Graphical Abstract

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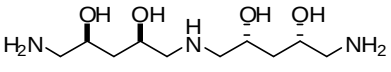

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Structure Elucidation and Synthesis of Pavettamine, the Causal Agent of Gousiekte

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pavettamine, gousiekte, total synthesis, polyamine

Abstract

The structure elucidation of a novel natural product pavettamine, the causal agent of the plant toxicosis gousiekte, is described. A synthetic strategy towards pavettamine, accommodating all possible stereoisomers, is discussed. The absolute configuration of the natural product, determined by total synthesis, is reported.

1. Introduction

Gousiekte ("quick" disease), one of the six most important plant toxicoses of livestock in South Africa, is a plant-induced cardiomyopathy of domestic ruminants that is characterized by the sudden death of animals within a period of 3-6 weeks after the initial ingestion of toxic plant material. The six species of the three genera of the Rubiaceae family *viz. Pachystigma pygmaeum*,[1] *P. thamnus*, and *P. latifolium*;[2] *Pavetta harborii*[3] and *P.schumanniana*, and *Fadogia homblei*[4] have been identified as the causative agents of the disease.[5] The disease was first identified in 1908 but because of the irregular outbreaks the matter was not pursued until a severe outbreak in 1915 was reported in which 1047 out of a flock of 1761 sheep died.[1] Gousiekte is the last of the major plant poisonings in southern Africa to be investigated and the causal toxin was not isolated until 1995.[6] Investigations were hampered by the variations in the clinical signs of the disease, variability in toxicity of the plants, differences in animal susceptibility to intoxication, and diminishing toxicity of the plants during drying. Although there is strong evidence that shows that a small dose of plant material is occasionally fatal, generally fairly large quantities of plant material have to be ingested for intoxication to occur.

2. Results and discussion

2.1 Structure elucidation

The same active principle was isolated from *Pachystigma pygmaeum*, *Pavetta harborii*, *Pavetta schumanniana* and *Fadogia homblei*.[6] Electrospray ionization mass spectrometry (ESI-MS) of this active principle, named pavettamine, established the molecular mass as 251 and the molecular formula as $C_{10}H_{25}N_3O_4$ by accurate mass determination of the $[M+H]^+$, $[M+Na]^+$ and $[2M+Na]^+$ ions as well as the fragment ions formed from the $[M+H]^+$ ion in an MS-MS analysis. The ^{13}C NMR spectrum showed only 5 signals for the proton-bearing carbon atoms (see Table 1) and the ^1H NMR spectrum multiplet signals for only 8 protons. It is evident from the NMR data that the pavettamine molecule contains a symmetry element: either a C_2 axis or a symmetry plane. The multiplicities of the different ^{13}C resonances were deduced from the proton-decoupled CH and CH_2 subspectra obtained using the DEPT pulse sequence.

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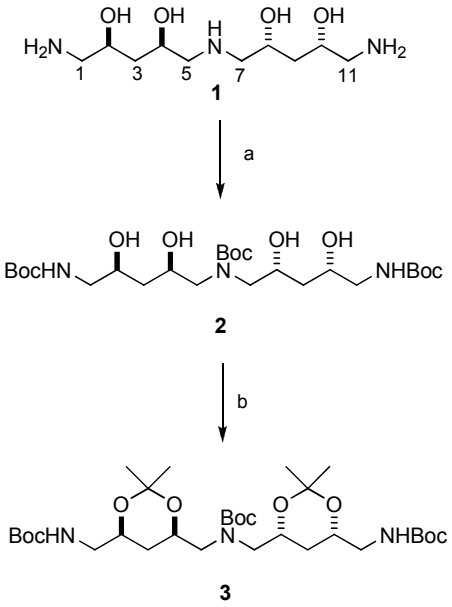
Table 1. NMR Data for pavettamine **1**[*]

δ_H	δ_C
H-1a 2.851 (dd, $J_{1a,1b}$ 13.2, $J_{1a,2}$ 9.5) H-1b 3.058 (dd, $J_{1a,1b}$ 13.0, $J_{1b,2}$ 3.0)	C-1 46.65 T
H-2 3.952 (m, $J_{1a,2}$ 9.4, $J_{1b,2}$ 3.1, $J_{2,3}$ 6.5)	C-2 67.18 D
H-3 1.679 (m)	C-3 40.97 T
H-4 4.057 (m, $J_{4,5a}$ 10.0, $J_{4,5b}$ 2.8, $J_{3,4}$ 6.3)	C-4 66.27 D
H-5a 3.000 (dd, $J_{5a,5b}$ 13.0, $J_{4,5a}$ 10.0) H-5b 3.143 (dd, $J_{5a,5b}$ 13.0, $J_{4,5b}$ 2.9)	C-5 54.56 T

[*] in D_2O.

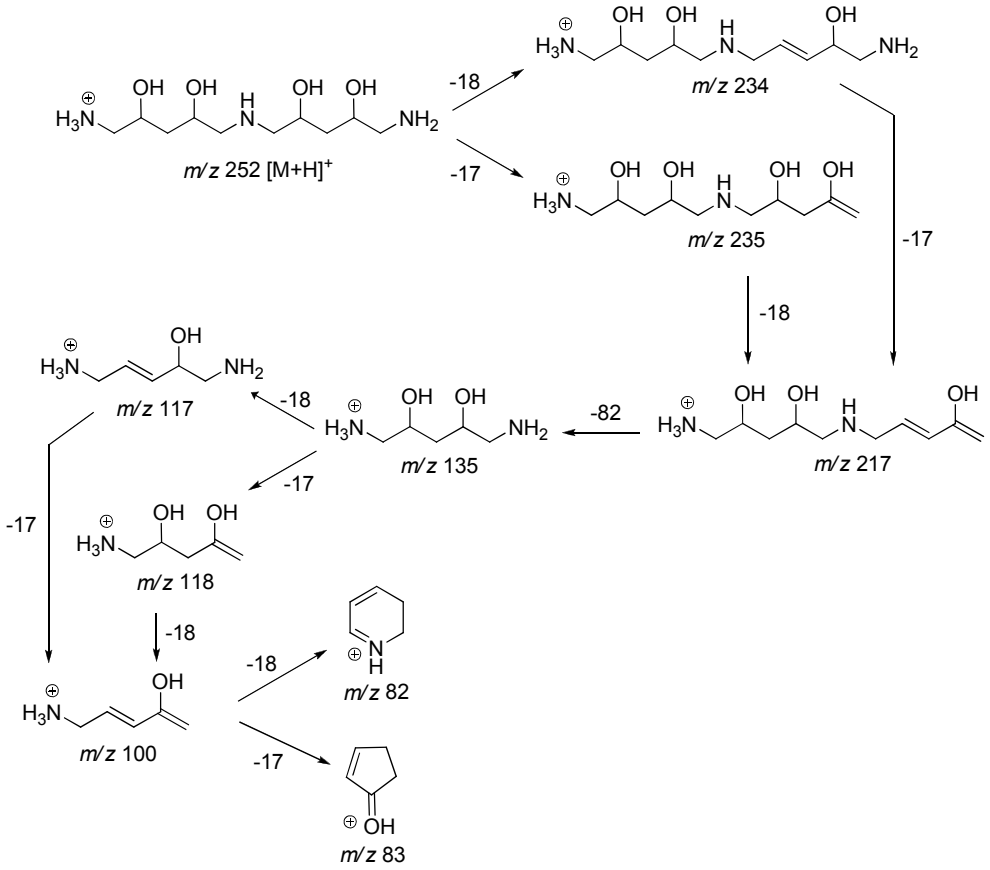
The signals of the proton-bearing carbon atoms were correlated with specific proton resonances in a two-dimensional (2-D) $^{13}C\{^1H\}$ heteronuclear chemical shift correlation experiment (HETCOR) utilizing the one-bond ($^{13}C,^1H$) spin-spin couplings. The assignments of the signals in the ^1H NMR spectrum are based on first-order analysis of the spin systems and chemical shift considerations and were confirmed by a two-dimensional (2D) ($^1H,^1H$) homonuclear chemical shift correlation (COSY) experiment and $^1H\{^1H\}$ spin-decoupling experiments. The assignment of the signal at δ_C 46.65T to C-1 in pavettamine **1**, and thus the corresponding signals at δ_H 2.851 and 3.058 to the C-1 protons, is based on the analysis of the NMR data for the tri-Boc derivative (**2**)(Scheme 1). The structure **1**, 1,11-diamino-6-aza-undecane-2,4,8,10-tetraol, was assigned to pavettamine on the basis of the above data.



Scheme 1. Determination of the relative stereochemistry of pavettamine **1**.

Reagents: (a) Boc_2O, Na_2CO_3; (b) 2,2-Dimethoxypropane, TsOH.

The proposed structure is in agreement with the fragmentation pattern (Scheme 2) derived from the analysis of the MS-MS spectrum of **1** (Table 2).



Scheme 2. MS-MS Fragmentation pattern for pavettamine **1**.

Table 2. MS-MS of pavettamine **1**

Observed Mass (*m/z*)	Formula	Theoretical Mass	DBE	Match (ppm)
252.191233	$C_{10}H_{26}N_3O_4$	252.191769	0	-2.13
235.165592	$C_{10}H_{23}N_2O_4$	235.165221	1	+1.58
234.181234	$C_{10}H_{24}N_3O_4$	234.181206	1	+0.12
217.154755	$C_{10}H_{21}N_2O_3$	217.154758	2	+0.45
135.112484	$C_5H_{15}N_2O_2$	135.112796	0	-2.31
118.085967	$C_5H_{12}NO_2$	118.086248	1	-2.39
117.102321	$C_5H_{13}N_2O$	117.102233	1	+0.75
100.075477	$C_5H_{10}NO$	100.075685	2	-2.09
83.049182	C_5H_7O	83.049137	3	+0.53
82.064992	C_5H_8N	82.065122	3	-1.59

The next step entailed the determination of the stereochemistry of pavettamine **1**. There are 6 possible stereoisomers that meet the symmetry criteria of the structure (see Figure 1). Two of the stereoisomers are *meso* compounds (**A** and **B**) and possess a plane of symmetry whereas the stereoisomers **C**-**F** have a C_2 symmetry axis. In addition **C** and **D**, as well as **E** and **F** are enantiomers. Differentiation between the two groups of stereoisomers is possible by determining whether pavettamine shows optical activity: *meso* compounds are optically inactive. The presence of a C_2 symmetry element in pavettamine was established by the fact that the compound was optically active and showed a specific rotation of –19.5. The magnitude remained in doubt as a result of solvent retained in the natural toxin obtained from the isolation procedure but the result excluded the presence of a symmetry plane and thus the two possible *meso* stereoisomers for pavettamine.

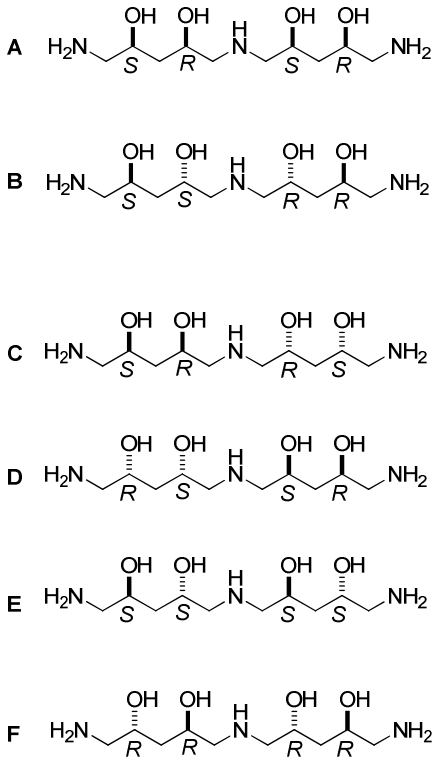


Figure 1: Stereoisomers of pavettamine meeting the symmetry requirements

The relative stereochemistry of pavettamine was established by ^{13}C NMR analysis of the acetonide derivative of the 1,3-diol system present in the compound, a method developed by Rychnovsky.[7,8] The amino groups present in pavettamine were first protected by converting the compound to the tri-Boc derivative **2** by treatment with Boc_2O and Na_2CO_3 in aqueous dioxane. The signals at δ_H 3.076 and 3.235 in the ^1H NMR spectrum of **2**, which correlated with the signal at δ_C 47.16T, showed coupling with the NH proton at δ_H 4.945 and thus provided the unambiguous assignment of the C-1 and C-5 (δ_C 56.02T) resonances in **2** and therefore in pavettamine **1** as well. The 1,3-diol system of **2** was protected as the acetonide **3** by acid-catalysed (TsOH) transacetalisation with 2,2-dimethoxypropane (Scheme 1). The signals at δ_C 30.00Q, 19.87Q and 19.71Q for the 2,2-dimethyl groups of the formed 1,3-dioxane rings as well as the signal at δ_C 98.73S in the ^{13}C NMR spectrum for the acetal carbon atom established the *syn* stereochemistry of pavettamine.[7,8] The absolute configuration as shown in **1** *i.e.* (2*S*,4*R*,8*R*,10*S*) (or *ent*-**1**) was therefore assigned to pavettamine.

2.2 Synthesis

The synthetic effort commenced before any information on the relative stereochemistry was available. Thus, a synthetic sequence was chosen that could accommodate all possible stereoisomers: both *syn*

and *anti* (Fig. 1). The C_2 symmetry of pavettamine lent itself to a synthetic approach involving the preparation of a common C_5 subunit identified by retrosynthetic analysis (Figure 2) that could then be functionalised and linked to prepare the final C_{10} product. The common approach used towards both the *syn* and *anti* C_5 units is outlined below and used chiral sulfoxide methodology as a means of controlling the relative stereochemistry of the two hydroxyl groups. The enantiomeric C_5 unit could in turn be obtained by an orthogonal protection-deprotection strategy of the primary hydroxyl groups in a C_5 unit. A synthesis for pavettamine was thus designed that could provide any one of the possible stereoisomers and which would then establish the absolute configuration of the natural product.

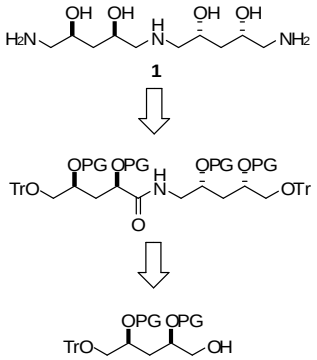
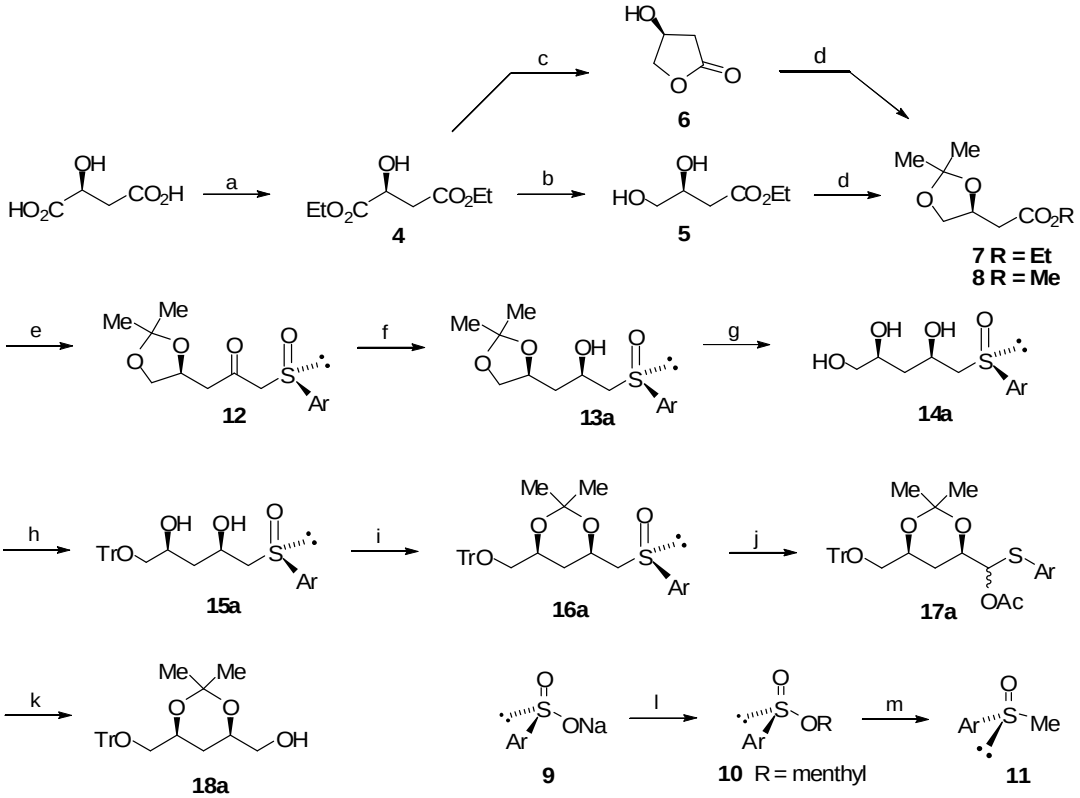


Figure 2: Retrosynthetic analysis of pavettamine **1** leading to a C_5 building block.

The starting material chosen was the four-carbon unit (2*S*)-malic acid, where stereochemistry at one position is already defined. Scheme 3 illustrates the synthetic sequence used to prepare both the *syn* and *anti* C_5 unit. The sequence involved esterification of (2*S*)-malic acid to give the diethyl ester **4.** Regioselective reduction of one of the esters using $BH_3.SMe_2$ complex and catalytic $NaBH_4$ (5 mol%) and workup of the reaction mixture with *p*-TsOH (5 mol%) gave the 3,4-dihydroxybutanoate ester **5.**[9] The use of excess *p*-TsOH resulted in the formation of the corresponding lactone **6**.[10,11] Treatment of the 3,4-dihydroxybutanoate ester **5** with 2,2-dimethoxypropane in acetone in the presence of *p*-TsOH gave the ethyl ester 3,4-*O*-isopropylidene derivative **7** whereas similar treatment of the lactone **6** gave the methyl ester **8**. The one-carbon chain extension of the esters **7** (or **8**) is based on the reaction of the ester group with two equivalents of the α-sulfinyl anion derived from (*R*)-(+)-methyl *p*-tolylsulfoxide **11**,[12] prepared from the anhydrous sodium salt of *p*-toluenesulfinic acid **9** via the menthyl ester **10**,[13,14] and yielded the β-ketosulfoxide **12** (ν_{max} 1720 cm^{-1}; δ_C 199.27S). The stereochemical course of the reduction of the carbonyl group of **12** with DIBALH is controlled by the configuration of the *p*-tolyl sulfoxide moiety: in the presence of $ZnCl_2$ only the 2,4-*syn* diol **13a** was formed whereas the 2,4-*anti* diol **13b** was obtained as a single diastereomer in the absence of $ZnCl_2$.[12,15,16] The acetonide protective group of both the *syn* **13a** and the *anti* diol **13b** were removed by acid catalysis using TsOH in aqueous MeOH to give the water-soluble triols **14a** and **14b**, respectively, that were isolated by continuous extraction with EtOAc. The primary hydroxyl group of each of these triols was selectively converted to the trityl ether to give **15a** and **15b**. The two secondary hydroxyl groups in both **15a** and **15b** were protected as the acetonide by treatment with 2,2-dimethoxypropane and TsOH to give **16a** and **16b**. The use of the acetonide protecting group confirmed the relative stereochemistry of the 2,4-diol system: the characteristic ^{13}C chemical shifts of the methyl groups and the C-2 quaternary carbon of the 1,3-dioxane ring in **16a** (δ_C 19.60Q, 29.69Q and 98.87S) and **16b** (δ_C 24.84Q, 24.53Q and 101.00S) established the *syn* and *anti* relative stereochemistry, respectively,[7,8] and provided a method of monitoring the stereochemical integrity of the 2,4-diol system in subsequent steps of the synthetic route.

All that remained for successful preparation of the C_5 unit was conversion of the chiral sulfoxide auxiliary into a primary hydroxyl group. This conversion was achieved in a two-step process. In the first step the Pummerer rearrangement[17,18] of the sulfoxide group in **16** using Ac_2O and NaOAc at 130–140 °C resulted in the transfer of chirality from the sulfur stereogenic centre to the C-1 carbon atom in **17** and gave rise to the formation of the *O,S*-acetal as a *ca*. 1:1 diastereomeric mixture as was

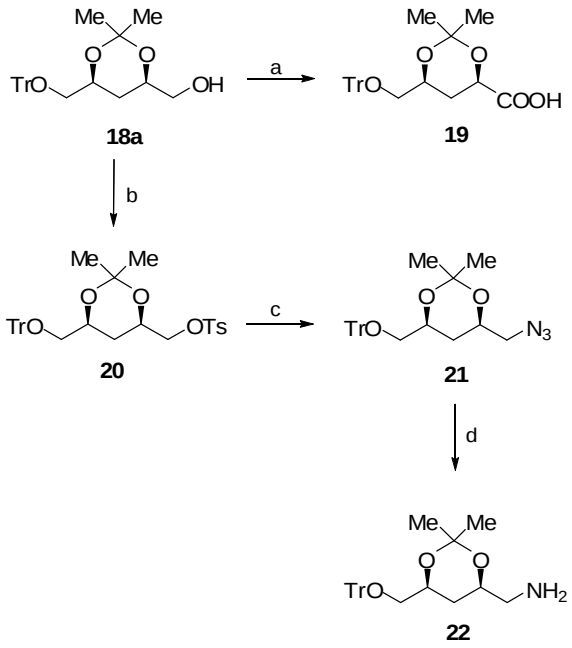
evident from the two sets of signals in the ^{1}H and ^{13}C NMR spectra of both **17a** and **17b**. The second step of the conversion was the $LiAlH_4$ reduction of the *O*,*S*-acetal **17** to give the required C_5 building block with either the *syn* **18a** or *anti* **18b** stereochemistry as the primary alcohol.



Scheme 3. Preparation of the C_5 unit with the *syn* 1,3-diol moiety (compounds **13a**–**18a**). Reduction of the ketosulfoxide **12** with DIBALH in step **f** gave the C_5 unit with the *anti* 1,3-diol moiety (compounds **13b**–**18b**)(see Experimental). (Ar ≡ *p*-tolyl)
Reagents: (a) Amberlite IR120 (H^+), $CHCl_3$-EtOH; (b) $BH_3.SMe_2$, $NaBH_4$ (5 mol%), THF; (c) $BH_3.SMe_2$, $NaBH_4$ (5 mol%), THF; (d) $Me_2C(OMe)_2$, TsOH, acetone; (e) **11**, LDA, THF; (f) DIBALH, $ZnCl_2$, THF; (g) TsOH, aq. MeOH; (h) TrCl, DMAP, pyridine, CH_2Cl_2; (i) $Me_2C(OMe)_2$, TsOH; (j) Ac_2O, NaOAc, 130ºC; (k) $LiAlH_4$, Et_2O; (l) i. $SOCl_2$, ii. (–)-menthol; (m) MeMgI.

At this point in the synthesis, sufficient natural product was available to determine the relative stereochemistry as *syn* and thus all subsequent efforts focused on this series. The synthetic route to pavettamine, identified by retrosynthetic analysis required the linkage of two of the C_5 building blocks by means of an amide bond. The formation of the amide bond in turn meant that the C_5 alcohol **18a** had to be converted to an amine as well as into a carboxylic acid.

The C_5 unit **18a** was firstly functionalised to the carboxylic acid **19** by oxidation with TEMPO[19] and $NaOCl$-$NaClO_2$ and, secondly, to an amine **22** by consecutive functional group transformations of the primary hydroxyl group in **18a** to the *O*-Ts derivative **20** followed by an S_N2 reaction with sodium azide to give the azido product **21** which yielded the required amine **22** on reduction with $LiAlH_4$ (Scheme 4).

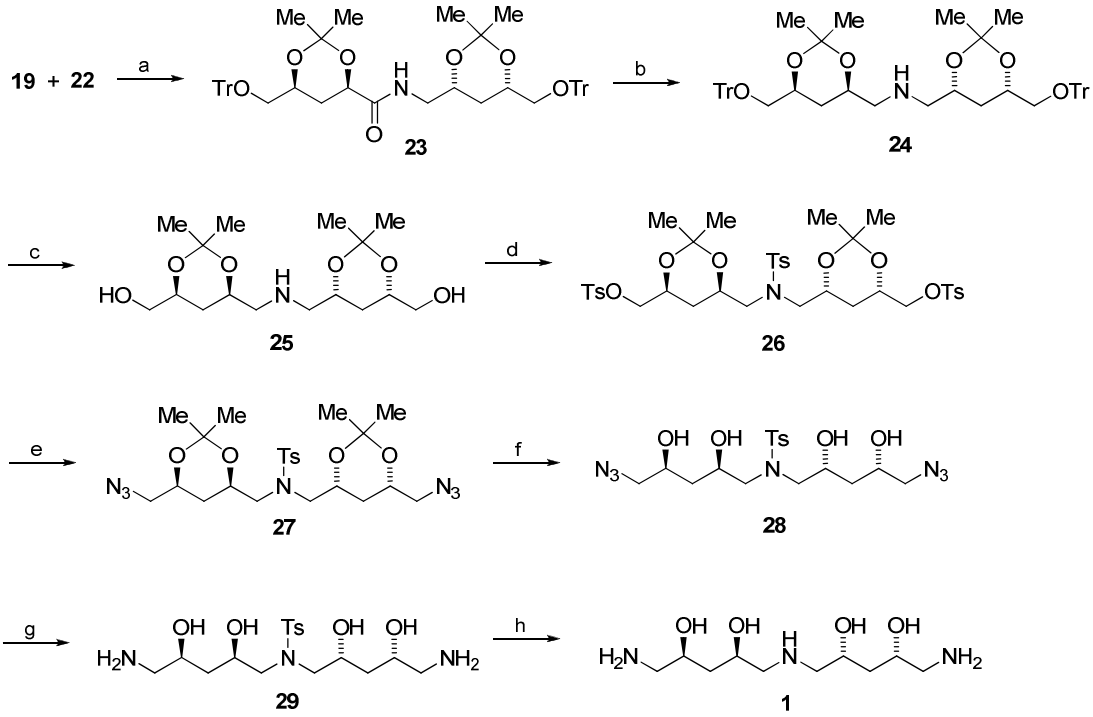


Scheme 4. Functionalisation of the C_5 unit in preparation of coupling

Reagents: (a) TEMPO, $NaClO_2$, NaOCl; (b) TsCl, DMAP, pyridine; (c) NaN_3, DMF; (d) $LiAlH_4$, Et_2O.

Preparation of the C_{10} unit is shown in Scheme 5. The amine and carboxylic acid were linked to give amide **23** using the peptide coupling agent 1,1′-carbonyldiimidazole. Reduction of the amide bond to the secondary amine **24** was achieved using $LiAlH_4$ in refluxing toluene. Attempted reduction using $LiAlH_4$ in THF or Et_2O failed and only starting material was recovered. Using $BH_3.SMe_2$ complex, the amide appeared to reduce as evidenced by the absence of the carbonyl ^{13}C signal, but the resulting product did not have the simplified ^1H and ^{13}C NMR spectra associated with the C_2 symmetrical product **24**. Apparently, an extremely stable boron complex was formed which on treatment with TMEDA gave the amine **24**, but in poor yield. Removal of the triphenylmethyl protecting group was achieved using sodium in liquid ammonia to give compound **25**. The only outstanding steps at this juncture were conversion of the hydroxyl termini to amino groups and acetonide deprotection. A number of possibilities existed for the sequence of functional group conversions and deprotection reactions.

Tosylation of compound **25** was first carried out, which resulted in both *O*- and *N*-tosylation to give compound **26**. Reaction with NaN_3 gave the diazide **27**. Initially, this diazide was reduced to the diamine using catalytic hydrogenation over Pd-C followed by *N*-tosyl removal by sodium in liquid ammonia reduction and attempted acetonide removal as the final step. This final acetonide removal proved to be unsuccessful and recovery of any product from the reaction was hampered by the complete water solubility of the desired product. This failure led to a change in the order of the steps and removal of the acetonide protecting group was carried out successfully on the diazide **27** to give the tetraol compound **28**. Reduction of this compound under H_2 pressure (5 atm) using Pd-C as catalyst yielded the diamine **29**. The final reductive cleavage of the *N*-tosyl group involved once again a sodium in liquid ammonia reduction. Clean-up of the final product was achieved using a nitrile SPE column to remove extraneous organic material and a Sephadex G10 column to separate inorganic salts.



Scheme 5. Preparation of C_{10} unit and functionalisation to pavettamine (**1**)
Reagents: (a) 1,1′-CDI, DMF; (b) $LiAlH_4$, toluene; (c) Na, liq. NH_3; (d) *p*-TsCl, DMAP; (e) NaN_3, DMF; (f) p-TsOH, aq. MeOH; (g) 10% Pd-C, H_2; (h) Na, liq. NH_3.

Thin layer chromatography of natural pavettamine **1** and the synthetic compound confirmed identical R_f values for both. ^1H and ^{13}C NMR data of the two compounds proved to be identical. In addition, optical rotation measurements on the synthetic compound showed the sign of rotation to be minus, as found for the natural product. Thus, through synthesis of this compound, the absolute stereochemistry of the natural product pavettamine is established as that shown in **1**.

3. Experimental

3.1 General methods

Air and/or moisture sensitive reactions were carried out under an atmosphere of argon in glassware pre-dried at temperatures above 100°C. All reagents were of reagent grade and were used without any further purification. When necessary, solvents and reagents were dried according to standard methods prior to use. Solvents used for chromatography or extractions were distilled. Analytical TLC was carried out with precoated aluminium-backed plates (Merck silicagel 60 F_{254}) visualised under UV light (λ=254 nm) and stained using aqueous acidic ammonium heptamolybdate(IV) reagent, cerium(IV) sulfate-sulfuric acid reagent or ninhydrin. Column chromatography was performed on Merck silica gel 60 (70-230 mesh).

Optical rotations were determined on a Perkin Elmer 341 polarimeter with a sodium lamp at 25°C. Specific rotations are given in units of 10^{-1} deg.g^{-1}.cm^2 and concentrations, *c* are reported in g/100 ml. High resolution fast atom bombardment (FAB) mass spectra were recorded by Dr. L. Fourie, University of Potchefstroom, on a VG 7070-E spectrometer (Xe beam, *m*-nitrobenzyl alcohol matrix, detection of positive ions with *m/z*>99). Electrospray-mass spectrometry (ES-MS) analyses were carried out in Cambridge, UK on a Bruker BioApex 47e Fourier-Transform Ion Cyclotron-Resonance mass spectrometer (Bruker Analytical Systems, Billerica, MA, USA) equipped with an infinity cell ion trap and using an external electrospray ion source (Analytica, Bamford, CT, USA) with an IRIS Hexapole ion guide.

Nuclear magnetic resonance (NMR) spectra were measured for $CDCl_3$ solutions (unless otherwise indicated) on Bruker AMX-300 (7.0 T) or AVANCE-500DRX (11.7 T) spectrometers. Proton-proton coupling constants (*J*) are given in Hz. Spectral coupling patterns are designated as follows: S/s: singlet; D/d: doublet; T/t: triplet; Q/q: quartet; m: multiplet; br: broad signal; The assignments of the signals in the ^{1}H NMR spectra are based on first-order analysis of the spin systems and when required were confirmed by ^{1}H{^{1}H} decoupling experiments and two-dimensional (2-D) (^{1}H,^{1}H) homonuclear chemical shift correlation (COSY) experiments. The ^{13}C chemical shifts were obtained from proton-decoupled spectra. The multiplicities of the different ^{13}C resonances were assigned through the proton-decoupled DEPT pulse sequence. The signals of the proton-bearing carbon atoms were correlated with specific proton resonances in 2-D heteronuclear chemical shift correlation (HETCOR) experiments utilizing the one-bond (^{13}C,^{1}H) spin-spin couplings. The long-range (^{1}H,^{13}C) connectivity patterns were established in inverse HMBC experiments. Standard Bruker programs were used in all experiments.

*3.2 (2S,4R,8R,10S)-1,11-Diamino-6-aza-undecane-2,4,8,10-tetraol (≡natural pavettamine) (**1**)*

$[\alpha]_D$ −19.5 (*c* 1.2, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 4.057 (ddd, 1H, $J_{4,5a}$ 10.0 $J_{4,5b}$ 2.8 $J_{4,3}$ 6.3, H-4), 3.952 (ddd, 1H, $J_{2,1a}$ 9.4 $J_{2,1b}$ 3.1 $J_{2,3}$ 6.5, H-2), 3.143 (dd, 1H, $J_{5a,5b}$ 13.0 $J_{5b,4}$ 2.9, H-5b), 3.058 (dd, 1H, $J_{1a,1b}$ 13.0 $J_{1b,2}$ 3.0, H-1b), 3.000 (dd, 1H, $J_{5a,5b}$ 13.0 $J_{5a,4}$ 10.0, H-5a), 2.851 (dd, 1H, $J_{1a,1b}$ 13.2 $J_{1a,2}$ 9.5, H-1a), 1.679 (2H, m, H-3); ^{13}C NMR (125 MHz, D_2O): δ 67.18D (C-2), 66.27D (C-4), 54.56T (C-5), 46.65T (C-1), 40.97T (C-3); HRMS (ESI): *m/z* 525.3559 $(2M+Na)^+$; calcd for $C_{20}H_{50}N_6O_8Na$: 525.3588. *m/z* 274.1743 $(M+Na)^+$; calcd for $C_{10}H_{25}N_3O_4Na$: 274.1743. *m/z* 252.1920 $(M+H)^+$; calcd for $C_{10}H_{26}N_3O_4$: 252.1923.

*3.3 (2S,4R,8R,10S)- 6-Aza-6-(t-butoxycarbonyl)-1,11-di[(t-butoxycarbonyl)amino]- undecane-2,4,8,10-tetraol (**2**)*

Di-*t*-butyl dicarbonate (Boc_2O)(120 mg, 0.55 mmol) was added to a solution of a sample of natural pavettamine (**1**) (20 mg) and K_2CO_3 (148 mg) in aqueous dioxane (1:1, 4 ml) and the reaction stirred for 16 h at rt. The solvents were evaporated under reduced pressure and the residue dried *in vacuo*. The solid residue was extracted with CH_2Cl_2 (2x10 ml), the CH_2Cl_2 solution dried (Na_2SO_4) and evaporated to give the tri-Boc derivative (**2**) (12 mg) as an oil. R_f = 0.28 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.945 (dd, 2H, $J_{NH,1a}$ 6.2, $J_{NH,1b}$ 5.6, NH), 4.117 (m, 2H, $J_{4,5}$ 3.7 $J_{4,3}$ 5.5, H-4), 3.952 (m, 2H, $J_{2,3}$ 5.7 $J_{2,1a}$ 3.5 $J_{2,1b}$ 6.7, H-2), 3.268 (d, 4H, $J_{5,4}$ 3.7, H-5), 3.235 (ddd, 2H, $J_{NH,1a}$ 6.2 $J_{1a,1b}$ 14.1 $J_{2,1a}$ 3.5, H-1a), 3.076 (ddd, 2H, $J_{NH,1b}$ 5.6 $J_{1a,1b}$ 14.1 $J_{2,1b}$ 6.7, H-1b), 1.524 (dd, 4H, $J_{3,4}$ 5.5 $J_{3,2}$ 5.7, H-3), 1.448 (s, 9H, C(CH_3)$_3$), 1.431 s (s, 18H, C(CH_3)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.08S (CO), 80.70S and 79.76S (O*C*$(CH_3)_3$), 71.69D (C-2), 71.08D (C-4), 56.02T (C-5), 47.16T (C-1), 37.94T (C-3), 28.49Q and 28.45Q (C(*C*H_3)$_3$). HRMS (ESI): *m/z* 574.3296 $(M+Na)^+$; calcd for $C_{25}H_{49}N_3O_{10}Na$: 574.3316.

*3.4 (2S,4R,8R,10S)-6-Aza-6-(t-butoxycarbonyl)-1,11-di[(t-butoxycarbonyl)amino]-2,4:8,10-di-O-iso-propylidene-undecane-2,4,8,10-tetraol (**3**)*

2,2-Dimethoxypropane (0.5 ml) and *p*-TsOH (1 mg) were added to a solution of the tri-Boc derivative (**2**) (12 mg) in acetone (2 ml) and the reaction stirred at rt for 1 h. The reaction was neutralised with Et_3N (0.1 ml) and the solvents evaporated. The residue was purified by column chromatography using EtOAc-hexane (2:3) as eluant to give the diacetonide (**3**) (6 mg) as an oil. R_f = 0.28 (EtOAc-hexane 2:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.77 (br, 2H, NH), 4.05 (br m, 2H, H-4), 3.900 (m, 2H, H-2), 3.37 (br m, 2H, H-5a), 3.267 (ddd br, 2H, $J_{1a,1b}$ 13.7, $J_{1a,NH}$ 6.5, $J_{1a,2}$ 3.4, H-1a), 3.15 (m br, 2H, H-5b), 3.014 (ddd, 2H, $J_{1a,1b}$ 13.7, $J_{1b,2}$ 6.7, $J_{1b,NH}$ 5.2, H-1b), 1.430 (s, 27H, C(CH_3)$_3$), 1.379 (s, 6H, C(CH_3)$_2$),

1.353 (s, 6H, C(C*H*$_3$)$_2$), 1.130 (ddd, 2H, $J_{3a,3b}$ 11.9, $J_{3b,2}$ 11.9, $J_{3b,4}$ 11.9, H-3b). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.06S and 155.70S (CO), 98.73S ((CH$_3$)$_2$*C*), 79.72S and 79.34S (O*C*(CH$_3$)$_3$), 68.12D (C-2 and C-4), 54.02T and 53.57T (C-5), 45.46T (C-1), 31.46T and 31.16T (C-3), 30.00Q ((*C*H$_3$)$_2$C), 28.44Q (C(*C*H$_3$)$_3$), 19.87Q and 19.71Q ((*C*H$_3$)$_2$C). HRMS (FAB): *m/z* 631.4042 (M^+); calcd for $C_{31}H_{57}N_3O_{10}$: 631.4044.

*3.5 Diethyl (2S)-malate (**4**)*

(2*S*)-Malic acid (100 g, 0.746 mol) was suspended in a mixture of $CHCl_3$-EtOH (3:4, 350 ml). Amberlite IR120 resin (H^+ form, 40 g) was added and the mixture was heated under Dean-Stark reflux conditions. After reaction the resin beads were removed by filtration and washed with $CHCl_3$. The washings were added to the filtrate and the solvent was removed under reduced pressure. High vacuum distillation (115°C/1 mmHg) afforded diethyl malate (**4**) (132 g, 94%). $[\alpha]_D$ –10.6 (neat). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.449 (dd, 1H, *J* 4.7, 6.0, H-2), 4.248 (dq, 1H, *J* 10.9, 7.2, OC*H*$_2$CH$_3$), 4.229 (dq, 1H, *J* 10.9, 7.2, OC*H*$_2$CH$_3$), 4.200 (q, 2H, *J* 7.0, OC*H*$_2$CH$_3$), 3.52 (s, 1H, OH), 2.808 (dd, 1H, *J* 16.3, 4.7, H-2a), 2.751 (dd, 1H, *J* 16.3, 6.0, H-2b), 1.270 (t, 3H, *J* 7.0, Me), 1.235 (t, 3H, *J* 7.0, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.26S and 170.38S (C-1 and C-4), 67.25D (C-2), 61.85T and 60.83T (2 x CH_2O), 38.69T (C-3), 14.00Q (2 x CH_3).

*3.6 Ethyl (3S)-3,4-dihydroxybutanoate **(5)***

BH_3-SMe_2 (251 mmol, 25.1 ml) was added dropwise over 30 min. to a stirred solution of diethyl (*S*)-malate (**4**) (46.4 g, 0.244 mol) in dry THF (500 ml). After 35 min the solution was cooled in an ice-bath for 10 min. $NaBH_4$ (0.462 g, 12.2 mmol) was added and when the exothermic reaction subsided, the reaction was removed from the ice-bath and stirred at rt for an additional 40 min. The reaction was quenched by addition of EtOH (85 ml) and *p*-TsOH (2.32 g, 12.2 mmol) and stirring at rt for 35 min. The mixture was then evaporated under reduced pressure on a rotary evaporator at 45°C. The resulting liquid was dissolved in benzene-EtOH (1:1, 500 ml) and concentrated. Benzene (400 ml) was added to the residue and concentrated again. This process was repeated twice more. The resulting oil was purified by column chromatography using EtOAc to afford ethyl (3*S*)-3,4-dihydroxybutanoate (**5**) (28.7 g, 79%). $[\alpha]_D$ +6.2 (*c* 1.3, $CHCl_3$)(lit.,[9] $[\alpha]_D$ +6.22 (*c* 1.22, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.117 (q, *J* 7.0, OCH_2), 4.083 (dddd, 1H, *J* 8.0, 6.5, 4.9, 3.4, H-3), 3.780 (m, 1H, OH), 3.610 (dd, 1H, *J* 11.4, 3.4, H-4a), 3.464 (dd, 1H, *J* 11.4, 6.5, H-4b), 3.171 (s, 1H, OH), 2.481 (dd, 1H, *J* 16.3, 8.0, H-2a), 2.429 (dd, 1H, *J* 16.3, 4.9, H-2b), 1.220 (t, 3H, *J* 7.2, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.41S (C-1), 68.57D (C-3), 65.68T (C-4), 60.77T (CH_2O), 37.77T (C-2), 14.02Q (CH_3).

*3.7 (3S)-3-Hydroxy-4-butanolide (**6**)*

The reduction of the diester **4** (38.0 g, 200 mmol) with BH_3.SMe_2, (10M, 20.6 ml, 206 mmol) and $NaBH_4$ (0.39 g, 10.3 mmol) as described above but using an excess of *p*-TsOH (2.96 g, 15.6 mmol) in the work-up, gave after column chromatography with hexane-EtOAc (1:18) as eluent, the lactone (**6**) as a colourless oil (14.7 g, 72%); R_f = 0.42 (hexane-EtOAc 1:18); $[\alpha]_D$ –40.8 (*c* 1.2, $CHCl_3$) (lit.,[10] $[\alpha]_D$ –80.2 (*c* 3.0, EtOH)); ν_{max} 1782 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.598 (m, 1H, *J* 5.9, 4.4, 1.8, 1.5, H-3), 4.354 (dd, 1H, *J* 10.4, 4.4, H-4b), 4.232 (ddd, 1H, *J* 10.4, 1.8, 1.0, H-4a), 3.82 (br s, 1H, 2-OH), 2.689 (dd, 1H, *J* 17.9, 5.9, H-2b), 2.433 (ddd, 1H, *J* 17.9, 1.6, 1.0 H-2a). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.32S (C-1), 76.33T (C-4), 67.17D (C-3), 37.60T (C-2). HRMS (FAB): *m/z* 102.0317 (M^+); calcd for $C_4H_6O_3$: 102.0317.

*3.8 Ethyl (3S)-3,4-dihydroxy-3,4-O-isopropylidene-butanoate (**7**)*

Ethyl (3*S*)-3,4-dihydroxybutanoate (**5**) (21.6 g, 0.146 mol) was dissolved in acetone (78 ml) and 2,2-dimethoxypropane (20 ml, 0.164 mol) and *p*-TsOH (1.4 g, 7.4 mmol) were added. The reaction was allowed to stir for 30 min at rt and then neutralized by addition of Et_3N (3 ml). The solvent was removed and the residue was purified by column chromatography (EtOAc) to afford ethyl (3*S*)-3,4-dihydroxy-3,4-*O*-isopropylidene-butanoate (**7**) (25.30 g, 92%). R_f = 0.70 (EtOAc). $[\alpha]_D$ +19.2 (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.373 (dddd, 1H, *J* 7.2, 6.2, 6.2, 5.9, H-3), 4.070 (q, 2H, *J* 7.2, OCH_2CH_3), 4.069 (dd, 1H, *J* 8.3, 5.9, H-4a), 3.568 (dd, 1H, *J* 8.3, 6.2, H-4b), 2.625 (dd, 1H, *J* 15.8, 6.2, H-2a), 2.426 (dd, 1H, *J* 15.8, 7.2, H-2b), 1.326 (s, 3H, $(CH_3)_2C$)), 1.269 (s, 3H, $(CH_3)_2C$)), 1.180 (t, 3H, *J* 7.2, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.46S (C-1), 109.05S ($(CH_3)_2C$), 71.98D (C-3), 69.07T (C-4), 60.53T (CH_2O), 38.89T (C-2), 26.78Q and 25.42Q ($(CH_3)_2C$), 14.05Q (CH_3CH_2). HRMS (FAB): *m/z* 189.1127 $(M+H)^+$; calcd for $C_9H_{17}O_4$: 189.1126.

*3.9 Methyl (3S)-3,4-O-isopropylidene-3,4-dihydroxybutanoate (**8**)*

p-TsOH (1.86 mmol, 0.35 g) was added to a solution of the lactone (**6**) (61.2 g, 600 mmol) in acetone (120 ml) and 2,2-dimethoxypropane (75 ml). The reaction was stirred at rt for 14 h and then neutralized by addition of Et_3N (10 ml). The solvent was evaporated and the residue was purified by column chromatography with hexane-EtOAc (2:3) to yield the methyl ester (**8**) (86.4 g, 83%) as a colourless liquid; R_f = 0.56 (hexane-EtOAc 2:3); $[\alpha]_D$ +17.7 (*c* 0.30, $CHCl_3$), (lit.,[9] $[\alpha]_D$ +18.2 (*c* 5.0, $CHCl_3$)); ν_{max} 1737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.417 (m, 1H, *J* 7.0, 6.5, 6.5, 5.9, H-3), 4.101 (dd, 1H, *J* 8.3, 5.9, H-4b), 3.649 (s, 3H, OMe), 3.596 (dd, 1H, *J* 8.3, 6.5, H-4a), 2.662 (dd, 1H, *J* 15.9, 6.4, H-2b), 2.474 (dd, 1H, *J* 15.9, 7.0, H-2a), 1.360 (s, 3H, $(CH_3)_2C$)), 1.303 (s, 3H, $(CH_3)_2C$)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.96S (C-1), 109.17S ($(CH_3)_2C$), 71.99D (C-3), 69.08T (C-4), 51.67Q (OMe), 38.73T (C-2), 26.81Q and 25.44Q ($(CH_3)_2C$). HRMS (FAB): *m/z* 175.0971 $(M+H)^+$; calcd for $C_8H_{15}O_4$: 175.0970.

*3.10 (1R,2S,5R)-(–)-Menthyl (S)-p-toluenesulfinate (**10**)*

The powdered sodium salt of anhydrous p-toluenesulfinic acid (**9**) (80.0 g, 0.44 mol) was added in small portions to a solution of thionyl chloride (100 ml, 1.40 mol) in benzene (300 ml) at 0°C. The reaction was allowed to reach rt and the solvent was removed under reduced pressure. Excess thionyl chloride was removed by addition of benzene (200 ml) and evaporation under reduced pressure. The residue was diluted with anhydrous Et_2O (500 ml) (formation of a white precipitate of sodium chloride) and cooled at 0°C. A solution of (–)-menthol (69.4 g, 0.44 mol) in pyridine (70 ml) was added dropwise. After the addition was complete the mixture was stirred for 1 h at rt and hydrolysed with H_2O (200 ml). The organic layer was washed with 10% HCl (200 ml) and saturated brine (100 ml), dried over Na_2SO_4 and concentrated. The residue was diluted with acetone (200 ml), ~5 drops 10M HCl were added, and allowed to crystallise at −20°C. After the filtration of the first crop of crystals, the mother liquor was concentrated to ~50 ml, 1 drop 10M HCl was added and this was again allowed to crystallise at −20°C. This operation was repeated 3-4 times in total. Hexane was used to dilute the increasingly viscous mother liquor to improve crystallisation. The combined crops were finally recrystallised from hot acetone to give the pure (*S*)-sulfinate (**10**) as a white crystalline material (102.5 g, 78%). mp 108-109°C (lit.,[20] 106-107°C). $[\alpha]_D^{21}$ −201 (*c* 2.5, acetone) (lit.,[21] $[\alpha]_D^{21}$ −201 (*c* 2.0, acetone)).

*3.11 (R)-(+)-Methyl p-tolylsulfoxide (**11**)*

A solution of methyl magnesium iodide [prepared from iodomethane (114 g, 803 mmol), and magnesium (16.0 g, 658 mmol)] in Et_2O (400 ml) was slowly added by cannula to a solution of (–)-(*S*)-menthyl-*p*-toluenesulfinate (**10**) (140 g, 475 mmol) in dry benzene (400 ml) between 0–10°C.

After addition, the mixture was stirred at rt for 2 h and then hydrolyzed with saturated aq. NH_4Cl solution (200 ml). The aqueous solution was extracted with Et_2O (2x400 ml). The organic layers were washed with saturated brine (200 ml), dried (Na_2SO_4) and concentrated in vacuo. The oily residue was mixed with hot hexane until formation of a light white cloudy precipitate and crystallization occured overnight on cooling to −5ºC. The solid material was recrystallised from Et_2O-hexane at −5 ºC affording white crystals of (**11**) (57.4 g, 78%), m.p. 75-76°C (lit.,[22] 73-74.5ºC). $[\alpha]_D^{21}$ +192 (*c* 4.0, $CHCl_3$), $[\alpha]_D^{21}$ +146 (*c* 2.0, acetone), (lit.,[13,14] $[\alpha]_D^{21}$ +192 (*c* 1.2, $CHCl_3$), lit.,[22] $[\alpha]_D^{21}$ +145.5 (acetone)).

*3.12 (S(R),4S)-4,5-O-Isopropylidene-1-(p-tolylsulfinyl)-2-pentanone (**12**)*

n-Butyllithium (1.5M in hexanes, 96.7 ml, 0.145 mol) was added to a solution of diisopropylamine (22.1 ml, 0.158 mol) in dry THF (160 ml) at –78°C under argon. The mixture was stirred for 30 min at –78°C and the solution was then allowed to reach –30°C and (*R*)-(+)-methyl *p*-tolyl sulfoxide (**11**) (20.77 g, 0.135 mol) in dry THF (160 ml) was added. The solution went bright yellow at this stage. The mixture was stirred for 30 min while warming to 0°C, after which it was cooled to –40°C and stirred for 5 min. Ethyl (3*S*)-3,4-dihydroxy-3,4-*O*-isopropylidene-butanoate (**7**) (12.37 g, 65.7 mmol) in dry THF (160 ml) was added slowly. On completion of addition the temperature was allowed to rise to rt and the reaction mixture was stirred for an additional 2 h. The reaction mixture was quenched by addition of saturated NH_4Cl solution and acidified with 1M HCl to pH 6. The mixture was extracted with EtOAc (3x100 ml), and the combined organic layers were washed with water and brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave viscous oil that was purified by column chromatography (hexane-EtOAc 1:9) to afford ketosulfoxide (**12**) (12.46 g, 64%), m.p. 77-79°C. R_f = 0.72 (hexane-EtOAc 1:9). $[\alpha]_D$ +150.0 (*c* 1.20, $CHCl_3$); ν_{max} 1720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48-7.24 (m, 4H, ArH), 4.333 (m, 1H, *J* 6.5, 6.3, 6.0, H-4), 4.037 (dd, 1H, *J* 8.3, 6.0, H-5b), 3.805 (s, 2H, H-1), 3.395 (dd, 1H, *J* 8.3, 6.5, H-5a), 2.888 (dd, 1H, *J* 17.1, 6.3, H-3b), 2.574 (dd, 1H, *J* 17.1, 6.5, H-3a), 2.355 (s, 3H, ArCH_3), 1.314 (s, 3H, (CH_3)$_2$C)), 1.256 (s, 3H, (CH_3)$_2$C). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.27S (C-2), 141.93S, 139.17S, 129.85D and 123.78D (ArC), 108.73S ((CH$_3$)$_2$*C*), 70.90D (C-4), 68.80T (C-5), 67.68T (C-1), 48.82T (C-3), 26.52Q and 25.17Q ((*C*H$_3$)$_2$C), 21.14Q (Ar*C*H$_3$). HRMS (FAB): *m/z* 297.1160 $(M+H)^+$; calcd for $C_{15}H_{21}SO_4$: 297.1161.

*3.13 (S(R),2R,4S)-4,5-O-Isopropylidene-1-(p-tolylsulfinyl)-pentane-2,4,5-triol (**13a**)*

$ZnCl_2$ (8.24 g, 60.5 mmol) was flame-dried under vacuum in a 2-necked flask and cooled and, dry THF (300 ml) was added. (S(*R*),4*S*)-4,5-*O*-isopropylidene-1-(*p*-tolylsulfinyl)-2-pentanone (**12**) (4.48 g, 15.1 mmol) in dry THF (100 ml) was added and this was allowed to stir at rt under argon for 2 h. The reaction mixture was cooled to –78°C. After stirring at –78°C for 10 min, DIBALH (8.60 g, 10.8 ml, 60.5 mmol) was added slowly. The reaction was allowed to stir at low temperature for 1.5 h (TLC control) and then quenched by careful addition of saturated NH_4Cl solution at –78°C. The reaction was allowed to warm to rt and was extracted once with Et_2O. The organic solvent was removed under reduced pressure and the residue partitioned between water (pH 5) and EtOAc (3x50 ml). The organic solution was washed with brine, dried (Na_2SO_4) and evaporated to give a white solid. This material was purified by column chromatography (elution EtOAc) to afford the triol (**13a**) (3.38 g, 75%) as a single diastereomer, m.p. 87-89°C. Starting material (9%) was recovered. R_f = 0.33 (EtOAc). $[\alpha]_D$ +131.1 (*c* 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.55-7.29 (m, 4H, ArH), 4.317 (m, 1H, *J* 8.2, 7.8, 4.4, 3.9, 1.6, H-2), 4.252 (m, 1H, *J* 7.1, 7.0, 5.9, 4.9, H-4), 4.064 (dd, 1H, *J* 8.3, 5.9, H-5b), 3.922 (d, 1H, *J* 1.6, 2-OH), 3.583 (dd, 1H, *J* 8.3, 7.1, H-5a), 3.035 (dd, 1H, *J* 13.2, 7.8, H-1b), 2.822 (dd, 1H, *J* 13.2, 3.9, H-1a), 2.397 (s, 3H, ArCH_3), 1.878 (ddd, 1H, *J* 14.2, 8.2, 7.0, H-3b), 1.837 (ddd, 1H, *J* 14.2, 4.9, 4.4, H-3a), 1.386 (s, 3H, (CH_3)$_2$C), 1.318 (s, 3H, (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.76S, 140.36S, 130.01D and 124.02D (ArC), 109.27S ((CH$_3$)$_2$*C*), 73.96D (C-4), 69.34T (C-5),

66.74D (C-2), 62.97T (C-1), 39.89T (C-3), 26.79 Q and 25.63Q ((CH_3)$_2$C), 21.35Q (ArCH_3). HRMS (FAB): *m/z* 299.1316 $(M+H)^+$; calcd for $C_{15}H_{23}SO_4$: 299.1317.

3.14 (S(R),2S, 4S)- 4,5-O-Isopropylidene-1-(p-tolylsulfinyl)-pentane-2,4,5-triol (***13b***)

DIBALH (3.98 g, 30.0 mmol) was added by syringe to a solution of (S(*R*),4*S*)-4,5-*O*-isopropylidene-1-(*p*-tolylsulfinyl)-2-pentanone (**12**) (7.00 g, 20.0 mmol) in THF (120 ml) at –78°C. The reaction mixture was stirred at –78°C for 1 h, and then quenched by careful addition of saturated NH_4Cl solution at –78°C. The reaction was allowed to warm to rt and worked-up as described for compound **13a** above. Column chromatography of the oily residue using EtOAc as eluent gave the hydroxysulfoxide **13b** (4.69 g, 67%) as a white solid; m.p 104-106°C; R_f = 0.35 (EtOAc); $[\alpha]_D$ +197.4 (*c*, 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.29 (m, 4H, ArH), 4.689 (d, 1H, 2-OH), 4.306 (m, 1H, H-2), 4.152 (dddd,1H, *J* 7.5, 7.2, 6.0, 4.7, H-4), 4.017 (dd, 1H, *J* 8.0, 6.0, H-5a), 3.510 (dd, 1H, *J* 8.0, 7.2, H-5b), 2.975 (dd, 1H, *J* 13.4, 9.0, H-1a), 2.786 (dd, 1H, *J* 13.4, 2.2, H-1b), 2.376 (s, 3H, ArCH_3), 1.763 (ddd, 1H, *J* 14.0, 8.0, 4.7, H-3a), 1.691 (ddd, 1H, *J* 14.0, 7,5, 4.1, H-3b), 1.319 (s, 3H, (CH_3)$_2$C), 1.213 (s, 3H, (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.47S, 139.73S, 130.00D, 123.93D (ArC), 108.69S (CH_3)$_2C$), 73.18D (C-4), 69.52T (C-5), 64.49D (C-2), 62.53T (C-1), 40.32T (C-3), 26.81Q and 25.61Q ((CH_3)$_2$C), 21.29Q (ArCH_3). HRMS (FAB): *m/z* 299.1317 $(M+H)^+$; calcd for $C_{15}H_{22}SO_4$: 299.1317.

*3.15 (S(R),2R,4S)-1-(p-Tolylsulfinyl)-pentane-2,4,5-triol (**14a**)*

(S(*R*),2*R*,4*S*)-4,5-*O*-Isopropylidene-1-(*p*-tolylsulfinyl)-pentane-2,4,5-triol (**13a**) (5.05 g, 16.9 mmol) was dissolved in MeOH (150 ml) and water (50 ml) and *p*-TsOH (0.32 g) was added. The reaction was heated under reflux for 1.5 h, after which TLC indicated that no starting material remained. Et_3N (1 ml) was added to neutralize the acid and the solvents were removed under reduced pressure. The residue was dissolved in water (60 ml) and extracted with EtOAc (50 ml) to remove any starting material. The aqueous layer was then continuously extracted with EtOAc for 2 d. The EtOAc solution was dried (Na_2SO_4) and evaporated to leave (S(*R*),2*R*,4*S*)-1-(*p*-tolylsulfinyl)-pentane-2,4,5-triol (**14a**) (3.93 g, 90%) as an oil that solidified after drying under high vacuum, m.p. 140-142°C. $[\alpha]_D$ +186.8 (*c* 0.53, $CHCl_3$), $[\alpha]_D$ +82.4 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.24 (m, 4H, ArH), 4.315 (m, 1H, H-2), 3.903 (m, 1H, H-4), 3.563 (dd, 1H, *J* 11.4, 3.6, H-5b), 3.454 (dd, 1H, *J* 11.4, 6.2, H-5a), 3.077 (dd, 1H, *J* 13.3, 7.4, H-1b), 2.819 (dd, 1H, *J* 13.3, 4.3, H-1a), 2.354 (s, 3H, ArCH_3), 1.768 (m, 1H, H-3b), 1.712 (m, 1H, H-3a); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.94S, 139.90S, 130.10D and 124.18D (ArC), 71.07D (C-4), 67.16D (C-2), 66.33T (C-5), 62.62T (C-1), 39.13T (C-3), 21.35Q (ArCH_3). HRMS (FAB): *m/z* 259.1004 $(M+H)^+$; calcd for $C_{12}H_{19}SO_4$: 259.1004.

3.16 (S(*R*),2*S*,4*S*)-*1-(p-Tolylsulfinyl)-pentane-2,4,5-triol (**14b**)*

p-TsOH (0.15 g) was added to a solution of the protected sulfoxide **13b** (3.70 g, 12.0 mol) in MeOH (90 ml) and water (30 ml). The reaction was heated under reflux for 1.5 h, neutralised by addition of Et_3N (0.5 ml) and concentrated under reduced pressure. The residue was dissolved in water (30 ml) and the product continuously extracted with EtOAc to yield pure white crystals of **14b** (2.84 g, 89%); m.p 139-141°C; R_f = 0.43 ($CHCl_3$-MeOH 4:1); $[\alpha]_D$ +196.8 (*c*, 0.53, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.30 (m, 4H, ArH), 4.202 (dddd, 1H, *J* 10.2, 9.3, 3.6, 2.8, H-2), 3.784 (dddd, 1H, *J* 9.6, 6.5, 4.1, 4.1, H-4), 3.447 (dd, 1H, *J* 11.6, 4.1, H-5a), 3.353 (dd, 1H, *J* 11.6, 6.5, H-5b), 3.006 (dd, 1H, *J* 13.7, 2.8, H-1a), 2.812 (dd, 1H, *J* 13.7, 10.2, H-1b), 2.237 (s, 3H, ArCH_3), 1.538 (ddd, 1H, *J* 14.6, 9.3, 4.1, H-3a), 1.445 (ddd, 1H, *J* 14.6, 9.6, 3.6, H-3b), ^{13}C NMR (75 MHz, D_2O): δ 143.81S, 137.82S, 130.82D, 124.98D (ArC); 68.56D (C-4); 66.23T (C-5); 64.34D (C-2); 62.84T (C-1); 39.85T (C-3); 21.00Q (ArCH_3). HRMS (FAB): *m/z* 259.1004 $(M+H)^+$; calcd for $C_{12}H_{18}SO_4$: 259.1004.

*3.17 (S(R),2R,4S)-1-(p-Tolylsulfinyl)-5-(triphenylmethyloxy)pentane-2,4-diol (**15a**)*

4-Dimethylaminopyridine (DMAP) (0.36 g, 2.96 mmol) and triphenylmethyl chloride (4.64 g, 16.31 mmol) was added to a solution of (S(*R*),2*R*,4*S*)-1-(*p*-tolylsulfinyl)-pentane-2,4,5-triol (**14a**) (3.83 g, 14.82 mmol) in CH_2Cl_2 (60 ml) and pyridine (4.8 ml, 59.3 mmol) and the reaction mixture stirred at rt for 2 d (TLC control). The reaction mixture was washed with 1M HCl (4x100 ml) and then with brine (100 ml). The organic layer was dried (Na_2SO_4) and evaporated to leave a yellow, viscous oil which was purified by column chromatography (elution hexane-EtOAc 1:4) to afford (S(*R*),2*R*,4*S*)-1-(*p*-tolylsulfinyl)-5-(triphenylmethyloxy)pentane-2,4-diol (**15a**) (7.26 g, 98%), m.p.74-76°C. R_f = 0.38 (hexane-EtOAc 1:4). $[\alpha]_D$ +89.3 (*c* 0.98, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.18 (m, 19H, ArH), 4.34 (m, 2H, H-2 and OH), 4.016 (m, 1H, H-4), 3.26 (br s, 1H, OH), 3.095 (m, 2H, H-5), 3.017 (dd, 1H, *J* 13.2, 8.0, H-1b), 2.772 (dd, 1H, *J* 13.2, 3.6, H-1a), 2.394 (s, 3H, ArC*H*$_3$), 1.690 (dd, 2H, *J* 6.2, 6.2, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.69S, 141.77S, 140.38S, 130.00D, 128.55D, 127.79D, 127.04D and 124.02D (ArC), 86.66S (Ph$_3$*C*O), 70.41D (C-4), 68.10D (C-2), 67.40T (C-5), 63.04T (C-1), 39.37T (C-3), 21.34Q (Ar*C*H$_3$). HRMS (FAB): *m/z* 501.2099 $(M+H)^+$; calcd for $C_{31}H_{33}SO_4$: 501.2100.

*3.18 (S(R),2S,4S)-1-(p-Tolylsulfinyl)-5-(triphenylmethyloxy)pentane-2,4-diol (**15b**)*

DMAP (0.26 g, 2.14 mmol) and triphenylmethyl chloride (3.21 g, 11.5 mmol) was added to a solution of the triol **14b** in CH_2Cl_2 (60 ml) and pyridine (4.2 ml, 54.2 mmol). The reaction mixture was refluxed for 6 h, allowed to cool, and washed with 3M HCl (100 ml) and then with brine (2x100 ml). The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography of the residue using EtOAc as eluent yielded the *O*-trityl derivative **15b** (4.98 g, 95%); m.p. 143-145°C; R_f = 0.58 (EtOAc); $[\alpha]_D$ +112.6 (*c*, 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 - 7.17 (m, 19H, ArH), 4.651 (d, 1H, *J* 4.1, 2-OH), 4.467 (m, 1H, H-2), 4.028 (m, 1H, H-4), 3.286 (d, 1H, *J* 3.9, 4-OH), 3.085 (d, 2H, *J* 5.4, H-5), 3.007 (dd, 1H, *J* 13.3, 9.8, H-1a), 2.748 (dd, 1H, *J* 13.3, 2.2, H-1b), 2.392 (s, 3H, ArCH_3), 1.624 (ddd, 1H, *J* 14.0, 9.1, 3.6, H-3a), 1.540 (ddd, 1H, *J* 14.0, 8.3, 2.8, H-3b); After D_2O exchange: 4.467 (dddd, 1H, *J* 9.8, 8.3, 3.6, 2.2, H-2), 4.028 (dddd, 1H, *J* 9.1, 6.5, 4.9, 2.8, H-4), 3.095 (dd, 1H, *J* 9.6, 4.9, H-5a), 3.073 (dd, 1H, *J* 9.6, 6.5, H-5b); ^{13}C NMR (75 MHz, $CDCl_3$): 143.84S, 141.50S, 139.58S, 130.00D, 128.58D, 127.70D, 126.89D, 123.98D (ArC), 86.49S (Ph$_3$*C*O), 67.65T (C-5); 67.39D (C-4), 63.49T (C-1), 63.30D (C-2), 40.05T (C-3), 21.28Q (ArCH_3). HRMS (FAB): *m/z* 501.2098 $(M+H)^+$; calcd for $C_{31}H_{33}SO_4$: 501.2100.

*3.19 (S(R),2R,4S)-2,4-O-Isopropylidene-1-(p-tolylsulfinyl)-5-(triphenylmethyloxy)pentane-2,4-diol (**16a**)*

p-TsOH (25 mg) was added to a stirred solution of (S(*R*),2*R*,4*S*)-1-(*p*-tolylsulfinyl)-5-(triphenylmethyloxy)pentane-2,4-diol (**15a**) (1.00 g, 1.997 mmol) in 2,2-dimethoxypropane (5 ml) and acetone (20 ml). Et_3N (1 ml) was added after 35 min and the solvent removed under reduced pressure. Column chromatography of the residue with hexane-EtOAc (1:1) as eluent afforded (S(*R*),2*R*,4*S*)-2,4-*O*-isopropylidene-1-(*p*-tolylsulfinyl)-5-triphenylmethyloxypentane-2,4-diol (**16a**) (0.96 g, 89%). R_f = 0.51 (hexane-EtOAc 1:1). $[\alpha]_D$ +25.2 (*c* 1.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.26 (m, 19H, ArH), 4.085 (m, 1H, H-2), 3.963 (m, 1H, H-4), 3.221 (dd, 1H, *J* 9.3, 5.2, H-5b), 3.140 (dd, 1H, *J* 13.2, 6.9, H-1b), 2.961 (dd, 1H, *J* 9.3, 6.0, H-5a), 2.752 (dd, 1H, *J* 13.2, 5.4, H-1a), 2.399 (s, 3H, ArC*H*$_3$), 1.736 (ddd, 1H, *J* 12.7, 2.3, 2.3, H-3), 1.370 (ddd, J 12.6, 12.6, 12.6, H-3), 1.325 (s, 3H, (C*H*$_3$)$_2$C), 1.293 (s, 3H, (C*H*$_3$)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.91S, 141.62S, 140.26S, 129.78D, 128.68D, 127.73D, 126.95D and 124.41D (ArC), 98.87S ((CH$_3$)$_2$*C*), 86.52S (Ph$_3$*C*O), 68.19D (C-4), 67.02T (C-5), 63.91D (C-2), 63.11T (C-1), 33.60T (C-3), 29.69Q ((*C*H$_3$)$_2$C), 21.36Q (Ar*C*H$_3$), 19.60Q ((*C*H$_3$)$_2$C). HRMS (FAB): *m/z* 540.2335 (M^+); calcd for $C_{34}H_{36}SO_4$: 540.2334.

*3.20 (S(R),2S,4S)-2,4-O-Isopropylidene-1-(p-tolylsulfinyl)-5-(triphenylmethyloxy)pentane-2,4-diol (**16b**)*

p-TsOH (0.15 g) was added to a stirred solution of (**15b**) (5.70 g, 11.4 mmol) in 2,2-dimethoxy-propane (28.6 ml) and acetone (120 ml). Et_3N (1 ml) was added after 35 min and the solvent removed under reduced pressure. Column chromatography of the residue with hexane-EtOAc (1:1) as eluent afforded the isopropylidene derivative (**16b**) (5.97 g, 97%) as a white solid, m.p. 113-115°C. R_f = 0.51 (hexane-EtOAc 1:1). $[\alpha]_D$ +68.0 (*c* 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 - 7.19 (m, 19H, ArH), 4.431 (dddd,1H, *J* 10.1, 9.8, 6.0, 3.2, H-2), 4.028 (dddd, 1H, *J* 9.1, 6.3, 6.3, 5.0, H-4), 3.285 (dd, 1H, *J* 9.8, 6.3, H-5a), 3.013 (dd, 1H, *J* 9.8, 5.0, H-5b), 2.814 (dd, 1H, *J* 13.2, 3.2, H-1a), 2.779 (dd, 1H, *J* 13.2, 10.1, H-1b), 2.387 (s, 3H, ArCH_3), 1.706 (ddd, 1H, J 12.9, 9.1, 6.0, H-3a), 1.594 (ddd, 1H, *J* 12.9, 9.8, 6.3, H-3b), 1.479 (s, 3H, (CH_3)$_2$C), 1.443 (s, 3H, (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.96S, 141.53S, 141.26S, 123.74D, 129.89D, 128.63D, 127.85D, 127.69D, 126.90D (ArC), 101.00S ((CH$_3$)$_2$*C*), 86.41S (Ph$_3$*C*O); 66.34T (C-5); 66.10D (C-4); 64.12T (C-1); 61.05D (C-2); 34.49T (C-3); 24.53Q and 24.84Q ((*C*H$_3$)$_2$C), 21.28Q (ArCH$_3$). HRMS (FAB): *m/z* 540.2334 (M^+); calcd for $C_{34}H_{36}SO_4$: 540.2334.

*3.21 (1RS,2R,4S)-1-Acetoxy-2,4-O-isopropylidene-1-(p-tolylsulfanyl)-5-(triphenylmethyloxy)-pentane-2,4-diol (**17a**)*

(S(*R*),2*R*,4*S*)-2,4-*O*-Isopropylidene-1-(*p*-tolylsulfinyl)-5-(triphenylmethyloxy)pentane-2,4-diol (**16a**) (0.40 g, 0.74 mmol) was dissolved in Ac_2O (20 ml) and NaOAc (0.43 g, 5.18 mmol) was added. The reaction was heated at 130-140°C in an oil bath for 4.5 h (TLC control). The Ac_2O was removed by repeated evaporation with toluene under reduced pressure. The residue was purified by column chromatography (elution hexane-EtOAc 4:1), to afford (1*RS*,2*R*,4*S*)-1-acetoxy-2,4-*O*-isopropylidene-1-(*p*-tolylsulfanyl)-5-triphenylmethyloxypentane-2,4-diol (**17a**) (0.36 g, 83%) as a mixture of diastereomers. R_f = 0.36 (hexane-EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.00 (m, 19H, ArH), 6.032 (d, *J* 5.7, H-1) and 5.992 (d, *J* 4.9, H-1), 4.14-3.94 (m, 2H, H-2 and H-4), 3.25 (m, 1H, H-5b), 3.00 (m, 1H, H-5a), 2.320 (s, 3H, ArCH_3), 2.053 (s, 3H, OAc), 1.399 (s, 6H, (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.77S and 169.61S (C=O), 144.00S, 138.52S, 138.42S, 134.16S, 133.72S, 129.80D, 129.69D, 128.72D, 128.31D, 127.74D and 126.96D (ArC), 99.15S ((CH$_3$)$_2$*C*), 86.50S (Ph$_3$*C*O), 83.24D and 82.84D (C-1), 70.52D and 69.92D (C-2), 68.18D (C-4), 67.28T and 67.15T (C-5), 30.51T (C-3), 29.87Q and 29.77Q ((*C*H$_3$)$_2$C), 21.13Q (Ar*C*H3), 20.96Q (OAc), 19.58 ((*C*H$_3$)$_2$C). HRMS (FAB): *m/z* 582.2440 (M^+); calcd for $C_{36}H_{38}SO_5$: 582.2440.

*3.22 (1RS,2S,4S)-1-Acetoxy-2,4-O-isopropylidene-1-(p-tolylsulfanyl)-5-(triphenylmethyloxy)-pentane-2,4-diol (**17b**)*

The protected sulfoxide **16b** (5.97 g, 11.0 mmol) was dissolved in (100 ml) and NaOAc (6.34 g) was added. The reaction was stirred for 5 h at 140°C. The Ac_2O was removed by repeated evaporation with toluene under reduced pressure. The residue was suspended in Et_2O (100 ml), filtered to remove salts and the filtrate evaporated. The residue was purified by column chromatography hexane-EtOAc (4:1) as eluent to give the *O*,*S*-acetal **17b**, an oil (4.50 g, 72%) as a mixture of diasteromers. R_f = 0.47 (hexane-EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 - 7.10 (m, 19H, ArH), 6.102 (d, *J* 4.1, H-1) and 6.084 (d, *J* 6.5, H-1), 4.15-4.00 (m, 2H, H-2 and H-4), 3.281 (dd, 1H, *J* 9.6, 6.5, H-5a), 3.277 (dd, 1H, *J* 9.6, 6.5, H-5a), 3.047 (dd, 1H, *J* 9.8, 4.7, H-5b), 2.342 (s, 3H, ArCH_3), 2.074 (s, 3H, OAc), 2.059 (s, 3H, OAc), 2.00-1.65 (m, 2H, H-3), 1.480 (s, 3H), 1.446 (s, 3H), 1.456 (s, 3H), and 1.376 (s, 3H) (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.63S and 169.56S (acetate CO); 144.04S, 138.45S, 138.36S, 133.81D, 129.74S, 129.72D, 129.68S, 128.67D, 127.69D, and 126.88D (ArC), 100.90S and 100.81S ((CH$_3$)$_2$*C*), 86.39S (Ph$_3$*C*O), 83.40D and 82.13D (C-1), 68.09D and 67.94D (C-4), 66.43T

(C-5), 66.22D and 66.38D (C-2), 31.67T and 30.84T (C-3), 24.96Q, 24.68Q, and 24.58Q ((CH_3)$_2$C), 20.89Q and 21.07Q (ArCH_3). HRMS (FAB): *m/z* 582.2442 (M^+); calcd for $C_{36}H_{38}SO_5$: 582.2440.

*3.23 (2R,4S)-2,4,O-Isopropylidene-5-(triphenylmethyloxy)pentane-1,2,4-triol (**18a**)*

(1*RS*,2*R*,4*S*)-1-Acetoxy-2,4-*O*-isopropylidene-1-(*p*-tolylsulfanyl)-5-(triphenylmethyloxy)pentane-2,4-diol (**17a**) (320 mg, 0.55 mmol) was dissolved in dry Et_2O (30 ml) and $LiAlH_4$ (44 mg, 1.10 mmol) was added. After 1.5 h (TLC control) 2 M NaOH was added dropwise until a white precipitate formed. Anhydrous Na_2SO_4 was added and the mixture filtered. The solid white residue was extracted twice more with Et_2O (50 ml) and the combined Et_2O solution evaporated to give a residue that was purified by column chromatography with hexane-EtOAc (3:2), to afford the triol (**18a**) (185 mg, 80%). R_f = 0.29 (hexane-EtOAc 3:2). $[\alpha]_D$ –28.6 (*c* 0.76, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.24 (m, 15H, ArH), 4.02 (m, 2H, H-2 and H-4), 3.602 (dd, 1H, *J* 11.4, 3.0, H-1b), 3.494 (dd, 1H, *J* 11.4, 6.3, H-1a), 3.259 (dd, 1H, *J* 9.2, 5.3, H-5b), 2.997 (dd, 1H, *J* 9.2, 6.1, H-5a), 2.06 (s, 1H, 1-OH), 1.546 (ddd, J 12.8, 2.6, 2.6, H-3b), 1.452 (s, 3H, (CH_3)$_2$C), 1.396 (s, 3H, (CH_3)$_2$C), 1.294 (ddd, 1H, J 12.0, 12.0, 12.0, H-3a); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.00S, 128.70D, 128.43S, 127.73D and 126.93D (ArC), 98.67S ((CH_3)$_2$*C*), 86.48S (Ph_3*C*O), 69.52D (C-2), 68.02D (C-4), 67.26T (C-5), 66.08T (C-1), 29.88Q ((CH_3)$_2$C), 29.81T (C-3), 19.84Q ((CH_3)$_2$C). HRMS (FAB): *m/z* 418.2144 (M^+); calcd for $C_{27}H_{30}O_4$: 418.2144.

*3.24 (2S,4S)-2,4-O-Isopropylidene-5-(triphenylmethyloxy)pentane-1,2,4-triol (**18b**)*

A solution of **17b** (6.90 g, 11.9 mmol) in Et_2O (50 ml) was added to a suspension of $LiAlH_4$ (0.90 g, 23.7 mmol) in Et_2O (200 ml) and the mixture stirred at rt for 4 h. The excess $LiAlH_4$ was destroyed by careful quenching of the reaction with 2M NaOH until a white precipitate formed. Anhydrous Na_2SO_4 was added and the mixture filtered. The solid white residue was extracted twice more with Et_2O (100 ml) and the combined Et_2O solutions evaporated to give a residue that was purified by column chromatography with hexane-EtOAc (1:1) as eluent to give the alcohol **18b** as a white powder (3.90 g, 79%); mp 63-65°C; R_f = 0.49 (hexane-EtOAc 1:1); $[\alpha]_D$ –32.9 (*c*, 1.04, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.21 (m, 15H, ArH), 4.002 (dddd, 1H, *J* 9.5, 7.1, 6.2, 3.2, H-2), 3.923 (dddd, 1H, *J* 9.5, 6.3, 6.3, 4.9, H-4), 3.591 (dd, 1H, *J* 11.4, 3.2, H-1a), 3.502 (dd, 1H, *J* 11.4, 7.1, H-1b), 3.276 (dd, 1H, *J* 9.6, 6.3, H-5a), 3.017 (dd, 1H, *J* 9.6, 4.9, H-5b), 1.627 (ddd, 1H, *J* 12.8, 9.5, 6.2, H-3a), 1.542 (ddd, 1H, *J* 12.8, 9.5, 6.3, H-3b), 1.420 (s, 3H, (CH_3)$_2$C), 1.394 (s, 3H, (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.09S, 128.70D, 127.70D, 126.90D (ArC), 100.40S ((CH_3)$_2$*C*), 86.41S (Ph_3*C*O), 67.48D (C-4), 66.57T (C-5), 66.27D (C-2), 65.36T (C-1), 30.37T (C-3), 24.99Q and 24.87Q ((CH_3)$_2$C). HRMS (FAB): *m/z* 419.2224 $(M+H)^+$; calcd for $C_{27}H_{31}O_4$: 419.2222.

*3.25 (2R,4S)-2,4-O-Isopropylidene-5-(triphenylmethyloxy)pentanoic acid (**19**)*

(2*R*,4*S*)-2,4-*O*-Isopropylidene-5-(triphenylmethyloxy)pentane-1,2,4-triol (**18a**) (0.50 g, 1.19 mmol) was dissolved in acetonitrile (10 ml). To this solution were added TEMPO (13 mg, 0.08 mmol), $NaClO_2$ (269 mg, 2.38 mmol) in water (1 ml), buffer (7.5 ml of a 1:1 mixture of a 0.67M NaH_2PO_4 and a 0.67M Na_2HPO_4 solution) and bleach solution (89 μl of a 2% m/v solution, 0.024 mmol) in 0.5 ml water. The reaction was allowed to stir overnight at 35°C. Water (10 ml) was added and the reaction was cooled on ice prior to addition of sodium disulfite (400 mg). After 30 min the reaction was extracted with EtOAc (20 ml) and the organic layer washed with brine and dried ($MgSO_4$). The material was purified by column chromatography (elution $CHCl_3$-MeOH 4:1) to afford the carboxylic acid (**19**) (0.49 g, 95%). R_f = 0.47 ($CHCl_3$-MeOH 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.24 (m, 15H, ArH), 4.595 (dd, 1H, *J* 12.3, 3.0, H-2), 4.153 (m, 1H, H-4), 3.361 (dd, 1-H, *J* 9.3, 5.2, H-5b), 3.138 (dd, 1H, *J* 9.3, 5.9, H-5a), 2.192 (ddd, 1H, *J* 13.2, 2.8, 2.6, H-3b), 1.48 (m, 1H, H-3a), 1.476 (s,

3H, (CH_3)$_2$C), 1.453 (s, 3H, (CH_3)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.74S (C-1), 143.87S, 128.74D, 127.87D and 127.10D (ArC), 99.79S ((CH$_3$)$_2$*C*), 86.67S (Ph$_3$*C*), 68.38D (C-4), 68.27D (C-2), 66.71T (C-5), 30.77T (C-3), 29.69Q ((*C*H$_3$)$_2$C), 19.63Q ((*C*H$_3$)$_2$C). HRMS (FAB): *m/z* 433.2015 $(M+H)^+$; calcd for $C_{27}H_{29}O_5$: 433.2015.

*3.26 (2R,4S)-2,4-O-Isopropylidene-1-(p-toluenesulfonyloxy)-5-(triphenylmethyloxy)pentane-2,4-diol (**20**)*

(2*R*,4*S*)-2,4-*O*-Isopropylidene-5-(triphenylmethyloxy)pentane-1,2,4-triol (**18**) (1.0g, 2.39 mmol) was dissolved in CH_2Cl_2 (30 ml) and 4-DMAP (0.38 g, 3.11 mmol) was added. The reaction was cooled to 0°C in an ice bath and *p*-toluenesulfonyl chloride (0.57 g, 2.99 mmol) was added. The mixture was allowed to stir at rt for 1 d. Water (25 ml) was added and the mixture stirred for 30 min. The organic layer was separated, dried (Na_2SO_4) and the solvent removed under reduced pressure. The product, a white solid, was purified by column chromatography (hexane-EtOAc 4:1 as eluant) to afford (2*R*,4*S*)-2,4-*O*-isopropylidene-1-(*p*-toluenesulfonyloxy)-5-(triphenylmethyloxy)-pentane-2,4-diol (**20**) (1.13 g, 83%). R_f = 0.31 (hexane-EtOAc 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90-7.22 (m, 19H, Ar*H*), 4.11 (m, 1H, H-4), 4.07 (m, 1H, H-2), 3.979 (dd, 1H, *J* 10.3, 5.7, H-1b), 3.928 (dd, 1H, *J* 10.3, 5.0, H-1a), 3.217 (dd, 1H, *J* 9.3, 5.2, H-5b), 2.948 (dd, 1H, *J* 9.3, 5.8, H-5a), 2.411 (s, 3H, ArCH_3), 1.594 (ddd, 1H, *J* 12.9, 2.6, 2.6, H-3b), 1.365 (s, 3H, (CH_3)$_2$C), 1.301 (s, 3H, (CH_3)$_2$C), 1.148 (ddd, 1H, *J* 12.9, 11.9, 11.9, H-3a); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.73S, 143.91S, 133.02S, 129.74D, 128.67D, 127.98D, 127.75D and 126.98D (ArC), 98.78S ((CH$_3$)$_2$*C*), 86.52S (Ph$_3$*C*), 72.37T (C-1), 67.85D (C-2), 67.05T (C-5), 66.86D (C-4), 30.18T (C-3), 29.64Q ((*C*H$_3$)$_2$C), 21.57Q (ArCH$_3$), 19.53Q ((*C*H$_3$)$_2$C). HRMS (FAB): *m/z* 572.2232 (M^+); calcd for $C_{34}H_{36}SO_6$ 572.2233.

*3.27 (2S,4R)-5-Azido-2,4-O-isopropylidene-1-(triphenylmethyloxy)pentane-2,4-diol (**21**)*

(2*R*,4*S*)-2,4-*O*-Isopropylidene-1-(*p*-toluenesulfonyloxy)-5-(triphenylmethyloxy)pentane-2,4-diol (**20**) (0.96 g, 1.68 mmol) was dissolved in DMF (50 ml) and NaN_3 (0.27 g, 4.19 mmol) was added. The reaction was heated at 90°C for 3.5 h. After cooling Et_2O (250 ml) was added and the organic layer was washed once with saturated brine. This brine washing was extracted once with a fresh portion of Et_2O (250 ml). The combined Et_2O layers were washed with saturated brine (6 x 400 ml), dried (Na_2SO_4) and evaporated under reduced pressure to give (2*R*,4*S*)-1-azido-2,4-*O*,*O*-isopropylidene-5-(triphenylmethyloxy)pentane-2,4-diol (**21**) (0.74 g, 100%) as a yellowish solid. The product was not purified but used in the next reaction. R_f = 0.56 (hexane-EtOAc 4:1)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.15 (m, 15H), 4.11-3.99 (m, 2H, H-2 and H-4), 3.284 (dd, 1H, *J* 9.3, 5.2, H-1a), 3.254 (dd, 1H, *J* 12.7, 6.5, H-5a), 3.180 (dd, 1H, *J* 12.7, 4.1, H-5b), 3.010 (dd, 1H, *J* 9.3, 6.0, H-1b), 1.605 (ddd, 1H, *J* 12.9, 2.6, 2.6, H-3a), 1.465 (s, 3H, (CH_3)$_2$C), 1.421 (s, 3H, (CH_3)$_2$C), 1.301 (ddd, 1H, *J* 12.9, 11.6, 11.6, H-3b); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.97S, 128.70D, 127.76D and 126.98D (ArC), 98.86S ((CH$_3$)$_2$*C*), 86.54S (Ph$_3$*C*), 68.48D (C-4), 68.12D (C-2), 67.16T (C-1), 55.18T (C-5), 31.32T (C-3), 29.66Q ((*C*H$_3$)$_2$C), 19.69Q ((*C*H$_3$)$_2$C). HRMS (FAB): *m/z* 443.2209 (M^+); calcd for $C_{27}H_{29}N_3O_3$ 443.2209.

*3.28 (2S,4R)-5-Amino-2,4-O-isopropylidene-1-(triphenylmethyloxy)pentane-2,4-diol (**22**)*

(2*S*,4*R*)-5-Azido-2,4-*O*-isopropylidene-1-(triphenylmethyloxy)pentane-2,4-diol (**21**) (0.65 g, 1.47 mmol) was dissolved in dry Et_2O (40 ml) and $LiAlH_4$ (59 mg, 1.47 mmol) was added in one portion. The reaction was stirred at rt for 2 h. The reaction was stopped by dropwise addition of 2M NaOH to give a white precipitate. After addition of solid Na_2SO_4, the solids were collected by filtration and extracted twice more with Et_2O (50 ml). The combined Et_2O solutions were evaporated to give a white solid which was purified by column chromatography (elution $CHCl_3$- MeOH 4:1) to afford the

amine (**22**) (0.51 g, 84%). R_f = 0.45 ($CHCl_3$-MeOH 4:1); $[\alpha]_D$ –25.2 (*c* 1.34, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.19 (m, 15H, Ar*H*), 4.020 (m, 1H, H-2), 3.832 (m, 1H, H-4), 3.248 (dd, 1H, *J* 9.2, 5.3, H-1a), 2.965 (dd, 1H, *J* 9.2, 6.0, H-1b), 2.700 (dd, 1H, *J* 13.0, 4.2, H-5a), 2.674 (dd, 1H, *J* 13.0, 6.8, H-5b), 1.553 (ddd, 1H, *J* 12.7, 2.4, 2.4, H-3a), 1.439 (s, 3H, $(CH_3)_2C$), 1.382 (s, 3H, $(CH_3)_2C$), 1.205 (m, 1H, H-3b); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.01S, 128.69D, 127.70D and 126.91D (ArC), 98.56S ($(CH_3)_2C$), 86.46S (Ph_3C), 70.32D (C-4), 68.19D (C-2), 67.30T (C-1), 47.23T (C-5), 31.47T (C-3), 29.94Q ($(CH_3)_2C$), 19.85Q ($(CH_3)_2C$). HRMS (FAB): *m/z* 418.2382 $(M+H)^+$; calcd for $C_{27}H_{32}NO_3$ 418.2382.

*3.29 (2R,4S)-N-{(2′R,4′S)-2,4-O-isopropylidene-5′-(triphenylmethyloxy)pentan-1′-yl}-2,4-O-isopropylidene-5-(triphenylmethyloxy)pentanamide (**23**)*

(2*R*,4*S*)-2,4-*O*-Isopropylidene-5-triphenylmethyloxypentanoic acid (**19**) (0.44 g, 1.01 mmol) was dissolved in dry DMF (8 ml) and 1,1′-carbonyldiimidazole (0.17 g, 1.06 mmol) was added. The reaction mixture was stirred at rt for 10 min. and then at 45°C for 20 min. After cooling, (2*S*,4*R*)-5-amino-2,4-*O*-isopropylidene-1-(triphenylmethyloxy)pentane-2,4-diol (**22**) (0.42 g, 1.01 mmol) in dry DMF (2 ml) was added and the reaction was stirred at rt for 3 h. The reaction was diluted with Et_2O (30 ml) and washed once with brine. This brine washing was extracted once with Et_2O (30 ml). The combined Et_2O solution was washed with brine (x 4), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (elution hexane-EtOAc 3:2) to afford the amide (**23**) as a white solid (0.69 g, 81%). R_f = 0.54 (hexane-EtOAc 3:2); $[\alpha]_D$ –22.6 (*c* 0.78, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.20 (m, 30H, Ar*H*), 6.903 (dd, 1H, *J* 6.8, 5.3, N*H*), 4.336 (dd, 1H, *J* 12.0, 2.8, H-2), 4.08-3.93 (m, 3H, H-2', H-4, H-4'), 3.512 (ddd, 1H, *J* 13.6, 6.8, 3.3, H-1'a), 3.247 and 3.233 (each a dd, 1H, *J* 9.3, 5.3, H-5a and H-5'a), 3.110 (ddd, 1H, *J* 13.5, 7.0, 5.3, H-1'b), 2.190 (ddd, 1H, *J* 13.2, 2.7, 2.7, H-3a), 1.596 (ddd, 1H, *J* 12.8, 2.6, 2.6, H-3'a), 1.490, 1.427, 1.421, and 1.387 (each s, 3H, (2x$(CH_3)_2C$), 1.38-1.13 (m, 2H, H-3'b and H-3b); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.53S (C-1), 143.99S, 143.89S, 128.70D, 127.73D and 126.95D (ArC), 99.02S and 98.70S (2 x $(CH_3)_2C$), 86.53S and 86.49S (2 x Ph_3C), 69.45D (C-2), 68.61D and 68.16D (C-4 and C-4'), 67.93D (C-2'), 67.22T and 66.90T (C-5 and C-5'), 43.43T (C-1'), 31.69T (C-3), 31.27T (C-3'), 29.87Q and 29.73Q ($(CH_3)_2C$), 19.85Q and 19.66Q ($(CH_3)_2C$). HRMS (FAB): *m/z* 831.4135 (M^+); calcd for $C_{54}H_{57}NO_7$ 831.4135.

*3.30 (2S,4R,8R,10S)-6-Aza-2,4:8,10-di-O,O-isopropylidene-1,11-di(triphenylmethyloxy)-undecane-2,4,8,10-tetraol (**24**)*

(2*R*,4*S*)-*N*-{(2′*R*,4′*S*)-2,4-*O*-Isopropylidene-5′-triphenylmethyloxypentan-1′-yl}-2,4-*O*-isopropylidene-5-triphenylmethyloxypentanamide **(23)** (0.266 g, 0.32 mmol) was dissolved in dry toluene (7 ml). $LiAlH_4$ (72 mg) was added and the reaction refluxed for 2 h (TLC control). The reaction was quenched by addition of a few drops of water. After stirring for 15 min Et_2O (30 ml) was added followed by solid anhydrous Na_2SO_4. The organic layer was filtered off and the solid material was extracted with Et_2O (4x20 ml). The combined Et_2O solutions gave a viscous oil that was purified by column chromatography (elution EtOAc-hexane 4:1) to give the title amine (**24**) (204 mg, 78%). R_f = 0.35 (EtOAc-hexane 4:1). $[\alpha]_D$ –33.5 (*c* 0.85, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.20 (m, 30H, Ar*H*), 4.03 (m, 4H, H-4 and H-2), 3.257 (dd, 2H, *J* 9.3, 5.2, H-1a), 2.972 (dd, 2H, *J* 9.3, 5.9, H-1b), 2.687 (dd, 2H, *J* 12.2, 7.2, H-5a), 2.612 (dd, 2H, *J* 12.2, 4.1, H-1b), 1.593 (ddd, 2H, *J* 12.6, 2.3, 2.3, H-3a), 1.452 (s, 6H, $(CH_3)_2C$), 1.385 (s, 6H, $(CH_3)_2C$), 1.215 (ddd, 2H, *J* 12.6, 11.6, 11.6, H-3b); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.05S, 128.72D, 127.71D and 126.92D (Ar*C*), 98.59S ($(CH_3)_2C$), 86.46S (Ph_3C), 68.31D (C-2), 68.00T (C-1), 67.37D (C-4), 54.90T (C-5), 32.17T (C-3), 29.99Q ($(CH_3)_2C$), 19.86Q ($(CH_3)_2C$). HRMS (FAB): *m/z* 818.4420 $(M+H)^+$; calcd for $C_{54}H_{60}NO_6$ 818.4421.

*3.31 (2S,4R,8R,10S)-6-Aza-2,4:8,10-di-O-isopropylidene-undecane-1,2,4,8,10,11-hexaol (**25**)*

(2*S*,4*R*,8*R*,10*S*)-6-Aza-2,4:8,10-di-*O*-isopropylidene-1,10-di(triphenylmethyloxy)-undecane-2,4,8,10-tetraol (**24**) (0.286 g, 0.35 mmol) was dissolved in dry THF (12 ml) and liquid ammonia (25 ml, distilled from sodium) was added to the solution kept at −78°C. Sodium metal (20 eq.) was added in small pieces in four batches until a permanent blue colour was obtained. After 1h a few drops of EtOH were added to the reaction, followed 5 min later by solid NH_4Cl (4 g). Ammonia was evaporated by gentle warming and the residue extracted with CH_2Cl_2 (20 ml). The CH_2Cl_2 was dried (Na_2SO_4) and evaporated. The product was purified by column chromatography (elution $CHCl_3$-MeOH 4:1) to afford the hexaol (**25**) (70 mg, 60%). R_f = 0.46 ($CHCl_3$-MeOH 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.06 (m, 2H, H-4), 3.97 (m, 2H, H-2), 3.575 (dd, 2H, *J* 11.4, 3.4, H-1a), 3.477 (dd, 2H, *J* 11.4, 6.0, H-1b), 2.732 (dd, 2H, *J* 12.0, 8.0, H-5a), 2.630 (dd, 2H, *J* 12.0, 4.0, H-5b), 2.55 (br s, 2H, 1-OH), 1.443 (s, 6H, (CH_3)$_2$C), 1.384 (ddd, 2H, *J* 12.9, 3.1, 3.1, H-3a), 1.371 (s, 6H, (CH_3)$_2$C), 1.309 (ddd, 2H, *J* 12.8, 11.1, 11.1, H-3b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.92S ((CH$_3$)$_2$*C*), 69.39D (C-2), 67.37D (C-4), 65.93T (C-1), 54.52T (C-5), 30.07T (C-3), 29.94Q ((*C*H$_3$)$_2$C), 19.92Q ((*C*H$_3$)$_2$C). HRMS (FAB): *m/z* 334.2229 (M+H)$^+$; calcd for $C_{16}H_{32}NO_6$ 334.2230.

*3.32 (2S,4R,8R,10S)-6-Aza-2,4:8,10-di-O-isopropylidene-N-(p-toluenesulfonyl)-1,11-di-(p-toluenesulfonyloxy)-undecane-2,4,8,10-tetraol (**26**)*

(2*S*,4*R*,8*R*,10*S*)-6-Aza-2,4:8,10-di-*O*-isopropylidene-undecane-1,2,4,8,10,11-hexaol (**25**) (58 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (5 ml) and DMAP (128 mg, 1.05 mmol) and tosyl chloride (194 mg, 1.02 mmol) were added. The reaction was allowed to stir for 24 h at rt. The reaction mixture was partitioned between CH_2Cl_2 and water and the organic layer dried (Na_2SO_4) and evaporated. The product was purified by column chromatography (elution hexane-EtOAc 3:2 to hexane-EtOAc 1:1) to afford the product (**26**) (127 mg, 92%). R_f = 0.42 (hexane-EtOAc 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.781 (d, 4H, *J* 8.4, ArH-3), 7.642 (d, 2H, *J* 8.4, ArH-3), 7.300 (d, 4H, *J* 8.4, ArH-2), 7.214 (d, 2H, *J* 8.4, ArH-2), 4.07-3.97 (m, 4H, H-2 and H-4), 3.928 (dd, 2H, *J* 10.1, 5.4, H-1a), 3.866 (dd, 2H, *J* 10.1, 4.7, H-1b), 3.278 (dd, 2H, *J* 14.8, 4.2, H-5a), 3.174 (dd, 2H, *J* 14.8, 7.2, H-5b), 2.419 (s, 6H, ArCH_3), 2.386 (s, 3H, ArCH_3), 1.446 (ddd, 2H, *J* 12.7, 2.3, 2.3, H-3a), 1.214 (s, 6H, (CH_3)$_2$C), 1.208 (s, 6H, (CH_3)$_2$C), 1.069 (ddd, 2H, *J* 12.7, 11.6, 11.6, H-3b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.82S, 143.38S, 137.29S, 132.90S, 129.80D, 129.60D, 127.95D and 127.18D (Ar*C*), 98.87S ((CH$_3$)$_2$*C*), 72.09T (C-1), 67.75D and 66.67D (C-2 and C-4), 54.15T (C-5), 30.06T (C-3), 29.63Q ((*C*H$_3$)$_2$C), 21.57Q (2x Ar*C*H$_3$) and 21.39Q (Ar*C*H$_3$), 19.38 ((*C*H$_3$)$_2$C). HRMS (FAB): *m/z* 795.2412 (M$^+$); calcd for $C_{37}H_{49}NS_3O_{12}$ 795.2417.

*3.33 (2S,4R,8R,10S)-6-Aza-1,11-diazido-2,4:8,10-di-O-isopropylidene-N-(p-toluenesulfonyl)-undecane-2,4,8,10-tetraol (**27**)*

(2*S*,4*R*,8*R*,10*S*)-6-Aza-2,4:8,10-di-*O*-isopropylidene-*N*-(*p*-toluenesulfonyl)-1,11-di-(*p*-toluenesulfonyloxy)-undecane-2,4,8,10-tetraol (**26**) (117 mg, 0.15 mmol) was dissolved in DMF (6 ml) and sodium azide (48 mg, 0.74 mmol) was added and the reaction heated at 95°C for 4 h. The reaction mixture was cooled, diluted with Et_2O (50 ml) and washed with brine. The brine layer in turn was extracted once with Et_2O (50 ml). The combined Et_2O solutions were washed with brine (7 x 100 ml), dried (Na_2SO_4) and evaporated to afford the azide (**27**) (70 mg, 89%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.681 (d, 2H, *J* 8.4, ArH-3), 7.267 (d, 2H, *J* 8.4, ArH-2), 4.110 (dddd, 2H, *J* 11.6, 7.1, 4.4, 2.7, H-4), 3.990 (dddd, 2H, *J* 11.6, 5.6, 4.4, 2.7, H-2), 3.339 (dd, 2H, *J* 14.7, 4.4, H-5a), 3.243 (dd, 2H, *J* 14.8, 7.1, H-5b), 3.208 (dd, 2H, *J* 13.0, 5.7, H-1a), 3.158 (dd, 2H, *J* 13.0, 4.4, H-1b), 2.394 (s, 3H, ArCH_3), 1.460 (ddd, 2H, *J* 12.8, 2.6, 2.6, H-3a), 1.331 (s, 6H, (CH_3)$_2$C), 1.308 (s, 6H, (CH_3)$_2$C), 1.223 (ddd, 2H, *J* 12.8, 11.6, 11.6, H-3b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.37S,,137.32S, 129.60D, and 127.24D (Ar*C*), 98.97S ((CH$_3$)$_2$*C*), 68.32D (C-2), 68.07D (C-4), 55.03T (C-1), 54.40T (C-5), 31.13T (C-3),

29.82Q ((CH_3)$_2$C), 21.41Q (ArCH_3), 19.54Q ((CH_3)$_2$C). HRMS (FAB): *m/z* 538.2451 $(M+H)^+$; calcd for $C_{23}H_{36}N_7SO_6$ 538.2447.

*3.34 (2S,4R,8R,10S)-6-Aza-1,11-diazido-N-(p-toluenesulfonyl)-undecane-2,4,8,10-tetraol (**28**)*

(2*S*,4*R*,8*R*,10*S*)-6-Aza-1,11-diazido-2,4:8,10-di-*O*,*O*-isopropylidene-*N*-(*p*-toluenesulfonyl)-undecane-2,4,8,10-tetraol (**27**) (0.104 g, 0.193 mmol) was dissolved in MeOH (5 ml) and water (1.5 ml) was added. To this mixture was added *p*-TsOH (8 mg) and the reaction was stirred at rt for 3 days. The solvent was removed under reduced pressure and the residue was purified by chromatography (elution EtOAc-hexane 9:1) to afford the deprotected tetraol (**28**) (80 mg, 90%); R_f = 0.45 (EtOAc-hexane 9:1). ^{13}C NMR NMR (75 MHz, $CDCl_3$): δ 143.96S, 134.93S, 129.89D and 127.39D (ArC), 70.91D and 70.61D (C-2 and C-4), 56.90T (C-1), 56.64T (C-5), 37.08T (C-3), 21.55Q (ArCH_3). HRMS (FAB): *m/z* 458.1822 $(M+H)^+$; calcd for $C_{17}H_{28}N_7SO_6$ 458.1822.

*3.35 (2S,4R,8R,10S)-1,11-Diamino-6-aza-N-(p-toluenesulfonyl)-undecane-2,4,8,10-tetraol (**29**)*

A solution of (2*S*,4*R*,8*R*,10*S*)-6-aza-1,11-diazido-*N*-(*p*-toluenesulfonyl)-undecane-2,4,8,10-tetraol (**28**) (129 mg, 0.281 mmol) in MeOH (5 ml) and 5% Pd-C (26 mg) in a small Parr reactor was stirred under H_2 at 5 atm at rt for 4 h. The reaction mixture was filtered to remove the catalyst and the solvent evaporated to afford the diamine (**29**) (0.116 mg, 100%) that was used without further purification. ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.55S, 135.17S, 129.77D, and 127.42D (Ar*C*), 70.96D (C-2), 69.17D (C-4), 56.72T (C-5), 47.26T (C-1), 38.45T (C-3), 21.50Q (ArCH_3). HRMS (FAB): *m/z* 406.2012 $(M+H)^+$; calcd for $C_{17}H_{32}N_3SO_6$ 406.2012.

*3.36 (2S,4R,8R,10S)-1,11-Diamino-6-aza-undecane-2,4,8,10-tetraol (synthetic pavettamine) (**1**)*

(2*S*,4*R*,8*R*,10*S*)-1,11-Diamino-6-aza-*N*-(*p*-toluenesulfonyl)-undecane-2,4,8,10-tetraol (**29**) (63 mg, 0.155 mmol) was partially dissolved in dry dioxane (1 ml) and dry THF (15 ml) was added. Liquid ammonia (15 ml) was added and Na metal (40 mg) was added in three portions to give a blue solution. The reaction was allowed to stir at –78°C for 1 h. A few drops of EtOH were added until the reaction turned colourless. The reaction mixture was removed from the cooling bath, the ammonia allowed to evaporate and 10M HCl (120µl) added to the residue. The reaction mixture was filtered and the precipitate was dissolved in a small volume of distilled water and loaded on a Strata CN phenomenex SPE column that had been prewashed with MeOH and then water. The sample was eluted with two column volumes of water, the solvent was removed under reduced pressure and two-thirds of the material was dissolved in a minimum amount of water before loading on a Sephadex G10 column (6 ml gel). The sample was eluted with distilled water. Fractions containing product eluted immediately before fractions containing salts. Combined fractions containing product were evaporated to give (2*S*,4*R*,8*R*,10*S*)-1,11-diamino-6-aza-undecane-2,4,8,10-tetraol (**1**) (11 mg, 40%). $[\alpha]_D$ –16.3 (*c* 0.49, H_2O); HRMS (FAB): *m/z* 251.18449 (M^+); calcd for $C_{10}H_{25}N_3O_4$ 251.18451. ^{1}H and ^{13}C NMR data identical to that of natural pavettamine, see Table 1.

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