UNIVERSITY OF SOUTHAMPTON

Synthesis of Carbasugar Derivatives *via* a "*pseudo*"-C_2-Symmetric Building Block Derived from Arabitol.

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DEPARTMENT OF CHEMISTRY
FACULTY OF SCIENCE

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This thesis and the work described therein are entirely my own, except where I have *either* acknowledged help from a named person *or* where a reference is given to a published source or thesis. Text taken from another source will be enclosed in quotation marks or written in italics and a reference will be given.

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Master of Philosophy

SYNTHESIS OF CARBASUGAR DERIVATIVES *VIA* A "*PSEUDO*"-C_2-SYMMETRIC BUILDING BLOCK DERIVED FROM ARABITOL.

By Alan James Boydell

Development of a kinetic protection protocol for arabitol affords the "*pseudo*"-C_2-symmetric bis-acetal **8** in good yield. Utilising a scavenging purification strategy greatly simplifies the separation of **8** from the thermodynamically more stable regioisomeric byproduct **7**.

The building block **8** is utilised in a series of syntheses to yield a "*pseudo*"-C_2-symmetric and C_2-symmetric 1,4-bis-epoxides in 3 and 5 steps, respectively, from **8**.

These bis-epoxides are then reacted with a dithiane stabilised carbanion in a Brook rearrangement mediated cyclisation to furnish carbasugar derivatives in enantiopure form. The "*pseudo*"-C_2-symmetric bis-epoxide gives a distereomeric mixture as expected, while the C_2–symmetric bis-epoxide reacts to form only one diastereomer.

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Thanks are due to my project students Richard and Thomas, both of whom managed to make my glassware disappear and my fume cupboard shrink but who have contributed much to this project and others.

Martin and Fred have my unending gratitude for setting me on the path, and putting up with me when I knew a lot less than I should.

I gratefully acknowledge Richard Whitby for useful discussions and much encouragement, Joan Street and Neil Wells for managing the NMR facilities and John Langley along with Julie Herniman for running the Mass Spectroscopy suite here at Southampton.

Lastly, and most importantly, I thank Marlies for all her love, tolerance, and encouragement – even if she does think I work too hard.

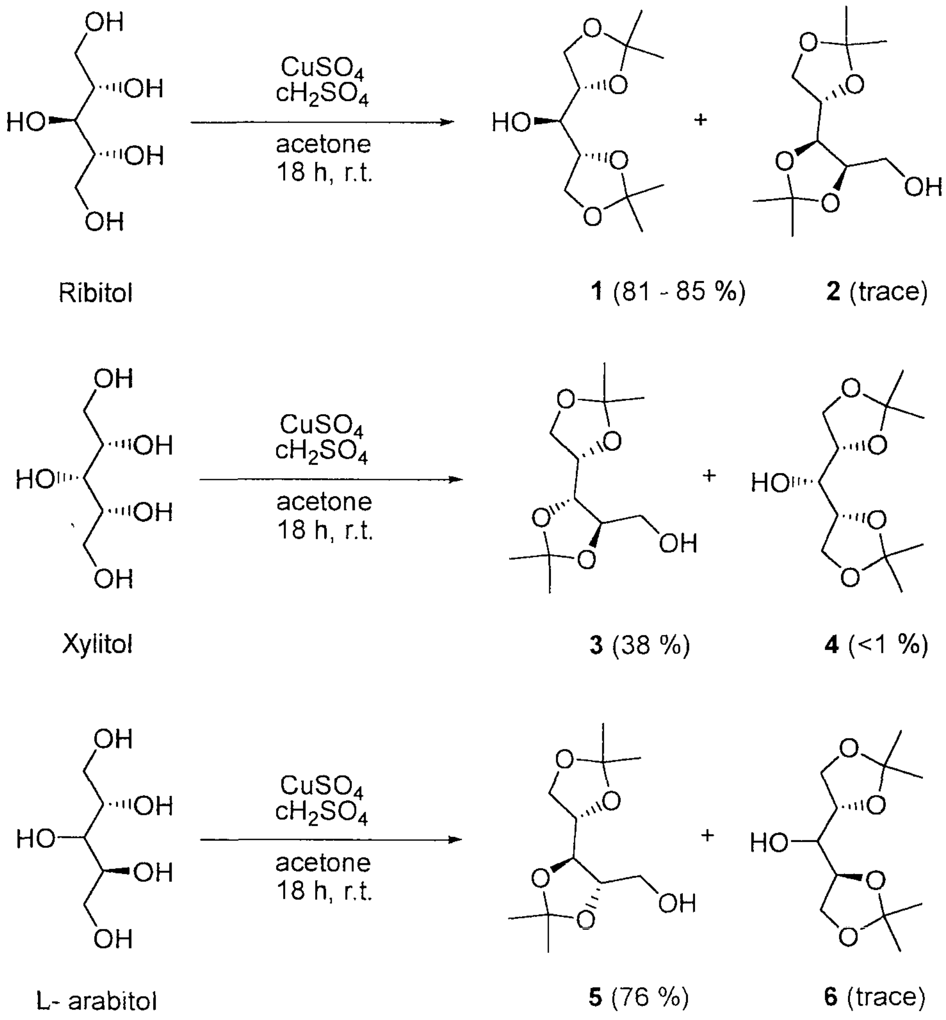
ABBREVIATIONS

CIMS	Chemical Ionisation Mass Spectrometry
CSA	(±)-Camphor-10-sulfonic acid
DMF	Dimethyl formamide
EIMS	Electron Ionisation Mass Spectrometry
ENT-**X**	Enantiomer of **X**
GC-MS	Gas Chromatography – Mass Spectrometry
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
NBS	*N*-Bromosuccinimide
NOE	Nuclear Overhauser Effect
NMR	Nuclear Magnetic Resonance
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
pTSA	*para*-Toluenesulfonic acid

1. KINETIC ARABITOL PROTECTION

1.1 INTRODUCTION

The selective protection of multifunctional substrates is of great importance in organic synthesis. For polyol structures, such as carbohydrates and their derivatives, acetal protection and deprotection protocols have proven to be of great value.[1] The reversible nature of these reactions, and the usually predictable relative stabilities of structurally different acetal subunits, have led to a number of synthetically useful procedures for the differentiation of hydroxyl groups present at various positions in carbohydrate starting materials.[2,4c]



Scheme 1: Literature protections of pentitols.

Typically, acetal forming reactions are under thermodynamic control.[3] Hence, product distribution is a consequence of the relative stabilities of the possible acetal structures. When comparing 2,2-disubstituted-1,3-dioxolanes, internal *trans*–acetals are more thermodynamically stable than terminal acetals, while internal *cis*–substituted acetals are the least stable.[4] This is elegantly illustrated with the pentitol protections shown in Scheme 1. In the case of ribitol, no internal *trans*–acetonide isomer is possible. Therefore, the symmetrical bis-acetonide **1** with its two terminal acetonides is the major product,[5] although, there have been confusing reports in the literature regarding this.[6] However, in the cases of arabitol[4a,6] and xylitol,[7] where the formation of a more stable internal *trans*–acetal is possible, the unsymmetrical bis-acetonides are isolated.

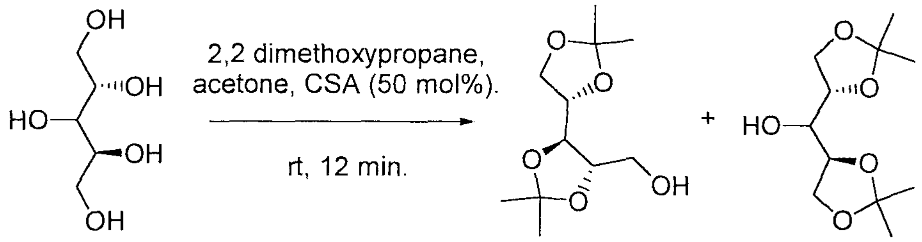
Based on its "*pseudo*"-C_2-symmetric nature, we became interested in the use of the bis-acetal **6** as a chiral building block in organic synthesis. The synthesis of **6** has been reported in 4 steps from mannose.[8] However, a direct protection protocol from arabitol is clearly more desirable in order for **6** to serve as a valuable building block.

As **6** is the thermodynamically less stable bis-acetal of arabitol, its successful isolation in high yield is dependent on the development of a suitable kinetic protection protocol. Kinetic protections depend on the difference in reaction rate between two or more functionalities. It is known that primary hydroxyl groups react faster in acetal forming reactions compared to secondary hydroxyls.[4b] Hence, initial protection of arabitol to form the terminal acetonide occurs first, but if allowed, subsequent acetal migration leads to the formation of the thermodynamically more stable 2,3:4,5-bis-acetal.

Through variation of reaction temperature, protecting group, reaction solvent and relative amounts of reagent, it was hoped that we could develop a reaction where the rate of initial protection of arabitol, as its symmetric bis-acetal, was higher than that of acetal isomerisation. A reaction of this type could be halted when all arabitol had undergone initial protection as **6** but before **6** could undergo isomerisation to form **5**.

1.2 PRELIMINARY RESULTS

Previous work within our research group has led to development of a direct arabitol acetonisation reaction, leading to a 3.6:1 mixture of regioisomers with **6** as the major component.



L- arabitol

5 (16 %)

6 (58 %)

Scheme 2: Existing protection protocol.

As can be seen in Scheme 2, even with a conversion of over 80%, already a substantial amount of thermodynamic bis-acetal product was formed. This indicates that under these conditions, the rate of rearrangement is too fast compared to the initial protection step.

A major disadvantage in this procedure is that arabitol is sparingly soluble in the reaction mixture, and only dissolves gradually as the reaction proceeds. This leads to extended reaction duration, which gives acetal rearrangement time to occur. A further problem was the preparative HPLC required to separate **5** and **6,** this is time consuming and expensive, making the procedure impractical on a large scale.

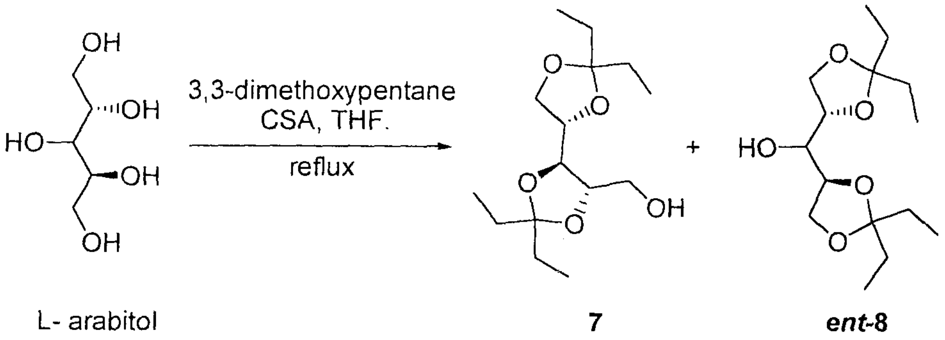
Due to the insolubility of arabitol in the previously used reaction solvent it was decided to attempt protections in different solvents and at elevated temperatures. A crucial factor would be the relative rate enhancement of acetal formation compared to acetal rearrangement at higher temperatures.

1.3 DEVELOPMENT OF A PRATICAL PROTECTION SYSTEM

In order to overcome the problem of the insolubility of arabitol a switch to a new reaction solvent was investigated. The range of solvents suitable for acetal forming reactions in which arabitol readily dissolves is narrow. However, arabitol is completely soluble in DMF and its use, with 2-methoxypropene, in acetonisations has been reported to inhibit acetal migration.[9]

In our hands, however, reactions of arabitol with 2-methoxypropene or 2,2-dimethoxypropane in DMF gave yields of **6** not greater than 30%. Moreover, **5** was still present in significant quantities (4% – 11%). Reaction times were unacceptably long, with reactions still being incomplete after 7 days at room temperature. Elevated temperatures gave an increased overall yield but gave **5** as the major product. The addition of drying agents such as ground molecular sieves, drierite or trimethyl orthoformate gave no increase in yield or reduction in reaction time.

One possible cause for the low yields of **6** in the existing procedure and the DMF experiments was the formation of 1,3:4,5 bis-acetals followed by fast rearrangement to **5**. Though 1,2-acetonides are more stable than 1,3-acetonides, the formation of the latter in a kinetically controlled process cannot be excluded. The formation of 3,3-pentylidenes is known to be more selective for 5 membered dioxolane rings[10] and hence it was hoped that the use of 3,3-dimethoxypentane as the reagent for the protection would benefit the desired kinetic process.



Scheme 3: Use of 3,3-dimethoxypentane in the protection reaction.

Replacing the acetone/2,2-dimethoxypropane with 3-pentanone/3,3-dimethoxypentane, whilst leaving the other reactions conditions as shown in scheme 2, the symmetrical bis-acetal ***ent*-8** was obtained in unsatisfactory yields. Moreover, the original problem of the insolubility of arabitol presenting itself once more, a radical change was needed.

A procedure for the selective protection of a triol substrate using 3,3-dimethoxypentane in refluxing THF has been reported.[10h] It was hoped that this elevated temperature would not only overcome the previous problem of arabitol's insolubility, but that it would increase the rate of initial protection to a greater degree than that of acetal isomerisation. The results are displayed in Table 1.

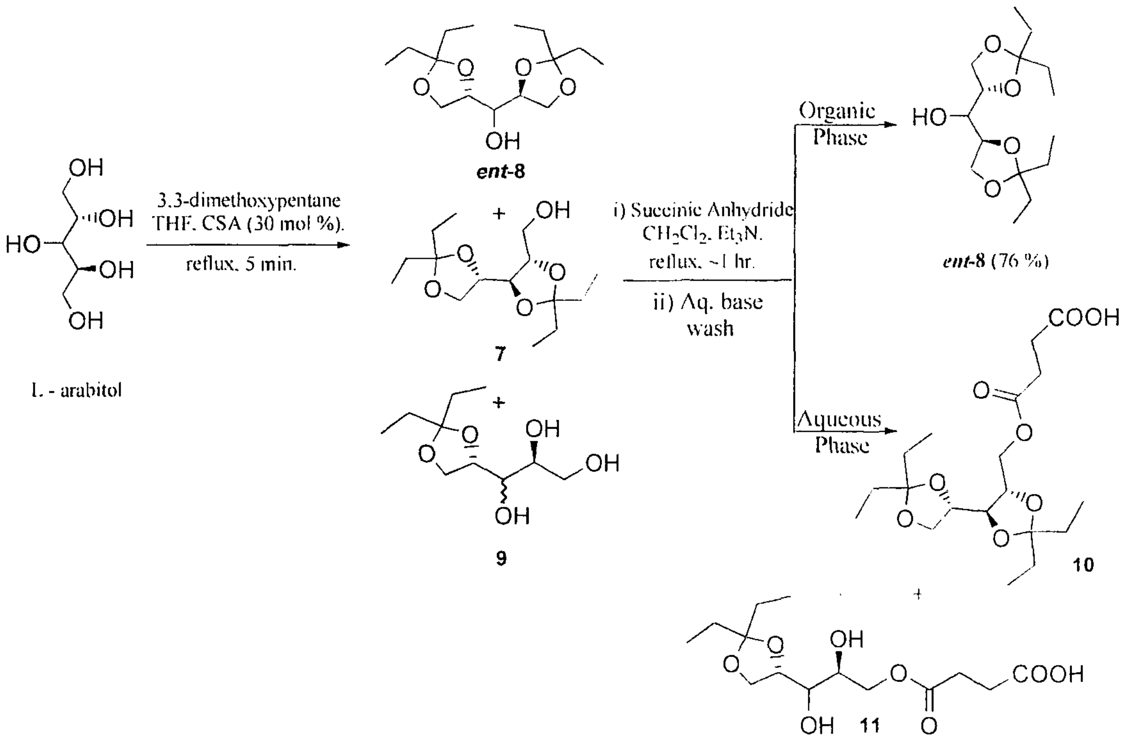
Entry	Time (min)	3,3-Dimethoxy-pentane (eq)	Acid Catalyst (mol %)	Yield ***ent*-8** (%)	Yield 7 (%)	Overall Yield (%)
1	240	2.2	4 (pTSA)	23	68	91
2	120	2.2	4 (pTSA)	46	44	90
3	30	2.2	4 (pTSA)	60	25	85
4	15	2.2	4 (pTSA)	65	19	84
5	10	2.2	4 (pTSA)	71	13	84
6	5	2.2	4 (pTSA)	69	9	78
7	5	2.2	35 (CSA)	37	31	68
8	5	2.2	25 (CSA)	69	15	84
9	5	2.2	15 (CSA)	70	11	81
10	5	2.2	10 (CSA)	71	10	81
11	5	2.2	5 (CSA)	69	8	77
12	5	4.4	35 (CSA)	71	15	86
13	5	4.4	30 (CSA)	80	12	92
14	5	4.4	25 (CSA)	73	12	85
15	5	4.4	15 (CSA)	74	6	80
16	5	4.4	10 (CSA)	66	6	72
17	5	4.4	5 (CSA)	68	5	73

Table 1: Results from optimisation of the protection.

First, a series of experiments was conducted to investigate the influence of the reaction time on the product outcome (entries 1 – 6). A clear trend was apparent in which the yield of the desired product ***ent*-8** increased with shorter reaction times. Conversely, longer reaction times resulted in predominant formation of the more thermodynamically stable product. These results indicate that even at higher temperatures (65°C) the reaction is kinetically controlled in case of short reaction times. Arabitol is once again not very soluble in the initial reaction mixture; however, its disappearance was observed after just a few minutes at reflux temperatures.

In the following set of experiments, the influence of the amount of acid catalyst was investigated (entries 7 – 11). While the combined yield seemed not too dependent on the relative amount of acid, at higher acid concentrations the yield of ***ent*-8** dropped while the yield of 7 increased accordingly.[11] It can also be seen that changing p-TSA for CSA does not influence the product outcome (entries 6 vs. 11). A significant improvement in the yield for **1** was obtained when the relative amount of 3,3-dimethoxypentane (entries 12 – 17) was increased. Screening for the optimum amount of acid catalyst showed that a higher quantity of acid was required with this increased amount of 3,3-dimethoxypentane (entries 8 vs. 14).

In summary, we had achieved a high yielding direct protection protocol to obtain the thermodynamically less stable bis-acetal of arabitol. However, preparative HPLC is still required to separate the regioisomeric bis-acetals, compromising the practical usefulness of the process on a large scale. Therefore, a study was undertaken in order to develop an alternative purification strategy (Scheme 4).



Scheme 4: Scavenging workup with succinic anhydride.

To develop such a strategy the nature of the crude reaction mixture from the protection must be considered. It contains a mixture of desired ***ent*-8**, undesired 7 and mono-protected arabitol **9**. Chemically, these compounds can be differentiated in terms of reactivity. Primary hydroxyls are more reactive than secondary and secondary more reactive than tertiary. 7 and **9** both contain a primary hydroxyl group whereas ***ent*-8** contains a secondary alcohol. This difference in reactivity will allow for the selective reaction of 7 and **9** with an anhydride to produce acidic byproducts, which can then be removed by basic aqueous workup to yield pure ***ent*-8**.

In order to provide a useful strategy for the removal of 7 without time consuming chromatography, trial reactions with mixtures of 7, ***ent*-8** and **9** were conducted. These showed the undesired products 7 and **9** reacted, leading to adducts **10** and **11** which could be removed by subsequent basic workup. Optimisation of the scavenging workup involved the crude mixture from the protection reaction being concentrated, taken up in CH_2Cl_2, and treated with succinic anhydride and Et_3N at a range of temperatures and reaction times. Furthermore, the neutralisation of the protection reaction with Et_3N was replaced in favour of a basic aqueous workup. This removed the acidic Et_3N salts previously present, any unreacted arabitol and much of the mono-protected product. Using this new workup protocol, followed by reaction with succinic anhydride in refluxing CH_2Cl_2 until disappearance of 7 by TLC, gave pure ***ent*-8** without chromatographic methods in 74% yield.

On scale up, further optimisation of the practical procedure was needed. The protection reaction had previously been quenched by the addition of saturated aqueous $NaHCO_3$, however, on a large scale, the effervescence caused by neutralisation was extremely violent, and so aqueous 2M NaOH is now used. Furthermore, two previously unobserved by-products have been isolated in 0.5% total yield. They have not been conclusively identified but are believed to be the 1,3;4,5 bis-acetals of arabitol, and are easily removed from the crude product by filtration through silica gel after the scavenging workup.

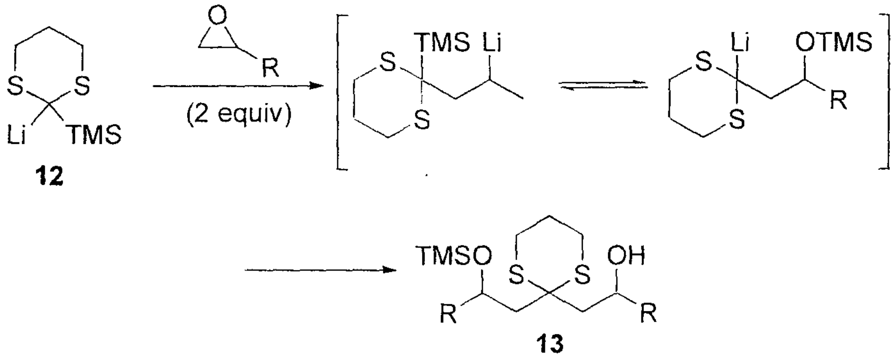
Our procedure allows us to synthesise 14g of **8** in less than a day. Unfortunately, the synthesis of **8** from arabitol was recently published by Maleczka in a communication.[12] Interestingly, they achieved a 90% yield using DMF as solvent.

2. DESYMMETRISATION OF 1,4-BIS-EPOXIDES *VIA* A LINCHPIN CYCLISATION

2.1 LINCHPIN CYCLISATIONS UTILISING 1,4 SILYL MIGRATION[13]

The 1,2-anionic migration of silyl groups from carbon atoms to oxygen atoms was recognized and studied by A.G. Brook in the mid 20th century.[14] It has been recognized that the reverse process can also occur,[15] and that there is a family of [1,n] migrations possible. These migrations are more commonly known as Brook (or retro-brook) rearrangements.[16]

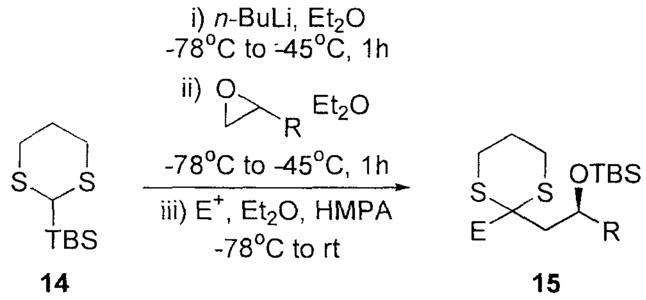
Several examples of tandem nucleophilic addition-1,4-silyl migration-intermolecular alkylations have been reported.[17] In general they entail addition of 2 equiv of an epoxide to the stabilized carbanion and result in the general formation of symmetrically bis-alkylated acyclic products (Scheme 5).



Scheme 5: Symmetrical bis-alkylation of silyl dithianes.

In a study by Oshima and co-workers it was found that the rate of 1,3 and 1,4-silyl migrations is highly solvent dependent.[18] When Et_2O was used as solvent, migration was completely suppressed but in THF migration was initiated by warming from -78°C to -40°C. Furthermore, addition of HMPA was effective in promoting rapid silyl migration even at -78°C.

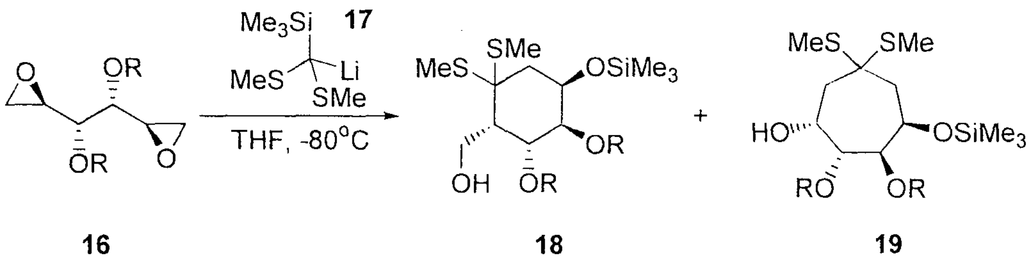
It is this solvent controlled nature of 1,4-Brook rearrangements that allowed, with further research by Smith and co-workers, development of a method for the synthesis of unsymmetrically bis-alkylated acyclic products.[19]



Scheme 6: Unsymmetrical bis-alkylation of silyl dithianes.

The protocol to yield the unsymmetrically bis-alkylated products, outlined in Scheme 6, involves initial deprotonation of **14** and alkylation with 1 equivalent of an epoxide. When the epoxide has been consumed, addition of HMPA and a second electrophile results in a rapid Brook rearrangement followed by alkylation thus providing compounds such as **15** in good yield.

Tandem nucleophilic addition-1,4-silyl migration-intramolecular alkylations provide and effective method for the one-pot synthesis of functionalised cyclic products. Schaumann and co-workers have utilised 1,5-bis-epoxides for the asymmetric synthesis of highly oxygenated carbocycles (Scheme 7).[20]



Scheme 7: Use of bis-epoxides for the asymmetric synthesis of carbocycles.

The carbohydrate derived bis-epoxide **16** undergoes ring opening and Brook rearrangement when reacted with **17**. As **16** is C_2-symmetric the epoxide moieties are homotopic, meaning that ring-opening by **17** can occur at either epoxide with both providing the same stereochemical outcome. However, the selectivity of the ring closure was only moderate with competing 6-*exo*-tet and 7-*endo*-tet cyclisations producing mixtures of **18** and **19**. In a related study by Le Merrer et al., using silated 1,3-dithianes, selectivity in the ring closure could be induced by the choice of the protecting groups present in the bis-epoxide.[21]

We envisage a similar procedure to the one outlined above in which we would utilise the "*pseudo*"-C_2-symmetric and C_2-symmetric-1,4-bis-epoxides shown below to yield functionalised cyclopentanes and carbasugars. We anticipate a cleaner cyclisation pathway, as the two competing cyclisations will be 5-*exo*-tet and 6-*endo*-tet. However, it should be noted that in epoxide ring opening reactions, the competition between 5-*exo*-tet and 6-*endo*-tet is much more equal than in other systems.[22] This is due to the fact that the epoxide oxygen can be considered just as much an *exo* as *endo* leaving group in the formation of 6-membered rings.

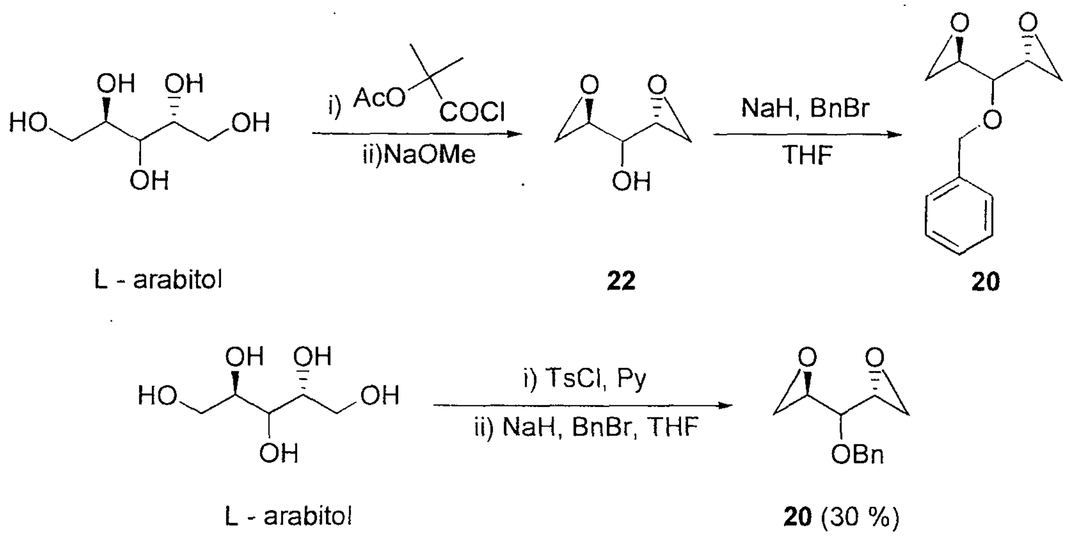
20 **21**

Figure 1: Symmetrical bis-epoxides **20** and **21**.

2.2 OVERVIEW OF 1,4 BIS-EPOXIDE SYNTHESIS

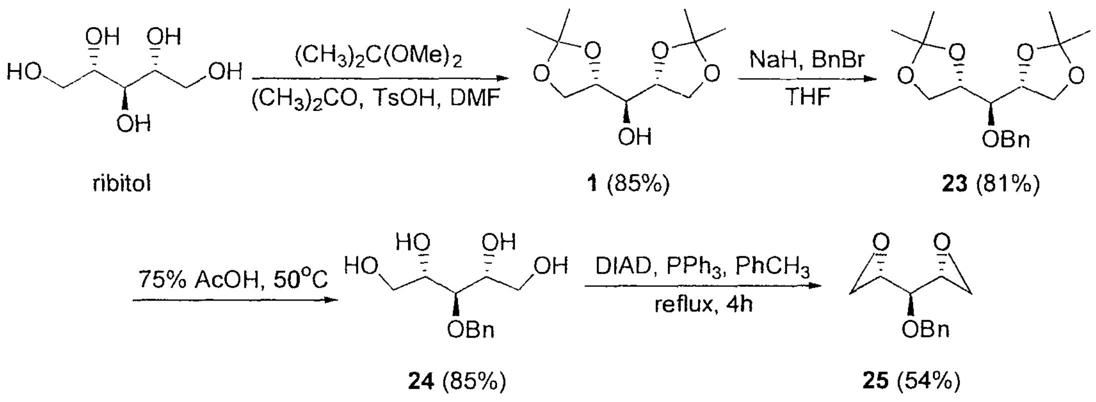
*2.2.1 Syntheses of 1,4 bis-epoxide **20***

Bis-epoxide **20** has been synthesised by a variety of methods from arabitol as outlined in Scheme 8.[23,24]



Scheme 8: Two literature routes to 20 from arabitol.[23, 24]

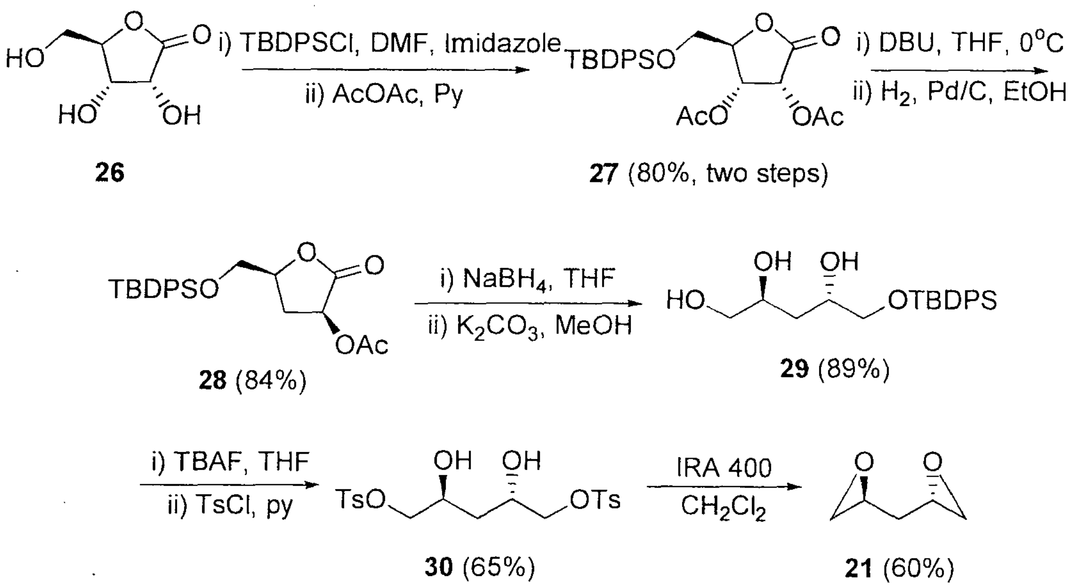
A longer route, in which a 1,4-bis-epoxide is synthesised from the symmetric bis-acetal of ribitol has been reported,[5d] and provides us with another potential route for the synthesis of **20** from arabitol.



Scheme 9: Preparation of a symmetrical 1,4-bis-epoxide from ribitol.

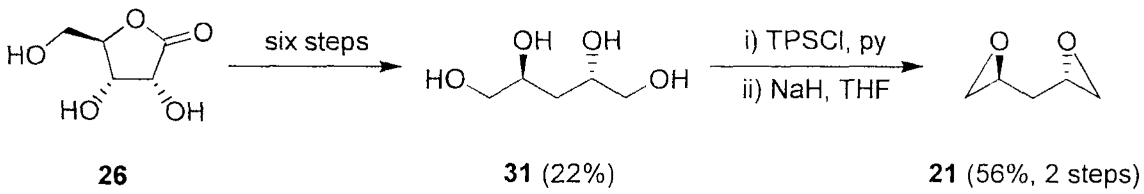
2.2.2 Syntheses of bis-epoxide 21

Bis-epoxide **21** has been synthesised by two main methods. The first method is one beginning from a D-ribonic acid γ-lactone derivative,[25] and is outlined in Scheme 10.



Scheme 10: Literature procedure for the preparation of **21**.

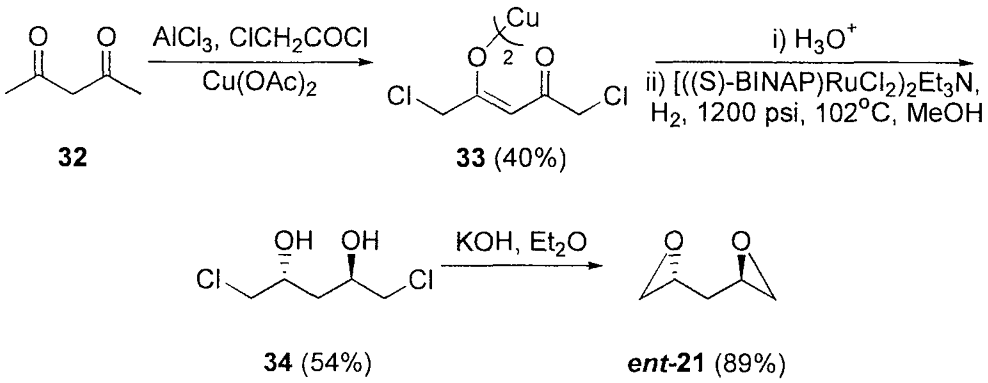
Alternatively, D-ribonic acid γ-lactone can be converted to the tetraol **31** in six steps. Sulfonylation of the primary alcohols followed by treatment with NaH yields **21** in 56% over 2 steps from **31** (Scheme 11).[26]



Scheme 11: Alternative route to **21**.

Although elegant, this synthesis was unsuitable for our needs, as we desired a synthesis allowing access to both enantiomers of **21**. Unfortunately, the D-ribonic acid γ-lactone is the only enantiomer commercially available.

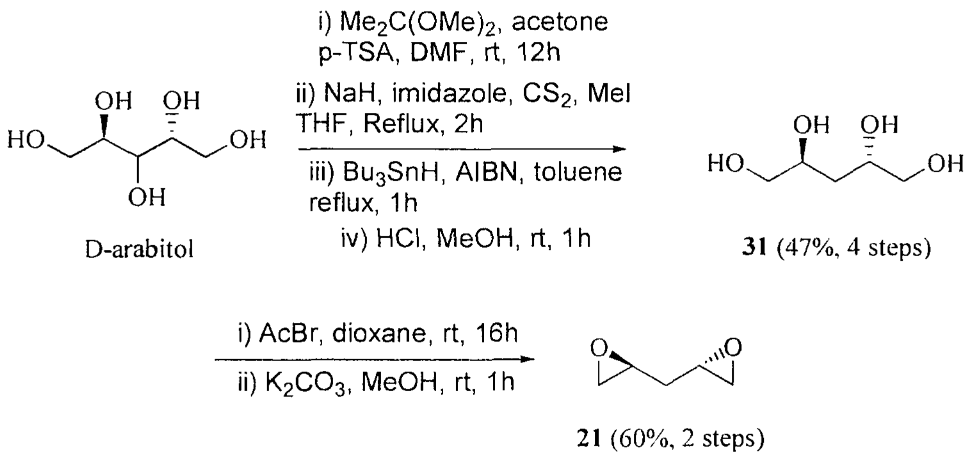
Rychnovsky reported the synthesis of **21** in 3 synthetic steps from 2,4-pentanedione based on an enantioselective reduction using Noyori's asymmetric hydrogenation catalyst, which, after recrystallisation of an intermediate, gave **21** in 19% overall yield with a >97% ee.[27]



Scheme 12: Literature preparation of **21**.

Both methods are frequently used and Jung reported that they gave similar results in terms of efficiency when employed on lab scale,[26] although Rychnovksy claimed that partial racemisation was observed in the route from the ribonic acid lactone.[27]

Very recently, Nakata communicated the synthesis of **21** from arabitol in 6 steps in 28% overall yield (Scheme 13).[28]

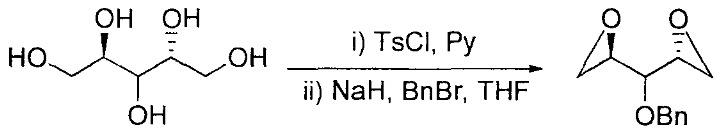


Scheme 13: Literature preparation of **21** from arabitol.

Using our own, higher yielding arabitol protection we should be able to utilise this route to produce large-scale quantities of **21** in both enantiomeric forms.

2.3 SYNTHESIS OF THE 1,4-BIS-EPOXIDES

*2.3.1 Synthesis of bis-epoxide **20***

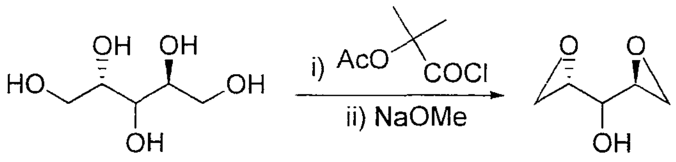


D-arabitol

20 (30%)

Scheme 14: Preparation of **20**.

Initial attempts to synthesis bis-epoxide **20** centred on the procedure reported by Dreyer *et al.*[24b] Despite several attempts the bis-tosylates were never successfully isolated. A procedure where the crude product of the tosylation reaction was reacted directly with NaH in THF, followed by treatment with benzyl bromide, yielded **20** in 30 % yield.[24a]



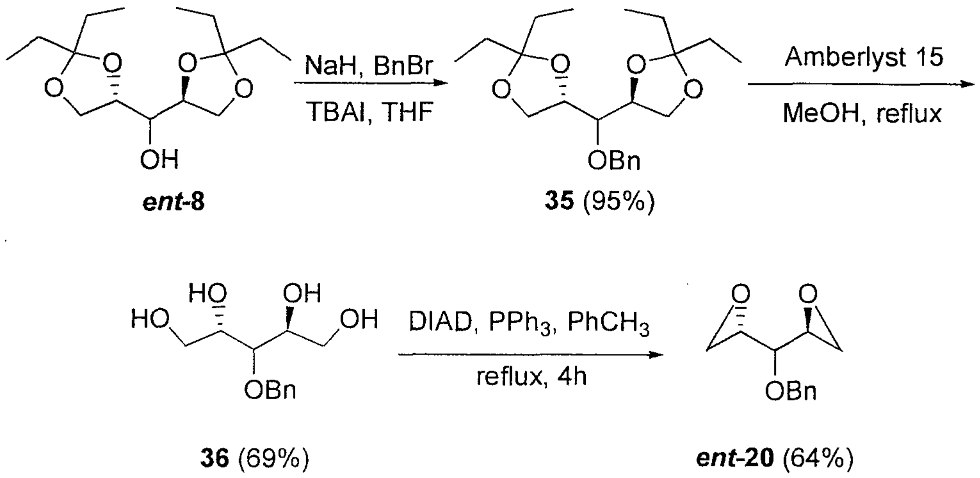
L-arabitol

22

Scheme 15: Attempted synthesis of **22**.

The synthesis of **22**, as described by Schreiber,[23] begins with treatment of arabitol with Moffat's reagent, followed by basic hydrolysis and elimination. In our hands this method proved unreliable, as treatment with Moffat's reagent returned an inseparable mix of regioisomers, as was expected from reports in the literature. However, in our hands, when treated with NaOMe, this mixture yielded none of the desired bis-epoxide.

A further synthesis of **20** from arabitol was attempted using the methodology described by Smith *et al.* for their synthesis of bis-epoxide **25** from ribitol.[5d]

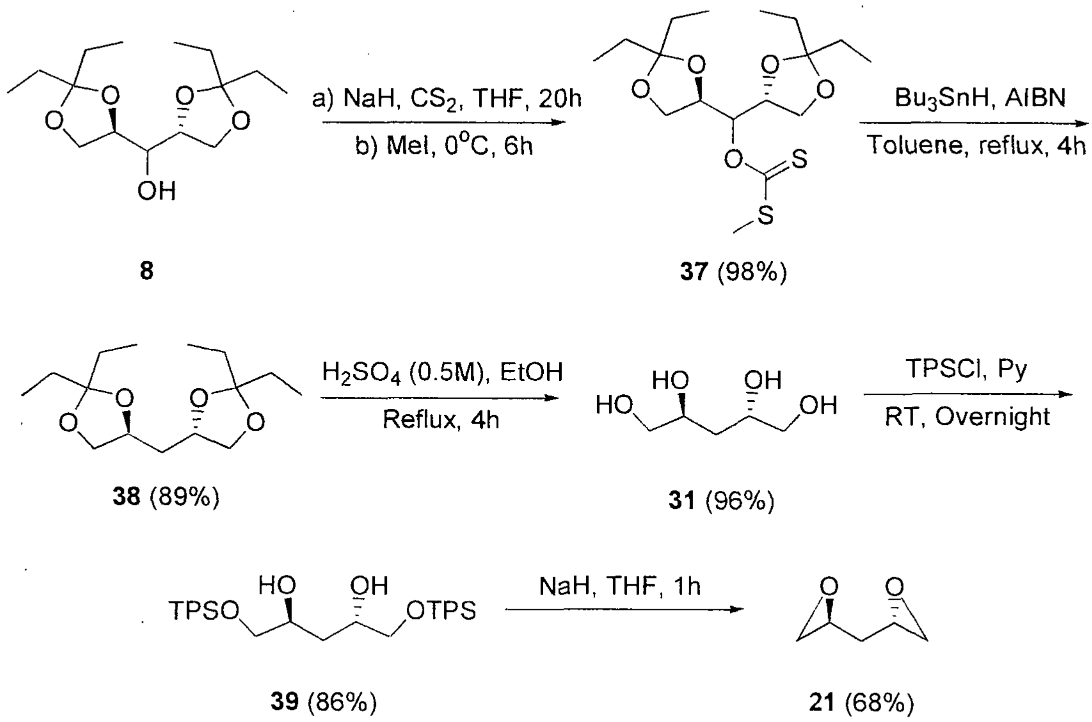


Scheme 16: Preparation of ***ent*-20**.

Arabitol was initially protected as its symmetric bis-acetal (see 1.3). The free hydroxyl group at C3 was then protected as a benzyl ether prior to deprotection of the acetals. This reaction was attempted using various methods, but the water solubility of the product made isolation through aqueous workup impossible. Treatment with acidic resin in wet methanol at reflux proved to be the best method. The bis-epoxide was formed via an intramolecular Mitsunobu reaction, which provided ***ent*-20** in good yield.

*2.3.2 Synthesis of bis-epoxide **21***

The synthesis of **21** from bis-protected arabitol involved the formation and subsequent reduction of the xanthate at C3, followed by deprotection of the acetals and epoxide formation.



Scheme 17: Synthesis of bis-epoxide **21**.

Protected arabitol was treated with NaH in the presence of CS_2, followed by a MeI quench to furnish the xanthate **37** in good yield. However, on a large scale, complete conversion of **8** was difficult to achieve despite an increase in the relative amount of NaH added and a decrease in the volume of solvent used.

Reduction of the xanthate with tributyltin hydride proceeded smoothly. However, on a large scale the stoichiometric amounts of tin reagent required make this process unattractive in the long term.[29]

It was clear from work carried out during the synthesis of **20**, that to deprotect **38**, a strong acid was required to remove the protecting groups within a reasonable timeframe. Thus, a series of experiments, all in alcohol solvents, using concentrated HCl and H_2SO_4 were attempted. TLC analysis showed consumption of the starting material within 1 hour and the reactions were quenched with solid $NaHCO_3$. However, after purification by column chromatography the product obtained was found to be impure with inorganic material. It was presumed that these were salts produced during quenching carried through the column by the polar solvent system employed. A quench with $BaCO_3$ however yielded pure **31**. It had been hoped that the insolubility of barium compounds would overcome previous difficulties, although their use as quenching agents produces other problems. Filtration of the reaction mixture to remove the excess barium carbonate and barium sulfate produced was challenging but when accomplished, the yield of isolated **31** was much improved.

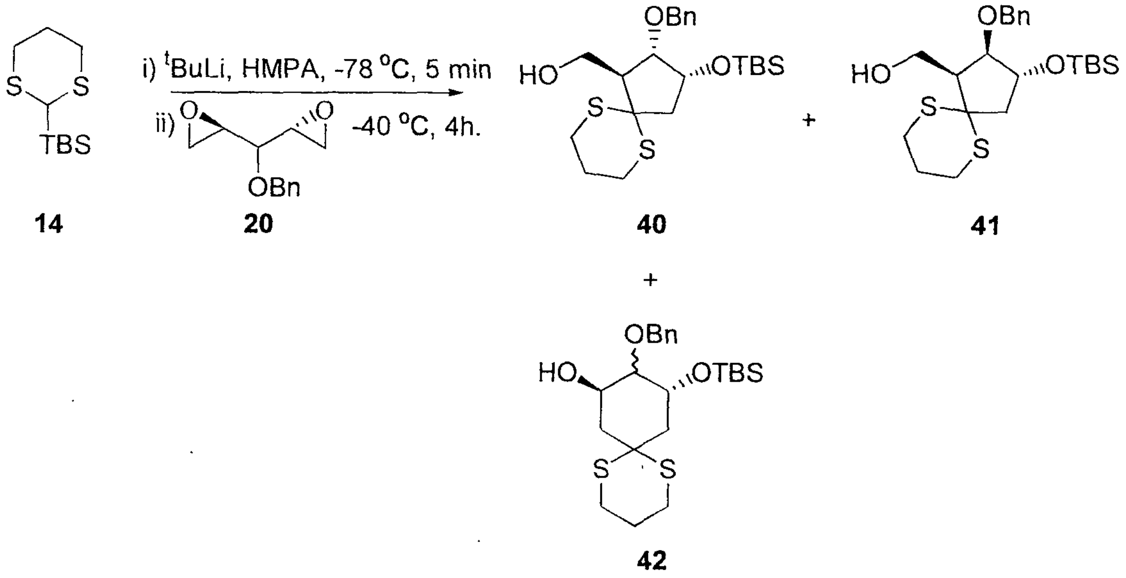
Sulfonylation of the primary alcohols of **31** with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) proceeded satisfactorily when undertaken with strict adherence to the method outlined in the literature,[26] with yields of approximately 70%. However, when the reaction was stirred overnight at ambient temperature a higher yield of **39** was obtained (86%). In an attempt to increase the yield of this reaction further, investigations into a recently reported system using catalytic Bu_2SnO has been conducted.[30] This however, offered no improvement.

The formation of the epoxide moieties present in **21** and subsequent isolation of the product proved challenging. Firstly, the reaction itself required vigorous stirring to overcome solidification of the reaction mixture by the precipitation of sodium sulfonates. Initial attempts to isolate **21** involved filtration of the reaction mixture, followed by concentration *in vacuo* and purification by chromatography. This yielded a small amount of product but was clearly an unsatisfactory method for its isolation. The first problem to overcome was that the sodium sulfonates filtered off at the very first stage were soluble in ether solvents so washings in subsequent experiments were done with pentane. Concentration of the filtrate was conducted by fractional distillation to prevent loss of the volatile product. Attempts to isolate the product directly from the concentrated filtrate by Kugelrohr distillation were unsuccessful. Hence, purification by column chromatography followed by fractional distillation of the appropriate fractions yielded pure **13** in 68% yield after Kugelrohr type distillation.

2.4 BROOK REARRANGEMENT MEDIATED CYCLISATION REACTIONS

*2.4.1 Formation of carbasugar derivatives **40** and **41** from bis-epoxide **20***

Application of a tandem epoxide opening – Brook rearrangement – epoxide opening sequence on a 1,4-bis-epoxide would lead to polysubstituted cyclopentane rings **40** and **41**, and possibly cyclohexane derivative **42**. To our surprise this procedure has not yet been reported.



Scheme 18: Desymmetrisation of bis-epoxide **20** to form **40**, **41** and **42**.

Reaction of the silyl stabilised carbanion of **14** with bis-epoxide **20** to form a carbasugar derivative, as a mixture of diastereomers was the first attempted reaction of this type. Initial reactions were conducted with a 2 hour period at -40°C between treatment with t-BuLi and addition of the epoxide after which the reaction was stirred for 30 min at -78°C. However, no product was seen when the crude material was analysed by GC-MS and ^{1}H NMR.

It was possible that the carbanion of **14** was unstable under the previously stated conditions so a shorter reaction time after addition of the ^{t}BuLi was required. When stirred at -78°C for 5 minutes before addition of the epoxide, the reaction proceeded as expected. When bis-epoxide **20** was added to the carbanion of **14** and the reaction stirred for 4 hours at -40°C, aqueous workup yielded a mixture of compounds. On purification by column chromatography a mixture of cyclisation products was obtained. These were separated by HPLC to give the two diastereomers, **40** and **41**, in 47% overall yield in a 2.4 : 1 ratio. HPLC of this mixture also gave a 3rd unidentified product assumed to be **42,** in 9% yield. The major diastereoisomer was found, from NOE data, to be the diastereomer in which the benzyl ether is *trans* to the hydroxymethyl group. As we do not expect the diastereotopic epoxide groups to have significantly different reactivities, and as the first step is not expected to be reversible, a possible explanation for the formation of **40** and **41** in different yields could be due to a difference in ease of cyclisation between the two diastereoisomeric intermediates. The reasoning for the product distribution observed is outlined below.

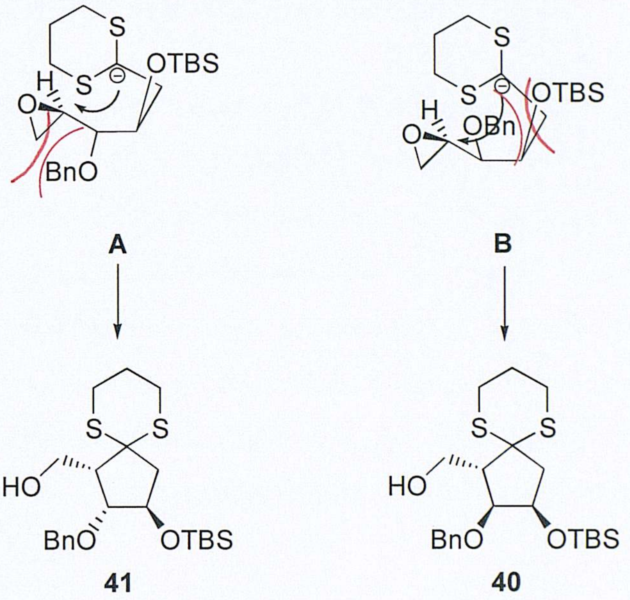
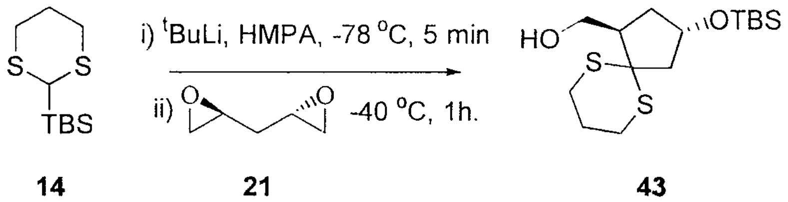


Figure 2: Transition states possible in the cyclisation to form **40** and **41**.

It can be seen from Figure 2 that in the first intermediate there is a steric clash (indicated in red) between the benzyl ether and the CH_2 group of the remaining epoxide moiety. In the second possible transition state the steric clash is between the benzyl ether and the silyl ether. As the major diastereomer has been shown to have the benzyl ether *trans* to the hydroxymethyl group, the most favourable interaction must be that in intermediate **B**. If intermediate **A** is unfavoured as we believe, we would expect to obtain the protonated product arising from **A**. This is not the case, and therefore it is believed that intermediate **A** can undergo a competing 6-*exo*-tet cyclisation to yield **42**. However, the yield of **41** and **42** combined is not equal to that of **40** which would be expected based on the above assumptions. This issue remains unclear and further investigations are required.

2.4.1 Formation of carbasugar derivative 43 from bis-epoxide 21



Scheme 19: Cyclisation reaction with bis-epoxide **21** to form **43**.

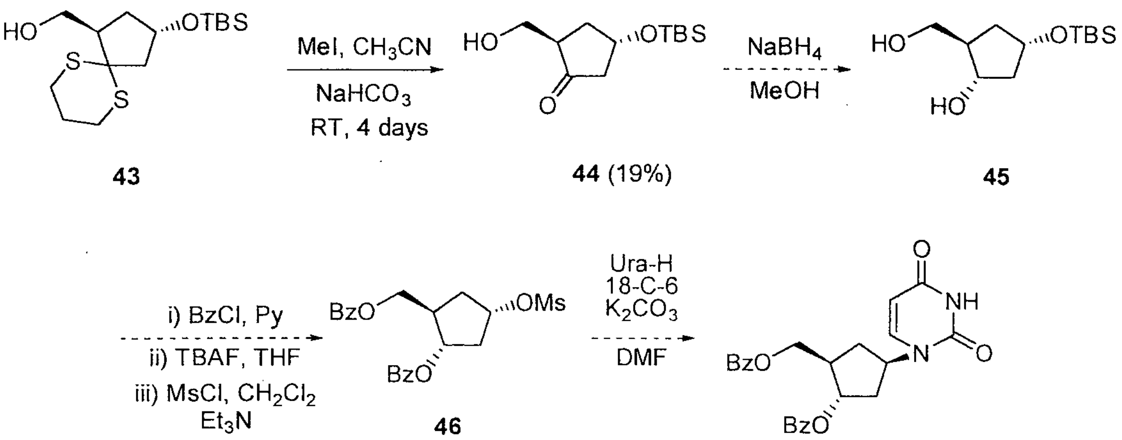
Initial reactions of bis-epoxide **21** with the carbanion of **14** were conducted using the conditions developed for bis-epoxide **20**. A reaction time of 4 hours after the addition of the epoxide gave the desired product **43** in 4% yield. However, isolation of the product was hampered by the presence of what appeared to be decomposition products though this remains unconfirmed. In an attempt to increase reaction yield, reaction scale was increased (previous reactions had been done on ≤ 0.04 g) and reaction time after epoxide addition was reduced to 2 hours. This increased the yield of **43** to 43%, with a further reduction in reaction time to 1 hour resulting in another increase in yield to an acceptable 56%.

Since **21** is C_2-symmetric, the reaction leads to a single diastereomer as predicted. Furthermore, the desymmetrisation can be conducted on either enantiomer of the bis-epoxide giving us access to both enantiomers of the product.

2.5 FURTHER TRANSFORMATION

An investigation to transform the obtained cyclopentane **43** to carbanucleosides has been commenced.

As can be seen from Scheme 20 **43** could act as a valuable intermediate in the synthesis of carbanucleosides



Scheme 20: Synthesis of a carbanucleoside from **43**.

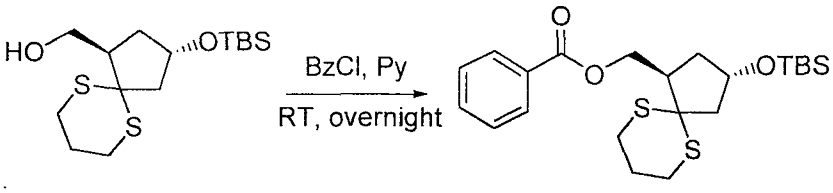
Investigation of the first step of this synthesis has as yet been relatively unsuccessful, with the hydrolysis of the thioketal only being achieved in low yield. Le Merrer et al. reported that a cyclic ketone with a silyl ether in the β position is prone to elimination to form an α,β unsaturated compound.[21] To this end they used NBS in aqueous acetone at -30°C to effect the hydrolysis and reduced the crude product with no isolation of the intermediate. All attempts to effect the hydrolysis of **43** using a NBS based system have yielded small amounts of the ketone **44**. Hence an alternative system using MeI in aqueous CH_3CN has been used, producing similar results.

Hydrolysis with NBS has been tried over various reaction times from 5 minutes to 30 minutes. As reaction time increases the amount of recovered starting material decreases but the yield of the desired product remains similar.

The hydrolysis system with MeI is used at ambient temperature but has a much longer reaction time. TLC analysis of the reaction after 4 days shows trace starting material, product and baseline material. However, when purified by column chromatography the yield of the ketone **44** is only 19%.

There are two possible explanations: the product **44** is unstable to silica and must be reduced directly without isolation, or the hydrolysis agents used, react with the primary hydroxyl in **43** and/or cause decomposition of the starting material through elimination or retro-aldol processes.

Direct reduction of the crude hydrolysis product has not yet been attempted. In an attempt to determine if NBS and MeI react with **43**'s free hydroxyl group, it has been protected as the benzoate ester (Scheme 21) and hydrolysis of the dithioketal will be attempted on this substrate.



43

48

Scheme 21: Protection of **43** as a benzoate ester.

3. CONCLUSIONS

In summary, we have accomplished the development of a novel protection / purification protocol for arabitol which allows access to the "*pseudo*"-C_2-symmetric bis-acetal in good yield without the need for extensive chromatographic purification.

We have utilised this bis-acetal in two separate syntheses for a "*pseudo*"-C_2-symmetric 1,4-bis-epoxide, and developed an improved route to the C_2-symmteric bis-epoxide **21**. Furthermore, due to the availability of both enantiomers of arabitol, these bis-epoxides have been synthesised in both enantiomeric forms.

These 1,4-bis-epoxides have been utilised in novel tandem nucleophilic addition-1,4-silyl migration-intramolecular alkylation reactions to form homochiral carbasugar derivatives. As was predicted, when a C_2-symmetric bis-epoxide is used only a single diastereomer is obtained, and when a "*pseudo*"-C_2-symmetric bis-epoxide is used a mixture of two diastereomers is observed.

Further functionalisation of these carbasugar derivatives to carbanucleoside structures has begun and continues to be an avenue for further research.

4. EXPERIMENTAL

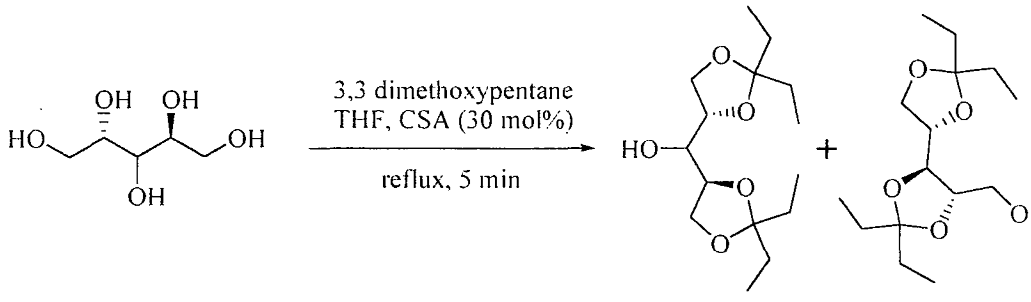
4.1 General methods

^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker DPX400 spectrometer. Chemical shifts are quoted in ppm relative to residual solvent peaks as appropriate. CIMS and EIMS were recorded on a Thermoquest Trace GCMS Quadrapole system. Infrared spectra were recorded as neat films on a Nicolet Impact 400 ATR spectrometer. Elemental analyses were conducted at Medac Ltd and HRMS were carried out in the Mass Spectrometry department at this university. Melting points were recorded on a Gallencamp Melting Point Apparatus and are uncorrected. Optical Rotations were measured on an Optical Activity PolAAr 2001.

Column chromatography was performed on 230-400 mesh Matrex silica gel (Fisher). Preparative HPLC was carried out using a Biorad Biosil D 90-10, 250×22mm column eluting at 20 mL min^{-1}, connected to a Kontron 475 refractive index detector. Reactions were monitored by TLC (Merck) with detection by alkaline $KMnO_4$ oxidation.

Arabitol was obtained from Pfanstiehl and used without further purification. Reaction solvents were dried before use as follows: THF was distilled from the sodium/benzophenone ketal; CH_2Cl_2, CS_2 and Et_3N were distilled from CaH_2; toluene was distilled from sodium; pyridine was double distilled from CaH_2 and stored in a Schlenk for later use; HMPA was distilled from CaH_2 and stored over 4A molecular sieves. All reaction vessels were flame dried under vacuum (2 mmHg) and cooled under nitrogen prior to use and all experiments were carried out under a nitrogen atmosphere.

(2*S*,4*S*)-1,2:4,5-di-*O*-(3,3-pentylidene)-arabitol (*ent*-8) and (2*S*,3*R*,4*S*)-2,3:4,5-di-*O*-(3,3-pentylidene)-arabitol (7)



L - arabitol   *ent*-**8** (80%)   **7** (12%)

To a refluxing suspension of L-arabitol (0.51 g, 3.35 mmol) and 3,3-dimethoxypentane (1.96 g, 14.8 mmol) in THF (5 mL) was added CSA (0.23 g, 0.99 mmol) and the reaction was stirred at reflux for 5 minutes. Triethylamine (1 mL) was added to the refluxing reaction, the mixture concentrated *in vacuo* and loaded directly onto a silica gel column (hexane / ethyl acetate, 8:2). The silica gel column was treated with eluent containing 1% Et_3N before use. This yielded a colourless oil which was further purified by preparative HPLC (hexane / acetone, 95:5) to give ***ent*-8** (0.76 g, 80%) and **7** (0.155 g, 12%) as colourless oils.

Data for ***ent*-8**:

$[\alpha]_D$ = -5.8 (*c* 0.9, $CHCl_3$, 20 °C).

IR (film): 3477 (m), 2973 (s), 2941 (s), 2883 (s), 1464 (m), 1082 (s), 919 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (1H, m, $CH_2C\underline{H}$); 4.14 (1H, dd, *J* = 7.8, 5.8 Hz, $C\underline{H}HCH$); 4.08 (1H, dd, *J* = 8.0, 6.5 Hz, $CH\underline{H}CH$); 3.98 (1H, m, $CH_2C\underline{H}$); 3.93 (1H, app. t, *J* = 8.0 Hz, $C\underline{H}HCH$); 3.86 (1H, app. t, *J* = 8.0 Hz, $CH\underline{H}CH$); 3.46 (1H, dt, *J* = 7.5, 5.3 Hz, $C\underline{H}OH$, simplifies to dd, J = 7.7, 4.9 Hz upon D_2O exchange); 2.39 (1H, d, *J* = 5.5 Hz, $CHO\underline{H}$, exchanges with D_2O); 2.4-1.56 (8H, m, 4 × $CH_3C\underline{H}_2$); 0.94-0.86 (12H, m, 4 × $C\underline{H}_3CH_2$).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 113.30 ($\underline{C}$), 112.92 ($\underline{C}$), 76.82 ($CH_2\underline{C}H$), 76.7 ($CH_2\underline{C}H$), 72.99 ($\underline{C}HOH$), 67.87 ($\underline{C}H_2CH$), 66.55 ($\underline{C}H_2CH$), 29.54 (2 × $CH_3\underline{C}H_2$), 29.05 ($CH_3\underline{C}H_2$), 28.96 ($CH_3\underline{C}H_2$), 8.19 ($\underline{C}H_3$), 8.17 ($\underline{C}H_3$), 8.04 (2 × $\underline{C}H_3$).

CIMS: m/z (%): 289 ((M+H)$^+$, 38), 259 (25), 203 (100), 173 (56).

HRMS (EI) for $C_{13}H_{23}O_5$ (M – CH_2CH_3)$^+$: calcd 259.15455, found 259.15484.

Anal. Calcd for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79. Found: C, 62.36; H, 9.49.

Data for 7:

$\mathbf{[\alpha]_D}$ = -7.1 (*c* 0.9, $CHCl_3$, 20 °C).

IR (film): 3493 (m), 2973 (s), 2941 (s), 2882 (s), 1464 (m), 1085 (s), 915 (s) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.20 (1H, dd, *J* = 8.3, 6.3 Hz, $\mathbf{C\underline{H}}HCH$); 4.05 – 3.99 (2H, m, $CH_2\mathbf{C\underline{H}}$ + $\mathbf{C\underline{H}}CH_2OH$); 3.91 (1H, dd, *J* = 8.3, 6.3 Hz, $\mathbf{CH\underline{H}}CH$); 3.85 – 3.74 (2H, m, $\mathbf{C\underline{H}_2}OH$); 3.62 (1H, t, *J* = 8.4 Hz, $CH\mathbf{C\underline{H}}CH$); 2.46 (1H, dd, *J* = 8.4, 4.3 Hz, $CH_2\mathbf{O\underline{H}}$); 1.70-1.59 (8H, m, $CH_3\mathbf{C\underline{H}_2}$); 0.92 – 0.86 (12H, m, $\mathbf{C\underline{H}_3}CH_2$).

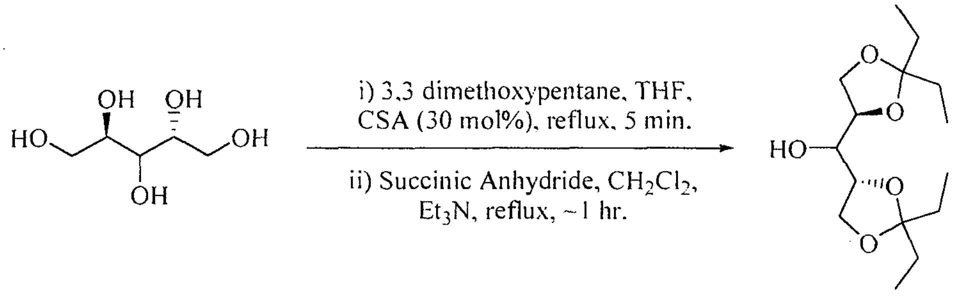
^{13}**C NMR + DEPT** (100 MHz, $CDCl_3$): δ 113.86 ($\underline{C}$), 113.10 ($\underline{C}$), 81.40 ($CH_2\mathbf{\underline{C}H}CH$), 79.75 ($CH\mathbf{\underline{C}H}CH_2OH$), 76.95 ($CH\mathbf{\underline{C}H}CH$), 68.74 ($\mathbf{\underline{C}H_2}CHCH$), 62.88 ($\mathbf{\underline{C}H_2}OH$), 30.39 ($\mathbf{\underline{C}H_2}CH_3$), 30.27 ($\mathbf{\underline{C}H_2}CH_3$), 29.50 ($\mathbf{\underline{C}H_2}CH_3$), 28.81 ($\mathbf{\underline{C}H_2}CH_3$), 8.15 ($\mathbf{\underline{C}H_3}$), 8.00 (2 × $\mathbf{\underline{C}H_3}$), 7.91 ($\mathbf{\underline{C}H_3}$).

CIMS: m/z (%): 289 ((M+H)$^+$, 44), 259 (86), 203 (100).

HRMS (EI) for $C_{13}H_{23}O_5$ (M – CH_2CH_3)$^+$: calcd 259.15455, found 259.15408.

Anal. Calcd for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79. Found: C, 62.37; H, 9.76.

The procedure including the scavenging type workup used to produce large scale quantities of (2*R*, 4*R*)-1,2:4,5-di-*O*-(3,3-pentylidene)-arabitol (8)



D - arabitol

8 (74%)

A refluxing suspension of D-arabitol (10.0 g, 65.72 mmol) and 3,3-dimethoxypentane (38.25 g, 0.29 mol) in THF (100 mL) was stirred for 15 min. CSA (4.58 g, 19.72 mmol) was added and the reaction was stirred at reflux for 5 minutes. The reaction was quenched by addition of NaOH (aq, 2M, 20 mL) at reflux. Diethyl ether (50 mL) and water (10 mL) were added and the layers separated. The aqueous solution was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. The crude product was taken up in CH_2Cl_2 (200 mL) and Et_3N (10 mL) was added. The reaction was brought to reflux and succinic anhydride (1.71 g, 17.09 mmol) was added. The reaction was stirred at reflux until the presence of **2** was undetectable by TLC (approximately 1 hour). The reaction was quenched with $NaHCO_3$ (aq, 5%, 100 mL). The layers were separated and the aqueous solution extracted with CH_2Cl_2 (2 × 100 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by quick column chromatography (hexane / ethyl acetate, 8:2) gave a colourless oil (14.09 g, 74%).

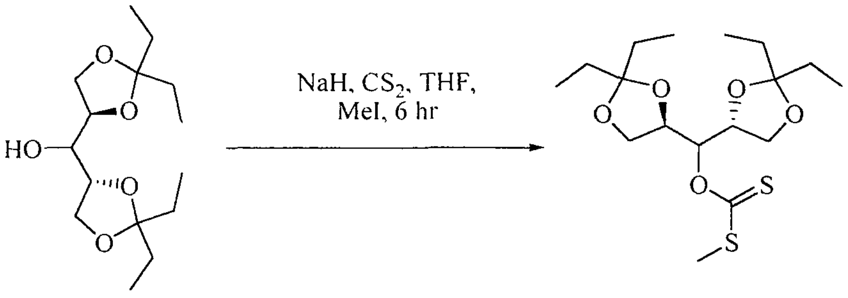
Data for **8**:

$[\alpha]_D = +5.6$ (*c* 0.8, $CHCl_3$, 20°C).

^{1}H and **^{13}C NMR, CIMS** and **IR** data all correspond to that for ***ent*-8.**

Anal. Calcd for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79. Found: C, 62.41; H, 9.98.

(2*R*,4*R*)-1,2:4,5-di-*O*-(3,3-pentylidene)-3-(methylthiothiocarbonyloxy)arabitol (37)



1

37 (98%)

To a solution of **1** (12.03 g, 41.7 mmol) in THF (150 mL) and CS_2 (32.0 mL, 0.53 mol) at 0°C was added NaH (2.0 g of a 60% dispersion in mineral oil, 50 mmol) and the reaction was stirred for 1 hour at 0°C. After warming to room temperature and stirring overnight the reaction was cooled to 0°C and MeI (3.3 mL, 54.21 mmol) was added the reaction warmed to room temperature and stirred for 6 hours. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl (200 mL) followed by diethyl ether (200 mL). The layers were separated and the aqueous solution extracted with diethyl ether (2 × 200 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil. This was purified by column chromatography (hexane / ethyl acetate 9 : 1) to give a yellow oil (15.47 g, 98%).

Data for **37**:

$[\alpha]_D$ = +56.1 (*c* 0.5, $CHCl_3$, 20°C).

IR (film): 2973 (s), 2940 (s), 2882 (m), 1463 (m), 1357 (w), 1209 (s), 1077 (s).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 6.13 (1H, dd, *J* = 5.7, 2.7 Hz, **CH**OCS); 4.45-4.37 (2H, m, CH_2**CH** + CH_2**CH**); 4.11 (1H, dd, *J* = 8.5, 6.5 Hz, **CH**HCH); 4.03 (1H, dd, *J* = 8.5, 6.5 Hz, **CH**HCH); 3.99 (1H, dd, *J* = 8.5, 6.6 Hz, **CHH**CH); 3.70 (1H, t, *J* = 8.0 Hz, CH**CHH**); 2.60 (3H, s, S**CH_3**); 1.71-1.57 (8H, m, CH_3**CH_2**); 0.95-0.87 (12H, m, **CH_3**CH_2).

^{13}**C NMR + DEPT** (100 MHz, $CDCl_3$): δ 217.17 (**C**S); 113.27 (CH_2**C**CH_2); 113.22 (CH_2**C**CH_2); 79.42 (**CH**OCS); 75.63 (CH_2**CH**); 75.40 (CH_2**CH**); 66.39 (**C**H_2CH);

65.64 ($\mathbf{\underline{C}H_2}$CH); 29.64 ($CH_3\mathbf{\underline{C}H_2}$); 29.33 ($CH_3\mathbf{\underline{C}H_2}$); 29.05 ($CH_3\mathbf{\underline{C}H_2}$); 28.95 ($CH_3\mathbf{\underline{C}H_2}$); 19.27 ($S\mathbf{\underline{C}H_3}$); 8.01 (2 × $\mathbf{\underline{C}H_3}CH_2$); 8.05 (2 × $\mathbf{\underline{C}H_3}CH_2$).

CIMS: m/z (%): 349 ($(M - CH_2CH_3)^+$, 36), 293 (100), 263 (46), 241 (66).

HRMS (ES^+) for $C_{17}H_{30}O_5S_2$ $(M + Na)^+$: calcd 401.1426865, found 401.1425750.

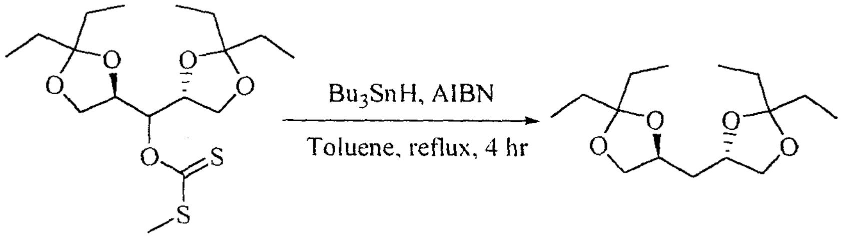
Data for ***ent*-37**

[α]ᴅ = -56.1 (*c* 0.6, $CHCl_3$, 20 °C).

^{1}H and **^{13}C NMR, CIMS** and **IR** data all correspond to that for **37.**

HRMS (ES^+) for $C_{17}H_{30}O_5S_2$ $(M + Na)^+$: calcd 401.1426865, found 401.1426660

(*2S, 4S*)-1,2:4,5-Bis-(3,3-pentylidenedioxy)-pentane (38)



37 **38** (89%)

AIBN (0.4 g, 2.5 mmol) and **37** (23.25 g, 61.42 mmol) were dissolved in toluene (350 mL) and the solvent degassed with dry N_2 for 30 minutes. Bu_3SnH (18.50 mL, 67.56 mmol) was added and the reaction brought to reflux, then stirred for 4 hours. The reaction was allowed to cool and concentrated *in vacuo*. Purification by column chromatography (hexane / ethyl acetate 9 : 1) yielded **38** as a colourless oil (14.92 g, 89%).

Data for **38**:

$[\alpha]_D$ = + 10.0 (*c* 0.5, $CHCl_3$, 20°C).

IR (film): 2973 (s), 2941 (s), 2881 (s), 1464 (m), 1355 (m), 1173 (s), 1078 (s) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.18 (2H, ddd, *J* = 12.3, 7.5, 6.3 Hz, $CH_2C\underline{H}$); 4.11 (2H, dd, *J* = 7.8, 6.0 Hz, $\mathbf{CH\underline{H}O}$); 3.52 (2H, t, *J* = 7.8 Hz, $\mathbf{C\underline{H}HO}$); 1.81 (2H, t, *J* = 6.4 Hz, $CH\mathbf{C\underline{H}_2}CH$); 1.67 – 1.58 (8H, m, $CH_3\mathbf{C\underline{H}_2}$); 0.90 (6H, t, *J* = 7.4 Hz, $\mathbf{C\underline{H}_3}CH_2$); 0.89 (6H, t, *J* = 7.4, $\mathbf{C\underline{H}_3}CH_2$).

^{13}**C NMR + DEPT** (100 MHz, $CDCl_3$): δ 112.61 ($\underline{\mathbf{C}}$); 73.99 ($CH_2\mathbf{\underline{C}H}$); 70.53 ($\mathbf{\underline{C}H_2}CH$); 37.68 ($CH\mathbf{\underline{C}H_2}CH$); 29.93 ($CH_3\mathbf{\underline{C}H_2}$); 29.70 ($CH_3\mathbf{\underline{C}H_2}$); 8.22 ($\mathbf{\underline{C}H_3}CH_2$); 7.95 ($\mathbf{\underline{C}H_3}CH_2$).

CIMS: m/z (%): 273 ($(M+H)^+$, 30), 243 (22), 187 (52), 157 (100), 129 (14).

Anal., Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.43; H, 10.23.

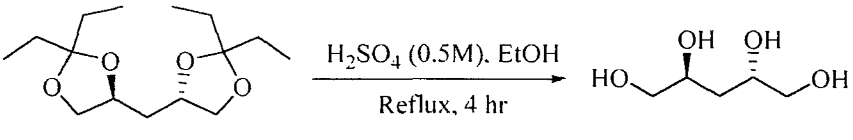
Data for ***ent*-38**:

$[\alpha]_D$ = -11.5 (*c* 0.60, CHC13, 20 °C).

^{1}**H** and ^{13}**C NMR**, **CIMS** and **IR** data all correspond to that for **38.**

Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.20; H, 10.08.

(2*S*, 4*S*)-Pentane-1,2,4,5-tetraol (31)



38 **31** (96%)

To a stirred solution of **38** (10.652 g, 39.11 mmol) in ethanol (50 mL) was added H_2SO_4 (50 mL of a 0.5 M solution in H_2O, 25 mmol) and the reaction was stirred at reflux for 4 hours. The reaction was quenched by addition of powdered $BaCO_3$ until neutral. After stirring at reflux for another 10 minutes the reaction mixture was cooled and filtered. The residue was stirred again with hot methanol, filtered and washed with methanol. The filtrate was concentrated *in vacuo* to give a white solid. This was purified by column chromatography (CH_2Cl_2/MeOH 7 : 3) to give a white solid (5.092 g, 96%).

Data for **31**:

m.p. = 104 – 106°C (EtOH / hexane), lit.[25a] 106 – 107°C.

[α]$_D$ = - 47.7 (*c* 0.5, EtOH, 20°C), lit.[25a] –46.0 (*c* 1.0, EtOH, 22°C).

The **^{1}H** and **^{13}C NMR** spectra corresponded to the literature values[25a]

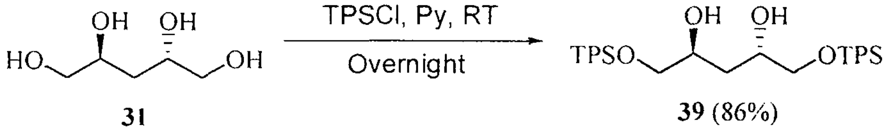
Data for ***ent*-31**:

m.p. = 105 – 107°C.

[α]$_D$ = + 47.2 (*c* 0.4, EtOH, 20°C).

The **^{1}H** and **^{13}C NMR** spectra correspond to that for **31**.

(2*S*, 4*S*)-2,4-Dihydroxypentane-1,5-diyl bis(2,4,6-tri-isopropylbenzenesulfonate) (39)



To a stirred solution of **31** (0.1 g, 0.73 mmol) in dry pyridine (2 mL) at 0°C was added 2,4,6-tri-isopropylbenzenesulfonyl chloride (0.49 g, 1.61 mmol). The reaction was stirred overnight at room temperature and the solvent removed under high vacuum rotary evaporation. The resulting pale yellow solid was purified by column chromatography (hexane / acetone, 75 : 25) to give a white solid. Recrystallisation from CH_2Cl_2 / hexane gave a fluffy white solid (0.422 g, 86 %).

Data for **39**:
m.p. = 154 – 156°C (CH_2Cl_2 / hexane), lit.[25a]154 – 155°C (CH_2Cl_2 / hexane).
[α]$_D$ = -7.5 (*c* 0.6, EtOH, 20°C), lit.[25a] –8.8 (*c* 0.2, EtOH, 22°C).
The ^{1}**H** and ^{13}**C NMR** spectra corresponded to the literature values.[25a]

Data for ***ent*-39**:
m.p. = 153 – 154°C (CH_2Cl_2 / hexane).
[α]$_D$ = +7.7 (*c* 0.4, EtOH, 22°C).
The ^{1}**H** and ^{13}**C NMR** spectra corresponded to those of **39**.

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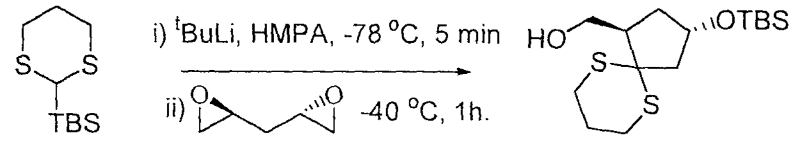
(1*R*, 3*S*)-{3-[(tert-Butyl-dimethyl-silanyl)-methyl]-6,10-dithia-spiro[4.5]dec-1-yl}-methanol (43)



14 **21** **43** (56%)

To a stirred solution of **14** (0.57 g, 2.43 mmol) and HMPA (1.74 mL, 10 mmol) in dry THF (15 mL) at -78°C was added ᵗBuLi (1.5M in pentanes, 2.15 mL, 3.225 mmol) and the reaction was stirred at -78°C for 5 minutes. A solution of **21** (0.25 g, 2.5 mmol) in dry THF (1 mL) was added, the reaction warmed to -40°C and stirred for 1 hour. Saturated aqueous NH_4Cl (20 mL) was added and the reaction stirred for a further 10 minutes. Et_2O (20 ml) was added and the layers separated. The aqueous phase was extracted with diethyl ether (4 × 20 mL), the organic phases combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (hexane / ethyl acetate, 8 : 2) gave a colourless oil (0.468 g, 56%).

Data for **43**:

$[\alpha]_D$ = +3.1 (*c* 0.5, $CHCl_3$, 20°C).

IR (film): 3444 (m), 2952 (s), 2926 (s), 2899(s), 2854 (s), 1471 (m), 1254 (s), 1087 (s), 835 (s).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 4.40 (1H, qd, *J* = 7.0, 4.0 Hz, $\mathbf{C}\underline{\mathrm{H}}$OSi); 3.90 (1H, ddd, *J* = 11.5, 8.0, 3.5 Hz, $\mathbf{CH}\underline{\mathbf{H}}$OH; simplifies to dd, *J* = 11.8, 8.0 Hz upon D_2O exchange); 3.70, (1H, ddd, *J* = 11.5, 8.5, 5.5 Hz, $\mathbf{C}\underline{\mathbf{H}}\mathbf{H}$OH; simplifies to dd, *J* = 11.8, 5.3 Hz upon D_2O exchange); 3.09 – 2.93 (2H, m, $\mathbf{SC}\underline{\mathbf{H}}\mathbf{H}$ + $\mathbf{SC}\underline{\mathbf{H}}\mathbf{H}$); 3.03 (1H, dd, *J* = 13.5, 6.5 Hz, $\mathrm{SSC}\mathbf{C}\underline{\mathbf{H}}\mathbf{H}$); 2.83 – 2.74 (2H, m, $\mathbf{SCH}\underline{\mathbf{H}}$ + $\mathrm{SCH}\underline{\mathrm{H}}$); 2.62 (1H, qd, *J* = 8.5, 5.5, $\mathbf{C}\underline{\mathbf{H}}\mathrm{CH_2OH}$); 2.33 (1H, m, $\mathrm{CH_2}\mathbf{O}\underline{\mathbf{H}}$; exchanges with D_2O); 2.14 (1H, dd, *J* = 13.5, 5.5 Hz, $\mathrm{SSC}\mathbf{CH}\underline{\mathbf{H}}$); 2.14 – 2.06 (1H, m, $\mathrm{CH_2}\mathbf{C}\underline{\mathbf{H}}\mathbf{H}\mathrm{CH_2}$); 1.98 – 1.82 (3H, m, $\mathrm{CH_2}\mathbf{CH}\underline{\mathbf{H}}\mathrm{CH_2}$ + $\mathrm{CH}\mathbf{C}\underline{\mathbf{H}}_2\mathrm{CH}$); 0.87 (9H, s, $\mathrm{C(C}\underline{\mathrm{H}}_3)_3$); 0.03 (6H, s, $\mathrm{Si(C}\underline{\mathrm{H}}_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 71.09 ($\underline{C}$OTBS), 63.38 ($\underline{\mathbf{C}}\mathbf{H}_2$OH), 56.56 (S$\underline{C}$S), 52.75 (C$\underline{\mathbf{C}}\mathbf{H}_2$CH), 51.35 ($\underline{\mathbf{C}}HCH_2$OH), 37.40 (CH$\underline{\mathbf{C}}\mathbf{H}_2$CH), 28.86 (S$\underline{\mathbf{C}}\mathbf{H}_2$), 26.89 (S$\underline{\mathbf{C}}\mathbf{H}_2$), 25.78 (C($\underline{\mathbf{C}}\mathbf{H}_3$)$_3$), 25.69 (CH$_2$$\underline{\mathbf{C}}\mathbf{H}_2CH_2$), 17.98 (Si$\underline{C}$), -4.80 (Si($\underline{\mathbf{C}}\mathbf{H}_3$)$_2$).

CIMS: m/z (%): 335 ((M + H)$^+$, 22), 317 (14), 277 (28), 259 (100), 203 (100), 185 (85).

Anal. Calcd for $C_{15}H_{30}O_2S_2Si$: C, 53.84; H, 9.04. Found: C, 54.20; H, 9.39.

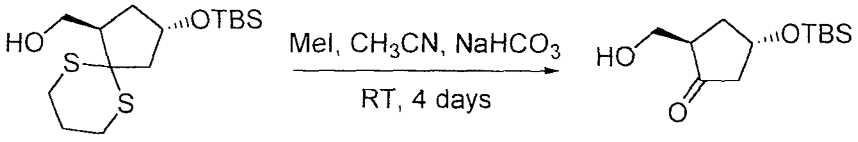
Data for ***ent*-43**:

$[\alpha]_D$ = -2.9 (*c* 0.8, $CHCl_3$, 20°C).

^{1}H and **^{13}C NMR**, **CIMS** and **IR** data all correspond to that for **43**.

Anal. Calcd for $C_{15}H_{30}O_2S_2Si$: C, 53.84; H, 9.04. Found: C, 53.90; H, 9.37.

(2*R*, 4*S*)-4-[(tert-Butyl-dimethyl-silanyl)-methyl]-2-hydroxymethyl-cyclopentanone (44)



43

44 (19%)

To a stirred solution of **43** (0.1 g, 0.3 mmol) in a mixture of acetonitrile / water 8 : 1 (2 mL) was added $NaHCO_3$ (0.13 g, 1.55 mmol) and MeI (0.19 mL, 3.1 mmol). The reaction was stirred at ambient temperature for 4 days. Diethyl ether (10 mL) and water (10 mL) were added and the layers separated. The organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography to give a white solid (0.014 g, 19%).

Data for **44**:

m.p. = 47 – 49°C.

$[\alpha]_D$ = + 99.0 (*c* 0.26, $CHCl_3$, 22°C).

IR (film): 3448 (s), 2954 (m), 2929 (m), 2856 (w), 1736 (m), 1472 (w), 1256 (m).

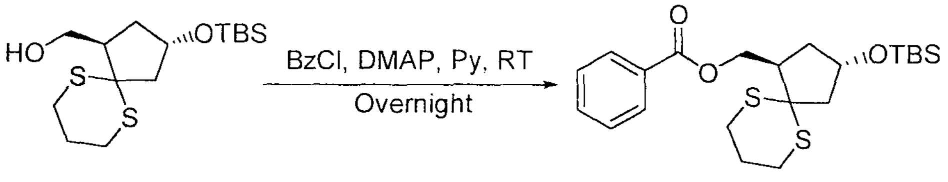
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57 (1H, tt, *J* = 4.0, 2.0 Hz, C$\underline{\text{H}}$OSi); 3.91 (1H, ddd, *J* = 11.5, 7.5, 4.5 Hz, **CH$\underline{\text{H}}$**OH); 3.70 (1H, ddd, *J* = 10.5, 6.5, 4.5 Hz, **C$\underline{\text{H}}$H**OH); 2.73 (1H, m, **C$\underline{\text{H}}$**CH_2OH); 2.33 (2H, m, **C$\underline{\text{H}}_2$**CO); 2.15 (1H, m, CH**CH$\underline{\text{H}}$**CH); 1.95 (1H, ddd, *J* = 13.0, 11.5, 4.0 Hz, CH**C$\underline{\text{H}}$H**CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 220.39 ($\underline{\text{C}}$O), 68.28 ($\underline{\text{C}}$HOSi), 61.70 ($\underline{\text{C}}H_2$OH), 48.72 ($\underline{\text{C}}H_2$CO), 47.48 (CO$\underline{\text{C}}$HCH_2OH), 35.67 (CH$\underline{\text{C}}H_2$COSi), 25.70 (3 × $\underline{\text{C}}H_3$), 17.96 (Si$\underline{\text{C}}$), -4.83 (Si$\underline{\text{C}}H_3$), -4.89 (Si$\underline{\text{C}}H_3$).

CIMS: m/z (%): 262 ($(M+NH_4)^+$, 7), 245 (13), 215 (5), 187 (7), 169 (54), 157 (86).

Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 58.93; H, 10.24.

(1*R*, 3*S*)-Benzoic acid 3-[(tert-butyl-dimethyl-silanyl)-methyl]-6,10-dithia-spiro[4.5]dec-1-ylmethyl ester (48)



43

48 (91%)

To a stirred solution of **43** (0.13 g, 0.37 mmol) in pyridine (2 mL) was added DMAP (0.002 g, 0.0185 mmol) and benzoyl chloride (0.05 mL, 0.45 mmol). The reaction was stirred for 16 hours at ambient temperature before concentration *in vacuo* to give a white solid. This was purified by chromatography on flash silica (hexane / ethyl acetate, 10 : 1) to give a colourless oil (0.15 g, 91%).

Data for **48**:

$[\alpha]_D$ = - 0.86 (*c* 1.8, $CHCl_3$, 22°C).

IR (film): 2953 (s), 2929 (s), 2897 (m), 2855 (m), 1720 (s), 1602 (w), 1270 (s).

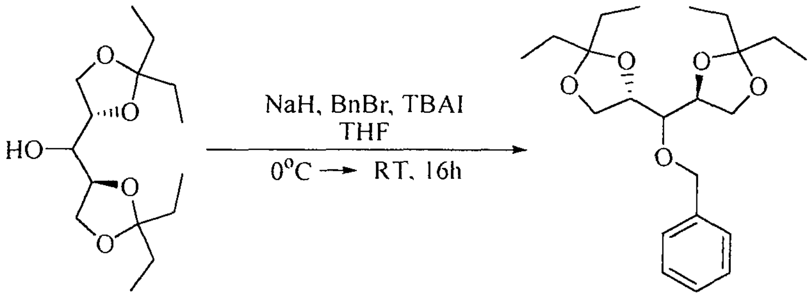
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.08 (2H, dd, *J* = 8.3, 1.3 Hz, $Ar\underline{H}$); 7.55 (1H, tt, *J* = 7.5, 1.7 Hz, $Ar\underline{H}$); 7.44 (2H, t, *J* = 7.5 Hz, $Ar\underline{H}$); 4.64 (1H, dd, *J* = 11.3, 5.3 Hz, $C\underline{H}HO$); 7.48 (1H, ddt, J = 7.3, 5.3, 3.5 Hz, $C\underline{H}OSi$); 4.39 (1H, dd, J = 11.3, 7.8 Hz, $CH\underline{H}O$); 3.07 – 2.79 (6H, m, 2 × $C\underline{H}_2S$, $C\underline{H}CH_2O$ + $CHC\underline{H}HCH$); 2.22 – 2.01 (4H, m, $CH_2C\underline{H}HCH_2$, $CC\underline{H}_2$+ $CHCH\underline{H}CH$); 1.98 – 1.88 (1H, m, $CH_2CH\underline{H}CH_2$); 0.89 (9H, s, $C(C\underline{H}_3)_3$), 0.059 (3H, s, $SiC\underline{H}_3$); 0.056 (3H, s, $SiC\underline{H}_3$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 166.33 ($\underline{C}O$), 132.79 ($Ar\underline{C}H$), 130.23 ($Ar\underline{C}$), 129.62 (2 × $Ar\underline{C}H$), 128.25 (2 × $Ar\underline{C}H$), 70.80 ($\underline{C}HOSi$), 65.08 ($\underline{C}H_2O$), 56.45 ($S\underline{C}S$), 52.61 ($SSC\underline{C}H_2$), 48.44 ($\underline{C}HCH_2O$), 38.31 ($CH\underline{C}H_2CH$), 28.65 ($S\underline{C}H_2$), 27.16 ($S\underline{C}H_2$), 25.78 ($C(\underline{C}H_3)_3$), 25.43 ($CH_2\underline{C}H_2CH_2$), 17.98 ($Si\underline{C}$), -4.80 ($Si(\underline{C}H_3)_2$).

EIMS: m/z (%): 381 ((M - ^{t}Bu)$^+$, 2), 316 (14), 259 (96), 185 (91), 165 (20).

Anal. Calcd for $C_{22}H_{34}O_3S_2Si$: C, 60.23; H, 7.81. Found: C, 60.30; H, 7.94.

(2*S*,4*S*)-1,2:4,5-di-*O*-(3,3-pentylidene)-3-(benzyloxy)-arabitol (35)



***ent*-8** **35** (95%)

To a stirred solution of ***ent*-8** (0.52 g, 1.8 mmol), benzyl bromide (0.34 mL, 2.8 mmol) and tetrabutylammonium iodide (0.066 g, 0.18 mmol) at 0°C was added NaH (0.079 g of a 60% dispersion in mineral oil, 1.9 mmol). The reaction was allowed to warm to room temperature overnight and was then quenched by the careful addition of saturated aqueous NH_4Cl (5 mL). Et_2O was added (10 mL) and the layers separated. The aqueous layer was extracted with ether (2 × 10 mL), the organic components combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting colourless oil was purified by column chromatography (hexane / ethyl acetate 95 : 5) to give a colourless oil (0.65 g, 95%).

Data for **35**:

[α]$_D$ = - 43.9 (*c* 0.8, $CHCl_3$, 24°C).

IR (film): 3089 (w), 3065 (w), 3031 (w), 2972 (s), 2940 (s), 2882 (s), 1497 (w), 1463 (m), 1090 (s), 920 (s).

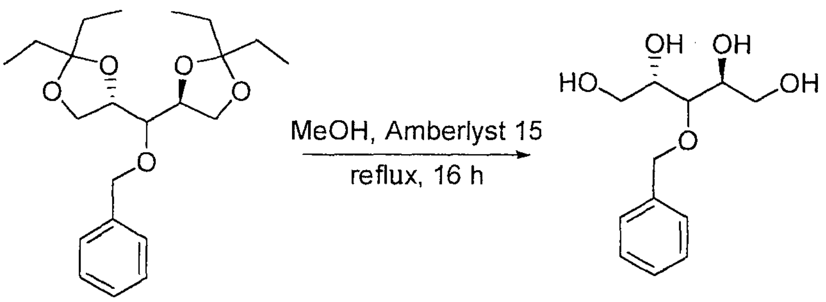
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.26 (5H, m, Ar$\underline{\mathrm{H}}$), 4.87 (1H, d, *J* = 11.5 Hz, **C$\underline{\mathrm{H}}$**HOPh); 4.72 (1H, d, *J* = 11.5 Hz, **CH$\underline{\mathrm{H}}$**OPh); 4.16 (1H, dt, *J* = 8.6, 6.0 Hz, CH_2C$\underline{\mathrm{H}}$); 4.11 – 4.00 (3H, m, **$\underline{\mathrm{H}}$HCCH**, CHCH$\underline{\mathrm{H}}$ + C$\underline{\mathrm{H}}$$CH_2$); 3.81 (1H, t, *J* = 7.5 Hz, **H$\underline{\mathrm{H}}$**CCH); 3.73 (1H, t, *J* = 8.5 Hz, CHC$\underline{\mathrm{H}}$H); 3.51 (1H, t, *J* = 6.5 Hz, CHC$\underline{\mathrm{H}}$CH); 1.72 – 1.54 (8H, m, 4 × C$\underline{\mathrm{H}_2}$$CH_3$); 0.94 – 0.85 (12H, m, 4 × CH_2C$\underline{\mathrm{H}_3}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.45 (Ar$\underline{\mathrm{C}}$), 128.31 (2 × Ar$\underline{\mathrm{C}}$H), 127.97 (2 × Ar$\underline{\mathrm{C}}$H), 127.67 (Ar$\underline{\mathrm{C}}$H), 113.09 ($CH_2$$\underline{\mathrm{C}}$$CH_2$), 112.67 ($CH_2$$\underline{\mathrm{C}}$$CH_2$), 80.40 ($\underline{\mathrm{C}}$HOBn), 78.96 ($CH_2$$\underline{\mathrm{C}}$H), 76.49 ($CH_2$$\underline{\mathrm{C}}$H), 74.55 (O$\underline{\mathrm{C}}$$H_2$Ph), 67.60 ($\underline{\mathrm{C}}$$H_2$CH), 66.91 ($\underline{\mathrm{C}}$$H_2$CH), 29.75 ($\underline{\mathrm{C}}$$H_2$$CH_3$), 29.62 ($\underline{\mathrm{C}}$$H_2$$CH_3$), 29.45 ($\underline{\mathrm{C}}$$H_2$$CH_3$), 28.81 ($\underline{\mathrm{C}}$$H_2$$CH_3$), 8.21 (2 × $\underline{\mathrm{C}}$$H_3$), 8.15 ($\underline{\mathrm{C}}$$H_3$), 8.12 ($\underline{\mathrm{C}}$$H_3$).

CIMS: m/z (%): 379 ((M + H)$^+$, 8), 349 (18), 293 (86), 263 (68), 207 (12).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.70; H, 9.26.

(2*S*,4*S*)-3-Benzyloxy-1,2,4,5-pentane tetraol (36)

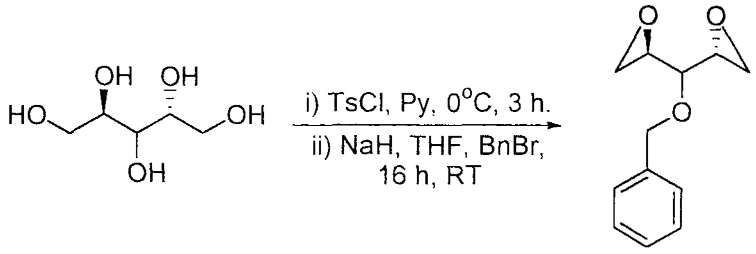


35 **36** (69%)

To a stirred solution of **35** (2.70 g, 7.1 mmol) in wet methanol (25 mL) was added Amberlyst 15 (1.9 g). Reaction heated to reflux and stirred for 40 h. Reaction allowed to cool, the resin removed by filtration and the filtrate concentrated *in vacuo* to yield a colourless oil. Purification by column chromatography (CH_2Cl_2 / MeOH, 10 : 1) yielded a white solid (1.19 g, 69%).

Data for **36**:
m.p. = 60 – 64°C.
$[\alpha]_D$ = - 6.7 (*c* 0.5, $CHCl_3$, 22°C).
IR (neat): 3395 (s), 3248 (s), 2926 (m), 2879 (w), 1320 (m), 1092 (m), 1054 (s).
^{1}**H NMR** (400 MHz, CH_3OD): δ 7.40 – 7.25 (5H, m, Ar$\underline{H}$); 4.77 (1H, d, *J* = 11.0 Hz, CH$\underline{H}$Ph); 4.66 (1H, d, *J* = 11.0 Hz, C$\underline{H}$HPh); 3.93 (1H, dt, *J* = 6.5, 2.5 Hz, $CH_2C\underline{H}$); 3.86 (1H, ddd, *J* = 7.0, 5.5, 3.6 Hz, $C\underline{H}CH_2$); 3.78 (1H, dd, *J* = 11.3, 3.8 Hz, CH$\underline{H}$CH); 3.68 – 3.63 (3H, m, $CHC\underline{H}_2$ + C$\underline{H}$HCH); 3.61 (1H, dd, *J* = 7.0, 2.5 Hz, CHC$\underline{H}$CH).
^{13}**C NMR** (100 MHz, CH_3OD): δ 139.86 (Ar$\underline{C}$), 129.31 (2 × Ar$\underline{C}$H), 129.18 (2 × Ar$\underline{C}$H), 128.71 (Ar$\underline{C}$H), 79.88 (CH$\underline{C}$HCH), 75.22 ($\underline{C}H_2Ph$), 73.03 ($CH_2\underline{C}H$), 72.94 ($\underline{C}HCH_2$), 64.45 ($\underline{C}H_2CH$), 64.31 ($CH\underline{C}H_2$).
ES$^+$: m/z (%): 260 ($(M+NH_4)^+$, 18), 251 (14), 221 (10), 151 (100), 135 (56).
Anal. Calcd for $C_{22}H_{34}O_5$: C, 59.49; H, 7.49. Found: C, 59.45; H, 7.69.

(2*R*,4*R*)-1,2:4,5-Dianhydro-3-(benzyloxy)-arabitol (20)[31]



D - arabitol

20

To a stirred solution of D-arabitol (1.0 g, 6.6 mmol) in pyridine (23 mL) at 0°C was added p-TsCl (2.55 g, 13.38 mmol). The reaction was stirred at 0°C for 3 h before warming to ambient temperature. The reaction was poured into cold HCl (6N aq. 25 mL), allowed to cool, Et$_2$O (35 mL) was added and the layers were separated. The aqueous layer was extracted with Et$_2$O (2 × 50 mL), the organic phases were combined, washed with a 3% aqueous solution of NaHCO$_3$, dried over MgSO$_4$, filtered and concentrated *in vacuo*. The resulting milky oil was taken up in THF (15 mL) and was added dropwise to a suspension of NaH (0.6 g of a 60% dispersion in mineral oil, 15.0 mmol) in THF (20 mL). The reaction was stirred for 1 hour at 0°C. benzyl bromide (0.78 mL, 6.6 mmol) was added, the reaction warmed to room temperature and then stirred for 16 h. H$_2$O (5 mL) and Et$_2$O (50 mL) were added and the layers separated. The aqueous phase was extracted with Et$_2$O (2 × 50 mL), the organic phases combined, dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (hexane / diethyl ether, 7 : 3) yielded **20** as a yellow oil (0.38 g, 28 %).

Data for **20**:

$[\alpha]_D$ = + 29.8 (*c* 1.0, CHCl$_3$, 22°C).

IR (film): 3062 (m), 3031 (m), 2998 (s), 2927 (m), 2873 (m), 1602 (w), 1496 (m), 1455 (s), 1251 (m), 1090 (s), 1028 (m).

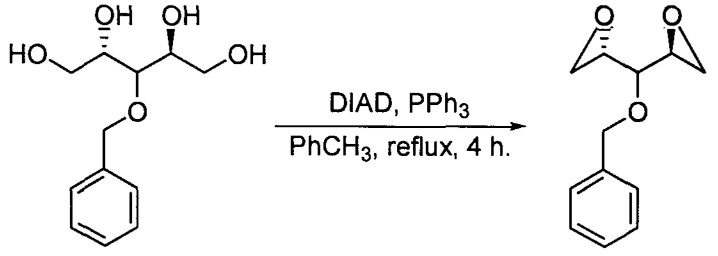
^{1}**H NMR** (400 MHz, CDCl$_3$): δ 7.37 – 7.25 (5H, m, Ar**H**); 4.76 (1H, d, *J* = 12.1 Hz, **CHH**Ph); 4.65 (1H, d, *J* = 12.1 Hz, **CHH**Ph); 3.17 (1H, ddd, *J* = 6.0, 4.5, 3.0 Hz, CH$_2$**CH**); 3.07 (1H, ddd, *J* = 5.5, 3.5, 2.5 Hz, **CH**CH$_2$); 2.99 (1H, dd, *J* = 6.5, 5.5, **CH**OCH$_2$); 2.84 – 2.79 (2H, m, **CHH**CH + CH**CHH**); 2.68 – 2.64 (2H, m, **CHH**CH + CH**CHH**).

^{13}C NMR (100 MHz, CDCl$_3$): δ 137.87 (Ar$\underline{\mathbf{C}}$), 128.34 (2 × Ar$\underline{\mathbf{C}}\mathbf{H}$), 127.72 (3 × Ar$\underline{\mathbf{C}}\mathbf{H}$), 79.65 ($\underline{\mathbf{C}}\mathbf{H}OCH_2$), 72.16 ($\underline{\mathbf{C}}\mathbf{H}_2$Ph), 52.59 (CH$_2\underline{\mathbf{C}}\mathbf{H}$), 50.93 ($\underline{\mathbf{C}}\mathbf{H}CH_2$), 45.24 ($\underline{\mathbf{C}}\mathbf{H}_2$CH), 43.10 (CH$\underline{\mathbf{C}}\mathbf{H}_2$).

CIMS: m/z (%): 224 ((M+NH$_4$)$^+$, 60), 181 (12), 131 (10), 108 (22), 91 (100).

HRMS: (ES$^+$) for C$_{12}$H$_{14}$O$_3$ (M + Na)$^+$: calcd 229.08406, found 229.08315.

(2*S*,4*S*)-1,2:4,5-Dianhydro-3-(benzyloxy)-arabitol (*ent*-20)



36 *ent*-**20**

A stirred solution of **36** (1.20 g, 4.95 mmol) and PPh_3 (2.99 g, 11.39 mmol) in toluene (70 mL) was brought to reflux and DIAD (2.26 mL, 11.39 mmol) was added. The reaction was stirred at reflux for 4 hours before removal of the solvent *in vacuo*. The residue was purified by column chromatography (hexane / diethyl ether, 7 : 3) to yield impure *ent*-**20** which was further purified by HPLC (hexane / ethyl acetate, 87 : 13) to give a colourless oil (0.654 g, 64 %).

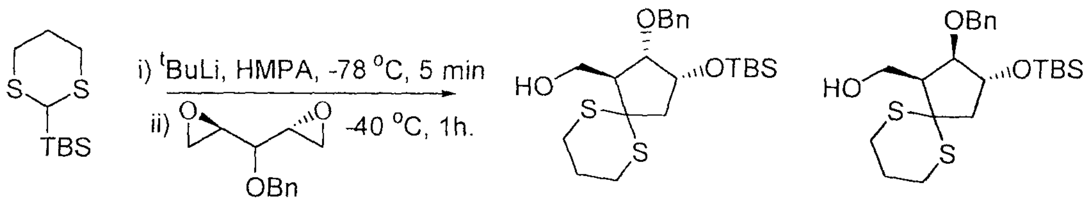
Data for *ent*-**20**:

$[\alpha]_D$ = - 29.0 (*c* 0.5, $CHCl_3$, 24°C).

^{1}**H** and ^{13}**C NMR**, **CIMS** and **IR** data all correspond to that for **20.**

HRMS (ES^+) for $C_{12}H_{14}O_3$ $(M + Na)^+$: calcd 229.08406, found 229.08352.

(1*S*, 2*S*, 3*R*)-{2-Benzyloxy-3-[(tert-butyl-dimethyl-silanyl)-methyl]-6,10-dithia-spiro[4.5]dec-1-yl}-methanol (40) and (1*S*, 2*R*, 3*R*)-{2-Benzyloxy-3-[(tert-butyl-dimethyl-silanyl)-methyl]-6,10-dithia-spiro[4.5]dec-1-yl}-methanol (41)



14 **20** **40** (33%) **41** (14%)

To a stirred solution of **14** (0.15 g, 0.65 mmol) in THF (7 mL) at -78°C was added HMPA (0.45 mL, 2.6 mmol)and ^{t}BuLi (1.5M in pentanes, 0.56 mL, 0.84mmol). The reaction was stirred for 5 min before the addition of **20** (0.14 g, 0.65 mmol) in THF (2 mL). The reaction was warmed to -40°C and stirred for 4 hours. Saturated aqueous NH_4Cl (5 mL) was added and the reaction stirred vigorously for 10 minutes. Et_2O (10 mL)added and the layers separated. The aqueous layer was extracted with Et_2O (2 × 10 mL), the organic phases combined, washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (hexane / ethyl acetate, 8 : 2)gave a yellow oil which was further purified by HPLC (hexane / acetone, 92 : 8) to yield a colourless oil **40** (0.094 g, 33%). a colourless oil **41** (0.040g, 14%) and a third product (0.026g, 9%).

Data for **40**:

$[\alpha]_D$ = -86.5 (*c* 1.0, $CHCl_3$, 19°C).

IR (film): 3530 (w), 2952 (s), 2928 (s), 2898 (s). 2856 (s), 1471 (w), 1253 (m).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.35 – 7.25 (5H, m, Ar**H**); 4.74 (1H, d, *J* = 12.0 Hz, **CHH**Ph); 4.45 (1H, d, *J* = 11.9 Hz, **CHH**Ph); 4.40 (1H, dd, *J* = 9.5, 4.5 Hz. **CH**OSi): 4.03 – 3.91 (2H, m, **CH**$_2$OH, simplifies to: 3.99 (1H, dd, *J* = 11.8, 7.2 Hz) and 3.94 (1H, dd, *J* = 11.8, 6.0 Hz) upon D_2O exchange); 3.79 (1H, dd, *J* = 9.5, 4.5, **CH**OCH_2): 3.10 (1H, ddd, *J* = 14.6, 12.1, 2.5 Hz, S**CHH**); 2.97 (1H, ddd, *J* = 14.6, 11.6, 2.5 Hz, S**CHH**); 2.87 – 2.74 (3H, m, **SCHH**, **SCHH** + SS**CCHH**); 2.68 (1H, dt, *J* = 9.0, 6.5 Hz, HOCH_2**CH**); 2.41 (1H, t, *J* = 6.5 Hz, CH_2**OH**, exchanges with D_2O); 2.38 (1H, dd, *J* = 14.0, 4.0 Hz, $\mathbf{CH\underline{H}}$CHO); 2.18 – 2.07 (1H, m, $SCH_2\mathbf{C\underline{H}H}$); 1.97 – 1.86 (1H, m, $SCH_2\mathbf{CH\underline{H}}$); 0.93 (9H, s, $C(\mathbf{C\underline{H}_3})_3$); 0.11 (3H, s, $Si\mathbf{C\underline{H}_3}$); 0.10 (3H, s, $Si\mathbf{C\underline{H}_3}$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 138.14 (Ar$\underline{\mathbf{C}}$), 128.35 (2 × Ar$\underline{\mathbf{C}}\mathbf{H}$), 127.63 (Ar$\underline{\mathbf{C}}\mathbf{H}$), 127.59 (2 × Ar$\underline{\mathbf{C}}\mathbf{H}$), 81.56 ($\underline{\mathbf{C}}\mathbf{H}OCH_2Ph$), 71.90 ($\underline{\mathbf{C}}\mathbf{H_2}Ph$), 70.10 ($\underline{\mathbf{C}}\mathbf{H}OSi$), 62.06 ($\underline{\mathbf{C}}\mathbf{H_2}OH$), 56.04 ($\underline{\mathbf{C}}\mathbf{H}CH_2OH$), 52.00 ($S\underline{\mathbf{C}}S$), 50.81 ($\underline{\mathbf{C}}\mathbf{H_2}CHO$), 28.63 ($S\underline{\mathbf{C}}\mathbf{H_2}$), 27.03 ($S\underline{\mathbf{C}}\mathbf{H_2}$), 25.80 ($C(\underline{\mathbf{C}}\mathbf{H_3})_3$), 25.50 ($CH_2\underline{\mathbf{C}}\mathbf{H_2}CH_2$), 18.09 ($Si\underline{\mathbf{C}}$), -4.49 ($Si\underline{\mathbf{C}}\mathbf{H_3}$), -4.73 ($Si\underline{\mathbf{C}}\mathbf{H_3}$).

CIMS: m/z (%): 441 ($(M+H)^+$, 10), 291 (8), 197 (20), 171 (47), 106 (36).

Anal. Calcd for $C_{22}H_{36}O_3S_2Si$: C, 59.96; H, 8.23. Found: C, 60.13; H, 8.50.

Data for **41**:

[α]$_D$ = -25.6 (*c* 1.1, $CHCl_3$, 19°C).

IR (film): 3495 (w), 2951 (s), 2928 (s), 2897 (s), 2855 (s), 1471 (w), 1254 (m).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.25 (5H, m, Ar$\underline{\mathbf{H}}$); 4.75 (1H, d, *J* = 11.6 Hz, $\mathbf{C\underline{H}H}Ph$); 4.57 (1H, d, *J* = 11.5 Hz, $\mathbf{CH\underline{H}}Ph$); 4.42 (1H, dt, *J* = 8.0, 5.5 Hz, $\mathbf{C\underline{H}}OSi$); 4.28 (1H, dd, *J* = 7.0, 4.5 Hz, $\mathbf{C\underline{H}}OCH_2Ph$); 3.93 (2H, m $\mathbf{C\underline{H}_2}OH$, simplifies upon D_2O exchange); 2.97 – 2.83 (4H, m, 2 × $\mathbf{S}\mathbf{C\underline{H}_2}$); 2.76 – 2.69 (2H, m, $\mathbf{C\underline{H}}CH_2OH$, $SS\mathbf{C\underline{H}H}$); 2.61 (1H, t, *J* = 6.5 Hz, $\mathbf{O\underline{H}}$, exchanges with D_2O); 2.04 (1H, dd, *J* = 14.1, 5.5 Hz, $SS\mathbf{CH\underline{H}}$); 2.01 – 1.96 (2H, m, $CH_2\mathbf{C\underline{H}_2}CH_2$); 0.91 (9H, s, $C(\mathbf{C\underline{H}_3})_3$); 0.10 (3H, s, $Si\mathbf{C\underline{H}_3}$); 0.08 (3H, s, $Si\mathbf{C\underline{H}_3}$).

^{13}**C NMR** (100 MHz, $CDCl_3$): δ 138.12 (Ar$\underline{\mathbf{C}}$), 128.44 (2 × Ar$\underline{\mathbf{C}}\mathbf{H}$), 127.71 (Ar$\underline{\mathbf{C}}\mathbf{H}$), 127.55 (2 × Ar$\underline{\mathbf{C}}\mathbf{H}$), 87.69 ($\underline{\mathbf{C}}\mathbf{H}OCH_2Ph$), 76.53 ($\underline{\mathbf{C}}\mathbf{H}OSi$), 72.66 ($\underline{\mathbf{C}}\mathbf{H_2}Ph$), 60.60 ($\underline{\mathbf{C}}\mathbf{H_2}OH$), 53.64 ($S\underline{\mathbf{C}}S$), 52.20 ($\underline{\mathbf{C}}\mathbf{H}CH_2OH$), 48.91 ($\underline{\mathbf{C}}\mathbf{H_2}CHO$), 28.79 ($S\underline{\mathbf{C}}\mathbf{H_2}$), 27.95 ($S\underline{\mathbf{C}}\mathbf{H_2}$), 25.74 ($C(\underline{\mathbf{C}}\mathbf{H_3})_3$), 24.89 ($CH_2\underline{\mathbf{C}}\mathbf{H_2}CH_2$), 17.87 ($Si\underline{\mathbf{C}}$), -4.41 ($Si\underline{\mathbf{C}}\mathbf{H_3}$), -4.79 ($Si\underline{\mathbf{C}}\mathbf{H_3}$).

CIMS: m/z (%): 441 ($(M+H)^+$, 6), 315 (13), 291 (8), 197 (22), 171 (52), 108 (32).

Anal. Calcd for $C_{22}H_{36}O_3S_2Si$: C, 59.96; H, 8.23. Found: C, 60.11; H, 8.45.

Data for ***ent*-40**:

[α]$_D$ = +87.3 (*c* 0.5, $CHCl_3$, 19°C).

^{1}**H** and ^{13}**C NMR**, **CIMS** and **IR** data all correspond to that for **40**.

Anal. Calcd for $C_{22}H_{36}O_3S_2Si$: C, 59.96; H, 8.23. Found: C, 59.91; H, 8.41.

Data for ***ent*-41**:

$[\alpha]_D$ = +24.9 (*c* 0.9, $CHCl_3$, 19°C).

^{1}**H** and ^{13}**C NMR**, **CIMS** and **IR** data all correspond to that for **41.**

Anal. Calcd for $C_{22}H_{36}O_3S_2Si$: C, 59.96; H, 8.23. Found: C, 59.75; H, 8.36.

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