Synthesis of (6*R*,7*R*,8*S*,8a*R*)-6,7,8-Trihydroxyperhydro[1,3]thiazolo[3,2-*a*]pyridine and Its 8a*S*-Epimer. Novel, Biologically Active Analogs of Castanospermine

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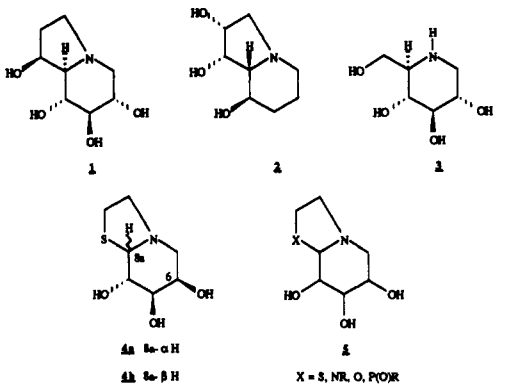
Concise syntheses of the title compounds **4a** and **4b** have been achieved from D-(−)-arabinose. In the first route the dithioacetal **9** was converted via the tosylate **10** to the hemiacetal **11** which was reacted with aminoethanethiol·HCl to give a mixture of compounds **4**. Alternatively, the thiazolidines **6** were cyclized (using Ph_3P, CCl_4, Et_3N) to give **4a,b** in a two-step approach without recourse to protecting groups. Castanospermine analogs **4** show in vitro activity against HIV at μM concentrations.

With the discovery that castanospermine **1**, swainsonine **2**, nojirimycin **3**, and a number of other naturally occuring polyhydroxylated indolizidine, piperidine, and pyrrolidine alkaloids are potent glycosidase inhibitors, intense efforts have been made to develop efficient syntheses of these compounds, as well as structural analogs.[1] For example, a wide range of castanospermine analogs has now been prepared in which the configuration of the chiral centers has been inverted either individually or several at a time.[2-11] Derivatization of the hydroxyl groups has also been studied in an effort to potentiate the therapeutic index of these compounds.[12,15g] Through such a systematic search the specificity of the castanospermine system to different glycosidases (e.g., glucosidases, mannosidases, and fucosidases) has been accentuated and potential application of these compounds as antidiabetic,[13] antitumor,[14] and anti-HIV agents[15] as well as antifeedants[16] has been revealed. However, it should be emphasized that despite the structural correspondence of castanospermine analogs to specific sugars, structure–activity relationships are not always straightforward.



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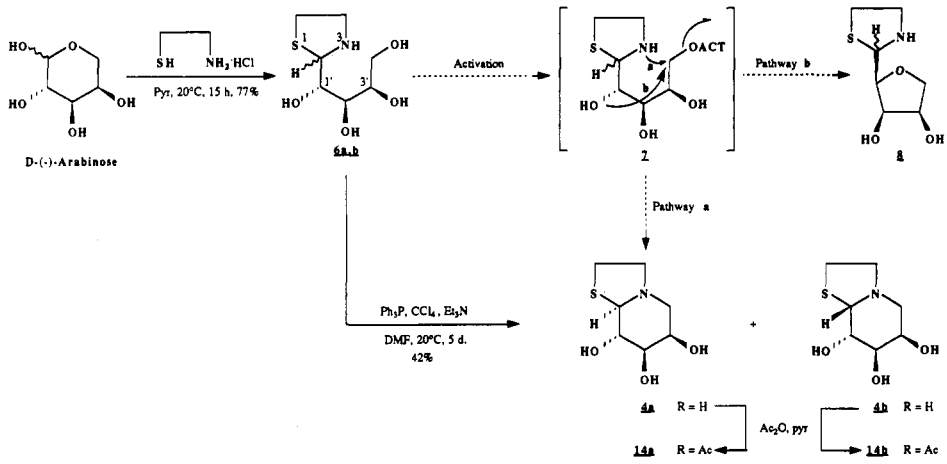
Scheme I

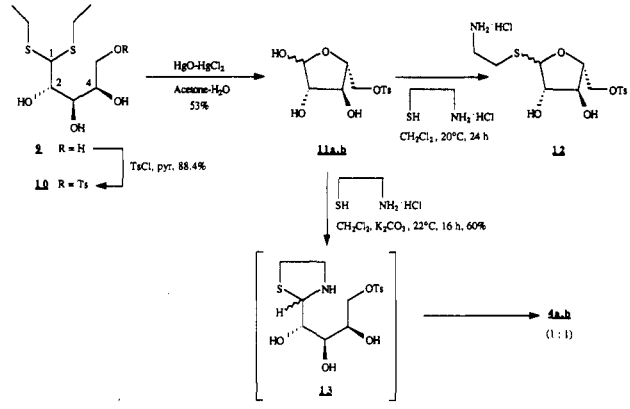


In this paper, we describe a particularly concise synthesis of the 6-epicastanospermine analog **4a** and its 8a-epimer **4b** from D-(−)-arabinose. These are lead molecules in a program to prepare and evaluate the biological activities of a new series of castanospermine analogs of general structure **5**, in which the C-1 carbon is replaced by a S, N, O, or P atom. It was felt that introduction of a heteroatom at this position will provide a successful mimic of the C-1 hydroxyl group while at the same time altering the geometry of the indolizidine system and the electronic properties of the bridgehead nitrogen. The possibility that an iminium ion could be generated in the enzyme-active site through nitrogen lone pair assisted cleavage of the C(8a)–S bond was also envisaged. Such an entity would represent a transition-state analog of the putative oxonium ion intermediate generated during glycoside bond cleavage.[17]

Two simple ideas are central to the synthesis of compounds **4** (Scheme I). Firstly, given that sugars can be trapped in their open-chain form, generally as a dithioacetal, it appeared attractive to transform of D-(−)-arabinose into its cyclic *N,S*-acetal, thereby forming the "thiazolidine equivalent" **6** of the hydroxy substituted pyrrolidine ring of castanospermine in a single operation.[18] Secondly, sufficient literature precedent exists to suggest that the primary hydroxyl group in thiazolidine **6** could be selectively activated without prior protection of the secondary hydroxyl groups.[19,20] Spontaneous cyclization of **7** would give the target molecule (pathway **a**). The preparation of **4** is thus envisaged in *two* steps *without* recourse to hydroxyl protecting groups, which is an acceptable number in view of the fact that three of the chiral centers are present in the starting sugar.[21]

To impliment this two-step strategy it was clear that reaction conditions would have to be carefully chosen in order to avoid a number of potential problems such as Amadori rearrangement, dehydration to a pyridinium salt,[22] or competitive intramolecular displacement of the activated primary alcohol function in **7** by the C-2 hydroxyl oxygen to give the anhydropentose derivative **8** (pathway **b**). However, unlike the other pentoses, acyclic acetals of D-(−)-arabinose such as the dithioacetal **10** adopt a conformation such that the latter cyclization reaction does not readily occur.[23]

Scheme II



Reaction of D-(−)-arabinose with 2-aminoethanethiol·HCl in pyridine overnight gave an inseparable 1.6:1 mixture of epimeric thiazolidines **6a,b**, isolated as their crystalline hydrochloride salts in 77% yield (Scheme I). Despite the complexity of the ^{1}H NMR spectrum of this mixture, the absorptions for H-2, H-1′, and H-2′ for both epimers could be identified since they appeared as simple doublets due to the absence of any coupling between H-2′ and H-3′. Compounds **6a,b** were reacted under a variety of conditions (Rh cat.,[24] Ph_3Br_2,[25] and phosphonium anhydrides[26]) in an attempt to effect ring closure to **4**. However, in these exploratory experiments either the recovered starting material or intractable tars were obtained.

At this juncture we decided to examine the alternative strategy whereby the primary alcohol function in arabinose was activated through tosylate formation prior to construction of the thiazolidine ring (Scheme II). The required tosylate intermediate **11** was prepared in two routine steps from the readily available acyclic arabinose

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dithioacetal derivative **9**.[27] This involved regioselective tosylation of **9** through reaction with *p*-TsCl in pyridine (22 °C, 18 h, 88%)[28] and liberation of the aldehyde function in **10** by treatment with mercury salts ($HgCl_2$–HgO) in acetone–water.[29] The furanose hemiacetal **11** (a mixture of anomers) was obtained as an amorphous solid (in 40% overall yield from arabinose) after column chromatographic purification on silica gel (EtOAc–heptane (4:1)). Only partial interpretation of the ^1H NMR spectrum of compounds **11** was possible [α-anomer: δ 5.14 (d, J = 4.1 Hz), δ 103.53; β-anomer: δ 5.03 (3, J = 2.36 Hz), δ 97.59 (C-1)[30]]. In contrast, the spectrum of its tosylate precursor **10** is well resolved due to the downfield position of the ABX system for the H-5 methylene protons [δ 4.06 (dd, J = 10, 6.12 Hz); 4.28 (dd, J = 10, 2.2 Hz)] and the well-separated signals for H-1: δ 3.99 (d), H-2: δ 3.77 (dd), and H-3: δ 3.93 (dd). Reaction of intermediates **11** with aminoethanethiol·HCl in CH_2Cl_2 at 20 °C for 24 h led to formation of a mixture of two new unstable products which could not be completely purified but whose NMR data indicate that they correspond to structure **12** (δ_{C-1} 90.89 and 90.29; δ_{C-4} 82.94 and 83.61; δ_{NCH_2} 43.47 and 41.06[30]) resulting from thioglycoside formation, and not to the expected thiazolidines **13**. To avoid this problem triethylamine was also added to the reaction mixture. In these experiments two different products possessing similar mobility on TLC (CH_2Cl_2–MeOH (9:1); R_f 0.27, 0.25) were formed. Interestingly, only small quantities of these products were recovered after attempted silica gel column purification. Furthermore, on standing in methanol solution they slowly converted to two new, slightly more polar components. These observations suggest that the thiazolidines **13** produced in the reaction were undergoing cyclization to the desired bicyclic compounds **4a,b**. Subsequent experiments showed that the transformation of the in situ generated thiazolidine **13** to a (1:1) mixture of compounds **4a,b** (tosylate salt) occurs at room temperature in CH_2Cl_2 containing triethylamine. Purification of these products presented problems, as they could not be separated by silica gel or ion-exchange chromatography from the Et_3N·HCl also formed in the reaction. This complication was overcome by employing the alternative base K_2CO_3. In this way compounds **4a,b** (a 1:1 mixture by ^1H NMR) were obtained in the form of their free bases as a syrup in 60% yield after purification by silica gel chromatography.

Having the castanospermine analogs **4a,b** in hand, we returned to the ring closure of thiazolidines **6a,b**. Indeed, it was found that this transformation could be achieved by reaction of intermediates **6** with triphenylphosphine, CCl_4, and triethylamine in DMF at 20 °C for 5 days (Scheme I).[19,31] Compounds **4a,b** (1:1 mixture) were isolated as their free bases in 42% yield after column chromatography on silica gel (CH_2Cl_2–MeOH (5:2)) followed by passage through an IRA-45 ion exchange column (OH^- form; H_2O). The structures of the two epimers were elucidated from their ^1H NMR spectrum (of the epimeric mixture) which was well resolved. The majority of protons could be assigned from the ^1H,^1H COSY 2D spectrum. The analysis started with the proton resonating furthest downfield [δ 4.74 (d, J = 4.2 Hz)] which, from its chemical shift and coupling constant, is assigned as H-8a of the 8a*S* epimer **4b**. The doublet resonating at δ 3.44 (d, J = 9 Hz) is assigned to the corresponding proton of the 8a*R* epimer,

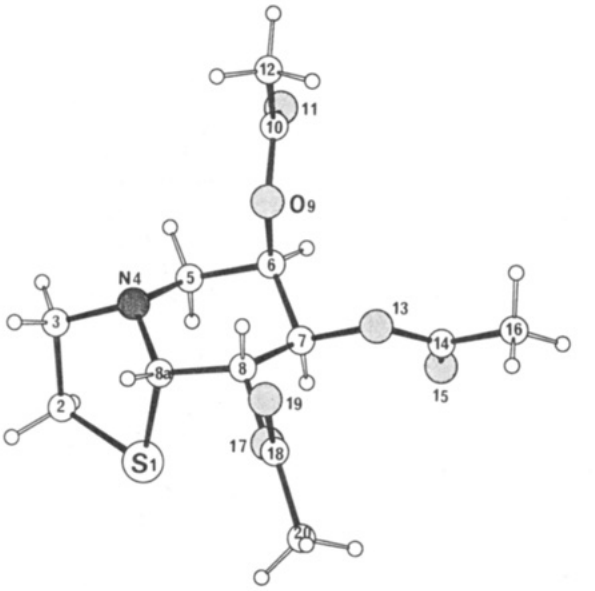

Figure 1. OETEP representation of the triacetate derivative **14b**.

its characteristic upfield position correlating well with its axial orientation antiperiplanar to the lone pair of electrons on nitrogen.[32] The assignment of the epimeric H-8a protons is supported by the magnitudes of their coupling constants. The connectivities of protons H-8 [δ 4.22 (dd, J = 8.5, 4.2 Hz)], H-7 [δ 3.81 (dd, J = 3.2 Hz)], and H-6 [δ 3.92 (m)] of the 8a*R* epimer **4a** and H-8 [δ 3.65 (t, J = 9 Hz)], H-7 [δ 3.35 (obscured by H-2 and 3)], and H-6 [δ 3.92 (m)] of the 8a*S* epimer **4b** follow from an analysis of the ^1H,^1H COSY 2D spectrum. The magnitudes of the coupling constants of each of these protons support the assignments made and are consistent with them being arranged in an axial–axial–equatorial sequence around a piperidine ring in a chair conformation. The ^{13}C NMR spectrum of **4a,b** was analyzed using a ^1H,^{13}C COSY 2D spectrum (solved using the assigned ^1H NMR spectrum) and a J-resolved spin echo spectrum. The spectrum comprises 14 peaks (eight downfield methine carbons and six upfield methylene carbons) and is consistent with the proposed bicyclic structures **4a** and **4b**.

To facilitate separation of the two epimeric castanospermine analogs **4**, they were converted to the corresponding triacetate derivatives **14a,b** (Ac_2O, pyridine). Highly enriched samples of compounds **14a** and **14b** could be obtained by silica gel column chromatography. However, subsequent NMR analysis revealed that, whereas both products were configurationally stable in C_6D_6, epimerization of the C-8a center was rapid in $CDCl_3$ solution.[33] Although the facility with which epimerization occurs hampered efforts to completely purify these compounds by flash chromatography, complete separation of the two products was achieved by preparative HPLC [silica gel; heptane–EtOAc (7:3) containing 0.2% Et_3N]. The structures of each of these products follows from an analysis of their ^1H NMR spectra. The downfield resonances were assigned to H-8: δ 6.09 (dd, J = 10.2 Hz), H-7:

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δ 5.71 (dd, J = 10.2, 3.2 Hz), and H-6: δ 5.5 (m) of the 8a*S* epimer **14b** and to H-8: δ 5.8 (t, J = 9.0 Hz), H-7: δ 5.05 (dd, J = 9.0, 3.5 Hz), and H-6: δ 5.41 (m) of the 8a*R* epimer **14a** by considering the magnitudes of their coupling constants and confirmed by ^{1}H,^{1}H COSY 2D NMR experiments. The chemical shifts of the H-8a protons are little changed upon acetylation and as expected the absorption for the axial hydrogen in **14a** [H-8a*R*: δ 3.52 (d, = 9.0 Hz)] occurs upfield with respect to the corresponding signal for **14b** [H-8a*S*: δ 5.13 (d, J = 4.9 Hz)]. Obtention of compound **14b** in crystalline form provided an opportunity to unequivocally confirm its bicyclic structure by X-ray diffraction (Figure 1). The diffraction data shows that the bridgehead nitrogen atom is pyramidal and that the five-membered sulfur-containing ring adopts an envelope conformation with the nitrogen atom deviated by 0.641 (6) Å from the mean plane of the other four atoms. The cis-fused ring system in this molecule is probably stabilized by an anomeric interaction, which results in the observed elongation of the C_{8a}–S bond [1.87 (1) Å] relative to the C_2–S bond [1.81 (1) Å].[34]

Having separated the epimeric acetates **14**, attempts were made to obtain pure **4a** or **4b** from their respective acetate under mild base hydrolysis conditions [NaOMe (cat.), MeOH]. In each instance, however, an epimeric mixture (1:1 by ^{1}H NMR before chromatography) of **4a,b** was obtained, despite the established stability of the starting acetates to epimerization in methanol. The biological tests were thus carried out on the mixture of compounds **4**.

A complete account of the biological activities of these new castanospermin analogs will be given ulteriorly, but it is interesting to note that in CEM c113 cells infected with the LAV_{Bru} strain of HIV they display no cytotoxicity up to 500 μM concentrations, and at concentrations above 6 μM a marked reduction of HIV-induced cytopathy is observed. Another interesting observation is that cytoprotection plateaus at 60% and remains essentially constant up to 500 μM concentrations. In parallel, a 50–60% reduction of reverse transcriptase in cell supernatant is found at concentrations from 18 to 500 μM. The activity displayed by the analogs **4** is intriguing when one considers that 6-epicastanospermine and 1,6-diepicastanospermine have been shown not to suppress HIV cytopathicity and that analogs possessing a D-*gluco*-configuration (and thus, expected to inhibit processing glucosidases) are usually those which have a pronounced effect on HIV replication.[15f]

Experimental Section

General. Melting points (mp) were determined using a Reichert Thermovar apparatus and are uncorrected. NMR spectra were recorded on Bruker WP-200, WP-250, or WP-400 instruments at 200.13, 250.13, or 400.13 MHz for ^{1}H and at 50.13 or 62.89 MHz for ^{13}C using deuterated solvents. Chemical shift data (obtained using standard software provided by the manufacturer) are reported in parts per million (δ in ppm) where s, d, dd, t, q, and m designate singlet, doublet, doublet of doublets, triplet, quartet, and multiplet, respectively. Infrared (IR) spectra were recorded on a Nicolet 205 FTIR spectrophotometer. Thin-layer chromatography (TLC) was performed using Merck 60 F_{254} (aluminum support, 0.2-mm thickness) plates. Flash column chromatography was done using Merck silica gel 60 (Art. 9385). Mass spectra (MS) were recorded on a MS-9 AEI spectrometer for chemical ionization (CI) (isobutane as carrier gas unless otherwise stated) and a Kratos MS80RF spectrometer for fast atom bombardment (FAB) (4 kV, pos, thioglycerol). Optical rotation data were obtained at 23 °C using a Perkin-Elmer 241 polarimeter. High-pressure liquid chromatography (HPLC) was performed using a Waters 600E pump, a UV484 detector, a Waters 410 differential refractometer, and a Wisp 710 injector. Elemental analyses were performed by the microanalysis laboratory at the ICSN.

2-(D-Arabino-1,2,3,4-tetrahydroxybutyl)thiazolidine HCl Salts (6a and 6b). D-Arabinose (5 g, 33 mmol) and 2-aminoethanethiol·HCl (4.16 g, 36.62 mmol) were stirred in dry pyridine (60 mL) at 22 °C for 20 h under argon. The reaction mixture was then filtered to remove solids and concentrated in vacuo to give a golden syrup. This mixture was taken up in hot methanol, treated with activated carbon, filtered through a short column of Celite, and cooled to 0 °C. Compounds **6a,b** separated out as a colorless crystalline solid. Concentration and further cooling gave a second crop. Recrystallization from methanol gave compounds **6a** and **6b** as an inseparable mixture of 2*R* and 2*S* epimers (6.3 g, 77.5%): mp 128–129 °C (from methanol); $[\alpha]_D$ −18.44° (*c* 1.1, water); IR (KBr) 3600–2300, 1584, 1463, 1449, 1412, 1377, 1332, 1315, 1290, 1243, 1222, 1192, 1102, 1074, 1061, 1032, 960, 929, 885, 771, 750, 634, 567 cm^{-1}; ^{1}H NMR indicates that the compound is a 1.6:1 mixture of major (maj) and minor (min) components; ^{1}H NMR (400.13 MHz, C_6D_5N) δ 3.06 (m, 2 H, H-5 min, ax and eq), 3.24 (m, 2 H, H-5 maj, ax and eq), 3.39 (m, 1 H, Hh4 min), 3.67 (m, 1 H, H-4 min), 3.75 (m, 1 H, H-4 maj), 3.8 (m, 1, H, H-4 maj), 4.49 (m, 2 H, H-4′), 4.58 (d, J = 7.5 Hz, 1 H, H-2′ maj), 4.62 (m, 2 H, H-4′), 4.67 (m, 1 H, H-3′ min), 4.77 (m, 1 H, H-3′ maj), 4.79 (d, J = 7.0 Hz, 1 H, H-2′ min), 5.04 (d, J = 7.0 Hz, 1 H, H-1′ min), 5.08 (d, J = 7.5 Hz, 1 H, H-1′ maj), 5.64 (d, J = 7.0 Hz, 1 H, H-2 min), 5.74 (d, J = 7.5 Hz, 1 H, H-2 maj); ^{13}C NMR (62.89 MHz, C_6D_5N) δ 73.85, 72.31, 73.17, 72.85, 72.58, 72.58 (C-1′, 2′, 3′ maj and C-1′, 2′, 3′ and 2 min), 70.4 5 (C-2 maj), 65.25 (C-4′ maj and min), 51.79 (C-4 min), 50.26 (C-4 maj), 33.59 (C-5 min), 32.36 (C-5 maj); MS (FAB) m/z (relative intensity) 210 (100) (M + H − HCl)$^+$. Anal. Calcd for $C_7H_{16}O_4NSCl$: C, 34.22; H, 6.56; N, 5.70. Found: C, 34.45; H, 6.63; N, 5.57.

5-*O*-(*p*-Toluenesulfonyl)-D-arabinose Diethyl Dithioacetal (10). Freshly recrystallized *p*-toluenesulfonyl chloride (7.2 g, 37 mmol) was added in one batch to a cooled (−10 °C) solution of D-arabinose diethyl dithioacetal (**9**) (9.0 g, 35 mmol)[27] in dry pyridine (54 mL), and the resulting mixture was stirred at −10 °C for 1 h and at 22 °C for 18 h (Ar atmosphere). The mixture was then poured into vigorously stirred ice–water. The crude product which crystallized within 15 min was collected by suction filtration and dissolved in CH_2Cl_2. This solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo until the odor of residual pyridine had almost completely disappeared. Crystallization from $CHCl_3$–petroleum ether (40–60 °C) gave compound **10** as a colorless solid (12.7 g, 88.4 %): mp 67–68 °C (from $CHCl_3$–petroleum ether (40–60 °C)) (lit.[28] mp 68 °C (from $CHCl_3$–petroleum ether)); $[\alpha]_D$ +21.2° (*c* 1.2, methanol) (lit.[28] $[\alpha]_D$ +20.4 (*c* 1.96, methanol)); IR (KBr) 3600–3200, 1352, 1188, 1170, 1169, 1083, 1066, 982, 909, 830, 817, 555 cm^{-1}; ^{1}H NMR (250.13 MHz, CD_3OD) δ 1.25 (m, 6 H), CH_3), 2.45 (s, 3 H, CH_3), 2.54–2.80 (m, 4 H, SCH_2), 3.77 (dd, J = 9.2, 1.13 Hz, 1 H, H-2), 3.84 (m, 1 H, H-4), 3.93 (dd, J = 9.2, 1.13 Hz, 1 H, H-3), 3.99 (d, J = 9.2 Hz, 1 H, H-1), 4.06 (dd, ABX, J = 10, 6.12 Hz, 1 H, H-5a), 4.28 (dd, ABX, J = 10, 2.2 Hz, 1 H, H-5b), 7.42 (d, J = 8.1 Hz, 2 H, Ar-H), 7.81 (d, J = 8.3 Hz, 2 H, Ar-H); ^{13}C NMR (62.89 MHz, CD_3OD) δ 14.83 (CH_3), 21.58 (CH_3), 25.22 and 25.31 (SCH_2), 55.96 (C-1), 70.58 (C-4), 71.25 (C-3), 72.22 (C-2), 73.98 (C-5) 129.05, 130.96, 134.15, 146.30 (ArC); MS (FAB) m/z (relative intensity) 433 (40) (M + Na)$^+$, 287 (40), 177 (50), 155 (35), 135 (100), 115 (45), 105 (75), 97 (40), 91 (45), 75 (70). Anal. Calcd for $C_{16}H_{26}O_6S_3$: C, 46.8; H, 6.20. Found: C, 46.68: H, 6.38.

5-*O*-(*p*-Toluenesulfonyl)-D-arabinofuranoses (11a,b). 5-*O*-(*p*-Toluenesulfonyl)-D-arabinose diethyl dithioacetal (**10**) (9.7 g, 23.63 mmol)[28] was stirred with $HgCl_2$ (9.2 g) and red HgO (9.2 g) in acetone–H_2O (4:1; 50 mL) at 50 °C for 5 h. The reaction mixture was then filtered through a short column of Celite, the residue was washed thoroughly with acetone, and the combined filtrate and washings were concentrated in vacuo. The solid material obtained was dissolved in EtOAc (200 mL), and this solution was washed with 10% aqueous KI (200 mL), dried over Na_2SO_4, and evaporated in vacuo to give a pale yellow syrup (6.5 g). Compounds **11a,b** were obtained as a colorless solid (3.6 g, 52.8%) after flash column chromatography on silica gel (Et-

(34) De Hoog, A. J.; Havinga, E. *Recueil* **1970**, *89*, 972.

OAc–heptane (4:1)): mp 80–85 °C; $[\alpha]_D$ +24.87° (c 0.94, methanol); ^1H NMR indicates a 1:1.7 mixture of anomers); IR (KBr) 3600–3200, 1368, 1360, 1190, 1171, 1095, 1055, 1040, 994, 987, 966, 955, 941, 833, 823, 788, 667 cm^{-1}; ^1H NMR (250.13 MHz, CH_3OD) δ 2.44 (s, 6 H, CH_3), 3.54– 3.92 and 4.00–4.35 (m, 12 H, H-2, 3, 4, 5a and 5b of both anomers), 5.03 (d, J = 2.4 Hz, 1 H, H-1 minor), 5.14 (d, J = 4.1 Hz, 1 H, H-1 major), 7.45 (d, J = 8.1 Hz, 2 H, Ar-H), 7.79 (d, J = 8.2 Hz, 2 H, Ar-H); ^{13}C NMR (50.13 MHz, CD_3OD) δ 21.50 (CH_3 × 2), 70.93 and 72.47 (C-5 a and b), 76.81, 77.95, 78.09, 80.58, 81.63 and 83.20 (C-2, 3 and 4 of both anomers), 97.59 (C-1 β), 103.52 (C-1 α), 128.81, 130.92, 133.89 and 146.44 (ArC); MS (FAB) m/z (relative intensity) 327 (80) $(M + Na)^+$, 287 (30), 217 (20), 202 (15), 195 (15), 181 (10), 173 (50), 155 (40), 139 (20), 123 (10), 115 (70), 102 (100). Anal. Calcd for $C_{12}H_{16}O_7S$: C, 47.00; H, 5.29; O, 36.80; S, 10.54. Found: C, 47.49; H, 5.32; O, 36.71; S, 10.49.

5-*O*-(*p*-Toluenesulfonyl)-2′-(aminoethyl)-1-thio-D-arabinofuranoside·HCl Salts (12). 2-Aminoethanethiol·HCl (0.14 g, 1.23 mmol) was added to a solution of the 5-*O*-(*p*-toluenesulfonyl)-D-arabinofuranoses (11) (0.37 g, 1.2 mmol) in CH_2Cl_2 (5 mL) and the mixture stirred at 22 °C for 48 h. The reaction was then concentrated in vacuo and applied directly to a silica gel flash column (CH_2Cl_2–MeOH (5:2)). Compound 12 (a mixture of anomers as indicated by ^1H NMR) was obtained as an unstable syrup (270 mg, 55.4%) and only partially characterized: ^1H NMR (200.13 MHz, CD_3OD) δ 2.5 (s, 3 H, CH_3), 2.6–2.8 (m, 4 H, SCH_2CH_2N), 3.6–4.4 (m, 5 H, H-2,3,4, 5a and 5b of both anomers), 4.88 (d, J = 4.1 Hz, H-1), 5.24 (d, J = 2 Hz, 1 H, H-1), 7.4 (d, J = 8.0 Hz, 2 H, ArH), 7.8 (d, J = 8 Hz, 2 H, ArH); ^{13}C NMR (50.13 MHz, CD_3OD) δ 21.30 (CH_3, maj), 21.30 (CH_3, min), 29.38 (SCH_2, maj), 29.89 (SCH_2, min), 41.06 (NCH_2, maj), 43.47 (NCH_2, min), 70.40 (C-5, min), 71.26 (C-5, maj), 77.73 (min), 78.09 (maj), 78.83 (maj), 81.34 (min), 82.93 (min), 83.61 (maj), (C-2, 3 and 4), 90.28 (C-1, maj), 90.89 (C-1, min), 126.70, 128.78, 129.83, 131.06, 131.34, 133.64, 146.66 (ArC); MS (FAB) m/z (relative intensity) 386 (35) $(M + Na)^+$, 364 (100) $(M + H - HCl)^+$, 237 (25), 131 (20), 91 (38), 73 (30).

Cyclization of 11 to 4. 2-Aminoethanethiol·HCl (0.149 g, 1.31 mmol), K_2CO_3 (0.182 g, 1.31 mmol), Na_2SO_4 (0.5 g), and 5-*O*-(*p*-toluenesulfonyl)-D-arabinofuranoses (**11a,b**) (0.20 g, 0.65 mmol) were stirred vigorously together in CH_2Cl_2 for 16 h at 22 °C. The mixture was then filtered through a short column of Celite and the column washed several times with fresh mechanol. The filtrates were combined, evaporated in vacuo, and purified by flash chromatography on silica gel (CH_2Cl_2–MeOH (5:2)) to give an inseparable mixture of compounds **4a** and **4b** in the form of their free bases (75 mg, 60%). ^1H NMR indicates a 1:1 mixture of the 8a*R* and the 8a*S* epimers. Data for the 8a*R* epimer **4a**: ^1H NMR (250.13 MHz, CD_3OD) δ 2.34 (dd, ABX, J = 12.2, 1 Hz, 1 H, H-5), 2.44 (m, 1 H, H-3), 2.82 (m, 1 H, H-2), 2.94–3.09 (m, 1 H, H-2), 3.22 (dd, ABX, J = 12.2, 3 Hz, 1 H, H-5), 3.31–3.43 (m, 2 H, H-3 and H-7), 3.44 (d, J = 9 Hz, 1 H, H-8a), 3.65 (t, J = 9 Hz, 1 H, H-8), 3.92 (m, 1 H, H-6); ^{13}C NMR (62.89, CD_3OD) δ 28.82 (C-2), 55.53 (C-5), 58.14 (C-3), 70.04 (C-6), 73.67 (C-8a), 75.17 (C-8), 76.54 (C-7). Data for the 8a*S* epimer **4b**: ^1H NMR (250.13 MHz, CD_3OD) δ 2.54 (dd, ABX, J = 12.0, 4.5 Hz, 1 H, H-5), 2.75 (dd, ABX, J = 12.0, 2.0 Hz, 1 H, H-5), 2.88 (m, 2 H, H-2 and 3), 2.94–3.09 (m, 1 H, H-2), 3.31–3.43 (m, 1 H, H-3), 3.81 (dd, J = 8.5, 3.2 Hz, 1 H, H-7), 3.92 (m, 1 H, H-6), 4.22 (dd, J = 8.5, 4.2 Hz, 1 H, H-8), 4.74 (d, J = 4.2 Hz, 1 H, H-8a); ^{13}C NMR (62.89, CD_3OD) δ 29.45 (C-2), 51.87 (C-5), 59.27 (C-3), 76.77 (C-8a), 71.39 (C-7), 69.58 (C-6), 69.44 (C-8). Data for combined mixture: MS (FAB) m/z (relative intensity) 237 (45) (2 thio + $Na)^+$, 215 (20) $(M + Na)^+$, 192 (60) $(M + H)^+$; MS (CI, NH_3) m/z 192 $(M + H)^+$, 174 $(M + H - H_2O)^+$.

Cyclization of 6 to 4. Thiazolidines **6a,b** (1.6 g, 6.51 mmol), triphenylphosphine (3.5 g, 13.3 mmol), dry carbon tetrachloride (1.3 mL, 13.5 mmol), and freshly distilled triethylamine (1.8 mL, 12.9 mmol) were stirred together in dry DMF at 22 °C for 5 d under an argon atmosphere, with exclusion of light. Methanol (20 mL) was then added and the mixture stirred for a further 30 min, concentrated in vacuo, and partitioned between CH_2Cl_2 and H_2O. The aqueous layer was evaporated and applied to a flash column (silica gel; CH_2Cl_2–MeOH (5:2)). The partially pure products 4 were further purified by ion-exchange chromatography on IRA 45 (OH^-) (elution with H_2O). Compounds 4 were obtained as an inseparable mixture as their free bases in the form of a colorless syrup (0.52 g, 41.6%). For data see preceeding experiment.

Preparation of 14a and 14b from 4a,b. 5-*O*-(*p*-Toluenesulfonyl)-D-arabinofuranoses 4 (0.30 g, 0.99 mmol) were added in one batch to a mixture of 2-aminoethanethiol·HCl (0.12 g, 1.1 mmol) and triethylamine (0.28 mL, 2.0 mmol) in CH_2Cl_2 (6 mL), and the reaction was stirred at 22 °C for 24 h. The mixture was then evaporated to dryness in vacuo and the residue treated at 0 °C with freshly distilled acetic anhydride (5 mL) and dry pyridine (5 mL). After being stirred at 22 °C for 3 d the reaction mixture was poured into ice–water and extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4 and concentrated. Compounds 14 were obtained as a mixture of colorless crystals (247 mg, 79%) after flash column chromatography on silica gel (EtOAc–heptane (2:1)). The two epimers (3:7 8a*R*:8a*S* by ^1H NMR) could be separated by HPLC [silica gel ultrasphere column (10 mm × 250 mm), 3 mL/min flow rate, EtOAc–heptane (7:3) containing 0.2% Et_3N].

Data for 8a*R* epimer **14a**: t_R 23.91 min; mp 152–154 °C; $[\alpha]_D$ +4.40° (c 0.48, benzene); IR (KBr) 1757, 1745, 1736, 1367, 1254, 1244, 1232, 1223, 1188, 1053, 1043, 1031 cm^{-1}; ^1H NMR (400.13 MHz, C_6D_6) δ 1.64 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3), 1.8 (dd, J = 12.9, 2.0 Hz, 1 H, H-5), 1.92 (m, 1 H, H-3), 2.35 (m, 1 H, H-2), 2.62 (m, 2 H, H-2 and H-3), 2.75 (dd, J = 12.9, 3.3 Hz, 1 H, H-5), 3.52 (d, J = 9.0 Hz, 1 H, H-8a), 5.05 (dd, J = 9.0, 3.5 Hz, 1 H, H-7), 5.41 (m, 1 H, H-6), 5.82 (t, J = 9.0 Hz, 1 H, H-8); ^{13}C NMR (62.89 MHz, C_6D_6) δ 20.26, 20.34, 20.47 (CH_3), 29.41 (C-2), 51.23, 56.67 (C-3 and C-5), 68.67, 69.50, 72.58, 72.95 (C-6,7,8 and 8a), 169.80, 169.79, 169.95 (C=O); MS (FAB) m/z (relative intensity) 340 (15) $(M + Na)^+$, 318 (70) $(M)^+$, 274 (18), 258 (70), 214 (22), 172 (20), 154 (100), 138 (85), 75 (96); MS (CI) m/z 413 $(M + 96)^+$, 374 (M + isobutane)$^+$, 318 $(M + H)^+$, 258 $(318 - AcOH)^+$, 198 $(318 - 2\ AcOH)^+$. Anal. Calcd for $C_{13}H_{19}O_6NS$: C, 49.20; H, 6.04; O, 30.25; N, 4.41; S, 10.10. Found: C, 49.56; H, 6.03; O, 29.20; N, 4.19; S, 9.82.

Data for 8a*S* epimer **14b**: t_R 30.27 min; mp 107–108 °C; $[\alpha]_D$ −218.7° (c 0.47, benzene); IR (KBr) 1744, 1383, 1371, 1256, 1246, 1229, 1048 cm^{-1}; ^1H NMR (400.13 MHz, C_6D_6) δ 1.63 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 2.15–2.31, 2.3–2.42, 2.44–2.51 (m, 6 H, H-2,3, 5 ax and eq), 5.13 (d, J = 4.9 Hz, 1 H, H-8a), 5.5 (m, 1 H, H-6), 5.71 (dd, J = 10.2, 3.2 Hz, 1 H, H-7), 6.09 (dd, J = 10.2 Hz, 4.9, 1 H, H-8); ^{13}C NMR (62.89 MHz, C_6D_6) δ 20.26, 20.34, 20.47 (CH_3), 28.86 (C-2), 47.84, 58.33 (C-3 and 5), 68.62, 68.67, 74.11 (C-6,7,8 and 8a), 169.80, 169.79, 169.95 (C=O).

Deacetylation of Compounds 14 To Give 4a,b as Their Free Bases. The tri-*O*-acetylated compounds 14 (0.10 g, 0.32 mmol) were dissolved in dry methanol (5 mL) containing NaOMe (0.01 g) and stirred at 22 °C for 3 h. The reaction mixture was then concentrated and applied directly to a silica gel flash column (CH_2Cl_2–MeOH (5:2)) to give **4a** and **4b** as an inseparable mixture (2:1) in the form of their free bases. For data see above.

X-ray Structure Determination of Compound 14b. X-ray crystal analysis: **14b** $C_{13}H_{19}O_6NS$, molecular weight 317.37, crystal obtained by slow crystallization from EtOAc–hexane, trigonal system, space group $P3_121$, Z = 6, a = b = 8.484 (4) Å, c = 37.287 (9) Å, γ = 120°; V = 2324.3 Å^3, d_{calcd} = 1.361 g·cm^{-3}, $F(000)$ = 1008, λ (MoKα) = 0.7107 Å, μ = 1.9 cm^{-1} (absorption ignored). A large pyramidal crystal (0.8 × 0.6 × 0.5 mm) has been for the data collection on a Phillips PW1100 diffractometer, using graphite-monochromated MoKα radiation and the θ–2θ scan, method, up to θ = 25°. 4448 reflections (hkl and $-hkl$) were measured of which 1524 were rejected because of the overlapping of the successive reflections in some directions, due to a large scan width (1.5°) and the use of the MoKα radiation with a large parameter value (c = 37.28 Å). The presence of one single crystal prevented us from registering with the CuKα radiation. So, from the 2083 unique remaining data, only 1701 were kept in the refinement calculations as observed, having $I > 3\ \sigma(I)$, $\sigma(I)$ from counting statistics. The structure was solved by direct methods, with SHELXS86,[35] and refined by full-matrix least-squares methods, minimizing the function $\Sigma w(F_o - F_c)^2$ with SHELX76.[36] The

(35) Sheldrick, G. M. SHELEXS86. Program for crystal structure solution; University of Götingen, Germany, 1986.

hydrogen atoms were introduced at theoretical positions (*d* C-H = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atoms, plus 10%. Convergence was reached at $R = 0.080$, $R_w = 0.129$ (with $R_w = \{\Sigma w(F_o - Fc)^2/\Sigma wF_o^2)^{1/2}$ and $w = 1/[\sigma^2(F_o) + 0.004\,901F_o^2]$). No residual was higher than 0.38 eÅ^{-3} in the final difference map.

(36) Sheldrick, G. M. SHELEXS76. Program for crystal structure solution; University of Cambridge, UK., 1976.

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Supplementary Material Available: X-ray data for **14b** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Rearrangement of Isoxazoline-5-spiro Derivatives. 8.[1] Selective Formation of Tetrahydropyridones from C,C-Disubstituted Nitrones

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The thermal rearrangement of isoxazolidines **3**, **7**, **9**, **17**, and **19** obtained by 1,3-dipolar cycloaddition of C,C-disubstituted nitrones and methylenecyclopropanes **1** and **6** has been studied. The lack of hydrogen at the C-3 position of the isoxazolidine ring leads selectively to azaheterocyclic ketones, structurally differentiated according to the starting dipoles and dipolarophiles. The process allows the "one-pot" synthesis of valuable perhydro pyridone, indolizinone, and pyrrolo[1,2-*a*]quinolinone ring systems with excellent overall yield and atom economy. A new entry to the functionalized 1-azaspiro[5.5]undecane **22** framework found in alkaloids of the histrionicotoxin family is also presented.

Introduction

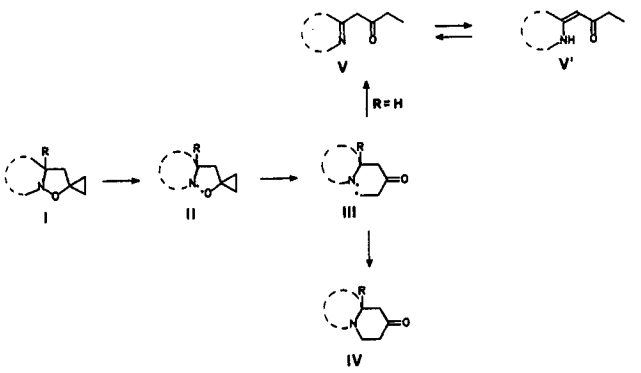
The thermal rearrangement of isoxazolidine-5-spirocyclopropanes has shown high versatility as a new method for the synthesis of azaheterocycles of pyridine, indolizine, and quinolizine type.[2] The method has been recently applied to the formal and total synthesis of alkaloids containing these skeletons.[3,4]

The mechanism proposed[2,5] for the process consists of a thermal homolytic cleavage of the N-O bond of the isoxazolidine **I** (Scheme I) obtained by 1,3-dipolar cycloaddition of a nitrone to methylenecyclopropane; the formed cyclopropyloxy diradical **II** then undergoes a rearrangement to the diradical **III** which cyclizes to the ketone **IV**.

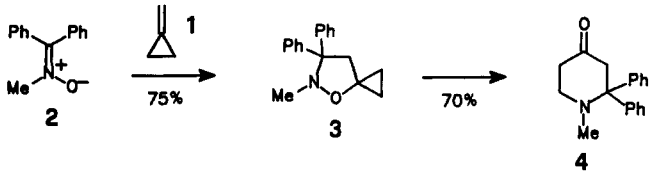
A serious drawback of the process is the possible transfer of the hydrogen α to nitrogen in the diradical **III** (R = H, Scheme I) to give the enaminone compounds **V'**. This side reaction invariably lowers the yield of cyclic ketones. The hydrogen abstraction might occur in an intermolecular fashion and possibly with participation of the solvent, but the intramolecular 1,5-hydrogen shift seems to be the most likely process. This is supported by the formation of enaminones in significant yields even under conditions of flash vacuum thermolysis (FVT).

If the proton on C-3 of isoxazolidine is replaced by a substituent (R ≠ H, Scheme I) this side reaction should be precluded, and cyclic ketones should form in higher yields. In the present study we report on the results obtained with structurally differentiated C-3 (isoxazolidine numbering) substituted isoxazolidines which substantiate our prediction.

Scheme I



Scheme II



Results and Discussion

C,C-Diphenyl-*N*-methylnitrone (**2**) reacted with **1** in a sealed tube to give the isoxazolidine **3** as the sole regioisomer in 75% yield (Scheme II). Upfield chemical shift for the isoxazolidine methylene (δ 3.08 ppm) is diagnostic for the assignment of the structure to **3**. The methylene of the 4-spirocyclopropane regioisomers usually resonate 1 ppm more downfield.[3,4] This high regioselectivity is unprecedented in the case of cycloadditions of nitrones to

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