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Enantiospecific Synthesis of 8-*O*-Methylthioswainsonine from a Derivative of *D*-Glucose[1]

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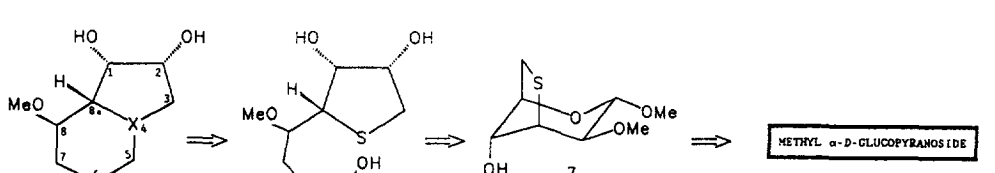
Abstract: The thioanalogue **1**, (1*R*,2*S*,4*S*,8*R*,8a*S*)-1,2,8-trihydroxy-8-*O*-methylthioindolizidine of 8-*O*-methylswainsonine **2** has been enantiospecifically synthesized from the important key intermediate methyl 2-*O*-methyl-3,6-thioanhydro-α-*D*-mannopyranoside **7**, in five steps. Formation of the bicyclic system in **1** took place with a high stereoselectivity. Compound **7** was obtained in eight steps from the readily available methyl α-D-glucopyranoside.

In recent years we have reported on the enantiospecific synthesis of some thioanalogues of important glycosidase inhibitors such as 1-deoxythiomanojirimycin[2] and polyhydroxythiolane derivatives[3], using 2,6- and 3,6-thioanhydrohexosides as starting chiral templates. On the other hand, Grierson *et al.*[4] have reported the synthesis of a thioanalogue of castanospermine, where the -CHOH- group at the 1-position was substituted by a sulfur. Our group is also interested in the enantiospecific synthesis of the thioanalogue **1** of 8-*O*-methylswainsonine **2**. In relation with such synthesis, an important key intermediate (2*R*,3*R*,4*S*)-3-benzyloxy-4-hydroxy-2-[(*R*)-1-benzyloxy-4-hydroxybutyl]thiolane has been described[3b], but because of some initial steps being troublesome, we decided to design a new synthetic route.

Scheme I

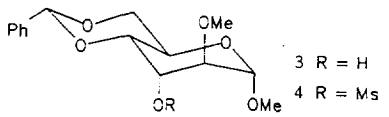


1 X = S+A-
2 X = N

The required methyl 2-*O*-methyl-3,6-thioanhydro-α-*D*-mannopyranoside **7** (Scheme I) was synthesized from the well-known methyl 2,3-anhydro-4,6-*O*-benzylidene-α-*D*-allopyranoside[5] in five steps, by regioselective

[1]Thioanhydro Sugar derivatives, Part VII. For Part VI, see Ref. 1.

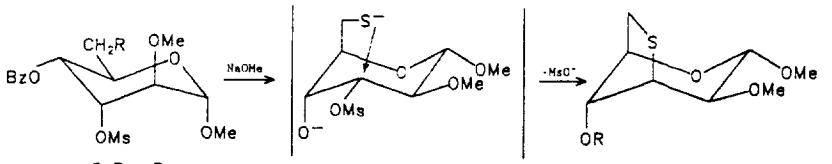
opening of the oxirane ring by methanolic sodium methoxide according to the Robertson and Griffith procedure[6] to give methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-altropyranoside **3** instead of the related 2-*O*-benzyl derivative used in the paper above mentioned[3b]. The change of the protecting group at C-2 was necessary because in a later opening of the 4,6-*O*-benzylidene group by NBS the bromine radical caused partial debenzylation to give a complex mixture. Although compound **3** has been mentioned by other authors[7] no precise ^{1}H and ^{13}C-NMR spectroscopic data have been reported, so they are included herein; the assignment of the ^{13}C resonance signals being made by running a 2D ^{13}C-^{1}H shift-correlation spectrum. Conventional methanesulfonylation of **3** gave the corresponding 3-*O*-methanesulfonyl derivative **4**.



Treatment of **4** with NBS in carbon tetrachloride afforded methyl 4-*O*-benzoyl-6-bromo-6-deoxy-3-*O*-methanesulfonyl-2-*O*-methyl-α-*D*-altropyranoside **5**. Reaction of **5** with potassium thioacetate in DMF proceeded smoothly and regiospecifically at C-6 to produce the related 6-acetylthio-6-deoxy derivative **6**, with no nucleophilic substitution product at C-3 was detected. The upfield-shift of the resonance signals showed by H-6,6' and C-6 in the NMR spectra of **6** were in accordance with the above substitution.

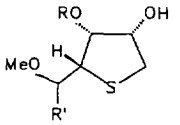
Treatment of compound **6** with methanolic sodium methoxide caused the loss of the acyl protecting group and a concomitant ring closure by nucleophilic displacement of the methanesulfonyloxy group by the mercaptide anion (Scheme II) to afford methyl 2-*O*-methyl-3,6-thioanhydro-α-*D*-mannopyranoside **7**. This new synthesis precluded the formation of elimination products during the required inversion at C-3 previously reported[3b]. The analytical and spectroscopic data of **7** agreed with the proposed structure.

Scheme II

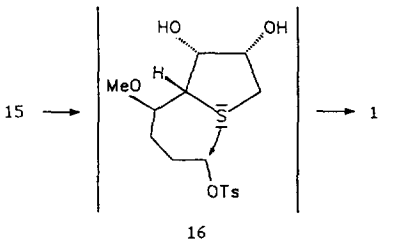


Conventional benzylation of **7** gave the corresponding 4-*O*-benzyl derivative **8** that was hydrolyzed in 70% aqueous trifluoroacetic acid to the uncharacterised aldehyde **9** that was subsequently reduced with $NaBH_4$ to give (2*R*,3*R*,4*S*)-3-benzyloxy-4-hydroxy-2-[(*R*)-2-hydroxy-1-methoxyethyl]thiolane **10**. Birch reduction [Na/NH_3(liq)] of **10** produced the related polyhydroxythiolane **11**. On the other hand, **9** reacted with methoxycarbonylmethylenetriphenylphosphorane in dichloromethane to afford methyl (*R*)-4-[(2'*R*,3'*R*,4'*S*)-3'-benzyloxy-4'-hydroxythiolan-2'-yl]-4-methoxy-2-butenoate **12** as an ≈1:1 *E*/*Z* mixture, which was subsequently

hydrogenated to the saturated ester **13**. Reduction of **13** with $LiAlH_4$ in ether gave (2*R*,3*R*,4*S*)-3-benzyloxy-4-hydroxy-2-[(*R*)-4-hydroxy-1-methoxybutyl]thiolane **14**.



9 R = Bn; R' = CHO
10 R = Bn; R' = CH_2OH
11 R = H; R' = CH_2OH
12 R = Bn; R' = $HC{=}CHCO_2Me$
13 R = Bn; R' = $(CH_2)_2CO_2Me$
14 R = Bn; R' = $(CH_2)_3OH$
15 R = H; R' = $(CH_2)_3OH$



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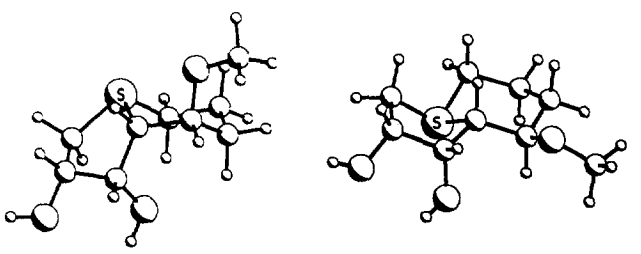
Debenzylation of **14** by the above method provided 3,4-dihydroxythiolane derivative **15**. Finally, reaction of **15** with *p*-toluenesufonyl chloride showed (TLC) the formation of a faster running product, presumably the corresponding *p*-toluenesulfonate of the 4-hydroxy-1-methoxybutylic side chain **16** not isolated. Attempts to purify **16** by column chromatography caused an internal nucleophilic displacement of the *p*-toluenesulfonyloxy group by the sulfur to produce the required sulfonium salt **1**. A similar cyclization process has been described by Urban *et al.*[8], where they obtained thiolanium salt from acyclic derivatives. ^1H, ^{13}C and 2D ^{13}C-^1H heteronuclear shift-correlation spectra as well as mass spectral fragmentation patterns were in agreement with the proposed structure for **1**.

Formation of bicyclic system in **1** could be proceeded either in a *cis* or *trans* manner. From the results obtained, we concluded that the process had occurred with a high stereoselectivity, since only one product was isolated. The configuration at the new stereogenic center (S-4) was tentatively assigned as 4*S* from the following data. The $J_{8,8a}$ value (3 Hz) was in accordance with a *trans*-diequatorial disposition for H-8,8a indicating a bicyclic system *cis*-fusioned, since a *trans*-fusioned system would require a higher $J_{8,8a}$ value due to their *trans*-diaxial disposition for such protons. In addition, theoretical calculations[9-11] on both epimers (see fig. 1), clearly showed the 4*S*-epimer to be of lower energy.



8-*O*-Methylthioswainsonine (*S*, 12.9 Kcal/mol) 8-*O*-Methylthioswainsonine (*R*, 16.5 Kcal/mol)

Figure 1

Experimental

General: Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin-Elmer 782 instrument and mass spectra with a Hewlett-Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds, for which elemental analyses were not obtained were shown to be homogeneous by chromatography and characterised by NMR and mass spectrometry.

Methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-*D*-altropyranoside 3: Compound **3** was obtained from methyl 2,3-anhydro-4,6-*O*-benzylidene-α-*D*-allopyranoside[5] by the Robertson procedure[6] and had m.p. 96-98°C, $[\alpha]_D^{25}$: +98 (c 1). [lit.[6], m.p. 98-99°C, $[\alpha]_D^{15}$: +102.7 (c 3.22)]. NMR data: ^1H, δ 7.51-7.34 (m, 5 H, Ph), 5.62 (s, 1 H, C<u>H</u>Ph), 4.74 (s, 1 H, H-1), 4.33 (dd, 1 H, $J_{5,6eq}$ 5.1, $J_{6ax,6eq}$ 10.2 Hz, H-6*eq*), 4.21 (m, 1 H, H-5), 4.17 (dd, 1 H, $J_{4,5}$ 5.1 Hz, H-4), 3.89 (dd, 1 H, $J_{3,4}$ 9.8 Hz, H-3), 3.83 (t, 1 H, $J_{5,6ax}$ 10.2 Hz, H-6*ax*), 3.52 (d, 1H, $J_{2,3}$ 2.9 Hz, H-2), 3.47 (s, 3H, OMe-2), and 3.45 (s, 3 H, OMe-1); ^{13}C, δ 137.36, 129.20, 128.35, and 126.32 (Ph), 102.34 (<u>C</u>HPh), 99.83 (C-1), 79.19 (C-2), 76.66 (C-3), 69.24 (C-6), 66.55 (C-5), 58.57 (OMe-2), 58.33 (C-4), and 55.74 (OMe-1).

Methyl 4,6-*O*-benzylidene-3-*O*-methanesulfonyl-2-*O*-methyl-α-*D*-altropyranoside 4: To an ice-water and stirred solution of **3** (2 g, 6.7 mmol) in dry pyridine (15 mL), methanesulfonyl chloride (0.7 mL, 9 mmol) was added dropwise and the mixture kept at room temperature for 24 h. TLC (3:1 ether-hexane) then revealed the presence of a faster-running compound. The mixtured was poured into ice-water, extracted with Cl_2CH_2 and the extracts washed with aqueous 10% hydrochloric acid, water, saturated $NaHCO_3$ solution, water and then concentrated. Column chromatography (2:1 ether-hexane) of the residue gave crystalline **4** (2.27 g, 91%), m.p. 115-117°C, $[\alpha]_D^{25}$: +84.4 (c 1); ν_{max}^{KBr} 3038 and 3025 (C-H, aromatic), 2946, 2920 and 2881 (C-H), 766 and 702 cm^{-1} (aromatic). NMR data: ^1H, δ 7.47-7.35 (m, 5 H, Ph), 5.59 (s, 1 H, C<u>H</u>Ph), 5.01 (t, 1 H, $J_{2,3} = J_{3,4}$ = 3 Hz, H-3), 4.69 (s, 1 H, H-1), 4.32 (dd, 1 H, $J_{5,6eq}$ 5.2, $J_{6ax,6eq}$ 10 Hz, H-6*eq*), 4.20 (dt, 1 H, H-5), 4.01 (dd, 1 H, $J_{4,5}$ 10 Hz, H-4), 3.77 (t, 1 H, $J_{5,6ax}$ 10 Hz, H-6*ax*), 3.66 (d, 1H, H-2), 3.50 (s, 3H, OMe-2), 3.40 (s, 3 H, OMe-1), and 2.94 (s, 3 H, OMs); ^{13}C, δ 137.20, 129.31, 128.40, and 126.11 (Ph), 102.25 (<u>C</u>HPh), 99.40 (C-1), 79.04 (C-2), 74.12 and 73.97 (C-3,4), 69.23 (C-6), 58.97 (OMe-2), 58.38 (C-5), 55.66 (OMe-1), and 38.62 (OMs). Mass spectrum: *m/z* 375 (0.22%, M^+), 374 (0.39, M^+-1), 373 (0.82, M^+-2), 265 (0.38, M^+-OMe-SO_2Me), 264 (2.49, M^+-1-OMe-SO_2Me), 165 (100), 105 (11.19, $C_7H_5O^+$), and 79 (34.86, $MeSO_2^+$). Anal. Calcd. for $C_{16}H_{23}O_8S$: C, 51.20; H, 6.17; S, 8.54. Found: C, 51.66; H, 6.02; S, 8.02.

Methyl 4-*O*-benzoyl-6-bromo-6-deoxy-3-*O*-methanesulfonyl-2-*O*-methyl-α-*D*-altropyranoside 5: A stirred suspension of **4** (2.07 g, 5.5 mmol), NBS (1.4 g, 7.8 mmol) and $BaCO_3$ (3.4 g, 17.26 mmol) in dry CCl_4 (40 mL) was heated under reflux for 2 h. During this time the initially red solution became colourless. TLC (3:1 ether-hexane) then revealed a new compound of lower mobility. The reaction mixture was filtered and the filtrate washed with 10% aqueous sodium thiosulfate and brine, then concentrated. Column chromatography (2:1 ether-hexane) of the residue gave **5** (2 g, 80%) as a colourless syrup; $[\alpha]_D^{25}$: +74 (c 1); ν_{max}^{film} 3105 and 3066 (C-H, aromatic), 2939 and 2838 (C-H), 1728 (C=O, benzoate), and 714 cm^{-1} (aromatic). NMR data: ^1H, δ 8.02-7.45 (m, 5 H, Ph), 5.30 (dd, 1 H, $J_{3,4}$ 3.4, $J_{4,5}$ 9.4 Hz, H-4), 5.15 (t, 1 H, H-3), 4.79 (s, 1 H, H-1), 4.40 (ddd, 1 H, $J_{5,6}$ 7.3 Hz, H-5), 3.67 (d, 1 H, $J_{2,3}$ 3 Hz, H-2), 3.60 (dd, 1 H, $J_{5,6}$ 2.6, $J_{6,6}$ 11 Hz, H-6), 3.54-3.40 (m, 1 H, H-6'), 3.51 and 3.47 (2 s, 6 H, 2 OMe), and 2.95 (s, 3 H, OMs); ^{13}C, δ 165.28 (Ph<u>C</u>O), 133.80, 129.86, 128.94, and 128.69 (Ph), 99.68 (C-1), 77.95, 73.90, 68.22, and 66.24 (C-2,3,4,5), 58.77 (OMe-2), 55.77 (OMe-1), 38.57 (OMs), and 32.16 (C-6). Mass spectrum: *m/z* 423 (28.4%, M^++1-OMe), 421 (28.4 M^+-1-OMe), 373 (1.2, M^++1-SO_2Me), 217 (12.4), and 105 (100, $C_7H_5O^+$). Anal. Calcd. for $C_{16}H_{21}BrO_8S$: C, 42.40; H, 4.66; S, 7.07. Found: C, 42.50; H, 4.74; S, 6.76.

Methyl 6-*S*-acetyl-4-*O*-benzoyl-3-*O*-methanesulfonyl-2-*O*-methyl-6-*thio*-α-*D*-altropyranoside 6: To a stirred solution of **5** (1.8 g, 4 mmol) in dry DMF (17 mL) was added potassium thioacetate (0.7 g, 6.1 mmol) portionwise under argon, and the mixture left at room temperature overnight. TLC (3:1 ether-hexane) then revealed a new compound of slightly lower mobility. The solvent was evaporated and the residue in CH_2Cl_2 (25 mL) washed with brine and water, then concentrated. Column chromatography (2:1 ether-hexane) of the residue gave **6** (1.7 g, quantitative) as a syrup; $[\alpha]_D^{25}$: +86 (c 1.5); ν_{max}^{film} 3065 (C-H, aromatic), 2939 and 2837 (C-H), 1729 (C=O, benzoate), 1694 (C=O, thioacetate), 736 and 714 cm^{-1} (aromatic). NMR data: ^1H, δ 8.09-4.47 (m, 5 H, Ph), 5.25 (dd, 1 H, $J_{3,4}$ 3.4, $J_{4,5}$ 9.3 Hz, H-4), 5.15 (t, 1 H, H-3), 4.71 (bs, 1 H, H-1), 4.27 (dt, 1 H, H-5), 4.20 (dd, 1 H, $J_{5,6}$ 3.2, $J_{6,6'}$ 14 Hz, H-6), 3.65 (dd, 1 H, $J_{1,2}$ 1.4, $J_{2,3}$ 3.7 Hz, H-2), 3.51 (s, 3 H, OMe-2), 3.42 (s, 3 H, OMe-1), 3.02 (dd 1 H, $J_{5,6'}$ 8.2 Hz, H-6'), 2.92 (s, 3 H, OMs), and 2.32 (s, 3 H, SAc); ^{13}C, 194.73 (S<u>C</u>OMe), 165.51 (<u>C</u>OPh), 133.70, 129.94, 129.21, and 128.70 (Ph), 99.58 (C-1), 78.05, 73.89,1 68.46, 66.05 (C-2,3,4,5), 58.87 (OMe-2), 55.70 (OMe-1), 38.47 (OMs), 30.68 (C-6), and 30.49 (SCO<u>Me</u>). Mass spectrum: *m/z* 448 (0.4%, M^+), 417 (14 M^+-OMe), 375 (9.6), 279 (12.8), 217 (21.6), 191 (33.6), and 105 (100, $C_7H_5O^+$). Anal. Calcd. for $C_{18}H_{24}O_9S_2$: C, 48.20; H, 5.40; S, 14.30. Found: C, 47.75; H, 5.25; S, 14.06.

Methyl 2-*O*-methyl-3,6-*thioanhydro*-α-D-mannopyranoside 7: To a stirred solution of **6** (11.25 g, 25 mmol) in dry benzene (60 mL), 1 *M* methanolic sodium methoxide (50 mL) was added dropwise, and the mixture maintained at room temperature for 3 h. TLC (2:1 EtOAc-hexane) of the deep brown solution showed the absence of **6** and the presence of a slower-running product. The mixture was neutralised with acetic acid, concentrated and the residue extracted with EtOAc. The combined extracts were washed with brine and concentrated to give a residue that was chromatographed (ether) to afford crystalline **7** (2.6 g, 51%), m.p. 87-

89°C, $[\alpha]_D^{28}$: +96 (c 1); ν_{max}^{KBr} 3243 (OH), 2953 and 2929 cm^{-1} (C-H). NMR data: ^1H, δ 4.78 (d, 1 H, $J_{1,2}$ 6.6 Hz, H-1), 4.40 (dd, 1 H, $J_{4,5}$ 2.6 Hz, H-5), 4.19 (dd, 1 H, $J_{3,4}$ 4.6 Hz, H-4), 3.55 (dd, 1 H, $J_{2,3}$ 3.2 Hz, H-2), 3.53 (s, 3 H, OMe-2), 3.49 (dd, 1 H, H-3), 3.44 (s, 3 H, OMe-1), 3.01 (dd, 1 H, $J_{5,6exo}$ 4.6, $J_{6exo,6endo}$ 12.5 Hz, H-6*exo*), and 2.82 (d, 1 H, H-6*endo*); ^{13}C, δ 102.33 (C-1), 77.53 (C-5), 77.10 (C-2), 75.72 (C-4), 58.40 (OMe-2), 57.82 (OMe-1), 47.35 (C-3), and 30.10 (C-6). Mass spectrum: *m/z* 207 (4.4%, M^+), 176 (0.3, M^+-2-MeOH), 175 (0.6, M^++1-MeOH), 174 (4.4, M^+-MeOH), 146 (8.3), 113 (11.7) and 87 (100). Anal. Calcd. for $C_8H_{14}O_4S$: C, 46.58; H, 6.84; S, 15.54. Found: C, 45.96; H, 6.63; S, 15.37.

Methyl 4-O-benzyl-2-*O*-methyl-3,6-*thioanhydro*-α-*D*-mannopyranoside 8: To an ice-water cooled and stirred solution of **7** (360 mg, 1.7 mmol) in anhydrous THF (15 mL) a solution of potassium *tert*-butoxide (315 mg, 2.8 mmol) in the same solvent (5 mL) and benzyl bromide (0.3 mL, 2.6 mmol) were added. The mixture was left at room temperature for 2 h. TLC (4:1 EtOAc-hexane) then revealed the absence of **7** and the presence of a faster-running compound. The mixture was neutralized with acetic acid, concentrated and the residue extracted with ether (25 mL). The combined extracts were washed with brine and then concentrated. Column chromatography (1:3 → 3:1 ether-hexane) of the residue yielded syrupy **8** (310 mg, 62%), $[\alpha]_D^{25}$: +55 (c 1); ν_{max}^{film} 3064 and 3033 (C-H, aromatic), 2954, 2938, and 2828 (C-H), 1455 (benzyl), 740 and 698 cm^{-1} (aromatic). NMR data: ^1H, δ 7.37-7.25 (m, 5 H, Ph), 4.80 (d, 1 H, $J_{1,2}$ 6.7 Hz, H-1), 4.72 and 4.60 (2 d, 2 H, J 12.2 Hz, C$\underline{H}_2$Ph), 4.56 (t, 1 H, H-4), 3.87 (dd, 1 H, $J_{4,5}$ 3 Hz, H-5), 3.57 (dd, 1 H, $J_{2,3}$ 3 Hz, H-2), 3.53 (s, 3 H, OMe-2), 3.46 (t, 1 H, $J_{3,4}$ 4 Hz, H-3), 3.39 (s, 3 H, OMe-1), 2.92 (dd, 1 H, $J_{5,6exo}$ 5, $J_{6exo,6endo}$ 12.3 Hz, H-6*exo*), and 2.78 (d, 1 H, H-6*endo*); ^{13}C, δ 137.67, 128.64, 128.14, and 128.05 (Ph), 102.21 (C-1), 81.71 (C-4), 76.11 (C-5), 74.24 (C-2), 72.34 (C$\underline{H}_2$Ph), 58.85 (OMe-2), 57.03 (OMe-1), 45.40 (C-3), and 30.19 (C-6). Mass spectrum: *m/z* 296 (0.4%, M^+), 265 (0.4, M^+-OMe), 236 (0.8), 177 (24.9), and 91 (100, $C_7H_7^+$). Anal. Calcd. for $C_{15}H_{20}O_4S$: C, 60.78; H, 6.80; S, 10.81. Found: C, 60.53; H, 6.80; S, 10.22.

(2*R*,3*R*,4*S*)-3-Benzyloxy-4-hydroxy-2-[(*R*)-2-hydroxy-1-methoxyethyl]thiolane 10: A solution of **8** (1 g, 3.3 mmol) in aqueous 70% trifluoroacetic acid (5 mL) was heated at 70° for 1 h. TLC (1:1 EtOAc-hexane) then revealed a slower running compound. The mixture was concentrated and the residue disolved in dry methanol (10 mL), neutralised (K_2CO_3) and filtered. The filtrate was treated with $NaBH_4$ (230 mg) portionwise. After 1 h, TLC (EtOAc) then showed the presence of a slower-running product. The mixture was neutralised with acetic acid, concentrated and the residue extracted with EtOAc and the combined extracts washed with brine and then concentrated. Column chromatography (2:1 ether-hexane) of the residue gave crystalline **10** (330 mg, 40%), m.p. 172-174°C, $[\alpha]_D^{27}$: +36 (c 1, methanol); ν_{max}^{KBr} 3286 (OH), 3088, 3068, and 3035 (C-H, aromatic), 2944, 2885, and 2828 (C-H), 1450 (benzyl), 730 and 693 cm^{-1} (aromatic). NMR data (methanol-d_4, 400 MHz): ^1H, δ 7.45-7.22 (m, 5 H, Ph), 5.02 and 4.66 (2 d, 2 H, J 11.3 Hz, C$\underline{H}_2$Ph), 4.28 (ddd, 1 H, H-4), 4.12 (t, 1 H, $J_{2,3} = J_{3,4}$ = 3.3 Hz, H-3), 3.87 (dd, 1 H, $J_{6,7}$ 2.2, $J_{7,7'}$ 12.5 Hz, H-7), 3.59 (dd, 1 H, $J_{2,6}$ 10 Hz, H-2), 3.53 (dt, 1 H, H-6), 3.40 (dd, 1 H, $J_{6,7'}$ 3.2 Hz, H-7'), 3.31 (s, 3 H, OMe), 2.90 (t, 1 H, $J_{4,5} = J_{5,5'}$ = 10 Hz, H-5),

and 2.82 (dd, 1 H, $J_{4,5'}$ 6.7 Hz, H-5'); ^{13}C, δ 140.49, 129.21, 128.56, and 128.36 (Ph), 83.49 (C-3), 82.41 (C-4), 78.49 (C-6), 75.32 ($\underline{C}H_2Ph$), 61.03 (C-7), 57.28 (OMe), 47.76 (C-2), and 33.45 (C-5). Anal. Calcd. for $C_{14}H_{20}O_4S$: C, 59.12; H, 7.00; S, 11.27. Found: C, 59.84; H, 6.89; S, 11.65.

(2*S*,3*R*,4*S*)-3,4-Dihydroxy-2-[(*R*)-2-hydroxy-1-methoxyethyl]thiolane 11: A solution of **10** (70 mg, 0.25 mmol) in anhydrous THF (5 mL) was added to a stirred and cooled (-40°) solution of sodium (130 mg) in liquid NH_3 (*ca.* 50 mL) under argon. The mixture was stirred for 3 h and then at room temperature for 1 h. The mixture was quenched with NH_4Cl (400 mg) and the NH_3 was evaporated. The residue was suported on silica and chromatographed (10:1 ether-methanol) to give **11** (30 mg, 62%) as a solid foam; $[\alpha]_D^{27}$: +32 (c 1.25, methanol). NMR data (methanol-d_4): ^{1}H, δ 4.21-4.11 (m, 2 H, H-3,4), 3.81 (dd, 1 H, $J_{6,7}$ 2.3, $J_{7,7'}$ 12.2 Hz, H-7), 3.55 (ddd, 1 H, H-6), 3.48 (s, 3 H, OMe), 3.46 (dd, 1 H, $J_{2,3}$ 3.5, $J_{2,6}$ 10 Hz, H-2), 3.39 (dd, 1 H, $J_{6,7'}$ 4 Hz, H-7'), 2.89 (t, 1 H, $J_{4,5} = J_{5,5'}$ = 10 Hz, H-5), and 2.81 (dd, 1 H, $J_{4,5'}$ 7 Hz, H-5'); ^{13}C, δ 82.55 (C-3), 77.74 (C-4), 74.57 (C-6), 62.22 (C-7), 58.28 (OMe), 48.06 (C-2), and 33.11 (C-5). Anal. Calcd. for $C_7H_{14}O_4S$: C, 43.28; H, 7.26; S, 16.50. Found: C, 43.32; H, 7.60; S, 16.30.

Methyl (*E/Z*) (*R*)-4-[(2'*R*,3'*R*,4'*S*)-3'-benzyloxy-4'-hydroxythiolan-2'-yl]-4-methoxy-2-butenoate 12: A solution of **8** (1 g, 3.3 mmol) in aqueous 70% trifluoroacetic acid (5 ml) was heated at 70°C for 1 h. TLC (1:1 EtOAc-hexane) then revealed the presence of a new slower-running product. The reaction mixture was concentrated and repeatly codistilled with dichloromethane. The residue was disolved in dichloromethane (25 mL), methoxycarbonylmethylenetriphenylphosphorane (1.33 g, 4 mmol) was added and the mixture was left at room temperature for 3 days. TLC (1:1 EtOAc-hexane) then showed the presence of a new compound of higher mobility. The solvent was evaporated and the residue chromatographed (1:3 EtOAc-hexane) to afford syrupy **12** (0.97 g, 87%) as a ≈ 1:1 *E/Z* mixture; $[\alpha]_D^{24}$: +59 (c 1); ν_{max}^{film} 3460 (OH), 3068 and 3032 (C-H, aromatic), 1725 (C=O, ester), 1662 (C=C), 1455 (benzyl), 750 and 699 cm^{-1} (aromatic). NMR data: ^{1}H, δ 6.73 (dd, $J_{2,3}$ 15.8, $J_{3,4}$ 7.7 Hz, H-3 (*E*-isomer)), 6.21 (dd, $J_{2,3}$ 11.7, $J_{3,4}$ 8.8 Hz, H-3 (*Z*-isomer)), 6.07 (dd, $J_{2,4}$ 0.8 Hz, H-2 (*E*-isomer)), 5.96 (dd, $J_{2,4}$ 1.2 Hz, H-2 (*Z*-isomer)); ^{13}C, δ 166.32, 166.14 (2 C-1), 148.06, 145.40 (2 C-3), 124.57, 122.33 (2 C-2), 74.69, 73.69 (2 CH_2Ph), 57.67, 56.92 (2 OMe), 51.82, 51.58 (2 $CO_2\underline{Me}$), 50.58, 50.51 (2 C-2'), 34.92, 33.98 (2 C-5'). Anal. Calcd. for $C_{17}H_{22}O_5S$: C, 60.29; H, 6.55; S, 9.46. Found: C, 60.39; H, 6.55; S, 9.26.

Methyl (*R*)-4-[(2'*R*,3'*R*,4'*S*)-3'-benzyloxy-4'-hydroxy-thiolan-2'-yl]-4-methoxybutanoate 13: A solution of **12** (660 mg, 1.95 mmol) in methanol (40 mL) was hydrogenated over Palladium hydroxide on carbon at 4 atm for 24 h. The mixture was filtered, the catalyst washed with methanol and the combined filtrate and washings concentrated. Column chromatography (1:3 EtOAc-hexane) of the residue afforded crystalline **13** (445 mg, 67%), m.p. 57-59°C, $[\alpha]_D^{25}$ -63 (c 1); ν_{max}^{KBr} 3461 (OH), 3090, 3067 and 3034 (C-H, aromatic), 1740 (C=O, ester), 1455 (benzyl), 740 and 699 cm^{-1} (aromatic). NMR data: ^{1}H, δ 7.37-7.25 (m, 5 H, Ph), 4.83 and 4.68

(2 d, 2 H, J 11.7 Hz, C$\underline{H}_2$Ph), 4.22 (ddd, 1 H, $J_{4',5'}$ 6.8, $J_{4',5''}$ 9.4 Hz, H-4'), 4.13 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 3.7 Hz, H-3'), 3.70 (m, 1 H, H-4), 3.66 (s, 3 H, CO_2Me), 3.43 (dd, 1 H, $J_{2',4}$ 9.4 Hz, H-2'), 3.32 (s, 3 H, OMe), 2.94-2.78 (m, 2 H, H-5,5'), 2.41-2.14 and 1.84-1.73 (2 m, 5 H, relative intensity 4:1, C$\underline{H}_2$C$\underline{H}_2$,OH); ^{13}C, δ 174.02 (C-1), 138.34, 128.73, 128.04, and 127.69 (Ph), 81.98 (C-4'), 78.70 (C-3'), 76.25 (C-4), 74.54 (C$\underline{H}_2$Ph), 56.16 (OMe), 51.72 ($CO_2\underline{Me}$), 49.01 (C-2'), 33.91 (C-5'), 28.05 (C-2), and 24.60 (C-3). Anal. Calcd. for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11; S, 9.42. Found: C, 60.57; H, 7.18; S, 9.27.

(2*R*,3*R*,4*S*)-3-Benzyloxy-4-hydroxy-2-[(*R*)-4-hydroxy-1-methoxybutyl]thiolane 14: To a stirred solution of **13** (415 mg, 1.22 mmol) in anhydrous ether (10 mL), lithium aluminium hydride (80 mg, 1.5 mmol) was added and the mixture refluxed for 3 h. TLC (2:1 EtOAc-hexane) then revealed the presence of a new slower-running product. The excess of hydride was decomposed by addition of ether saturated with water, and water. The organic phase was separated, washed with brine and concentrated. Column chromatography (1:3 EtOAc-hexane) of the residue gave **14** (170 mg, 50%) as a syrup; $[\alpha]_D^{23}$: -76 (c 1); ν_{max}^{film} 3386 (OH), 3091, 3066 and 3033 (C-H, aromatic), 1455 (benzyl), 737 and 699 cm^{-1} (aromatic). NMR data (methanol-d_4): ^{1}H, δ 7.43-7.25 (m, 5 H, Ph), 5.01 and 4.66 (2 d, 2 H, J 11.4 Hz, C$\underline{H}_2$Ph), 4.27 (ddd, 1 H, $J_{3,4}$ 3.3 Hz, H-4), 4.10 (t, 1 H, $J_{2,3}$ 3.3 Hz, H-3), 3.65 (dt, 1 H, $J_{1',2'} = J_{1',2''}$ = 4.3 Hz, H-1'), 3.52 (t, 2 H, J 6.5 Hz, C$\underline{H}_2$OH), 3.44 (dd, 1 H, $J_{1,2}$ 10 Hz, H-2), 3.25 (s, 3 H, OMe), 2.97 (dd, 1 H, $J_{4,5}$ 10.3, $J_{5,5'}$ 9.3 Hz, H-5), 2.82 (dd, 1 H, $J_{4,5'}$ 6.8 Hz, H-5'), 1.84-1.73 (m, 1 H, H-2'), and 1.60-1.34 (m, 3 H, H-2'',3',3''); ^{13}C, δ 140.49, 129.22, 128.63, and 128.37 (Ph), 82.42, 80.43, and 78.55 (C-3,4,1'), 75.27 (C$\underline{H}_2$Ph), 63.17 (C-4'), 56.57 (OMe), 50.45 (C-2), 33.32 (C-5), 27.60 and 27.33 (C-2',3'). Anal. Calcd. for $C_{16}H_{24}O_4S$: C, 61.50; H, 7.74; S, 10.26. Found: C, 61.72; H, 7.73; S, 10.31.

(2*S*,3*R*,4*S*)-3,4-Dihydroxy-2-[(*R*)-4-hydroxy-1-methoxybutyl]thiolane 15: A solution of **14** (280 mg, 0.9 mmol) in anhydrous THF (15 mL) was added to a stirred and cooled (-50°) solution of sodium (300 mg) in liquid NH_3 (*ca.* 50 mL) under argon. The mixture was stirred for 2 h and then at room temperature for 1 h. TLC (EtOAc) then showed the presence of a new compound of lower mobility. The mixture was quenched with NH_4Cl and the NH_3 was evaporated. The residue was suported on silica and chromatographed (10:1 ether-methanol) to give **15** (170 mg, 85%) as a syrup; $[\alpha]_D^{24}$: +32 (c 1.2). ν_{max}^{film} 3376 (OH), 2939 and 2836 cm^{-1} (C-H). NMR data (methanol-d_4): ^{1}H, δ 4.20-4.10 (m, 2 H, H-3,4), 3.62 (ddd, 1 H, H-1'), 3.54 (t, 2 H, J 6.4 Hz, C$\underline{H}_2$OH), 3.44 (s, 3 H, OMe), 3.34 (dd, 1 H, $J_{1',2}$ 10, $J_{2,3}$ 3.4 Hz, H-2), 2.90-2.77 (m, 2 H, H-5,5'), and 1.78-1.30 (m, 4 H, H-2',2'',3',3''); ^{13}C, δ 80.84, 77.82, and 74.46 (C-3,4,1'), 63.14 (C-4'), 58.04 (OMe), 51.79 (C-2), 32.94 (C-5), 29.06 and 28.37 (C-2',3'). Mass spectrum: *m/z* 223 (4.7%, M^++1), 205 (7.7, M^++1-H_2O), 191 (5.9, M^++1-MeOH), 174 (11.5, M^++1-OMe-H_2O), 173 (100, M^+-OMe-H_2O), 156 (1.4, M^++1-OMe-2H_2O), and 155 (14.2, M^+-OMe-2H_2O). Anal. Calcd. for $C_9H_{18}O_4S$: C, 48.62; H, 8.16; S, 14.40. Found: C, 48.20; H, 7.89; S, 14.26.

8-*O*-Methylthioswainsonine 1: To a cooled (ice-water) and stirred solution of **15** (145 mg, 0.65 mmol) in dry pyridine (10 mL), *p*-toluenesulfonyl chloride (170 mg, 0.89 mmol) was added. The mixture was kept at room temperature overnight and then was poured into ice-water, extracted with Cl_2CH_2 (2 x 20 mL) and the extracts washed with aqueous 10% hydrochloric acid, water, saturated $NaHCO_3$ solution, water and then concentrated. Column chromatography (20:4:1 MeCN-AcOH-H_2O) of the residue gave crystalline **1** (80 mg, 39%); $[\alpha]_D^{26}$: -11 (c 0.4, methanol); ν_{max}^{KBr} 3415 (OH), 2928 and 2857 cm^{-1} (C-H). NMR data (methanol-d_4): ^1H, δ 3.93 (m, 1 H, H-8), 3.71 (ddd, 1 H, $J_{1,2}$ 2.5, $J_{2,3}$ 11, $J_{2,3'}$ 4.3 Hz, H-2), 3.39 (m, 2 H, H-5,5'), 3.37 (dd, 1 H, $J_{1,8a}$ 10 Hz, H-1), 3.31 (s, 3 H, OMe), 2.92 (dd, 1 H, $J_{8,8a}$ 3 Hz, H-8*a*), 2.86 (dd, 1 H, $J_{3,3'}$ 12.8 Hz, H-3), 2.27 (dd, 1 H, H-3'), and 2.12-1.23 (4 m, 4 H, H-6,6',7,7'); ^{13}C, δ 76.49 (C-1), 74.82 (C-8), 73.70 (C-5), 73.01 (C-2), 58.66 (OMe), 41.33 (C-8*a*), 28.82 (C-3), 28.03 and 27.87 (C-6,7). Mass spectrum (c.i. CH_4): *m/z* 206 (6.8%, M^++1), 205 (62.4, M^+), 188 (7.2, M^++1-H_2O), 187 (69.2, M^+-H_2O), 174 (8.1, M^++1-MeOH), 173 (90.1, M^+-MeOH), 170 (4.3, M^++1-2H_2O), 169 (45.0, M^+-2H_2O), and 155 (100, M^+-MeOH-H_2O).

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