A Convenient Route to Alkaloid Lipids: Application for the Synthesis of a Leptophylline A Analogue

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Abstract: A synthetic route for efficient access to alkaloid lipids, using the chiral 2,3,6-trisubstituted piperidine acetaldehyde 9 as an intermediate, is reported. The utility of the synthetic route was demonstrated in the asymmetric synthesis of an unnatural analogue of Cassia leptophylla alkaloid lipid, leptophyllin A, in 16 steps and 15% overall yield starting from D-glucal.

Key words: piperidines, alkaloids, asymmetric synthesis

Alkaloid lipids are natural compounds isolated from the leaves, stems and roots of various Prosopis, and Cassia species.1 Their structural framework consists of a polar head group (a 2,6-disubstituted-3-piperidinol) and a lipid tail group (Figure 1, compounds 1–7). Besides their unique structural features, these compounds and their synthetic analogues were also found to possess a wide range of antibiotic, anesthetic and CNS stimulating properties.2 Consequently, they have attracted increasing scientific interest.3 Intense research activity directed towards the efficient and stereoselective synthesis of these compounds and their derivatives has been initiated, producing a large number of biologically active compounds.4

Recently, bioassay-guided fractionation of a bioactive leaf extract of the Brazilian legume Cassia leptophylla5 led to the isolation and structure elucidation of three new alkaloid lipids named leptophylline B (5), leptophylline A (6), and 3-acetylleptophylline (7). These new structures represent the first example of alkaloid lipids that display significant anticancer activity5 and differ from other Prosopis and Cassia alkaloid lipids in the length and unusual dihydroxy functionality of their aliphatic side chains.

As part of our ongoing studies on the asymmetric synthesis of biologically interesting piperidine alkaloid derivatives,6 these intriguing molecules have attracted our attention. Aiming to develop a general synthetic route for the preparation of such compounds, our retrosynthetic strategy envisioned the use of the chiral 2,6-disubstituted-piperidin-3-ol 9 as a key intermediate (Scheme 1). This molecule has the desired cis-configuration and an aldehyde functionality on carbon atom C-6 that allows for the facile attachment of various lipid side chains. Furthermore, this compound is easily obtained by diastereoselective transformation of the corresponding 6-hydroxy-2S-hydroxymethyl-dihydropyridone 10, which can be prepared efficiently from the readily available D-glucal according to our recently reported synthetic route.7

Figure 1

Scheme 1

Scheme 2 Reagents and conditions: (a) NaH, BnBr, Bu,N, THF; (b) allylttrimethylsilane, TiCl4, CH2CL2, -78 °C; (c) i. K2Fe(CN)6; K2OsO4(OH)2; CH3SO2NH2; t-BuOH=H2O (1:1), ii. NaIO4, H2O=EtOH (1:1).
The synthesis of compound 9 was accomplished as depicted in Scheme 2. Enantioselective transformation of D-glucal to the trisubstituted piperidine 11 was achieved by an 8-step synthetic sequence in high yield, via the intermediate 6-hydroxy-2S-hydroxymethyl-dihydrotripyrone 10. Protection of the hydroxyl group and reaction with allyltrimethylsilane in the presence of a catalytic amount of titanium tetrachloride at −78 °C resulted in the exclusive formation of the all cis-diastereomer of 6-allyl-piperidine 13. The diastereoselectivity of this transformation can be rationalized, assuming an N-acyliminium ion intermediate (Figure 2). The strong A (1,2) strain between the tert-butyl-diphenyl-silyloxymethyl group on carbon atom C-2 and the N-tosyl group favors conformer II over conformer I. Exclusive formation of the 2,6-cis-isomer was revealed by HPLC and 1H NMR analysis and could be attributed to the stereoelectronically preferred axial attack by the silane nucleophile on II.

**Figure 2**

The stereochemistry of carbon atom C-6 in aldehyde 9 was assigned on the basis of 2D COSY and NOESY NMR spectroscopic studies. The aldehyde 9 was obtained in excellent yield after dihydroxylation and subsequent periodate cleavage of olefin 13. Thus, the strong NOE correlation among the CH2 protons of acetaldehyde, H-5eq and the methylenic protons of the silyloxyethyl group are indicative of the α-axial orientation of the acetaldehyde moiety at carbon atom C-6 (Figure 3). Furthermore, the small coupling constants observed between H-6 and the two protons H-5 are consistent with the β-equatorial orientation of H-6, reinforcing the previous assignment.

**Figure 3**

The all cis aldehyde 9 was envisioned to be the key intermediate for the preparation of a broad variety of natural and unnatural alkaloid lipids. To demonstrate the synthetic utility and versatility of this aldehyde, we targeted the novel chimeric alkaloid lipid analog 8 (Scheme 1). This compound would combine in a single molecule, the aliphatic side of leptophylline A with the polar head group of Prosopsis alkaloids. To this end, the chiral aliphatic substrate 18 was derived from the readily available 1,9-nonanediol, according to the reaction sequence outlined in Scheme 3. The 1,9-nonanediol 14 was transformed to the corresponding bromoalcohol and oxidized to aldehyde 15. Subsequent Wittig olefination afforded the bromo-alkene 16. Asymmetric dihydroxylation and subsequent acetalization provided the desired substrate 18 in very good chemical yield (85%) with 80% ee.

**Scheme 3** Reagents and conditions: (a) HBr, PhCH3; (b) PCC, CH2Cl2; (c) CH2PPh3Br, n-BuLi, THF; (d) (DHQD)2-PYR, K2Fe(CN)6, K2OsO4(OH)2, K2CO3, t-BuOH–H2O (1:1); (e) (CH3)2C(OC(OH)2)n–p-TSA, acetone.

Introduction of the aliphatic side chain onto the piperidine ring was performed via Wittig reaction of aldehyde 9 with the enantiomerically enriched triphenylphosphonium ylide. This ylide was derived from bromide 18, furnishing the corresponding alkenol 19, which was purified by chromatography and selective crystallization. Subsequent sequential removal of the silyl protective group, catalytic hydrogenation-hydrogenolysis and cleavage of the acetone and tosyl protective groups provided the desired synthetic alkaloid lipid 8 in 16 steps and 15% overall yield (from D-Glucal).

**Scheme 4** Reagents and conditions: (a) PPh3, 18, n-BuLi; (b) TBAF, THF; (c) H2, Pd/C, MeOH; (d) HCl, EtOH; (e) Na, naphthalene, DME.

In conclusion, we have described the efficient and stereoselective preparation of the all cis-aldehyde 9, a useful and versatile intermediate for the synthesis of alkaloid lipids. In addition, the convenient preparation of a novel alkaloid
lipid analog, incorporating in a single molecule the alliphatic tail chain of *leptophylline* A and the polar head group of a *Prospis* alkaloid, is presented. The described approach is highly convergent and is generally applicable since the side chain at carbon atom C-6 can be easily modified to provide access to a broad variety of natural and synthetic alkaloid lipids of structural and biological importance.

All reactions were carried out under an argon atmosphere unless otherwise noted. Solvents were distilled prior to use. THF was distilled from sodium-benzophenone and CHCl₃ was distilled over CaH₂ immediately prior to use. Starting materials and reagents were purchased from Aldrich (analytical reagent grades) and used without further purification. The (2S,3S,6R)-2-(tert-butyldiphenylsilyloxy)methyl-6-ethoxy-1-tosylpiperidin-3-ol (11) ([α]D²⁻⁻² = +60.4 (c 0.90, MeOH); mp 111–112 °C) was prepared according to literature procedure. Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Nicolet Magna 750, series II spectrometer. ¹H NMR spectra were recorded in CDCl₃ on Bruker AM-250 or DRX-400 spectrometers (250 MHz and 400 MHz, respectively) using TMS as internal standard. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at ambient temperature. Elemental analyses were provided by the University of Illinois microanalytical service laboratory. HPLC separations were performed using a Hewlett Packard 1100 series instrument with a variable wavelength UV detector and coupled to HP Chem-Station utilizing the manufacturer’s 5.01 software package. TLC was conducted on Merck glass plates coated with silica gel 60 F₂₅₄. Flash column chromatography was performed using Merck silica gel silicagel 60 (230–400 mesh ASTM).

The title compound was obtained by a general procedure. 7 Melting points were determined on a Büchi apparatus IR: 1640 cm⁻¹ (CH=CH). Anal. Calcd for C₃₉ H₄₇ NO₄ SSi (653.95): C, 71.63; H, 7.24; N, 2.14. Yield: 222 mg (87%).

(2S, 3S, 6R)-6-Allyl-3-benzyloxy-2-(tert-butyl-diphenyl-silyloxy-methyl)-1-tosyl piperidine (13)

To a stirred soln of TiCl₄ (45 µL, 0.41 mmol) in anhyd CH₂Cl₂ (1 mL) at –78 °C, a soln of 12 (256 mg, 0.39 mmol) and allylmethylenesilane (0.12 mL, 0.75 mmol) in CH₂Cl₂ (1.5 mL) was added dropwise over a 5 min period. The soln was allowed to gradually warm to 0 °C and stirred for a total period of 90 min. Then the reaction was quenched with H₂O (2 mL) and the ag layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated under reduced pressure to give a colorless oil which was purified by chromatography (EtOAc–hexane, 1:4; Rf = 0.57) to give 13 as white crystals. Yield: 222 mg (87%).
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Anal. Calc'd for C_{38}H_{45}NO_{5}SSi (655.9): C, 69.58; H, 6.92; N, 2.14.
Found: C, 69.38; H, 7.01; N, 2.10.

9-Bromo-nonanal (15)
A soln of 1.9-nonanol (8 g, 50 mmol) and 48% HBr (6 mL) in benzene (100 mL) was refluxed for 24 h in a Dean Stark apparatus. The resulting soln was washed successively with NaOH (6 N, 50 mL), HCl (10%, 50 mL) and H_{2}O (2 × 150 mL). The organic layer was separated, washed with brine, dried (MgSO_{4}) and evaporated to a colorless oil which was purified by chromatography (Et_{2}O–hexane, 1:4) to yield 15 (7 g). The latter was dissolved in CH_{2}Cl_{2} (75 mL) and PCC (16.2 g, 75 mmol) was added. After 30 min of stirring, the supernatant was decanted and filtered through a short pad of silica gel. The insoluble residue remaining in the reaction vessel was washed several times with Et_{2}O and the combined washings were washed with brine, dried (MgSO_{4}) and concentrated under reduced pressure. To a suspension of methyltriphenylphosphonium bromide (14.3 g, 47.63 mmol) in THF (10 mL) was added. The reaction was allowed to reach rt. and stirred for 1 h. The mixture was extracted with EtOAc (2 × 60 mL) and the combined organic layers were washed with brine, dried (MgSO_{4}) and concentrated under reduced pressure. The resulting colorless oil was purified by flash chromato- 

10-Bromo-dec-1-ene (16)
To a suspension of methyltriphenylphosphonium bromide (14.3 g, 47.63 mmol) in THF (10 mL) was added. The mixture was stirred for 1 h, cooled to –78 °C and a soln of aldehyde (Et_{2}O–hexane, 1:4) to yield 16 (8 g). The latter was dissolved in CH_{2}Cl_{2} (75 mL) and PCC (16.2 g, 75 mmol) was added. After 30 min of stirring, the supernatant was decanted and filtered through a short pad of silica gel. The insoluble residue remaining in the reaction vessel was washed several times with Et_{2}O and the combined washings were washed with brine, dried (MgSO_{4}) and concentrated under reduced pressure. To a suspension of methyltriphenylphosphonium bromide (14.3 g, 47.63 mmol) in THF (10 mL) was added. The reaction was allowed to reach rt. and stirred for an additional 1 h. The mixture was extracted with EtOAc (2 × 60 mL) and the combined organic layers were washed with brine, dried (MgSO_{4}) and concentrated under reduced pressure. The resulting colorless oil was purified by chromatography (EtOAc–hexane, 1:4; R_{f} = 0.58). Yield: 7.18 g (65%).

IR (KBr): 1720 cm^{-1} (C=O), 3391 cm^{-1} (CH=CH).
(2S, 3S, 6R, 4'R) -[3-Benzoyl oxy-6-[10'-2', 2'-dimethyl-[1', 3'-di o xo lan-4'-yl]-dec-2'-enyl]-1-tosyl piper id in-3-ol (20)

To a soln of olefin 19 (145 mg, 0.17 mmol) in THF (2 mL), TBAF (1.0 M soln in THF, 0.25 mL) was added. The mixture was stirred at 40 °C for 12 h, then the solvent was evaporated under reduced pressure to yield a yellowish oil which was purified by chromatography (EtOAc-acetone, 3:2; Rf = 0.67) to give alcohol 20 as a colorless oil. Yield: 97 mg (93%).

[alpha]$_D^{22}$ = +2.7 (c 0.7, EtOAc).

IR: 3445 cm$^{-1}$ (OH), 1354, 982 (COC).

1H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.20-1.35 (m, 11 H, H-5, CH$_2$), 1.33 (s, 3 H, CCH$_3$), 1.38 (s, 3 H, CCH$_3$), 1.45-1.70 (m, 5 H, H-4, CH$_2$), 1.98–2.11 (m, 2 H CH$_2$CH$_2$), 2.33-2.42 (m, 2 H CHCH$_2$CH), 2.43 (s, 3 H, ArCH$_3$), 2.62 (t, $J$ = 7.0 Hz, 1 H, OH), 3.17–3.25 (m, 1 H, H-3), 3.47–3.55 (m, 1 H, OCH), 3.64–3.74 (m, 1 H, CH$_2$), 3.98–4.14 (m, 4 H, H-6, OCH$_2$, CH$_2$OH), 4.31 (dd, $J$ = 13.5, 6.8 Hz, 1 H-2), 4.43 (d, $J$ = 11.9 Hz, 1 H, CHPh), 4.48 (d, $J$ = 11.9 Hz, 1 H, CH$_2$), 5.38 (dt, $J$ = 10.6, 6.8 Hz, 1 H, CH), 5.51 (dt, $J$ = 10.6, 7.2 Hz, 1 H, CH), 7.23 (d, $J$ = 8.3 Hz, 2 H, ArH), 7.25-7.30 (m, 2 H, ArH), 7.34–7.41 (m, 3 H, ArH), 7.63 (d, $J$ = 8.3 Hz, 2 H, ArH).

Anal. Calcd for C$_{35}$H$_{51}$NO$_6$S (613.9): C, 68.48; H, 8.37; N, 2.28.

(2R, 2'R, 5S, 6'S) -12-(5'-Hydroxy-6'-hydroxy methyl-piperidin-2'-yl)-dodecane-1,2-diol (8)

To a soln of naphthalene (50 mg, 0.39 mmol) in freshly distilled DME (2 mL), sodium (9 mg, 0.38 mmol) was added. The mixture was stirred at ambient temperature for 45 min (dark-green color), cooled to −78 °C and a soln of 20 (30 mg, 0.062 mmol) in DME (1 mL) was added. The reaction mixture was stirred at −78 °C for 30 min, quenched with brine (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure to give a colorless oil which was purified by chromatography (EtOAc-MeOH, 10:1; Rf = 0.63) to furnish the desired product 8. Yield: 16 mg (64%).

[alpha]$_D^{22}$ = +4.7 (c 1.2, EtOAc).

IR: 3407 cm$^{-1}$ (OH).

1H NMR (250 MHz, CDCl$_3$): $\delta$ = 1.15–1.69 (m, 22 H, CH$_2$), 2.07 (s br, 1 H, OH), 2.25 (s br, 1 H, OH), 2.63 (s br, 1 H, OH), 2.85 (s br, 1 H, OH), 3.15 (m, 2 H, H-2', H-5'), 3.32–3.37 (m, 2 H, H-6', CHOH), 3.55–3.72 (m, 4 H, CH$_2$OH, CH$_2$OH).

Anal. Calcd for C$_{31}$H$_{49}$NO$_7$ (531.49): C, 63.82; H, 8.37; N, 2.28. Found: C, 63.88; H, 8.21; N, 2.25.

References


(8) For a recent review on this subject see: Speckamp, W. N.; Moollenaar, M. J. Tetrahedron 2000, 56, 3817.