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A Facile Route to Diastereomerically Pure Analogues of Castanospermine and Australine.

D. Marek, A. Wadouachi, R. Uzan, D. Beaupere*

Laboratoire de Chimie Organique, Université de Picardie Jules Verne, 33 rue Saint-Leu
80039 Amiens

G. Nowogrocki#, G. Laplace

Laboratoire de Cristallochimie et Physicochimie du Solide,
E.N.S.C. de Lille , B.P. 108, 59652 Villeneuve D'Ascq

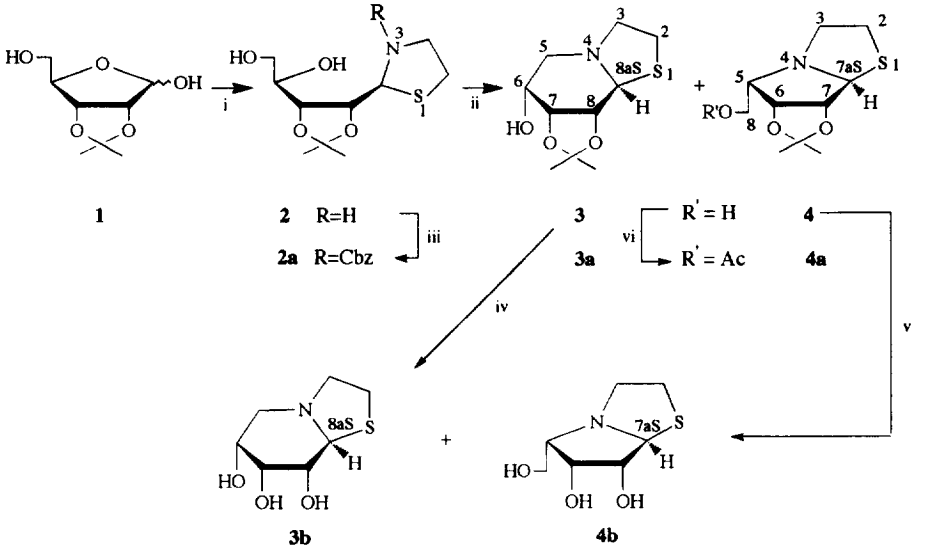
Abstract : Reaction of cysteamine with D-ribofuranose in which a 2,3-*O*-isopropylidene group was introduced, yielded the 2-(*S*)-thiazolidine derivative stereoselectively. The following step of cyclisation led to castanospermine and australine analogues, **3** and **4**, in good yields. It was shown that the ratio castanospermine / australine analogues was depending on the activating reagent used for the cyclisation step.

Polyhydroxylated indolizidine, piperidine and pyrrolizidine alkaloids, such as castanospermine, swainsonine, australine and their derivatives continue to attract considerable interest due to their potent activity as glycosidase inhibitors.[1] Intense efforts have been made to develop efficient syntheses of these compounds, as well as structural analogues.[2]

Recently, a particularly concise route for synthesis of an analogue of 6-*epi*castanospermine was described in which a thiazolidine derivative derived from D-arabinose and aminoethanethiol (cysteamine) is a key intermediate.[3] However, as no provision was made for control of stereochemistry during the thiazolidine forming step in this approach, a mixture of 8a*S* / 8a*R* diastereomers of (6*R*,7*R*,8*S*,8a)-6,7,8-trihydroxyperhydro[1,3]thiazolo[3,2a]pyridine was produced (1:1; 42%) during the subsequent ring closure reaction involving OTs displacement by nitrogen. In a previous report, we showed that the condensation of cysteamine with aldoses possessing stericaly bulky isopropylidene groups at the appropriate location occurs stereoselectively to provide diastereomerically enriched aldothiazolidines. For instance, 2-(*S*)-(1,2;4,5-di-*O*-isopropylidene-D-*manno*pentahydroxypentyl)thiazolidine was obtained in this manner as a single product in quantitative yield from 2,3;5,6-di-*O*-isopropylidene-α-D-mannofuranose.[4] In this paper we describe an extention of this work to the ribose series to prepare diastereomerically pure indolizidine and pyrrolizidine derivatives.

The treatment of 2,3-*O*-isopropylidene-D-ribofuranose **1**[5] with cysteamine in methanol, at room temperature, led to a mixture of **2** (*S*:*R* = 92:8) in 75% yield. It is noteworthy that, under the same conditions, ribose reacts with this aminothiol to give the corresponding unprotected thiazolidine as a 60:40 mixture of C-2 epimers. Thus, the highly stereoselective formation of *S*-**2** can be attributed to the presence of the isopropylidene moiety.

The subsequent cyclisation of **2** produced the (6*S*,7*S*,8*S*,8a*S*)-6,7,8-trihydroxy-7,8-*O*-isopropylidene perhydro[1,3]thiazolo[3,2-a]pyridine **3** (castanospermine analogue) and the (5*S*,6*S*,8*S*,7a*S*)-6,7-dihydroxy-6,7-*O*-isopropylidene-5-hydroxymethyl perhydro[1,3]thiazolo[3,2-a]pyrrole **4** (australine analogue) in yields which were found to depend upon the reagents and reaction conditions employed (Table 1). In all cases, the corresponding epimers 8a*R* -**3** and 7a*R* -**4** were detected in only trace quantities.



i: $HSCH_2CH_2NH_2.HCl$, MeONa, MeOH, reflux; ii: See Table 1; iii: CbzCl, Na_2CO_3, H_2O-CH_3COCH_3: 1:1 = v:v, RT; iv: HCl 1N-THF: 1:2 = v:v, RT; v: HCl 1N-THF: 1.5:2 = v:v, RT; vi: Ac_2O, Pyridine, RT.

Table 1 : Influence of experimental conditions on the intramolecular cyclisation.

Activating System	Equiv.	Solvent	Temperature	Time (h)	Yield*(%) **3a**	**4a**
nBu_3P/DIAD	1.5/1.5	CH_2Cl_2	Reflux	7	50	26
nBu_3P/DIAD	1.5/1.5	THF	Reflux	7	42	42
$PPh_3/CCl_4/Et_3N$	1.2/1.3/1	CH_3CN	R.T.	24	60	14
nBuLi/TsCl	1/1	THF	R. T.	24	41	6

* : Isolated yield (7:3 Hexane-EtOAc)

When **2** was treated with nBu_3P/DIAD in CH_2Cl_2 [6] followed by acetylation, compounds **3a** and **4a** were readily isolated in a 2:1 ratio by silica column chromatography. Structure assignment of these products was made from ^1H and ^{13}C NMR data.[7] Unexpectedly, the formation of chlorine containing by-products (approx. 10%) was observed. However, this problem could be avoided by using THF as solvent. Under these conditions, the yield of **4** increased from 26 to 42%, and after acetylation, **3a** and **4a** were obtained in the same yield.

Furthermore, when the N-carbobenzyloxy thiazolidine **2a** was reacted under Mitsunobu conditions, we observed the formation of the corresponding 4,5-anhydro derivative.[8] The observed formation of this anhydro derivative led us to postulate that **3** and **4** were obtained *via* such an epoxide.[6a]

With the activating system PPh_3-CCl_4[9] in acetonitrile,[10] the mixture of **3a** and **4a** were produced from **2** in 4:1 ratio. This result contrasts with what was formed under Mitsunobu conditions. This seems to indicate that the reaction intermediate is not only the anhydro derivative. To favour the formation of castanospermine analogue, the OH-5 of the compound **2** was activated by nBuLi/TsCl[11] in THF. The use of a strong base as nBuLi allowed the regioselective tosylation of the primary hydroxyl group, in the presence of the secondary amino group.

To confirm the *S*-absolute configuration at the C-2 center in the thiazolidine intermediate **2**, the X-ray crystal stuctures of compounds **4a** (Figure 1) and **3** (Figure 2) were obtained.[13]

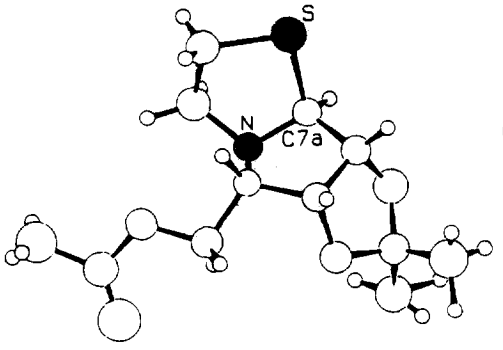


Figure 1

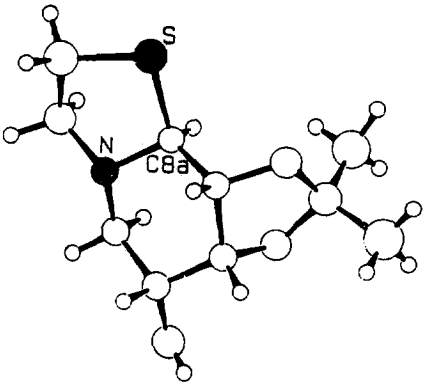


Figure 2

The deprotection of **3** and **4** was achieved in THF/HCl 1N (1,2 and 1.5,2 v:v respectively) at room temperature in 80% yield.[9b,12] The unmodified configurations of C-8a*S* and C-7a*S* were confirmed by NMR spectroscopy.[14]

In summary, it was found that, depending upon the experimental conditions, cyclisation of thiazolidine **2** results in the formation of an equimolar mixture of castanospermine/australine analogues, or the preponderant formation of castanospermine analogue. Biological tests for glycosidase inhibitory activity are in progress, and studies are presently extended to other monosaccharides.

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7. **3'** : crystal ; mp 156-157° C ; $[\alpha]_D$= - 52 (c = 1,.03, CH_2Cl_2) ; ^1H NMR (300MHz, $CDCl_3$) δ 1.27 (3H, s, CH_3), 1.45 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.5 (1H, dd, $J_{5,6}$ = 8.8 Hz, H-5), 2.6 (1H, m H-3), 2.78-2.94 (3H, m, H-2, H-2', H-5'), 3.3 (1H, dd, $J_{3,3}$=10 Hz, $J_{3,2}$=6 Hz, H3'), 3.95 (1H, d, $J_{8a,8}$=5.9, H-8a), 4.17 (1H, t, $J_{8,7}$=5.5 Hz, H-8), 4.32 (1H, t, $J_{7,6}$=5, H-7), 5.1 (1H, m H-6). ^{13}C NMR (300MHz, $CDCl_3$) δ 20.1 ($\underline{C}H_3CO$), 24.9 (CH_3), 26.6 ($\underline{C}H3$), 28.4 (C-2), 47.5, (C-5), 56.9 (C-3), 66.9 (C-6), 69.1 (C-8a), 71.4 (C-7), 76.9 (C-8), 109.2 (C iso), 169.2 (CO). Anal. Calcd for $C_{12}H_{19}O_4NS$: C 52.73, H 6.95, N 5.12, S 11.73. Found : C 52.70, H 6.98, N 5.34, S 11.81.
4' : crystal ; mp 120-121° C ; $[\alpha]_D$ +10 (c = 1,.01, CH_2Cl_2) ; ^1H NMR (300MHz, $CDCl_3$) δ 1.25 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.0 (3H, s, CH_3), 2.74 (1H, m, H-5), 2.79-2.95 (3H, m, H-2, H-2', H-3), 3.65 (1H, m, H-3'), 4.1 (1H, dd, $J_{8,5}$ = 7 Hz, H-8), 4.27 (1H, dd, $J_{8',5}$ = 5.4 Hz, $J_{8,8'}$ = 11.1 Hz,H-8'), 4.75 (3H, s, H-7a, H-7, H-6). ^{13}C NMR (300MHz, $CDCl_3$) δ 19.9 ($\underline{C}H_3CO$), 24.2 (CH_3) , 25.2 (CH_3), 29.6 (C-2), 54.2 (C-3), 60.5 (C-5), 62.1 (C-8), 79.6, 79.7, 82.1
(C-7a, C-7, C-6), 111.0 (C iso), 169.7 (CO). Anal Calcd for $C_{12}H_{19}O_4NS$: C 52.73, H 6.95, N 5.12, S 11.73. Found : C 52.77, H 6.83, N 5.38, S 11.62.

8. ^{13}C NMR analysis ($CDCl_3$) revealed two signals at 47,0 ppm et 49,2 ppm corresponding respectively to C-4 and C-3 of N-carbobenzyloxy-2-(3,4-anhydro-1,2-*O*-isopropylidene-D-*ribo*tetrahydroxybutyl)thiazolidine.

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10. Replacement of acetonitrile by DMF [3] reduced to 37% the overall yield and favored the formation of by-product as chlorinated derivative.

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13. X-ray Data : **3** : Empirical formula $C_{10}H_{17}O_3NS$, M = 231.31. Orthorhombic space group $P2_12_12_1$ (#19), a=6.048 (1), b=8.782 (1), c=21.420 (5) Å, V=1137.7 (3) Å3, Z=4, D_0=1.35 g/cm^3, μ=2.7 cm^{-1}, F(000)=124. Data collected at 294K on a Nonius CAD4 diffractometer with graphite monochromated Mo Kα radiation and θ/2θ scans to a 2θ max of 56°, -7<h<7, -11<k<11, 0<l<28. Reflections measured : 5602 ; number of unique reflections with I>3σ(I) : 1790 ; Solution by direct methods ; hydrogen atoms localized on difference Fourier maps. Last least-square with 32 atoms and 188 parameters gave R_f=0.033, R_W=0.026 and GoF=2.235. The enantiomorph configuration gave GoF=2.315
X-ray Data : **4'** : Empirical formula $C_{12}H_{19}O_4NS$, M = 273.35. Monoclinic, space group $P2_1$ (#4), a=9.14 (1), b=8.99 (1), c=8.43 (1) Å, β=98.32 (9)°. V=686 (1) Å3, Z=2 D_c=1.32 g/cm^3, μ=2.46 cm^{-1}, F(000)=146. Data collected at 294K on a Nonius CAD4 diffractometer with graphite monochromated Mo Kα radiation and θ/2θ scans to a 2θ max of 60°, -12<h<12, 0<k<12, -11<l<11. Reflections measured : 3569 ; number of unique reflections with I>3σ(I) : 796 ; Solution by direct methods ; hydrogen atoms localized on difference Fourier maps. Last least-square with 37 atoms and 219 parameters gave R_f=0.048, R_W=0.028 and GoF=1.97. The enantiomorph configuration gave GoF=1.98.

14. ^1H NMR data (solvent: DMSO):
For **3a** and **3b**, $J_{7a,7}$=0 and 0.5 Hz respectively.
For **4a** and **4b**, $J_{8a,8}$=6.2 and 6.9 Hz respectively.

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