observed ^{13}C chemical shift value for the spiro carbon atom in (**86a**) (δ_C 108.29S) and in (**86b**) (δ_C 109.49S) is consistent with the respective axial and equatorial orientations of the C–O bond in the two compounds.

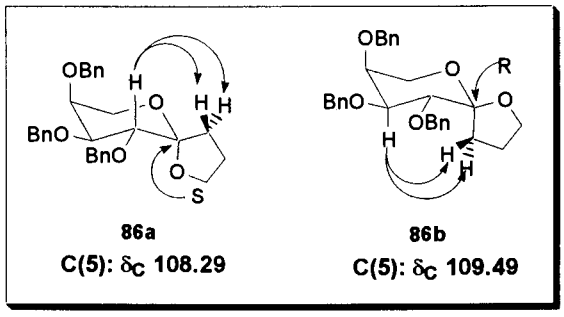
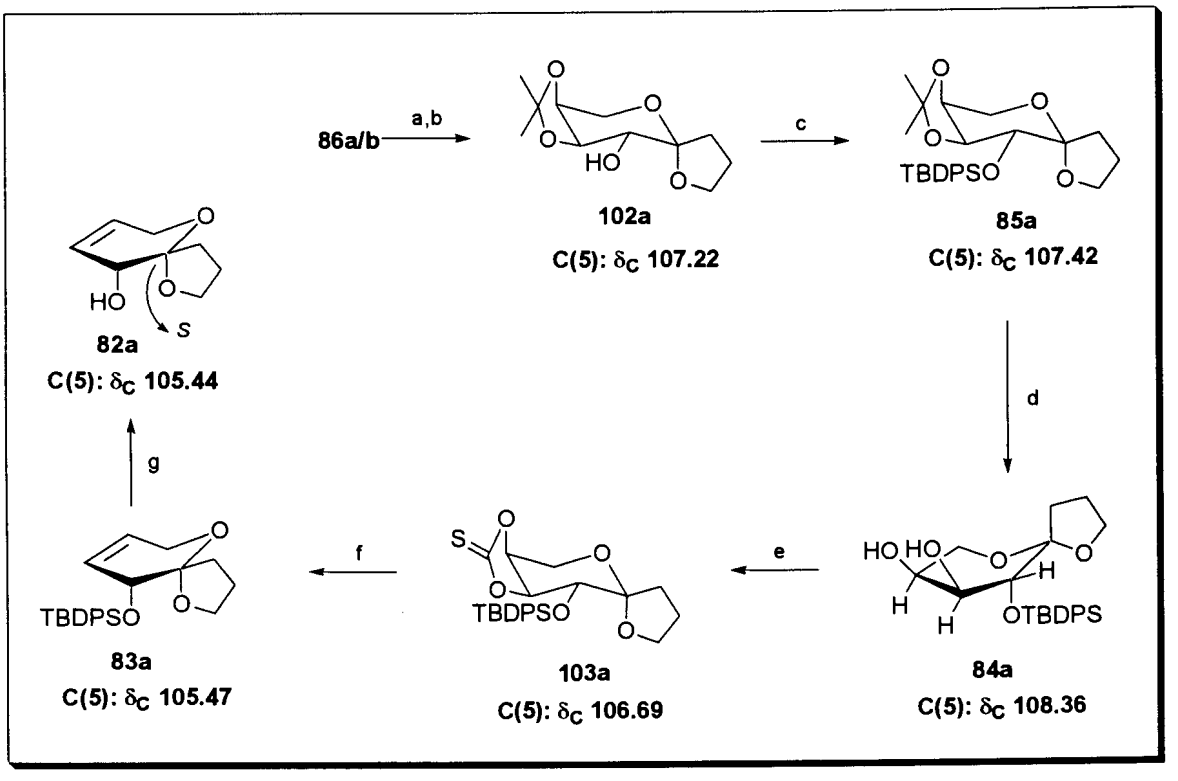


Figure 3.6: NOE data for the spiroacetal compounds.

Benzyl ethers are efficiently cleaved by a variety of reagents. Catalytic hydrogenation using 10% Pd-C or a catalytic hydrogen transfer reaction using $Pd(OH)_2$ and cyclohexene are among the best methods. In the present study the hydrogen transfer method for the deprotection of the benzyl-protected spiroacetals (**86**) was found to be more efficient as the reaction was faster. It is, however, of vital importance to remove the stabilizer that is present in commercial samples of cyclohexene, the hydrogen donor in the reaction. The tri-*O*-benzyl dioxaspiro[4.5] compounds (**86a**) or (**86b**) (Scheme 3.6), initially in separate experiments, were dissolved in ethanol and cylohexene in the presence of a catalytic amount of $Pd(OH)_2$. After refluxing for 4 h the catalyst was removed by filtration and the crude triol product, due to its polar nature, was converted to the acetonide derivative (**102a**) using 2,2-dimethoxypropane and *p*-toluenesulfonic acid as catalyst for the

transacetalisation reaction. In each case the same single diastereomer (**102a**) was formed in 75% yield. In subsequent debenzylation reactions the anomeric mixture of (**86**) was used.



Scheme 3.6: Synthesis of the (5*S*)-1,6-dioxaspiro[4.5]dec-8-en-10-ol (**82a**).

Reagents: a) $Pd(OH)_2$-C, cyclohexene, EtOH; b) 2,2-Dimethoxypropane, TsOH (75% for 2 steps); c) TBDPS-Cl, imidazole, DMAP, CH_2Cl_2 (92%); d) aq. MeOH, TsOH (83%); e) 1,1′-thiocarbonyldiimidazole, CH_3CN (96%); f) $(MeO)_3P$, reflux (68%); g) TBAF, THF (77%).

The configuration of the acetonide (**102a**) was deduced once again by analysis of the proton-proton spin systems and NOEs observed in its ^1H NMR spectrum. The C(10) proton appeared at δ_H 3.649 (dd, $J_{9,10}$ 7.5, $J_{10,OH}$ 7.6 Hz) and served as starting point in the analysis. The connectivity pattern of the protons was deduced from the cross-peaks in the COSY spectrum and the subsequent analysis of the spin systems provided the chemical shift values and coupling constants for the protons of the tetrahydropyran ring *viz.* H(9) δ_H 4.058 (dd, $J_{9,10}$ 7.5, $J_{8,9}$ 5.7 Hz), H(8) δ_H 4.142 (ddd, $J_{8,9}$ 5.7, $J_{7ax,8}$ 2.6, $J_{7eq,8}$ 1.0 Hz), H(7ax) δ_H 3.962 (dd, $J_{7ax,7eq}$ 13.3, $J_{7ax,8}$ 2.6 Hz), H(7eq) δ_H 3.884 (dd, $J_{7ax,7eq}$ 13.4, $J_{7eq,8}$ 1.0 Hz). The *J* values established the $^4C_1$ conformation for (**102a**). The 5S configuration followed from the NOEs observed between the C(10) and C(4) protons

which established that the anomeric C–O bond is in the axial position (Figure 3.7). The methyl groups of the acetonide group appeared as singlets at δ_H 1.299 (*Re* methyl group) and 1.480 (*Si* methyl group). The assignments followed from the NOE observed between the signal at δ_H 1.480 and the C(10) proton.

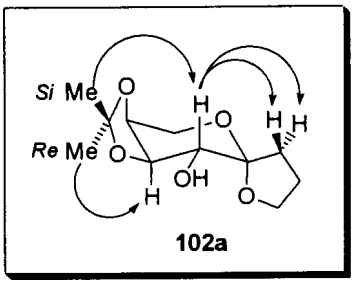


Figure 3.7: Partial NOE connectivity pattern for the 5*S* spiroacetal acetonide (**102a**).

The signals of the acetal carbon atoms in (**102a**) appeared as singlets at δ_C 109.04 and 107.22 [C(5)] in the ^{13}C NMR spectrum. The assignment of the δ_C 109.04 signal to the acetal carbon atom of the dioxolane ring is based on the correlation observed between the signals for the protons of the acetonide methyl groups and the signal for this carbon atom in the HMBC spectrum.

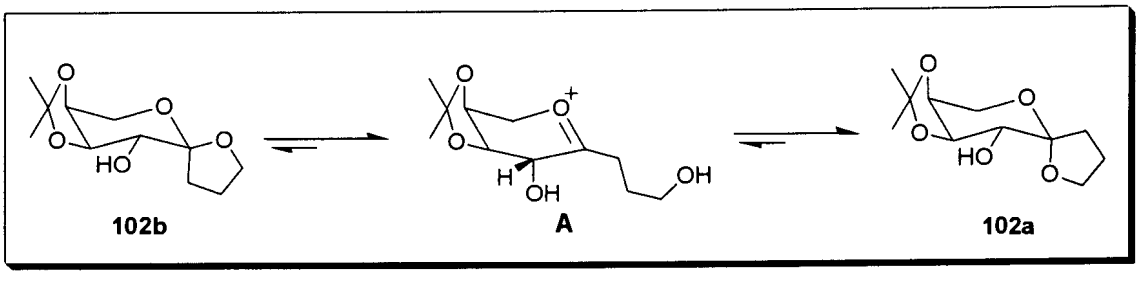


Figure 3.8: Acid-catalysed isomerisation.

It is evident that under the conditions employed for the acid-catalysed formation of the acetonide derivative, the (5*R*)-spiroacetal moiety (*i.e.* the one with the C–O bond of the tetrahydrofuran ring in the equatorial position) of (**102b**) is converted to the thermo-dynamically more stable (5*S*) spiroacetal of (**102a**). This acid-catalysed isomerisation involves the protonation of the furanose oxygen atom and subsequent ring-opening using the lone pair electrons of the oxygen of the tetrahydropyran ring to give the oxonium ion

intermediate **A** in Figure 3.8. Ring closure is then driven by the anomeric effect to give preferentially the (5*S*) spiroacetal.

A protection–deprotection strategy was used next in the synthesis in order to convert the acetonide protected 8,9-*cis*-diol group into an 8,9-olefin. As a first step the C(10) hydroxy group of (**102a**) was converted to the *t*-butyldiphenylsilyl (TBDPS) ether (**85a**) in 92% yield by treatment with TBDPS-Cl and imidazole as reported by Hanessian *et al.*[13] The presence of the TBDPS group in (**85a**) was evident from the ^{1}H and ^{13}C NMR spectra: the protons of the *t*-butyl group appeared as a singlet at δ_H 1.092 (9H) and the carbon atoms at δ_C 19.75S and 26.55Q. The acid-stability of the TBDPS protecting group allowed for the acid-catalysed cleavage of the acetonide group of (**85a**) in aqueous methanol and a catalytic amount of TsOH to give the diol (**84a**) in 83% yield. The analysis of the spin systems in the ^{1}H NMR spectrum in order to establish the conformation of the tetrahydropyran ring proved difficult as a result of the chemical shift equivalence of the C(9) and C(10) protons. The C(7) protons appeared at δ_H 3.831 (ddd, *J* 12.6, $J_{7a,OH}$ 1.6, $J_{7a,8}$ 1.5 Hz) and 3.548 (dd, *J* 12.6, 1.7 Hz) and H(8) was a broad unresolved multiplet with $w_{½}$ ~ 6Hz. The *J* values preclude both the $^1C_4$ and $^4C_1$ conformations as neither one of the C(7) protons nor the C(8) proton would be in a diaxial relationship with *J* 9-10 Hz. The proton of the C(8) hydroxy group appeared as a double doublet ($J_{8,OH}$ 2.8, $J_{7a,OH}$ 1.6 Hz) at δ_H 2.349 and that of the C(9) hydroxy group at δ_H 1.973 (dd, $J_{9,OH}$ 2.4, *J* 2.4 Hz). These signals disappeared upon addition of D_2O to the sample, the signal at δ_H 3.831 changed to a double doublet and the overlapping H(9) and H(10) signals were simplified but still not amenable to first-order analysis. It would appear as if the tetrahydropyran ring adopts a boat or distorted boat conformation as a result of hydrogen-bonding between the two *cis* hydroxy groups. The NOEs observed between the C(10) proton and the two C(4) protons in a ROESY experiment are consistent with a boat conformation (Figure 3.9). The spiroacetal carbon atom C(5) appeared at δ_C 108.36S in the ^{13}C NMR spectrum.

The problems associated with the analysis of the spin systems were resolved by a change of solvent from $CDCl_3$ to DMSO-d_6 but at a price. All the signals were well resolved in

[13] S. Hanessian and N.R. Plessas, *J. Org. Chem.*, 1969, **34**, 1035.

the ^{1}H NMR spectrum at 500 MHz but it was evident from the coupling constants that the tetrahydropyran ring in (**84a**) exists in the $^4C_1$ conformation in DMSO-d_6: $J_{9,10}$ 9.5, $J_{8,9}$ 3.6, $J_{7ax,8}$ 2.2, $J_{7eq,8}$ 1.0, $J_{7ax,7eq}$ 12.2 Hz. The proton of the C(9) hydroxy group resonated as a sharp doublet at δ 3.855 ($J_{9,OH}$ 7.3 Hz) and that of the 8-OH at δ 4.498 ($J_{8,OH}$ 3.5, $J_{8,7eq}$ 1.0 Hz) as hydrogen exchange is slower in DMSO between the two *cis* hydroxy groups. The spiroacetal carbon atom C(5) appeared at δ_C 107.99S in the ^{13}C NMR spectrum.

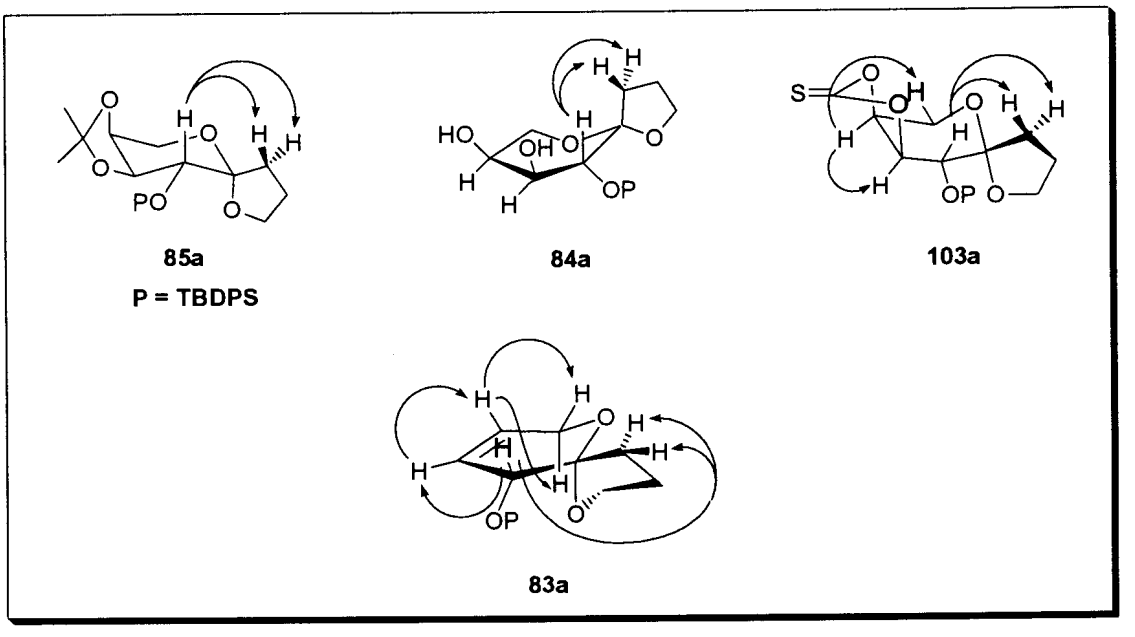


Figure 3.9: NOE connectivity pattern of the 5*S* spiroacetals.

The *cis*-diol (**84a**) was converted quantitatively to the cyclic thiocarbonate (**103a**) by reaction with 1,1′-thiocarbonyldiimidazole in acetonitrile at room temperature for 5 h. The signals at 190.77S and 106.69S in the ^{13}C NMR spectrum were assigned to the thionocarbonate carbon and the spiroacetal carbon atom, respectively. The $^6H_1$ chair conformation was deduced from the *J* values for the protons of the tetrahydropyran ring in the ^{1}H NMR spectrum and especially the C(10) proton at 3.743, a doublet with $J_{9,10}$ 7.2 Hz, and H(9) and H(8) at δ_H 5.033 (dd, $J_{9,10}$ 7.2, $J_{8,9}$ 7.0 Hz) and δ_H 4.798 (ddd, $J_{7ax,7eq}$ 14.2, $J_{7ax,8}$ 2.3, $J_{7eq,8}$ 1.0 Hz. This result was confirmed by the NOEs between H(10) and both the C(4) protons (Figure 3.9).

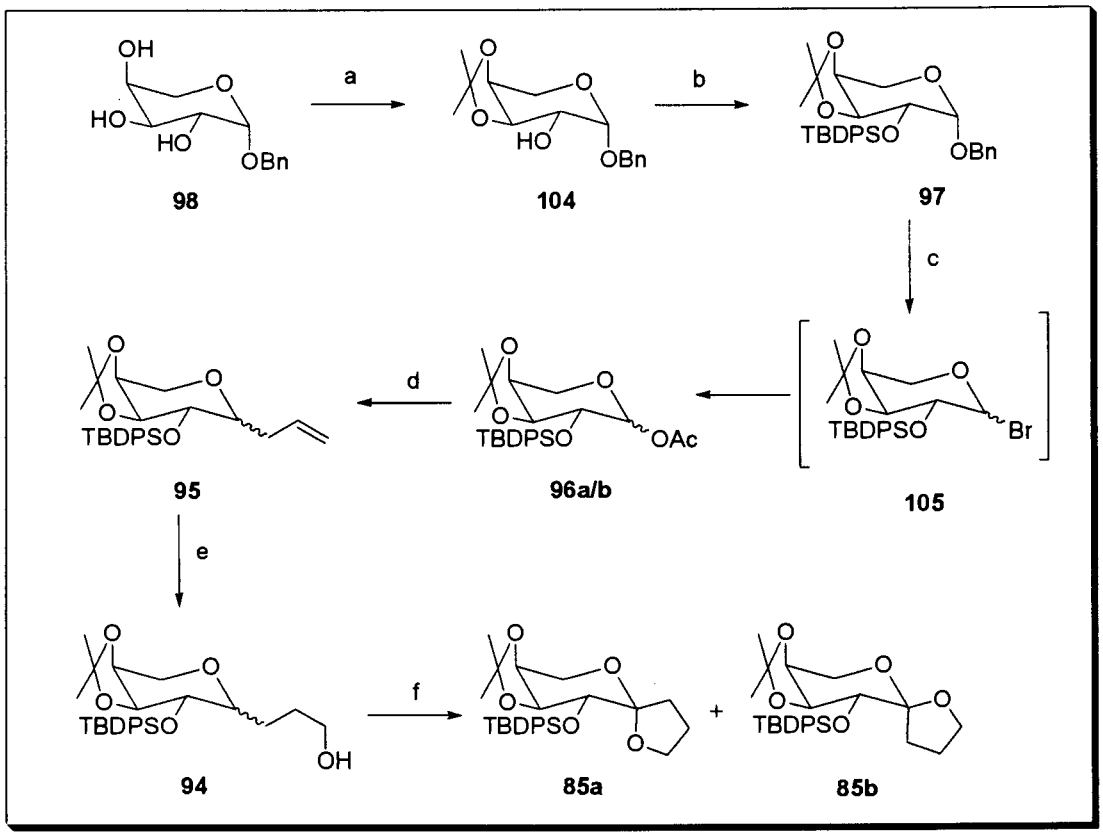
Cyclic thiocarbonates such as (**103a**) can be converted to olefins using the Corey-Winter procedure.[3.14] The reaction involves a *syn* stereospecific elimination and is best carried out on *cis*-1,2-diols when this moiety is present in a six-membered ring. Thus (**103a**) was refluxed in trimethyl phosphite for 24 h under argon to give the olefin (**83a**). A feature of the ^{1}H NMR spectrum of (**83a**) was the extensive allylic and homoallylic coupling observed for the protons of the dihydropyran ring. The small difference in chemical shift values for H(8) (δ_H 5.630m) and H(9) (δ_H 5.651m) in $CDCl_3$ made a first-order analysis of the spectrum impossible. A better resolved ^{1}H spectrum was obtained in C_6D_6. The coupling constant of 10.3 Hz for the olefinic protons at δ_H 5.817 [($J_{8,9}$ 10.3, and J 2.6, 1.8, 1.8 Hz, H(9)] and δ_H 5.384 [($J_{8,9}$ 10.3, and J 3.6, 1.8, 1.8 Hz, H(8)] is characteristic of the *Z* configuration. The C(7) protons appeared as complex multiplets at δ_H 4.323 ($J_{7a,7b}$ 16.6, and J 3.8, 2.7, 1.8 Hz) and δ_H 3.837 ($J_{7a,7b}$ 16.6, and J 3.0, 2.1, 2.1 Hz). The C(10) proton appeared as a complex multiplet at δ_H 4.845. The NOE connectivities for the sample in $CDCl_3$ are shown in Figure 3.9 and are in agreement with a boat or half-chair conformation and the assignment of the 5*S* configuration *i.e.* with the furanose C–O in the axial position. The signal for the spiroacetal carbon atom appeared at δ_C 105.47S in (**83a**) and confirms the above assignment as the C(5) signal for the 5*R* spiroacetal compound (**83b**), prepared simultaneously via Route 2 as reported in Chapter 3.4.2 below, appeared at δ_C 107.58S. The result is consistent with the finding that the anomeric carbon atom with an axial C–O bond appears at higher field strength (smaller δ_C values) than the one with an equatorial C–O bond due to the operation of the anomeric effect.

The final step in the synthesis involved the cleavage of the TBDPS group in (**83a**) with TBAF to give the alcohol (**82a**) in 77% yield. The signal of the C(5) spiroacetal carbon at δ_C 105.44S in the ^{13}C NMR spectrum in conjunction with the signal observed for C(5) in (**82b**) (δ_C 107.34S) as well as the same comparison for compounds (**83a**) and (**83b**), established the 3*S* absolute configuration for stenocarpin (**12**) and its derivatives (**13**) and (**14**).

3.4.2 Route 2 (Acetonide and TBDPS protecting groups)

[14] E.J. Corey, F.A. Carey and R.A.E. Winter, *J. Am. Chem. Soc.*, 1965, **87**, 934.

As reported in Chapter 3:4.1 above only the 5S spiroacetal model compound (**83a**) is formed by Route 1. The investigation of an alternative synthetic route that would provide samples of both the 5*S* (**83a**) and 5*R* (**83b**) spiroacetal diastereomers was carried out in parallel with Route 1 and is outlined in Scheme 3.7. In this approach the acetonide and TBDPS protecting groups are installed prior to the formation of the spiro ring system.



Scheme 3.7: Synthesis of the spiroacetals using acetonide and TBDPS protecting groups.

Reagents: a) 2,2-Dimethoxypropane, TsOH (68%); b) TBDPS-Cl, imidazole, DMAP, CH_2Cl_2 (90%); c) i. NBS, HMPA, $BaCO_3$, CCl_4, reflux; ii. AcOH, NaOAc (83%); d) $H_2C{=}CHCH_2SiMe_3$, $BF_3.OEt_2$, CH_3CN (66%); e) i. $BH_3.SMe_2$, THF, ii. 3M NaOH, 30% H_2O_2 (70%); f) DIB/I_2, cyclohexane, hν (60%).

The *cis*-diol group in *O*-benzyl β-L-arabinopyranoside (**98**) was protected as the acetonide by acid-catalysed transacetalisation using 2,2-dimethoxypropane and TsOH to give the acetonide (**104**). The remaining C(2) hydroxy group was then protected as the TBDPS ether using TBDPS-Cl and imidazole to give (**97**). Both the acetonide and TBDPS groups are incompatible with the reaction conditions used for the cleavage of the benzyl

glycoside bond in Route 1 *viz.* 1M HCl in HOAc and it was decided to use NBS instead. A solution of the protected benzyl glycoside (**97**) in CCl_4 containing HMPA was treated with NBS in the presence of $BaCO_3$ (an acid scavenger). The reaction proceeds *via* a radical mechanism to give the arabinopyranosyl bromide (**105**) as intermediate which was converted *in situ* to a 1:8 α:β anomeric mixture of the 1-*O*-acetyl compound (**96**) by addition of an excess of sodium acetate in acetic acid. This mixture could be separated by chromatography although this is not strictly necessary for the following steps in the synthetic route. The α-isomer can be easily identified by ^1H NMR as the coupling constant, $J_{1,2}$ of 7.5 Hz for H(1) (δ_H 5.543) and H(2) (δ_H 3.735) is typical for *trans* diaxial protons. In contrast the coupling constant of 3.6 Hz for H-1 (δ_H 4.734) and H(2) (δ_H 3.789) of the β-isomer corresponds to an equatorial-axial orientation. The signal for the C(1) carbon atom appears at δ_C 94.04S for the α-isomer whereas that of the β-isomer resonates at δ_C 91.27S.

The *C*-allylation of the anomeric mixture of the protected L-arabinopyranosyl acetate (**96**) followed the method described by Kishi[11] using allyltrimethylsilane and $BF_3.OEt_2$ to give compound (**95**) as a 1:1 C(1) epimeric mixture. The difference in this ratio compared to the 1:7 α:β ratio observed for the benzyl protected analogue (**88**) is rationalised in terms of restricted conformational mobility that arises from the presence of the acetonide group as well as the steric bulk of the TBDPS ether. Under the reaction conditions the pyranosyl acetate (**96**) is converted to a tetrahydropyran oxonium intermediate, which undergoes preferential (β) axial nucleophilic attack due to the anomeric effect from the ring oxygen, to give the *C*-allyl product. In the case of a C(2) benzyloxy group as in (**88**) the steric strain arising from axial nucleophilic attack can be relieved through a ring-flip to a $^1C_4$ conformer (**88a**). In the present case the steric strain introduced by the C(2) OTBDPS group to axial β-attack, favoured by the anomeric effect, is much greater and can only be relieved once again by a conformational change. Axial α-attack is sterically and thus energetically less demanding and formation of the C(1) α-epimer is favoured leading to the observed 1:1 α: β ratio.

The analysis of the ^{1}H NMR spectrum of the mixture of anomers (**95**) is complicated by overlap of signals but it was possible to identify the resonances of each of the anomers using COSY and HETCOR experiments. Analysis of the spin systems for the α-anomer (**95b**) is complicated by the overlap of the C(3) and C(4) proton signals. However, the coupling constants obtained from the analysis for the other protons *viz.* $J_{1,2}$ 9.3, $J_{4,5eq}$ 1.8, $J_{4,5ax}$ ~0, $J_{5ax,5eq}$ 13.2 Hz, are consistent with a $^4C_1$ conformation. In contrast the coupling constants for the β-anomer (**95a**) point to a half-chair conformation, $^1H_6$: $J_{1,2}$ 2.3, $J_{2,3}$ 3.3, $J_{3,4}$ 5.7, $J_{4,5a}$ 5.2, $J_{4,5b}$ 6.5, $J_{5a,5b}$ 11.9 Hz (Figure 3.10).

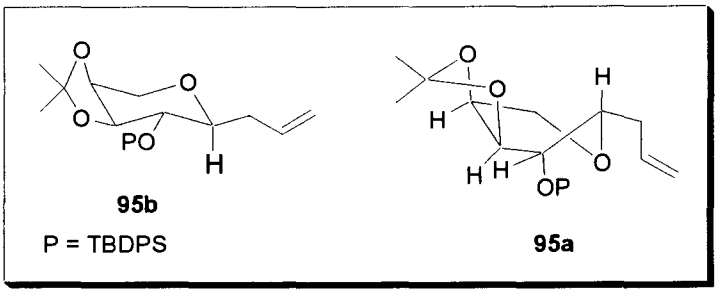


Figure 3.10: Conformations for the 1-*C*-allyl anomers.

The 1-*C*-allyl diastereomeric mixture (**95**) was used as such in the hydroboration/oxidation step: treatment of (**95**) with $BH_3.SMe_2$ followed by addition of 3M NaOH and H_2O_2, gave the primary alcohol (**94**) with the same 1:1 α:β ratio.

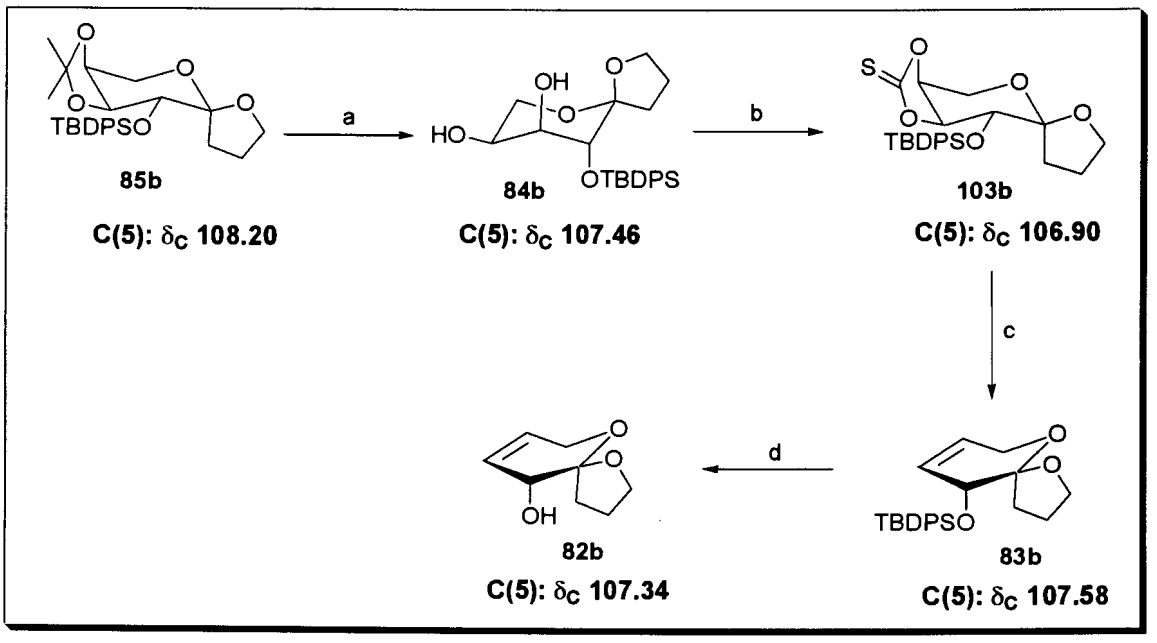
The spirocyclisation reaction of the 3-hydroxypropan-1-yl side-chain of the anomeric mixture (**94**) involves an intramolecular hydrogen abstraction and occurs when the alcohol (**94**) is irradiated with a 300 W tungsten-filament lamp for 45 min in the presence of diacetoxyiodobenzene and iodine. A mixture of the two C(5) epimeric dioxaspiro-[4.5]decanyl derivatives (**85a**) and (**85b**) were formed in a 1.0:1.7 ratio and 65% yield. The two compounds could be separated by chromatography. The configuration and conformation for each one was deduced by analysis of the proton-proton spin systems and NOEs observed in their ^{1}H NMR and ^{13}C NMR spectra. The C(10) proton in (**85a**) appeared at δ_H 3.773 (d, $J_{9,10}$ 7.2 Hz) and served as starting point in the analysis. The connectivity pattern of the protons was deduced from the cross-peaks in the COSY spectrum and the subsequent analysis of the spin systems provided the chemical shift values and coupling constants for the protons of the tetrahydropyran ring *viz.* H(9) δ_H

4.335 (dd, $J_{9,10}$ 7.2, $J_{8,9}$ 5.8 Hz), H(8) δ_H 4.155 (ddd, $J_{8,9}$ 5.8, $J_{7ax,8}$ 2.7, $J_{7eq,8}$ 1.0 Hz), H(7ax) δ_H 3.989 (dd, $J_{7ax,7eq}$ 13.2, $J_{7ax,8}$ 2.7 Hz), H(7eq) δ_H 3.812 (dd, $J_{7ax,7eq}$ 13.2, $J_{7eq,8}$ 1.0 Hz). The J values established the $^4C_1$ conformation for (**85a**). The 5S configuration followed from the NOEs observed between the C(10) and C(4) protons. A similar analysis of the spin systems for (**85b**) gave the coupling constants: $J_{9,10}$ 5.7, $J_{8,9}$ 5.4, $J_{7a,8}$ 6.1, $J_{7b,8}$ 5.1, $J_{7a,7b}$ 12.6 Hz which are indicative of the $^{2,5}B$ boat conformation This result was confirmed by the NOEs observed between H(9) and both the C(4) protons (Figure 3.11). The signals of the acetal carbon atoms in (**85a**) appeared as singlets at δ_C 108.51 and 107.56 [C(5)] and for (**85b**) at δ_C 109.20 and 108.24 [C(5)] in the ^{13}C NMR spectra. The assignment of the δ_C 108.51 and 109.20 signals to the acetal carbon atoms of the dioxolane ring in (**85a**) and (**85b**), respectively, is based on the correlation observed between the signals for the protons of the acetonide methyl groups and the signal for this carbon atom in the HMBC spectra. This long-range (^1H,^{13}C) correlation method was used to identify the acetal carbon atom of the acetonide group in all compounds.

The availability of both C(5) epimers and the assignment of the C(5) signal in their ^{13}C NMR spectra confirmed the observation that the chemical shift value of the anomeric carbon atom of the anomer with an axial C– O bond is lower relative to that of the anomer with the equatorial C–O bond: δ_C 107.56S in (**85a**) (5*S*) and δ_C 108.24S for (**85b**) (5*R*). This relationship was used to identify the presence of an anomeric axial or equatorial C–O bond in those compounds for which both anomers were available. It was for this reason that the TBDPS protecting group in a small sample of (**85b**) was cleaved by treatment with TBAF to give the alcohol (**102b**) in 79% yield. The C(5) signal appeared at δ_C 108.39S in the ^{13}C NMR spectrum compared to δ_C 107.22S for (**102a**).

Attention now turned to the conversion of the two spiroacetal compounds (**85a**) and (**85b**) to the target compounds (**82a**) and (**82b**). The sequence of reactions in the 5*S* series *i.e.* (**85a**)→(**82a**) has been described in Route 1 (see Chapter 3.4.1 above). The same sequence of reactions was used in the 5*R* series for the conversion (**85b**)→(**82b**) (Scheme3.8). Acid-catalysed cleavage of the acetonide group of (**85b**) in aqueous methanol and a catalytic amount of TsOH gave the diol (**84b**) in 83% yield. The C(5) signal appeared at δ_C 107.46S in the ^{13}C NMR spectrum [compared to δ_C 108.36S for

(**84a**)] and points to a C(5) axial C–O bond. This result indicated that a change in conformation, from a $^{2,5}B$ boat in (**85b**) to a $^{1}C_4$ chair in the diol (**84b**), occurs on cleavage of the acetonide group. The $^{1}C_4$ conformation for (**84b**) was identified by analysis of the proton spin system that yielded the following coupling constants: $J_{9,10}$ 4.0, $J_{8,9}$ 3.4, $J_{7ax,8}$ 10.5, $J_{7eq,8}$ 5.7, $J_{7ax,7eq}$ 11.4 and a w–coupling with $J_{7eq,9}$ 1.0 Hz. The 10.5 Hz coupling between the C(8) proton and one of the C(7) protons is characteristic of a *trans* diaxial arrangement for these protons. The NOEs observed between H(10) and the C(4) protons is in agreement with the proposed conformation (Figure 3.11).



Scheme 3.8: Synthesis of the 5*R* spiroacetal model compound (**82b**).

Reagents: a) aq. MeOH, TsOH (83%); b) 1,1'-thiocarbonyldiimidazole, CH_3CN (94%); c) $(MeO)_3P$, reflux (68%): d) TBAF, THF (84%).

The reaction of the *cis*-diol (**84b**) with 1,1'-thiocarbonyldiimidazole in acetonitrile resulted in the formation of the thiocarbonate derivative (**103b**) and once again a change in conformation occurs in order to accommodate the steric constraints of the 5-membered ring. The C(5) signal appeared at δ_C 106.90S compared to δ_C 106.69S for (**103a**) in the 5*S* series. The latter compound is present as the $^{6}H_1$ conformer with an axial C–O bond. It would thus appear from the chemical shift values for the C(5) spirocentre that (**103b**) also possesses an axial C–O bond. The connectivity pattern for the protons in (**103b**) was deduced from the cross-peaks in the COSY spectrum and the subsequent analysis of

the spin systems provided the chemical shift values and coupling constants for the protons of the tetrahydropyran ring *viz.* H(10) δ_H 4.001 (d, $J_{9,10}$ 4.0 Hz), H(9) δ_H 4.780 (dd, $J_{9,10}$ 4.0 $J_{8,9}$ 8.0 Hz), H(8) δ_H 4.874 (dt, $J_{8,9}$ 8.0, $J_{7,8}$ 4.6 Hz), H(7) δ_H 4.028 (d, $J_{7,8}$ 4.7 Hz). The J values established the $^1H_6$ conformation for (**103b**).

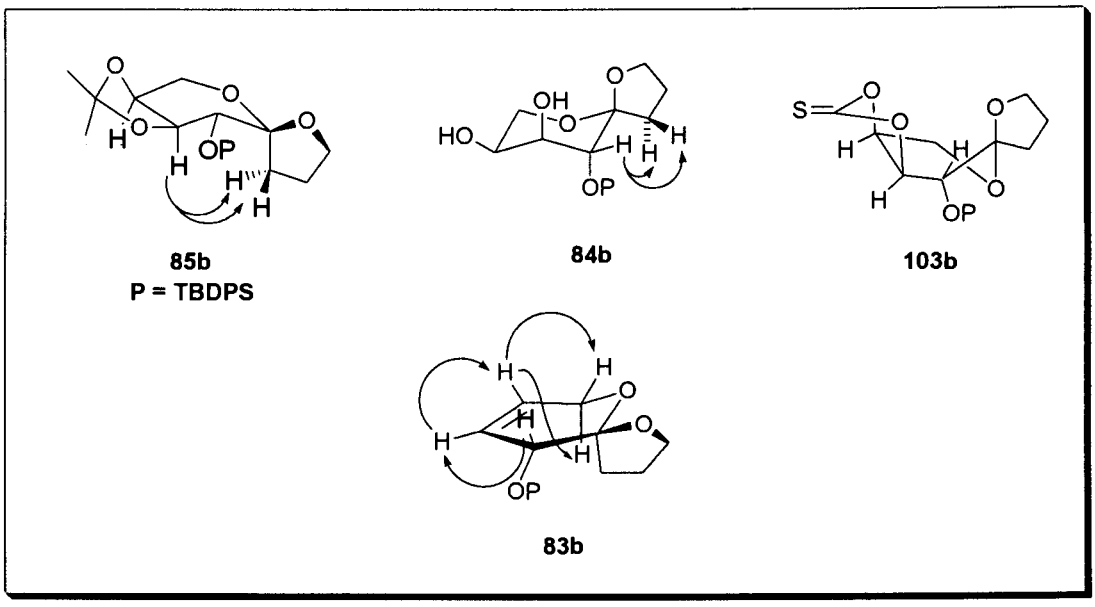


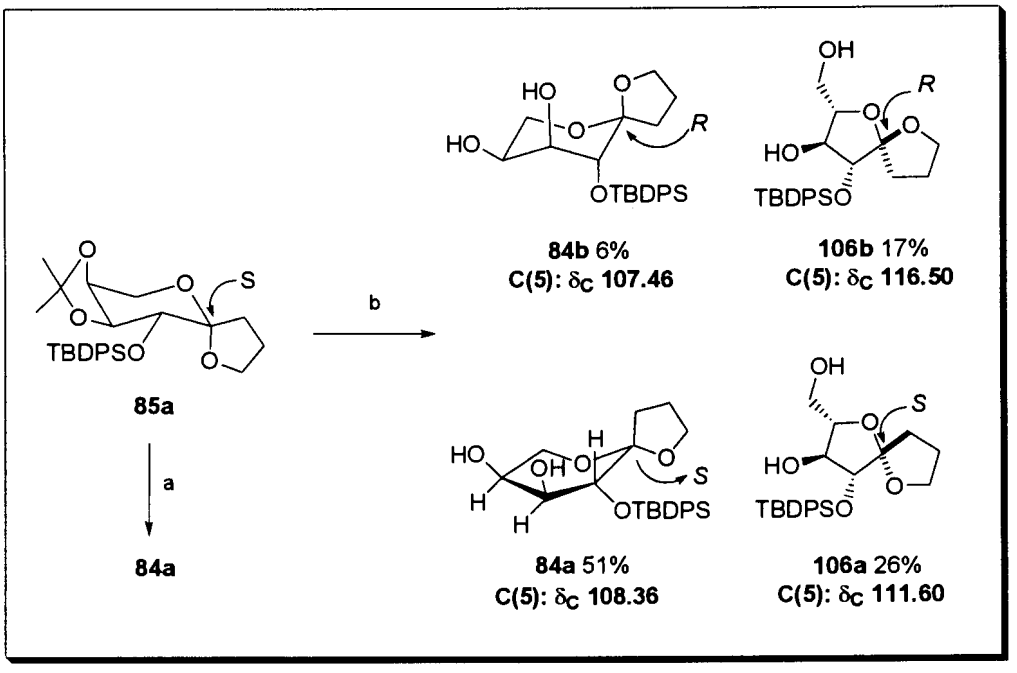
Figure 3.11: Conformations and NOE connectivities for the 5*R* spiroacetals.

The Corey-Winter procedure,[3,14] in which a solution of the thiocarbonate (**103b**) in trimethyl phosphite was refluxed for 24 h, was used to form the olefin (**83b**) in 68% yield. A feature of the ^{1}H NMR spectrum of (**83b**) was the extensive allylic and homoallylic coupling observed for the protons of the dihydropyran ring. The coupling constant of 10.4 Hz for the olefinic protons at δ_H 5.678 [H(8), dddd] and δ_H 5.462 [H(9), dddd] is characteristic of the *Z* configuration. The C(7) protons appeared as the AB part of a complex spin system with $J_{7a,7b}$ 17.1 Hz at δ_H 4.207 [(H(7a)] and δ_H 4.092 [H(7b)]. The C(10) proton appeared as a multiplet at δ_H 4.438. The coupling constants obtained from the analysis of these resonances established that extensive allylic and homoallylic coupling occurs: $J_{7a,8}$ 2.1, $J_{7a,8}$ 3.0, $J_{7a,9}$ 2.3, $J_{7b,9}$ 2.3, $J_{7a,10}$ 2.3, $J_{7b,10}$ 1.3, $J_{8,10}$ 0.8, $J_{9,10}$ 4.4 Hz. The NOE connectity pattern is shown in Figure 3.10: no NOE was observed between H(10) and the C(4) protons. The signal for the C(5) spiroacetal carbon of (**83b**) at δ_C 107.58S, when compared with δ_C 107.58S for (**83a**), points to the presence of an equatorial C–O bond in (**83b**).

The final step in the synthesis involved the cleavage of the TBDPS group in (**83b**) with TBAF to give the alcohol (**82b**). The signal of the C(5) spiroacetal carbon at δ_C 107.34S in the ^{13}C NMR spectrum in conjunction with the signal observed for C(5) in (**82a**) (δ_C 105.44S) established the 3*S* absolute configuration for stenocarpin (**12**) and its derivatives.

3.4.3 Acid-catalysed cleavage of the acetonide group.

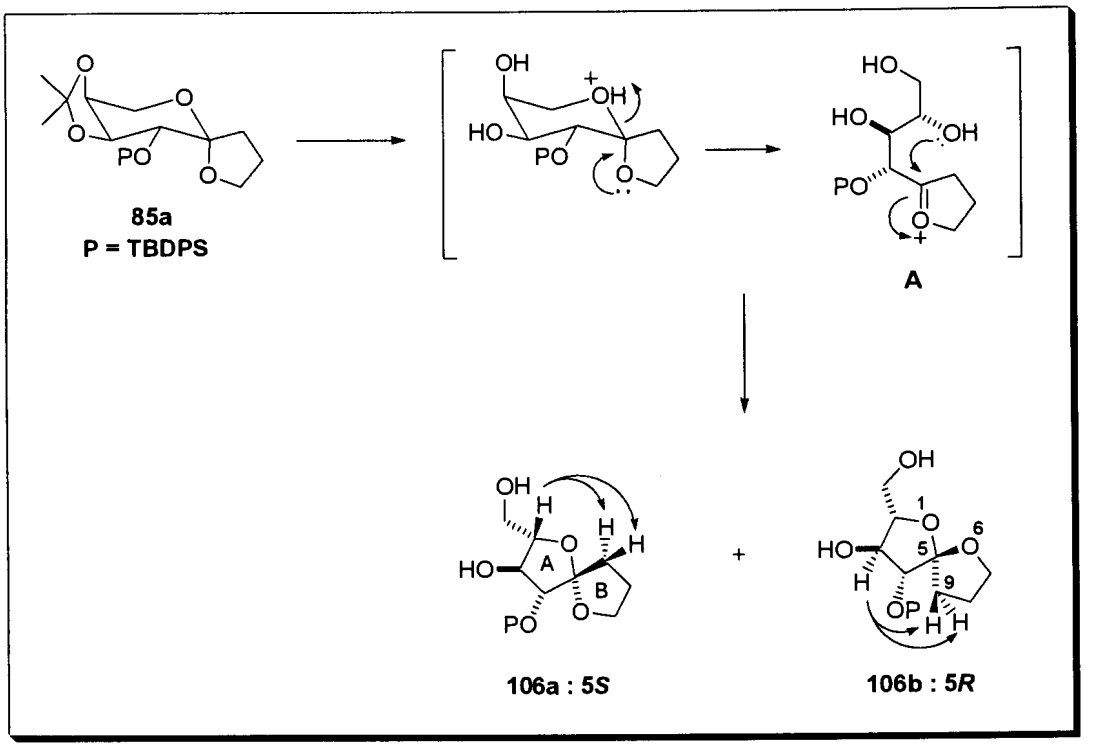
The cleavage of the acetonide protecting group in (**85a**) using TsOH in aqueous methanol gave only the diol (**84a**)(see Chapter 3.4.1). Initial studies of this reaction used only MeOH as solvent and led to the formation of an inseparable mixture of the two 1,6-dioxaspiro[4.5]decan-8,9-diols (**84a**) and (**84b**) (ratio 10:1) as the major component and two additional compounds identified as the two 1,6-dioxaspiro[4.4]nonane-3-ols (**106a**) and (**106b**) (ratio 1.4:1) as minor components in a 4:3 ratio (Scheme 3.9).



Scheme 3.9: Acid-catalysed acetonide cleavage.

Reagents: a) 5% aq.MeOH, TsOH, 6 h (83%); b) MeOH, TsOH, 6 h (77%).

The reaction proceeds by cleavage of the acetonide group to give the major diol (**84a**). Acid-catalysed isomerisation of (**84a**) involves the protonation of either the furanose or the pyranose oxygen atom. The former case has been described in Figure 3.8 and leads to the formation of a small quantity of (**84b**) and the latter is shown in Scheme 3.10. Thus protonation of the pyranose oxygen atom and subsequent ring-opening using the lone pair electrons of the oxygen of the tetrahydrofuran ring leads to the oxonium ion A. Subsequent ring-closure using the secondary hydroxy group, the C(3) hydroxy group in the side-chain of intermediate A, results in the formation of the [4.4]spiroacetals (**106a**) and (**106b**).



Scheme 3.10: Reaction mechanism and configuration analysis via NOEs

The proton connectivity pattern for the diol (**106a**) was established by analysis of the spin systems in the ^{1}H NMR spectrum and the COSY spectrum. The presence of a primary and secondary hydroxy group in (**106a**) was evident from the disappearance of the signals at δ_H 2.14 (t br) and 2.247 (d, J 9.0 Hz) upon addition of D_2O to the sample as well as the simplification of the signals for H(3) at δ_H 3.893 (dd, $J_{2,3}$ 3.5, $J_{3,4}$ 2.1 Hz) and H(10) at δ_H 3.740 (dd, $J_{10a,10b}$ 11.6, $J_{10a,2}$ 3.4 Hz) and 3.696 (dd, $J_{10a,10b}$ 11.6, $J_{10b,2}$ 4.6 Hz). The C(2) protons appeared at δ_H 3.938 (ddd, $J_{2,3}$ 3.5, $J_{10a,2}$ 3.4, $J_{10b,2}$ 4.6 Hz)

and H(4) at δ_H 4.097 (d, $J_{2,3}$ 3.5 Hz). The NOEs observed between H(2) and the C(9) protons established the 5*S* configuration for (**106a**) (Scheme 3.10). The chemical shift values for the diol (**106b**) obtained by a similar analysis are reported in Chapter 4. The coupling constants $J_{2,10a}$ 2.6, $J_{2,10b}$ 1.6, $J_{2,3}$ 6.5, $J_{3,4}$ 7.9, $J_{10a,10b}$ 12.2 Hz as well as the NOEs differ from those obtained for (**106a**). The NOEs observed for (**106b**) are between the H(3) signal at δ_H 4.468 and the C(9) protons and established the 5*R* configuration. The correlation between the coupling constants for the protons of the A-ring and the corresponding dihedral angles, together with the observed NOEs, defined the conformation of this ring in both compounds. Thus the ^1E conformation is assigned to the A-ring of (**106a**): All three substituents are in equatorial positions and the C(5)–O(6) bond is equatorial. The C(5) signal appears at δ_C 116.50S in the ^{13}C NMR spectrum. The A-ring of (**106b**) has the ^3E conformation and all three substituents are once again in equatorial positions but each ring oxygen is now axial with respect to the adjacent ring, thereby gaining stability from the anomeric effect.[7,8] The C(5) resonance now appears at δ_C 111.80S.

3.5 Epoxidation of the spiroacetals

3.5.1 Background

Epoxides (oxiranes) are versatile and important intermediates in organic reactions due to their ease of formation, which results in the creation of two contiguous stereogenic centers with known absolute configuration, and their ready reactivity towards stereospecific nucleophilic ring opening reactions to form bifunctional compounds. The regiochemistry of ring opening depends on the reaction conditions. Thus epoxide ring opening by an ionic nucleophile occurs by an S_N2 mechanism at the less substituted site in unsymmetrical epoxides whereas acid catalysed ring opening occurs primarily by an S_N1-like mechanism by attack at the more substituted epoxide carbon.[15] In order to utilize the spiroacetal model compounds (**82**) and (**83**) in a total synthesis of stenocarpin, the double bond has to be transformed to a functional group that can be used in a regioselective and stereospecific carbon-carbon bond forming reactions *i.e.* an epoxide.

3.5.2 Epoxidation using peracids.

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[15] J.G. Smith, *Synthesis*, 1994, 629.

The most commonly used epoxidising reagents are peroxycarboxylic acids (peracids).[16] Peracids are halfesters of hydrogen peroxide and are less acidic than the corresponding acid because their conjugate base is not stabilised by delocalisation into the carbonyl group. They are, however, electrophilic at oxygen because attack there by a nucleophile displaces a carboxylate, a good leaving group. In 1909, the Russian chemist N. Prileschajew[17] discovered epoxidation by organic peracids and found that the olefinic unit acts as the nucleophile and the peroxy acid as the electrophile. Thus, either increasing the electron density of the olefin or decreasing that of the peracid serves to increase the rate of the reaction. The most commonly used peracid is *m*-chloroperbenzoic acid (MCPBA). The essence of the mechanism is nucleophilic attack of the double bond π orbital on the outer oxygen atom of the weak, polarised O–O bond. The proton of the epoxide oxygen is transferred to the carboxylic acid by-product (see Figure 3.12). The reaction is stereospecific as both new C–O bonds are formed on the same face of the alkene's π bond and the geometry of the alkene is therefore reflected in the stereochemistry of the epoxide. Thus *cis* alkenes give rise to *cis* epoxides whereas the *trans* alkene leads to the formation of the *trans* epoxide.

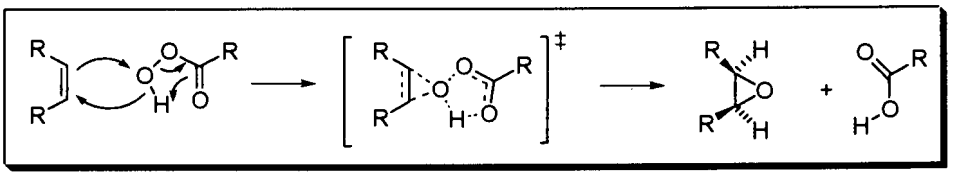

Figure 3.12: General mechanism of epoxidation by peracids.

Epoxidation of an allylic alcohol (both cyclic and acyclic) with MCPBA occurs by attack of the face of the alkene *syn* to the hydroxy group and the *syn* epoxy-alcohol is formed as the major diastereomer (95:5).[18] The reason for the diastereoselectivity is shown in the transition state for the reaction in Figure 3.13. The only important conformer in the transition state has the hydrogen of the stereogenic centre eclipsing the double bond. The hydrogen of the hydroxy group can then form a hydrogen bond to the oxygen of the peracid, stabilising the transition state when *syn* epoxidation occurs.[19] This hydrogen

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[16] G. Helmchen, R.W. Hoffman, J. Mulzer and E. Schaumann, *Stereoselective Synthesis, Methods of Organic Chemistry* (Houben-Weyl), Thieme Stuttgart, 4th Ed., Vol. **E21e**, 1995, p. 4599.
[17] N. Prileschajew, *Chem. Ber.*, 1909, **42**, 4811.
[18] H.B. Henbest and R.A.L. Wilson, *J. Chem. Soc.* (B), 1957, 1958.
[19] P. Chautemps and J.L. Pierre, *Tetrahedron*, 1976, **32**, 549.

bonding means that peracid epoxidations of alkenes with adjacent hydroxy groups are much faster than simple alkenes even when no stereochemistry is involved.[20]

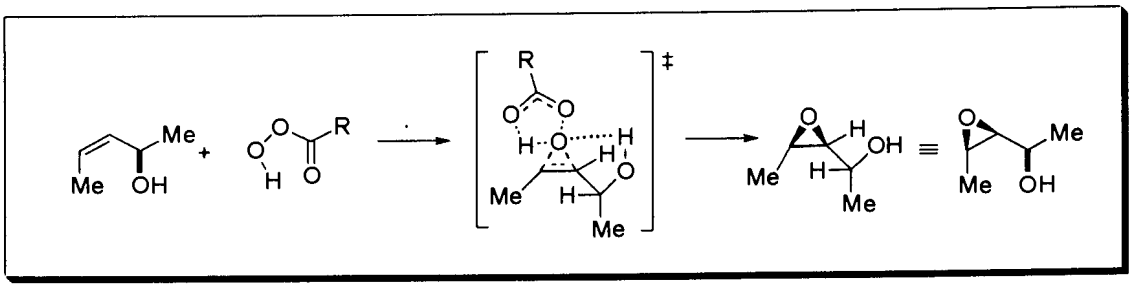


Figure 3.13: Stereofacial selectivity in the epoxidation of allylic alcohols.

3.5.3 Epoxidation using dimethyldioxirane(DMD).

Dimethyldioxirane has found numerous applications in organic synthesis as a valuable olefin epoxidation reagent, as well as in C–H insertion and heteroatom oxidation reactions. Numerous investigations have been undertaken to elucidate the reaction mechanism of the DMD epoxidation reaction and the general consensus favours a mechanism that involves a concerted electrophilic attack of the DMD on the alkene double bond (S_N2 reaction of the π-nucleophile on the peroxide bond).[21] The mechanism of epoxidation by DMD can also be viewed in terms of the transition state geometries of the two mechanistic extremes of electrophilic oxygen atom transfer, *i.e.* a *planar* or a *spiro* arrangement of the reactants (Figure 3.14).[22] Epoxidation of substituted alkenes by DMD showed a remarkable dependence on steric interactions: the reactivity of a *cis* alkene is about an order of magnitude higher than that of the *trans* analogue. This result suggests a spiro transition state geometry for the DMD approach on the double bond in which the plane of the three-membered peroxide ring is orthogonal to the π-bond.[23] The proximity of the dioxirane methyl groups to the oxygen atom that is being transferred, indicated by the tetrahedral structure of the dioxirane in Figure 3.14, allows the DMD to respond to the substitution pattern of the alkene. In contrast, for peracids such as m-chloroperbenzoic acid (M-CPBA), no steric discrimination between the spiro and planar geometry is expected since the substituent R is too far away to interact sterically with the alkene substituents. Thus for peracids[23] it is the nucleophilicity of the double bond rather

[20] W. Adam and T. Wirth, *Acc. Chem. Res.*, 1999, **32**, 703.
[21] L.A. Baumstark and P.C. Vasquez, *J. Org. Chem.*, 1988, **53**, 3437.
[22] R.W. Murray, R. Jeyarama and M.K. Pillay, *J. Org. Chem.*, 1987, **52**, 746.
[23] L.A. Baumstark and C. J. McCloskey, *Tetrahedron Lett.*, 1987, **28**, 3311.

than steric effects, that is the decisive factor in the epoxidation rate. For peracids each additional group enhances the rate by about an order of a magnitude due to the increased nucleophilicity of the alkene. For the sterically more demanding DMD the rate enhancement is much less because each additional substituent also increases the unfavourable steric interactions. These steric factors played a decisive role in the epoxidation of compounds (**83a**) and (**83b**) in both the DMD and m-CPBA reactions.

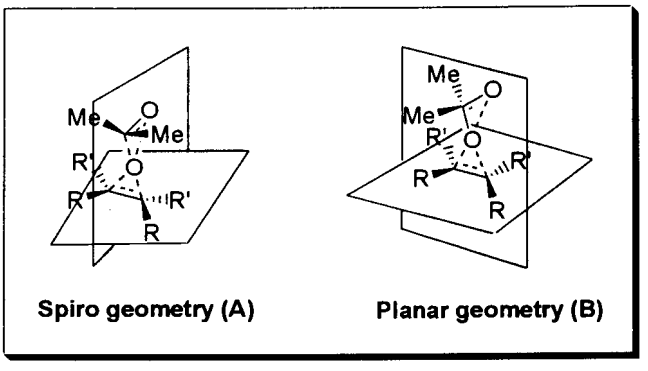


Figure 3.14: Possible geometries for the DMD epoxidation transition state.

Diastereoselective epoxidation of chiral allylic alcohols by DMD is dependent on solvent. Epoxidation in a polar solvent such as an acetone-methanol mixture occurs preferentially *anti* to the hydroxy functionality. Methanol can form a hydrogen bond with the hydroxy group of the allyl alcohol and this disfavours the approach of the steric-sensitive DMD reagent from the side *syn* to the allyl hydroxy group. The *syn* selectivity is favoured in less polar solvent mixtures such as acetone-CCl_4.as the association between the DMD and the substrate is promoted.

3.5.4 Epoxidation of the olefins (83).

Epoxidation of (**83a**) using MCPBA in dichloromethane gave the two epoxides (**107a**) and (**108a**) in a 8:5 ratio. The signal for the spiroacetal carbon atom C(5) of the two epoxides shows a significant difference *i.e* in (**107a**) the signal appears at δ_C 104.46S but at δ_C 106.36S for (**108a**) indicating that the C–O bond in (**108a**) has the equatorial orientation. The change in conformation in going from the starting material (**83a**) to the α-epoxide (**108a**) can be attributed to the steric strain between the epoxy oxygen and the axial C–O bond in the five-membered ring as well as the bulky OTBDPS group. The different conformations for the two epoxides are also clearly indicated by the coupling

constants obtained by analysis of the spin systems in the ^{1}H NMR spectra. The C(10) proton in (**107a**) appears as a singlet at δ_H 3.914 whereas H(9) (δ_H 3.263) is a doublet ($J_{8,9}$ 3.9 Hz) and H(8) (δ_H 3.102) is a broadened double doublet ($J_{8,9}$ 3.9, $J_{7a,8}$ 1.3 Hz). The C(7) protons appear at δ_H 3.812 (d, $J_{7a,7b}$ 13.2 Hz, H-7b) and δ_H 3.987 (dd, $J_{7a,7b}$ 13.2, $J_{7a,8}$ 1.3 Hz, H-7a). In the COSY spectrum correlations were observed between the C(8) proton and H(10) as well as both the C(7) protons and between H(9) and both H(10) and H(7b). For the epoxide (**108a**) the H(10) signal δ_H 3.996 (d, $J_{9,10}$ 2.3 Hz) also served as starting point in the analysis and identified the following coupling constants: $J_{8,9}$ 4.4, $J_{7a,8}$ 0.8, $J_{7b,8}$ 4.4, $J_{7a,9}$ 0.8, and $J_{7a,7b}$ 13.2 Hz.

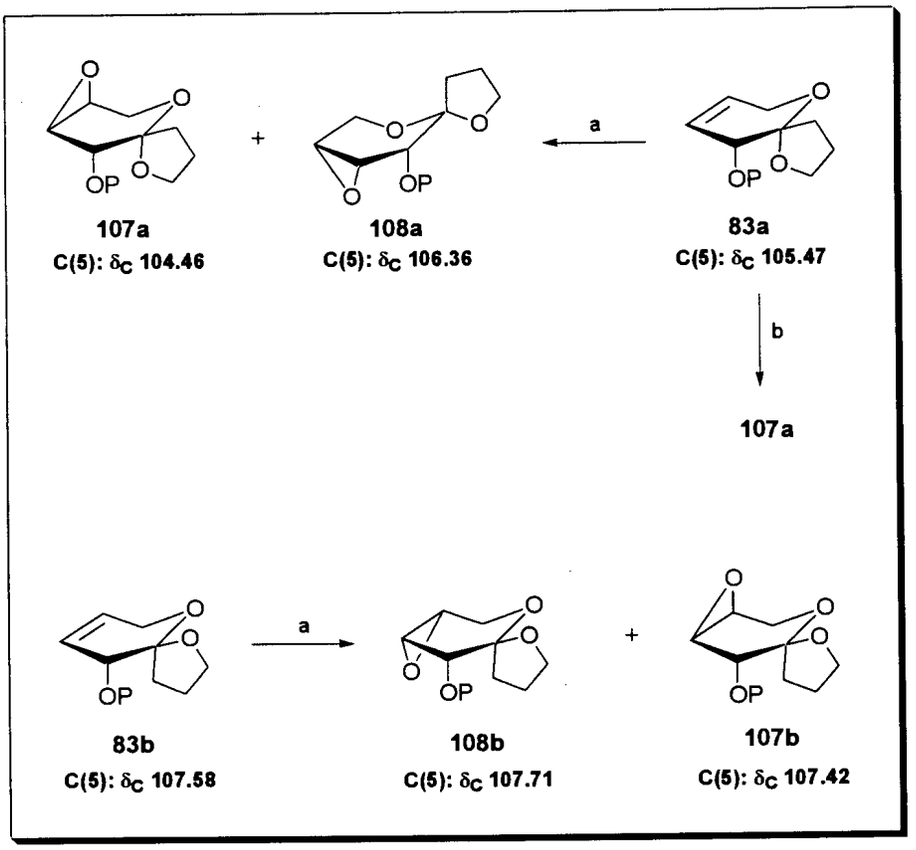
Epoxidation of (**83b**) using MCPBA gave the two epoxides (**107b**) and (**108b**) in a 1:1 ratio. The chemical shift values for the spiro carbon atom, C(5) of these two epoxides differ little and the signal appeared at δ_C 107.42S for (**107b**) and at δ_C 107.71S for (**108b**). Little difference is observed for the proton coupling constants and it is only the ones for H(10) that differ: $J_{9,10}$ 0.8, $J_{8,10}$ 0.6 Hz for (**107b**) and $J_{9,10}$ 3.6 Hz for (**108b**).

In contrast to the mixtures of epoxides that are formed when MCPBA is used, the reaction of the olefin (**83a**) with dimethyl dioxirane (DMD) in acetone leads to the formation of a single epoxide (**107a**). The outcome of the reaction is due to the sensitivity of the DMD reagent to steric factors in the transition state: the bulky OTBDPS group shields the α-face of the olefin and preferential (or exclusive) β-attack by the DMD reagant occurs. The assignment of the stereochemistry of the epoxides is based on this result and unambiguous proof using X-ray crystallography must await the availability of a suitable crystal.

3.6 Conclusion

The results reported in this dissertation show that a synthetic route to the model spiro-acetals using benzyl protecting groups is viable and can provide gram quantities of the spiroacetal compound with the stereochemistry that corresponds to the natural product, stenocarpin. The timing and sequence of the introduction of the acetonide and TBDPS protecting groups as well as the formation of the spiroacetal C–O bond in the synthetic route is of importance as it affects the distribution of the two model compounds. The

presence of the five-membered dioxolane ring causes constraints in the products that are minimized by conformational changes. These changes were detected through the proton-proton NOE effects and the ^{13}C chemical shift values of the anomeric carbon atom. The ready availability of the corresponding epoxy spiroacetals opens the way to a project on the total synthesis of stenocarpin.



Scheme 3.11: Epoxidation of the spiroacetal model compounds.

Reagents: a) m-CPBA, CH_2Cl_2 (78%); b) Dimethyldioxirane, acetone (77%).

4 EXPERIMENTAL

4.1 Introduction

Air- and/or moisture-sensitive reactions were carried out under positive argon pressure in oven-dried (120 °C) glassware. Room temperature (RT) refers to 20-25 °C. Evaporations were done under reduced pressure on a Büchi rotary evaporator. All reagents were synthetic grade and were used without any further purification. When necessary, solvents and reagents were dried according to standard methods prior to use.[1]

Melting points (mp) were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined with a Perkin Elmer 241 polarimeter for solutions in chloroform ($CHCl_3$). Specific rotations are given in units of 10^{-1} deg.g^{-1}.cm^2 High resolution fast atom bombardment (FAB) mass spectra were recorded by Dr. L. Fourie, University of Potchefstroom, on a VG 7070-E spectrometer (Xe beam, *m*-nitrobenzyl alcohol matrix, detection of positive ions with $m/z > 99$).

Nuclear magnetic resonance (NMR) spectra were measured for $CDCl_3$ solutions (unless otherwise indicated) on a Bruker AMX-300 (7.0 T) spectrometer operating at 300 MHz for ^1H, 75.47 MHz for ^{13}C or an AMXR-500 (11.7 T) spectrometer. All chemical shifts are reported as δ values downfield from Me_4Si using $CHCl_3/CDCl_3$ as internal standard (δ_H 7.24 and δ_C 77.00, respectively). Proton-proton coupling constants (*J*) are given in Hz. Spectral coupling patterns are designated as follows: S/s: singlet; D/d: doublet; T/t: triplet; Q/q: quartet; m: multiplet; br: broad signal; The assignments of the signals in the ^1H NMR spectra are based on first-order analysis[2] of the spin systems and when required were confirmed by $^1H\{^1H\}$ decoupling experiments and two-dimensional (2-D) (^1H,^1H) homo-nuclear chemical shift correlation (COSY) experiments. The ^{13}C chemical shifts were obtained from proton-proton decoupled spectra. The multiplicities of the different ^{13}C resonances were assigned through the proton-decoupled DEPT pulse sequence. The

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1 D.D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, Oxford, **1992.**

2 R.J. Abraham, J. Fisher and P. Loftus, in *Introduction to NMR Spectroscopy*, John Wiley & Sons, New Delhi, **1988.**

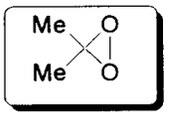
signals of the proton-bearing carbon atoms were correlated with specific proton resonances in 2-D heteronuclear chemical shift correlation (HETCOR) experiments utilizing the one-bond ($^{13}C,^{1}H$) spin-spin couplings. The proton-proton NOE connectivity patterns were established in 2D ROESY experiments and the long-range ($1H,^{13}C$) connectivity pattern in a 2D heteronuclear correlation experiment optimized to detect long-range ($^{1}H,^{13}C$) couplings or the HMBC experiment. Standard Bruker programs were used in these experiments.

The course of reactions was followed by thin-layer chromatography (TLC) performed on Merck silica gel $60F_{254}$ coated aluminum sheets. Column chromatography was performed on Merck silica gel 60 (60-200 m, 70-230 mesh). Eluant volumes are given as v/v. TLC plates were examined under UV light (254 and 366 nm) and/or after colouring with cerium(IV) sulfate/ammonium heptamolybdate reagent and subsequent heating at 120 °C.

4.2 Preparation of reagents

4.2.1 Spraying reagent

A spray solution containing ammonium heptamolybdate (5%) and cerium(IV) sulfate (0.2%) in 3M sulfuric acid was prepared by heating and continuous stirring. The solution was cooled and filtered. Chromatograms were immersed in the solution and heated with a heating gun until the appearance of coloured spots as a positive indication of the presence of compounds.



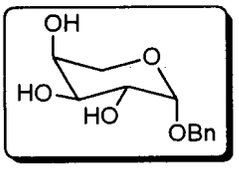
4.2.2 Preparation of dimethyldioxirane.

A two-necked, round-bottomed reaction flask (1000 ml) equiped with an efficient mechanical stirrer and an addition funnel for solids was connected by a means of a U-tube to a two-necked receiving flask cooled to -78 °C. The reaction flask was charged with a mixture of water (80 ml), acetone (70 ml), and $NaHCO_3$ (14.9 g) and cooled to 5-10 °C. Oxone (30.0 g) was added in three portions at 3 min intervals with vigorous stirring and cooling. Three minutes after the last addition the cooling bath was removed

from the reaction flask, a moderate vacuum was applied and the dimethyldioxirane–acetone mixture was distilled and collected.

4.3 Procedures

4.3.1 Synthesis of the 1,6-dioxaspiro[4.5]dec-8-en-10-ols: Route 1 Benzyl protecting group strategy



Benzyl β-L-arabinopyranoside (98)

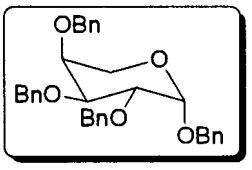
Thionyl chloride (24.2 ml) was added dropwise to a solution of L-arabinose (50.0 g, 0.33 mol) in benzyl alcohol (250 ml) at 0 °C. The reaction mixture was stirred for 24 h at room temperature and then diluted with diethyl ether (500 ml). The crystals were collected by filtration and recrystallized from ethanol to give the *O*-benzyl glycoside (**98**) (56.7 g, 71%), mp.170-173°C (Lit.,[3] 171-173 °C).

δ_H 3.484 (dd, 1H, $J_{4,5b}$ 2.9, $J_{5b,5a}$ 11.7, H-5b)
3.667 (m, 2H, H-2 and H-3)
3.747 (m, 1H, H-4)
3.686 (dd, 1H, $J_{4,5a}$ 2.9, $J_{5a,5b}$ 11.7, H-5a)
4.444 (br s, 3H, OH)
4.452 (d, 1H, $J_{b,a}$ 12.4, OCH_2Ph)
4.656 (d, 1H, $J_{a,b}$ 12.4, OCH_2Ph)
4.777 (m, 1H, H-1)
7.45-7.27 (m, 5H, aromatic protons)

δ_C 63.30T (C-5), 68.33D (C-4), 68.48T (OCH_2Ph), 68.70D, 69.13D (C-2 and C-3), 98.94D (C-1), 127.32D, 127.45D, 128.16D (aromatic carbons); 138.21S (*ipso* aromatic carbon).

[3] J.E. McCormick, *Carbohyd. Res.*, 1967, **4**, 262.

FAB-MS: *m/z* 241 $[M+H]^+$. Exact mass: Calculated for $C_{12}H_{17}O_5$, 241.1076; Found, 241.1076.



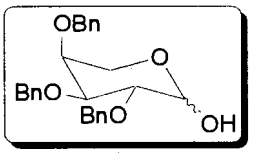
Benzyl 2,3,4-tri-*O*-benzyl-β-L-arabinopyranoside (99)

A mixture of benzyl-β-L-arabinose (**98**) (40.0 g), powdered potassium hydroxide (162 g) and dioxane (118 ml) was efficiently stirred and slowly warmed to the boiling point while benzyl chloride (53.8 ml) was added dropwise. Additional benzyl chloride (107.6 ml) was added dropwise to the refluxing and vigorously stirred mixture and the heating continued for 2 h after the addition was completed. The reaction mixture was cooled to *ca.*70°C and steam-distilled to remove dioxane, benzyl chloride and benzyl alcohol. The crude product was purified using column chromatography with hexane-EtOAc (4:1) as eluent to give the tribenzyl derivative (**99**) (74.0 g, 87%), mp 59-61°C; R_f 0.62 (hexane-EtOAc), $[\alpha]_D$ +88.1 (*c* 0.67, $CHCl_3$).

δ_H 3.708 (d, 2H, $J_{5,4}$ 2.1, H-5)
3.805 (dd, 1H, $J_{4,3}$ 3.0, $J_{4,5}$ 2.1, H-4)
3.967 (dd, 1H, $J_{3,2}$ 9.7, $J_{3,4}$ 3.0, H-3)
4.040 (dd, 1H, $J_{2,1}$ 3.4, $J_{2,3}$ 9.7, H-2)
4.577 (d, 1H, $J_{b,a}$ 12.0, OCH_2Ph)
4.626 (d, 1H, $J_{a,b}$ 12.0, OCH_2Ph)
4.658 (d, 1H, $J_{b,a}$ 12.0, OCH_2Ph)
4.728 (s, 2H, OCH_2Ph)
4.747 (d, 1H, $J_{b,a}$ 11.6, OCH_2Ph)
4.772 (d, 1H, $J_{a,b}$ 12.0, OCH_2Ph)
4.786 (d, 1H, $J_{a,b}$ 11.6, OCH_2Ph)
4.943 (d, $1H_{1,2}$ 3.4, H-1)
7.426-4.240 (m, 20H, aromatic protons)

δ_C 60.55T (C-5), 69.06T, 71.72T, 72.71T, 73.29T (OCH_2Ph); 74.05D (C-4), 76.42D (C-2), 77.31D (C-3), 96.70D (C-1), 127.40-128.28D (aromatic carbons); 137.48S, 138.38S, 138.73S, 138.81S (*ipso* aromatic carbons).

FAB-MS: *m/z* 510 $[M]^+$. Exact mass: Calculated for $C_{33}H_{34}O_5$, 510.2406; Found, 510.2406.



2,3,4-Tri-*O*-benzyl-L-arabinose (100)

A solution of (**99**) (19.0 g, 19.6 mmol) in a mixture of AcOH–1 M HCl (7:2, 224 ml) was stirred and heated at 75 °C for 4 h. The solution was diluted with chloroform and washed with $NaHCO_3$ and dried (Na_2SO_4). The crude product was purified by column chromatography with hexane-EtOAc (1:1) to give an inseparable diastereomeric mixture of sugar (**100**) (12.7 g, 81%); mp. 80-81 °C; R_f 0.54 (hexane-EtOAc 1:1) $[\alpha]_D$ +39.2 (*c* 0.46, $CHCl_3$).

α-Isomer (100a):

δ_H 3.571 (dd, 1H, $J_{5b,5a}$ 11.6, $J_{5b,4}$ 3.4, H-5b)
3.715 (m, 1H, H-2)
3.761 (m, 1H, H-3)
3.904 (m, 1H, H-4)
3.909 (br s, 1H, 1-OH)
4.066 (dd, 1H, $J_{5a,5b}$ 11.6, $J_{5a,4}$ 7.4, H-5a)
4.794-4.578 (m, 6H, OCH_2Ph)
5.229 (m, 1H, H-1)
7.387-7.310 (m, 15H, aromatic protons)

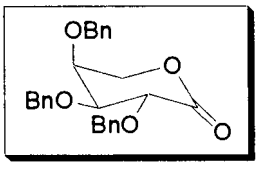
δ_C 59.02T (C-5), 72.03D (C-3), 71.33T, 73.04T, 73.29T, 75.60D (C-4), 76.75D (C-2), 94.33D (C-1), 127.43-128.30D (aromatic-carbons); 137.50-138.35S (*ipso* aromatic-carbons).

β-Isomer (100b)

δ_H 3.739 (m, 1H, H-2)
3.797 (m, 1H, H-3)
3.817 (m, 1H, H-5b)
3.852 (m, 1H, H-4)
3.878 (m, 1H, H-5a)
4.794-4.578 (m, 6H, OCH_2Ph)
4.841 (d, 1H, $J_{1,2}$ 3.9, H-1)
7.387-7.310 (m, 15H, aromatic protons)

δ_C, 60.60T (C-5), 71.39T, 72.44T, 73.34T (OCH_2Ph); 73.10D (C-3), 76.55D (C-4), 76.94D (C-2), 91.93D (C-1), 127.43-128.30D (aromatic-carbons); 137.50-138.35 S (*ipso* aromatic-carbons).

FAB-MS: *m/z* 420 $[M]^+$. Exact mass: Calculated for $C_{26}H_{28}O_5$, 420.1937; Found, 420.1937.



2,3,4-Tri-*O*-benzyl-L-arabino-1,5-lactone (93)

To a stirred solution of 2,3,4-tri-*O*-benzyl arabinose (**100**) (6.05 g, 14.3 mmol) in dichloromethane (300 ml) containing powdered molecular sieves (3Å, 14.3 g) was added pyridinium chlorochromate (PCC) (14.3 g, 65.8 mmol) in one portion. After 1 h the dark suspension was diluted with diethyl ether (300 ml) and hexane (150 ml), and filtered through a silica gel column. The column was washed with a further portion of diethyl ether (400 ml) and the combined filtrates were evaporated to give the lactone (**93**) (5.03 g, 80%) as a yellowish syrup: $[\alpha]_D$ +51.9 (*c* 0.36, $CHCl_3$); R_f 0.64 (EtOAc-hexane, 2:3)

δ_H, 3.880 (dd, 1H, $J_{3,2}$ 8.0, $J_{3,4}$ 2.5, H-3)
3.997 (ddd, 1H, $J_{4,3}$ 2.6, $J_{4,5a}$ 4.4, $J_{4,5b}$ 2.6, H-4)
4.107 (dd, 1H, $J_{5b,5a}$ 12.2, $J_{5b,4}$ 2.6, H-5b)
4.405 (dd, 1H, $J_{5a,5b}$ 12.2, $J_{5a,4}$ 4.1, H-5a)

4.405 (d, 1H $J_{2,3}$ 8.0; H-2)

4.637 (d, 1H, $J_{b,a}$ 12.1, OCH_2Ph)

4.704 (d, 1H, $J_{a,b}$ 12.1, OCH_2Ph)

4.683 (s, 2H, OCH_2Ph)

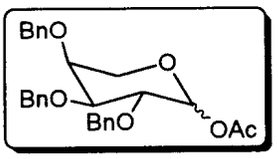
4.744 (d, 1H, $J_{b,a}$ 11.4, OCH_2Ph)

5.106 (d, 1H, $J_{a,b}$ 11.4, OCH_2Ph)

7.278-7.420 (m, 15H, aromatic protons)

δc 67.33T (C-5), 71.59D (C-4), 71.95T, 72.64T, 74.79T (OCH_2Ph), 76.57D (C-2) 77.59D (C-3), 127.62-128.47D (aromatic carbons), 137.34S, 137.43S, 137.69S, (*ipso* aromatic carbons), 169.74S (C-1).

FAB-MS: *m/z* 419 $[M+H]^+$. Exact mass: Calculated for $C_{26}H_{27}O_5$, 419.1858; Found, 419.1858.



2,3,4-*O*-Tri-O-benzyl-L-arabinopyranosyl acetate (89)

A solution of 2,3,4-tri-*O*-benzyl arabinose (**100**) (10.0 g, 240 mmol) in acetic anhydride (40 ml) and pyridine (25 ml) was stirred for 16 h. The solution was poured onto ice and the excess acetic anhydride allowed to hydrolyse. The aqueous solution was extracted with $CHCl_3$ and the combined organic phase was washed with 3M HCl, saturated $NaHCO_3$ solution and dried (Na_2SO_4). The solvent was evaporated and the residue purified by column chromatography (EtOAc-hexane 1:4) to give compound (**89**) (8.01 g, 75%), (α:β 1:2): R_f 0.63 (EtOAc-hexane 1:4); $[\alpha]_D$ +40.2, (*c* 0.60, $CHCl_3$).

α-Isomer (89b)

δ_H 2.111 (s, 3H, acetate Me)

3.479 (dd, 1H, $J_{5b,5a}$ 12.4, $J_{4,5b}$ 2.1, H-5b)

3.656 (dd, 1H, $J_{3,4}$ 3.2, $J_{3,2}$ 8.0, H-3)

3.787 (m, 1H, $J_{4,3}$ 3.2, $J_{4,5b}$ 2.1, H-4)

3.913 (dd, 1H, $J_{2,3}$ 8.0, $J_{2,1}$ 6.3, H-2)

4.075 (dd 1H, $J_{5a,4}$ 4.4, $J_{5a,5b}$ 12.4, H-5a)

4.625 (d, 1H, $J_{b,a}$ 12.0, OCH_2Ph)

4.648 (d. 1H, $J_{a,b}$ 12.0, OCH_2Ph)

4.681 (d, 1H, $J_{b,a}$ 13.5, OCH_2Ph)

4.727 (d, 1H, $J_{a,b}$ 13.5, OCH_2Ph)

4.733 (d, 1H, $J_{b,a}$ 11.4, OCH_2Ph)

4.786 (d, 1H, $J_{a,b}$ 11.4, OCH_2Ph)

5.634 (d, 1H, $J_{1,2}$ 6.3, H-1)

7.374-7.293 (m, 15H, aromatic protons)

δ_C 21.99Q (acetate Me) 62.91T (C-5), 71.77T, 72.54T, 74.51T (OCH_2Ph), 73.46D (C-4), 76.85D (C-2), 78.83D (C-3), 93.92D (C-1), 127.46-128.49D (aromatic carbons), 138.01-138.50S (*ipso* aromatic carbons), 169.53S (acetate CO).

β-Isomer (89a)

δ_H 2.049 (s, 3H, acetate Me)

3.758 (m, 1H, H-4)

3.834 (m, 2H, H-5a and H-5b)

3.876 (dd, 1H, $J_{2,3}$ 9.3, $J_{3,4}$ 2.8, H-3)

4.145 (dd, 1H, $J_{2,3}$ 9.3, $J_{2,1}$ 3.4, H-2)

4.625 (d, 1H, $J_{b,a}$ 12.0, OCH_2Ph)

4.648 (d. 1H, $J_{a,b}$ 12.0, OCH_2Ph)

4.681 (d, 1H, $J_{b,a}$ 13.5, OCH_2Ph)

4.727 (d, 1H, $J_{a,b}$ 13.5, OCH_2Ph)

4.733 (d, 1H, $J_{b,a}$ 11.4, OCH_2Ph)

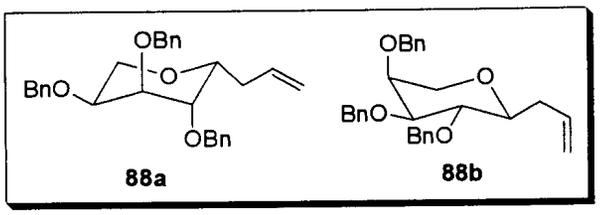
4.786 (d, 1H, $J_{a,b}$ 11.4, OCH_2Ph)

6.357 (d, 1H, $J_{1,2}$ 3.5, H-1)

7.374-7.293 (m, 15H, aromatic protons)

δ_C 20.91Q (acetate Me), 62.43T (C-5), 71.35T, 72.31T, 73.46T (OCH_2Ph), 71.93D (C-4), 75.20D (C-2), 76.94D (C-3), 91.25D (C-1), 127.46-128.49D (aromatic carbons), 138.01-138.50 S (*ipso* aromatic carbons), 169.53S (acetate CO).

FAB-MS: *m/z* 461 $[M-H]^+$. Exact mass: Calculated for $C_{28}H_{29}O_6$, 461.1964; Found, 461.1965.



2,3,4-Tri-*O*-benzyl-1-deoxy-1-(prop-2-enyl)-L-arabinopyranose (88)

To a magnetically stirred solution of **(89)** (7.61 g, 17.7 mmol) and allyltrimethylsilane (2.37 g, 20.7 mmol) in acetonitrile (80 ml) at 0 °C was added dropwise $BF_3.OEt_2$ (4.79 g, 35 mmol). The reaction mixture was allowed to warm to 25 °C after 1 h and the stirring was continued for 4 h. The reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ solution (70 ml) and diethyl ether (250 ml). The organic layer was separated and washed with additional $NaHCO_3$ solution (70 ml), H_2O (60 ml) and brine (50 ml) and dried ($MgSO_4$). Solvent evaporation gave the product as a 1:7 α:β anomeric mixture of **(88b):(88a)** (6.22 g, 84%). A small sample was separated by column chromatography using hexane-EtOAc (9:2) as eluant to give the two anomers.

β-Anomer (88a)

R_f 0.38 (hexane-EtOAc 9:2); $[\alpha]_D$ +11.7 (*c* 0.53, $CHCl_3$).

δ_H 2.222 (m, 1H, $J_{1b',2'}$ 7.6, $J_{1b',1}$ 7.6, $J_{1a',1b'}$ 14.2, $J_{1b',3b'}$ 1.3, $J_{1b',3a'}$ 1.0, H-1b')
2.434 (m, 1H, $J_{3a',1a'}$ 1.5, $J_{1a',1b'}$ 14.2, $J_{1a',2'}$ 6.5, $J_{1a',1}$ 6.5, $J_{1a',3b'}$ 1.5 H-1a')
3.406 (dd, 1H, $J_{2,3}$ 3.9, $J_{1,2}$ 1.6, H-2)
3.800 (ddd, 1H, $J_{1,2}$ 1.6 $J_{1,1a'}$ 6.5, $J_{1,1b'}$ 7.6, H-1)
3.936 (ddd, 1H, $J_{4,5eq}$ 5.0, $J_{4,5ax}$ 10.6, $J_{4,3}$ 2.7, H-4)
3.800 (dd, 1H, $J_{5ax,5eq}$ 10.6, $J_{5ax,4}$ 10.6, H-5b)
3.903 (dd, 1H, $J_{5eq,5ax}$ 10.6, $J_{5eq,4}$ 5.0, H-5a)
3.888 (dd, 1H, $J_{3,4}$ 2.7, $J_{3,2}$ 3.9, H-3)
4.343 (d, 1H, $J_{a,b}$ 11.9, OCH_2Ph)
4.456 (d, 1H, $J_{b,a}$ 11.9, OCH_2Ph)
4.551 (d, 1H, $J_{a,b}$ 12.2, OCH_2Ph)

4.516 (d, 1H $J_{b,a}$ 12.2, OCH_2Ph)

4.573 (d, 1H, $J_{a,b}$ 12.4, OCH_2Ph)

4.780 (d, 1H, $J_{b,a}$ 12.4, OCH_2Ph)

5.080 (m, 1H, $J_{3a',2'}$ 17.1, $J_{3a',3b'}$ 4.9, $J_{3a',1a'}$ 1.5, $J_{3a',1b'}$ 1.0, H-3a′)

5.044 (m, 1H, $J_{3b',2'}$ 10.1, $J_{3a',3b'}$ 4.9, $J_{3b',1b'}$ 1.3, $J_{3b',1a'}$ 1.5, H-3b′)

5.739 (m, 1H, $J_{1b',2'}$ 7.5, $J_{1a',2'}$ 6.5, $J_{2',3a'}$ 17.1, $J_{2',3b'}$ 10.1, H-2′)

7.391-7.212 (m, 15H, aromatic protons)

δ_C 34.99T (C-1′), 64.45T (C-5), 71.30T, 72.67T, 72.98T (OCH_2Ph); 72.44D (C-4), 72.93D (C-3), 74.16D (C-1), 76.29D (C-2), 116.82T (C-3′), 127.54-128.44D (aromatic carbons); 134.84D (C-2′), 138.58S, 138.35S, 137.87S (*ipso* aromatic carbon).

FAB-MS: *m/z* 444 $[M]^+$. Exact mass: Calculated for $C_{29}H_{32}O_4$, 444.2301; Found, 444.2302.

α-Anomer (88b):

R_f 0.48 (hexane-EtOAc 9:2); $[\alpha]_D$+23.1 (*c* 0.81, $CHCl_3$).

δ_H 2.400 (m, 1H, $J_{1,1b'}$ 8.0, $J_{1a',1b'}$ 14.7, $J_{1b',3b'}$ 1.3, $J_{1b',2'}$ 7.5, $J_{1b',3a'}$ 1.0, H-1b′)

2.679 (m, 1H, $J_{1a',1b'}$ 14.8 $J_{1a',1}$ 3.1, $J_{1a',3a'}$ 1.6, $J_{1a',2'}$ 6.2, H-1a′)

3.266 (dd, 1H, $J_{5ax,5eq}$ 12.7, $J_{5eq,4}$ 1.3, H-5b)

3.279 (ddd, 1H, $J_{1,1a'}$ 3.1, $J_{1,2}$ 9.3, $J_{1,1b'}$ 8.0, H-1)

3.582 (dd, 1H, $J_{3,4}$ 3.4, $J_{3,2}$ 9.3, H-3)

3.765 (dd, 1H, $J_{2,1}$ 9.3, $J_{2,3'}$ 9.3, H-2)

3.780 (ddd, 1H, $J_{4,5ax}$ 2.3, $J_{4,3}$ 3.4, $J_{4,5eq}$ 1.3, H-4)

4.101 (dd, 1H, $J_{5ax,4}$ 2.3, $J_{5ax,5eq}$ 12.7, H-5a)

4.594 (d, 1H, $J_{b,a}$ 11.6, OCH_2Ph)

4.659 (d, 1H, $J_{a,b}$ 11.6, OCH_2Ph)

4.687 (d, 1H, $J_{a,b}$ 10.1, OCH_2Ph)

4.700 (d, 1H, $J_{b,a}$ 12.7, OCH_2Ph.)

4.815 (d, 1H, $J_{a,b}$ 12.7, OCH_2Ph)

5.026 (d, 1H, $J_{b,a}$ 10.1, OCH_2Ph)

5.109 (m, 1H, $J_{3b',2'}$10.6, $J_{3b',1b'}$1.3, $J_{3b',3a'}$ 5.0, $J_{3b',1a'}$2.3, H-3b′)

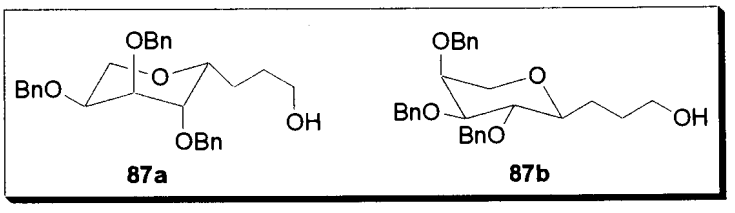
5.141 (m, 2H, $J_{3a',2'}$ 17.8, $J_{3a',3b'}$5.0, $J_{3a',1a'}$ 1.7, $J_{3a',1b}$ 3.6, H-3a′)

5.964 (m, 1H, $J_{2',3b'}$ 10.3, $J_{2',3a'}$ 17.8, $J_{2',1a'}$ 6.2, $J_{2',1b'}$ 8.0, H-2′)

7.454-7.300 (m, 15H, aromatic protons)

δ_C 36.19T (C-1′), 66.81T (C-5), 71.01T, 71.41T, 75.24T (OCH_2Ph); 78.27D (C-2), 79.59D (C-1), 82.89D (C-3), 116.75T (C-3′), 127.53-128.27D (aromatic carbons); 135.02D (C-2′), 138.25S, 138.27S, 138.56S (*ipso* aromatic carbons).

FAB-MS: *m/z* 444, $[M]^+$. Exact mass: Calculated for $C_{29}H_{32}O_4$, 444.2301; Found, 444.2302.



2,3,4-Tri-*O*-benzyl-1-deoxy-1-(3-hydroxypropan-1-yl)-L-arabinopyranose (87)

To a stirred solution of the 1-*C*-allyl compound (**88**) (5.50 g, 11.9 mmol) in THF (15. ml) at 25°C was added $BH_3.SMe_2$ (18 1 mmol, 2.10 ml) in THF over 30 min. After 40 min the reaction mixture was cooled to 0°C and treated dropwise with 3M NaOH (114 ml, 34.2 mmol), and 30% H_2O_2 (3.6 ml, 129 mmol) over 20 min. The cooling bath was removed and the reaction mixture was stirred for another 30 min. The reaction was diluted with diethyl ether (80 ml), washed with water (100 ml), dried ($MgSO_4$) and concentrated. Chromatography with EtOAc-hexane 1:1 gave the alcohols (**87a/b**) (3.81 g, 69%) as an oil.

β-Anomer (87a):

R_f 0.38 (EtOAc-hexane 1:1); $[\alpha]_D$ –2.7, (*c* 0.51, $CHCl_3$).

δ_H 1.407 (m, 1H, H-1a′)

1.556 (m, 2H, H-2′)

1.708 (m, 1H, H-1b′)

2.072 (br s, H, OH)

3.312 (dd, 1H, $J_{2,1}$ 1.5, $J_{2,3}$ 3.8, H-2)

3.564 (dd, 2H, $J_{3',2a'}$ 5.9, $J_{2b',3'}$ 6.2, H-3′)

3.671 (m, 1H, $J_{1,2}$ 1.6, $J_{1,1a'}$ 6.2, $J_{1,1b'}$ 5.7, H-1)

3.731 (dd, 1H, $J_{5b,4}$ 10.6, $J_{5b,5a}$ 10.6, H-5b)

3.845 (dd, 1H, $J_{5a,4}$ 10.6, $J_{5a,4}$ 5.0, H-5a)

3.873 (ddd, 1H, $J_{4,3}$ 2.8, $J_{4,5a}$ 5.0, $J_{4,5b}$ 10.6, H-4)

3.878 (m, 1H, H-3)

4.386 (d, 1H, $J_{b,a}$ 12.0, OCH_2Ph)

4.450 (d, 1H, $J_{a,b}$ 12.0, OCH_2Ph)

4.505 (d, 1H, $J_{b,a}$ 12.2, OCH_2Ph)

4.536 (d, 1H, $J_{a,b}$ 12.2, OCH_2Ph)

4.555 (d, 1H, $J_{a,b}$ 12.4, OCH_2Ph)

4.762 (d, 1H, $J_{a,b}$ 12.4, OCH_2Ph)

7.349-7.174 (m, 15H, aromatic protons)

δ_C 27.29T (C-1′), 29.43T (C-2′), 62.57T (C-3′), 64.32T (C-5), 71.35T, 72.74T 72.03T (OCH_2Ph); 72.44D (C-4), 72.94D (C-3), 74.57D (C-1), 77.06D (C-2) 127.53-128.31D (aromatic carbons); 137.81S, 138.31S, 138.54S (*ipso* aromatic carbons).

FAB-MS: *m/z* 463 $[M+H]^+$. Exact mass: Calculated for $C_{29}H_{35}O_5$, 463.2485; Found, 463.2485.

α-Anomer (87b):

R_f, 0.25 (EtOAc-hexane 1:1); $[\alpha]_D$ +25.8, (*c* 0. 16, $CHCl_3$)

δ_H 1.601 (m, 1H, H-2b′)

1.698 (m, 1H, H-2a′)

1.699 (m, 1H, H-1b′)

1.994 (m, 1H, H-1a′)

3.178 (ddd, 1H $J_{1,1b'/1a'}$ 8.3, 2.6, $J_{1,2}$ 9.3, H-1)

3.250 (dd, 1H,$J_{5b,5a}$ 12.7, $J_{5b,4}$ 1.0, H-5b)

3.542 (dd, 1H, $J_{3,2}$ 9.1 $J_{3,4}$ 3.1, H-3)

3.611 (ddd, 2H, $J_{3',2'_s}$ 5.9, 6.2, H-3')

3.707 (dd, 1H, $J_{2,3}$ 9.1, $J_{2,1}$ 9.3, H-2)

3.758 (ddd, 1H, $J_{4,5a}$ 2.1, $J_{4,5b}$, 1.0, $J_{4,3}$ 3.1, H-4)

4.045 (dd, $1H_{5b,4}$ 2.1, $J_{5a,5b}$ 12.7, H-5a)

4.568 (d, 1H, $J_{b,a}$ 11.9, OCH_2Ph)

4.628 (d, 1H, $J_{a,b}$ 11.9, OCH_2Ph)

4.660 (d, 1H, $J_{b,a}$ 10.9, OCH_2Ph)

4.683 (d, 1H, $J_{b,a}$ 12.7, OCH_2Ph)

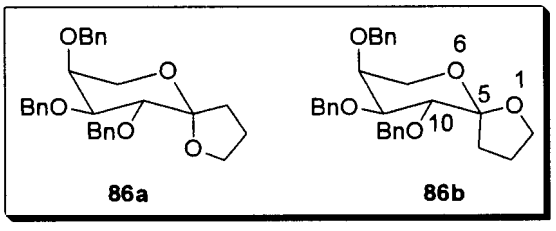
4.781 (d, 1H, $J_{a,b}$ 12.7, OCH_2Ph)

4.998 (d, 1H, $J_{a,b}$ 10.9, OCH_2Ph)

7.238-7.420 (m, 15H, aromatic protons)

δ_C 28.45T (C-1'), 29.056T (C-2'), 62.74T (C-3'), 66.94T (C-5), 71.14T, 71.49T, 75.41T (OCH_2Ph.); 72.48D (C-4), 78.51D (C-2), 80.08D (C-1), 82.95D (C-3), 127.56–128 .30D (aromatic carbons); 138.20S, 138.23S, 138.49S (*ipso* aromatic carbons).

FAB-MS: *m/z* 463, $[M+H]^+$. Exact mass: Calculated for $C_{29}H_{35}O_5$, 463.2485; Found, 463.2492.



86a **86b**

(5*SR*,8*S*,9*S*,10*R*)-8,9,10-Tri-(benzyloxy)-1,6-dioxaspiro[4.5]decane (86)

A solution of compound (**87**) (2.05 g, 4.76 mmol) in cyclohexane (300 ml) containing (diacetoxyiodo)benzene (DIB) (1.75 g, 5.24 mmol) and iodine (1.12 g, 4.76 mmol) under argon was irradiated with a 300 W tungsten filament lamp for 45 min. The reaction mixture was then poured into a saturated aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. Chromatography of the residue using hexane-

EtOAc (2:1) afforded the two diastereomeric spiro compounds (**86a**) (0.69g, 34%) and (**86b**) (0.58 g, 28%),(overall yield 62%).

(5*S*,8*S*,9*S*,10*R*)-8,9,10-Tri-(benzyloxy)-1,6-dioxaspiro[4.5]decane (86a)

R_{fa} 0.67 (EtOAc-hehane 2:1); $[\alpha]_D$ +59.7, (*c* 0.40, $CHCl_3$).

δ_H 1.838 (m, 1H, H-3b)
1.886 (m, 1H, H-4b)
1.950 (m, 1H, H-4a)
1.997 (m, 1H, H-3a)
3.689 (m, 2H, H-7)
3.769 (m, 1H, $J_{8,9}$ 3.1, $J_{8,7}$ 1.9, H-8)
3.868 (m, 1H, $J_{2b,2b}$ 7.9, $J_{2b,3a/3b}$ 8.0, 6.5, H-2b)
3.940 (dd, 1H, $J_{9,10}$ 10.0, $J_{9,8}$ 3.1, H-9)
3.983 (m, 1H, $J_{2a,2b}$ 7.9, $J_{2a,3a/3b}$ 7.7, 4.9, H-2a)
4.038 (d, 1H, $J_{10,9}$ 9.9, H-10)
4.624 (d, 1H, $J_{b,a}$ 11.6, OCH_2Ph)
4.661 (d, 1H, $J_{a,b}$ 11.6, OCH_2Ph)
4.699 (d, 1H, $J_{b,a}$ 11.5, OCH_2Ph)
4.723 (d, 1H, $J_{b,a}$ 12.5, OCH_2Ph)
4.777 (d, 1H, $J_{a,b}$ 12.5, OCH_2Ph)
5.022 (d, 1H, $J_{a,b}$ 11.5, OCH_2Ph)
7.243-7.418 (m, 15H, aromatic protons)

δ_C 24.12T (C-4), 33.83T (C-3), 61.12T (C-7), 68.26T (C-2), 71.54T, 72.21T 75.60T (OCH_2Ph); 73.84D (C-8), 77.12D (C-10), 80.35D (C-9), 108.29S (C-5), 127.48-128.28D (aromatic carbons); 138.50S 138.56, 138.60S (aromatic carbons).

FAB-MS: *m/z* 460 $[M]^+$. Exact mass Calculated for $C_{29}H_{32}O_5$, 460.2250; Found, 460.2249.

(5*R*,8*S*,9*S*,10*R*)-8,9,10-Tri-(benzyloxy)-1,6-dioxaspiro[4.5]decane (86b)

R_f 0.52 (EtOAc-hexane 1:2); $[\alpha]_D$ +15.4, (*c* 0.81, $CHCl_3$)

δ_H 1.879 (m, 2H, H-4)

1.994 (m, 2H, H-3)

3.330 (dd, 1H, $J_{7(eq),8}$ 2.3, $J_{7(eq),7(ax)}$12.4, H-7b)

3.552 (dd, 1H, $J_{9,8}$ 3.4, $J_{9,10}$ 8.3, H-9)

3.731(m, 1H, $J_{8,7(eq)}$ 2.3 $J_{8,9}$ 3.4, $J_{8,7\,(ax)}$ 4.9, H-8)

3.909 (d, 1H, $J_{10,9}$ 8.3, H-10)

3.946 (ddd, 1H, $J_{2a,2b}$ 7.9, $J_{2a,3a/3b}$ 8.0, 6.2, H-2b)

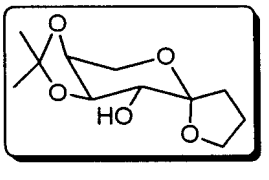
4.00 (dd, 1H, $J_{7(ax),7(eq)}$ 12,4, $J_{7(ax),8}$ 4.9, H-7a)

4.06 (ddd, 1H, $J_{2a,2b}$ 7.9, $J_{2a,3a/3b}$ 7.7, 5.9, H-2a)

7.257-7.393 (m, 15H, aromatic protons)

δ_C 24.03T (C-4), 9.51T (C-3), 61.08T (C-7), 68.34T (C-2), 71.03T, 72.40T, 74.67T (OCH_2Ph); 72.73D (C-8), 77.856D (C-9), 78.79D (C-10), 109.49S (C-5) 127.43-128.26D (aromatic carbons); 138.39S, 138.66S, 138.72S, (aromatic carbons).

FAB-MS: *m/z* 461 $[M+H]^+$. Exact mass: Calculated for $C_{29}H_{32}O_5$, 461.2328; Found, 461.2328.



(5*S*,8*S*,9*S*,10*R*)-8,9-*O*-Isopropylidene-1,6-dioxaspiro[4.5]decan-10-ol (102a)

Debenzylation of (5*S*,8*S*,9*S*,10*R*)- (86a) and (5*R*,8*S*,9*S*,10*R*)-8,9,10-Tri-(benzyloxy)-1,6-dioxaspiro[4.5]decane (86b)

a. Pd/C (10%, 200 mg) was added to a solution of the spiro compound (**86a**) [or (**86b**)] (2 03g, 4.42 mmol) in methanol (20 ml) and the suspension stirred in a H_2 atmosphere (80 psi) for 24 h. The catalyst was removed by filtration and the solvent was evaporated to give the crude product.

b. $Pd(OH)_2/C$ (20%, 200 mg) was added to a solution of the tri-*O*-benzyl spiro compound (**86b**) [or (**86a**)] (2.01 g, 4.41 mmol) in cyclohexene:ethanol (1:2, 24 ml)

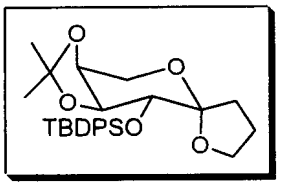
mixture and the suspension refluxed for 4 h. The catalyst was removed by filtration and the solvent was evaporated to give the crude product.

p-Toluenesulfonic acid (88 mg) was added in separate experiments, to a solution of each of the crude triols obtained above, in acetone (1.5 ml) and 2,2-dimethoxypropane (5.2 ml). The reaction mixture was stirred for 2 h at room temperature when Et_3N (2 ml) was added to the solution. The solvent was evaporated and the residue partitioned between diethyl ether and water. The ether solution was dried (Na_2SO_4) and the solvent evaporated. Column chromatography using hexane-EtOAc (1:1) gave in each case only the acetonide (**102a**) (0.75 g, 75% yield) from the hydrogen-transfer reaction and (0.71g, 70%) from catalytic hydrogenation. Recrystallisation from diethyl ether-hexane gave colourless crystals of the acetonide, mp 58-60 °C; R_f 0.61 (hexane-EtOAc 1:1), $[\alpha]_D$ +167.1, (*c* 0.85, $CHCl_3$).

δ_H 1.299 (s, 3H, acetonide Me)
1.480 (s, 3H, acetonide Me)
1.812 (m, 1H, H-3b)
1.830 (m, 1H, $J_{4b,3a/3b}$ 8.3, $J_{4b,4a}$ 17.1, H-4b)
1.975 (m, 1H-3a)
2.177 (ddd, 1H, J, 9.3, J, 3.6, $J_{4a,4b}$ 17.1, H-4a)
2.388 (d, 1H, $J_{OH,10}$ 8.0, OH)
3.649 (dd, 1H, $J_{10,OH}$, 7.6, $J_{10,9}$ 7.5, H-10)
3.859 (m, 1H, $J_{2b,a}$ 8,3, $J_{2b,3a/3b}$ 8.3, 6.5, H-2b)
3.884 (m, 1H, $J_{7b,7a}$ 13.2, $J_{7b,8}$ 1.0, H-7b)
3.919 (ddd, 1H, $J_{2a,2b}$ 8.3, $J_{2a,3a/3b}$ 2.6, 7.5, H-2a)
3.962 (dd, 1H, $J_{7a,8}$ 2.6, $J_{7a,7b}$ 13.2, H-7a)
4.058 (dd, 1H, $J_{9,8}$ 5.7, $J_{9,10}$ 7.5, H-9)
4.142 (ddd, 1H, $J_{8,9}$ 5.7, $J_{8-,7a}$ 2.6, $J_{8,7b}$ 1.0, H-8)

δ_C 23.74T (C-3), 26.07Q (acetonide Me), 28.09Q (acetonide Me), 33.37T (C-4), 59.58T (C-7), 68.66T (C-2), 71.86D (C-10), 73.80D (C-8), 77.96D (C-9), 107.22S (C-5), 109.04S (acetonide acetal).

FAB-MS: *m/z* 231 $[M+H]^+$. Exact mass: Calculated for $C_{11}H_{19}O_5$, 231.1233; Found, 231.1234.



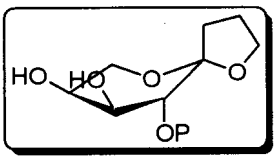
(5*S*,8*S*,9*S*,10*R*)-8,9-*O*-Isopropylidene-10-[(*t*-butyldiphenylsilyl)oxy]-1,6-dioxaspiro-[4.5]decane (85a)

To a stirred solution of the alcohol (**102a**) (0.42 g, 1.73 mmol) and imidazole (0.55 g, 8.17 mmol), in dry dichloromethane (3 ml) and a catalytic amount of DMAP (40. mg) was added TBDPS-Cl (0.54 ml, 2.07 mmol). After 6 h the reaction mixture was partitioned between water and dichloromethane and the organic phase was dried (Na_2SO_4). Column chromatography with EtOAc-hexane (1:7) gave compound (**85a**) (0.75 g, 92%) as a colourless oil; R_f 0.56 (EtOAc-hexane 1:7); $[\alpha]_D$ +51.3, (*c* 0.69, $CHCl_3$).

δ_H 1.092 (s, 9H, CMe_3)
1.161 (s, 3H, acetonide Me)
1.272 (s, 3H, acetonide Me)
1.491 (ddd, 1H, J 4.4, 9.0, 12.7, H-4b)
1.730 (m, 1H, H-3b)
1.888 (m, 1H, H-3a)
1.967 (m, 1H, H-4a)
3.773 (d, 1H, $J_{10,9}$ 7.2, H-10)
3.814 (d, 1H, $J_{7b,7a}$ 13.2, H-7b)
3.927 (ddd, 1H, $J_{2b,2a}$ 8.1, $J_{2b,3a/3b}$ 8.3, 5.6, H-2b)
3.985 (dd, 1H, $J_{7a,8}$ 2.6, $J_{7a,7b}$ 13.7, H-7a)
4.073 (ddd, 1H, $J_{a,b}$ 8.1, $J_{2a,3b}$ 7.8, $J_{2a,3a}$ 6.6, H-2a)
4.151 (dd, 1H, $J_{8,9}$ 5.7, $J_{8,7a}$ 2.6, H-8)
4.335 (dd, 1H, $J_{9,8}$ 5.7, $J_{9,10}$ 7.2, H-9)
7.779-7.703 and 7.443-7.340 (m, 10H, aromatic protons)

δ_C 19.75S (CMe_3), 22.99T (C-3), 26.26Q (acetonide Me), 26.55Q (CMe_3), 27.67Q (acetonide Me), 33.26T (C-4), 59.23T (C-7), 68.41T (C-2), 73.68D (C-10) 74.00D (C-8) 78.13D (C-9) 107.56S (C-5), 108.51S (acetonide acetal), 136.48-127.21D (aromatic carbons), 132.58S, 134.58S, (*ipso* aromatic carbons).

FAB-MS: *m/z* 468 $[M]^+$. Exact mass: Calculated for $C_{27}H_{36}SiO_5$, 468.2332; Found, 468.2333.



(5*S*,8*S*,9*S*,10*R*)-10-[(*t*-Butyldiphenylsilyl)oxy]-1,6-dioxaspiro[4.5]decan-8,9-diol (84a)
The acetonide (**85a**) (0.20 g, 0.40 mmol) and *p*-toluenesulfonic acid (20 mg) in 5% aqueous methanol (3 ml) was stirred for 6 h. Et_3N (x ml) was added and the solvent was evaporated. The residue was partitioned between water and EtOAc. The aqueous phase was extracted three times with EtOAc and the combined organic extracts dried over Na_2SO_4. The solvent was evaporated and the residue purified by column chromatography (EtOAc-hexane 2:1) to give the diol (**84a**) (0.15 g, 83%). The compound was recrystallized from acetone-water to give white crystals with mp 132-133 °C; R_f 0.70; (EtOAc-hexane 2:1) $[\alpha]_D$ +59.9. (*c* 0.51, $CHCl_3$).

δ_H 1.039 (s, 9H, CMe_3)
1.689 (ddd, 1H, $J_{4b,3b}$ 3.6, $J_{4b,3a}$ 8.4, $J_{4a,4b}$ 12.4, H-4b)
1.823 (m, 1H, $J_{3b,2a}$ 8.0, $J_{3b,2b}$ 5.8, $J_{3b,3a}$ 16.0, $J_{3b,4a}$ 9.8, $J_{3b,4b}$ 3.6, H-3b)
1.965 (m, $1H_{3a,2a}$ 6.6, $J_{3a,2b}$ 8.3, $J_{3a,3b}$ 16.0, $J_{3a,4a}$ 8.4, $J_{3a,4b}$ 8.4, H-3a)
1.974 (dd, 1H, J 2.3, J 2.6, HO-9)
2.054 (ddd, 1H, $J_{4a,4b}$ 12.4, $J_{4a,3a}$ 8.4, $J_{4a,3b}$ 9.8, H-4a)
2.349 (dd, 1H, $J_{OH,8}$ 2.6, $J_{OH,7a}$ 1.6, OH-8)
3.548 (dd, 1H, $J_{7b,7a}$ 12.4, $J_{7b,8}$ 1.7, H-7b)
3.754 (ddd, 1H, $J_{8,7b}$ 1.7, $J_{8,7a}$ 1.6, $J_{8,OH8}$ 2.6, H-8)
3.831 (ddd, 1H, $J_{7a,8}$ 1.6, $J_{7a,OH8}$ 1.6 $J_{7a,7b}$ 12.4, H-7a)
3.926 (m, 2H, H-9 and H-10)

3.948 (ddd, 1H, $J_{2b,3b}$ 5.8, $J_{2b,2a}$ 8.2, 8.3, H-2b)

4.046 (ddd, 1H, $J_{2a,3b}$ 8.0, $J_{2a,3a}$ 6.6 , $J_{2a,2b}$ 8.2, H-2a)

7.762-7.347 (m, 10H, aromatic protons)

δ_C 19.67S (CMe_3), 23.44T (C-4), 27.06Q (CMe_3), 33.47T (C-3), 62.57T (C-7), 68.59T (C-2), 69.80D (C-8), 71.58D, 72.85D (C-10&C-9); 108.36S (C-5), 127.71D-135.98D (aromatic carbons); 132.85S, 134.31S (*ipso* aromatic carbons).

δ_H (DMSO-d_6)

0957 (s, 9H, CMe_3)

1.373 (ddd, 1H, $J_{4b,3a/3b}$ 3.9, 8.7, $J_{4b,4a}$ 12.3, H-4b)

1.567 (m, 1H, H-3b)

1.767 (m, 1H, H-3a)

1.858 (ddd, 1H, $J_{4a,3a/ab}$ 8.4, 10.0, $J_{4a,4b}$ 12.3, H-4a)

3.332 (dd, 1H, $J_{7b,7a}$ 11.8, $J_{7b,8/8OH}$ 1.7, H-7b)

3.619 (m,1H, $J_{8,9}$ 3.5, $J_{8,8OH}$, 3.5, $J_{8,7a/7b}$ 1.7, H-8)

3.622 (m, 1H, $J_{7a,7b}$, 11.8, H-7a)

3.719 (ddd, 1H, $J_{9,8}$ 3.5, $J_{9,-9OH}$ 7.3, $J_{9,10}$ 9.5, H-9)

3.777 (ddd, 1H, $J_{2b,2a}$ 8.0, $J_{2b,3a/3b}$ 8.0, 5.9, H-2b)

3.855 (d, 1H, $J_{9HO,9}$ 7.3, 9-OH)

3.888 (d, 1H, $J_{10,9}$ 9.5, H-10)

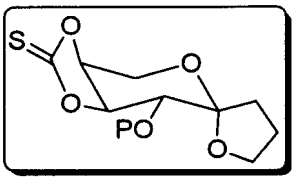
3.936 (ddd, 1H, $J_{2a,2b}$ 8.0, $J_{2a,3a/3a}$ 6.0, 8.0, H-2a)

4.498 (d, 1H, $J_{8,OH,8}$ 3.5, 8-OH)

7.703-7.374 (aromatic protons)

δ_C 19.57S (CMe_3), 22.81T (C-4), 26.89Q (CMe_3), 32.99T (C-3), 63.12T (C-7), 67.24T (C-2), 69.08D (C-8), 70.55D (C-9) 72.36D (C-9); 107.99S (C-5), 127.30-135.50D (aromatic carbons); 133.62S, 134.30S (*ipso* aromatic carbons).

FAB-MS: *m/z* 428 $[M]^+$. Exact mass: Calculated for $C_{24}H_{32}SiO_5$, 428.2019; Found, 428.2020.



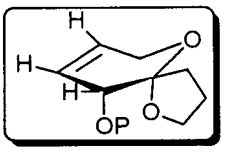
(5*S*,8*S*,9*S*,10*R*)-10-[(*t*-Butyldiphenylsilyl)oxy]-8,9-*O*-thiocarbonyl-1,6-dioxaspiro-[4.5]decane (103a)

1,1′-Thiocarbonyldiimidazole (1.60 g, 8.81 mmol) was added to a solution of the diol (**84a**) (1.31 g, 3.02 mmol) in dry acetonitrile (20 ml) under argon and the solution was stirred at room temperature for 5 h. The reaction mixture was poured into brine and extracted with $CHCl_3$. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (hexane-EtOAc, 2:1) gave compound (**103a**) (1.36 g, 96%); R_f. 0.67 (hexane-EtOAc, 2:1); $[\alpha]_D$ +42.3, (*c* 0.53, $CHCl_3$).

δ_H 1.081 (s, 9H, CMe_3)
1.439 (m, 1H, H-4b)
1.733 (m, 1H, H-3b)
1.884(m, 2H, H-3a and H-4a)
3.743 (d, 1H, $J_{10,9}$ 7.2, H-10)
3.918 (ddd, 1H,$J_{2a,2b}$ 14.1, $J_{2b,3a/3b}$ 8.0, 5.4, H-2b)
4.062 (ddd, 1H, $J_{2a,2b}$ 14.1, $J_{2a,3a/3b}$ 8.0, 6.2, H-2a)
3.950 (d, 1H, $J_{7b,7a}$ 14.2, H-7b)
3.995 (dd, 1H, $J_{7a,7b}$ 14.2, $J_{7a,4}$ 2.3, H-7a)
4.789 (ddd, 1H, $J_{8,9}$ 7.0, $J_{8,7a}$ 2.3, $J_{8,7b}$ 1.0, H-8)
5.033 (dd, 1H, $J_{9,8}$ 7.0, $J_{9,10}$ 7.2, H-9)
7.748-7.357 (m, 10H, aromatic protons)

δ_C 19.64S (CMe_3), 23.02D (C-3), 26.99Q (CMe_3), 33.11D (C-4), 57.60D (C-7), 69.04T (C-2), 71.65D (C-10), 80.31D (C-8), 83.30D (C-9), 106.69S (C-5), 127.57-136.11D (aromatic carbons), 131.14S, 132.83S (*ipso* aromatic carbon); 190.77S (C=S).

FAB-MS: *m/z* 470 $[M]^+$. Exact mass: Calculated for $C_{25}H_{31}SiO_5$, 471.1662; Found, 471.1661.



(5*S*,10*R*)-10-[(*t*-Butyldiphenylsilyl)oxy]-1,6-dioxaspiro[4.5]dec-8-en (83a)

A solution of the thiocarbonate (**103a**) (210 mg, 0.42 mmol) in trimethyl phosphite (12 ml) under argon was heated at reflux temperature for 24 h (TLC control). The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography hexane-EtOAc, 7:1) to give the olefin (**83a**) (0.11 g, 68%); R_f 0.55 (hexane-EtOAc 7:1); $[\alpha]_D$ –5.8, (*c* 0.93, $CHCl_3$).

δ_H 1.064 (s, 9H, CMe_3)
1.588 (m, 1H, H-4b)
1.836 (m, 1H, H-3b)
1.991 (m, 1H, H-3a)
2.013 (m, 1H, H-4a)
3.887 (m, 1H, $J_{7b,7a}$ 15.8, J 1.6, J 3.4, J 1.1, H-7b)
4.043 (ddd, 1H, $J_{2b,2a}$ 8.1, $J_{2b,3a/3b}$ 8.2, 5.4, H-2b)
4.088 (ddd, 1H, $J_{2a,2b}$ 8.1, $J_{2a,3a/3b}$ 6.9, 8.2, H-2a)
4.235 (m, 1H, $J_{7a,7b}$ 15.8, J 0.8, J 1.1, J 4.4, H-7a)
4.436 (m, J, 1.6, J 1.1, J 4.9, H-10)
5.616 (m, 1H, $J_{8,9}$ 10.5, J 1.3, J 2.1, H-8)
5.662 (m, 1H, $J_{9,8}$ 10.5, J 1.3, J 2.6, H-9)
7.333-7.731 (m, 10H, aromatic protons)

δ_C 19.42S (CMe_3), 24.07T (C-3), 26.98Q (CMe_3), 33.73T (C-4), 60.99T (C-7), 68.07D (C-10), 69.02T (C-2), 105.47S (C-5), 126.31D (C-9), 127.61D (C-8), 127.56-136.01D (aromatic carbons); 133.55S, 133.87S (*ipso* aromatic carbons).

δ_H (D_6C_6)
1.274 (s, 9H, CMe_3)
1.78o (m, 1H, H-3a)
1.914 (m, 1H, H-4b)
1.972 (m, 1H, H-3a)

2.321 (m, 1H, H-4a)

3.837 (ddd, J 2.1, 2.1, 3.0, $J_{7b,7a}$ 16.6, H-7b)

4.054 (ddd, 1H, $J_{2b,2a}$ 8.0, $J_{2b,3a/3b}$ 5.7, 8.0, H-2b)

4.091 (ddd, 1H, $J_{2a,2b}$ 8.0, $J_{2a,3a/3b}$ 7.0, 8.0, H-2a)

4.323 (m, 1H, J 1.8, 2.7, 3.8, $J_{7a,7b}$ 16.6, H-7a)

4.845 (ddd, 1H, J 1.8, 2.3, 2.3, 3.6, H-10)

5.384 (m, 1H, J 1.8, J 1.8, J 2.6, $J_{8,9}$ 10.3, H-8)

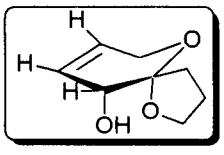
5.817 (m, 1H, J 1.8, 1.8, 3.6, $J_{9,8}$ 10.3, H-9)

7.342-7.307 (m, 10H, aromatic protons)

δ_C (D_6C_6)

20.07S (CMe_3), 24.99T (C-3), 27.44Q (CMe_3), 34.76T (C-4), 61.447T (C-7), 69.37T (C-2), 69.53 (C-10), 106.13S (C-5), 130.22D (C-9), 130.34D (C-8), 128.00-128.64D, 136.42D, 136.67D (aromatic carbons), 134.62S, 135.16S (*ipso* aromatic protons).

FAB-MS: *m/z* 394 $[M]^+$. Exact mass: Calculated for $C_{24}H_{30}SiO_3$, 394.1964; Found, 394.1964.



(5*S*,10*R*)-1,6-Dioxaspiro[4.5]dec-8-en-10-ol (82a)

A solution of (**83a**) (0.11 g, 0.25 mmol), in THF (5 ml) was stirred at RT with tetra-butylammonium fluoride (19 mg, 0.50 mmol) for 2 h. The solvent was evaporated and the residue partitioned between water and chloroform, and dried over Na_2SO_4. After column chromatography with hexane-EtOAc (1:1) the alcohol (**82a**) (30 mg, 77%) was obtained as a colourless oil: R_f 0.55 (hexane-EtOAc 1:1)

δ_H 2.25-1.86 (m, 4H, H-3 and H-4)

4.07-3.94 (m, 3H, H7b and H-2)

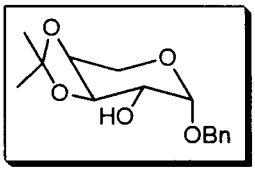
4.24-4.14 (m, 2H, H7a and H-10)

5.715 (ddd, 1H, J 1.3, J 1.3, J 2.1, J 10.3 Hz, H-9)

5.786 (ddd, 1H, J 1.5, J 1.5, J 2.8, J 10.3 Hz, H-8)

δ_C 24.34T (C-3), 33.99T (C-4), 60.80T (C-7), 66.01D (C-10), 69.19T (C-2), 126.96D (C-9), 127.59D (C-8).

4.3.2 Synthesis of the 1,6-dioxaspiro[4.5]dec-8-en-10-ols: Route 2: Acetonide and TBDPS protecting group strategy.



Benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (104)

2.2-Dimethoxypropane (82 ml) and TsOH (0.5 g) were added to a solution of (**98**) (20.0 g, 83.3 mmol) in dry acetone (20 ml). The reaction mixture was stirred for 2 h at room temperature and Et_3N (20 ml) was added to the solution. The solvent was evaporated and the residue partitioned between diethyl ether and water. The ether solution was dried (Na_2SO_4) and the solvent evaporated. Recrystallisation from diethyl ether-hexane gave colourless crystals of the acetonide (**104**) (15.9 g, 68%); mp 64–66 °C, R_f 0.67 (EtOAc-hexane 1:1).

δ_H 1.46 (s, 3H, acetonide Me)

1.63 (s, 3H, acetonide Me)

2.72 (d, H, $J_{H2,OH}$ 6.2, OH)

3.77 (m, H, H-2)

3.88 (dd, H, $J_{5a,5b}$ 13.2, $J_{5a,4}$ 1.0, H-5a)

3.96 (dd, H, $J_{5b,5a}$ 13.1, $J_{5e,4}$ 1.0, H-5b)

4.187-4.172 (m, 2H, H3 and H4)

4.510 (d, 1H, $J_{b,a}$ 11.9, OCH_2Ph)

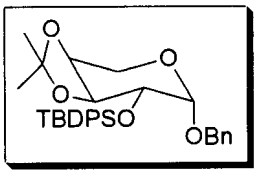
4.740 (d, 1H, $J_{a,b}$ 11.9, OCH_2Ph)

4.89 (d, 1H, $J_{1,2}$ 3.6, H-1)

7.35-7.22 (m, 5H, aromatic carbon)

δ_C 26.32Q (acetonide Me), 28.28Q (acetonide Me), 60.26D (C-2), 70.37T (OCH_2Ph), 70.37T (C-5), 76.30D and 73.32 2D (C-3 and C-4), 97.42D (C-1), 109.54S (acetonide acetal); 127.82-128.37D (aromatic carbons), 136.97S (*ipso* aromatic carbon).

FAB-MS: *m/z* 281 $[M+H]^+$. Exact mass: Calculated for $C_{15}H_2O_5$, 281.1389; Found, 281.1389.



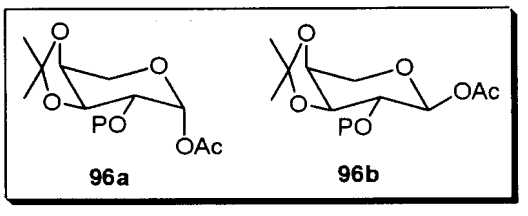
Benzyl 2-[(*t*-butyldiphenylsilyl)oxy]-3,4-*O*-isopropylidene-β-L-arabinopyranoside (97)

t-Butyldiphenylsilyl chloride (21.7 g, 78.9 mmol) was added to a stirred solution of imidazole (17.9 g, 263 mmol), DMAP (200 mg) and (**104**) (18.4 g, 65.7 mmol) in CH_2Cl_2 (500 ml). After 6 h water (100 ml) was added to the reaction. The organic solution was dried (Na_2SO_4) and evaporated. The crude product was recrystallised from hexane to give the white crystalline TBDPS ether (**97**) (30.6 g, 90 %); R_f 0.68 (EtOAc:Hexane 1:4), mp 91-92°C, $[\alpha]_D$ +32.9 (*c* 0.63, $CHCl_3$).

δ_H 1.113 (s, 9H, CMe_3)
1.270 (s, 3H, acetonide Me)
1.341 (s, 3H, acetonide Me)
3.830 (dd, H, $J_{2,3}$ 7.5, J 3.6, H-2)
3.872 (dd, H, $J_{5a,5b}$ 13.9, $J_{5a,4}$ 0, H-5a)
3.948 (dd, H, $J_{5b,5a}$ 13.2, $J_{5b,4}$ 2.9,H-5b)
4.204 (dd, H, $J_{3,4}$ 5.7, $J_{5b,4}$ 2.1, H-4)
4.408 (dd, H, $J_{3,2}$ 7.5, $J_{3,4}$ 5.7, H-3)
4.321 (d, H, $J_{b,a}$ 11.9, OCH_2Ph)
4.442 (d, H, $J_{1,2}$ 3.6, H-1)
4.643 (d, H, $J_{a,b}$ 11.9, proton)
7.931-7.554 (m, 15H, aromatic protons)

δ_C 19.30S (CMe_3) 26.33Q (acetonide Me) 26.93Q (CMe_3) 27.90Q (acetonide Me) 58.85T (C-5); 69.50T (OCH_2Ph); 72.52T (C-2); 73.56D (C-4); 76.60D (C-3); 97.97D (C-1); 108.58S (acetonide acetal); 127.50-129.70D, 135.80D, 136.19D (aromatic carbons); 133.06S, 134.42S, 137.43S (*ipso* aromatic carbons).

FAB-MS: *m/z* 518 $[M]^+$. Exact mass: Calculated for $C_{31}H_{38}O_5Si$ 518.2488; Found, 518.2488.



2-[(*t*-Butyldiphenylsilyl)oxy]-3,4-*O*-isopropylidene-L-arabinopyranosyl acetate (96)

A mixture of freshly prepared benzyl glycoside (**97**) (10.1 g, 19.3 mmol) and barium carbonate (3.94 g, 20.0 mmol) in carbon tetrachloride (120 ml) was refluxed for 30 min. NBS (7.89 g, 55.1 mmol) and after a further 2.5 h HMPA (4 ml) was added. After another 40 min. acetic acid (35 ml) and sodium acetate (15.8 g, 193 mmol) were added and the reaction refluxed for another 90 min. The solution was diluted with chloroform and washed with $NaHCO_3$ solution. The crude product (α:β 1:7) obtained from the organic solution was purified by column chromatography (EtOAc-hexane 1:4) to give the two anomers (7.50 g, 83%)

α-Isomer (96b)

R_f 0.55 (EtOAc-hexane 1:4); $[\alpha]_D$ +29.2 (*c* 0.51, $CHCl_3$).

δ_H 1.061 (s, 9H, CMe_3)
1.167 (s 3H, acetonide Me)
1.277 (s, 3H, acetonide Me)
1.501 (s, 3H, OAc)
3.735 (dd, 1H, $J_{2,3}$ 7.5, $J_{2,1}$ 7.5, H-2)
3.859 (dd, 1H $J_{5b,4}$ 2.6, $J_{5b,5a}$13.2, H-5b)
3.973 (dd, 1H, $J_{5a,4}$ 2.9, $J_{5a,5b}$ 13.2, H-5a)

4.247 (m, 2H, H-3&H-4)

5.543 (d, 1H, $J_{1,2}$ 7.5, H-1)

7.770-7.239 (m, 10H, aromatic protons)

δ_C 19.35S (CMe_3), 20.39Q (acetate Me), 26.76Q (CMe_3), 25.92Q and 27.21Q (acetonide Me) 63.39T (C-5), 72.56D (C-2), 73.17D (C-4), 78.84D (C-3), 94.04D (C-1), 109.84S (acetonide acetal), 127.39-129.91D, 135.52D and 136.40D (aromatic carbons), 131.90-134.183S (*ipso* aromatic carbons), 169.75S (acetate CO).

FAB-MS: *m/z* 470 $[M]^+$. Exact mass: Calculated for $C_{26}H_{34}SiO_6$, 470.2125; Found, 470.2126.

β-Isomer (96a)

R_f 0.48 (EtOAc-hexane 1:4); $[\alpha]_D$ +62.3 (*c* 0.59, $CHCl_3$)

δ_H 1.064 (s, 9H, CMe_3)

1.209 (s, 3H, acetonide Me)

1.289 (s, 3H, acetonide Me)

2.058 (s, 3H, acetate Me)

3.789 (dd, 1H, $J_{2,3}$ 6.3, $J_{2,1}$ 3.6, H-2)

3.908 (dd, 1H, $J_{5,4}$ 1.3, $J_{5b,5a}$ 13.2, H-5b)

4.025 (dd, 1H, $J_{5b,4}$ 2.9, $J_{5a,5b}$ 13.2, H-5a)

4.227 (ddd, 1H, $J_{4,3}$ 6.1, $J_{4,5a}$ 2.9, $J_{4,5b}$ 1.3, H-4)

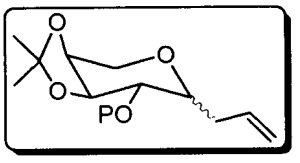
4.333 (dd, 1H, $J_{3,2}$ 6.2, $J_{3,4}$ 6.1, H-3)

4.734 (d, 1H, $J_{1,2}$ 3.6, H-1)

7.736-7.314 (m, 10H, aromatic protons)

δ_C 19.26S (CMe_3), 20.80Q (acetate Me), 27.49Q and 25.954Q (acetonide Me), 26.85Q (CMe_3), 61.16T (C-5), 70.52D (C-2), 72.72D (C-4), 75.76D (C-3), 91.27D (C-1), 109.148S (acetonide acetal), 127.54-129.96D, 135.55-136.43D (aromatic carbons), 132.85S, 133.28S (*ipso* aromatic carbons), 169.38S (acetate CO).

FAB-MS: *m/z* 470 $[M]^+$. Exact mass: Calculated for $C_{26}H_{34}SiO_6$, 470.2125; Found, 470.2131.



2-[(*t*-Butyldiphenylsilyl)oxy]-1-deoxy-1-(prop-2-enyl)-3,4-*O*-isopropylidene-L-arabino-pyranose (95)

To a stirred solution of the 1-*O*-acetate (**96**) (0.50 g, 1.06 mmol) and allyltrimethylsilane (0.22 ml, 1.26 mmol) in acetonitrile (5 ml) at 0 °C was added dropwise $BF_3.OEt_2$ (0.3 ml, 2.2 mmol). After 1 h the reaction was allowed to warm to 25 °C and the stirring was continued for another 1 h. The reaction mixture was poured into a mixture of saturated $NaHCO_3$ solution (4 ml), and diethyl ether (15 ml). The organic layer was separated and washed again with $NaHCO_3$ solution, brine, and dried ($MgSO_4$). Solvent evaporation followed by column chromatography (hexane-EtOAc 10:1) gave a 1:1 anomeric mixture of the 1-*C*-allyl substituted sugar as an oil (0.32 g, 66%); R_f 0.64 (hexane-EtOAc 10:1) $[\alpha]_D$ +15.8 (*c* 0.92, $CHCl_3$).

α- Isomer (95b)

δ_H 1.074 (s, 9H CMe_3)

1.109 (s, 3H, acetonide Me)

1.162 (s, 3H, acetonide Me)

1.869 (m, 1H, $J_{1b',1a'}$ 14.5, $J_{1b',1}$ 8.0, $J_{1b',2'}$ 6.5, $J_{1b',3'a/b}$ 2.5, 1.3, H-1b′)

2.397 (m, 1H, $J_{1a',1b'}$ 14.5, $J_{1a',1}$ 2.8, $J_{1'a,2'}$ 7.2, $J_{1a',3'a/b}$ 4.4, 1.3, H1a′)

3.208 (ddd, 1H, $J_{1,2}$ 9.3, $J_{1,1b'}$ 8.0, $J_{1',1a'}$ 2.8, H-1)

3.545 (m, 1H, H-2)

3.690 (dd, 1H, $J_{5b,5a}$, 13.2, $J_{5b,4}$ 1.8, H-5b)

4.079 (d, 1H, $J_{5a,5b}$ 13.2, H-5a)

4.154-4.141 (m, 2H, H-4 and H-3)

4.948 (m, 2H, H-3′)

5.725 (m, 1H, $J_{2',3'a/3b}$ 17.1, 9.4, $J_{2',1b'}$ 6.6, $J_{2',1a'}$ 2.3, H-2′)

7.31-7.72 (m, 10H, aromatic protons)

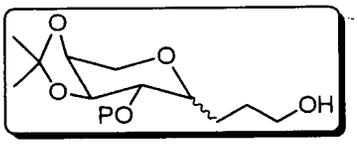
δ_C 19.55S (CMe_3), 25.53Q (acetonide Me), 27.08Q (CMe_3), 27.25Q (acetonide Me), 36.73T (C-1′), 66.36T (C-5), 73.72D (C-3), 78.76D (C-4), 74.42D (C-2), 79.72D (C-1), 108.78S (acetonide acetal), 116.68T (C-3′), 127.40-136.40D (aromatic carbons), 133.16S, 133.73S (*ipso* aromatic carbons); 135.08D (C-2′).

β-Isomer (95a)

δ_H 1.100 (s, 9H, CMe_3)
1.242 (s, 3H, acetonide Me)
1.353 (s, 3H, acetonide Me)
2.178 (m, 1H, $J_{1b',1a'}$ 14.5, $J_{1b',1'}$ 6.2, $J_{1b',2'}$ 4.7, $J_{1b',3'}$ 2.6, $J_{1b',3'}$ 1.3, H-1b′)
2.641 (m, 1H, $J_{1'a',1b'}$ 14.5, $J_{1a',1'}$ 8.3, $J_{1a',2'}$ 7.0, $J_{1a',3'}$ 2.8, $J_{1a',3'}$ 1.3, H-1′)
3.503 (dd, $J_{5a,5b}$, 11.9, $J_{5a,4}$ 6.7, H-5b)
3.945 (dd 1H, $J_{2,3}$ 3.3, $J_{2,1}$ 2.3 H-2)
4.013 (dd, 1H, $J_{5b,5a}$ 11.9, $J_{5b,4}$ 5.2, H-5a)
4.073 (dd, 1H, $J_{3,4}$ 5.7, $J_{3,2}$ 3.3, H-3)
4.178 (m, 1H, H-4)
3.545 (m, 1H, H-1)
5.702 (m, 1H, $J_{2',3'}$ 16.8, $J_{2',3'}$ 10.0, $J_{2'1a'}$ 7.0, $J_{2',1b'}$ 2.6, H-2′)
4.948 (m, 2H, H-3′)
7.318-7.723 (m, 10H, aromatic protons)

δ_C 19.58S (CMe_3), 26.10Q (acetonide Me), 27.08Q (CMe_3), 27.63Q (acetonide Me), 34.71T (C-1′) 65.44T (C-5), 74.82D (C-3), 74.72D (C-1), 70.25D (C-2), 70.41D (C-4), 109.21S (acetonide acetal), 116.52S (C-3′), 127.40-136.40D (aromatic carbons), 132.85S, 134.01S (*ipso* aromatic carbons); 135.12D (C-2′).

FAB-MS: *m/z* 452 $[M]^+$. Exact mass: Calculated for $C_{27}H_{36}SiO_4$, 452.2383; Found, 452.2383.



2-[(*t*-Butyldiphenylsilyl)oxy]-1-deoxy-1-(3-hydroxypropan-1-yl)-3,4-*O*-isopropylidene-L-arabinopyranse (94)

$BH_3.SMe_2$ (0.33 ml, 3.50 mmol) was added dropwise to a stirred solution of the isomeric mixture of the 1-*C*-allyl sugar (**95**) (0.81 g, 1.80 mmol) in THF (5 ml) at 25°C. After 1 h the reaction mixture was cooled to 0°C and treated dropwise with 3M NaOH (2.2 ml, 6.7 mmol) and 30% H_2O_2 (0.7 ml, 5.6 mmol) for 20 min. The cooling bath was removed and the reaction mixture was stirred for another 20 min, diluted with diethyl ether and washed with H_2O, dried over $MgSO_4$ and concentrated. Column chromatography with hexane-EtOAc (1:2) the alcohol (**94**) as an oil (0.58 g, 70%); R_f 0.21 (hexane-EtOAc 1:2); $[\alpha]_D$ +36.0 (*c* 0.19, $CHCl_3$).

α-Isomer (94b)

δ_H 1.052 (s, 9H, CMe_3)
1.0465 (m, 1H, H-1b′)
1.144 (s, 3H, acetonide Me)
1.237 (s, 3H, acetonide Me)
1.474 (m, 2H, H-2′)
1.727 (m, 1H, and H-1a′)
1.892 (br s, 1H, OH)
3.124 (ddd, 1H, $J_{1,2}$ 9.3, $J_{1,1'}$ 8.0, $J_{1,1'}$ 2.3, H-1)
3.439-3487 (m, 3H, H-3′ and H-2)
3.678 (dd, 1H, $J_{5b,a}$ 13.3, $J_{5b,4}$ 1.8, H-5b)
4.074 (d, 1H, $J_{5a,b}$ 13.3 H-5a)
4.137 (m, 2H, H-3 and H-4)
7.702 (m, 10H, aromatic protons)

δ_C 14.16S (CMe_3), 26.13Q (acetonide Me) 27.05Q (CMe_3), 27.11T (C-1′), 27.29Q (Me), 27.63Q (acetonide Me), 28.83T (C-2′), 62.61T (C-3′), 66.33T (C-5), 73.69D (C-3), 74.88D (C-2), 78.95D (C-4), 79.96D (C-1), 109.21S (actonide

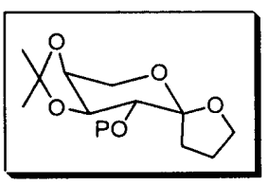
acetal), 127.38-136.38D (aromatic carbons), 132.80S, 134.10S (*ipso* aromatic carbons).

β-Isomer (94a)

δ_H 1.077 (s, 9H, CMe_3)
1.114 (s, 3H, acetonide Me)
1.349 (s, 3H, acetonide Me)
1.474 (m, 3H, H-2′ and H-1b′)
1.727 (m, 1H, H-1a′)
1.892 (br s, 2H, OH)
3.487 (dd, 1H, $J_{5,4}$ 6.5, $J_{5a,5b}$ 11.9, H-5b)
3.504 (m, 1H, H-1)
3.506 (dd, 2H, $J_{3',2a/2b}$ 6.5, 5.9 H-3a′)
3.904 (dd, 1H, $J_{2,1}$ 3.4, $J_{2,3}$ 2.3, H-2)
4.066 (dd, 1H, $J_{3,2}$ 2.3, $J_{3,4}$ 5.3, H-3)
4.099 (dd, 1H, $J_{5a,4}$ 5.0, $J_{5a,b}$ 11.9, H-5a)
4.198 (ddd, H, $J_{4,5a}$ 5.0, $J_{4,5b}$ 6.5, $J_{4,3}$ 5.3, H-4)
7.702 (m, 10H, aromatic protons)

δ_C 19.54S (CMe_3), 25.53Q and 27.28Q (acetonide Me), 27.05Q (CMe_3), 27.11T (C-1'), 29.44T (C-2'), 62.67T (C-3'), 65.37T (C-5), 70.35D (C-4), 70.60D (C-2) 74.88D (C-3), 74.93D (C-1), 108.83S (acetonide acetal), 127.38-136.38D (aromatic carbons), 133.18S, 133.68S (*ipso* aromatic carbons).

FAB-MS: *m/z* 471, $[M+H]^+$. Exact mass; Calculated for $C_{27}H_{39}SiO_5$, 471.2567; Found, 471.2567.



(5*R*,8*S*,9*S*,10*R*)-8,9-*O*-Isopropylidene-10-[(*t*-butyldiphenylsilyl)oxy]-1,6-dioxaspiro-[4.5]decane (85b)

A solution of compound (**94**) (6.51 g, 13.9 mmol) in cyclohexane (450 ml) containing (diacetoxyiodo)benzene (DIB) (1.75 g, 5.24 mmol) and iodine (3.50 g, 13.9 mmol) under argon was irradiated with a 300W tungsten filament lamp for 45 min. The reaction mixture was then poured into a saturated aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated. Chromatography of the residue using hexane-EtOAc (4:1) as eluant gave the two diastereomeric spiro compounds (**85a**) (1.40 g, 21%) and (**85b**) (2.42 g, 44%). Rf_a 0.77 (hexane-EtOAc 4:1).

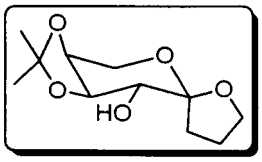
Spiroacetal (85b)

R_f 0.61 (hexane-EtOAc 4:1); $[\alpha]_D$ -13. 5 (*c* 0.25, $CHCl_3$)

δ_H 1.066 (s, 9H, CMe_3)
1.087 (s, 3H, acetonide Me)
1.110 (s, 3H, acetonide Me)
1.813 (m, 1H, H-4b)
1.961 (m, 2H, H-3)
2.059 (m, 1H, H-4a)
3.681 (dd, 1H, $J_{7,8}$ 5.1, $J_{7b,7a}$ 12.6, H-7b)
3.686 (ddd, 1H, $J_{2b,3a/3b}$ 6.4, J 8.5, $J_{2b,2a}$ 8.2, H-2b)
3.814 (dd, 1H, $J_{7a,7b}$ 12.6, $J_{7a,8}$ 6.1, H-7a)
3.855 (ddd, 1H, $J_{2a,3}$ 5.7, $J_{2a,3a/b}$ 8.1, $J_{2a,2b}$ 8.2, H-2a)
4.016 (d, 1H, $J_{10,9}$ 5.7, H-10)
4.045 (dd, 1H, $J_{9,10}$ 5.7, $J_{9,8}$ 5.4, H-9)
4.156 (ddd, 1H, $J_{8,9}$ 5.4, $J_{8,7b}$ 5.1, $J_{8,7a}$ 6.1, H-8)
7.754-7.307 (m, 10H, aromatic protons)

δ_C 19.61S (CMe_3), 23.46T (C-3), 25.69Q (acetonide Me), 27.01Q (CMe_3), 27.19Q (acetonide Me), 30.29T (C-4), 60.97T (C-7), 67.60T (C-2), 71.16D (C-8), 73.18D (C-10), 77.63D (C-9), 108.24S (C-5), 109.20S (acetonide acetal), 127.33-136.21D (aromatic carbons) 133.55S, 133.60 (*ipso* aromatic carbons).

FAB-MS: *m/z* 468 $[M]^+$. Exact mass: Calculated for $C_{27}H_{36}SiO_5$, 468.2332; Found, 468.2332.



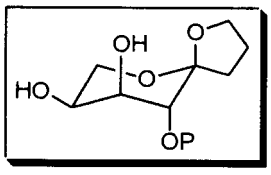
(5*R*,8*S*,9*S*,10*R*)-8,9-*O*-Isopropylidene-1,6-dioxaspiro[4.5]decan-10-ol (102b)

A solution of the 10-*O*-TBDPS ether (**85b**) (90 mg, 0.19 mmol) and TBAF (10 mg, 0.38 mmol) in THF (3 ml) was stirred for 4 h. The solvent was evaporated and the residue partitioned between water and chloroform, and dried (Na_2SO_4). Purification by column chromatography (hexane-EtOAc 1:1) gave the alcohol (**102b**) (35 mg, 79%) as a white solid; R_f 0.39 (hexane-EtOAc 1:1); $[\alpha]_D$ +11.9 (*c* 0.52, $CHCl_3$).

δ_H 1.325 (s, 3H, acetonide Me)
1.502 (s, 3H, acetonide Me)
1.815 (m, 1H, H-4b)
1.916 (m, 2H, H-3)
2.023 (m, 1H, H-4a)
3.757 (dd, 1H, $J_{7b,7a}$ 12.7, $J_{7b,8}$ 5.2, H-7b)
3.939 (m, 2H, H-2)
3.868 (d, 1H, $J_{10,9}$ 7.5, H-10)
3.949 (dd, 1H $J_{7a,7b}$ 12.7, $J_{7a,8}$ 5.4, H-7a)
4.022 (dd, 1H, $J_{9,8}$ 6.0, $J_{9,10}$ 7.5, H-9)
4.237 (ddd, 1H, $J_{8,7a}$ 5.4, $J_{8,7b}$ 5.2, $J_{8,9}$ 6.0, H-8)

δ_C 24.42T (C-3), 25.76Q (acetonide Me), 27.87Q (acetonide Me), 28.76T (C-4), 61.73T (C-7), 68.08T (C-2), 71.80D (C-8), 72.17D (C-10), 77.30D (C-9), 108.39S (C-5), 109.99S (acetonide acetal).

FAB-MS: *m/z* 231 $[M+H]^+$. Exact mass: Calculated for $C_{11}H_{19}O_5$, 231.1233; Found, 231.1237.



(5*R*,8*S*,9*S*,10*R*)-10-[(*t*-Butyldiphenylsily)oxy]-1,6-dioxaspiro[4.5]decan-8,9-diol (84b)

The acetonide (**85b**) (4.02 g, 8.50 mmol) and *p*-toluenesulfonic acid (0.4 g) in 5% aqueous methanol (64 ml) was stirred for 6 h. Et_3N (3.0 ml) was added and the solvent was evaporated. The residue was partitioned between water and EtOAc. The aqueous phase was extracted three times with EtOAc and dried over Na_2SO_4. Solvent evaporation followed by column chromatography of the residue using EtOAc-hexane (2:1) gave the diol (**84b**) (3.21 g, 83%); R_f 0.68 (EtOAc-hexane 2:1). The compound was recrystallized from acetone-water as white crystals, mp. 99–101 °C, $[\alpha]_D$ –19.6 (*c* 0.24, $CHCl_3$).

δ_H 1.069 (s, 9H, CMe_3)
1.456 (m, 1H, H-4b)
1.600 (m, 1H, H-3b)
1.856 (m, 1H, H-3a)
1.926 (ddd, 1H, $J_{4a,b}$ 19.9, $J_{4a,3a/3b}$ 8.0, 2.9, H-4a)
3.558 (dd, 1H, $J_{7b,8}$ 10.5, $J_{7b,7a}$ 11.4, H-7b)
3.664 (ddd, 1H, $J_{7a,7b}$ 11.4, $J_{7a,8}$ 5.7, $J_{7a,10}$ 0.8 H-7a)
3.783 (ddd, 1H, $J_{2b,2a}$ 8.1, $J_{2b,3a/3b}$ 6.5 , 8.0, H-2b)
3.796 (dd, 1H, $J_{9,10}$ 7.4, $J_{9,8}$ 3.4, H-9)
3.821 (dd, 1H, $J_{10,9}$ 7.4, $J_{10,7a}$ 0.8, H-10)
3.901 (ddd, 1H, $J_{2a,2b}$ 8.1, $J_{2a,3a/3b}$ 8.0, 5.2, H-2a)
4.088 (ddd, 1H, $J_{8,7b}$ 10.5, $J_{8,7a}$ 5.7, $J_{8,9}$ 3.4, H-8)
7.710-7.343 (m, 10H, aromatic protons)

δ_C 19.36S (CMe_3), 22.71T (C-3), 26.92Q (CMe_3), 35.00T (C-4), 60.43T (C-7), 63.56D (C-8), 68.71T (C-2), 71.48D (C-10), 73.09D (C-9), 107.46S (C-5), 135.93-127.62D (aromatic carbons), 132.86S (*ipso* aromatic carbons).

δ_H (DMSO-d_6)
1.002 (s, 9H, CMe_3)
1.623 (m, 1H, H-4b)
1.721 (m, 2H, H-3b and H-3a)
1.890 (m, 1H, H-4a)
3.416 (dd, 1H, $J7_{b,7a}$ 11.6, $J_{7b,8}$ 3.1, H-7b)

3.534 (ddd, 1H, $J_{2b,2a}$ 8.0, $J_{2b,3a/3b}$ 1.5, 8.0, H-2b)

3.570 (d, 1H, $J_{7a,7b}$ 11.6, H-7a)

3.573 (m, 1H, $J_{9,8}$ 9.8, $J_{9,10}$ 6.7, $J_{9,9OH}$ 6.7, H-9)

3.689 (ddd, 1H, $J_{2a,2b}$ 8.0, $J_{2a3a/3b}$ 5.4, 8.0, H-2a)

3.734 (ddd, 1H, $J_{8,9}$ 9.8, $J_{8,7b}$ 3.2, $J_{8,OH8}$ 5.4, H-8)

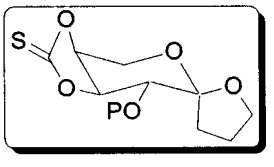
3.807 (d, 1H $J_{10,9}$ 6.7, H-10)

3.910 (dd, 1H, $J_{9,9OH}$ 6.7, J 0.8, 9-OH)

4.467 (d, 1H, $J_{OH8,8}$ 5.4, 8-OH)

δ_C 19.15S (CMe_3), 22.61T (C-3), 26.85Q (CMe_3), 30.07T (C-4), 62.13T (C-7), 65.90D (C-8), 67.02T (C-2), 71.62D (C-9), 73.63D (C-10), 108.35S (C-5), 127.40-135.57D (aromatic carbons), 133.31S, 133.50S (*ipso* aromatic carbons).

FAB-MS: *m/z* 428. $[M]^+$. Exact mass: Calculated for $C_{24}H_{32}SiO_5$, 428.2019; Found, 428.2017.



(5*R*,8*S*,9*S*,10*R*)-10-[(*t*-Butyldiphenylsilyl)oxy]-8,9-*O*-thiocarbonyl-1,6-dioxaspiro-[4.5]decane (103b)

1,1′-Thiocarbonyldiimidazole (0.7 g, 1.60mmol) was added to a solution of the diol (**84a**) (0.24 g, 0.54mmol) in dry acetonitrile (5 ml) under argon and the solution was stirred at room temperature for 5 h. The reaction mixture was poured into brine and extracted with $CHCl_3$. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (hexane-EtOAc, 2:1) gave compound (**103b**) (0.72 g, 94%). The compound was recrystallized from ether to give a well-developed crystals of mp 121-122°C; R_f. 0.47 (hexane-EtOAc 2:1); $[\alpha]_D$ –8.9 , (*c* 0.47, $CHCl_3$).

δ_H 1.074 (s, 9H, CMe_3)

1.732 (m, 1H, H-3b)

1.846 (m, 1H, H-4b)

1.954 (m, 1H, H-3a)

1.993 (m, 1H, H-4a).

3.702 (ddd, 1H, $J_{2b,2a}$ 8.2, $J_{2b,3a/3b}$ 2.9, 6.5, H-2b)

3.787 (ddd, 1H, $J_{2a,2b}$ 8.2, $J_{2a,3a/3b}$ 4.1, 3.1 H-2a)

4.001 (d, 1H, $J_{10,9}$ 4.1, H-10)

4.028 (d, 2H, $J_{7,8}$ 4.7, H-7)

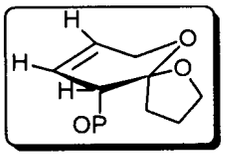
4.777 (dd, 1H, $J_{9,10}$ 4.1, $J_{9,8}$ 8.0, H-9)

4.876 (ddd, 1H, $J_{8,9}$ 8.0, $J_{8,7}$ 4.7, H-8)

7.680-7.361 (m, 10H, aromatic protons)

δ_C 19.44S (CMe_3), 23.00T (C-3), 26.94Q (CMe_3), 33.43T (C-4), 59.39T (C-7), 68.46T (C-2), 70.10D (C-10), 76.11D (C-8), 80.38D (C-9), 106.90S (C-5), 127.93-135.90D (aromatic carbons); (aromatic carbons); 131.88S, 132.38S (*ipso* aromatic carbons); 190.86S (C=S).

FAB-MS: *m/z* 471 $[M+H]^+$. Exact mass: Calculated for $C_{26}H_{31}SSiO_5$, 471.1662; Found, 471.1661.



(5*R*,10*R*)-10-[(*t*-Butyldiphenylsilyl)oxy]-1,6-dioxaspiro[4.5]dec-8-ene (83b)

A solution of the thiocarbonate (**103b**) (0.21 g, 0.42 mmol) in trimethyl phosphite (12 ml) under argon was refluxed for 24 h (TLC control). The reaction mixture was concentrated under *in vacuo* and the residue was purified by column chromatography (hexane-EtOAc 7:1) to give **103b**) (0.11 g, 68%). R_f 0.55 (hexane-EtOAc 7:1); $[\alpha]_D$ –159.9, (*c* 0.85, $CHCl_3$).

δ_H 1.064 (s, 9H, CMe_3)

1.892 9m, 2H, H-3b and H-4b)

2.106 (m, 2H, H-3a and H-4a)

3.892 (ddd, 1H, $J_{2b,2a}$ 8.0, $J_{2b,3a3b}$ 3.8, 4.9, H-2b)

3.985 (ddd, 1H, $J_{2a,2b}$ 8.0, $J_{2a,3a/3b}$ 3.2, 4.8, H-2a)

4.028 (m, 1H, $J_{10,9}$ 6.6, $J_{10,7b}$ 1.1, J 1.8, H-10)

4.085 (dddd, 1H, $J_{7b,7a}$ 17.1, $J_{7b,8}$ 3.0, $J_{7b,9}$ 2.2 $J_{7b,10}$ 1.1, H-7b)

4.215 (ddd, 1H, $J_{7a,7b}$ 17.1, 4.1, $J_{7a,8}$ 2.2, H-7a)

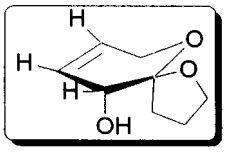
5.461 (ddd, 1H, $J_{9,8}$ 10.3, $J_{9,10}$ 6.6, $J_{9,7b}$ 2.2, H-9)

5.678 (dddd, 1H, $J_{8,9}$ 10.3, $J_{8,7b}$ 3.0, $J_{7a,8}$ 2.2, $J_{8,10}$ 0.8, H-8)

7.327-7.754 (m, 10H, aromatic protons)

δ_C 19.40S (CMe_3), 23.78T (C-3), 26.91Q (CMe_3), 33.58T (C-4), 61.43T (C-7), 68.18D (C-10), 68.79T (C-2), 107.58S (C-5), 125.60D (C-9), 128.27D (C-8),); 127.27-135.98D (aromatic carbons). 133.84S, 134.65S (*ipso* aromatic carbons

FAB-MS: *m/z* 394 $[M]^+$. Exact mass: Calculated for $C_{24}H_{30}SiO_3$, 394.1964; Found, 394.1965.



(5*R*,10*R*)-1,6-Dioxaspiro[4.5]dec-8-en-10-ol (82b)

A solution of (**83b**) (60 mg, 0.15 mmol), in THF (3 ml) and TBAF (8 mg, 0.30 mmol) was stirred at RT for 2 h. The solvent was evaporated and the residue partitioned between water and ethyl acetate, and dried over Na_2SO_4. Column chromatography with hexane-EtOAc (1:1) as eluant gave (**82b**) (20 mg, 84%); R_f 0.45 (hexane-EtOAc 1:1)

δ_H 1.714 (br s, 1H, 10-OH)

2.18-1.89 (m, 4H, H-3 and H-4)

3.691 (br s, 1H, H-10)*

4.019-3.962 (m, 2H, H-2)

4.059 (ddd, 1H, $J_{7b,7a}$ 17.1, J 1.3, J 2.3, H-7a)

4.277 (ddd, 1H, $J_{7a,7b}$ 17.1, J 2.1, J 3.4, H-7a)

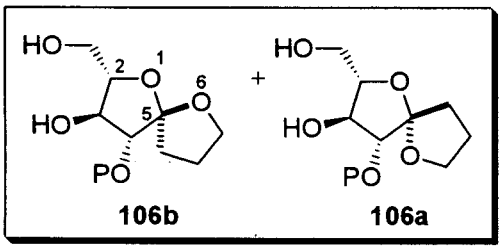
5.917 (ddd , 1H, $J_{9,8}$ 10.1, J 1.5, J 2.9, H-9)

6.480 (dddd, 1H, $J_{8,9}$ 10.1, J 1.8, J 1.8 J 4.67, H-8)

* After D_2O exchange: δ_H 3.686 (dd, 1H, J 1.5, J 4.7, H-10)

δ_C 23.73T (C-3), 34.31T (C-4), 61.22T (C-7), 66.49D (C-10), 69.27T (C-2), 107.30S (C-5), 127.43D (C-9), 129.50D (C-8).

4.3.3 Acid-catalysed cleavage of the acetonide group



(2*S*,3*S*,4*R*,5*RS*)-4-[(*t*-Butyldiphenylsilyl)oxy]-1,6-dioxaspiro[4.4]nonan-2,10-diol (106)
The acetonide (**85a**) (0.21 g, 0.42 mmol) and TsOH (20 mg) in absolute methanol (3 ml) was stirred for 6 h at RT. Et_3N (0.5 ml) was added and the solvent was evaporated. The residue was partitioned between water and EtOAc. The aqueous phase was extracted three times with EtOAc and dried over Na_2SO_4. Solvent evaporation followed by column chromato-graphy (EtOAc-hexane 2:1) gave (**84a/b**) (80 mg, 44%) as a 9:1 inseparable mixture as well as the two epimeric 1,6-dioxaspiro[4.4]nonanediols (**106b**) (25 mg, 14%);(R_f 0.37) (EtOAc-hexane 2:1) and (**106a**) (35 mg, 19%) (R_f, 0.29). (EtOAc-hexane 2:1)

(5*R*) Spiroacetal (106b)

δ_H 1.068 (s, 9H, CMe_3)
1.805 (m, 3H, H-3a,3b and H-9b)
1.979 (m, 1H, H-9a)
1.422 (d,1H, J 4.4, 3-OH)
2.927 (dd, 1H, J 1.8, J 9.3, 10-OH)
3.522 (dd, 1H, $J_{b,2}$ 2.6, $J_{10b,10a}$ 12.2, H-10b)
3.636 (dd, 1H, $J_{10a,2}$ 2 2.6, $J_{10a,10b}$ 12.2, H-10a)
3.725 (ddd, m, 1H, $J_{2,10b}$ 2.6, $J_{8,10a}$ 2.6, $J_{2,3}$ 6.5, H-2)
3.941 (m, 1H, H-7b)
4.088 (m 1H, H-7a)

4.077 (d, 1H, $J_{4,3}$ 7.7, H-4)

4.468 (dd, 1H, $J_{3,4}$ 7.7, $J_{3,2}$ 6.5, H-3)

7.467-7.368 (m, 10H, aromatic protons)

δ_C 19.38S (CMe_3), 24.51T (C-4), 26.93Q (CMe_3), 32.61T (C-3), 62.04T (C-7), 68.98T (C-2), 74.51D (C-9), 80.91D (C-10), 81.41D (C-8), 111.80S (C-5), 127.77-136.03D (aromatic carbons); 132.91, 133.98S (*ipso* aromatic carbons).

(5*S*) Spiroacetal (106a)

δ_H 1.088 (S, 9H, CMe_3)

1.598 (ddd, 1H, $J_{7b,8a}$ 7.2, $J_{7b,8b}$ 7.2, $J_{8b,8a}$ 10.9, H-8b)

1.901 (ddd, 1H, $J_{7a,8a}$ 3.4, $J_{7a,8b}$ 4.7, $J_{8a,8b}$ 10.9, H-8a)

1.978 (m, 2H, H-9)

2.14 (t,br, 1H, 10-OH)

2.247 (d, 1H, J 9.0, 3-OH)

3.697 (m, 2H, H-10)

3.725 (ddd, 1H, $J_{7b,7a}$ 11.6, $J_{7b,8a}$ 7.2, $J_{7b,8b}$ 3.4, H-7b)

3.914 (m, 2H, H-3&H-2)

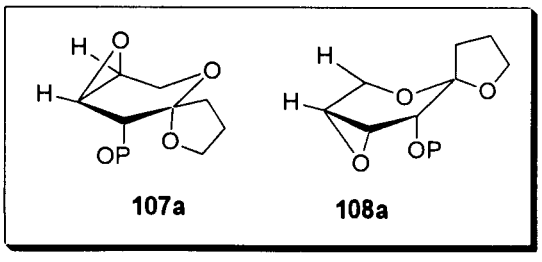
3.917 (ddd, 1H, $J_{7a,7b}$ 11.6, $J_{7a,8a}$ 4.7, $J_{7a,8b}$ 7.2, H-7a)

4.097 (d, 1H, $J_{4,3}$ 2.1, H-4)

7.68-7.35 (m, 10H, aromatic protons)

δ_C 19.26S (CMe_3), 23.87T (C-8), 27.01Q (CMe_3), 31.34T (C-9), 62.74T (C-10), 68.08T (C-7), 82.10D (C-4), 84.81D and 78.40D (C-3 and C-2); 116.50S (C-5), 127.88-135.93D (aromatic carbons), 132.77S and 133.17S (*ipso* aromatic carbons).

FAB-MS: *m/z* 428, $[M]^+$. Exact mass: Calculated for $C_{24}H_{32}SiO_5$, 428.2019; Found, 428.2109.



107a **108a**

4.3.4 Epoxidation of the spiroacetal model compounds

(5*S*,8*S*,9*S*,10*R*)- (107a) and (5*S*,8*R*,9*R*,10*R*)-10-[(*t*-Butyldiphenylsilyl)oxy]-8,9-epoxy-1,6-dioxaspiro[4.5]decane 108a.

A solution of the (5*S*) alkene (**83a**) (80 mg, 0.20 mmol) and MCPBA (150 mg, 0.41 mmol) in dichloromethane (2 ml) was stirred at room temperature for 8 h. The reaction mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and dried (Na_2SO_4). The product mixture was separated by chromatography using hexane-EtOAc (4:1) as eluent to afford the two diastereomeric epoxides (**107a**) and (**108a**) (Ratio 8:5) in 78% yield.

(5*S*) Series: (8*S*,9*S*)-Epoxide (107a)

Yield: 40 mg; R_f 0.62 (hexane-EtOAc (4:1); $[\alpha]_D$ +21.6 (*c* 0.70, $CHCl_3$).

δ_H 1.102 (s, 9H, CMe_3)
1.521 (m, 1H, H-4b)
1.760 (m, 1H, H-3b)
1.847 (m, 1H, H-4a)
1.891 (m, 1H, H-3a)
3.102 (br dd, 1H, $J_{8,9}$ 4.2, $J_{8,7a}$ 1.3, H-8)
3.263 (d, 1H, $J_{9,8}$ 4.2, H-9)
3.812 (d, 1H, $J_{7b,7a}$ 13.2, H-7b)
3.914 (s, 1H, H-10)
3.987 (dd, 1H, $J_{7a,8}$ 1.3, $J_{7a,7b}$ 13.2, H-7a)
4.011 (m, 2H, H-2)
7.754-7.711, 7.449-7.327 (m, 10H, aromatic protons)

δ_C 19.48S (CMe_3), 23.97T (C-3), 27.00Q (CMe_3), 33.41T (C-4), 50.60D (C-8), 54.91D (C-9), 58.53T (C-7), 68.26D (C-10), 69.08T (C-2), 104.46S (C-5), 127.74-135.91D (aromatic carbons); 133.11S and 133.27S (*ipso* aromatic carbons).

FAB-MS: *m/z* 411 $[M+H]^+$. Exact mass: Calculated for $C_{24}H_{31}SiO_4$, 411.1992; Found, 411.1998.

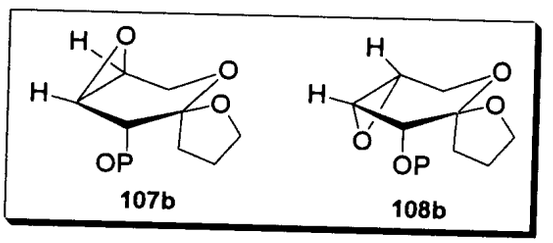
(5*S*) Series: (8*R*,9*R*)-Epoxide (108a)

Yield: 25 mg; R_f 0.39 (hexane-EtOAc (4:1); $[\alpha]_D$ -6.5 (*c* 0 .34, $CHCl_3$).

δ_H 1.073 (s, 9H, CMe_3)
1.557 (ddd, 1H, $J_{4b,4a}$ 12.0, $J_{4b,3a/3b}$ 3.4, 8.0, H-4b)
1.830 (m, 2H, H-3)
2.047 (ddd, 1H, $J_{4a,4b}$ 12.0, $J_{4a,3a/3b}$ 3.4, 9.3, H-4a)
3.074 (ddd, 1H, $J_{9,8}$ 5.4, $J_{9,10}$ 2.3, $J_{7a,9}$ 0.8, H-9)
3.312 (ddd, 1H, $J_{8.7b}$ 4.4, $J_{8,9}$ 4.4, $J_{8,7a}$ 0.8, H-8)
3.686 (dd, 1H, $J_{7b,8}$ 4.4, $J_{7b,7a}$ 13.2, H-7b)
3.988 (ddd, 1H, $J_{2a,2b}$ 8.3, $J_{2b,3a}$ 8.3, $J_{2b,3b}$ 5.2 Hz, H-2b)
3.996 (d, 1H, $J_{10,9}$ 2.3, H-10)
4.045 (ddd, 1H $J_{7a,7b}$ 13.2, $J_{7a,8}$ 0.8, $J_{7a,9}$ 0.8, H-7a)
4.116 (m, 1H, H-2a)
7.34-7.79 (m, 10H, aromatic protons)

δ_C 19.38S (CMe_3), 22.93T (C-3), 26.92Q (CMe_3), 35.12T (C-4), 52.98D (C-9), 55.04D (C-8), 59.12T (C-7), 69.59D (C-10), 69.99T (C-2), 106.36S (C-5), 127.66-135.96D (aromatic carbons); 132.98S and 133.33S (*ipso* aromatic carbons).

FAB-MS: *m/z* 411 $[M+H]^+$. Exact mass: Calculated for $C_{24}H_{31}SiO_4$, 411.1992; Found, 411.1992.



(5*R*,8*S*,9*S*,10*R*)- (107b) and (5*S*,8*R*,9*R*,10*R*)-10-[(*t*-Butyldiphenylsilyl)oxy]-8,9-epoxy-1,6-dioxaspiro[4.5]decane.

A solution of the (5*R*) alkenol) and MCPBA (150 mg, 0.41 mmol) in dichloromethane (2 ml) was stirred at room temperature for 8 h. The reaction mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and dried (Na_2SO_4). The product mixture was separated by chromatography using hexane-EtOAc (4:1) as eluent to afford the two diastereomeric epoxides (**107b**) and (**108b**) (Ratio 1:1) in 80% yield.

(5*R*) Series: (8*R*,9*R*)-Epoxide (108b)

Yield: 34 mg; R_f 0.53 (hexane-EtOAc (4:1); $[\alpha]_D$ –53.0 (*c* 0.16, $CHCl_3$).

δ_H 1.090 (s, 9H, CMe_3)
1.830 (m, 1H, H-3b)
1.968 (m, 1H, H-3a)
2.058 (m, 2H, H-4)
2.942 (ddd, 1H, $J_{9,8}$ 4.2, $J_{9,10}$ 3.6, $J_{9,7a/7b}$ 0.6, H-9)
3.115 (ddd, 1H, $J_{8,9}$ 4.2, $J_{8,7b}$ 1.9, $J_{8,7a}$ 0.8, H-8)
3.824 (m, 2H, H-2)
3.885 (dd, 1H, $J_{7b,7a}$ 13.4, $J_{7b,8}$ 1.9, H-7b)
3.946 (dd, 1H, $J_{7a,7b}$ 13.4, $J_{7a,8}$ 0.8, H-7a)
3.974 (d, 1H, $J_{10,9}$ 3.6, H-10)
7.33-7.79 (m, 10H, aromatic protons)

δ_C. 19.52S (CMe_3), 24.00T (C-3), 26.96Q (CMe_3), 31.13T (C-4), 52.52D (C-8), 53.13D (C-9), 59.45T (C-7), 68.02S (C-2), 69.58D (C-10), 107.71S (C-5), 127.57-136.09D (aromatic carbons); 133.18S and 133.89S (*ipso* aromatic carbons).

FAB-MS: *m/z* 411 $[M+H]^+$. Exact mass: Calculated for $C_{24}H_{31}SiO_4$, 411.1992; Found, 411.1992.

(5*R*) Series: (8*S*,9*S*)-Epoxide (107b)

Yield: 34 mg; R_f 0.40 (hexane-EtOAc 4:1); $[\alpha]_D$ –39.0 (*c* 0.36, $CHCl_3$).

δ_H 1.083 (s, 9H, CMe_3)

1.920 (m, 2H, H-3)

2.054 (m, 2H, H-4)

2.976 (dddd, 1H, $J_{8,7a}$ 0.8, $J_{8,10}$ 0.6, $J_{8,7b}$ 1.7, $J_{9,8}$ 4.0, H-8)

3.019 (ddd, 1H, $J_{9,10}$ 0.8, $J_{9,7b}$ 1.7, $J_{9,8}$ 4.0, H-9)

3.852 (ddd, 1H, $J_{2b,2a}$ 13.7, $J_{2b,4a/4b}$ 6.5, 7.5, H-2b)

3.903 (dd, 1H, $J_{7b,8}$ 2.7, $J_{7b,7a}$ 13.5, H-7b)

3.933 (ddd, 1H, $J_{2a,2b}$ 13.5, $J_{2a,3a/3b}$ 8.2, 5.9, H-2a)

4.024 (dd, 1H, $J_{10,9}$ 0.8, $J_{10,8}$ 0.6, H-10)

4.073 (ddd, 1H, $J_{7a,8}$ 0.8, $J_{7a,9}$ 1.7, $J_{7a,7b}$ 13.7, H-7a)

δ_C 19.45S (CMe_3), 23.74T (C-3), 26.93Q (CMe_3), 30.85T (C-4), 49.82D (C-8), 54.36D (C-9), 60.77T (C-7), 68.85T (C-2), 69.46D (C-10), 10.42S (C-5), 127.67-135.93D (aromatic carbon); 132.84, 133.97S (aromatic carbons).

FAB-MS: *m/z* 411 $[M+H]^+$. Exact mass: Calculated for $C_{24}H_{31}SiO_4$, 411.1992; Found, 411.1991.

Alternative method of epoxidation: use of dimethyldioxirane/acetone

A solution of the (5*S*) alkene (**83a**) (50 mg, 0.12 mmol) in CH_2Cl_2 (5 ml) under argon at 0 °C was allowed to react with an excess of a freshly prepared solution of dimethyldioxirane in acetone. The reaction mixture was stirred at 0 °C for 2 h (TLC control) and the solvent evaporated with a stream of nitrogen. The residue was purified by column chromatography using hexane-EtOAc (4:1) as eluent to give only (**107a**) (40 mg, 77% yield).