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Synthesis of 2-Hydroxymethyl-1-oxaquinolizidine

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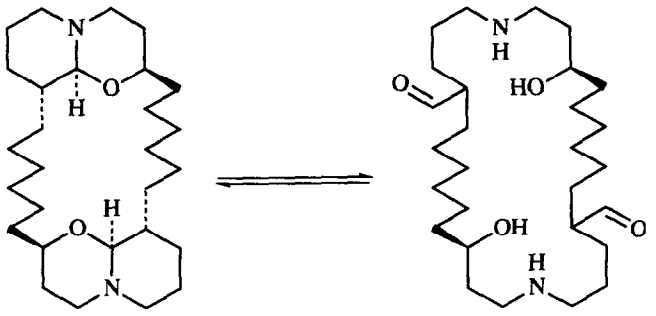
Abstract: *The synthesis of 2-hydroxymethyl-1-oxaquinolizidine from L-malic acid and 1,5 pentanediol, is reported.*

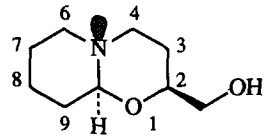
Araguspongine D (**1**), also known as Xestospongine A, isolated from the marine sponge *Xestospongia* has been reported to possess vasodilatory properties.[1, 2] The mechanism by which these properties are expressed is as yet not known. However one can speculate that such macrocyclic compounds containing both nitrogen and oxygen should exhibit metal ion chelating properties, both in solution and even on the surface of receptor proteins. The nature of the biological activity of the xestospongines and their potential use in the development of new medicinal compounds makes them particularly interesting targets for chemical synthesis. We are currently involved in the development of a general strategy for the synthesis of xestospongines and a number of analogues. The appearance of studies aimed at similar goals prompted us to report our results.[3 - 6]



1 **2**

Figure 1.

Xestospongine contains a C_2 symmetry axis, the major part of the synthetic problems should therefore be encountered through the synthesis of one half of the molecule. It is expected that the pentacyclic xestospongine is in equilibrium with the monocyclic compound, **2** (Figure 1). The consequences of this equilibrium are found in the stereochemistry of the xestospongine. The asymmetry at the 2 and 2' positions are unaffected whereas the asymmetries at 5, 5', 9, 9' and 10, 10' are lost due to the possibility of inversion at nitrogen, inversion due to tautomerism and the prochirality of the carbonyl carbon respectively. A stereospecific synthesis of xestospongine may therefore be based solely on one asymmetric centre. We chose to commence our studies with the synthesis of 2-hydroxymethyl-1-oxaquinolizidine (**3**) from (L)-malic acid (**4**) and 1,5-pentanediol (**5**). In so doing the ease with which the oxaquinolizidine forms can be demonstrated, and a method which can be extended for the total synthesis of xestospongine A may be established.



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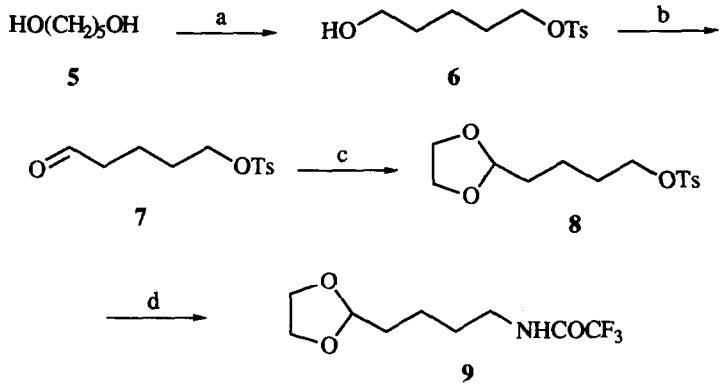
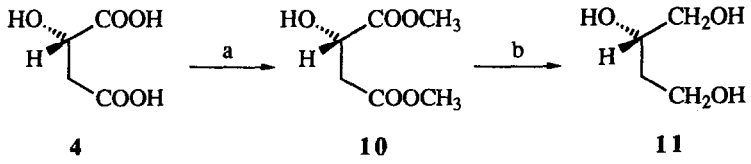
Results and discussion.

In order to synthesise 2-hydroxymethyl-1-oxaquinolizidine from (L)-malic acid and 1,5-pentanediol, trifluoroacetamide was used as the source of nitrogen. The two alkyl chains should be modified in such a way as to allow coupling to the nitrogen before the cyclisation reaction. 1,5-Pentanediol was converted to the monotosylate (**6**) using a previously reported procedure.[7] Swern oxidation[8] of **6** gave 5-tosyloxy pentanal (**7**) in 93 % yield (Scheme 1). The aldehyde function was protected as the 1,3-dioxolane by reaction with ethylene glycol and p-toluenesulphonic acid.[9] The 5-tosyloxy pentanal ethylene acetal (**8**) thus formed was used to alkylate trifluoroacetamide in *N,N*-dimethylformamide with sodium hydride as base,[10] giving a 57 % yield of the monoalkylated trifluoroacetamide (**9**).

(L)-Malic acid was converted to (S)-1,2,4-butanetriol (**11**), first by formation of the dimethyl ester (**10**) followed by reduction with lithium aluminium hydride (Scheme 2). This reaction sequence gave a quantitative yield, but required great care during work up in order to prevent the loss of unnecessarily large amounts of product due to complexation with the metal ions. In order to achieve selective alkylation at the 4-position, the 1- and 2 positions were protected as the acetonide.[10] This protective group was chosen partly because of the favourable formation over the 2,4-acetonide, and partly because deprotection can be achieved simultaneously with the removal of the ethylene acetal.

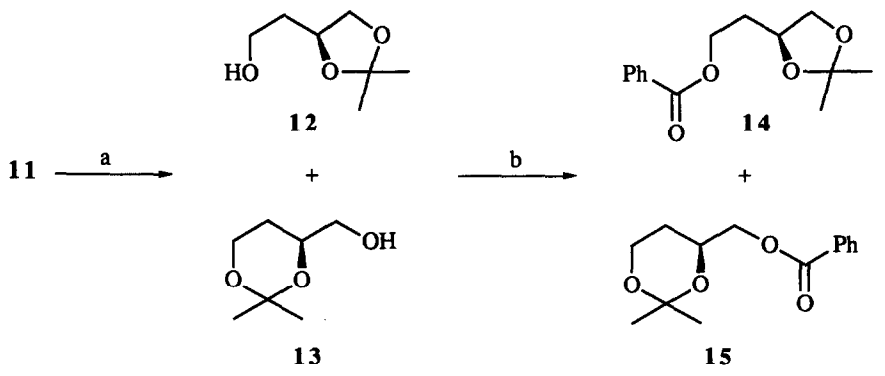


Scheme 1. (a) p-Toluenesulphonyl chloride, NEt_3, 4-dimethylaminopyridine, CH_2Cl_2, 86 %. (b) Oxalyl chloride, DMSO, CH_2Cl_2, 93 %. (c) Ethylene glycol, p-toluenesulphonic acid, C_6H_6. (d) Trifluoroacetamide, NaH, DMF, 57 %.



Scheme 2. (a) $SOCl_2$, CH_3OH, 98 %. (b) $LiAlH_4$, THF, 100 %

Reaction of (S)-1,2,4-butanetriol with acetone and p-toluenesulphonic acid gave a 9:1 mixture of (S)-1,2-*O*-isopropylidene-1,2,4-butanetriol (**12**) and (S)-2,4-*O*-isopropylidene-1,2,4-butanetriol (**13**) which were not easily separable by standard chromatographic techniques (Scheme 3). It was found that the benzoyl esters **14** and **15** could be separated with relative ease by chromatography on silica gel with dichloromethane as solvent. The pure (S)-4-benzoyl-1,2-*O*-isopropylidene-1,2,4-butanetriol was then hydrolysed to give pure **12** with only small losses of material. The identity of this compound was established by ^{1}H-NMR spectroscopy and comparison with literature data.[11, 12] The isomeric and optical purities were determined by ^{31}P-NMR spectroscopy.[13] It is worth noting that tosylation of the mixture of compounds **12** and **13** gives a mixture of tosylates which are also separable by chromatography on silica gel.

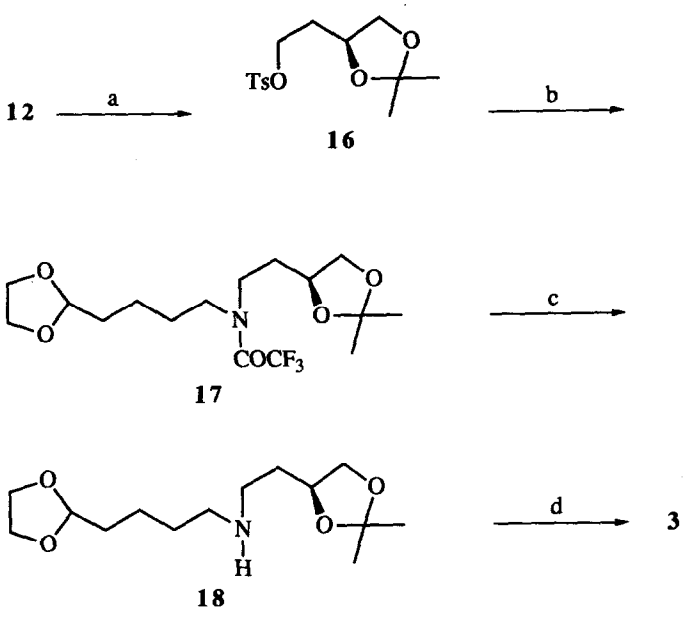


Scheme 3. (a) Acetone, p-toluenesulphonic acid, 98 %. (b) PhCOCl, NEt_3, 4-dimethylaminopyridine, 74 %.

(S)-1,2-*O*-isopropylidene-1,2,4-butanetriol (**12**) was converted to the tosylate (**16**) by reaction with p-toluenesulphonyl chloride and triethylamine with a catalytic amount of 4-dimethylaminopyridine (Scheme 4). Compound **16** could then be used for alkylation of the trifluoroacetamide (**9**). This reaction was carried out in *N,N*-dimethylformamide using sodium hydride as base.[10] The product (**17**), which was isolated in 42 % yield was characterised by ^1H, ^{13}C and ^{19}F-NMR spectroscopy. In the proton NMR spectrum a characteristic triplet at 4.81 ppm showed the ethylene acetal on the pentyl chain, while singlets at 1.30 and 1.38 ppm showed the isopropylidene group. The ^{19}F-NMR spectrum showed a single peak at -62.0 ppm. ^{13}C-NMR spectra however showed a series of double peaks, indicating the presence of *cis* and *trans* isomers of the amide.

Treatment of **17** with potassium hydroxide in methanol[14] gave the secondary amine (S)-6-Aza-9,10-dihydroxy-9,10-*O*-isopropylidenedecanal ethylene acetal (**18**) quantitatively. Removal of the two acid labile protecting groups was achieved using p-toluenesulphonic acid monohydrate in dichloromethane. The reaction was worked up with saturated sodium hydrogen carbonate solution and the product isolated was the cyclised 2-hydroxymethyl-1-oxaquinolizidine (**3**).

^1H-NMR analysis of the product (Figure 2) showed there to be only one isomer present. The ^1H and ^{13}C signals were assigned by a combination of COSY and HETCOR spectra. H-10 was easily assigned as the double doublet at 3.48 ppm as this signal was coupled to the ^{13}C signal at 92.2 ppm. The signals at 2.80 and 2.07 ppm were shown by COSY to belong to the same spin system as H-10 and therefore assigned as H-6 equatorial and axial respectively. Assignment of the signal at 2.80 ppm as equatorial H-6 was confirmed by the small w-coupling to equatorial H-8. The coupling patterns of the protons at positions 4 and 6 showed that the product adopted a *trans* conformation. The coupling pattern of H-10 shows that it is in an axial position, indicating the presence of a single conformer and causing the 2-hydroxymethyl group to be in an equatorial position. The absence of a small w-coupling between H-2 and H-4 also indicates that the hydroxymethyl group adopts an equatorial position.



Scheme 4. (a) p-Toluenesulphonyl chloride, NEt_3, 4-dimethylaminopyridine, CH_2Cl_2, 84 %. (b) **9**, NaH, DMF, 42 %. (c) KOH, CH_3OH, 100 %. (d) p-Toluenesulphonic acid, CH_2Cl_2, 50 %.

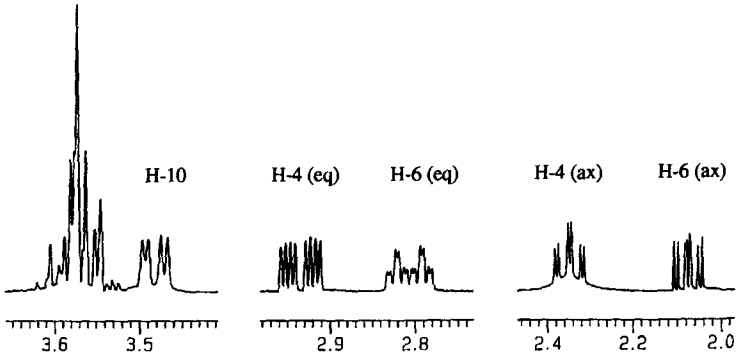


Figure 2. Portion of the 400 MHz ^{1}H-NMR spectrum of compound **3**.

Preliminary results obtained by molecular mechanics calculations, using the MM2 force field, were in agreement with the conclusions drawn from the NMR spectra. A conformation with an axial hydroxymethyl group would have an energy 3.1 kcal mol^{-1} higher than a conformation with an equatorial

hydroxymethyl group. Conformations with a *cis* configuration showed steric energies ranging from 4.8 to 5.6 kcal mol^{-1} higher than the equatorial conformer. None of the high energy conformers would be expected to be present at room temperature.

Conclusions.

The synthesis presented herein represents a route for the synthesis of 1-oxaquinolizidine natural products. The stereochemistry of the one asymmetric centre in the precursors is sufficient to control the stereochemistry of the three asymmetric centres in the product during the spontaneous cyclisation reaction. The readily available starting materials and the ease with which they can be modified makes this a particularly attractive approach for the synthesis of xestospongines. Work in this direction is continuing in our laboratory.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Jeol EX270 spectrometer at 270.05 MHz and 67.8 MHz respectively and on a Jeol EX400 spectrometer at 398.5 MHz. Chloroform, δ=7.26, or methanol, δ=3.35, were used as internal references in ^{1}H NMR. Chloroform, δ=77, or dimethyl sulphoxide, δ=39.5 were used as internal references in ^{13}C NMR spectra. ^{19}F NMR spectra were recorded on a Jeol FX90Q spectrometer at 84.2 MHz, using trifluoroacetic acid, δ=–76.5, as internal reference. Low-resolution electron-impact mass spectra were recorded on a Hewlett-Packard mass spectrometer HP5971A MSD connected with a gas chromatograph HP GC5890 Series 2. IR spectra were recorded on a Perkin-Elmer 298 instrument. Optical rotation was measured with a Perkin-Elmer 241 polarimeter at 22 °C. TLC was performed using silica gel plates (F_{254}, Merck) or aluminium oxide plates (F_{254}, Merck) and the spots were detected with either UV light or H_2SO_4. Column chromatography was performed on silica gel 60 (0.040-0.063 mm, Merck) or on aluminium oxide 90 (0.063-0.200 mm). The elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden. Melting points are uncorrected. Sodium hydride was used as an 80% oil suspension. *N,N*-Dimethylformamide was dried and distilled over calcium hydride. Tetrahydrofuran was dried and distilled from sodium and benzophenone. Trifluoroacetamide was recrystallised in chloroform. All other commercial chemicals were used without further purification.

5-Tosyloxypentanal (7). Oxalyl chloride (1.4 ml, 16.5 mmol) was dissolved in dichloromethane (45 ml) and cooled to -78 °C under nitrogen atmosphere. Dimethyl sulphoxide (2.3 ml, 33.0 mmol) was dissolved in dichloromethane (15 ml) and added to the cold solution under a 25 minutes period. 5-Tosyloxy-1-pentanol (**6**) (3.87 g, 15.0 mmol) was dissolved in dichloromethane (30 ml) and added dropwise under a 10 minutes period. This mixture was stirred for 40 minutes at -78 °C. The reaction was quenched by adding diisopropylethylamine (13 ml, 75.0 mmol). The solution was heated to room temperature and washed with water and saturated citric acid solution. The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (silica, dichloromethane) giving a colourless oil. 3.58 g, 93% yield. ^{1}H NMR ($CDCl_3$) δ: 9.72 (s, 1H), 7.77 (d,

J=8 Hz, 2H), 7.35 (d, J=8 Hz, 2H), 4.03 (t, J=6 Hz, 2H), 2.44 (s, 3H), 2.42 (t, J=6 Hz, 2H), 1.70-1.64 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 201.9, 145.2, 133.2, 130.2, 128.2, 70.2, 43.2, 28.4, 21.9, 18.3. IR (film) 1715 cm^{-1}. Anal calcd. for $C_{12}H_{16}O_4S$: C: 56.2%; H: 6.3%; O: 25.0%; S:12.5%. Found: C: 57.2%; H: 6.5%.

5-Tosyloxypentanal ethylene acetal (8). Ethylene glycol (2.0 ml, 37.1 mmol) and p-toluenesulphonic acid (catalytic amount) were refluxed in benzene with a Dean-Stark apparatus for 30 min. 5-Tosyloxypentanal (**7**) (6.34 g, 24.7 mmol) was dissolved in benzene (20 ml), added to the mixture and refluxed for 3 hours. This solution was extracted with saturated sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated to dryness, giving a colourless oil. 6.81 g, 92% yield. ^1H NMR ($CDCl_3$) δ: 7.78 (d, J=8 Hz, 2H), 7.34 (d, J=8 Hz, 2H), 4.79 (t, J=5 Hz, 1H), 4.01 (t, J=6 Hz, 2H), 3.96-3.79 (m, 4H), 2.44 (s. 3H), 1.74-1.40 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 144.6, 133.0, 129.8, 127.8, 104.0, 70.3, 64.8, 33.0, 28.6, 21.6, 19.8. IR (film) 1590 cm^{-1}. Anal calcd for $C_{14}H_{20}O_5S$: C: 56:0%; H: 6.7%; O: 26.6%; S:10.7%. Found C:55.9%; H:6.7%.

N-(Trifluoroacetyl)-5-aminopentanal ethylene acetal (9). Trifluoroacetamide (2.25 g, 20.0 mmol) was dissolved in dry *N,N*-dimethylformamide (100 ml) under nitrogen atmosphere. Sodium hydride (0.78 g, 26.0 mmol) was added and the slurry was heated to 70 °C for 45 minutes. 5-Tosyloxypentanal ethylene acetal (**8**) (6.0 g, 20.0 mmol) was dissolved in dry *N,N*-dimethylformamide (25 ml) and added dropwise to the mixture and stirred at 70 °C for 8 hours. The solution was partitioned between dichloromethane and brine. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (aluminiumoxide, dichloromethane) giving white crystals. 2.74 g, 57% yield. Mp: 25 °C. ^1H NMR ($CDCl_3$) δ: 6.84 (b.1H), 4.82 (t, J=5 Hz, 1H), 3.99-3.77 (m, 4H), 3.33 (q, J= 7 Hz, 2H), 1.71-1.40 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 157.2 (q, J_{CF}=37 Hz), 115.8 (q, J_{CF}=288 Hz), 104.1, 64.8, 39.8, 32.8, 28.4, 20.9. ^{19}F NMR ($CDCl_3$) δ: -76.7. IR 3320, 1710 cm^{-1}. Anal calcd. for $C_9H_{14}F_3NO_3$: C: 44.8%; H: 5.8%; F: 23.6%; N: 5.8%; O: 19.9%. Found: C: 44.8%; H: 5.8%.

(S)-Dimethylmalate (10). (S)-Malic acid (26.8 g, 200 mmol) was dissolved in methanol (500 ml) and cooled to 0 °C. Thionyl chloride (32.2 ml, 440 mmol) was added dropwise during a one hour period and the solution was stirred in room temperature for 24 hours. The solvent was evaporated almost to dryness and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution, The organic phase was dried ($MgSO_4$) and evaporated, giving a colourless oil. 31.7 g, 98% yield. ^1H NMR ($CDCl_3$) δ: 4.50 (m, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.24 (d, J=6 Hz, 1H), 2.83 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 173.5, 170.8, 66.7, 52.5, 51.8, 38.0. IR (film) 3480, 1740 cm^{-1}. $[\alpha]_D$ -8.9° (c=1.0, methanol).

(S)-1,2,4-Butanetriol (11). Lithium aluminium hydride (4.5 g, 118 mmol) was added to cold (0 °C) tetrahydrofuran (250 ml) under nitrogen atmosphere. (S)-Dimethyl malate (**10**) (5.0 g, 30.8 mmol) was

dissolved in tetrahydrofuran (10 ml) and added dropwise to the cold slurry. This mixture was heated to 65 °C for 3 days. Water (35 ml) was added dropwise and the mixture was filtered through Celite. The solvent was evaporated and the residue was purified by flash chromatography (silica, dichloromethane-ethanol 0-50%), giving a yellowish oil 1.3 g, 100% yield. ^{1}H NMR (MeOH-d_4) δ: 3.78 (m, 3H), 3.52 (m, 2H), 1.70 (m, 2H). ^{13}C NMR (DMSO-d_6) δ: 68.9, 66.2, 58,1, 36.8. IR (film) 3320 cm^{-1}. $[\alpha]_D$ -26.9° (c=1.0, methanol).

(S)-1,2-O-isopropylidene-1,2,4-butanetriol (12) and (S)-2,4-O-isopropylidene-1,2,4-butanetriol (13). (S)-1,2,4-Butanetriol (**11**) (10.0 g, 94.2 mmol) was dissolved in acetone (500 ml) and a catalytic amount of p-toluenesulphonic acid was added. This solution was stirred in room temperature for 14 hours. Five drops of triethylamine was added and the solvent evaporated. The residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated, giving a yellowish oil. 13.5 g, 98% yield. ^{1}H NMR analysis of the product showed it to consist of a 9:1 mixture of **12** and **13**.

(S)-1,2-O-isopropylidene-1,2,4-butanetriol benzoyl ester (14) and (S)-2,4-O-isopropylidene-1,2,4-butanetriol benzoyl ester (15). The 9:1 mixture of (S)-1,2- and (S)-2,4-*O*-isopropylidene-1,2,4-butanetriol (**12** and **13**) (13.0 g, 88.9 mmol), triethylamine (37.0 ml, 267 mmol) and 4-dimethylaminopyridine (0.11 g, 0.9 mmol) were dissolved in dichloromethane (300 ml) and cooled to 0 °C. Benzoyl chloride (15.5 ml, 133 mmol) was dissolved in dichloromethane (100 ml) and added dropwise to the cold solution during a 40 minutes period. This solution was stirred in room temperature for 14 hours and washed with saturated sodium bicarbonate and citric acid solutions. The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (silica, dichloromethane), R_f: **14**: 0.64; **15**: 0.70 with 2% ethanol in dichloromethane as eluent, giving a yellowish oil. 16.35 g, 74% yield. ^{1}H NMR ($CDCl_3$) δ: 7.95 (arom, 2H), 7.48 (arom, 1H), 7.37 (arom, 2H), 3.35 (m, 3H), 4.05 (dd, J=8 Hz, J=6 Hz, 1H), 3.57 (dd, J=8 Hz, J=6 Hz, 1H), 1.98 (m, 2H), 1.36 (s, 3H), 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 166.4, 133.0, 130.1, 129.5, 128.4, 108.9, 73.3, 69.4, 61.9, 32.9, 26.9,25.7. IR (film): 1715 cm^{-1}. $[\alpha]_D$ -14.2° (c=1.0, dichloromethane). Anal calcd. for $C_{14}H_{18}O_4$: C: 67.2%; H: 7.2%; O: 25.6%. Found: C: 67.2%; H: 7.3%.

(S)-1,2-O-isopropylidene-1,2,4-butanetriol (12). Aqueous sodium hydroxide solution (4%, 14 ml) and methanol (60 ml) were mixed and poured over the benzoyl ester (**14**) (2.5 g, 10.0 mmol). This solution was stirred in room temperature for 45 minutes and then partitioned between dichloromethane and brine. The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (silica, dichloromethane-ethanol 0-5%) giving a colourless oil. 1.31 g, 90% yield. ^{1}H NMR ($CDCl_3$) δ: 4.27 (qv, J=6 Hz, 1H), 4.08 (dd, J=8 Hz, J=6 Hz, 1H), 3.80 (q, J=6 Hz, 2H), 3.59 (dd, J=8 Hz, J=6 Hz, 1H), 2.27 (t, J=6 Hz, 1H), 1.79 (q, J=6 Hz, 2H), 1.42 (s, 3H), 1.36 (s, 3H). ^{13}C

NMR ($CDCl_3$) δ: 109.0, 75.0, 69.5, 60.5, 35.6, 26.8, 25.6. IR (film) 3460 cm^{-1}. $[\alpha]_D$ -3.2° (c=1.0, methanol).

(S)-4-Tosyloxy-1,2-O-isopropylidene-1,2-butanediol (16). (S)-1,2-*O*-isopropylidene-1,2,4-butanetriol (4.0 g, 27.4 mmol), triethylamine (11.4 ml, 82.0 mmol) and 4-dimethylaminopyridine (catalytic amount) were dissolved in dichloromethane (175 ml) and the solution was cooled to 0 °C. p-toluenesulphonyl chloride (7.9 g, 41.0 mmol) was dissolved in dichloromethane (100 ml) and added dropwise to the cold solution under an one hour period. This solution was stirred in room temperature for 14 hours and then washed with saturated sodium bicarbonate and citric acid solutions. The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (silica, dichloromethane-ethanol 0-15%) giving a yellowish oil. 6.9 g, 84% yield. ^1H NMR ($CDCl_3$) δ: 7.79 (d, J=8 Hz, 2H), 7.35 (d, J=8 Hz, 2H), 4.15 (m, 3H), 4.04 (dd, J=8 Hz, J=6 Hz, 1H), 3.51 (dd, J=8 Hz, J=6 Hz, 1H), 2.45 (s, 3H), 1.88 (m, 2H), 1.34 (s, 3H), 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 144.8, 132.8, 129.8, 127.9, 109.0, 72.2, 69.0, 67.4, 33.1, 26.8, 25.5, 21.6. IR (film) 1600 cm^{-1}. $[\alpha]_D$ -15.3° (c=1.0, dichloromethane). Anal calcd, for $C_{14}H_{20}O_5S$: C: 56.0%; H: 6.7%; O: 26.6%; S:10.8%. Found: C: 56.5%; H: 7.1%.

(S)-6-Aza-9,10-dihydroxy-9,10-O-isopropylidene-6-(trifluoroacetyl)-decanal ethylene acetal (17). Sodium hydride (0.3 g, 10.0 mmol) was added to *N,N*-dimethylformamide (8 ml) under nitrogen atmosphere. *N*-(5-pentylal ethylene acetal)-trifluoroacetamide (**9**) (2.0 g, 8.3 mmol) was dissolved in *N,N*-dimethylformamide (5 ml) and added dropwise to the slurry. This mixture was heated to 80 °C for 35 minutes. (S)-Tosyloxy-1,2-*O*-isopropylidene-1,2-butanediol (2.5 g,8.3 mmol) was dissolved in *N,N*-dimethylformamide (10 ml) and added dropwise to the heated solution, which was stirred at 80 °C for 14 hours. This mixture was partitioned between dichloromethane and brine. The organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (aluminium oxide, petroleum ether-ethyl acetate 0-70%) giving a colourless oil. 1.28 g, 42% yield. ^1H NMR ($CDCl_3$) δ: 4.81 (t, J=5 Hz, 1H), 4.06-4.01 (m, 2H), 3.94-3.78 (m, 4H), 3.57-3.32 (m, 5H), 1.90-1.73 (m, 6H), 1.70-1.40 (m, 2H), 1.38 (s; 3H), 1.30 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 156.6 (q, J=28 Hz), 116.4 (q, J=288 Hz), 109.3, 109.0, 104.1, 104.0, 73.4, 73.1, 69.0, 68.9, 64.8, 47.9, 47.0, 44.5, 33.2, 33.1, 30.8, 28.5, 26.8, 26.6, 25.4, 21.1, 20.8. ^{19}F NMR ($CDCl_3$) δ: -62.0. IR (film): 1680 cm^{-1}. $[\alpha]_D$ -1.6° (c=1.0, dichloromethane). Anal calcd. for $C_{16}H_{26}F_3NO_5$: C: 52.0%; H: 7.1%; F:15.4%; O 21.6%; N: 3.8%. Found C: 52.7% ;H: 7.3%.

(S)-6-Aza-9,10-dihydroxy-9,10-O-isopropylidenedecanal ethylene acetal (18). Aqueous potassium hydroxide (6%, 8 ml) and methanol (16 ml) were mixed and poured over the trifluoroacetamide (**17**) (1.0 g, 2.71 mmol). This solution was stirred in room temperature for four hours and extracted with dichloromethane. The organic phase was dried and evaporated to dryness giving a colourless oil. 0.74 g, 100% yield. ^1H NMR ($CDCl_3$) δ: 4.79 (t, J=5 Hz, 1H), 4.09 (q, J=6 Hz, 1H), 4.01 (dd, J=8 Hz, J=6

Hz, 1H), 3.93-3.77 (m, 4H), 3.48 (dd, J=8 Hz, J=6 Hz, 1H), 2.71-2.55 (m, 4H), 2.02 (b, 1H), 1.76-1.39 (m, 8H), 1.35 (s, 3H), 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 108.7, 104.4, 74.8, 69.5, 64.8, 49.9, 46.7, 34.0, 33.7, 30.0, 26.9, 25.7, 21.8. IR (film) 3320 cm^{-1}. $[\alpha]_D$ 2.9° (c=1.0, dichloromethane). Anal calcd. for $C_{14}H_{27}NO_4$: C: 61.5%; H: 9.9%; N: 5.1%; O: 23.4%. Found C: 61.3%; H: 9.9%. MS: m/z (relative intensity) 272(2), 258(25), 158(54), 101(25), 100(100), 87(37), 73(33), 44(29).

(2S, 5R, 10S)-2-hydroximethyl-1-oxaquinolizidine (3). The amine (**18**) (0.26 g, 0.95 mmol) was dissolved in dichloromethane (25 ml). p-Toluenesulphonic acid mono hydrate (0.20 g, 1.05 mmol) and water (0.55 g) were added. This mixture was stirred in room temperature for 48 hours and extracted with saturated sodium bicarbonate solution. The organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (aluminium oxide, dichloromethane-ethanol 0-25%) giving pale yellow crystals. 80 mg, 50% yield. Mp 53-54 °C. ^1H NMR ($CDCl_3$) δ: 3.60-3.54 (m, 3H), 3.48 (dd, J=12 Hz, J=3 Hz, 1H), 2.93 (ddd, J=12 Hz, J=5 Hz, J=2 Hz, 1H), 2.80 (dddd, J=8 Hz, J=8 Hz, J=4 Hz, J=1 Hz, 1H), 2.34 (ddd, J=12 Hz, J=12 Hz, J=3 Hz, 1H), 2.34 (b, 1H), 2.07 (ddd, J=12 Hz, J=10 Hz, J=4 Hz, 1H), 1.83-1.23 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 92.2, 77.3, 65.7, 53.0, 52.6, 31.3, 26.1, 25.0, 22.5. IR 3360 cm^{-1}. $[\alpha]_D$ 1.9°(c=1.0, dichloromethane). Anal calcd. for $C_9H_{17}NO_2$: C: 63.1%; H: 10.0%; N: 8.2%; O: 18.7%. Found C: 63.7%;H: 10.2%.MS: m/z (relative intensity) 170(18), 140(100).

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