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STEREOCHEMICAL CONTROL OF NATURE'S BIOSYNTHETIC PATHWAYS: A GENERAL STRATEGY FOR THE SYNTHESIS OF POLYPROPIONATE-DERIVED STRUCTURAL UNITS FROM A SINGLE CHIRAL PROGENITOR †

S. HANESSIAN* and P.J. MURRAY

Department of Chemistry, Université de Montréal
Montréal, Québec, Canada H3C 3J7

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Abstract - A general strategy that permits the stereocontrolled construction of acyclic chains containing vicinal and/or alternating alkyl and hydroxy substitutents is presented. Structural subunits of ionomycin were synthesized from a common chiral intermediate.

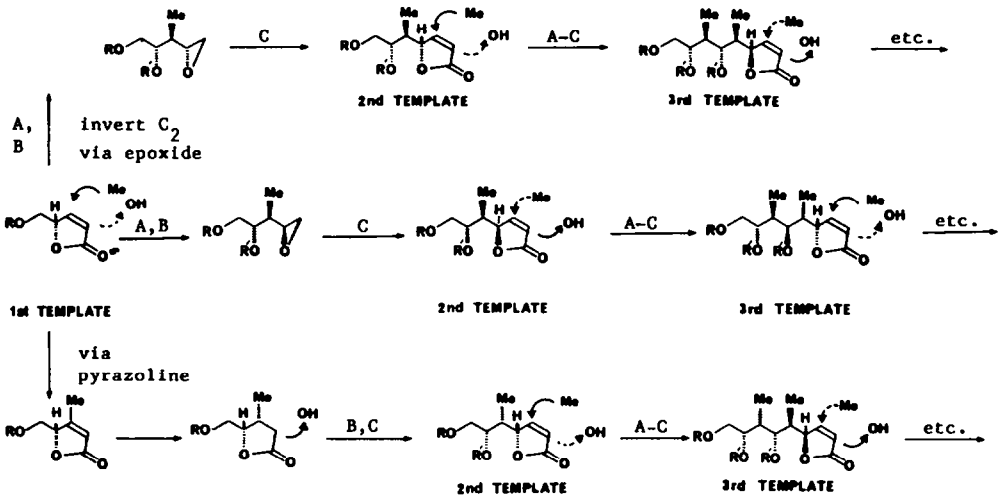
The polypropionate pathway is an important biosynthetic tool by which nature assembles a multitude of products that contain combinations of carbon and hydroxy substituents.[1] The quest to match and surpass nature's stereochemical virtuosity has brought forth a number of innovative methods for the synthesis of products formally derived from the propionate and related pathways. One of the more frequently adopted strategies has centered around the aldol condensation.[2] A number of other methods have also been recently reported for the assembly of carbon chains containing alternating 1,3-dimethyl substituents, with or without intervening hydroxyl groups.[3] Other approaches have relied on the utilization of cyclic and acyclic templates (chiral synthons or chirons)[4] derived from carbohydrates, terpenes, amino acids, hydroxy acids and related compounds.[5] In spite of their respective merits, these methods normally address specific sets of substitution patterns in the intended target structures. A general method that can provide access to any number of combinations of structural subunits derived from the propionate, butyrate, etc. pathways, particularly from a common progenitor, is not presently available.

We describe herein a protocol for the synthesis of virtually any combination of alternating alkyl and hydroxy substitution patterns on chains of seven carbons or more. The method[6,7] is based on the utilization of the readily available[8] (S)-5-hydroxymethyl 5(H)-furan-2-one* as a template, in such a way so as to permit a systematic, stereocontrolled introduction of methyl and hydroxy groups at predetermined positions.[9] A two-carbon acetate extension, replication of the butenolide template, and reiteration of the process affords after one such cycle, a seven-carbon lactone, harboring a full complement of substituents. By virtue of the difference in the nature of the terminal groups, and the possibility to extend in either direction, and/or to adjust stereochemistry in the process, each reiteration can produce several diastereomeric structural units, with predetermined patterns of *syn* or *anti* substituents. Scheme 1 illustrates one of several working examples taken from current work in our laboratory. For the sake of clarity of presentation, chain

† Dedicated to Professor Hans Wynberg on the occasion of his 65th birthday.

* This compound can also be named (4S)-4-hydroxymethyl-2-buten-4-olide, or as a carbohydrate, 2,3-dideoxy-D-*glycero*-pent-2-eno-1,4-lactone.

Scheme 1



A. Conjugate addition, then hydroxylation; B. epoxide formation; C. acetate extension, then lactonization/elimination

extension and replication is done in a unidirectional manner starting at C-1 of the original (and reiterated) butenolides. It should be noted that the sense of chirality and orientation of the C-4 substituents in the butenolides are the controlling elements in this stereochemically predictive, tunable and linear process. We demonstrate the general applicability of this strategy for the construction of a number of stereochemically defined acyclic carbon chains with diverse combinations of methyl and hydroxyl groups. A number of these correspond to the chiral subunits of well known propionate-derived natural products.[1]

ACCESS TO OPTICALLY PURE LACTONES 1 AND 4 (Scheme 2)

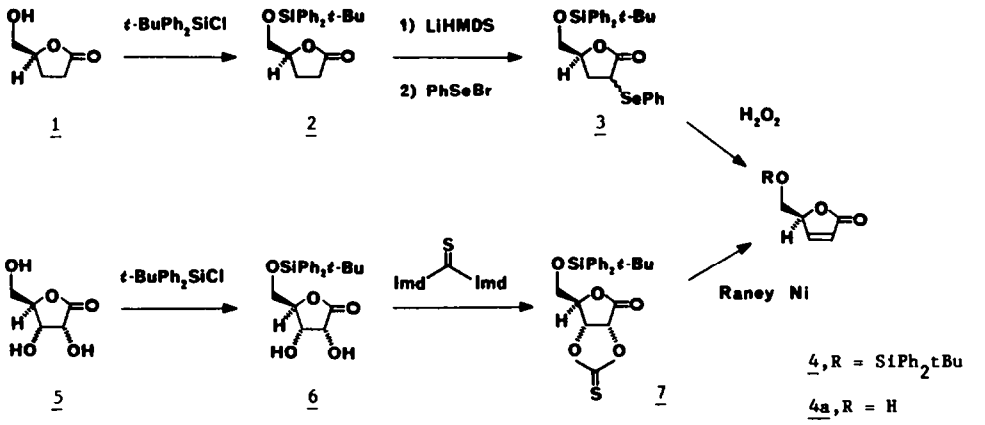
The preparation of (S)-5-hydroxymethyl butyrolactone 1[10] and (S)-5-hydroxymethyl (5)-H-furan-2-one[8] 4a has been described in the literature. Our need for large quantities of these precursors prompted us to reexamine their reported preparations. Our efforts were focused on the 5-O-t-butyldiphenylsilyl derivatives 2 and 4, since this silyl protective group is ideally suited for subsequent operations (Scheme 2).[6,7] One of the literature procedures[11] for the preparation of 1 consists in the nitrous acid deamination of (S)-glutamic acid to give (S)-butyrolactone-γ-carboxylic acid, followed by reduction of the carboxyl group.[10] We have found that reduction with borane dimethylsulfide complex and work-up in the presence of triethylamine provided 1 in consistently higher yields than the recommended procedure[10]. The versatile lactone 1 has been utilized as an important precursor in natural product synthesis,[10,12] and as a template for an alternative approach to acyclic stereoselection.[6]

A number of procedures for the preparation of 5-O-trityl and 5-O-t-butyldimethylsilyl 2,3-dideoxy D-glycero-pent-2-eno-1,4-lactone have been reported.[8] Application of the orthoester pyrolysis[8g] procedure to the orthoester of 6 gave low yields of product.[8c] A recent report[13] using the corresponding 2-dimethylamino(methylene) acetal[14] is more encouraging. Adapting the Ireland procedure[8a] which consists in the reductive elimination of a cyclic thionocarbonate such as 7 with Raney nickel did produce the desired 4. However, this crystalline material was invariably contaminated (up to 20%) with the over-reduction product 2.* Since 2 and 4 have identical chromatographic properties and n.m.r. detection of the minor component based on integration is not sufficiently accurate, its presence in such reactions may have gone undetected also in the reported preparation

* A similar observation has been made by Prof. S.V. Ley, Imperial College, London. Private communication.

of 4,[8c] and other derivatives related to 4.[8a] Thus, depending on the activity of the Raney nickel used, the extent of over-reduction may vary. In our experience, the most reliable method for the preparation of 4 having the highest optical purity consists in the oxidative elimination[15] of the 2-phenylseleno derivative 3 easily obtained from 2 in 95% yield.[8f,10] In this manner, the desired compound 4 was obtained as a crystalline solid having, mp 83-84° and $[\alpha]_D$ -85.2° (compare, mp 79-80° and $[\alpha]_D$ -76.6°; -81.8° from the thionocarbonate route).[8c] In spite of the presence of some unwanted 2 in the reductive elimination of 7, it is possible to use the mixture for large-scale operations particularly if a separation of products could be effected at a later stage.

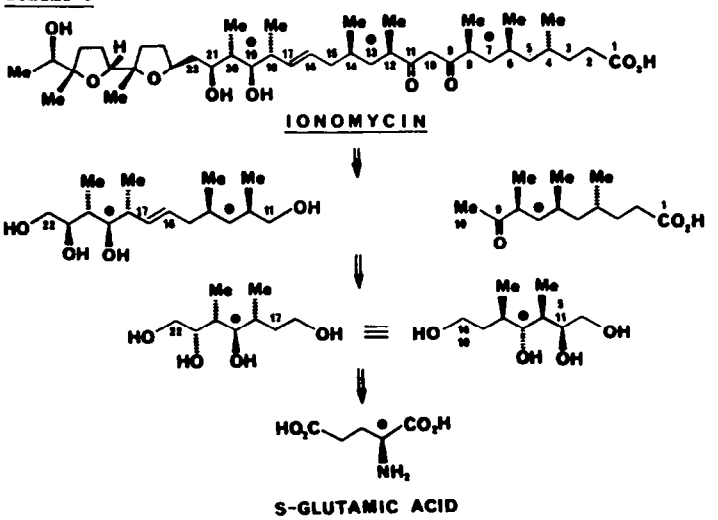
Scheme 2



ACCESS TO POLYPROPIONATE-DERIVED SUBUNITS

Examination of the basic strategy outlined in Scheme 1 reveals that stereoselective sequential bond formation is possible in reactions involving a butenolide template such as 4, by virtue of the orientation of substituents already present. Thus, an incoming carbon nucleophile will approach the conjugated systems at C-3 from a side opposite to the side-chain[6,8f,9]. Provided that the C-3 substituent is bulky enough, the introduction or trapping of an electrophile at C-2 via the corresponding enolate will also be highly stereoselective.[16,17] We had already shown this strategy to be highly efficient in the construction of seven-carbon chains containing methyl and hydroxy substitution.[6,7,18] We demonstrate the application of this technology to the synthesis of a number of acyclic subunits found in the ionophore antibiotic ionomycin[7,19] (Scheme 3).

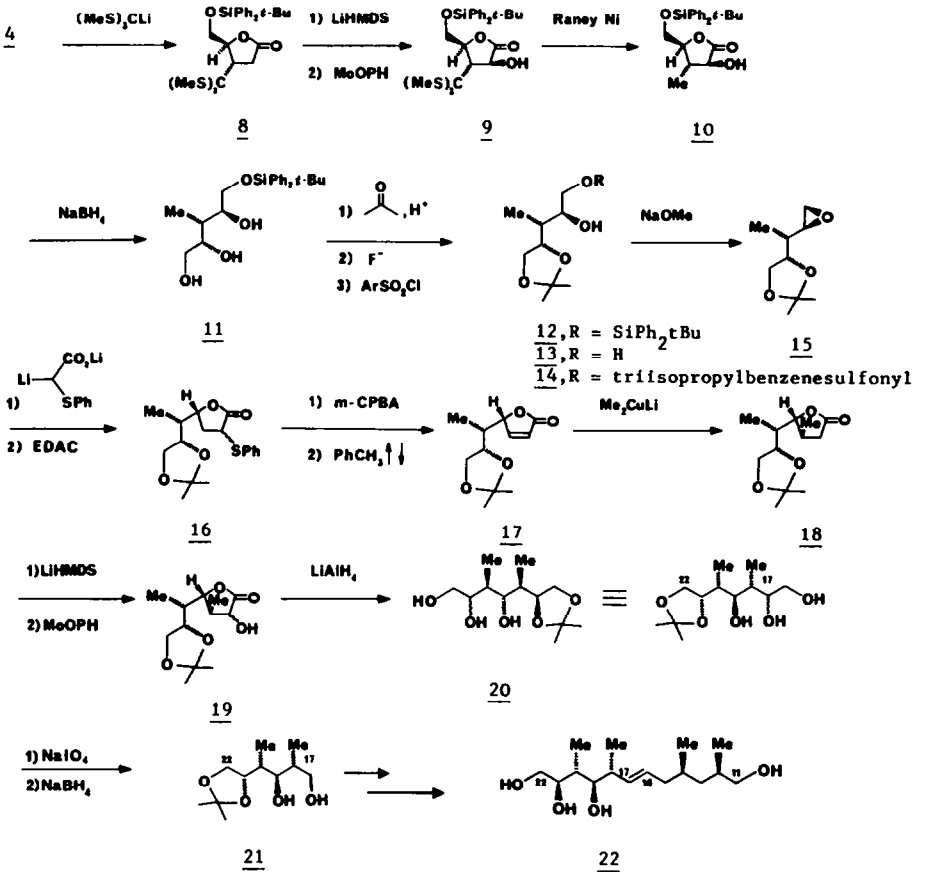
Scheme 3



THE C_{17}-C_{22} SUBUNIT OF IONOMYCIN

The anti-anti arrangement of methyl and hydroxy groups in this subunit can be attained by adopting the general method shown in Scheme 1 (top sequence). An alternative sequence which demonstrates the versatility of the approach is also possible. Thus, treatment of 4 with the anion of tris-trimethylthiomethane[17a] led to the exclusive formation of the conjugate addition product 8. Formation of the corresponding enolate and treatment with oxodiperoxomolybdenum IV-pyridine-HMPA complex (MoOPH)[20,21] led to the desired substitution pattern as shown in structure 9. (Scheme 4). The conjugate addition and hydroxylation could also be done in a "one-pot" reaction in 78% overall yield.*

Scheme 4



Reductive desulfurizaton then led to 10 in good overall yield. In the case where the bulky substituent at C-3 was replaced with a C-methyl group (ex. cuprate on 4), the introduction of the hydroxy group was less stereoselective (2:1 ratio). Reduction of 10 with sodium borohydride afforded the tetrol derivative 11 which was subjected to preferential acetal formation, desilylation, and selective arylsulfonylation to give 14 in good overall yield. Treatment of 14 with sodium methoxide led to the epoxide 15. It should be noted that the terminal carbon atom of the epoxide corresponds to the original C-5 of the butenolide 4. The reiteration could now be done at this end which represents an operational variant of the unidirectional linear chain-elongation sequence shown in Scheme 1 (top sequence). Treatment of 15 with the dilithio salt of phenylthioacetic acid[22] (or phenylselenoacetic acid),[23] followed by lactonization,[24] gave the corresponding 2-phenylthio (or phenylseleno) lactone 16. Oxidative elimination then led to the replicated butenolide 17 in excellent yield. As anticipated, conjugate addition with lithium dimethyl cuprate occurred in a totally stereoselective manner to give the lactone 18 in high yield.

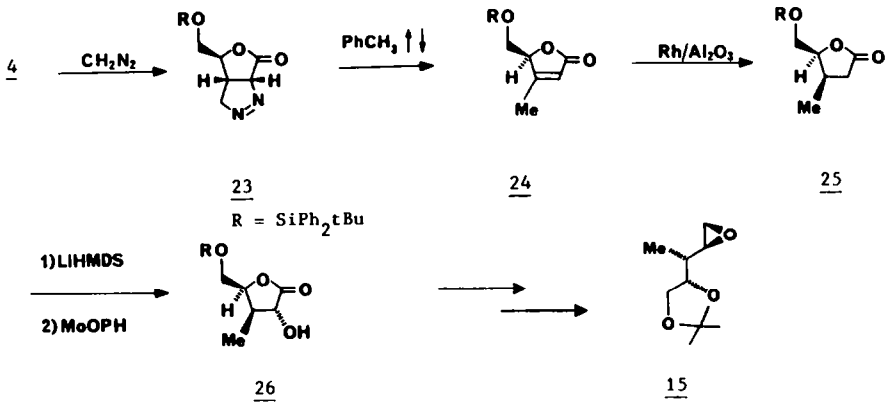
* This reaction was performed by Dr. G. McCraw. The methodology for sequential conjugate addition and hydroxylation was developed by Dr. S.P. Sahoo in our laboratory, see ref. 6.

In order to secure the C_{17}–C_{22} subunit, the enolate derived from **18** was hydroxylated to give **19** and the latter was reduced to the pentol derivative **20**. This chiron had been previously converted to the C_{11}–C_{22} segment **22** of ionomycin by adjustment of functionality and coupling based on sulfone anion methodology.[7]

It should be noted that the butenolide **17** and related ones resulting from the thermal elimination of the sulfoxides did not undergo racemization to any detectable extent. For example, the 5-O-trityl derivative of **4a**, prepared by the thermal elimination of the corresponding 2-phenylsulfinyl derivative, is reported to be of low optical purity.[8f]

Subunit **21** is also accessible by a different strategy which demonstrates the versatility in manipulating butenolide templates such as **4**. Thus treatment of **4** with diazomethane[16,25] afforded the crystalline pyrazoline **23**, which upon heating in toluene, led to the butenolide **24** in excellent yield (Scheme 5). Catalytic reduction over rhodium-on-alumina gave the butyrolactone derivative **25** as the only detectable isomer (400 MHz n.m.r.), in which the two substituents have a *syn* disposition. It should be noted that reduction of the 5-O-trityl derivative corresponding to **24** with PtO_2 led to 4:1 mixture of diastereomeric butyrolactones.[25a] Thus, the utility of the t-butyldiphenylsilyl group and the choice of catalyst in this instance are evident. Formation of the enolate and treatment with MoOPH gave the lactone **26**, which is diastereomeric with **10**. In view of the inherent symmetry and different substitution patterns at both extremities, lactone **26** can be easily converted into the desired **15**, hence **21**, by chain-elongation and reiteration at C-1 (instead of at C-5).

Scheme 5

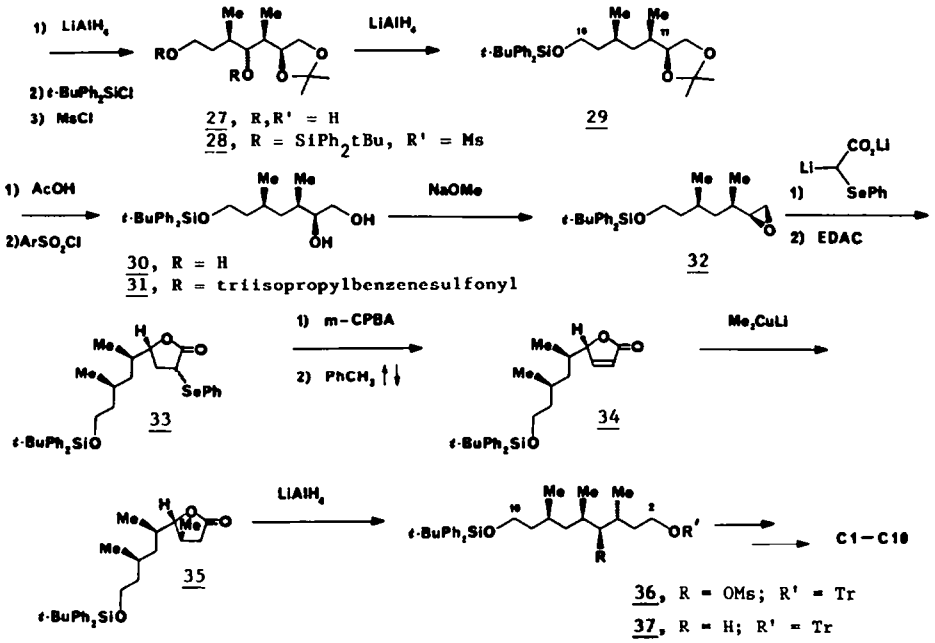


ACCESS TO DEOXYGENATED POLYPROPIONATE UNITS

The pattern of substitution in the C_2–C_{16} segment of ionomycin provides the opportunity to explore methodology for the construction of polypropionate-derived carbon chains lacking the intervening hydroxy groups.

Reduction of **18** afforded the tetrol derivative **27**, where convergence of the two asymmetric centers with C-4/C-6 and C-12/C-14 of ionomycin is evident except for the presence of the intervening hydroxyl group. Selective silylation, mesylation and reductive desulfonylation gave the desired chiron **29** (Scheme 6). The presence of the diol group was convenient since oxidative cleavage could generate an aldehyde precursor necessary for eventual coupling at C-11. Alternatively, the diol group could be used as a means for a third reiteration via the corresponding epoxide **32**, which could be obtained by conventional methodology. The two-carbon chain extension as previously described afforded the lactone **33** which was cleanly transformed into the corresponding butenolide **34**. Once again, treatment with lithium dimethylcuprate delivered the incoming methyl group from the side opposite to the bulky side-chain to afford **35**. Reduction followed by tritylation and mesylation gave **36**. Reductive desulfonyloxylation then led to the nine-carbon diol derivative

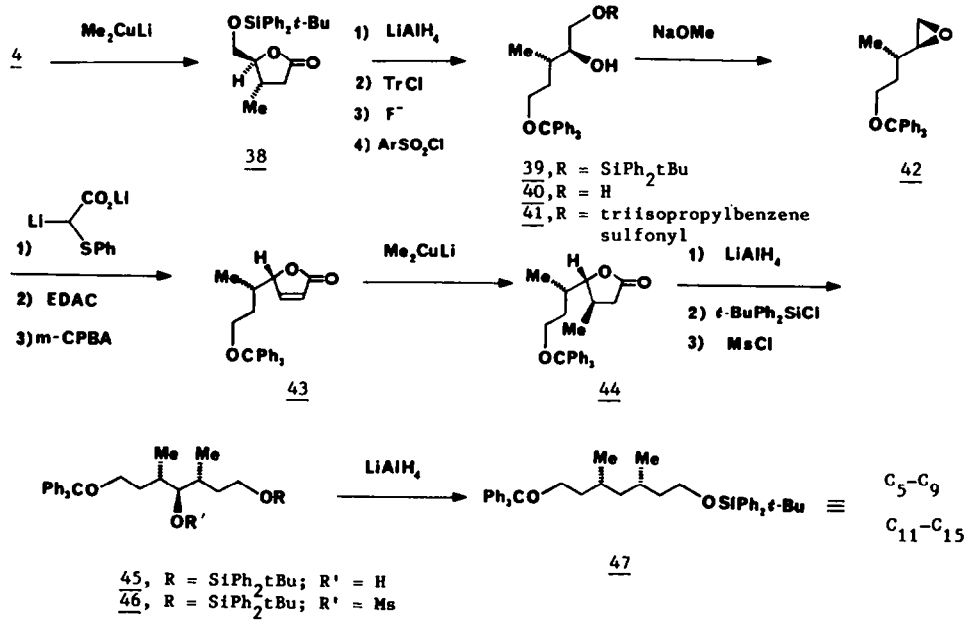
Scheme 6



37 harboring three alternating C-methyl substituents with the desired anti/syn orientation. This chiron had been previously converted to the C_2-C_{10} subunit of ionomycin.[7]

Scheme 7 illustrates the application of the replicating lactone strategy for the construction of seven carbon diols and triols containing a syn arrangement of alternating C-methyl substituents[6] as can be found in the C_5-C_9 and C_{11}-C_{15} subunits of ionomycin.[7] By virtue of the fact that these subunits have a plane of symmetry, it becomes imperative to construct carbon chains in which the terminal positions are easily distinguishable and independently manipulatable. Treatment of 4 with lithium dimethylcuprate gave the lactone 38 in 87% yield. Reduction, tritylation and replacement of the silyl protective

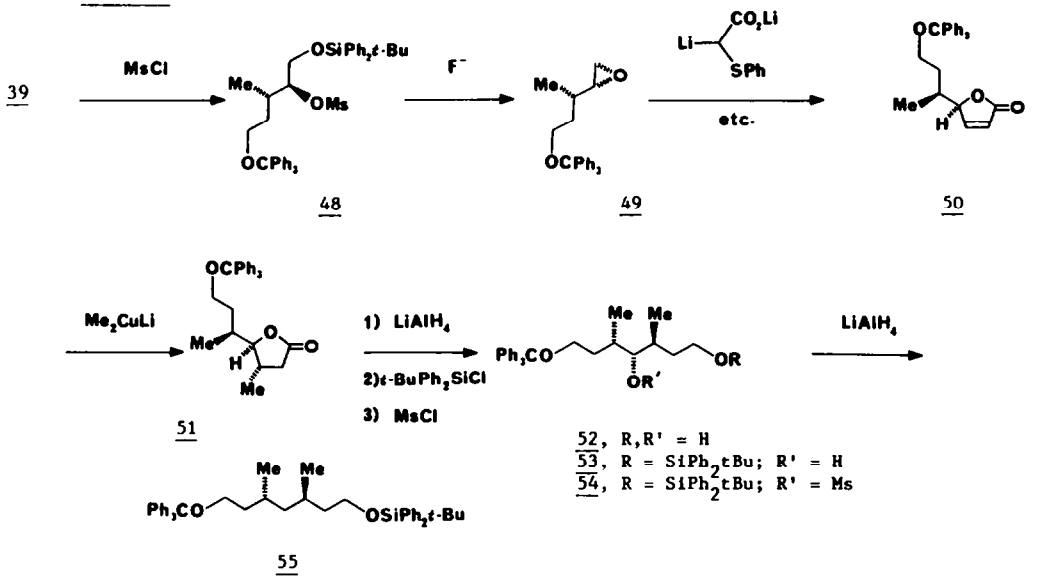
Scheme 7



group by a bulky arylsulfonate led to the triol derivative 41. Treatment with sodium methoxide afforded the epoxide 42, which, upon extension and lactonization gave the replicated butenolide 43. The latter was now poised for a second conjugate addition with lithium dimethylcuprate. As anticipated, this reaction was highly stereoselective to give 44. Reduction and selective silylation gave 45, which was converted to the mesylate 46. Reductive desulfonyloxylation gave the seven-carbon diol derivative 47 in very good overall yield. As previously alluded to, this inherently symmetrical molecule is easily convergent with two possible syn 1,3-dimethyl substitution patterns ("up-up" or "down-down") by virtue of the differentiation of the protective groups.

The versatility of the strategy to provide diastereomeric compounds in the same series is evident in Scheme 8. Thus, mesylation of 39 and treatment of the mesylate 48 with fluoride ion gave the epoxide 49 with inversion of configuration. Replication through the sequence shown above led to the butenolide 50 in which the side-chain is disposed "above" the plane of the ring. Consequently, treatment with lithium dimethylcuprate resulted in the delivery of the methyl group from the side opposite to the side-chain exclusively to afford the lactone 51. Following the same operations as in Scheme 7, the latter was converted into the triol derivative 52, and finally into the seven-carbon diol derivative 55, harboring a set of anti 1,3-dimethyl substituents. Here again, the different protective groups allow exploitation of the C_2 symmetrical pattern in either direction.

Scheme 8



Thus, the butenolide-based replicating lactone strategy[6] provides a powerful and operationally different alternative to a number of methods recently reported[2,3,5] for the assembly of carbon chains containing alternating 1,3-dimethyl substituents, with or without intervening hydroxyl groups.

CONCLUSION

The replicating butenolide template technology[6,7] is a powerful tool for the construction of acyclic carbon chains containing virtually any combination of vicinal or alternating carbon and hydroxy substituents with complete stereocontrol.[26] It is also adaptable to the synthesis of vicinal secondary and tertiary centers.[16] The inherent symmetry and functional group diversity in the products, coupled with the possibility to adjust stereochemistry prior to each replication, offers numerous possibilities for convergence with a host of propionate-derived structural subunits found in natural products. The approach described in this and our previous papers has the following attributes: a. stereochemical flexibility; b. functional diversity; c. choice of linearity

of operation or convergence; d. utilization of common intermediates from a single chiral progenitor; and e. high predictive power. It is our contention that this practical alternative to acyclic stereoselection will find widespread utility in the synthesis of polyfunctional natural products.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H n.m.r. spectra were recorded in $CDCl_3$ on a Brucker 400 MHz spectrometer. Infrared spectra were obtained as neat films from syrups, or films obtained by gentle melting the solids on a sodium chloride pellet on a Perkin Elmer model 781 spectrometer. Optical rotations were measured at room temperature with a Perkin Elmer model 141 polarimeter. Mass spectra were obtained on a VG-1212 low resolution and Kratos-50 high resolution spectrometers by the chemical ionization technique. EDAC is the abbreviation for 1-ethyl 3-[3'-diethylaminopropyl]carbodiimide hydrochloride. Work-up in the usual manner signifies, washing the organic phase with water or dil. hydrochloric acid, washing with aq. bicarbonate, brine, water, drying ($MgSO_4$) and evaporation to dryness under vacuo. Chromatography was done by the flash column technique[27] utilizing ethyl acetate and hexanes (gradient or by % volume).

(S)-5-Hydroxymethyl-1,4-butyrolactone, 1 - A quantity of (S)-5-carboxy-1,4-butyrolactone,[11] (30.2g, 0.232 mole) prepared from (S)-glutamic acid in 74% yield,* was dissolved in THF (500 mL) and the solution was cooled to 0°. A solution of 2N borane-dimethylsulfide (Aldrich) (120 mL) was added dropwise over a period of 40 min. and the solution was stirred at 0° for 15 h. The solution was stirred overnight at room temperature, methanol (500 mL) containing triethylamine (20 mL) was added dropwise while cooling. The solution (pH ~7-8) was evaporated to dryness, the residue was dissolved in MeOH, and the solution evaporated several times, to afford a pale yellow oil which was purified by flash column chromatography (1% MeOH-CH_2Cl_2) to give 22.8 g (83%) of the title compound as an oil, $[\alpha]_D$ + 34.2° (c 3, EtOH); reported[10] $[\alpha]_D$ + 32.5° (c 2.9, EtOH); λ film/max 1760 cm^{-1}, (C=O).

(S)-O-tert-Butyldiphenylsilyl-5-hydroxymethyl-1,4-butyrolactone, 2 - To a solution of 1 (20.8 g, 0.177 mmol) in 180 mL of dichloromethane was added 37.5 mL of triethylamine at 0°. After stirring for 10 min., t-butyldiphenylsilyl chloride (51 mL) and 4-dimethylamino-pyridine (0.275 g) were added, and the solution was stirred at room temperature for 3.5 h. The suspension containing crystalline triethylamine hydrochloride was diluted with 680 mL of ether and 350 mL of water. Extraction, washing with water, 1N HCl, aq. bicarbonate and finally brine, then water, drying, and evaporation of the organic layer gave a syrup which was dissolved in 350 mL of warm hexane. Upon cooling, the product crystallized. Filtration and washing with hexane (100 mL) gave 45.37 g (71.5%) of crystalline product 2, mp 75-76°; $[\alpha]_D$ +28.95° (c 2, $CHCl_3$); λ film/max 1770 cm^{-1} (C=O). The mother liquors from the crystallization were evaporated to dryness, and the residue was chromatographed (EtOAc-hexane, 1:10→1:20) to give a second crop of crystals, 7.64 g, mp 75-76°; $[\alpha]_D$ + 28.6° (c 2.05, $CHCl_3$); ^{1}H n.m.r. δ = 7.68-7.64 (4H, m); 7.48-7.38 (6H, m); 4.61 (1H, dddd, J=6.6, 5.3, 3.3, 3.3 Hz); 3.87 (1H, dd, J=11.4, 3.3 Hz); 3.87 (1H, dd, J=11.4, 3.3 Hz); 3.68 (1H, dd, J=11.4, 3.3 Hz); 2.69 (1H, ddd, J=17.6, 10.1, 7.2 Hz); 2.52 (1H, ddd, J=17.6, 10.0, 6.6 Hz); 1.06 (9H, s). Anal. calcd. for $C_{21}H_{26}O_3Si$; c 71.14; H, 7.40. Found C, 71.03; H, 7.33.

5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-D-glycero-pent-2-eno-1,4-lactone, 4 - A. From D-Ribono-1,4-lactone - To D-ribono-1,4-lactone, 5 (50 g, 0.337 mmol) in DMF (250 mL) containing imidazole (13.8 g, 0.6 equiv.) at -20°C was added t-butyldiphenylsilyl chloride (46.31 g, 0.5 equiv.) dropwise over 30 min. The mixture was stirred at -20 to -15°C for 1 h and then poured into ether (1.5 L) and water (1 L). The organic phase was washed several times with water (4 x 1 L), then processed in the usual manner. Evaporation in vacuo gave syrupy 6 (in essentially quant. yield (based on silyl chloride) which was not contaminated with di-silyl ether; mp 71-76° (softening), melts 83-84°C, $[\alpha]_D$ + 46.5° (c 1.1, $CHCl_3$); reported[8b] mp 65-70°; reported[8c] mp 72-74° (softening), melts 83-84°C.

Compound 6 (28.5 g, 73.8 mmol) prepared as above, and without purification, was redissolved in THF (100 mL), cooled in a water-bath and treated with 1,1'-thiocarbonyldiimidazole (15.6 g, 87.6 mmol, 1.2 equiv.) in THF (75 mL) added dropwise over 5 min. The orange solution was stirred at room temperature for 15 min., and then poured into ether(750 mL) and water (500 mL). The ethereal layer was washed several times with water (5 x 500 mL), sat. brine (1 x 500 mL) and dried ($MgSO_4$). Evaporation gave 7 as a syrup, which was used directly. The product crystallizes on standing.** The thionocarbonate prepared above was redissolved in THF (400 mL) and brought to reflux. Raney nickel (washed with 2% AcOH, H_2O, acetone and finally THF) was added in 15-20 g portions over a period of about 4 hrs at 45 min. intervals (tlc). The resulting suspension was diluted with $CHCl_3$ (400 mL) in order to reduce the risk of fire and filtered (with great care!) through a

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* The crude preparation which crystallized on standing was used in the next step, mp. 67-70°; $[\alpha]_D$ + 1.5° (c 2, EtOH). A sample was recrystallized from ether-hexane to give material showing mp 72-73°; $[\alpha]_D$ + 16.3° (c 2, EtOH). See ref. 11, note 15.

** Purification by flash chromatography gave material with mp. 115.5-116.5°; $[\alpha]_D$ -20° (c 2, $CHCl_3$); $[\alpha]_D$ - 4.32 (c 17.3 ether); reported[8c], mp 116.5-117°; $[\alpha]_D$ - 2.1 (c 10.9, ether).

celite pad. The solid was immediately washed with $CHCl_3$ then thoroughly doused with water. The solvent was evaporated and the crude product purified by flash column chromatography (15-25% EtOAc in hexane) to provide 4 as a white crystalline solid (15.1 g 65%); mp 77-78° $[\alpha]_D$ - 75°; reported, mp 79-80°, $[\alpha]_D$ - 76.6°; -81.8°[8c]; compare with material obtained under B (see below). This material is contaminated with about 10-15% of over-reduction product 1.

B. From (S)-O-tert-Butyldiphenylsilyl-5-hydroxymethyl-1,4-butyrolactone, 2 - The lactone 2 (17.7 g, 50 mmol) in THF (75 mL) was added dropwise to a THF solution (200 mL) containing lithium hexamethyldisilazide (prepared from HMDS, 11.6 mL, 1.1 equiv. and n-BuLi, 31.2 mL of a 1.6 M solution in hexane, 1.0 equiv.) at -78° over 5 min. After 25 min. the enolate was quenched by the addition of phenylselenenyl bromide (11.7 g, 1.0 equiv.) in THF (50 mL) and immediately afterwards with 1 N hydrochloric acid (200 mL). The reaction was poured into ether (500 mL) and the ethereal layer worked up in the usual manner to afford a crude mixture of epimeric monoselenides (~quant.).* Chromatography (1:10 EtOAc-hexane) provided the two monoselenides 3 as yellow oils (23.58 g, 95%). For the less polar isomer (78%); $[\alpha]_D$ +17.63° (c 2.2 $CHCl_3$); more polar isomer (22%); $[\alpha]_D$ +43.3 (c 2.12, $CHCl_3$). This mixture of selenides (13.1 g, 25.7 mmol) in CH_2Cl_2 (200 mL) was added dropwise to a vigorously stirred solution of ice-cold 30% hydrogen peroxide (20 mL) over 40 min. The heterogeneous reaction was stirred for a further 15 min and the organic phase was then washed with water (4 x 100 mL), sat. brine (1 x 100 mL), dried ($MgSO_4$) and evaporated to an oil. Chromatography (20% EtOAc in hexane) gave the butenolide 4 as a white crystalline solid (8.85 g, 97%), mp. 83-84°; $[\alpha]_D$ -85.2° (c 1.2, $CHCl_3$). On larger runs, the yield of oxidation varied between 72 and 90%.; λ film/max 1700 cm^{-1} (C=O); mass spectral data. Found m/e 295.0787 (M-t-Bu); ^1H n.m.r.;7.65-7.61 (4H, m); 7.47-7.37 (7H, m); 6.17 (1H, dd, J=5.7, 2.0 Hz); 5.08-5.05 (1H, m); 3.90 (1H, dd, J=10.9, 4.4 Hz); 3.87 (1H, dd, J=10.9, 4.9 Hz); 1.04 (9H, s).

2,3-Dideoxy-3-tris(methylthio)methyl-5-O-tert-butyldiphenylsilyl-D- erythro-pentono-1,4-lactone, 8 - To a solution of tris(methylthio)methane (1.13 mL, 1.31 g, 8.5 mmole) in THF (100 mL) at -78°C was added n-butyl lithium (5.3 mL of a 1.6 M solution in hexane, 1.0 equiv.) over 3-4 min. After 20 min. a solution of the 4 (3.0 g, 1.0 equiv.) in THF (20 mL) was added dropwise and the reaction stirred at -78°C for 30 min. The mixture was then poured into ether (250 mL) and dil. hydrochloric acid (250 mL) and processed in the usual manner. Flash chromatography of the crude product yielded the title compound 8 as a colorless crystalline solid (3.7 g, 86%); mp 140-142°C; $[\alpha]_D$ + 20.5° (c 1.1, $CHCl_3$); ν film/max 1785, 1185, 1120, 1010, 950, 715 and 710 cm^{-1}; m/e (CI) 507 $(M+1)^+$, 459, 449, 429, 381, 329, 221, 203, and 163; ^1H n.m.r.; δ = 7.67-7.63 (4H, m); 7.47-7.37 (6H, m); 4.84 (1H, ddd, J=2.7, 2.3, 2.3 Hz); 3.95 (1H, dd, J=11.4, 2.7 Hz); 3.62 (1H, dd, J=11.4, 2.3 Hz); 2.99 (1H, ddd, J=10.1, 2.8, 2.3 Hz); 2.95 (1H, dd, J=18.3, 2.8 Hz); 2.83 (1H, dd, J=18.3, 10.1 Hz); 2.11 (9H, s); 1.04 (9H, s). Anal. calcd for $C_{25}H_{34}O_3SiS_3$: C, 59.04; H, 6.72 S, 18.97. Found: C, 59.11; H, 6.70; S, 19.02.

3-Deoxy-3-tris(methylthio)methyl-5-O-tert-butyldiphenylsilyl-D- arabino-1,4-lactone, 9 - A. From 8 - To a solution of hexamethyldisilizane (HMDS) (464 µl, 355 mg, 2.2 mmole) in THF (50 mL) at 0°C was added n-butyl lithium (1.25 mL of a 1.6 M solution, 2.0 mmol) and the mixture stirred at this temperature for 10 min. The solution was then cooled to -78°C, and the lactone 8 (508 mg, 1.0 mmol) in THF (10 mL) added over 2-3 min. The enolate was allowed to form for 20 min, after which oxodiperoxomolybdenum-pyridine-HMPA complex (MoOPH) (477 mg, 1.1 equiv.) was added rapidly as the solid in a single portion. After the addition, the temperature was maintained at -60°C for 45 min. during which time the initially yellow suspension became a green, and finally a blue solution. The cold solution was poured directly into a freshly prepared saturated solution of sodium sulphite (50 mL) and ether (50 mL) and the complex decomposed by vigorous shaking. The ethereal layer was then separated, given a standard work-up and the residue chromatographed (5+50% EtOAc in hexane) to provide the title compound as a pale yellow oil (445 mg, 85%); $[\alpha]_D$ + 8.1°, (c 1.36, $CHCl_3$); ν max (neat oil) 3460, 2940, 2865, 1780, 1435, 1195, 1130, 1120, 1080 and 705 cm^{-1}; m/e (CI) 523 $(M+H)^+$, 475 $(M-{}^tBu)^+$ 457, 329, 281, 241, 207; Found 475.1410, $C_{24}H_{31}O_4S_2Si$ (M^+-MeS); requires 475.1433; ^1H n.m.r., δ = 7.71-7.67 (4H, m); 7.48-7.38 (6H, m); 4.78 (1H, dd, J=6.0, 4.8 Hz); 4.77 (1H, ddd, J=4.5, 2.5, 2.3 Hz); 4.00 (1H, dd, J=11.7, 2.3 Hz); 3.73 (1H, dd, J=11.7, 2.5 Hz); 3.16 (1H, d, J=6.0 Hz); 3.14 (1H, dd, J=4.8, 4.5 Hz); 2.20 (9H, s);

B - From 4 in "one-pot" - A solution of tris(methylthio)methane (0.76 mL, 7.7 mmol) in tetrahydrofuran (25 mL) was treated dropwise with 1.55 M n-butyl lithium (3.7 mL) at -78°C. After 30 min, 4 (2 g, 5.67 mmol)** dissolved in 5 mL of THF was added dropwise. Following an additional 30 min., oxodiperoxomolybdenum-pyridine-HMPA complex (MoOPH)(2.7 g, 6.2 mmol) was added as the solid and the temperature was allowed to slowly warm to -30°C. A solution of satd. sodium sulfite (5 mL) was added at -30°C, and the solution was warmed to room temperature. The organic phase was diluted with ether (50 mL) and washed with satd. sodium sulfite (in 10 mL portions until the aqueous layer was colorless), water (2 x 10 mL), 1% hydrochloric acid (2 x 25 mL) and water again. After drying over magnesium sulfate and flash chromatography (4:1 hexane-EtOAc) the product 9 (1.86 g, 78.8%) was obtained as an oil.

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* When phenylselenelyl chloride was utilized under the same conditions, the yield was 52% with formation of the diselenide and recovery of starting material.

** This compound was contaminated with ~15% of 2 as a result of over-reduction in the Raney-nickel desulfurization of 7.

3-Deoxy-3-C-methyl-5-O-tert-butyldiphenylsilyl-D-arabino-1,4-lactone, 10 - The previous compound (445 mg, 0.85 mmol) was stirred with Raney nickel (previously washed with 5% AcOH in water, water, and methanol) in methanol (20 mL) at room temperature for 18 h. The suspension was then diluted with $CHCl_3$ (20 mL), filtered (caution!) through a celite pad and evaporated to an oil. The residue was purified by chromatography (10-20% EtOAc in hexane) to provide **10** as a colorless oil (212 mg, 62%); $[\alpha]_D$ +12.5°. (c 2.25, $CHCl_3$); νmax (neat oil) 3440, 2930, 2860, 1780, 1430, 1115, 1035, 705 cm^{-1}; m/e (CI) 385 $(M+H)^+$, 279, 261, 241, 221, 201; ^1H n.m.r. δ = 7.70-7.65 (4H, m); 7.46-7.38 (6H, m); 4.07 (1H, dd, J=10.5, 3.5 Hz); 4.03 (1H, ddd, J=9.6, 4.1, 2.8 Hz); 3.92 (1H, dd, J=12.0, 2.8 Hz); 3.75 (1H, dd, J=12.0, 2.8 Hz); 2.96 (1H, bd.s); 2.47 (1H, ddt, J=10.5, 9., 6.6 Hz); 1.17 (3H, d, J=6.6 Hz); 1.05 (9H, s).

1-O-tert-Butyldiphenylsilyl-3-deoxy-4,5-O-isopropylidene-3-C-methyl-D-arabinitol, 12 - The lactone **10** (21.8 g, 56.7 mmol) in THF/H_2O (4:1, 250 mL) was reduced with sodium borohydride (4.28 g, 2.0 equiv.) at room temperature for 1 h. The reaction was quenched by the cautious addition of dil. hydrochloric acid (50 mL) and the mixture evaporated to remove most of the THF. The residue was then saturated with aq. NaCl and the solution was extracted with ether (3 x 250 mL). Evaporation of the combined ethereal layers provided the triol **11** which was used directly in the next step. It was dissolved in acetone (250 mL) and dimethoxypropane (50 mL), two drops of conc. hydrochloric acid were added and the mixture was stirred at room temperature for 15 h. The solution was evaporated to an oil, the latter dissolved in ether and processed as usual by washing with aq. bicarbonate, then water, etc. The crude product was then chromatographed (5→7.5% EtOAc in hexane) to afford the product **12** as a colorless oil (15.7 g, 65%); $[\alpha]_D$ - 0.3°, (c 3.3, $CHCl_3$); ν max (neat oil) 3500, 2940, 2860, 1435, 1120, 1065, 705, 620 cm^{-1}; m/e (CI) 371 $(M^+-{}^tBu)$, 353, 335, 313, 293, 275, 235, 215; ^1H n.m.r. δ = 7.68-7.64 (4H, m); 7.47-7.36 (6H, m); 4.25 (1H, ddd, J=7.4, 6.5, 5.1 Hz); 4.04 (1H, dd, J=8.3, 6.5 Hz); 3.76 (1H, dd, J=13.9, 7.6 Hz); 3.67 (1H, dd, J=8.3, 7.4 Hz); 3.67 (1H, dd, J=8.3, 7.4 Hz); 3.61 (2H, m); 2.83 (1H, bd.d, D_2O exch., J=2.6 Hz); 1.80-1.71 (1H, m); 1.38 (3H, s); 1.33 (3H, s); 1.06 (9H, s); 0.83 (3H, d, J=6.9 Hz).

3-Deoxy-3-C-methyl-4,5-O-isopropylidene-D-arabinitol, 13 - To the silyl ether **12** (15.7 g, 36.7 mmol) was added tetra n-butylammonium fluoride (55 mL of a 1.0 M solution in THF, 1.5 equiv.) and the solution stirred at room temperature for 2 h. The mixture was then concentrated and the residue chromatographed directly (50→100% EtOAc in hexane) to give the title compound as a colorless oil (6.6 g, 95%), $[\alpha]_D$ + 8.8°, (c 3, $CHCl_3$) ν max (neat oil) 3410, 2990, 1370, 1215, 1160, 1060, 860 cm^{-1}; m/e (CI) 191 $(M+H)^+$, 175, 133, 115, 101, 97.

3-Deoxy-3-C-methyl-1-O-(2,4,6-trisopropyl)benzenesulfonyl-D-arabinitol, 14 - The previous compound **13** (6.6 g, 34.7 mmol) in pyridine (10 mL) and CH_2Cl_2 (14 mL) was treated with 2,4,6-(triisopropyl)benzenesulphonyl chloride (21.8 g, 2.0 equiv.) at room temperature for 15 h. Excess sulphonyl chloride was destroyed with water (5 mL) at room temperature for 1 h and the mixture then subjected to a standard work-up. Chromatography of the crude product (5→10% EtOAc in hexane) gave the sulphonate **14** as a colorless oil (14.5 g, 92%); ^1H n.m.r., 7.20 (2H, s); 4.32 (1H, ddd, J=7.2, 6.6, 4.0 Hz); 4.20 (1H, dd, J=10.4, 4.0 Hz); 4.13 (2H, sept., J=6.7 Hz); 4.05 (1H, dd, J=10.4, 6.2 Hz); 4.04 (1H, dd, J=8.4, 6.6 Hz); 3.81 (1H, ddd, J=7.0, 6.2, 4.0 Hz); 3.71 (1H, dd, J=8.4, 7.2 Hz); 2.92 (1H, sept., J=6.9 Hz); 2.73 (1H, bd.s); 1.95-1.87 (1H, m); 1.38 (3H, s); 1.32 (3H, s); 1.27 (12H, d, J=6.7 Hz); 1.26 (6H, d, J= 6.9 Hz); 0.95 (3H, d, J=7.0 Hz).

1,2-Anhydro-3-deoxy-3-C-methyl-4,5-O-isopropylidene-D-arabinitol, 15 - The sulphonate ester **14** (15.5 g, 31.8 mmol) in methanol (50 mL) and CH_2Cl_2 (50 mL) was treated with sodium methoxide (35 mL of 1.0 M solution in methanol, 1.1 equiv.) at 0°C for 30 min. The reaction mixture was then poured into water (150 mL) and ether (150 mL), worked-up as usual and concentrated (at 20°) to a mobile yellow liquid. Chromatography (50% ether in pentane) provided the epoxide **15** (ca 5 g) as a rather volatile, pale yellow liquid which was not free of residual solvent; m/e (CI) 173 $(M+H)^+$, 157, 155, 97; ^1H n.m.r. δ = 4.14-4.08 (2H, m); 3.79-3.74 (1H, m); 2.80-2.76 (2H, m); 2.51-2.49 (1H, m); 1.43-1.32 (1H, m); 1.41 (3H, s); 1.37 (3H, s); 1.06 (3H, d, J=6.9 Hz).

2,3,5-Trideoxy-5-C-methyl-6,7-O-isopropylidene-D-arabino-hept-2-eno-1,4-lactone, 17 - To a solution of hexamethyldisilazane (24.6 mL, 116 mmol) in THF (200 mL) at 0°C was added a solution of n-butyl lithium (72.8 mL of a 1.6 M soln. in hexane, 1.0 equiv.) After 15 min. a solution of phenylthioacetic acid (9.8 g, 63.4 mmole) in THF (50 mL) as then introduced and the mixture allowed to attain room temperature over 1 h. The initially clear solution became a white suspension over 5-10 min as the dianion formed and precipitated. The epoxide **15** (5.47 g, 31.7 mmol) containing a small amount of residual solvent (ether) was added in THF (20 mL) and the mixture stirred for 15 h. The resulting pale yellow solution was then poured into 2M hydrochloric acid (100 mL) and extracted with ether (3 x 200 mL). The combined ethereal layers were washed with water (2 x 50 mL) and satd.brine (1 x 200 mL), dried ($MgSO_4$) and evaporated to provide the γ-hydroxyacid as a pale-yellow oil. This was dissolved in dichlormethane (150 mL) and treated with EDAC (8.0 g, 41.7 mmol, 1.3 equiv.) and DMAP (150 mg) for 20 min. The mixture was then poured into (500 mL) and given a standard aq. work-up. Evaporation of the organic layer gave a syrup which was chromatographed (20% EtOAc in hexane) to give the α-phenylthiolactone **16** as a mixture of epimers (8.03 g, 77%, 2 steps); ν max (neat oil) 1780 cm^{-1}.

This compound (8.03 g, 24.5 mmol) was dissolved in dichloromethane (150 mL) and treated with mCPBA (6.8 g of 85% purity oxidant, 1.3 equiv.) at -23°C for 20 min. Excess oxidant was then destroyed by quenching with a large excess of dimethylsulphide (10-15 mL) and the mixture brought to room temperature for 10 min. The reaction was poured into ether (500 mL) and satd. bicarbonate (100 mL), the ethereal layer extracted with a second portion of bicarbonate solution (100 mL), dried ($MgSO_4$) and evaporated to give the crude sulphoxides as a yellow oil. The mixture of sulphoxides was redissolved in toluene (250 mL) and pyridine (1 mL) containing $CaCO_3$ powder (5 g) and heated to reflux for 1 h. After cooling, the suspension was filtered, and the solvent removed to provide the crude product as a yellow oil. Chromatography (15→25% EtOAc in hexane) gave the α,β-unsaturated lactone **17** as a white crystalline solid (4.6 g, 89%); mp 78-79°C; $[\alpha]_D$ + 91.3°, (C 6.3, $CHCl_3$) m/e (CI) 213 $(M+H)^+$, 155; Found 197.0858, M-CH_3 = $C_{10}H_{13}O_4$ requires 197.0814; ^{1}H n.m.r. δ = 7.30 (1H, dd, J=5.8, 1.6 Hz); 6.15 (1H, dd, J=5.8, 2.0 Hz); 5.00 (1H, ddd, J=7.1, 2.0, 1.6 Hz); 4.34 (1H, ddd, J=6.7, 6.7, 3.8 Hz); 4.11 (1H, dd, J=8.5, 6.7 Hz); 3.71 (1H, dd, J=8.5, 6.7 Hz); 1.98 (1H, ddt, J=7.1, 3.8, 6.8 Hz); 1.41 (3H, s); 1.36 (3H, s); 0.95 (3H, d, J=6.8 Hz). Anal. calcd for $C_{11}H_{16}O_4$: C, 62.54; H, 7.59. Found: C, 62.19; H, 7.53.

2,3,5-Trideoxy-3,5-Di-C-methyl-D-talo-heptono-1,4-lactone, 18 - To a suspension of CuBr.Me_2S (7.75 g, 37.7 mmol) in ether (200 mL) was added a solution of methyl lithium (44.35 mL of a 1.7 M soln. in ether 2.0 equiv.) at 0° over 5-10 min. The initial yellow precipitate redissolved to give a pale-buff colored solution. After cooling the solution to -23°C the enone **17** (1.6 g, 7.5 mmol, 0.2 equiv.) in ether (25 mL) was added, and the reaction stirred for 10 min. before being quenched by the cautious addition of satd. ammonium chloride solution. After vigorous extraction to remove copper compounds, the colorless ethereal layer was evaporated to give the crude product. Flash column chromatography (15→20% EtOAc in hexane) gave pure **18** as a colorless oil (1.56 g, 91%); $[\alpha]_D$ - 32°(c 2.1, $CHCl_3$); ν max (neat oil) 2990, 1785, 1215, 1060, 1005 cm^{-1}; m/e (CI) 229 (M+H) †, 213, 171;Found 213.1099 M-CH_3 = $C_{11}H_{17}O_4$; required 213.1127; ^{1}H n.m.r. δ = 4.25 (1H, ddd, J=7.0, 6.6, 4.6 Hz); 4.09 (1H, dd, J=8.4, 6.6 Hz); 3.98 (1H, dd, J=8.9, 5.7 Hz); 3.65 (1H, dd, J=8.4, 7.0 Hz); 2.72 (1H, dd, J=17.8, 8.9 Hz); 2.42 (1H, dddq, J=8.9, 7.2, 5.7, 6.7); 2.19 (1H, dd, J=17.8, 7.2 Hz); 1.79 (1H, ddq, J=8.9, 4.6, 6.7 Hz); 1.40 (3H, s); 1.34 (3H, s); 1.21 (3H, d, J=6.7 Hz); 1.03 (3H, d, J=6.7 Hz).

3,5-Dideoxy-3,5-di-C-methyl-6,7-O-isopropylidene-D-glycero-D-talo- heptono-1,4-lactone 19, (and its C-2 epimer) - To a solution of hexamethyldisilazane (2.90 mL, 13.7 mmol) in THF (75 mL) at 0°C was added n-butyl lithium (7.8 mL of a 1.6 M soln., 12.5 mmol) and the base allowed to form for 20 min. The solution was then cooled to -78° and the lactone **18** (1.42 g, 6.23 mmol) added in THF (15 mL) over 1-2 min. The enolate was generated at this temperature for 30 min. and then treated with solid oxodiperoxomolybdenum-pyridine-HMPA complex (MoOPH) (3.24 g, 7.47 mmol) added as the solid in a single portion. The temperature was allowed to rise to -50°C for 40 min. and the resulting blue-green solution poured into ether (250 mL) and freshly prepared sat. sodium sulphite solution (100 mL). The organic layer was then worked up in the usual manner to provide the crude epimeric α-hydroxy lactones. Purification by column chromatography (30% EtOAc in hexane) afforded **19** as an inseparable mixture (4:1) of epimers (2α the major product) as a colorless oil (1.17 g, 77%); ν max (neat oil) 3430, 2980, 1785, 1210, 1060 cm^{-1}; m/e (CI) 245, $(M+H)^+$, 229, 159, 141; Found 229.1061 M^+-CH_3=$C_{11}H_{17}O_5$; requires 229.1176; ^{1}H n.m.r. δ = 4.31 (1H, ddd, J=6.9, 6.7, 4.1 Hz); 4.08 (1H, dd, J=8.4, 6.7 Hz); 4.07 (1H, d, J=10.1 Hz); 3.98 (1H, dd, J=9.2, 8.2 Hz); 3.68 (1H, dd, J=8.4, 6.9 Hz); 3.63 (1H, bd.S); 2.24 (1H, ddq, J=10.1, 9.2, 6.5 Hz); 1.89 (1H, ddq, J=8.2, 4.1, 7.0 Hz); 1.41 (3H, s); 1.31 (3H, s); 1.33 (3H, d, J=6.5 Hz); 1.03 (3H, d, J=7.0 Hz).

3,5-Dideoxy-3,5-di-C-methyl-5,6-O-isopropylidene-D-talitol, 21 - The α-hydroxylactone mixture **19** (343 mg, 1.43 mmol) in THF/H_2O (4:1, 15 mL) was treated with sodium borohydride (216 mg, 4.0 equiv.) at room temperature for 1 h. The reaction was quenched with 2 M hydrochloric acid, the mixture saturated with sodium chloride and then extracted with ethyl acetate (4 x 50 mL). The combined organic layers were extracted with water (1 x 20 mL) and sat. brine (1 x 20 mL), dried ($MgSO_4$) and evaporated to a crude oily product. Chromatography (EtOAc-1% MeOH) provided the triol as a colorless oil (258 mg, 73%). The previous compound was dissolved in methanol (20 mL) and treated with sodium metaperiodate (335 mg, 1.5 equiv.) in water (10 mL) at room temperature for 10 min. A voluminous white precipitate formed during this time. The aldehyde formed *in situ* was then reduced directly with sodium borohydride (197 mg, 5.0 equiv.) at room temperature for 10 min. The reaction was quenched by the cautious addition of 2M hydrochloric acid, the solution was saturated with sodium chloride and extracted with EtOAc (4 x 20 mL). The organic phase was washed with water (1 x 10 mL), satd. bicarbonate (10 mL) and satd. brine (20 mL). Drying, evaporation and flash chromatography (30% EtOAc in hexane) provided **21** as a colorless oil (165 mg, 72%); ν_{max} (neat oil) 3440, 2990, 1430, 1410, 1380, 1060 cm^{-1}. The corresponding 3-O benzyl ether showed $[\alpha]_D$ - 38.4° (c 4.2, $CHCl_3$); m/e Found 293.1748 (M^+); requires, 293.1708, ^{1}H n.m.r. δ = 7.37-7.26 (5H, m); 4.66 (1H, d, J=10.9 Hz); 4.65 (1H, d, J=10.9 Hz); 4.40 (1H, ddd, J=7.2, 6.7, 3.8 Hz); 4.01 (1H, dd, J=8.1, 6.7 Hz) 3.82 (1H, dd, J=11.1, 3.7 Hz); 3.67 (1H, dd, J=8.1, 7.2 Hz); 3.58 (1H, dd, J=11.1, 4.6 Hz); 3.39 (1H, dd, J=8.9, 3.1 Hz); 2.84-2.60 (1H, bds, D_2O exch.); 1.98-1.87 (2H, m); 1.43 (3H, s); 1.35 (3H, s); 1.17 (3H, d, J=7.1 Hz); 0.95 (3H, d, J=6.8 Hz).

3,5,6-Trideoxy-1,2-O-isopropylidene-3,5-di-C-methyl-7-O-tert-butyldiphenylsilyl-D-altro-heptitol, 27 - To the lactone **18** (1.56 g, 6.84 mmol) in ether (50 mL) was added lithium aluminium hydride (0.52 g, 2.0 equiv.) at 0°, the reaction was allowed to warm up to 25° and then stirred for 1 h. Excess reductant was destroyed by the cautious addition at 0°C of ethyl acetate (25 mL, dropwise) followed by water (10 mL, dropwise) and finally dil. hydrochloric acid (50 mL). The ethereal layer was subjected to a standard aqueous work-up and the organic phase was evaporated to provide the diol as a colorless oil which was used directly in the next step. The product (1.46 g, 6.3 mmol) in DMF (20 mL) was treated with t-butyldiphenylsilyl chloride (1.96 mL, 1.2 equiv.) in the presence of imidazole (0.65 g, 1.5 equiv.) at room temperature for 20 min. The reaction mixture was then poured in ether (100 mL) and water (100 mL), the ethereal layer worked-up in the usual manner and evaporated to a crude syrup. Chromatography (15→25% EtOAc in hexane) furnished the title compound as a colorless oil (2.76 g, 86%, 2 steps); $[\alpha]_D$ + 5.5° (c 1.9, $CHCl_3$); ν max (neat oil) 3500, 2940, 1430, 1115, 1090, 1060, 705 and 615 cm^{-1}; m/e (CI) 471 $(M+H)^+$, 396, 355, 335, 199, 157, ^1H n.m.r., δ = 7.69-7.65 (4H, m); 7.45-7.36 (6H, m); 4.37 (1H, ddd, J=7.7, 6.5, 4.1 Hz); 4.03 (1H, dd, J=8.2, 6.5 Hz); 3.80-3.75 (1H, m); 3.73 (1H, dd, J=8.2, 7.7 Hz);3.65 (1H, ddd, J=10.3, 8.2, 5.2 Hz); 3.37 (1H, ddd, J=8.2, 5.8, 3.9 Hz); 2.86 (1H, d, J=5.9 Hz); 1.98-1.75 (3H, m); 1.45-1.37 (1H, m); 1.43 (3H, s); 1.35 (3H, s); 1.04 (9H, s); 0.93 (3H, d, J=6.9 Hz); 0.91 (3H, d, J=7.0 Hz).

3,4,5,6-Tetradeoxy-1,2-O-isopropylidene-3,5-di-C-methyl-7-O-tert-butyldiphenylsilyl-D-arabino-heptitol, 29 - The previous compound (2.30 g, 4.89 mmol) in dichloromethane (25 mL) was treated with methanesulphonyl chloride (0.57 mL, 1.5 equiv.) in the presence of triethylamine (1.36 mL, 2.0 equiv.) at 0° for 40 min. After quenching the reaction with water (5 mL) and stirring at room temperature for 10 min., the mixture was poured into ether (150 mL) and dil. hydrochloric acid (75 mL), given a standard aqueous work-up and evaporated to give the crude mesylate as a yellow oil which was used directly in the next step. To the crude mesylate (2.3 g, 4.9 mmol) in ether (50 mL) was added lithium aluminium hydride (0.74 g, 4.0 equiv.) at room temperature and the reaction stirred for 2 h. Excess reductant was destroyed by the dropwise addition of ethyl acetate (25 mL) followed by water (10 mL) and dil. hydrochloric acid (50 mL). The organic layer was worked-up to provide the crude deoxy compound which was chromatographed (2→6% EtOAc in hexane) to give **29** as a colorless oil (1.66 g, 75%, 2 steps); $[\alpha]_D$ + 21.6° (c 2.1, $CHCl_3$); ν max (neat oil) 2940, 1430, 1115, 1090, 1070, 705, 615 cm^{-1}; m/e (CI) 455 $(M+H)^+$, 439 $(M-CH_3)$ 397 (M-t-Bu) 379, 339, 319; Found 397.2232 (M-t-Bu) = $C_{28}H_{42}O_3Si$; requires 397.2199; ^1H n.m.r., δ = 7.70-7.66 (4H, m); 7.44-7.35 (6H, m); 3.97 (1H,dd, J=7.8, 6.2 Hz); 3.84 (1H, ddd, J= 7.5, 6.5, 6.2 Hz); 3.72 (1H, ddd, J=10.2, 7.1, 5.2 Hz); 3.66 (1H, ddd, J=10.2, 7.4, 6.4 Hz); 3.56 (1H, dd, J=7.8, 6.5 Hz); 1.78-1.60 (3H, m); 1.40 (3H, s); 1.34 (3H, s); 1.23-1.10 (2H, m); 1.05 (9H, S); 1.05-0.99 (1H, m); 0.94 (3H, d, J-6.6 Hz); 0.83 (3H, d, J=6.6 Hz).

3,4,5,6-Tetradeoxy-3,5-di-C-methyl-7-O-tert-butyldiphenylsilyl-D-arabino-heptitol, 30 - The acetonide **29** (780 mg, 1.72 mmol) was stirred in 80% aqueous acetic acid (75 mL) at room temperature for 15 h. The mixture was then concentrated at the water pump, and co-evaporated several times with toluene (50 mL). Chromatography of the crude product (20-30% EtOAc in hexane) gave the diol **30** as a colorless oil (697 mg, 98%), $[\alpha]_D$ + 17.0°, (c 2.1, $CHCl_3$); ν max (neat oil) 3380, 2940, 1435, 1120, 1095, 705 cm^{-1}; m/e (CI) 415 $(M+H)^+$, 339, 319, 259, 199.

1,2-Anhydro-3,4,5,6-tetradeoxy-3,5-di-C-methyl-5-O-tert-butyldiphenyl- silyl-D-arabino-heptitol, 32 - To the diol **30** (44 mg, 0.106 mmol) in CH_2Cl_2 (1 mL) was added pyridine (22 μL, 2.5 equiv.) and 2,4,6-(triisopropyl)benzenesulphonyl chloride (64 mg, 2.0 equiv.) and the mixture stirred at room temperature for 1 h. After quenching with water (1 mL) for 1 h, the solution was worked up in the usual manner and the residue obtained after evaporation was chromatographed (5-10% EtOAc in hexane) to give the pure 1-O-sulphonate **31** as a colorless oil which was epoxidized directly. The sulphonate prepared above, in MeOH (5 mL) and dichloromethane (5 mL) was treated with sodium methoxide (1 mL of a 1 M soln. in methanol) at room temperature for 20 min. The resulting solution was then poured into ether (25 mL) and water (25 mL), the ethereal layer worked up in the usual way and the crude product chromatographed to give the epoxide **32** as a colorless oil, (31 mg, 70%, 2 steps); ^1H n.m.r. δ = 7.69-7.65 (4H, m); 7.45-7.35 (6H, m); 3.71 (1H, ddd, J=10.2, 6.8, 5.6 Hz); 3.67 (1H, ddd, J=10.2, 7.3, 6.3 Hz); 2.73 (1H, dd, J=5.0, 4.0 Hz); 2.62 (1H, ddd, J=7.0, 4.0, 2.8 Hz); 2.51 (1H, dd, J=5.0, 2.8 Hz); 1.82-1.71 (1H, m); 1.63-1.55 (1H, m); 1.39-1.24 (3H, m); 1.13-1.05 (1H, m); 1.04 (9H, s); 1.01 (3H, d, J=6.4 Hz); 0.82 (3H, d, J=6.6 Hz).

Lactone 34 - To a solution of hexamethyldisilizane (70.2 μl, 0.333 mmol) in THF (5 mL) at 0°C was added n-butyl lithium (208 μl of a 1.6 M soln., 1.0 equiv.) and the base was allowed to form for 20 min. This was treated with phenylselenoacetic acid (35.8 mg, 0.167 mmole, 0.5 equiv.) in THF (500 μl) and the dianion allowed to form at room temperature for 1 h. The epoxide **32** (35.8 mg, 0.0833 mmol, 0.25 equiv.) was then added in THF (1 mL) and the mixture stirred at room temperature for 15 h. The resulting yellow solution was partitioned between ether (35 mL) and 2 M hydrochloric acid (2 mL), the ethereal layer washed with H_2O (2 x 5 mL) and satd. brine (10 mL), dried ($MgSO_4$) and evaporated to a yellow oil. The crude hydroxyacid obtained above was immediately redissolved in CH_2Cl_2 (10 mL) and treated with EDAC (31.9 mg, 2.0 equiv.) and DMAP (~5 mg, catalytic) at room temperature for 30 min. The mixture was poured into ether (50 mL) and water (50 mL), given a standard aq. work-up and evaporated to give the crude epimeric mixture of α-phenylselenolactones **33** which were oxidized directly.

The mixture of epimeric selenides obtained above, in CH_2Cl_2 (20 mL), was added dropwise to an ice-cold solution of 30% H_2O_2 (5 mL) with vigorous stirring. After the addition was complete, stirring was continued at room temperature for 45 min., after which the organic layer was separated and washed several times with H_2O (3 x 20 mL), dried ($MgSO_4$) and evaporated to a crude oil. Column chromatography (5→10% EtOAc in hexane) afforded the lactone **34** as a colorless oil (29 mg, 69%); ^{1}H n.m.r. δ = 7.69-7.64 (4H, m); 7.45-7.37 (7H, m); 6.6 (1H, bds); 4.93-4.90 (1H, m); 3.77-3.63 (2H, m); 1.98-1.89 (1H, m); 1.80-1.70 (1H, m); 1.70-1.60 (1H, m); 1.38 (1H, ddd, J=14.0, 8.0, 5.5 Hz); 1.28-1.18 (1H, m); 1.14-1.06 (1H, m); 1.04 (9H, s); 0.87 (3H, d, J=6.8 Hz); 0.84 (3H, d, J=6.7 Hz).

Lactone 35 - To a suspension of CuBr.Me_2S complex (158 mg, 0.77 mmol) in ether (10 mL) at 0°C was added methyl lithium (0.9 mL of a 1.7 M soln. in ether, 2.0 equiv.) dropwise over 5 min. To the resulting buff-colored solution at-23°C was then added the enone **34** (15 mg, 0.034 mmol) in ether (3 mL) and the mixture stirred for 20 min. at-23°C. The reaction was diluted with ether (10 mL) and quenched with satd. ammonium chloride solution (10 mL) added dropwise at -23°C over 2 min. The ethereal layer was re-extracted with satd. ammonium chloride (10 mL) water (10 mL) and satd. brine (10 mL), dried ($MgSO_4$), and evaporated to give the crude product. Chromatography (7% EtOAc in hexane) gave the lactone **35** as a colorless oil (14 mg, 90%); $[\alpha]_D$ - 8.4°, (c 0.5, $CHCl_3$); m/e (CI) 395 (M-t-Bu), 375, 317, 179; Found 395.2042 M-t-Bu = $C_{24}H_{31}O_3Si$; requires 395.2043.

(3R,4S,5R,7S)-1,4,9-Trihydroxy-3,5,7-trimethyl-9-O-tert-butyldiphenylsilyl-nonane, 36 - The lactone **35** (14 mg, 0.031 mmol) in ether (5 mL) was treated with lithium aluminium hydride (11.8 mg, 10.0 equiv.) at room temperature for 1 h. The reaction was quenched successively with ethyl acetate (5 mL, dropwise) water (5 mL, dropwise) and dilute hydrochloric acid (5 mL); the ethereal layer was given a standard aqueous work-up and evaporated to a crude oil. Chromatography (10→25% EtOAc in hexane) gave the diol as a colorless oil (12.3 mg, 88%).

(3R,5S,7S)-1,9-Dihydroxy-3,5,7-trimethyl-9-O-tert-butyldiphenylsilyl-1-O-triphenylmethyl nonane 37 - The diol **36** (12.3 mg, 0.027 mmol) in acetonitrile (5 mL) was treated with tritylpyridinium tetrafluoroborate[28] (22 mg, 2.0 equiv.) at room temperature for 1 h. The mixture was diluted with ether (25 mL) and water (25 mL) the ethereal layer subjected to a standard aqueous work-up and evaporated to afford the trityl ether (together with Ph_3COH) as a yellow oil.

This product (~15 mg) in CH_2Cl_2 (5 mL) was treated with methanesulfonyl chloride (50 µl) in the presence of triethylamine (200 µl) at 0° for 1 h. The reaction was quenched with water (100 µl) and allowed to reach room temperature, stirred for 20 min and then partitioned between ether (25 mL) and water (25 mL). The organic phase was processed in the usual manner to give the crude mesylate as a yellow oil which was reduced directly. The product was dissolved in ether (5 mL) and reduced with lithium aluminum hydride (50 mg) at room temperature for 3 h. After careful dropwise addition of ethyl acetate (5 mL) at 0°C, the mixture was diluted with ether (10 mL), water (10 mL, dropwise) and dil. hydrochloric acid (10 mL). The ethereal layer was then processed in the usual manner to give the deoxygenated compound **37** which was chromatographed (2% EtOAc in hexane) to provide a pale yellow oil.[7]

Pyrazoline, 23 - The butenolide **4** (250 mg, 0.71 mmol) was dissolved in a freshly prepared, ethereal solution of diazomethane (25 mL) and allowed to stand for 15 h. Excess diazomethane was destroyed with glacial acetic acid (3 mL) and the ethereal layer concentrated to give the crude pyrazoline. Chromatography (20% EtOAc in hexane) provided **23** as a white crystalline compound (274 mg, 98%); mp 105-106°; $[\alpha]_D$ - 215.4° (c 1.2, CCl_4); ν max (melt) 2970, 1785, 1430, 1115, 705 cm^{-1}; ^{1}H n.m.r. δ = 7.67-7.62 (4H, m); 7.49-7.39 (6H, m); 5.76 (1H, ddd, J=9.2, 2.5, 1.2 Hz); 4.96 (1H, ddd, J=18.7, 9.5, 1.2 Hz); 4.68 (1H, ddd, J=18.7, 4.1, 2.5 Hz); 4.18 (1H, ddd, J=2.9, 2.8, 2.3 Hz); 3.89 (1H, dd, J=11.4, 2.9 Hz); 3.68 (1H, dd, J=11.4, 2.9 Hz); 2.93 (1H, q, J=9.5, 9.2, 4.1, 2.8 Hz); 1.05 (9H, s). Anal. calcd for $C_{22}H_{26}N_2O_3S_i$; C, 66.97; H, 6.42; N, 7.10. Found, C, 66.88; H, 6.39; N, 7.11.

2,3-Dideoxy-3-C-methyl-5-O-tert-butyldiphenylsilyl-D-glycero-pent-2-eno-1,4-lactone, 24 - The pyrazoline **23** (274 mg, 0.695 mmol) in toluene (15 mL) containing calcium carbonate powder (0.5 g) was brought to reflux for 3 h. After cooling, the suspension was filtered and evaporated to give the crude enone. Purification by chromatography (15→20% EtOAc in hexane) gave the α,β-unsaturated lactone **24** as a colorless oil (234 mg, 92%); $[\alpha]_D$ - 20° (C 2.6, $CHCl_3$); ν max (neat oil) 2940, 1765, 1430, 1135, 1120, 900, 710 cm^{-1}; m/e (CI) 367 $(M+H)^{\cdot+}$, 289, 117; Found 309.0957, (M-tBu) $C_{18}H_{22}O_3Si$; requires 309.0947; ^{1}H n.m.r. δ = 7.67-7.63 (4H, m); 7.48-7.37 (6H, m); 5.80 (1H, m); 4.84 (1H, m); 4.01 (1H, dd, J=11.4, 3.5 Hz); 3.86 (1H, dd, J=11.4, 3.4 Hz); 2.07 (3H, m); 1.09 (9H, s).

2,3-Dideoxy-3-C-methyl-5-O-tert-butyldiphenylsilyl-D-threo-pentono-1,4- lactone, 25 - The enone **24** (234 mg, 0.639 mmole) in EtOAc (20 mL was catalytically reduced (5% Rh/Al_2O_3, H_2O, 50 psi) for 1 h. Evaporation and chromatography (20%) ethyl acetate in hexane gave the lactone **25** as a colorless solid (230 mg, = quant.); mp 88-89°C; $[\alpha]_D$ + 50.8° (c 2.3, $CHCl_3$); ν max (neat oil) 2930, 1785, 1430, 1170, 1115, 705 cm^{-1}; m/e (CI) 369 $(M+H)^+$, 311

7.70-7.67 (4H, m); 7.48-7.39 (6H, m); 4.45 (1H, ddd, J=7.5, 3.6, 2.8 Hz); 3.86 (1H, dd, J=11.6, 3.6 Hz); 3.70 (1H, dd, J=11.6, 2.8 Hz); 2.78 (1H, q, J=9.9, 8.6, 7.5, 6.9 Hz); 2.59 (1H, dd, J=17.0, 8.6 Hz); 2.52 (1H, dd, J=17.0, 9.9 Hz); 1.22 (3H, d, J=6.9 Hz); 1.05 (9H, s). Anal. calcd. for $C_{22}H_{28}O_3Si$; C, 71.69; H, 7.65. Found: C, 71.66; H, 7.61.

3-Deoxy-3-C-methyl-5-O-tert-butyldiphenylsilyl-D-xylono-1,4-lactone 26 - To a solution of **25** (100 mg, 0.27 mmol) in THF (15 mL) at -78° was added potassium hexamethyldisilazide (1.35 mL of a 0.5 M soln. in toluene, 2.5 equiv.) and the enolate allowed to form for 30 min. Solid MoOPH (140 mg, 1.2 equiv.) was added in a single batch and the oxidation allowed to proceed at -55° for 40 min. The solution was then poured into ether (50 mL) and satd. sodium sulphite solution (50 mL, freshly prepared), the organic phase was worked up in the usual manner, and the crude product chromatographed 15→20% EtOAc in hexane) to give **26** as a white crystalline solid (83 mg, 83%); mp 96-97°C; $[\alpha]_D$ + 90.6° (c 4.5, $CHCl_3$); ν max (melt) 3450, 2940, 1780, 1120, 710 cm^{-1}.

The above compound was converted to the 2-acetate **26a** in the standard manner; mp 81-82°C $[\alpha]_D$ + 82.4° (c 1.60, $CHCl_3$); m/e (CI) 427 $(M+H)^+$, 370 (M-t-Bu), 349, 290, 241, 221; ^1H n.m.r. δ = 7.72-7.63 (4H, m); 7.49-7.37 (6H, m); 5.89 (1H, d, J=10.9 Hz); 4.45 (1H, ddd, J=8.5, 2.4, 1.0 Hz); 3.89 (1H, dd, J=12.0, 2.4 Hz); 3.72 (1H, dd, J=12.0, 1.0 Hz); 2.79 (1H, q, J=10.9, 8.5, 6.9 Hz); 2.19 (3H, s); 1.30 (3H, d, J=6.9 Hz); 1.07 (9H, s).

2,3-Dideoxy-3-C-methyl-5-O-tert-butyldiphenylsilyl-D-erythro-pentono-1,4-lactone, 38 - To a vigorously stirred suspension of CuBr.Me_2S complex (19.0 g, 92.3 mmol) in ether (250 mL) at 0°C was added methyl lithium (132 mL of 1.4 M solution in hexane, 184.6 mmol) over 5-6 min. The resulting solution (pale yellow to colorless) was cooled to -23°C (carbon tetrachloride, dry ice bath) and a solution of **4** (6.5 g, 18.5 mmol) in ether (50 mL) added in one portion. A yellow precipitate was produced over several seconds. The suspension was stirred for 20 min. at this temperature and then quenched by the cautious addition of sat. ammonium chloride solution (100 mL), transferred to a separatory funnel and shaken vigorously to break down excess reagent. The organic layer was then extracted with satd. brine (50 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (7% EtOAc in hexane), and then recrystallized (hexane) to afford **38** as a white crystalline solid (5.88 g, 87%), mp 71-72°C; $[\alpha]_D$ + 30.5° (c 1.2, $CHCl_3$); ν max (neat oil 2940, 2860, 1785, 1430, 1175, 1120, 740, and 705 cm^{-1}; m/e (EI) 311 (M-t-Bu), 268, 223, 199, 183; Found 311.1107 (M-t-Bu) = $C_{18}H_{19}O_3Si$; requires 311.1104; ^1H n.m.r. δ = 7.68-7.65 (4H, m); 7.47-7.38 (6H, m); 4.10 (1H, ddd, J=5.7, 3.6, 3.3 Hz); 3.86 (1H, dd, J=11.5, 3.3 Hz); 3.71 (1H, dd, J=11.5, 3.6 Hz); 2.81 (1H, dd, J=17.5, 7.0 Hz); 2.57 (1H, q, J=8.8, 7.0, 5.7, 6.9 Hz); 2.17 (1H, dd, J=17.5, 7.0 Hz); 1.13 (3H, d, J=6.9 Hz); 1.05 (9H,s).

2,4-Dideoxy-3-C-methyl-5-O-tert-butyldiphenylsilyl-D-erythro-pentitol, 39 - The lactone **38** (5.0 g, 13.6 mmol) in THF (50 mL) was treated with borane-dimethylsulphide complex (27.2 mL of a 2.0 M solution in THF, 4.0 equiv) dropwise over 10 min. and then stirred at room temperature for 15 h. Excess reductant was destroyed by the cautious addition of methanol (150 mL) at 0°C and the mixture concentrated to an oil. The trituration, evaporation procedure was repeated four times (4 x 150 mL) and the residue purified by column chromatography (15→30% EtOAc in hexane) to give **39** as a colorless oil (4.8 g, 96%); $[\alpha]_D$ +4.0° (c 2.4, $CHCl_3$); ν max (neat oil) 3060, 2940, 1430, 1110, 705, and 615 cm^{-1}; m/e (EI) 315 (M-t-Bu), 229, 199, 163 and 139; Found 315.1385, M-t-Bu=$C_{18}H_{23}O_3Si$; requires 315.1406; ^1H n.m.r. δ = 7.69-765 (4H, m); 7.46-7.37 (6H, m); 3.77-3.68 (2H, m); 3.65-3.47 (3H, m); 3.10 (1H, bd.s, D_2O exch.); 2.81 (1H, bd.s, D_2O exch.) 1.78-1.64 (2H, m); 1.61-1.49 (1H, m); 1.05 (9H, s); 0.81 (3H, d, J=6.5 Hz).

2,3-Dideoxy-3-C-methyl-5-O-triphenylmethyl-D-erythro-pentitol, 40 - The preceding compound (4.8 g, 12.90 mmole) in CH_2Cl_2 (25 mL) was treated with trityl chloride (4.31 g, 1.2 equiv.) and pyridine (3 mL), catalyzed with 4-dimethylaminopyridine (DMAP) (200 mg, 12 mmol%) at room temperature for 15 h. The mixture was partitioned between ether (100 mL) and water (100 mL) and the organic phase extracted sequentially with dil. hydrochloric acid (2 x 100 mL), water (1 x 100 mL), sat. bicarbonate solution (1 x 50 mL) and satd. brine (1 x 100 mL). The solution was dried ($MgSO_4$) and concentrated to give crude product as a pale orange oil which was used directly in the next step. The crude alcohol (12.90 mmol) in THF (25 mL) was desilylated by stirring with tetra n-butylammonium fluoride (19.35 mL of a 1.0 M soln. in THF, 1.5 equiv.) at room temperature for 2h. After concentrating at the water aspirator the residue was purified by column chromatography (40% EtOAc in hexane) providing **40** as a colorless crystalline solid, (4.4 g, 92%); mp 119-120°C; $[\alpha]_D$ - 4.0° (c 1.2, $CHCl_3$); ν max (neat oil, melt) 3400, 1450, 1070, 760, 745, 705 and 630 cm^{-1}; m/e (CI) 299 (M-77, C_6H_5), 285, 243, 183, 167, 135, 115; ^1H n.m.r. δ = 7.45-7.41 (6H, m); 7.32-7.21 (9H, m); 3.65 (1H, dd, J=10.1, 2.1 Hz); 3.50-3.41 (2H, m); 3.25-3.20 (1H, m); 3.12 (1H, ddd, J=9.4, 7.7, 4.9 Hz); 3.05-4.95 (1H, bd.s, D_2O exch.); 2.20-2.05 (1H, bd.s, D_2O exch.); 1.84-1.68 (2H, m); 1.61-1.56 (1H, m); 0.78 (3H, d, J=6.9 Hz).

4,5-Anhydro-2,3-dideoxy-3-C-methyl-D-erythro-pentitol, 42 - Compound **40** (3.51 g, 9.33 mmol) in pyridine (15 mL) was stirred with 2,3,5-(triisopropyl)benzenesulphonyl chloride (3.38 g, 1.2 equiv.) at room temperature for 48 h. Excess acid chloride was destroyed with water (1 mL) and the reaction then poured into ether (100 mL) and water (100 mL). A standard aq. work-up provided a pale yellow oil which was chromatographed to afford the hydroxysulphonate **41**. This product was dissolved in methanol (25 mL) and treated dropwise with sodium meethoxide in methanol (15.0 mL of a 1.0 mL soln. 1.5 equiv.) at 0°C. The reaction was stirred at this temperature for 15 min, then poured into ether and water. A standard work-up provided an oil which was chromatographed (3% EtOAc in hexane) to afford the epoxide **42** as colorless crystals, (2.5 g, 75%, 2 steps); mp 62-63°C; $[\alpha]_D$ - 9.0° (c 1.1, $CHCl_3$); ν max (neat oil, melt) 2940, 1490, 1450, 1075, 760, 710, and 635 cm^{-1}; m/e (EI) 358, 341, 327, 243,

183, 165, 105; Found M^+ 358.1954 $C_{25}H_{26}O_2$; requires 358.1932; ^1H n.m.r. δ= 7.47-7.43 (6H, m); 7.32-7.20 (9H, m); 3.18 (1H, ddd, J=9.2, 7.3, 5.0 Hz); 3.12 (1H, ddd, J=9.2, 6.9, 6.7 Hz); 2.72 (1H, ddd, J=6.4, 4.0, 2.8 Hz); 2.66 (1H, dd, J=4.9, 4.0 Hz); 2.47 (1H, dd, J=4.9, 2.8 Hz); 1.87-1.98 (1H, m); 1.61-1.50 (2H, m); 0.83 (3H, d, J=6.4 Hz).

Lactone 43 - To a solution of hexamethyldisilazane (4.6 mL, 22.0 mmol) in THF (50 mL) at 0°C was added n-butyl lithium (14.0 mL of 1.5 M soln. in hexane, 21.0 mmol) over 2-3 min. After 20 min. a solution of phenylthioacetic acid (1.76 g, 10. 5 mmole, 0.5 equiv.) in THF (20 mL) was added and the mixture allowed to reach room temperature. A white precipitate of the dianion was produced over 10-15 min. At the end of 1 h the epoxide **42** (2.5 g, 7.0 mmol) in THF (15 mL) was introduced and the mixture stirred for 15 h, resulting in a clear yellow solution. The reaction was poured into ether (200 mL) and dilute hydrochloric acid (200 mL), extracted with water (2 x 50 mL) and satd. brine (1 x 100 mL); dried ($MgSO_4$ and evaporated to give the crude hydroxy acid as a yellow oil.

This product in dichloromethane (100 mL) was lactonized with EDAC (2.0 g, 1.5 equiv.) and DMAP (200 mg) at room temperature for 20 min. A standard aqueous work-up gave a crude product which was chromatographed (5→10% EtOAc in hexane) to give the corresponding lactone as a pale yellow oil, (3.0 g, 85% two steps); ν max (neat oil) 3060, 2940, 1800, 1455, 1190, 1075, 745, and 710 cm^{-1}; m/e Found (M^+) 508.2101 $C_{33}H_{32}O_3S$; requires 508.2072.

The epimeric sulphides (3.0g, 5.9 mmol) in CH_2Cl_2 (50 mL) were oxidized with m-CPBA (1.56 g of 85% purity oxidant, 1.3 equiv.) at -23°C for 10 min. The reaction was quenched at this temperature by the addition of dimethylsulfide (10 mL) and then poured into ether 200 mL and satd. sodium bicarbonate solution (50 mL). The organic phase was extracted several times with satd. bicarbonate (3 x 50 mL), washed with satd. brine (50 mL), dried ($MgSO_4$) and evaporated to give a mixture of sulphoxides as a yellow oil which was employed directly in the next reaction. The sulphoxides were brought to reflux in toluene (25 mL) containing powdered $CaCO_3$ (1 g) and pyridine (0.5 mL) for 40 min. The suspension was then cooled, diluted with $CHCl_3$ (50 mL), filtered, and evaporated to a yellow oil. Column chromatography of the residue (10 % EtOAc in hexane) afforded the lactone **43** as a colorless oil, (1.90 g, 81%, 2 steps); $[\alpha]_D$ + 54.1° (c 1.3, $CHCl_3$); ν max (neat oil) 2940, 1755, 1450, 1165 1090, 1070, and 710 cm^{-1}; m/e (EI) 398 (M^+) 321, 243, 165, 139, 105; Found (M^+) 398.1855 ($C_{27}H_{26}O_3$); requires 398.1882; ^1H n.m.r. δ = 7.45-7.41 (6H, m); 7.36 (1H, dd, J=5.9, 1.5 Hz); 7.32-7.20 (9H, m); 6.08 (1H, dd, J=5.9, 2.1 Hz); 4.93 (1H, ddd, J=5.3, 2.1, 1.5 Hz); 3.23-3.18 (1H, m); 3.09 (1H, ddd, J=9.3, 7.9, 5.5 Hz); 2.21-2.14 (1H, m); 1.81-1.73 (1H, m); 1.49-1.41 (1H, m); 0.81 (3H, d, J=6.9 Hz).

Lactone 46 - To a suspension of CuBr.Me_2S complex (5.1 g, 24.8 mmol) in ether (100 mL) at 0°C was added dropwise methyl lithium (34.1 mL of a 1.4 M soln in ether, 47.7 mmol, 1.9 equiv.) over 10 min. After stirring at this temperature for 20 min. the suspension was cooled to -23°C and the lactone **45** (1.90 g, 4.8 mmol) in ether (20 mL) introduced in one portion. The mixture was stirred for 20 min., cooled to -23°, then quenched by the cautious addition of satd. ammonium chloride solution (50 mL). The organic phase was re-extracted with ammonium chloride solution (2 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), and evaporated to an oil which was chromatographed (13% EtOAc in hexane) to give the lactone **44** as a colorless oil (1.80 g, 93%), which crystallized; mp 122-123°C; $[\alpha]_D$ -34.7° (c 2.1, $CHCl_3$); ν max (neat oil, melt) 2970, 1780, 1450, 1220, 1075, 1005, 765 and 710 cm^{-1}. m/e (EI) 414 (M^+), 337, 243, 155, 105; Found (M^+) 414.2194 ($C_{28}H_{30}O_3$); requires 414.2195; ^1H n.m.r. δ = 7.45-7.42 (6H, m); 7.32-7.20 (9H, m); 3.90 (1H, dd, J=6.6, 5.2 Hz); 3.21 (1H, ddd, J=9.2, 6.5, 5.2 Hz); 3.06 (1H, ddd, J=9.2, 8.2, 5.8 Hz); 2.67 (1H, dd, J 17.6, 8.8 Hz); 2.41-2.30 (1H, m); 2.16 (1H, dd, J=17.6, 8.2 Hz); 2.05-1.93 (1H, m); 1.86 (1H, ddd, J=13.7, 8.2, 6.5, 3.8 Hz); 1.45-1.37 (1H, m); 1.12 (3H, d, J=6.6 Hz); 0.86 (3H, d, J=6.8 Hz).

(3R,4S,5S)-3,4-Dimethyl-1-O-tert-butyldiphenylsilyl-7-O-triphenylmethyl heptane 1,4,7-triol, 45 - Lactone **44** (1.80g, 4.35 mmol) in ether (50 mL) at 0°C was reduced with lithium aluminium hydride (330 mg, 2.0 equiv.) for 1 h. Excess reductant was destroyed by dropwise addition of ethyl acetate (5 mL) followed by dil. hydrochloric acid (50 mL). A standard work-up gave the crude product which was chromatographed (30% EtOAc in hexane) to give a colorless syrup, (1.7 g, 94%); $[\alpha]_D$ - 5.7° (c 1.5, $CHCl_3$); ν max (neat oil) 3350, 2960, 1450, 1170, 760, 710, and 635 cm^{-1}; m/e (EI) 243, 165, 105. This diol derivative (1.7 g, 4.07 mmol) in CH_2Cl_2 and pyridine (5 mL) was treated with t-butyldiphenylsilyl chloride (1.27 mL, 1.2 equiv.) and DMAP 100 mg) at room temperature for 15 h. The reaction was then poured into ether (50 mL) and water (50 mL), given an aqueous work-up, and the crude product chromatographed (5→7% EtOAc in hexane) to provide the title compound as a colorless crystalline solid (2.3 g, 84%); mp 76-78°C; $[\alpha]_D$ - 4.4°C (c 1.5, $CHCl_3$); ν max (neat oil) 3440, 2940, 1430, 1115, 1075, 745 and 705 cm^{-1}.

(3S,5R)-3,5-Dimethyl-1-O-tert-butyldiphenylsilyl-7-O-triphenylmethyl-heptane 1,7-diol, 47 - Compound **45** (100 mg, 0.15 mmol) in pyridine (5 mL) was esterified with methanesulphonyl chloride (24 μL, 2.0 equiv.) and DMAP (5 mg) at room temperature for 1 h. The reaction was given a standard aqueous work-up and chromatographed quickly on a short column (7% EtOAc in hexane) to the mesylate **46** as a pale yellow oil which was reduced immediately. The mesylate (100 mg) in ether (15 mL) was stirred with lithium aluminum hydride (28.5 mg, 5.0 equiv) at room temperature for 2 h. The reaction was quenched with ethyl acetate (5 mL) and then dil. hydrochloric acid (15 mL), given a standard work-up and the residue chromatographed (2% EtOAc in hexane) to afford the title compound as a colorless oil (70 mg, 73%, 2 steps);

$[\alpha]_D$ - 3.6° (c 1.8, $CHCl_3$); ν max (neat oil) 2940, 1455, 1435, 1115, 790 and 710 cm^{-1}; ^1H n.m.r. δ = 7.69-7.65 (4H, m); 7.47-7.19 (21H, m); 3.73-3.62 (2H, m); 3.15-3.00 (2H, m); 1.72-1.57 (4H,m); 1.36-1.03 (3H, m); 1.05 (9H, s); 0.95-0.87 (1H, m); 0.79 (3H, d, J=6.5 Hz); 0.74 (3H, d, J=6.5 Hz).

4,5-Anhydro-2,3-dideoxy-3-C-methyl-5-O-triphenylmethyl-D-threo- pentitol, 49 - The alcohol **39** (1.9 g, 3.15 mmol) was esterified with methanesulphonyl chloride (0.48 mL, 2.0 equiv.) in CH_2Cl_2 (20 mL) and pyridine (5 mL) containing DMAP (100 mg) at room temperature for 4 h. The reaction was then poured into ether (100 mL) and water (100 mL), the organic phase worked up in the usual manner and the crude product purified by flash column chromatography (2→8% EtOAc in hexane) to give the mesylate **51** as a pale yellow oil which was epoxidized directly. The mesylate in THF (25 mL) was treated with tetra n-butylammonium fluoride (4.7 mL of a 1.0 M soln. in THF, 1.5 equiv.) at room temperature for 2 h. Evaporation and chromatography of the oily residue gave the epoxide **49** as a colorless oil (800 mg, 71%); $[\alpha]_D$ - 1.6° (c 0.9, $CHCl_3$); ν max (neat oil), 2930, 1450, 1080, 760, 710 and 635 cm^{-1}; m/e (EI) 358, 281, 243, 165, 105; Found (M^+) 358. 1970 ($C_{25}H_{26}O_2$); requires 358.1932; ^1H n.m.r. δ = 7.44-7.42 (6H, m); 7.30-7.20 (9H, m); 3.15-3.07 (2H,m); 2.62 (1H, ddd, J=7.0, 3.9, 2.8 Hz); 2.57 (1H, dd, J=4.9, 2.9 Hz); 2.39 (1H, dd, J=4.9, 2.8 Hz); 1.74-1.50 (3H, m); 0.97 (3H, d, J=6.7 Hz).

Lactone 50 - To a solution of hexamethyldisilazane (1.0 mL, 4.7 mmol) in THF (12 mL) was added n-butyl lithium (3.0 mL of 1.5 M soln. in hexane, 4.5 mmol) at 0°C and the mixture stirred for 20 min. A solution of phenylthioacetic acid (390 mg, 2.3 mmol) in THF (12 mL) was introduced, the mixture brought to room temperature and the dianion allowed to form over 1 h. To the resulting white suspension was added the epoxide **49** (600 mg, 1.67 mmol) in THF (10 mL) and the reaction stirred for 15 h. The yellow solution was then poured into ether (100 mL), and dilute hydrochloric acid (100 mL), extracted with water (2 x 25 mL) and satd. brine (1 x 50 mL), dried ($MgSO_4$) and evaporated to afford the crude hydroxy acid as a yellow oil. This product in CH_2Cl_2 (30 mL) was lactonized with EDAC (900 mg, 1.5 equiv.) and DMAP (50 mg) at room temperature during for 20 min. After a standard aqueous work-up the crude product was chromatographed (5→10% EtOAc in hexane) to furnish the epimeric 2-phenylthio lactones as a pale yellow oil (710 mg, 84%); Found (M^+) 508.2101, ($C_{33}H_{32}O_3S$); requires 508.2072

The mixture of epimeric sulphides (610 mg, 1.20 mmol) was oxidized with m-CPBA (317 mg of 85% purity oxidant, 1.3 equiv.) in CH_2Cl_2 (25 mL) at -23° for 20 min. Excess oxidant was destroyed at this temperature by the addition of dimethylsulphide (5 mL) and the mixture poured into ether (100 mL) and satd. bicarbonate (50 mL). The organic phase was re-extracted with bicarbonate solution (3 x 50 mL) and brine (1 x 50 mL), dried ($MgSO_4$) and evaporated to an oil. A solution of the crude sulphoxides in 25 mL toluene was brought to reflux in the presence of powdered $CaCO_3$ (≈1g) and pyridine (0.5 mL) for 40 min. The suspension was then cooled, diluted with $CHCl_3$ (50 mL), filtered and evaporated to give the impure lactone. Column chromatography (10% EtOAc in hexane) provided the pure lactone **50** as a colorless oil (439 mg, 92%, 2 steps); $[\alpha]_D$ - 48.4° (c 1.9, $CHCl_3$); ν max (neat oil) 1755, 1450, 1160, 1070, 765, 710 and 635 cm^{-1}; m/e (EI) 398 (M^+), 321, 243, 165, 139, 105; Found (M^+) 398.1854 ($C_{27}H_{26}O_3$); requires 398.1882; ^1H n.m.r. 7.45-7.42 (6H, m); 7.35 (1H, dd, J=5.7, 1.4 Hz); 7.31-7.21 (9H,m); 6.08 (1H, dd, J=5.7, 2.0 Hz); 4.89 (1H, ddd, J=4.1, 2.0, 1.4 Hz); 3.24-3.19 (1H, m); 3.14 (1H, ddd, J=9.4, 7.3, 5.5 Hz); 2.20-1.91 (1H, m); 1.87-1.78 (1H, m); 1.58-1.49 (1H, m); 0.77 (3H, d, J=6.9 Hz).

Lactone 51 - To a suspension of $CuBr.Me_2S$ (870 mg, 4.25 mmol) in ether (20 mL) at 0°C was added methyl lithium (6.1 mL of 1.4 M soln. 8.50 mmol) over 5-10 min. The solution was then cooled to -23°C and the lactone **50** (340 mg, 0.85 mmol) in ether (10 mL) added in one portion and stirred for 20 min. Excess reagent was destroyed by quenching with satd. ammonium chloride solution (20 mL) at this temperature. The organic phase was re-extracted with ammonium chloride solution (2 x 20 mL), and sat. brine (1 x 20 mL), dried ($MgSO_4$) and evaporated to a crude oil. Purification by column chromatography (10→15% EtOAc in hexane) gave the lactone **51** as a colorless oil (341 mg, 97%); $[\alpha]_D$ + 12.2° (c 1.2, $CHCl_3$); ν max (neat oil) 1780, 1450, 1215, 1165; m/e (EI) 414 (M^+), 337 ($M-C_6H_5$), 243, 155; Found (M^+) 414.2223 ($C_{28}H_{30}O_3$); requires 414.2194; ^1H n.m.r. δ = 7.45-7.42 (6H, m); 7.30-7.20 (9H, m); 3.90 (1H, dd, J=7.2, 3.9 Hz); 3.19 (1H, ddd, J=9.4, 6.1, 6.1 Hz); 3.11 (1H, ddd, J=9.4, 7.1, 5.7 Hz); 2.64 (1H, dd, J=17.5, 8.6 Hz); 2.40-2.28 (1H, m); 2.12 (1H, dd, J=17.5, 8.6 Hz); 2.03-1.92 (1H, m); 1.82-1.74 (1H, m); 1.60-1.51 (1H, m); 1.07 (3H, d, J=6.7 Hz); 0.84 (3H, d, J=6.8 Hz).

(3S,4R,5S)-3,5-Di-C-methyl-1-O-tert-butyldiphenylsilyl-7-O-triphenylmethyl-heptane 1,4,7-triol, 53 - The lactone **51** (341 mg, 0.824 mmol) in ether (20 mL) at 0°C was reduced with lithium aluminium hydride (62.5 mg, 2.0 equiv.) for 1.5 h. Excess reductant was destroyed by the dropwise addition of ethyl acetate (5 mL) followed by dil. hydrochloric acid (25 mL). After a standard aq. work-up the crude diol was purified by chromatography (20-30% EtOAc in hexane), yielding **52** as a colorless oil (327 mg, 96%); $[\alpha]_D$ + 1.6° (c 1.2, $CHCl_3$). The diol (327 mg, 0.782 mmol) in CH_2Cl_2 (10 mL) and pyridine (1 mL) was treated with t-butyldiphenylsilyl chloride (242 μL, 256 mg, 1.3 equiv.) and DMAP (50 mg) at room temp. for 15 h. The reaction was then poured into water (50 mL) and ether (50 mL), processed in the usual manner and the crude oily product chromatographed (5→7% EtOAc in hexane) to affordthe title compound **53** as a colorless oil (507 mg, 98%); $[\alpha]_D$ - 0.8° (c 1.2, $CHCl_3$); ν max (neat oil) 3440, 2940, 1460, 1115, 1090, 1070, 745 and 705 cm^{-1}.

(3R,5R)-3,5-Di-C-methyl-1-O-tert-butyldiphenylsilyl-7-O-triphenylmethyl-heptane 1,7-diol, 55 - The product 53 (507 mg, 0.773 mmol) in pyridine (5 mL) was esterified with methanesulphonyl chloride (120 µL, 177 mg, 2.0 equiv.) and DMAP (5 mg) at room temperature for 1 h. The reaction was given a standard aq. work-up and filtered through a short column (7% EtOAc in hexane) to give the mesylate 54 as a pale yellow oil which was reduced immediately. The mesylate prepared above (500 mg) in ether (30 mL) was stirred with lithium aluminum hydride, (147 mg, 5.0 equiv.) at room temperature for 2 h. The reaction was quenched by the dropwise addition of ethyl acetate (5 mL) and then dil. hydrochloric acid (25 mL), given an aq. work-up, and the residue chromatographed (2% EtOAc in hexane) to provide the title compound 55 as a colorless oil (350 mg, 71%, 2 steps); $[\alpha]_D$ + 3.1° (c 1.7, $CHCl_3$); ν max (neat oil) 2930, 1450, 1430, 1115, 1090, 1075, 705, and 615 cm^{-1}; m/e (CI) 563 ($M^+ - C_6H_5$), 285, 244; ^1H n.m.r., δ = 7.68-7.65 (4H, m); 7.47-7.19 (21H, m); 3.73-3.62 (2H, m); 3.13-3.01 (2H, m); 1.75-1.27 (6H, m); 1.05 (9H, s); 1.02-0.98 (2H, m); 0.77 (3H, d, J=6.5 Hz); 0.75 (3H, d, J=6.5 Hz).

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