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A Concise Diastereoselective Synthesis of the Natural (2*R*, 3*S*)-2-Hydroxymethyl-3-Hydroxy Pyrrolidine

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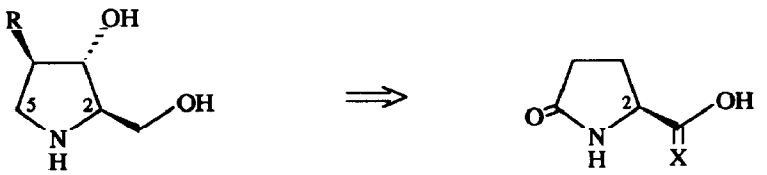
Key Words : pyroglutamic acid, hydroxylated pyrrolidine, epoxidation, epoxide opening, Castanospermum.

Abstract. *(2R, 3S)-2-hydroxymethyl-3-hydroxy pyrrolidine 4, a constituent of Castanospermum australe,[1] was synthesized from (S)-pyroglutamic acid through diastereoselective epoxidation of α, β-unsaturated pyrrolidone 8.*

Optically active polyhydroxylated pyrrolidines have recently received considerable attention due to their role as intermediates for the synthesis of more complex bioactive molecules or to their own biological activities.[2] Some of them, as DBA1 **1** (D-1,4-dideoxy-1,4-iminoarabinitol), are selective glycosidase inhibitors[3] whereas the enantiomer LBA1 exhibit anti-HIV properties.[4]

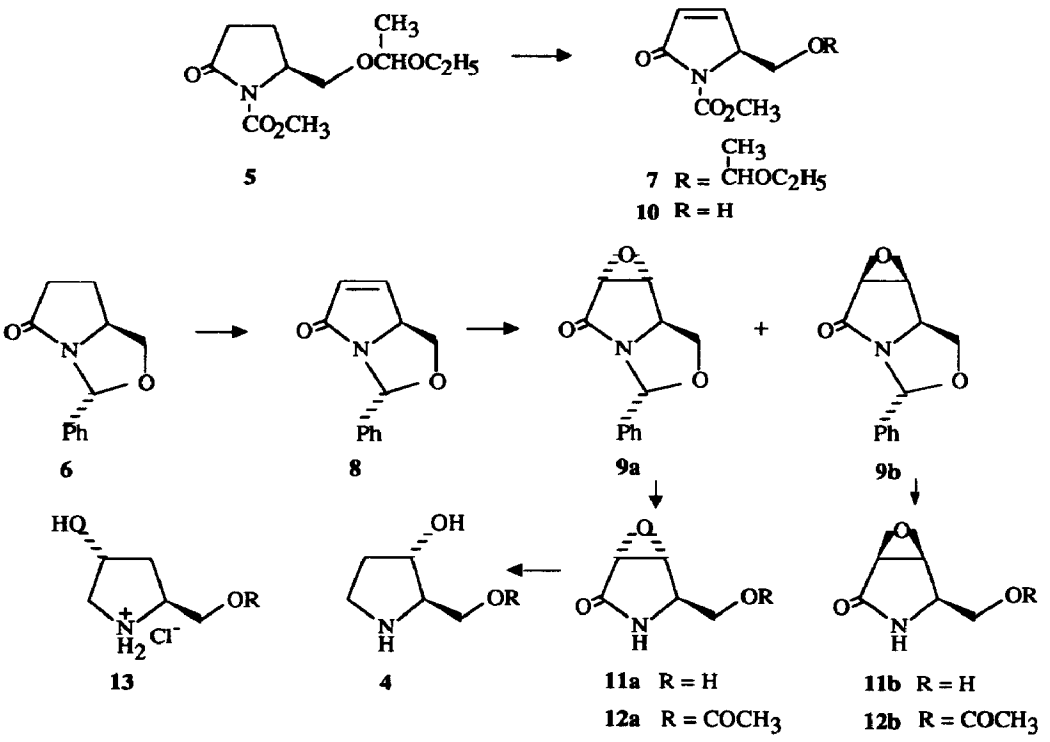


1 R = OH
4 R = H

2 X = O
3 X = H_2

Both enantiomers of pyroglutamic acid **2** have already proven to be useful in the syntheses of many substituted pyrrolidines with defined configurations. In continuation of our work starting from **2** as a chiral source in synthesis[5], we postulated that several interesting hydroxylated pyrrolidines could be easily accessible from (*S*) (or *R*) pyroglutaminol **3**[6]. For this purpose, we planned to prepare conveniently protected 3, 4-epoxy derivatives. These oxiranes could constitute versatile intermediates, depending on the nucleophile used to open the epoxide ring. This approach is illustrated here by the synthesis of the natural (2*R*, 3*S*)-2-hydroxymethyl-3-hydroxy pyrrolidine **4**[7], isolated from *Castanospermum australe*.[1]

The known pyrrolidones **5**[8] and **6**[9] were deprotonated respectively by LiHMDS and LDA (1 equiv, 78°) to introduce the conjugated double bond by classical phenylselenation (PhSeCl), followed by selenoxide elimination. In both cases hydrogen peroxide was used as an oxidant of the phenylselenides, leading respectively to **7**[10] and to the previously described compound **8**.[11]



The epoxidation of these α, β-unsaturated pyrrolidones proved to be more difficult than anticipated, which is also supported by recent results.[12] Several methods of electron deficient alkene epoxidation were investigated :

Dimethyldioxirane is known to epoxidize the double bond of α, β-unsaturated ketones, acids and esters.[13] This method was applied to the compound **7**, the *N*-methoxycarbonyl substitution of which provided some ketonic character to the conjugated γ-lactam carbonyl, but it was ineffective, and gave rise to only O-deprotected pyrrolidone **10**. The compound **8** lacked reactivity towards hydrogen peroxide in presence of sodium bicarbonate.[14] The use of sodium perborate[15] led to **9a** in poor yield (11%), but all attempts to improve yield by increasing the reaction time failed.

Better results were obtained with conjugate addition of lithium *tert*-butylhydroperoxide[16,17], which led to the epoxides **9** in 46% isolated yield. The ratio of diastereomers **9a** and **9b** (**9a** : **9b** = 87 : 13) was determined by ^1H NMR in C_6D_6, the chemical shift of the amino acetal proton was rather different in **9a** (6.46ppm)[18] and **9b** (6.04 ppm).[19] These diastereoisomers were separated chromatographically. The nitrogen and the hydroxymethyl groups of the major epoxide **9a** were deprotected by acidic hydrolysis without opening of the epoxide ring (CF_3CO_2H,THF-H_2O), leading to primary alcohol **11a**, which was characterized through its

acetate **12a** (57% isolated yield from **9a**).[20] In the same conditions, the isomer **9b** gave rise to **12b**. Thus **9a** and **9b** differ by relative configuration of the epoxide ring. The diastereoselectivity was interpreted as a consequence of the steric hindrance due to the oxazolidine methylene of the constrained compound **8** and the configurations were confirmed by X ray analysis of **9a** [21], but the stereocontrol was not so efficient[22] as observed in the conjugate addition of dialkyllithiocuprates.[23]

It is noteworthy that no epoxide could be isolated in the same conditions starting from the unsaturated pyrrolidinone **7** which was recovered along with several degradation products.[24]

$LiAlH_4$ reduction of **12a** gave rise to (2*R*, 3*S*)-2-hydroxymethyl-3-hydroxy pyrrolidine **4** in 80% yield. Its hydrochloride was spectroscopically identical with the natural product isolated from *Castanospermum australe* ;[1,25] (2*S*,4*R*)-4-hydroxy prolinol hydrochloride **13**, prepared by deprotection[26] of its N-BOC derivative[27], was not detected in the NMR spectra of the reduction product of **12a**, indicating a high stereoselectivity of the opening of epoxide ring by the hydride ion.

The use of optically pure 3, 4-epoxy pyrrolidone **9a** in further syntheses are under current investigation in our laboratory.

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References and Notes

1. Nash, R. J.; Bell, E. A.; Fleet, G.W.J.; Jones, R. H.; Williams J.M. J. *Chem. Soc. Chem. Comm.* **1985**, 738-740. For clarity, the same numbering of the pyrrolidine ring was used for all derivatives leading to pyrrolidine **4**.
2. Fleet, G.W.J.; Witty, D. R. *Tetrahedron Asymmetry* **1990**, *1*, 119-136.
3. Robinson, K. M.; Rhinehart B. L.; Ducep, J. B.; Danzin, C. *Drugs of the Future* **1992**, *17*, 705-720.
4. Karpas, A.; Fleet, G.W.J.; Dwek, R. A.; Petursson, S.; Namgoong S. K.; Ramsden, N. G.; Jacob, B. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 9229-9233.
5. Langlois, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77-80 and references therein. (*S*)-Pyroglutamic acid was kindly provided by UCIB (Usines Chimiques d'Ivry-la-Bataille).
6. Saijo, S.; Wada, M.; Himizu, J.; Ishida, A. *Chem. Pharm. Bull.* **1980**, *28*, 1449-1458.
7. a) Ikota, N.; Hanaki, A. *Heterocycles* **1988**, *27*, 2535-2537. b) Hirai, Y.; Chintani, M.; Yamazaki, T.; Momose, T. *Chem. Lett.* **1989**, 1449-1452.
8. Langlois, N.; Andriamialisoa, R. Z. *Tetrahedron Letters* **1988**, *29*, 3259-3262.
9. a) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.;Wong, M. K. Y.;Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140-3143. b) Thottathil, J. K.; Przybyla, C.; Malley, M.; Gougoutas, J. Z. *Tetrahedron Letters* **1986**, *27*, 1533-1536.
10. 7 : $[\alpha]_D^{20}$ = -197 (c = 0.8, $CHCl_3$) ; IR : 2987, 1792, 1736, cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, δ = 0, TMS, J = Hz) : 7.33 (m, 1H, C-3-H), 6.16 (dd, 1H, $J_{3,4}$ = 6 and J = 1, C-4-H), 4.77 (m, 1H, C-2-H), 4.68 (m, 1H,

OCHO), 4.06 and 3.68 (2m, 2H, OCH_2), 3.91 (s, 3H, CO_2CH_3), 3.58 and 3.46 (2m, 2H, CH_2), 1.29 (2d, 3H, J ~ 5.5, $CHCH_3$), 1.19 (t, 3H, J = 7, CH_2CH_3).; MS (m/z) : 228 ($M^{+\cdot}$ - CH_3), 213, 198, 154 (100%), 141, 109, 73 ; HRMS calcd for $C_{10}H_{14}NO_5$: 228.0872, obsd : 228.0900.

11. Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635-8652.
12. Woo, K. C.; Jones, K. *Tetrahedron Letters* **1991**, *32*, 6949-6952.
13. Adam, W.; Hadjiarapoglou, L.; Nestler, B. *Tetrahedron Letters* **1990**, *31*, 331-334.
14. Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460-3467.
15. Reed, K. L.; Gupton, J. T.; Solarz, T. L. *Synthetic Comm.* **1989**, *19*, 3579-3587.
16. Meth-Cohn, O.; Moore, C.; Taljaard H. C. *J. Chem. Soc. Perkin Trans I* **1988**, 2663-2674.
17. Lanier, M.; Haddach, M.; Pastor, R.; Riess, J. G. *Tetrahedron Letters* **1993**, *34*, 2469-2472.
18. **9a** : mp : 90-2° C; $[\alpha]_D^{30}$ = +237 (c = 0.9, $CHCl_3$) ; IR : 1729, 850 ; ^1H NMR (300 MHz, C_6D_6) : 7.38 and 7.06 (2m, aromatic H), 6.45 (s, 1H, OCHN), 3.46 (dd, 1H, $J_{2,6a}$ = 7, $J_{2,6b}$ = 9, C-2-H), 3.27 (dd, 1H, $J_{6a,6b}$ ~ 8, $J_{2,6a}$ = 7, C-6-Ha), 3.18 and 2.73 (2d, 2H, $J_{3,4}$ = 2.5, C-3-H and C-4-H), 2.63 (dd, 1H, $J_{6a,6b}$ ~ 8, $J_{2,6b}$ = 9, C-6-Hb) ; ^{13}C NMR (75 MHz, C_6D_6) : 175.44 (CO), 139.94 (C*), 129.28 (CH), 129.22 (CH), 126.85 (CH), 88.92 (OCHN), 66.02 (CH_2O), 60.09 (C-2-H), 57.27 and 53.63 (C-3 and C-4) ; MS (m/z) : 217 ($M^{+\cdot}$ weak), 216, 147, 105 (100%) ; HRMS : calcd for $C_{12}H_{11}NO_3$: 217.0739, obsd : 217.0730.
19. **9b** : mp : 140-2° C (ether) ; $[\alpha]_D^{30}$ = +181 (c = 0.4, $CHCl_3$) ; IR : 1722, 870 ; ^1H NMR (300 MHz, C_6D_6) : 7,49 and 7.1 (2m, aromatic H), 6.04 (s, 1H, OCHN), 3.50 (dd, 1H, $J_{6a,6b}$ ~$J_{2,6a}$ ~ 8, , C-6-Ha), 3.44 (dd, 1H, $J_{6a,6b}$ ~ 8, $J_{2,6b}$ ~ 7, C-6-Hb), 3.06 (d, 1H, $J_{3,4}$ = 2.5) and 2.53 (dd, 1H, J = 2.5, J' ~ 2) : C-3-H and C-4-H, 3.02 (m, 1H, C-2-H).^{13}C NMR (75 MHz, C_6D_6) : 171.5 (CO), 138.2(C*), 128.8 (CH), 128.5 (CH), 126.0 (CH), 86.9 (OCHN), 65.5 (CH_2O), 58.9 (CH), 57.1 (CH), 49.7 (CH) ; MS (m/z) : 217 ($M^{+\cdot}$ weak), 216, 147, 105 (100%) ; Analyse : $C_{12}H_{11}NO_3$, calcd% : C = 66.35, H = 5.10, N = 6.45 , found : C = 66.45, H = 5.32, N = 6.32.
20. **12a**: mp : 66° C ; $[\alpha]_D^{25}$ = +26 (c = 0.8, $CHCl_3$) ; IR : 3437, 1725, 848 ; ^1H NMR (400 MHz, $CDCl_3$) : 5.91 (bs, 1H, NH), 4.19 (dd, 1H, $J_{6a,6b}$ = 11.5, $J_{2,6a}$ ~ 5.4, C-6-Ha), 4.13 (dd, 1H, $J_{6a,6b}$ = 11.5, $J_{2,6b}$ ~ 5, C-6-Hb), 4.03 (m, 1H, C-2-H), 3.92 (m, 1H) and 3.63, (m, 1H) : C-3-H and C-4-H, 2.12 (s, 3H, COCH3) ; MS (m/z) : 171 ($M^{+\cdot}$), 111 (100%), 98 ; HRMS : ($M^{+\cdot}$) calcd for $C_7H_9NO_4$: 171.0531, obsd: 171.0529.
21. Riche, C.; Chiaroni, A. to be published.
22. The stereoselectivity was improved starting from the α, β-unsaturated bicyclic lactam protected with pivalaldehyde, but the chemical yields are lower.
23. Hanessian, S.; Ratovelomanana, V. *Synlett* **1990**, 501-503.
24. An attack of the carbonyl group by lithium *tert*-butylhydroperoxide could explain these results.
25. **4** (hydrochloride) : $[\alpha]_D^{20}$ = + 43.5 (c = 0.3, H_2O), lit : $[\alpha]_D^{21}$ = + 46.5 (c = 1, H_2O)[1], $[\alpha]_D^{23}$ = + 43.8 (c = 1, H_2O)[7a] ; comparison of ^1H NMR (300 MHz), ^{13}C NMR (75 MHz, D_2O), and CIMS data.[1]
26. Stahl, G. L.; Walter, R.; Smith, C. W. *J. Org. Chem.* **1978**, *43*, 2285-2286.
27. Baker, G.L.; Fritschel, S.J.; Stille, J. R.; Stille J. K. *J. Org. Chem.* **1981**, *46*, 2954-2960.

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