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CHIRAL AND STEREOSELECTIVE TOTAL SYNTHESIS OF (-)-DEOXOPROSOPININE AND (-)-DEOXOPROSOPHYLLINE[1)]

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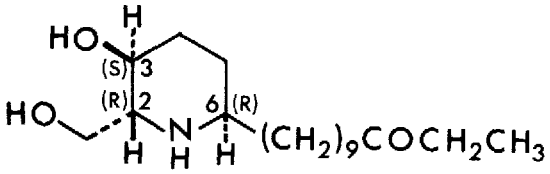
(-)-Deoxoprosopinine and (-)-deoxoprosophylline were synthesized starting from L-serine by a route involving the intramolecular aminomercuration of a chiral $\mathcal{E},\zeta$-unsaturated amine.

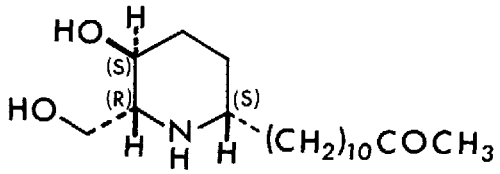
(+)-Prosopinine (1) and (±)-prosophylline (2) are two of the seven piperidine alkaloids isolated from Prosopis africana TAUB.,[2)] and some approaches to the synthesis of these Prosopis alkaloids have been reported.[3)] We wish to describe a chiral and stereoselective total synthesis of (-)-deoxoprosopinine (3) and (-)-deoxoprosophylline (4) from L-serine (5); the synthesis involves a cyclization of an ethylenic amine (6) by intramolecular aminomercuration.[4)]

L-serine (5) was transformed in 4 steps into (2S)-3-acetoxy-2-phthalimidopropanal (7) via (2S)-3-acetoxy-2-phthalimidopropanoic acid (8) by the known procedures.[5)] An elongation of the carbon chain of 7 by C_{15}-unit was carried out by the Grignard reaction. A bromide (9) used for the Grignard reaction was prepared as follows. 3-Pentadecyn-1-ol[6)] in ethanol was hydrogenated in the presence of Pd-$BaSO_4$ (deactivated with quinoline) to give (Z)-3-pentadecen-1-ol[7)] (10; mp 12-13 °C, bp 105 °C/0.1 kPa; yield quantitative). Bromination of 10 with dibromotriphenylphosphine in dichloromethane at room temperature afforded (Z)-3-pentadecenyl bromide[7)] (9; bp 156-156.5 °C/0.4 kPa; yield 89%).

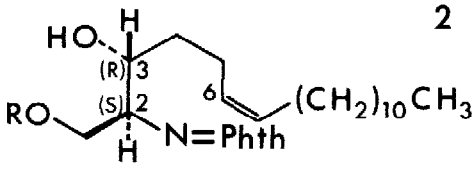
Reaction of the chiral aldehyde (7) [in THF-ether (2:1), -70 ~ -45 °C] with the Grignard reagent prepared from 9 gave a mixture of diol monoacetates[8)] (11 and 12). This mixture was subjected to hydrolysis (hydrochloric acid-MeOH, under reflux) and then separation by silica gel column chromatography to afford (2S, 3R,6Z)-2-phthalimido-6-octadecene-1,3-diol[7)] (13; erythro-form; yield from 8 16.5%) and (2S,3S,6Z)-2-phthalimido-6-octadecene-1,3-diol (14; threo-form; yield from 8 2.4%) in a ca. 7:1 ratio. Treatment of the diols (13 and 14) with 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid gave their acetonides



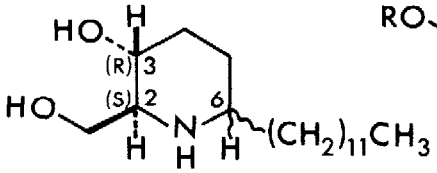
1



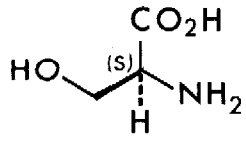
2 (racemic)



11 R = Ac
13 R = H



3 (6S) : 6β — H
4 (6R) : 6α — H



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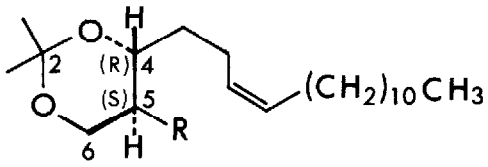
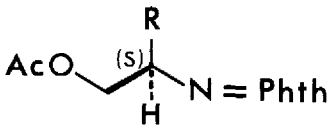
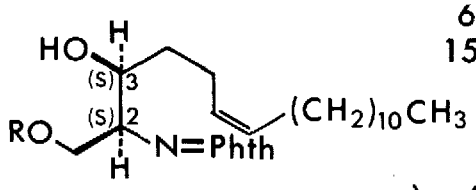


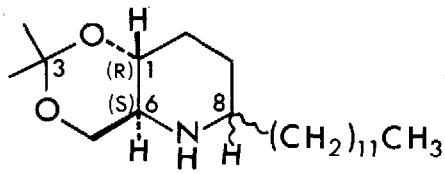
6 R = NH_2
15 R = —N=Phth



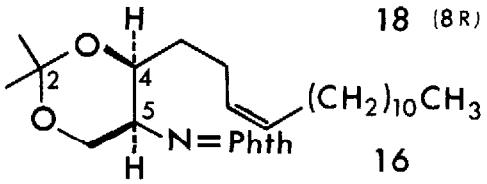
7 R = CHO
8 R = CO_2H
(Phth : phthaloyl)



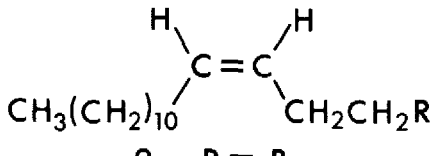
12 R = Ac
14 R = H



17 (8S) : 8β — H
18 (8R) : 8α — H



16



9 R = Br
10 R = OH

[15[7] (yield 97%) and 16 (yield 70%)], respectively. The erythro and threo configurations were shown for the diols (13 and 14), respectively, on the basis of the coupling constant values between $C_{(4)}$-H and $C_{(5\alpha)}$-H (15, 10 Hz; 16, 5 Hz) determined by NMR measurements of the acetonides (15 and 16). The observation described above shows that a stereoselective attack[5] of the Grignard reagent to

the aldehyde (7) effected preferentially from the less hindered side of 7 to give predominantly the desired erythro derivative (11).

The N-protective phthaloyl group of 15 was removed by hydrazinolysis to give (4R,5S)-2,2-dimethyl-4-[(Z)-3-pentadecenyl]-1,3-dioxan-5-amine (6; yield quantitative). The aminomercuration of this ξ,ζ-unsaturated amine (6) was effected by treatment with mercuric acetate in methanol at room temperature, followed by demercuration with sodium borohydride, giving rise to two piperidine acetonides, (1R,6S,8S)- and (1R,6S,8R)-8-dodecyl-3,3-dimethyl-2,4-dioxa-7-azabicyclo[4.4.0]-decane [17 (yield 4%) and 18 (yield 85%)][9] in a ca. 1:21 ratio.[10]

Finally, acid hydrolysis (hydrochloric acid-MeOH, under reflux) of the acetonides (17 and 18) afforded (-)-deoxoprosopinine (3; yield from 17 58%, total yield from 5 0.15%) and (-)-deoxoprosophylline (4; yield from 18 86%, total yield from 5 4.8%), respectively. These synthetic piperidines (3 and 4) were found to be identical, except optical property, with authentic (+)-deoxoprosopinine[2a,b] and (±)-deoxoprosophylline[2c] derived from natural (+)-prosopinine (1)[2a,b] and (±)-prosophylline (2),[2c] respectively. The absolute value of optical rotation ($[\alpha]_D$ -14.7°) of synthetic deoxoprosopinine (3) is almost the same as that ($[\alpha]_D$ +12°) of deoxoprosopinine derived from natural 1; this shows that no isomerization occurred during the synthesis described above.

This work constitutes the first example of stereoselective total synthesis of optically active prosopis alkaloids, and presents a useful synthetic route applicable to the other piperidine alkaloids.

Characterization of the products (3, 4, 6, 13-17, and 18) are as follows;
3: mp 89.5-90 °C, $[\alpha]_D$ -14.7° (c 0.3, $CHCl_3$); NMR ($CDCl_3$) δ 0.89 (3H, t, J=6 Hz, $-CH_2\underline{CH_3}$), 1.9 (br. s, OH), 2.82 (1H, m, $C_{(6\beta)}$-H), 3.14 (1H, m, $C_{(2\alpha)}$-H), 3.62 and 3.66 (each 1H, m, $HO\underline{CH_2}$-); MS m/e 299.2780 (M^+), calcd for $C_{18}H_{37}O_2N$: M 299.2822;
4: mp 90-91 °C [(±)-4 mp 83 °C[2c]], $[\alpha]_D$ -14° (c 0.24, $CHCl_3$); NMR ($CDCl_3$) δ 0.88 (3H, t, J=6 Hz, $-CH_2\underline{CH_3}$), 2.3 (br. s, OH), 2.50 (1H, br. s, $C_{(6\alpha)}$-H), 2.56 (1H, m, $C_{(2\alpha)}$-H), 3.44 and 3.71 (each 1H, m, $HO\underline{CH_2}$-); MS m/e 299.2800 (M^+), calcd for $C_{18}H_{37}O_2N$: M 299.2822;
6: an oil; IR (neat) 3350 (NH), 1660 cm^{-1} (-CH=CH-), absence of absorption around 965 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (3H, t, J=6 Hz; $-CH_2\underline{CH_3}$), 1.38 and 1.40 (each 3H, s, t-CH_3), 2.60 (1H, m, $C_{(5\alpha)}$-H), 3.40 (1H, dd, J=11 and J=9.5 Hz, $C_{(6\beta)}$-H), 3.80 (1H, dd, J=11 and J=5 Hz, $C_{(6\alpha)}$-H), 5.34 (2H, m, $-CH_2\underline{CH_A}=\underline{CH_B}CH_2$-; a J_{AB}=11 Hz value was determined by double irradiation experiments), and 2.00 (4H, m, allylic H's); MS m/e 339 (M^+);
13: mp 32.5-34.5 °C, $[\alpha]_D$ -15° (c 0.20, $CHCl_3$); IR (Nujol) 3450 cm^{-1} (OH), absence of absorption around 965 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (3H, t, J=6 Hz, $-CH_2\underline{CH_3}$), ca. 4.2 [4H, m, $HO\underline{CH_2}$-C<u>H</u>(NPhth)-C<u>H</u>(OH)-], 5.35 (2H, m, -CH=CH-), and 7.82 (4H, m, phthaloyl);
14: an oil, $[\alpha]_D$ +5° (c 0.23, $CHCl_3$), IR (Nujol) 3450 cm^{-1} (OH), absence of absorption around 965 cm^{-1}; NMR ($CDCl_3$) δ ca. 4.0 [4H, m, $HO\underline{CH_2}$-C<u>H</u>(NPhth)-

CH(OH)-], 5.36 (2H, m, -CH=CH-), and 7.83 (4H, m, phthaloyl);
15: mp 47-48 °C, $[\alpha]_D$ -6° (c 0.23, $CHCl_3$); NMR ($CDCl_3$) δ 1.45 and 1.64 (each 3H, s, t-CH_3), 3.70 (1H, dd, J=10 and J=5 Hz, $C_{(6\alpha)}$-H), 4.20 (1H, td, J=10 and J=5 Hz, $C_{(5\alpha)}$-H), 4.51 (1H, t, J=10 Hz, $C_{(6\beta)}$-H), 4.65 (1H, m, $C_{(4\beta)}$-H), 5.26 (2H, m, -CH=CH-), and 7.80 (4H, m, phthaloyl);
16: mp 56-56.5 °C, $[\alpha]_D$ +2° (c 0.43, $CHCl_3$); NMR ($CDCl_3$) δ 1.24 and 1.61 (each 3H, s, t-CH_3), 3.95 (1H, dd, J=11 and J=7 Hz, $C_{(6)}$-H), 4.15 (1H, ddd, J=9, J=5, and J=4.5 Hz, $C_{(4\alpha)}$-H), 4.38 (1H, dd, J=11 and J=7 Hz, $C_{(6)}$-H), 4.66 (1H, td, J=7 and J=5 Hz, $C_{(5\alpha)}$-H), 5.26 (2H, m, -CH=CH-), and 7.81 (4H, m, phthaloyl);
17: an oil, $[\alpha]_D$ +2° (c 0.10, $CHCl_3$); MS m/e 339.3090 (M^+), calcd for $C_{21}H_{41}O_2N$: M 339.3135; NMR ($CDCl_3$; 270 MHz): signals due to $C_{(1\beta)}$-H and $C_{(6\alpha)}$-H were observed at δ 3.58 and 2.80, respectively, and the $J_{(1\beta,6\alpha)}$-value was determined to be 10 Hz; the $C_{(8\beta)}$-H signal appeared at δ 2.99 as a broad signal ($W_{1/2}$=21 Hz[2b]);
18: mp 45-47.5 °C, $[\alpha]_D$ +9° (c 0.27, $CHCl_3$); MS m/e 339.3114 (M^+), calcd for $C_{21}H_{41}O_2N$: M 339.3135; NMR (C_6D_6; 270 MHz): the $C_{(1\beta)}$-H and $C_{(6\alpha)}$-H signals appeared at δ 3.47 and 2.56, respectively, and the $J_{(1\beta,6\alpha)}$-value was determined to be 10 Hz; the $C_{(8\alpha)}$-H resonated at δ 2.33 as a broad signal ($W_{1/2}$=25 Hz[2c]).

REFERENCES AND NOTES

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1) Part V of "Piperidine Alkaloids (Alcaloïdes Pipéridiniques)" by Q. Khuong-Huu; Part IV: reference 4b.
2) a) G. Ratle, X. Monseur, B. C. Das, J. Yassi, Q. Khuong-Huu, and R. Goutarel, Bull. Soc. Chim. France, 1966, 2945. b) Q. Khuong-Huu, G. Ratle, X. Monseur, and R. Goutarel, Bull. Soc. Chim. Belges, 81, 425 (1972). c) Idem, ibid., 81, 443 (1972).
3) a) G. Fodor, J.-P. Fumeaux, and V. Sankaran, Synthesis, 1972, 464. b) A. J. G. Baxter and A. B. Holmes, J. Chem. Soc. Perkin I, 1977, 2343.
4) a) J. J. Périé, J. P. Laval, J. Roussel, and A. Lattes, Tetrahedron, 28, 675 (1972) and references cited therein. b) This method was successfully applied to the synthesis of (±)-solenopsin A; Y. Moriyama, H.-D. Doan, C. Monneret, and Q. Khuong-Huu, Tetrahedron Lett., 1977, 825.
5) H. Newman, J. Am. Chem. Soc., 95, 4098 (1973).
6) D. E. Ames, A. N. Covell, and T. G. Goodburn, J. Chem. Soc., 1965, 894.
7) A satisfactory result of elementary analysis was obtained for this compound.
8) Separation of 11 and 12 by means of column and thin-layer chromatographies was unsuccessful.
9) Stereochemistry at $C_{(8)}$ of 17 and 18 was determined by their hydrolysis to give 3 and 4, respectively, as described below.
10) The reaction proved to proceed stereoselectively.

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