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New Synthetic Approach to Enantiopure Bicyclic Sulfonium Salts: Swainsonine Analogues

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Abstract: The enantioselective synthesis of bicyclic sulfonium salts **8** or **9**, thioanalogues of swainsonine derivatives, is described. The synthetic strategy is based on a stereo- and regiospecific transannular cyclization reaction of nine-membered cyclic sulfides, mediated by Me_3SiI or carried out under acidic catalysis.

Glycosidase enzymes play an important role in the biochemical processes,[1] and their abnormal activity leads to serious diseases. The compounds 1-deoxy-nojirimycin (**A**), castanospermine (**B**), and swainsonine (**C**), depicted in Figure 1, are among the most important therapeutic agents used as glycosidase inhibitors.[2]

As piperidine analogues of glucopyranose, these compounds inhibit several glucosidases and display antidiabetic and antiviral activities, including activity against HIV viruses.[3] In addition their ability to reduce tumor cell metastasis is well documented.[4] Glycosidases and their inhibitors have attracted the interest of many groups of researchers. In particular the development of new synthetic methods and the studies directed to understand the role played by molecular shape and charge on biological activity remain important problems to be investigated.[5]

Many strategic routes for the synthesis of swainsonine derivatives are reported in the literature but only a few examples of analogous compounds in which the bridgehead nitrogen atom is replaced by a sulfur atom have been described so far. The increasing interest toward these sulfonium salts stems from their ability to create electrostatic interactions: the effect of a positively charged

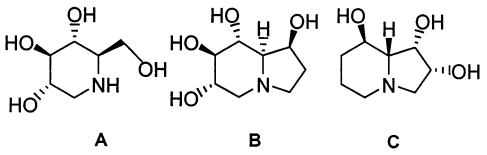

FIGURE 1.

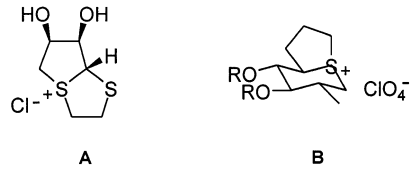

FIGURE 2.

moiety, such as a sulfonium ion in a bicyclic polyhydroxylated system, is likely to increase its potency as a glycosidase inhibitor since the charge separation would mimic the putative oxonium ion transition state that is generated during the carbohydrate hydrolysis by glycosidases. Moreover these sulfur-based compounds exhibit high water solubility and good stability, features of major importance for their evaluation as glycosidase inhibitors.

Several years ago a bicyclic [3.3.0] sulfonium salt was synthesized and tested as a glycosidase inhibitor by Grierson (Figure 2, A).[6]

More recently Pinto et al.[7] (Figure 2, B) described an interesting bicyclic [4.3.0] sulfonium salt derivative that can act as a mimic of castanospermine. All these authors outlined, however, the scarcity of polyhydroxylated cyclic sulfonium salts previously reported in the literature.[8] Moreover, in the last years numerous synthetic and biological studies related to Salacinol and Kotalanol,[9] natural inner-sulfonium salts of therapeutic relevance extracted from the Salacia Reticulata, have been reported and successfully adopted in traditional Ayurvedic medicine for the treatment of diabetes.

All these findings prompted us to direct our efforts on a new synthetic strategy aimed to synthesize a range of bicyclic sulfonium salts, thioanalogues of the swainsonine derivatives, which might constitute new therapeutic targets.

Previous work from this laboratory has described the transannular cyclization of medium-sized sulfurated compounds under acidic conditions by interaction be-

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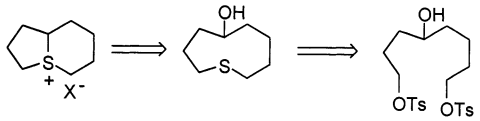
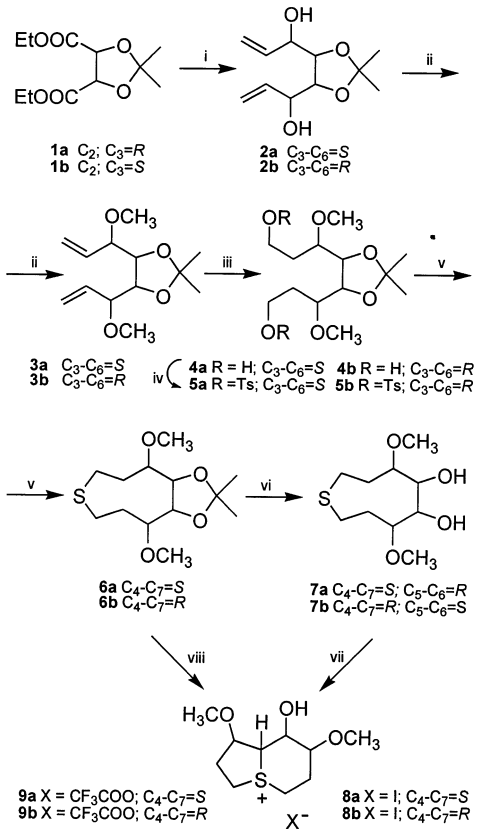


FIGURE 3. Retrosynthetic plan.

SCHEME 1[a]



[a] Reagents and conditions: (i) Dibal-H, $Zn(CH{=}CH_2)_2$, ref 12 (83%); (ii) NaH, MeI (98%); (iii) $BH_3{\cdot}Me_2S$, H_2O_2, NaOH (65%); (iv) pTsCl, Py (95%); (v) $Na_2S{\cdot}9H_2O$ (65%); (vi) 0.1 N H_2SO_4, 30 min, 50 °C (98%); (vii) Me_3SiI (90%); (viii) CF_3COOH in CH_3CN, 2 h, 90°C (90%).

tween the S atom and a double bond.[10] Further on we have reported that a transannular nucleophilic substitution by a sulfur atom on a carbon bearing an hydroxy group also can be achieved, under very mild conditions, by means of the Me_3SiI.[11] With these results in hand, we envisioned a simple new retrosynthetic plan to synthesize a thio-swainsonine analogue by using as a key step in the synthesis a stereo- and regiospecific transannular cyclization of a suitable thiacyclononane derivative (Figure 3).

To address this problem a suitable and straightforward approach to a configurationally homogeneous cyclic sulfide **6** was needed (Scheme 1). Thus, starting from diethyl L- and D-tartrate, enantiopure inexpensive and easily available compounds from the natural pool, we obtained the isopropylidene diene derivatives **2a**,**b**[12] (Scheme 1; compounds deriving from the L-configuration are noted as **a**, and those deriving from the D-configuration are noted as **b**) which were di-*O*-methylated under standard conditions with NaH and CH_3I, to give, in 98% yield, **3a**,**b**. Hydroxylation of the two double bonds by means of $BH_3{\cdot}Me_2S$ followed by treatment with alkaline hydrogen peroxide led to **4a**,**b** in 65% yield. The ditosyl derivatives **5a**,**b** obtained from **4a**,**b**, using *p*-TsCl in pyridine (95%), gave the thiacyclononane derivatives **6a**,**b** (65%) by intramolecular cyclization with $Na_2S{\cdot}9H_2O$. The thiacyclononane derivatives **7a**,**b**, obtained in 98% yield, using 0.1 N H_2SO_4 for 30 min at 50 °C, were submitted to Me_3SiI-mediated[11] transannular nucleophilic substitution leading in 90% yield to the bicyclic systems **8a**,**b**. To avoid in iodide **8a,b** possible equilibration with a form deriving from the five-membered ring-opening and darkening after long-term storage, bicyclic systems bearing nonnucleophilic counterions in the sulfonium salts were taken into consideration as well. Accordingly compounds **9a,b** were obtained in good yields (90%) by treatment of **6a**,**b** with CF_3COOH in CH_3CN for 2 h at 90 °C (CF_3SO_3H and H_2SO_4 also can be used).

Compounds **8** and **9**, obtained in both enantiomeric pure forms, can be considered di-*O*-methylated thia mimics of swainsonine.

In conclusion we have developed a conceptually new approach that should, at least in part, overcome the difficulties often encountered in the synthesis of functionalized thioswainsonine. A good asset of this method that nicely complements the previously reported strategies[6,7] lies in the fact that by using the nine-membered thiacyclo derivatives **6a**,**b**, the presence of a C_2 axis and the complete regio- and stereoselectivity of the transannular substitution leads to a single configurationally homogeneous product irrespective of the fact that the sulfur atom would attack C_5 or C_6. Moreover, the reduced number of steps and the easy availability of the starting materials make this route highly practical and suitable to be applied in a more general way to the synthesis of new thionia derivatives as compounds with potential interesting biological activities. An extensive study ongoing in our laboratory is aimed at the synthesis of new eight- and nine-membered polyhydroxylated sulfurated cycles.

Experimental Section

All moisture-sensitive reactions were performed in flame-dried glassware equipped with rubber septa under positive pressure of dry nitrogen. Organic extracts were dried over $CaSO_4$. Melting points are uncorrected. Preparative flash chromatographic experiments were performed with ICN Silica gel 230−400 mesh. For TLC precoated glass plates were used (Stratochrom SIF_{254}, 0.25 mm thick) and the spots were developed at 110 °C with an aqueous solution of $(NH_4)_6Mo_7O_{24}$ (2.5%) and $(NH_4)_4Ce(SO_4)_4$ (1%) in 10% H_2SO_4 or 0.1 M $KMnO_4$/1 M H_2SO_4 1/1. Yields are for isolated compounds. Unless specified otherwise, ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ as solvent. Chemical shifts are in ppm downfield of TMS and signal multiplicities were established by DEPT experiments. Signal assignments, if necessary, were elucidated by decoupling ^1H NMR. Optical rotations were measured at 589 nm. Infrared spectra were recorded on a FT IR spectrophotometer. Mass spectra were recorded by using electron impact at

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70 eV (EIMS), or electron spray ionization (ESIMS). CH_3CN was distilled from CaH_2 and pyridine from KOH. NaI was heated at 100 °C and 0.1 mmHg for 48 h. Light petroleum had bp 35−60 °C.

(+)-(4*S*,5*S*)-4,5-Bis[(1*S*)-1-methoxy-2-propenyl]-2,2-dimethyl-1,3-dioxolane (3a). The suspension of 1.0 g (22.3 mmol) of 50% NaH, previously washed with light petroleum under N_2, was treated with 4.8 g (22.3 mmol) of (−)-(1*S*)-1-{(4*S*,5*S*)-5-[(1*S*)-1-hydroxy-2-propenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-2-propen-1-ol[12] (**2a**) dissolved in 180 mL of THF. After 10 min 2.8 mL (44.6 mmol) of CH_3I was added, and the reaction mixture was stirred for 1 h. Then 1.0 g of 50% NaH and 2.8 mL of CH_3I were added again, using the same procedure. The residue, obtained by evaporation of the solvent, was treated with 20 mL of H_2O and extracted three time with 30 mL of CH_2Cl_2. The evaporation of the dried organic layer gave a crude product that was purified by flash chromatography (SiO_2−CH_2Cl_2/EtOAc 100/1) obtaining 5.4 g (98%) of the title compound **3a** as a colorless oil. ^{1}H NMR: δ 5.85−5.63 (m, 2H), 5.48−5.16 (m, 4H), 3.90 (m, 2H), 3.59 (d, 2H, J = 7.49 Hz), 3.27 (s, 6H), 1.33 (s, 6H). ^{13}C NMR: δ 134.3, 120.2, 83.9, 80.0, 56.6, 27.0. $[\alpha]_D^{26}$ +10.1 ($CHCl_3$, *c* 1.020). IR (neat): 2986, 2937, 2894, 2823, 1643, 1458, 1424, 1380, 1370, 1242, 1216, 1168, 1092, 1001, 928, 894, 863 cm^{-1}. (EIMS) *m/e* (rel intensity): 242 (<1), 227 (11), 171 (19), 113 (64), 85 (48), 71 (100). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.60; H, 9.10.

(−)-(4*R*,5*R*)-4,5-Bis[(1*R*)-1-methoxy-2-propenyl]-2,2-dimethyl-1,3-dioxolane (3b). The application of the above-described procedure, starting from the diethyl D-tartrate, led to the enantiopure compound **3b**. $[\alpha]_D^{26}$ −10.2 ($CHCl_3$, *c* 1.130).

(−)-(3*S*)-3-{(4*S*,5*S*)-5-[(1*S*)-3-hydroxy-1-methoxypropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-3-methoxy-1-propanol (4a). To 242 mg (1 mmol) of **3a**, dissolved in 5 mL of *n*-hexane and cooled at 0−5 °C, was added 78 μL (0.83 mmol) of BH_3·Me_2S maintaining the temperature at 5 °C. To the reaction mixture, stirred for 3 h at room temperature, was added 2 mL of EtOH and 0.6 mL of 3 N NaOH. After the solution was cooled at 0−5 °C, 270 μL of 30% H_2O_2 was added dropwise without exceeding the internal temperature of 35 °C. The mixture was refluxed for 3 h then, after cooling, was poured into 1 mL of cold brine. The aqueous phase was extracted three time with 10 mL of CH_2Cl_2 and the combined organic layers were dried on $MgSO_4$, filtered ,and evaporated to dryness to give 180 mg (65%) of **4a**. The crude product could be used without further purification. A sample was purified by flash chromatography (SiO_2−Et_2O/MeOH 9/1) to afford the analitically pure title compound as a white oil. ^{1}H NMR: δ 3.97 (m, 2H), 3.73 (t, 4H, J = 5.86 Hz), 3.45 (m, 2H), 3.40 (s, 6H), 2.92 (br s, 2H), 1.81 (m, 4H), 1.35 (s, 6H). ^{13}C NMR: δ 110.2, 81.1, 79.6, 60.0, 58.4, 32.9, 27.5. $[\alpha]_D^{20}$ − 46.5 ($CHCl_3$; *c* 1.381). IR (neat): 3417, 2974, 2930, 2827, 1650, 1454, 1373, 1252, 1215, 1167, 1078, 890, 865, 806 cm^{-1}. (EIMS) *m/e* (rel intensity): 189 (7), 157 (10), 131 (100), 113 (18), 99 (23), 89 (52), 85 (13), 71 (28), 59 (54). Anal. Calcd for $C_{13}H_{26}O_6$: C, 56.10; H, 9.42. Found: C, 56.22; H, 9.39.

(+)-(3*R*)-3-{(4*R*,5*R*)-5-[(1*R*)-3-Hydroxy-1-methoxypropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-3-methoxy-1-propanol (4b). The title compound was obtained, analogously to **4a**, from **3b**. $[\alpha]_D^{20}$ +46.4 ($CHCl_3$; *c* 1.272).

(3*S*)-3-{(4*S*,5*S*)-5-[(1*S*)-3-(4-methylbenzenesulfonate)-1-methoxypropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-3-methoxypropyl 4-methylbenzenesulfonate (5a). To 259 mg (0.93 mmol) of **4a**, dissolved in 2 mL of dry pyridine and cooled at 0 °C, was added 530 mg (2.78 mmol) of *p*-toluenesulfonyl chloride. After 14 h at 5 °C the solution was poured into 3 mL of H_2O and extracted with CH_2Cl_2. By evaporation of the dried organic layer 516 mg (95%) of **5a** was obtained as a white oil and used without further purification. ^{1}H NMR: δ 7.75 (d, 4H), 7.30 (d, 4H), 4.15 (m, 4H), 3.77 (m, 2H), 3.28 (m, 2H), 3.30 (s, 6H), 2.40 (s, 6H), 1.86 (m, 4H), 1.28 (s, 6H). ^{13}C NMR: δ 145.3, 133.5, 130.4, 128.4, 112.0, 79.6, 78.5, 67.7, 58.7, 30.3, 27.4, 22.1. IR (neat): 3063, 2982, 2827, 1922, 1805, 1598, 1454, 1359, 1174, 1097, 960, 872, 835, 813, 761, 735, 662 cm^{-1}. (EIMS) *m/e* (rel intensity): 586 (<1), 343 (8), 186 (12), 155 (23), 113 (24), 101 (48), 91 (70), 71 (100). Anal. Calcd for $C_{27}H_{38}O_{10}S_2$: C, 55.27; H, 6.53. Found: C, 55.21; H, 6.55.

(3*R*)-3-{(4*R*,5*R*)-5-[(1*R*)-3-(4-Methylbenzenesulfonate)-1-methoxypropyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-3-methoxypropyl 4-Methylbenzenesulfonate (5b). The title compound was synthesized as described for the above-reported enantiomer **5a**.

(−)-(3a*S*,4*S*,10*S*,10a*S*)-4,10-Dimethoxy-2,2-dimethyloctahydrothionino[5,6-*d*][1,3]dioxole (6a). To 100 mL of absolute EtOH, bubbled at reflux with N_2 for 10 min, was added 637 mg (2.65 mmol) of Na_2S·$9H_2O$. In this solution was slowly added dropwise and under reflux 518 mg (0.89 mmol) of **5a** dissolved in 80 mL of absolute EtOH. The reaction mixture was successively refluxed for 48 h and then evaporated. The residue was finally treated with 10 mL of H_2O and extracted with CH_2Cl_2. The evaporation of the dried organic layer gave a crude product that was purified by flash chromatography (SiO_2−light petroleum/Et_2O; 2/1.6) obtaining 159 mg (65%) of **6a** as a white solid, mp 84−85 °C. ^{1}H NMR: δ 4.53 (br s, 2H), 3.59 (m, 2H), 3.38 (s, 6H), 2.76 (m, 2H), 2.50 (m, 2H), 1.98 (m, 4H), 1.40 (s, 6H).^{13}C NMR: δ 107.9, 79.5, 76.9, 58.5, 30.9, 28.7, 27.1. $[\alpha]_D^{20}$ −12.2 ($CHCl_3$, *c* 1.081). IR (KBr) 2982, 2930, 2863, 2827, 1458, 1447, 1373, 1359, 1244, 1214, 1167, 1108, 1089, 1052, 850 cm^{-1}. (EIMS) *m/e* (rel intensity): 276(4), 261 (21), 218 (18), 203 (16), 117 (18), 85 (41), 72 (100). Anal. Calcd for $C_{13}H_{24}O_4S$: C, 56.49; H, 8.75. Found: C, 56.40; H, 8.73.

(+)-(3a*R*,4*R*,10*R*,10a*R*)-4,10-Dimethoxy-2,2-dimethyloctahydrothionino[5,6-*d*][1,3]dioxole (6b). The title compound was obtained with use of the same procedure adopted for the synthesis of **6a**. $[\alpha]_D^{20}$ +12.2 ($CHCl_3$, *c* 1.077).

(−)-(4*S*,5*R*,6*R*,7*S*)-4,7-Dimethoxy-5,6-thionanediol (7a). To 276 mg (1 mmol) of **6a**, dissolved in 3.5 mL of CH_3CN, was added 2 mL of 0.1 N H_2SO_4. The reaction mixture was stirred at 50 °C for 30 min, neutralized with Na_2CO_3, and evaporated. The residue extracted with CH_2Cl_2 gave 231 mg (98%) of crude **7a**, which was purified by flash chromatography (SiO_2−CH_2Cl_2/CH_3OH 30/0.5) obtaining a colorless oil. ^{1}H NMR (CD_3OD): δ 4.22 (br s, 2H), 3.60 (m, 2H), 3.40 (s, 6H), 2.82 (m, 2H), 2.43 (m, 2H), 2.07 (m, 4H). ^{13}C NMR (CD_3OD): δ 83.8, 73.4, 58.0, 33.4, 29.6. $[\alpha]_D^{20}$ − 45.0 (CH_3OH, *c* 1.185). IR (neat): 3432, 2930, 2819, 2539, 1451, 1370, 1263, 1093, 938, 798 cm^{-1}. (EIMS) *m/e* (rel intensity): 218 (17), 187 (37), 146 (16), 115 (12), 87 (22), 72 (100), 71 (75). Anal. Calcd for $C_{10}H_{20}O_4S$: C, 50.82; H, 8.53. Found: C, 50.75; H, 8.55.

(+)-(4*R*,5*S*,6*S*,7*R*)-4,7-Dimethoxy-5,6-thionanediol (7b). This compound was obtained analogously to **7a**. $[\alpha]_D^{20}$ + 44.9 (CH_3OH, *c* 1.164).

Synthesis of the Bicyclic Sulfonium Salts (1*S*,7*S*,8*S*,8a*S*)-8-Hydroxy-1,7-dimethoxyoctahydrothieno-[1,2-a]thiopyranium Iodide (8a). To 236 mg (1 mmol) of **7a** dissolved in 2 mL of dry CH_3CN was added 165 mg (1,1 mmol) of dried NaI, followed by dropwise addition of 140 μL (1.1 mmol) of freshly distilled Me_3SiI. The mixture was refluxed for 2 h and after cooling to room temperature, a few drops of aqueous 10% NH_4Cl was added. The organic layer, obtained by extraction with CH_2Cl_2, was sequentially washed with 5 mL of aqueous 20% $Na_2S_2O_3$ and brine. The evaporation of the dried organic layer gave 311 mg (90%) of the title compound (**8a**) as a pale yellow oil that darkened on standing.^{1}H NMR (CD_3OD): δ 4.62 (m, 1H), 4.55 (m, 1H), 4.04 (m, 1H), 3.95−3.52 (m, 3H), 3.44 (s, 3H), 3.40 (s, 3H), 3.35 (m, 2H), 2.83 (dd, 1H, J = 7.16, 14.86 Hz), 2.15 (m, 3H). ^{13}C NMR ($(CD_3)_2CO$): δ 85.0, 77.3, 66.4, 65.6, 57.5, 57.0, 44.6, 41.7, 33.1, 22.8. ES$^+$ MS 219, ES-MS 127. Anal. Calcd for $C_{10}H_{19}IO_3S$: C, 34.69; H, 5.53. Found: C, 34.75; H, 5.55.

(1*R*,7*R*,8*R*,8a*R*)-8-Hydroxy-1,7-dimethoxyoctahydrothieno[1,2-*a*]thiopyranium Iodide (8b). 8b was synthesized with use of the same procedure adopted for **8a**.

(+)-(1*S*,7*S*,8*S*,8a*S*)-8-Hydroxy-1,7-dimethoxyoctahydrothieno[1,2-*a*]thiopyranium Trifluoroacetate (9a). To 236 mg (1 mmol) of **6a** dissolved in 2 mL of CH_3CN was added 200 μL of CF_3COOH to obtain **9a**. The reaction mixture was heated at 50 °C for 2 h then directly evaporated to gave a crude

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product that was purified by dissolution in CH_2Cl_2 and precipitation with light petroleum obtaining 299 mg (90%) of **9a** as a colorless viscous oil. ^1H NMR and ^{13}C NMR are identical with those reported for **8a**. $[\alpha]_D^{20}$ +17.9 (CH_3OH, *c* 1.635). IR (Nujol): 3417, 2546, 1701, 1133, 990. ES^+ MS 219, ES-MS 113. Anal. Calcd for $C_{12}H_{19}F_3O_5S$: C, 43.37; H, 5.76. Found: C, 43.40; H, 5.78.

(−)-(1*R*,7*R*,8*R*,8a*R*)-8-Hydroxy-1,7-dimethoxyoctahydrothieno[1,2-*a*]thiopyranium trifluoroacetate (9b). This bicyclic compound was obtained analogously to **9a**. $[\alpha]_D^{20}$ −17.8 (CH_3OH, *c* 1.433).

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