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ScienceDirect
Tetrahedron 62 (2006) 9942–9948
Tetrahedron

An asymmetric aminohydroxylation route to *cis*-2,6-disubstituted piperidine-3-ol: application to the synthesis of (−)-deoxocassine

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Received 13 April 2006; revised 18 July 2006; accepted 3 August 2006
Available online 22 August 2006

Abstract—A highly efficient, flexible, and convergent route to *cis*-2,3,6-trisubstituted piperidines has been developed employing the Sharpless asymmetric aminohydroxylation and stereoselective reductive amination by catalytic hydrogenation as the key steps. Its usage is illustrated by the short synthesis of the piperidine-3-ol alkaloid, (−)-deoxocassine.

1. Introduction

Functionalized piperidines are among the most ubiquitous heterocyclic building blocks in natural products and synthetic compounds with important activities.[1] Hydroxylated piperidine alkaloids are frequently found in living systems and display a wide range of biological activities due to their ability to mimic carbohydrates in a variety of enzymatic processes.[2] Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids as important tools in the study of biochemical pathways.[3] 2,6-Disubstituted 3-piperidinols are abundantly found in nature and have received much attention from the synthetic community.[4] Typical representative of this class of compounds includes deoxocassine (**1**), prosafrinine (**2**), cassine (**3**), spectaline (**4**), azimic acid (**5**), and carpamic acid (**6**) etc. (Fig. 1). Consequently, much effort has been directed to the syntheses of these alkaloids including cassine[5] and deoxocassine.[6] Besides the interesting structural features, these compounds are also of pharmaceutical interest as they exhibit a wide range of biological activities.[7]

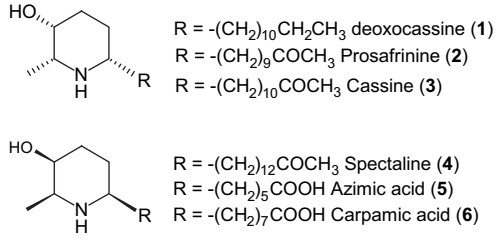

Figure 1.

In connection with our ongoing program aimed at developing enantioselective syntheses of naturally occurring lactones[8] and amino alcohols,[9] we became interested in developing a simple and feasible route to *cis*-2,6-disubstituted piperidine-3-ols. Here, we present an enantioselective synthesis of (−)-deoxocassine as a representative example for a general synthetic strategy to all 2,6-dialkyl 3-piperidinols.

2. Results and discussion

Our approach for a general synthetic strategy to *cis*-2,6-disubstituted 3-piperidinols was envisioned via the synthetic route as shown in Scheme 1. Compound **7** was visualized as an immediate precursor for the basic alkaloid skeleton, which in turn would be obtained by the coupling of fragments **8** and **12**. Lactone **8** could be derived from aminohydroxy ester **9**, which in turn would be prepared from the Sharpless asymmetric aminohydroxylation of *tert*-butyl crotonoate **11**. The sulfone fragment **12** could be easily derived from alcohol **13**.

In order to demonstrate the application of this general strategy for the *cis*-2,6-disubstituted 3-piperidinols, we first attempted at the total synthesis of (−)-deoxocassine (**1**). The synthesis of the target compound **1** started from commercially available *tert*-butyl crotonoate **11**. As shown in Scheme 2, compound **11** was subjected to Sharpless asymmetric aminohydroxylation[10] using benzyl carbamate as a nitrogen source, potassium osmate as an oxidant, and $(DHQD)_2PHAL$ as a chiral ligand in *n*-propanol/water (1:1) to give the amino alcohol **10** in high regioselectivity as well as in excellent enantioselectivity. The ratio of the regioisomer was about 9:1 based on ^1H NMR spectrum of the crude product, and the initial ee of 90% could be easily raised to >99% by a single recrystallization from

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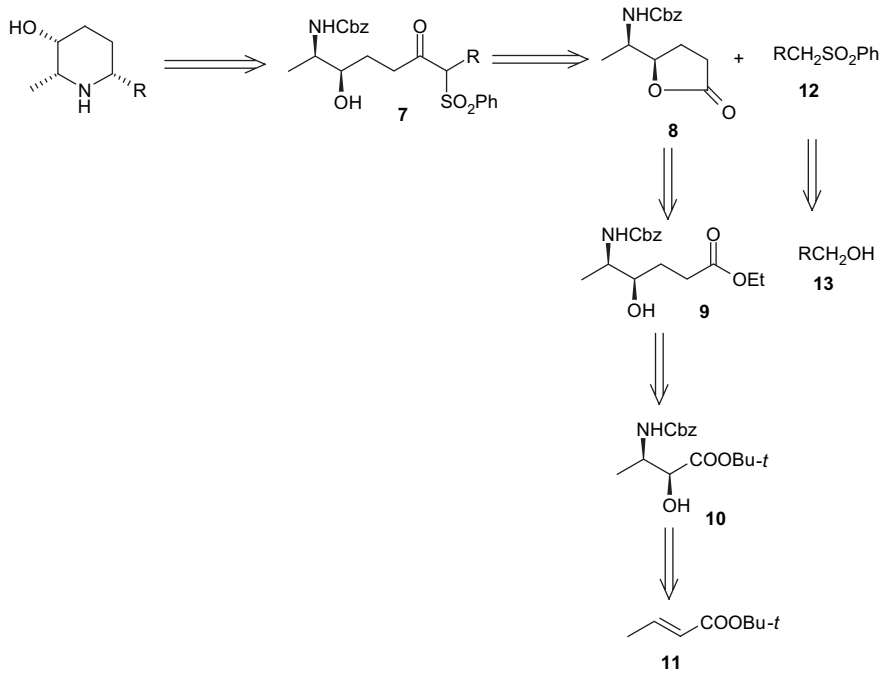
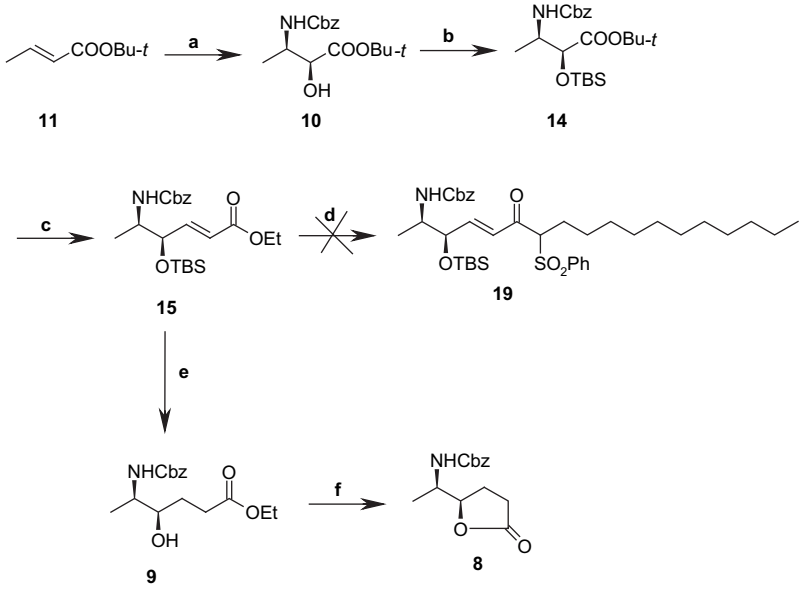
doi:10.1016/j.tet.2006.08.014



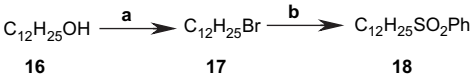
Scheme 1. Retrosynthetic analysis for a general synthetic strategy to *cis*-2,6-disubstituted piperidin-3-ol.



Scheme 2. Reagents and conditions: (a) $K_2OsO_2(OH)_4$, *t*-BuOCl, NaOH, benzyl carbamate, $(DHQD)_2PHAL$, *n*-PrOH/H_2O, 5 h, 67%, 9:1 regioisomer, >99% ee; (b) TBSCl, imidazole, DMAP (cat), dry DCM, 67%; (c) (i) DIBAL-H, dry DCM, −78 °C, 1 h; (ii) $Ph_3P{=}CHCOOEt$, dry THF, rt, 24 h, 73%; (d) $C_{12}H_{25}SO_2Ph$ (**18**), *n*-BuLi, dry THF, −78 °C; (e) (i) 10% Pd/C, MeOH, H_2, 6 h; (ii) CbzCl, Et_3N, dry DCM, 12 h, 78%; (f) *p*-TSA, MeOH, 30 min, 76%.

hexane/ethyl acetate.[10a,11] Subsequently, the free hydroxyl group of **10** was protected as silyl ether using TBSCl, imidazole, and catalytic amount of DMAP to give **14** in good yield. The ester group of **14** was then reduced to the corresponding aldehyde using 1 equiv of DIBAL-H at −78 °C followed by Wittig olefination to give the α,β-unsaturated ester **15** in 73% yield.[12]

The sulfone moiety, another fragment required in the synthesis of (−)-deoxocassine **1**, was synthesized as shown in Scheme 3. Thus, dodecane-1-ol **16** was treated with CBr_4 and TPP to give the bromo compound **17**, which was reacted with $PhSO_2Na$[13] in dry DMF to furnish the sulfone **18** in excellent yield.



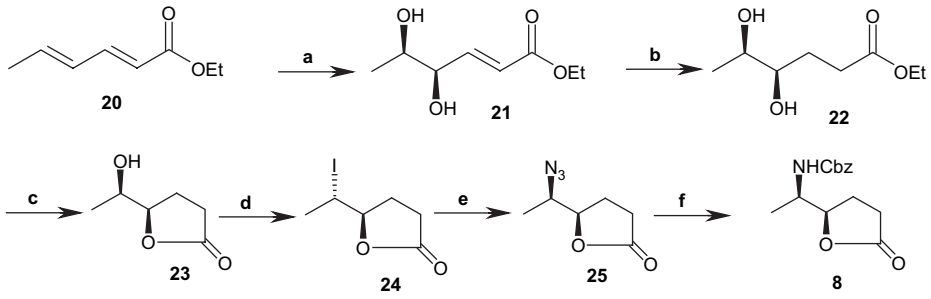
Scheme 3. Reagents and conditions: (a) CBr_4, TPP, dry DCM, 2 h, 85%; (b) $PhSO_2Na$, dry DMF, 8 h, 98%.

With substantial amount of both the fragments in hand, we then attempted at the coupling reaction of ester **15** with sulfone **18** under varied reaction conditions using different types of bases such as *n*-BuLi, NaH, and LDA in dry THF, however, the desired coupled product **19** could not be obtained[14] (Scheme 2). The reason for reaction failure could probably be attributed to the less reactivity of the α,β-unsaturated ester **15** as an electrophile. We then decided to use a more reactive electrophile such as **8** as a coupling partner instead of α,β-unsaturated ester **15**. The lactone **8** can be easily obtained from **15** simply by double bond reduction and subsequent cyclization. Accordingly, the double bond of **15** was reduced using H_2-10% Pd/C in methanol under hydrogenation conditions, which led to an intermediate resulting through concomitant deprotection of TBS and Cbz group. The free amine was subsequently protected using benzyloxycarbonyl chloride and triethyl amine to give **9**, which on treatment with 10 mol % *p*-TSA in methanol afforded the lactone **8** in 76% yield.

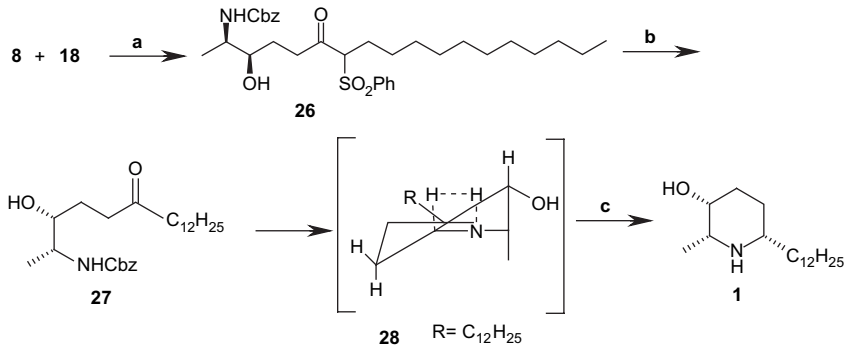
Alternatively, the lactone **8** could be prepared starting from easily available starting material sorbate **20** following a sequence of reaction as illustrated in Scheme 4. Thus, selective dihydroxylation of **20**[15] using osmium tetraoxide as oxidant and $(DHQD)_2PHAL$ as chiral ligand gave the diol **21** in good yield as well as in good enantioselectivity $[\alpha]_D^{25}$ +51.87 (*c* 1.1, EtOH) [lit.[15] $[\alpha]_D^{25}$ −52.0 (*c* 1.17, EtOH) for *S*-enantiomer]. Subsequently, the olefinic double bond was reduced to the corresponding saturated system **22** using H_2-10% Pd/C in methanol under hydrogenation conditions followed by treatment with 10 mol % *p*-TSA in methanol to give the lactone **23** in excellent yield. In order to introduce the azido group with retention of configuration, we carried out double inversion following a two-step reaction sequence as shown in Scheme 4.

Thus the lactone **23** was first reacted with methanesulfonyl chloride to give the *O*-mesyl derivative, which was subsequently treated with NaI under reflux conditions to furnish the iodide **24** with inversion of configuration. The introduction of azido group in S_N2 fashion led to the formation of desired *syn*-azido lactone **25** in good yield. Subsequent treatment with TPP in THF/H_2O afforded the free amine, which was protected with benzyloxycarbonyl chloride and triethyl amine to give the desired lactone **8**. The physical and chemical properties of **8** exactly matched with the one prepared earlier through aminohydroxylation approach (Scheme 2). The advantage of the aminohydroxylation over the dihydroxylation approach is that the desired fragment **8** could be prepared in relatively less number of steps.

Having completed the synthesis of both fragments **8** and **18**, we needed to couple the two fragments by lactone ring opening and subsequent reductive cyclization (Scheme 5). To this end the opening of the lactone **8** (prepared through the aminohydroxylation method) was carried out with a carbanion derived from **18** using *n*-BuLi at −78 °C to give the coupled product **26**. Reductive removal of the sulfonyl group with 6% Na/Hg in dry methanol at −10 °C furnished **27**, which was subjected to cyclization under hydrogenation conditions using H_2-20% $Pd(OH)_2$. This reaction proceeded through the formation of imine **28** as an intermediate, the catalytic hydrogenation of which under standard conditions afforded stereoselectively the target compound **1** as the only product.



Scheme 4. Reagents and conditions: (a) $(DHQD)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 12 h, 0 °C, 84%; (b) 10% Pd/C, H_2, MeOH, 1 h, 99%; (c) 10% *p*-TSA, MeOH, 30 min, rt, 83%; (d) (i) CH_3SO_2Cl, Et_3N, DMAP, dry DCM, rt, 30 min; (ii) NaI, acetone, reflux, 24 h, 60%; (e) NaN_3, dry DMF, 24 h, 70 °C, 74%; (f) (i) TPP, THF/H_2O (5:2), 24 h; (ii) CbzCl, Et_3N, dry DCM, 12 h, 73%.



Scheme 5. Reagents and conditions: (a) *n*-BuLi, dry THF, −78 °C, 50 min, 80%; (b) 6% Na/Hg, dry MeOH, −10 °C, 4 h, 68%; (c) 20% $Pd(OH)_2$, H_2, dry MeOH, 24 h, 100%.

The assigned stereochemistry at the newly created center was based on the assumption that the hydrogenation of imine **28** will occur from the less hindered β-face of the molecule, resulting in the all *syn*-configuration.[16] The physical and spectroscopic data of **1** were in accord with those described in literature.[6c]

3. Conclusion

In summary, we have achieved the synthesis of (−)-deoxocassine using Sharpless asymmetric aminohydroxylation/dihydroxylation and stereoselective reductive amination as the key steps. The synthetic strategy described would allow an easy access to a wide variety of related 2,6-disubstituted 3-piperidinols, for example, **2**–**6**.

4. Experimental

4.1. General methods

All reactions requiring anhydrous conditions were performed under positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. DCM and triethyl amine were distilled from CaH_2 and stored over molecular sieves and KOH, respectively. THF was distilled over sodium benzophenone ketyl. Solvents used for chromatography were distilled at respective boiling points using known procedures. Infrared spectra were recorded with an ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker MSL-300, and Brucker DRX-500 instruments using deuterated solvent. Chemical shifts are reported in parts per million. All melting points are uncorrected in degree celsius and recorded on a Thermonik melting point apparatus. Optical rotations were measured using the sodium D line of a JASCO-181 digital polarimeter. Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined using chiral HPLC and Mosher's analyses.

4.1.1. (2*S*,3*R*)-*tert*-Butyl-2-hydroxy-3-(*N*-benzyloxycarbonyl)-aminobutanoate (10). Benzyl carbamate (6.6 g, 43.60 mmol) was dissolved in 56 mL of *n*-propyl alcohol in a single-necked round bottom flask (250 mL) equipped with a magnetic stir bar. To this stirred solution was added a freshly prepared solution of NaOH (1.71 g, 42.89 mmol) in 105 mL of water followed by freshly prepared *tert*-butyl hypochlorite (4.7 mL, 42.89 mmol). Next, a solution of the ligand $(DHQD)_2PHAL$ (0.54 g, 5 mol %) in 49 mL of *n*-propyl alcohol was added. The reaction mixture was homogeneous at this point. Then the reaction mixture was immersed in a room temperature water bath and stirred for 3 min, and the *tert*-butyl crotonoate **11** (2.0 g, 14.06 mmol) was added followed by the osmium catalyst ($K_2OsO_2(OH)_4$) (0.20 g, 4 mol %). The reaction mixture was stirred until consumption of the starting material, when the light green color turned to light yellow. After completion of reaction, 30 mL of ethyl acetate was added and the phases were separated. The lower aqueous phase was extracted with ethyl acetate (4×60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to near dryness to afford the crude product, which was contaminated with excess of benzyl carbamate. Purification by flash chromatography using petroleum ether/EtOAc (6:4) as eluant provided **10** (2.92 g, 67%) as a white solid. The enantiomeric excess was found to be >99%.[11] Mp: 82–85 °C [lit.[10a] mp: 82–85 °C]; $[\alpha]_D^{25}$ −9.7 (*c* 0.34, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3522, 3311, 1721, 1692; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, *J*=6.6 Hz, 3H), 1.45 (s, 9H), 3.20 (br s, 1H, OH), 3.92–4.01 (m, 1H), 4.23–4.31 (m, 1H), 4.70 (s, 2H), 5.20 (br s, 1H, NH), 7.33–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.1, 27.6, 48.9, 66.4, 73.2, 83.3, 126.8, 127.4, 127.9, 128.3, 136.3, 155.5, 172.2.

4.1.2. (2*S*,3*R*)-*tert*-Butyl-2-(*tert*-butyldimethylsilanyloxy)-3-(*N*-benzyloxycarbonyl)-aminobutanoate (14). To a stirred solution of alcohol **10** (0.5 g, 1.61 mmol) in dry DCM (10 mL), imidazole (0.11 g, 1.61 mmol), TBSCl (0.36 g, 2.42 mmol), and catalytic amount of DMAP were added sequentially. The reaction mixture was stirred at ambient temperature. After TLC diagnosis, water was added to the reaction mixture and aqueous layer was extracted with dichloromethane (3×10 mL) and combined organic layers were washed with brine solution and dried over Na_2SO_4. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluant to give **14** (0.42 g, 67%) as a colorless liquid. $[\alpha]_D^{25}$ −14.6 (*c* 0.56, $CHCl_3$) [lit.[10b] $[\alpha]_D^{25}$ −14.6 (*c* 0.8, CH_2Cl_2)]; IR ($CHCl_3$, cm^{-1}) ν_{max} 3392, 1702, 1682; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.89 (d, *J*=5.4 Hz, 3H), 0.96 (s, 9H), 1.46 (s, 9H), 4.13 (t, *J*=6.6 Hz, 1H), 4.76 (s, 2H), 4.83–4.89 (m, 1H), 5.17 (s, 1H), 7.33–7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, −5.3, 10.1, 25.3, 25.5, 25.7, 25.9, 64.9, 69.3, 69.6, 125.9, 126.8, 127.5, 128.1, 128.2, 128.3, 128.5, 158.0, 170.2.

4.1.3. 5-Benzyloxycarbonylamino-4-(*tert*-butyldimethylsilanyloxy)-hex-2-enoic acid ethyl ester (15). To a stirred solution of **14** (1.0 g, 2.36 mmol) in dry DCM (10 mL) was added DIBAL-H (2.36 mL, 1 M solution in toluene, 2.36 mmol) at −78 °C and the mixture was stirred for 1 h at the same temperature. After completion of the reaction, the reaction mixture was quenched with saturated sodium potassium tartrate (5 mL) and filtered through Celite pad, dried over Na_2SO_4, and concentrated to near dryness. The crude product was used as such in the next Wittig reaction.

To a stirred solution of (ethoxycarbonylmethylene)-triphenylphosphorane (0.98 g, 2.83 mmol) in dry THF (10 mL) was added the crude aldehyde in dry THF (3 mL) and the reaction mixture was stirred for 24 h at room temperature and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluant to give **15** (0.62 g, 73%) as a light yellow liquid. $[\alpha]_D^{25}$ −12.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3369, 1723, 1682, 1603; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 1.12 (s, 9H), 1.23 (t, *J*=6.4 Hz, 3H), 1.30 (d, *J*=7.1 Hz, 3H), 3.70 (qn, *J*=6.2 Hz, 1H), 4.03–4.05 (m, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 6.10 (dd, *J*=15.7, 1.6 Hz, 1H), 6.94 (dd, *J*=15.8, 5.2 Hz, 1H), 4.72 (s, 2H), 4.98 (s, 1H), 7.28–7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.3, −3.4, 13.9, 18.7, 20.7, 52.3, 60.5, 70.0, 75.3, 122.0, 126.5, 127.3, 127.9, 140.9, 146.8,

157.2, 166.6. Anal. Calcd for $C_{22}H_{35}NO_5Si$ (421.60): C, 62.67; H, 8.37; N, 3.32. Found: C, 62.63; H, 8.31; N, 3.30.

4.1.4. 5-Benzyloxycarbonylamino-4-hydroxyhexanoic acid ethyl ester (9). To a stirred solution of **15** (0.5 g, 1.18 mmol) in dry methanol (10 mL) was added 10% Pd/C (50 mg) and the reaction mixture was stirred under hydrogen atmosphere for 6 h. The reaction mixture was filtered through Celite pad and concentrated to near dryness. The crude product thus obtained was dissolved in dry DCM (10 mL). Et_3N (0.25 mL, 1.78 mmol) and benzyloxycarbonyl chloride (0.22 mL, 1.54 mmol) were added at 0 °C. After consumption of the starting material (12 h), the reaction mixture was quenched with water (5 mL) and organic layer was extracted with dichloromethane (3×10 mL), dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (4:5) as eluant to give **9** (0.28 g, 78%) as a viscous liquid. $[\alpha]_D^{25}$ −32.4 (*c* 0.76, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3522, 3306, 1712, 1682; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.4 Hz, 3H), 1.99–2.23 (m, 2H), 2.47–2.58 (m, 2H), 2.99 (br s, 1H), 3.69 (q, *J*=7.1 Hz, 1H), 3.70–3.76 (m, 1H), 4.29 (q, *J*=7.3 Hz, 2H), 4.76 (s, 2H), 4.88 (s, 1H), 7.22–7.29 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 18.7, 27.8, 28.3, 52.5, 57.3, 70.1, 74.6, 127.3, 127.8, 128.8, 140.4, 155.2, 173.8. Anal. Calcd for $C_{16}H_{23}NO_5$ (309.36): C, 62.12; H, 7.49; N, 4.53. Found: C, 62.08; H, 7.43; N, 4.51.

4.1.5. [1-(5-Oxo-tetrahydrofuran-2-yl)-ethyl]-carbamic acid benzyl ester (8). Compound **9** (0.5 g, 1.62 mmol) was dissolved in bottle grade methanol (10 mL) and catalytic amount of *p*-TSA was added to this. The reaction mixture was stirred till completion of the reaction. Saturated sodium bicarbonate solution (3 mL) was added to the reaction mixture and stirred for 5 min. Methanol was removed in vacuo and the aqueous layer was extracted with dichloromethane (3×10 mL), washed with brine solution, dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluant to give the lactone **8** (0.32 g, 76%) as a light yellow solid. Mp: 122–124 °C; $[\alpha]_D^{25}$ −28.61 (*c* 0.92, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3323, 1721, 1696, 1321, 1225, 1032; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, *J*=6.8 Hz, 3H), 1.92–2.11 (m, 2H), 2.55 (t, *J*=8.5 Hz, 2H), 3.84–3.98 (m, 1H), 4.50 (q, *J*=7.1 Hz, 1H), 5.10 (s, 2H), 5.03 (br s, 1H), 7.31–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.3, 23.9, 28.0, 49.4, 66.5, 82.3, 127.7, 128.2, 131.7, 155.7, 176.7. Anal. Calcd for $C_{14}H_{17}NO_4$ (263.29): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.84; H, 6.50; N, 5.29.

4.1.6. 1-Bromododecane (17). To a solution of alcohol **16** (5.5 g, 29.51 mmol) in dry DCM (50 mL) were added TPP (15.48 g, 59.03 mmol) and CBr_4 (14.68 g, 44.27 mmol) sequentially at 0 °C. The reaction mixture was stirred (2 h) until disappearance of the starting material. Then, water was added to the reaction mixture and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (9.9:0.1) as eluant to give **17** (6.24 g, 85%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.3 Hz, 3H), 1.17–1.43 (m, 20H), 3.90 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.6, 26.9, 28.1, 28.7, 29.3, 29.4, 29.5, 29.6, 31.9, 32.8, 33.8.

4.1.7. (Dodecane-1-sulfonyl)-benzene (18). To a stirred solution of **17** (1 g, 4 mmol) in dry DMF (10 mL) was added $PhSO_2Na$ (0.98 g, 6 mmol) and then the reaction mixture was stirred for 8 h at ambient temperature. To the reaction mixture were added water (10 mL) and ethyl acetate (10 mL) and organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×10 mL) and combined organic layers were washed thoroughly with water and dried over Na_2SO_4. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) to give **18** (1.21 g, 98%) as a light yellow solid. Mp: 62 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, *J*=5.9 Hz, 3H), 1.12–1.33 (m, 20H), 3.04–3.12 (m, 2H), 7.53–7.68 (m, 3H), 7.91 (d, *J*=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 22.4, 28.0, 28.7, 28.9, 29.1, 29.2, 29.3, 31.6, 56.0, 127.8, 129.0, 133.4, 139.0.

4.1.8. (6-Benzenesulfonyl-2-hydroxy-1-methyl-5-oxo-heptadecyl)-carbamic acid benzyl ester (26). To a stirred solution of sulfone **18** (0.7 g, 2.28 mmol) in dry THF (10 mL) was added *n*-BuLi (1.4 mL, 2.28 mmol, 1.6 M solution in hexane) at −78 °C and stirring was continued for 20 min. Then, the lactone **8** (0.3 g, 1.14 mmol) in dry THF (3 mL) was added dropwise at the same temperature and stirring was continued for further 30 min. After TLC diagnosis, the reaction mixture was quenched with saturated NH_4Cl (5 mL) and aqueous layer was extracted with ethyl acetate (3×20 mL) and washed with brine solution, dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (4:6) as eluant to give **26** (0.52 g, 80%) as a light yellow solid. Mp: 165 °C; $[\alpha]_D^{25}$ −6.3 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3492, 3352, 1734, 1432; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, *J*=4.3 Hz, 3H), 1.22 (d, *J*=6.6 Hz, 3H), 1.13–1.26 (m, 20H), 1.76–1.88 (m, 2H), 2.02 (s, 1H), 2.24 (t, *J*=10.5 Hz, 2H), 3.06 (t, *J*=9.1 Hz, 1H), 3.81–3.95 (m, 1H), 4.35 (q, *J*=6.6 Hz, 1H), 4.79 (d, *J*=7.9 Hz, 1H), 5.11 (s, 2H), 7.36–7.38 (m, 5H), 7.49–7.60 (m, 3H), 7.85 (dd, *J*=7.7, 1.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.5, 26.3, 26.7, 27.1, 28.5, 29.1, 29.4, 29.9, 31.7, 49.3, 66.8, 85.8, 111.3, 126.7, 127.9, 128.9, 128.4, 129.2, 132.3, 134.2, 136.3, 142.6, 155.6, 167.8. Anal. Calcd for $C_{32}H_{47}NO_6S$ (573.78): C, 66.98; H, 8.26; N, 2.44. Found: C, 66.96; H, 8.23; N, 2.42.

4.1.9. (4*R*,5*R*,*E*)-Ethyl 4,5-dihydroxyhex-2-enoate (21). To a mixture of $K_3Fe(CN)_6$ (35.20 g, 0.1 mol), K_2CO_3 (14.76 g, 0.1 mol), and $(DHQD)_2PHAL$ (278 mg, 1 mol %) in *t*-BuOH/H_2O (1:1) cooled at 0 °C was added osmium tetraoxide (1.43 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methane sulfonamide (3.38 g, 35.66 mmol). After stirring for 5 min at 0 °C, olefin **20** (5 g, 35.66 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 12 h and then quenched with solid sodium sulfite (5 g). The stirring was continued for an additional 45 min and then the solution was extracted with ethyl acetate (5×100 mL). The combined organic phases were washed

with 10% aq KOH, brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluant gave the diol **21** (5.2 g, 84%) as a light yellow oil. $[\alpha]_D^{25}$ +51.87 (*c* 1.1, EtOH) [lit.[15] $[\alpha]_D^{25}$ −52.0 (*c* 1.17, EtOH) for *S*-enantiomer]; IR ($CHCl_3$, cm^{-1}) ν_{max} 3544, 3469, 1720, 1619; ^1H NMR (200 MHz, $CDCl_3$) δ 1.2 (d, *J*=6.5 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H), 3.25 (br s, 2H), 3.63–3.76 (m, 1H), 4.03 (ddd, *J*=11.4, 6.3, 1.6 Hz, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 6.06–6.15 (dd, *J*=15.6, 1.6 Hz, 1H), 6.92 (dd, *J*=15.7, 5.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 18.7, 60.5, 70.1, 75.3, 122.0, 146.8, 166.6. Anal. Calcd for $C_8H_{14}O_4$ (174.19): C, 55.16; H, 8.10. Found: C, 55.14; H, 8.18.

4.1.10. (4*R*,5*R*)-Ethyl 4,5-dihydroxyhexanoate (22). To a stirred solution of **21** (2.5 g, 14.35 mmol) in dry methanol (20 mL) was added 10% Pd/C (150 mg) and the reaction mixture was stirred under hydrogen atmosphere for 1 h. The reaction mixture was filtered through Celite pad and concentrated to near dryness. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluant gave the diol **22** (2.51 g, 99%) as a colorless oil. $[\alpha]_D^{25}$ +8.56 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3533, 1719; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (t, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.4 Hz, 3H), 1.99–2.23 (m, 2H), 2.47–2.58 (m, 2H), 2.99 (br s, 2H), 3.60 (q, *J*=7.1 Hz, 2H), 3.69–3.76 (m, 1H), 4.30 (q, *J*=7.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 18.7, 27.8, 30.2, 60.1, 70.1, 74.6, 173.8. Anal. Calcd for $C_8H_{16}O_4$ (176.21): C, 54.53; H, 9.15. Found: C, 54.50; H, 9.13.

4.1.11. 5-(1-Hydroxyethyl)-dihydrofuran-2-one (23). Compound **22** (2.0 g, 11.35 mmol) was dissolved in bottle grade methanol (20 mL) and catalytic amount of *p*-TSA was added to this. The reaction mixture was stirred at room temperature till completion of the reaction. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and stirred for 5 min. Methanol was removed in vacuo and the aqueous layer was extracted with dichloromethane (3×10 mL), washed with brine solution, dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluant to give the lactone **23** (1.22 g, 83%) as a light yellow solid. Mp: 92 °C; $[\alpha]_D^{25}$ −52.8 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3463, 1699; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, *J*=6.6 Hz, 3H), 1.97–2.29 (m, 2H), 2.47–2.57 (m, 2H), 3.03 (br s, 1H), 3.71–3.83 (m, 1H), 4.29–4.38 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.0, 23.5, 28.2, 68.9, 83.9, 177.6. Anal. Calcd for $C_6H_{10}O_3$ (130.14): C, 55.37; H, 7.74. Found: C, 55.34; H, 7.72.

4.1.12. 5-(1-Iodoethyl)-dihydrofuran-2-one (24). To a solution of **23** (2 g, 15.36 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added methanesulfonyl chloride (1.43 mL, 18.44 mmol), Et_3N (3.2 mL, 23.0 mmol), and DMAP (cat). The reaction mixture was stirred at room temperature for 30 min and then poured into Et_2O/H_2O mixture. The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water, brine, dried (Na_2SO_4), and concentrated to a white solid, which was dissolved in dry acetone (20 mL). Sodium iodide (21.6 g, 0.14 mol) was added and the reaction mixture was refluxed for 24 h. It was then cooled and poured into water and extracted with ethyl acetate. The organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated. Column chromatography on silica gel using petroleum ether/EtOAc (9.3:0.7) as eluant gave **24** (2.2 g, 60%) as a light yellow liquid. $[\alpha]_D^{25}$ −28.36 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 1722, 1519; ^1H NMR (200 MHz, $CDCl_3$) δ 1.98 (d, *J*=7.1 Hz, 3H), 2.02–2.06 (m, 2H), 2.28–2.31 (m, 1H), 4.19 (qn, *J*=6.6 Hz, 1H), 4.33 (q, *J*=7.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8, 20.8, 26.1, 34.9, 91.5, 172.0. Anal. Calcd for $C_6H_9IO_2$ (240.04): C, 30.02; H, 3.78; I, 52.87. Found: C, 30.01; H, 3.76; I, 52.85.

4.1.13. 5-(1-Azidoethyl)-dihydrofuran-2-one (25). Compound **24** (1.0 g, 4.16 mmol) was dissolved in dry DMF (10 mL). Sodium azide (1.62 g, 25 mmol) was added to the above solution and stirred at 80 °C for 24 h. The solution was then cooled and poured into water and extracted with ethyl acetate. The organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated. Column chromatography on silica gel using petroleum ether/EtOAc (1:9) as eluant gave **25** (0.48 g, 74%) as a colorless liquid. $[\alpha]_D^{25}$ −32.3 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 2122, 1738; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (d, *J*=6.7 Hz, 3H), 2.12–2.35 (m, 2H), 2.51–2.62 (m, 2H), 3.76–3.84 (m, 2H), 4.34–4.43 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.9, 22.3, 27.8, 59.2, 81.3, 176.3. Anal. Calcd for $C_6H_9N_3O_2$ (155.15): C, 46.45; H, 5.85; N, 27.08. Found: C, 46.41; H, 5.83; N, 27.05.

4.1.14. [1-(5-Oxo-tetrahydrofuran-2-yl)-ethyl]-carbamic acid benzyl ester (8). To a stirred solution of **25** (0.5 g, 3.2 mmol) in THF/H_2O (5:2) was added TPP (0.76 g, 2.9 mmol). The reaction mixture was stirred at ambient temperature for 24 h. The reaction mixture was concentrated to near dryness. The crude product thus obtained was dissolved in dry DCM (10 mL). Et_3N (0.65 mL, 4.64 mmol) and benzyloxycarbonyl chloride (0.60 mL, 4.02 mmol) were added at 0 °C. After consumption of the starting material (12 h), the reaction mixture was quenched with water (5 mL) and organic layer was extracted with dichloromethane (3× 10 mL), dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluant to give **8** (0.62 g, 73%) as a light yellow solid. The physical and spectroscopic data were in accord with those described earlier.

4.1.15. (2-Hydroxy-1-methyl-5-oxo-heptadecyl)-carbamic acid benzyl ester (27). To a stirred solution of **26** (0.25 g, 0.43 mmol) in dry methanol (5 mL) were added 6% Na/Hg (1.3 g) and Na_2HPO_4 (0.12 g, 0.87 mmol) at −10 °C and stirring was continued at the same temperature for further 4 h. After disappearance of the starting material the reaction mixture was quenched with water and methanol was removed in vacuo, water layer was extracted with ethyl acetate (3×5 mL) and washed with brine solution, dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluant to afford **27** (0.13 g, 68%) as a white solid. Mp: 141 °C; $[\alpha]_D^{25}$ −28.6 (*c* 0.92, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3499, 3296, 1696; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.6 Hz, 3H), 1.12 (d, *J*=6.6 Hz, 3H), 1.18–1.34 (m, 20H), 1.56–1.59 (m, 2H), 1.66–1.71 (m, 2H), 2.42 (t, *J*=7.3 Hz, 2H), 2.5

(br s, 1H), 3.56–3.73 (m, 1H), 4.08–4.10 (m, 1H), 4.71 (br s, 1H), 5.10 (s, 2H), 7.35–7.52 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 15.5, 22.4, 23.8, 24.1, 24.5, 29.0, 29.1, 29.3, 29.4, 31.5, 33.3, 44.9, 53.6, 69.5, 71.9, 126.6, 127.8, 128.8, 128.9, 142.4, 155.7, 210.8. Anal. Calcd for $C_{26}H_{43}NO_4$ (433.62): C, 72.02; H, 10.00; N, 3.23. Found. C, 72.0; H, 9.96; N, 3.20.

4.1.16. Synthesis of (−)-deoxocassine (1). In a single neck round bottom flask was placed **27** (0.1 g, 0.23 mmol) in methanol (2 mL) followed by addition of 20% $Pd(OH)_2$ (20 mg). The reaction mixture was stirred under hydrogen atmosphere for 24 h and filtered through Celite pad, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (7:4) as eluant to give **1** (65 mg, 100%) as a white solid. Mp: 48 °C [lit.[6b] Mp: 47–48 °C]. The physical and spectroscopic data of **1** were in full agreement with those reported.[6c] $[\alpha]_D^{25}$ −12.2 (*c* 0.68, $CHCl_3$) [lit.[6c] $[\alpha]_D^{25}$ −12.3 (*c* 0.19, $CHCl_3$)]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75 (t, *J*=6.8 Hz, 3H), 1.0 (d, *J*=6.5 Hz, 3H), 1.12–1.17 (m, 22H), 1.34–1.42 (m, 2H), 1.83–1.95 (m, 2H), 2.44–2.55 (m, 2H), 2.72–2.74 (m, 1H), 3.90 (d, *J*=6.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 16.3, 23.5, 26.2, 27.9, 30.2, 30.4, 30.5, 39.2, 56.5, 58.0, 58.2, 68.3.

Acknowledgements

S.R.V.K. thanks CSIR, New Delhi for senior research fellowship. Financial support from DST, New Delhi (Grant no. SR/S1/OC-40/2003) is gratefully acknowledged. We are grateful to Dr. M. K. Gurjar for his support and encouragement. This is NCL communication no. 6695.

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