Pergamon

Tetrahedron Letters 40 (1999) 6869–6870

TETRAHEDRON LETTERS

Asymmetric total synthesis of (−)-prosophylline

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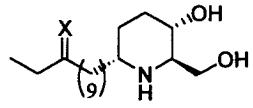
Received 18 June 1999; accepted 13 July 1999

Abstract

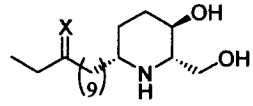
The asymmetric total synthesis of (−)-prosophylline from D-glucal via (2*S*)-hydroxymethyl-dihydropyridone **6** by a 17-step synthesis and 12% overall yield is presented.

Keywords: asymmetric synthesis; piperidine alkaloids; (−)-prosophylline.

Multifunctionalized piperidine alkaloids are widely found in nature and many of them exhibit significant biological activities of medicinal interest.[1] Prosopis alkaloids constitute a small subgroup of alkaloid lipids, which contain the 2,6-disubstituted-3-piperidinol skeleton. These compounds are isolated from the leaves of *Prosopis africana*[2] and possess noteworthy antibiotic and anesthetic properties.[3] Thus several endeavors directed towards their synthesis have been reported, including the asymmetric total syntheses of (+)-prosopinine **1**,[4] (+)-deoxoprosopinine **2**[5] and (−)-deoxoprosophylline **4**.[5b,6] Surprisingly, the synthesis of (−)-prosophylline **3** is less documented and only one racemic stereoselective synthesis of this molecule has been reported to date.[7] Herein we report an asymmetric total synthesis of **3** from D-glucal, based on our recently reported (five steps, 61% overall yield) enantioselective transformation to (2*S*)-hydroxymethyl-dihydropyridone **6** via α-furfurylamine **5**.[8]



X = O : (+)-prosopinine (**1**)
X = 2H : (+)-deoxoprosopinine (**2**)



X = O : (−)-prosophylline (**3**)
X = 2H : (−)-deoxoprosophylline (**4**)

Protected dihydropyridone **7** ($[\alpha]_D^{22}$=+100, *c*=1, MeOH) was hydrogenated over palladium and reduced with sodium cyanoborohydride in acetic acid/methanol to afford, after crystallization, (3*R*)-piperidinol **8** as a single diastereomer (Scheme 1). The configuration of C-3 was revealed by COSY and ^{1}H NMR analysis of its corresponding benzyl ether **9** ($[\alpha]_D^{22}$=+15, *c*=0.7, MeOH). The desired 2,6-*cis* stereochemistry was achieved by a variation of Speckamp's protocol[4b] which require a Lewis acid promoted allylsilane addition to an acyliminium ion intermediate, generated in situ from **9**. Thus, reaction with allyltrimethylsilane in the presence of 0.7 equivalents of titanium tetrachloride at −78°C

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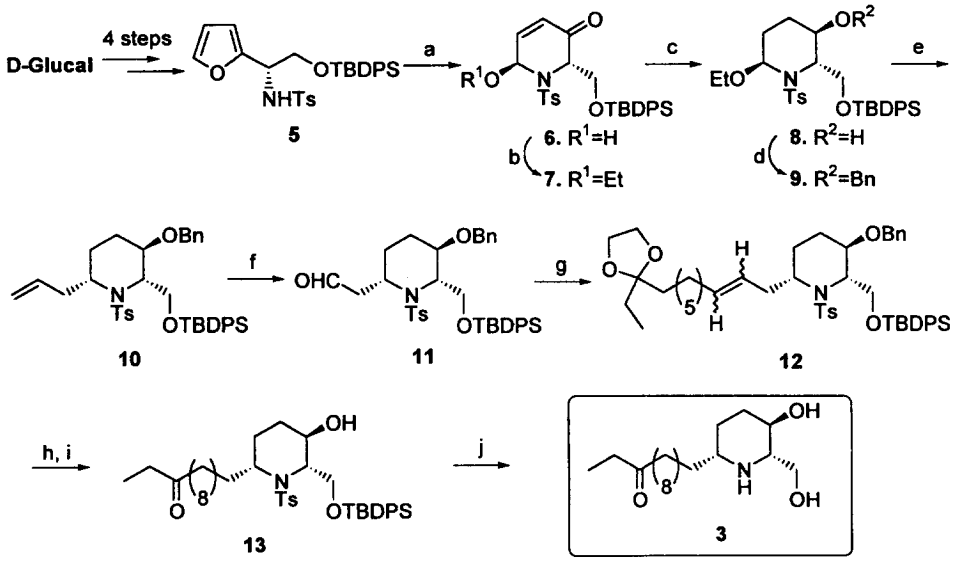
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01387-8

furnished **10** in 87% yield ($[\alpha]_D^{22}$=–2.1, *c*=1, MeOH). Dihydroxylation and subsequent periodate cleavage produced aldehyde **11**, while elongation of C-6 chain was carried out through the introduction of the 8-oxo-*n*-decanyl[9] side-chain by Wittig reaction. Finally, deprotection of the carbonyl group, hydrogenation and removal of the protecting groups provided (–)-prosophylline **3** (mp 75–76°C; lit.[7] mp 79°C of racemate, $[\alpha]_D^{22}$=–13.4, *c*=1.5, MeOH). Spectral and physical data are identical with those in the literature.[2,7,10]



Scheme 1. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2 (91%). (b) $HC(OEt)_3$, $BF_3 \cdot OEt_2$, 4 Å mol. sieves, THF, 0°C (95%). (c) i) H_2, Pd/C, AcOEt (91%); ii) $NaBH_3CN$, AcOH, MeOH, 0°C to rt (85%). (d) NaH, BnBr, Bu_4NI, THF (91%). (e) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, –78°C (87%). (f) i) $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_2$, Na_2SO_3, *t*-BuOH/H_2O (1:1); ii) $NaIO_4$, H_2O/EtOH (1:1) (96%, two steps). (g) PPh_3, $CH_3CH_2C(OCH_2)_2C_7H_{14}Br$, *n*-BuLi (68%). (h) HCl, H_2O. i) H_2, Pd/C, EtOH (88%, two steps). (j) i) TBAF, THF (91%); ii) Na, naphthalene (64%)

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9. $CH_3CH_2C(OCH_2)_2C_7H_{14}Br$ was prepared from 1,8-octanediol by the following sequence: (i) HBr, benzene, reflux (59%); (ii) PCC, CH_2Cl_2 (75%); (iii) CH_3CH_2MgBr, Et_2O (95%); (iv) PCC, CH_2Cl_2 (80%); and (v) $HOCH_2CH_2OH$, H_2SO_4, toluene (75%).
10. IR (neat): ν_{max}=3381, 3255, 1710 cm^{-1}; NMR ($CDCl_3$, 300 MHz): δ=1.05 (t, 3H, *J*=7.1 Hz), 1.28 (br s, 13H), 1.30–1.58 (m, 5H), 1.68–1.72 (m, 1H), 2.01–2.05 (m, 1H), 2.40 (t, 2H, *J*=7.2 Hz), 2.42 (t, 2H, *J*=7.2 Hz), 2.50 (m, 1H), 2.55 (dt, 1H, *J*=9.1, 4.7 Hz), 3.42 (td, 1H, *J*=10.5, 4.7 Hz), 3.63 (d, 1H, *J*=5.2 Hz), 3.63 (d, 1H, *J*=5.2 Hz); Anal. calcd for $C_{18}H_{35}NO_3$: C, 68.97; H, 11.25; N, 4.47. Found: C, 69.09; H, 11.18; N, 4.45.