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Asymmetric total synthesis of (–)-prosophylline

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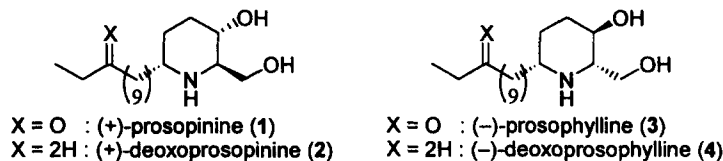
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Abstract

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. © 1999 Elsevier Science Ltd. All rights reserved.

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

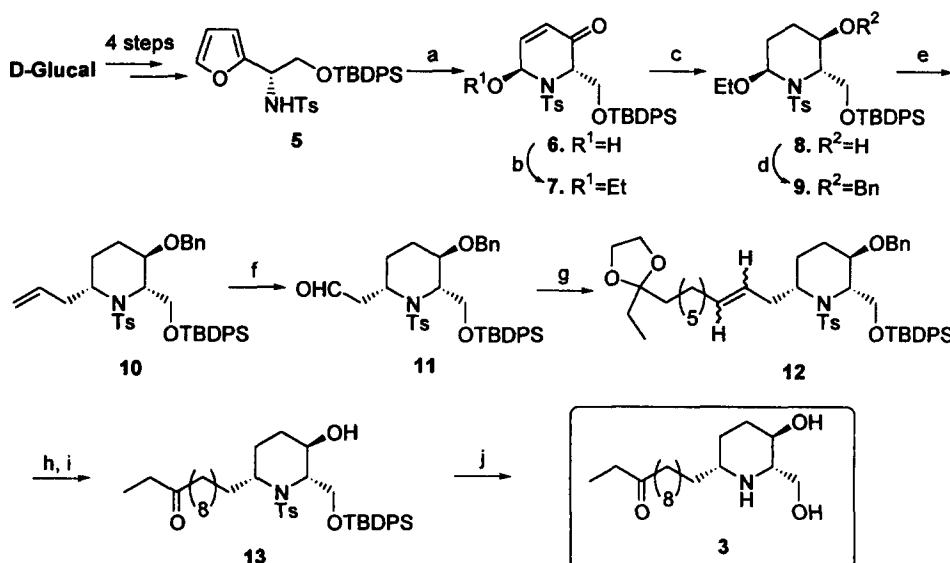
Multifunctionalized piperidine alkaloids are widely found in nature and many of them exhibit significant biological activities of medicinal interest.¹ Prosopis alkaloids constitute a small subgroup of alkaloid lipids, which contain the 2,6-disubstituted-3-piperidinol skeleton. These compounds are isolated 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



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 ¹H 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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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*-decanyl⁹ 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, CH₂Cl₂ (91%). (b) HC(OEt)₃, BF₃·OEt₂, 4 Å mol. sieves, THF, 0°C (95%). (c) i) H₂, Pd/C, AcOEt (91%); ii) NaBH₃CN, AcOH, MeOH, 0°C to rt (85%). (d) NaH, BnBr, Bu₄NI, THF (91%). (e) allyltrimethylsilane, TiCl₄, CH₂Cl₂, –78°C (87%). (f) i) K₃Fe(CN)₆, K₂CO₃, K₂OsO₂(OH)₂, Na₂SO₃, *t*-BuOH/H₂O (1:1); ii) NaIO₄, H₂O/EtOH (1:1) (96%, two steps). (g) PPh₃, CH₃CH₂C(OCH₂)₂C₇H₁₄Br, *n*-BuLi (68%). (h) HCl, H₂O. i) H₂, Pd/C, EtOH (88%, two steps). (j) i) TBAF, THF (91%); ii) Na, naphthalene (64%)

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- CH₃CH₂C(OCH₂)₂C₇H₁₄Br was prepared from 1,8-octanediol by the following sequence: (i) HBr, benzene, reflux (59%); (ii) PCC, CH₂Cl₂ (75%); (iii) CH₃CH₂MgBr, Et₂O (95%); (iv) PCC, CH₂Cl₂ (80%); and (v) HOCH₂CH₂OH, H₂SO₄, toluene (75%).
- IR (neat): $\nu_{\max} = 3381, 3255, 1710$ cm⁻¹; NMR (CDCl₃, 300 MHz): $\delta = 1.05$ (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 C₁₈H₃₅NO₃: C, 68.97; H, 11.25; N, 4.47. Found: C, 69.09; H, 11.18; N, 4.45.