Tetrahedron: *Asymmetry* 24 (2013) 758–763

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Total synthesis of the 2,6-disubstituted piperidine alkaloid (−)-andrachcinidine

Palakodety Radha Krishna *, Bonepally Karunakar Reddy

D-211, Discovery Laboratory, Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 15 April 2013
Accepted 10 May 2013
Available online 6 June 2013

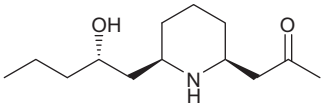
ABSTRACT

The total synthesis of the 2,6-disubstituted piperidine alkaloid (−)-andrachcinidine is reported using Keck's asymmetric allylation, Sharpless epoxidation, nucleophilic substitution, and intramolecular aza-Michael addition as the key steps.

1. Introduction

Natural alkaloid products, which contain a piperidine ring skeleton, are of great importance due to their potential biological activities.[1] Some piperidine derivatives are in clinical and preclinical studies.[2] The development of new methods for the synthesis of the piperidine ring skeleton is also important due to it being present in a large number of alkaloid natural products.[3]

(−)-Andrachcinidine **1** is a 2,6-disubstituted piperidine alkaloid that is isolated from *Andrachne aspera* spreng along with other piperidine alkaloids.[4] The plant *Andrachne aspera* spreng is a small perennial commonly found under shrubs in Karachi. The crude alkaloidal mixture showed activity in various biological tests with predominant antibacterial activity.[5] Chutian et al. reported on the first total synthesis of **1** by employing the desymmetrization of a *meso*-η-(3,4,5)-dihydropyridinylmolybdenum complex,[6] Hyung et al. reported on (+)-andrachcinidine using gold-catalyzed synthesis from alkynyl ethers.[7] Recently we reported on its synthesis using cross-metathesis and nucleophilic substitution reactions as the key steps.[8]



(-)-andrachcinidine **1**

However, due to its potent biological activity and interesting *cis*-2,6-disubstituted piperidine core skeleton, we revisited the synthesis of **1**, by using a linear synthetic strategy wherein a highly diastereoselective intramolecular aza-Michael addition strategy was used as the crucial reaction for construction of the piperidine ring. An asymmetric allylation, Sharpless epoxidation and nucleophilic substitution were the other key reactions employed to build the requisite carbon chain as well as the stereogenic centers.

2. Results and discussions

Retrosynthetic analysis (Scheme 1) revealed that the synthesis of target compound (−)-andrachcinidine **1** could be obtained from α,β-unsaturated ketone **14** via an intramolecular aza-Michael addition reaction[9,10] and hydrogenation reactions; α,β-unsaturated ketone **14** could be obtained from alcohol **10** using an oxidation/Wittig olefination/saturation/reduction reaction set, followed by oxidation and Wittig olefination reactions; alcohol **10** was synthesized from compound **9** by a reduction and benzyl carbamate protection, compound **9** could be generated from compound **6** followed by regioselective 1,3-epoxide ring opening reaction and general functional group transformations. Epoxy alcohol **6** could be generated from homoallylic alcohol **2** by a one-pot dihydroxylation, oxidative cleavage followed by Wittig olefination, reduction, and Sharpless asymmetric epoxidation reactions, and the homoallylic alcohol **2** could be synthesized from *n*-butyraldehyde using Keck's asymmetric allylation reaction.[11]

Our envisaged synthetic strategy (Scheme 2) started from commercially available *n*-butyraldehyde, which upon Keck's asymmetric allylation[11] {(*R*,*R*)-BINOL, 4 Å MS, Ti(O^iPr)$_4$, allyltri-*n*-butyltin, CH_2Cl_2, −78 to −20 °C, 24 h} gave homoallylic alcohol **2** (82%); its ee was found to be 97% (as determined by chiral HPLC: Chiralcel OBH; ^{i}PrOH/hexane, 1:99).[11] Homoallylic alcohol **2**[11b,c] was protected as its benzyl ether (BnBr, NaH, THF, 0 °C to rt, 4 h) to yield compound **3** (93%).[11b,c] Compound **3** upon one-pot dihydroxylation and oxidative cleavage {OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane:H_2O (3:1), rt, 4.5 h}, followed by Wittig olefination ($Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0 °C to rt, 5 h) furnished the α,β-unsaturated ester **4** (75% yield over two steps). Ester **4** was further reduced (DIBAL-H, CH_2Cl_2, 0 °C, 2 h) to allylic alcohol **5** (82%). Allylic alcohol **5** was

* Corresponding author. Tel.: +91 4027193158; fax: +91 4027160387.
E-mail address: prkgenius@iict.res.in (P. Radha Krishna).

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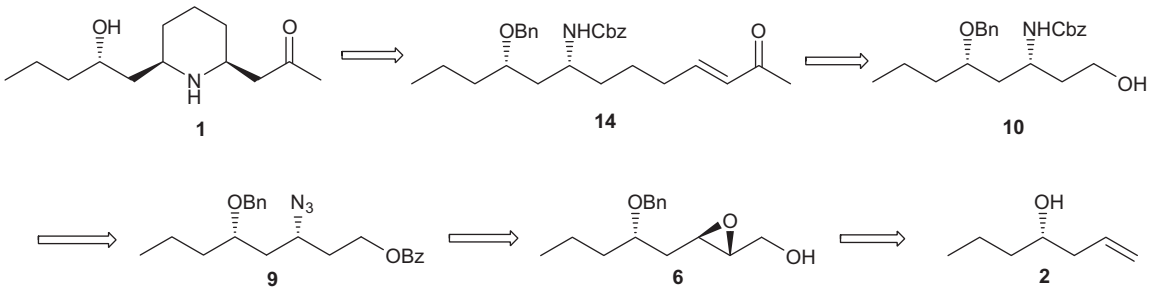
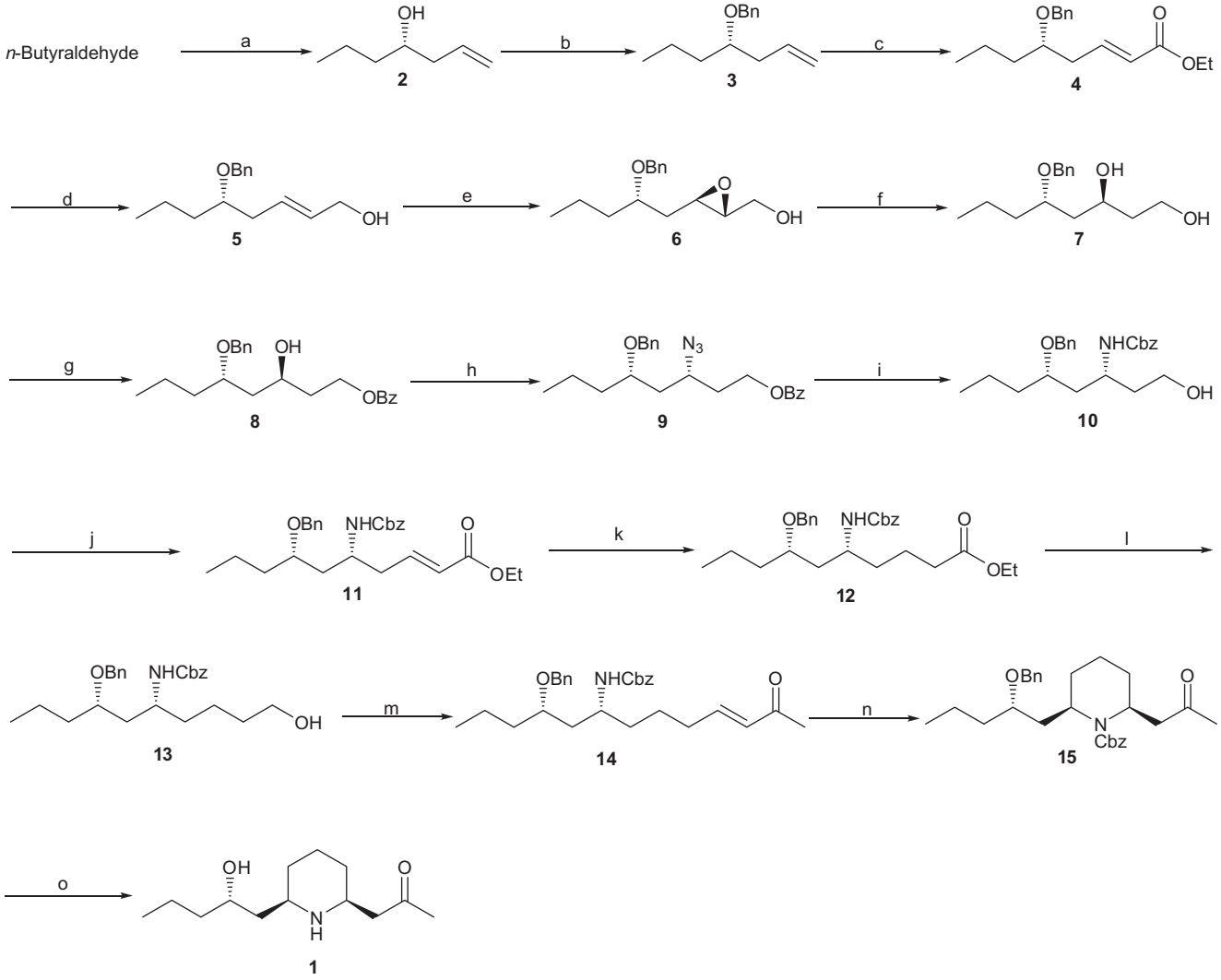
http://dx.doi.org/10.1016/j.tetasy.2013.05.004



Scheme 1. Retrosynthetic analysis of (−)-andrachcinidine.



Scheme 2. (a) (*R*,*R*)-BINOL, 4 Å MS, Ti(O^iPr)$_4$, allyltri-*n*-butyltin, CH_2Cl_2, −78 to −20 °C, 24 h, 82%; (b) BnBr, NaH, THF, 0 °C to rt, 4 h, 93%; (c) (i) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane:H_2O (3:1), rt, 4.5 h; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0 °C to rt, 5 h, 75% (over two steps); (d) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 82%; (e) (−)-DIPT, Ti(O^iPr)$_4$, CHP, CH_2Cl_2, −20 °C, 12 h, 84%; (f) Red-Al, THF, 0 °C, 5 h, 80%; (g) Bz-Cl, Et_3N, CH_2Cl_2, 0 °C to rt, 6 h, 92%; (h) (i) Mesyl chloride, Et_3N, 0 °C, 1 h; (ii) NaN_3, DMF, 50 °C, 5 h, 78%, (over two steps); (i) (i) $LiAlH_4$, THF, 0 °C, 2 h; (ii) Cbz-Cl, $NaHCO_3$, EtOAc:H_2O (1:1), 0 °C to rt, 5 h, 72% (over two steps); (j) (i) IBX, DMSO, CH_2Cl_2, rt, 8 h; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0 °C to rt, 5 h, 85%; (k) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C, 1 h, 92%; (l) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 76%; (m) IBX, DMSO, CH_2Cl_2, rt, 6 h; (ii) 1-(Triphenylphosphoranylidene)-2-propanone, THF, 65 °C, 12 h, 72% (over two steps); (n) (i) TFA, ^iPrOH, 65 °C, 6 h; (ii) Cbz-Cl, $NaHCO_3$, EtOAc:H_2O (1:1), 0 °C to rt, 6 h, 60% (over two steps); (o) Pd/C, H_2, MeOH, 12 h, 89%

converted into epoxy alcohol **6** under Sharpless asymmetric epoxidation conditions {(−)-DIPT, Ti(O^iPr)$_4$, CHP, CH_2Cl_2, −20 °C, 12 h} to give **6** in 84% yield; its diastereoselectivity was measured by LCMS (dr, 95.414:4.586) {Column: XDB-C18, acetonitrile/water (80:20)}. Next, epoxy alcohol **6** was subjected to a regioselective ring opening reaction using Red-Al (Red-Al, THF, 0 °C, 5 h) to afford 1,3-diol **7** in 80% yield. The thus obtained 1, 3-diol **7** was then subjected to a selective primary benzoylation reaction (Bz-Cl, Et_3N, CH_2Cl_2, 0 °C to rt, 6 h, 92%) to afford hydroxy benzoyl ester **8**. Compound **8** upon mesylation (mesyl chloride, Et_3N, 0 °C, 1 h) followed by nucleophilic substitution with azide (NaN_3, DMF, 50 °C, 5 h, 78%, over two steps) in an S_N2 fashion gave azide **9**. In order to obtain

the hydroxy benzyl carbamate functionality, we planned to reduce both the ester and azide functional groups in one-pot under LAH reaction conditions ($LiAlH_4$, THF, 0 °C, 2 h) to give the aminoalcohol, which could then be transformed into a carbamate {Cbz-Cl, $NaHCO_3$, EtOAc:H_2O (1:1), 0 °C to rt, 5 h} with protection of the amine functionality to selectively furnish the hydroxy benzyl carbamate **10** (72% yield over two steps). The hydroxy carbamate **10** was subjected to oxidation (IBX, DMSO, CH_2Cl_2, rt, 8 h) followed by Wittig olefination ($Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0 °C to rt, 5 h) to afford α,β-unsaturated ester **11** (85% yield over two steps). The olefin in compound **11** was saturated by selective reduction ($NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 °C, 1 h) to furnish ester **12** (92%). The ester was reduced to alcohol **13** (DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 76%), followed by oxidation (IBX, DMSO, CH_2Cl_2, rt, 6 h) and Wittig olefination [1-(triphenyl phosphoronylidene)-2-propanone/THF/reflux] to give the α,β-unsaturated keto carbamate **14** (72% yield over two steps).

With the α,β-unsaturated keto carbamate **14** in hand, our next step was to synthesize the piperidine ring skeleton using an intramolecular aza-Mchael addition reaction.[9] Accordingly, the key step was attempted under acidic conditions in a protic solvent (TFA, isopropanol, 65 °C, 6 h) to produce the piperidine derivative, which was reprotected as its benzyl carbamate {Cbz-Cl, $NaHCO_3$, EtOAc/H_2O (1:1), 0 °C to rt, 5 h} to afford the 2,6-disubstituted derivative exclusively as the *cis*-isomer **15** (69%), whose diastereoselectivity was measured by LCMS {Column: XDB-C18, acetonitrile/water (70:30)}. Its structure was confirmed by ^1H NMR, ^{13}C NMR and NOE experiments. Global deprotection of the benzylether group and benzyl carbamate under hydrogenation reaction conditions (Pd/C, H_2, MeOH, 12 h) on compound **15** furnished the target compound (−)-andrachcinidine **1** (89%) whose data matched with the data of natural[4] as well as the reported data.[6–8]

3. Conclusion

In conclusion, we have reported on the total synthesis of (−)-andrachcinidine **1** via a linear strategy using asymmetric allylation, Sharpless epoxidation, regioselective epoxide opening, nucleophilic substitution reaction and intramolecular aza-Michael addition reaction as the key steps. This strategy is general and amenable for the synthesis of related *aza*-analogues by changing the Michael acceptor moiety of the skeleton via the Wittig olefination reaction.

4. Experimental

4.1. General

Column chromatography was performed on silica gel, Acme grade 60–120 mesh. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenoneketyl. Unless stated otherwise, optical rotations were measured with a JASCO P-1020 instrument at 25 °C. ^1H NMR and ^{13}C NMR spectra were recorded either on a Bruker 300 in $CDCl_3$ as solvent with TMS as reference unless otherwise indicated. Unless stated otherwise, HRMS spectra were recorded on a QTOF analyser (QSTAR XL, Applied Biosystems/MDS Sciex) at NCMS-IICT, Hyderabad. Unless stated otherwise, Elemental Analysis was carried on a Vario Micro Cube Elementar at the Analytical Chemistry Division CSIR-IICT, Hyderabad. The software ACD/Name Version 1.0, developed by M/s Advanced Chemistry Development Inc., Toronto, Canada, assisted nomenclature was used in the experimental section. Unless stated otherwise, all reactions were performed under an inert atmosphere.

4.1.1. (*S*)-Hept-1-en-4-ol 2

A mixture of (*R*,*R*)-BINOL (5.04 g, 16.56 mmol) and $Ti(O^iPr)_4$ (5.04 mL, 16.56 mmol) in CH_2Cl_2 (120.0 mL) in the presence of 4 Å molecular sieves (12.0 g) was stirred at reflux. After 1 h, the reaction mixture was cooled to room temperature and the commercially available butyraldehyde (12.0 g, 165.6 mmol) in CH_2Cl_2 (60.0 mL) was added and stirred for a further 10 min. The reaction mixture was then cooled to −78 °C, allyltri-*n*-butyltin (56.88 mL, 183.36 mmol) was added and the stirring continued at −20 °C for 24 h. Next, satd aq $NaHCO_3$ solution (180.0 mL) was added to quench the reaction mixture, which was then stirred for an additional 30 min and then extracted with CH_2Cl_2 (2 × 200.0 mL). The organic phase was washed with water (100.0 mL), dried (Na_2SO_4), and the solvent was evaporated and the residue was purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.75, EtOAc/*n*-hexane 1:9) to give **2** (15.6 g, 82%) as a clear oil (ee was found to be 97%, determined by chiral HPLC: Chiralcel OBH; ^{i}PrOH/hexane, 1:99). $[\alpha]_D^{25} = +22.8$ (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.87–5.72 (m, 1H), 5.14–5.08 (m, 2H), 3.66–3.58 (m, 1H), 2.32–2.23 (m, 1H), 2.16–2.06 (m, 1H), 1.51–1.33 (m, 4H), 0.94 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 134.9, 118.1, 70.4, 42.2, 38.9, 18.7 14.1; IR (Neat) υ_{max} 3330, 3055, 1620, 1497, 1208, 769, 732 cm^{-1}; EIMS (*m*/*z*): $[M]^+$ 114.

4.1.2. (*S*)-((Hept-1-en-4-yloxy)methyl)benzene 3

To a cooled (0 °C) suspension of NaH (5.89 g, 147.37 mmol, 60% w/w dispersion in paraffin oil) in THF (100.0 mL), a solution of (*S*)-hept-1-en-4-ol **2** (14.0 g, 122.8 mmol) in THF (20.0 mL) was added dropwise. After 15 min. BnBr (16.04 mL, 135.09 mmol) was added dropwise at 0 °C and stirred for 4 h. at room temperature. The reaction mixture was quenched with satd aq NH_4Cl solution (120.0 mL) and extracted with EtOAc (2 × 200.0 mL). The combined organic layers were washed with water (100.0 mL), brine (80.0 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography (Silica gel 60–120 mesh, R_f 0.90, EtOAc/*n*-hexane, 1:19) to afford **3** (21.46 g, 93%) as a colorless liquid. $[\alpha]_D^{25} = -15.8$ (*c* 0.59, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.31 (m, 5H), 5.88–5.74 (m, 1H), 5.09–5.00 (m, 2H), 4.50 (dd, *J* = 11.5 Hz, 2H), 3.44–3.37 (m, 1H), 2.30 (br s, 2H), 1.54–1.24 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 139.0, 135.1, 128.3, 127.7, 127.3, 116.8, 78.4, 70.9, 38.3, 36.1, 18.7, 14.2; IR (Neat) υ_{max} 3060, 2890, 1610, 1475, 1160, 810, 735 cm^{-1}.

4.1.3. (*S*,*E*)-Ethyl 5-(benzyloxy)oct-2-enoate 4

To a stirred solution of **3** (20.0 g, 106.38 mmol) in 1,4-dioxane/H_2O (3:1, 150.0 mL) at 0 °C was added OsO_4 (15.0 mL, 0.5 M in toluene) drop wise. After 5 min. 2,6-lutidine (14.71 mL, 127.66 mmol) and $NaIO_4$ (34.13 g, 159.57 mmol) were added at 0 °C and stirred for 4.5 h at rt. The reaction mixture was quenched with Na_2SO_3 (15.0 g) and extracted with EtOAc (2 × 100.0 mL). The combined organic layers were washed with water (80.0 mL), brine (50.0 mL), dried, (Na_2SO_4) and evaporated. The obtained crude aldehyde was used directly for the next reaction.

To a solution of aldehyde (16.5 g, 88.71 mmol) in CH_2Cl_2 was added (ethoxycarbonylmethylene) triphenyl phosphorane ($Ph_3P{=}CHCO_2Et$) (37.04 g, 106.45 mmol) at 0 °C and allowed to stir at room temperature for approximately 5 h, after which the solvent was evaporated and adsorbed on silica, purified by column chromatography (Silica gel 60–120, R_f 0.8, EtOAc/*n*-hexane 1:9) to afford the α,β-unsaturated ester **4** (22.0 g, 75%) over two steps as a colorless syrup. $[\alpha]_D^{25} = -10.1$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24–7.37 (m, 5H), 6.99 (dt, *J* = 7.2, 15.1 Hz, 1H), 5.88 (d, *J* = 15.5 Hz, 1H), 4.52 (dd, *J* = 6.8, 11.3 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.52 (qt, *J* = 5.3 Hz, 1H), 2.45 (t, *J* = 6.4 Hz, 2H), 1.26–1.77 (m, 7H), 0.90 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 145.4, 138.5, 128.3, 127.7, 127.5, 123.4, 77.6,

71.1, 60.2, 36.8, 36.3, 18.6, 14.2, 14.1; IR (Neat) υ_{max} 3035, 1720, 1630, 1210 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{17}H_{25}O_3$ $[M+H]^+$ 277.1798, found 277.1797, Calcd for $C_{17}H_{29}NO_3$ $[M+NH_4]^+$ 294.2064. Found: 294.2060.

4.1.4. (*S*,*E*)-5-(Benzyloxy)oct-2-en-1-ol 5

To a stirred solution of ester **4** (18.0 g, 65.22 mmol) in dry CH_2Cl_2 (150.0 mL), DIBAL-H (102.0 mL, 143.48 mmol, 20% solution in hexane) was added at 0 °C and stirred at the same temperature for 2 h. Methanol (12.0 mL) was then added to the reaction mixture at 0 °C and stirred for 10 min. Next, a satd aq solution of sodium potassium tartrate (30.0 mL) was added and after 10 min methanol was evaporated. The reaction mixture was diluted with water (80.0 mL) and extracted with dichloromethane (2 × 100.0 mL). The combined organic layers were washed with brine (40.0 mL), dried (Na_2SO_4), concentrated, and the residue purified by column chromatography (Silica gel 60–120, R_f 0.50, EtOAc/*n*-hexane 2:8) to afford allylic alcohol **5** (12.5 g, 82%) as a colorless syrup. $[\alpha]_D^{25} = +3.2$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.38 (m, 5H), 5.68–5.73 (m, 2H), 4.52 (dd, *J* = 7.9, 11.3 Hz, 2H), 4.07 (d, *J* = 3.0 Hz, 2H), 3.44 (qt, *J* = 5.3 Hz, 1H), 2.31 (t, *J* = 5.3 Hz, 2H), 1.68–1.83 (br s, 1H), 1.25–1.60 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8, 131.4, 128.9, 128.3, 127.7, 127.4, 78.3, 70.9, 63.5, 36.5, 36.0, 18.6, 14.1; IR (Neat) υ_{max} 3450, 3020, 1590, 1560 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{15}H_{26}NO_2$ $[M+NH_4]^+$ 252.1958. Found 252.1958.

4.1.5. ((2*R*,3*R*)-3-((*S*)-2-(Benzyloxy)pentyl)oxiran-2-yl)methanol 6

To a suspension of thoroughly dried molecular sieves 4 Å (4.8 g) in dry CH_2Cl_2 (80.0 mL) was added (−)-DIPT (2.4 g, 10.26 mmol), followed by the slow addition of $Ti(O^iPr)_4$ (1.5 mL, 5.1 mmol) at −20 °C. After stirring for 30 min, cumene hydroperoxide (10.7 mL, 56.4 mmol, 80% in cumene) was added slowly and the resulting solution was stirred at −20 °C for a further 30 min. Allylic alcohol **5** (12.0 g, 51.2 mmol) in CH_2Cl_2 (30.0 mL) was then added and the reaction mixture was stirred at −20 °C for 12 h, then warmed up to 0 °C, and quenched with an aq. basic solution (6.0 g NaOH in 60.0 mL of brine). After stirring for 1 h, the reaction mixture was filtered through a pad of Celite and the pad was further washed with CH_2Cl_2. The filtrate was concentrated and purified by column chromatography (Silica gel 60–120 mesh, R_f 0.30, EtOAc/*n*-hexane 3:7) to afford hydroxy epoxide **6** (10.76 g, 84%) as a colorless oil (diastereoselectivity was measured by LCMS (dr, 95.414:4.586) {Column: XDB-C18, acetonitrile/water (80:20)}. $[\alpha]_D^{25} = +43.5$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.34 (m, 5H), 4.55 (dd, *J* = 11.3, 15.5 Hz, 2H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.54–3.66 (m, 2H), 3.07–3.12 (m, 1H), 2.90–2.95 (m, 1H), 2.11–2.26 (br s, 1H), 1.26–1.98 (m, 6H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 128.3, 127.7, 127.5, 76.6, 71.3, 61.7, 59.0, 53.5, 36.6, 36.5, 18.3, 14.1; IR (Neat) υ_{max} 3500, 3025, 1610, 1580 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1640, Calcd for $C_{15}H_{26}NO_3$ $[M + NH_4]^+$ 268.1913. Found: 268.1906.

4.1.6. (3*S*,5*S*)-5-(Benzyloxy)octane-1,3-diol 7

To a stirred solution of epoxide **6** (9.0 g, 36.0 mmol) in dry THF (90.0 mL) was added Red-Al (18.2 mL, 54.0 mmol, 60 wt % in toluene) at 0 °C. After 5 h the reaction mixture was quenched with sat. Na_2SO_4 solution (15 mL) and filtered through a Celite pad. The residue was washed with EtOAc (2 × 150 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (Silica gel 60–120 mesh, R_f 0.2, EtOAc/*n*-hexane, 4:6) to obtain 1,3-diol **7** (7.2 g, 80%) as a colorless liquid. $[\alpha]_D^{25} = +27.4$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.29–7.37 (m, 5H), 4.56 (dd, *J* = 11.3, 17.7 Hz, 2H), 4.19 (td, *J* = 2.3, 8.9 Hz, 1H), 3.83 (q, *J* = 4.5 Hz, 2H), 3.69–3.77 (m, 1H), 3.51 (d, *J* = 2.1 Hz, 1H), 2.76–2.84 (br s, 1H), 1.47–1.89 (m, 6H), 1.29–1.43 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.1, 128.5, 127.9, 127.8, 77.0, 71.2, 69.2, 61.8, 39.6, 38.7, 35.5, 18.7, 14.2; IR (Neat) υ_{max} 3500, 3400, 3050, 1590, 1250 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{15}H_{25}O_3$ $[M+H]^+$ 253.1798. Found: 253.1794.

4.1.7. (3*S*,5*S*)-5-(Benzyloxy)-3-hydroxyoctyl benzoate 8

To a well stirred and cooled (0 °C) solution of **7** (6.0 g, 23.8 mmol) and Et_3N (6.59 mL, 47.62 mmol) in CH_2Cl_2 (120.0 mL) was added benzoyl chloride (2.77 mL, 23.80 mmol) over 40 min. After the completion of the reaction, the reaction mixture was poured into water, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 50.0 mL). The combined organic extracts were washed with water (2 × 20.0 mL), brine (50.0 mL), dried, and evaporated. The crude product was purified by column chromatography (Silica gel 60–120 mesh, R_f 0.70, EtOAc/*n*-hexane, 1.5:8.5) to obtain hydroxyl benzoate **8** (7.80 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = +8.6$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.03–8.05 (m, 2H), 7.54–7.60 (m, 1H), 7.41–7.50 (m, 2H), 7.25–7.30 (m, 5H), 4.36–4.61 (m, 4H), 4.09 (tt, *J* = 2.8, 8.5 Hz, 1H), 3.74 (tt, *J* = 3.4, 6.6 Hz, 1H), 1.61–1.91 (m, 5H), 1.31–1.58 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 138.2, 132.9, 129.5, 128.4, 128.3, 127.9, 127.7, 76.4, 71.2, 65.2, 62.0, 40.1, 36.6, 35.6, 18.6, 14.2; IR (Neat) υ_{max} 3500, 3040, 1740, 1610, 1550, 1240 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{22}H_{29}O_4$ $[M+H]^+$ 357.2060, found 357.2055, Calcd for $C_{22}H_{28}O_4Na[M+Na]^+$ 378.1879. Found: 378.1874.

4.1.8. (3*R*,5*S*)-3-Azido-5-(benzyloxy)octyl benzoate 9

To a stirred solution of alcohol **8** (5.1 g, 14.33 mmol) in CH_2Cl_2 (55.0 mL), were added Et_3N (3.96 mL, 28.66 mmol) and methanesulfonyl chloride (1.11 mL, 15.76 mmol) at 0 °C after which the mixture was allowed to stir at 0 °C for 1 h. After completion of reaction, the reaction mixture was diluted with CH_2Cl_2 (20.0 mL), washed with satd $NaHCO_3$ (1 × 15.0 mL), 1 M HCl (1 × 15.0 mL), and water (2 × 20.0 mL) and brine solution (1 × 16.0 mL). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4. The reaction mixture was then concentrated under reduced pressure and the crude mesylate was used as such without further purification.

To a stirred solution of the above mesylate in dry DMF (25.0 mL), was added NaN_3 (1.40 g, 21.49 mmol) after which the mixture was heated to 55 °C and stirring continued for 5 h. After completion of the reaction, the reaction mixture was extracted with EtOAc/*n*-hexane (6:4) (2 × 35.0 mL), the organic phase was washed with brine (20.0 mL), dried (Na_2SO_4), the solvent was evaporated, and the residue was purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.90, EtOAc/*n*-hexane 1:19) to afford **9** (4.26 g, 78% over two steps) as a colorless syrup. $[\alpha]_D^{25} = +31.4$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.05 (dd, *J* = 1.2, 7.1 Hz, 2H), 7.6 (tt, *J* = 1.2, 8.6 Hz, 1H), 7.41–7.46 (m, 2H), 7.27–7.34 (m, 5H), 4.37–4.60 (m, 4H), 3.72 (tt, *J* = 4.2, 11.0 Hz, 1H), 3.57 (qt, *J* = 5.4 Hz, 1H), 1.97–2.09 (m, 2H), 1.82–1.90 (m, 1H), 1.53–1.77 (m, 3H), 1.38–1.48 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.3, 138.3, 132.9, 133.0, 129.5, 128.3, 127.7, 127.6, 75.4, 70.8, 61.6, 56.7, 38.5, 35.8, 33.1, 18.2, 14.2; IR (Neat) υ_{max} 3040, 3010, 2150, 1730, 1640, 1580, 1090 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{22}H_{28}N_3O_3$ $[M+H]^+$ 382.2125. Found: 382.2127. Calcd for $C_{22}H_{31}N_4O_3$ $[M+NH_4]^+$ 399.2396. Found: 399.2388.

4.1.9. Benzyl (3*R*,5*S*)-5-(benzyloxy)-1-hydroxyoctan-3-ylcarbamate 10

To a stirred solution of LAH (0.39 g, 11.14 mmol) in dry THF (35.0 mL) at 0 °C was added compound **9** (4.2 g, 11.02 mmol) in

THF (10.0 mL) and the reaction allowed to stir at rt for 2 h. The reaction mixture was then quenched with satd aq Na_2SO_4 (10.0 mL) at 0 °C, filtered through a Celite pad, and the Celite pad was washed with ethyl acetate (30.0 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was used for the next reaction without further purification.

To the above compound (2.5 g, 9.96 mmol) was added EtOAc/water (1:1, 20.0 mL), followed by Cbz-Cl (1.49 mL, 10.49 mmol) at 0 °C and stirred for 5 h. at room temperature. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20.0 mL) and extracted with ethyl acetate (2 × 10.0 mL). The combined organic layers were washed with brine (15.0 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.60, EtOAc/*n*-hexane 3:7) to afford **10** (3.05 g, 72% over two steps) as a viscous liquid. $[\alpha]_D^{25} = +30.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.34 (m, 10H), 5.06–5.18 (m, 3H), 4.43 (2 × d, AB pattern, *J* = 10.9 Hz, 2H), 3.87–4.03 (m, 1H), 3.31–3.71 (m, 4H), 1.22–1.90 (m, 8H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.5, 138.2, 136.3, 128.5, 128.3, 128.2, 128.1, 128.0, 127.6, 70.8, 67.0, 58.6, 47.1, 39.6, 39.5, 35.9, 18.1, 14.2; IR (Neat) υ_{max} 3650, 3480, 3020, 1640, 1590, 980 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{23}H_{32}NO_4$ $[M+H]^+$ 386.2326. Found: 386.2327. Calcd for $C_{23}H_{31}NO_3Na$ $[M + Na]^+$ 408.2145. Found: 408.2137.

4.1.10. (5*R*,7*S*,*E*)-Ethyl 7-(benzyloxy)-5-(benzyloxycarbonylamino) dec-2-enoate 11

To a stirred solution of compound **10** (3.0 g, 7.79 mmol), in CH_2Cl_2 (30.0 mL) and dimethyl sulfoxide (1.0 mL, 12.82 mmol) was added 2-iodoxy benzoic acid (2.62 g, 9.35 mmol) at 0 °C, and stirred for 8 h. After completion of the reaction, the reaction mixture was filtered through a Celite pad and washed with CH_2Cl_2 (30.0 mL). The organic layer was washed with satd aq $NaHCO_3$ (15.0 mL). The organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude aldehyde was used for the next reaction without further purification.

To a solution of above obtained aldehyde (2.80 g, 7.31 mmol) in CH_2Cl_2 (30.0 mL) was added (ethoxycarbonylmethylene)triphenyl phosphorane ($Ph_3P{=}CHCO_2Et$) (3.25 g, 9.35 mmol) at 0 °C and allowed to stir at room temperature for approximately 5 h. After completion of the reaction, the solvent was evaporated, adsorbed on silica, and purified by column chromatography (Silica gel 60–120, R_f 0.70, EtOAc/*n*-hexane 1:9) to afford the α,β-unsaturated ester **11** (2.99 g, 85% over two steps) as a pale yellow syrup. $[\alpha]_D^{25} = +1.2$ (*c* 0.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.37 (m, 10H), 6.79–6.92 (m, 1H), 5.82 (d, *J* = 15.7 Hz, 1H), 5.04–5.13 (m, 3H), 4.43, (2 × d AB pattern, *J* = 11.1 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.86 (m, 1H), 3.47 (qt, *J* = 5.5 Hz, 1H), 2.36–2.50 (m, 2H), 1.53–1.71 (m, 5H), 1.25–1.41 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 155.7, 144.2, 138.1, 128.6, 128.4, 128.1, 127.7, 124.3, 70.7, 66.5, 60.2, 49.2, 38.1, 37.8, 35.7, 17.9, 14.2; IR (Neat) υ_{max} 3650, 3035, 1730, 1650, 1610, 1080 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{27}H_{36}NO_5$ $[M + H]^+$ 454.2588. Found: 454.2587.

4.1.11. (5*R*,7*S*)-Ethyl 7-(benzyloxy)-5-(benzyloxycarbonylamino) decanoate 12

To a stirred solution of **11** (2.5 g, 5.52 mmol) and $NiCl_2{\cdot}6H_2O$ (0.37 g, 1.10 mmol) in MeOH (30.0 mL) under an H_2 atmosphere at 0 °C, $NaBH_4$ (0.20 g, 5.52 mmol) was added in small portions (the solution turned black). After the addition was complete, the reaction mixture was stirred at room temperature for 1 h. The black precipitate formed was filtered through a Celite pad and washed with EtOAc (3 × 20.0 mL). The solvent was evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, R_f 0.8, EtOAc:*n*-hexane, 1:9) to obtain **12** (2.31 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = +14.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24–7.36 (m, 10H), 5.06 (s, 2H), 4.89 (d, *J* = 7.93 Hz, 1H), 4.42 (2 × d, AB pattern, *J* = 11.1 Hz, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.65–3.78 (m, 1H), 3.45 (qt, *J* = 5.7 Hz, 1H), 2.19–2.35 (m, 2H), 1.31–1.71 (m, 10H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.2, 156.1, 138.4, 136.5, 128.4, 128.3, 128.0, 127.9, 127.5, 76.9, 70.6, 66.5, 60.3, 49.6, 39.2, 35.6, 35.1, 34.0, 20.9, 18.1, 14.2; IR (Neat) υ_{max} 3600, 3030, 1750, 1640, 1610, 1070 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{27}H_{38}NO_5$ $[M+H]^+$ 456.2745. Found: 456.2728.

4.1.12. Benzyl (5*R*,7*S*)-7-(benzyloxy)-1-hydroxydecan-5-ylcarbamate 13

To a solution of **12** (2.0 g, 4.39 mmol) in dry CH_2Cl_2 (20.0 mL) at 0 °C, DIBAL-H (7.1 mL, 9.67 mmol, 20% solution in hexane) was slowly added for 15 min. The reaction mixture was stirred at the same temperature for 2 h, quenched with methanol (10.0 mL) and sodium potassium tartrate solution (5.0 mL), after which it was diluted with water (10.0 mL) and extracted with dichloromethane (2.0 × 25 mL). The combined organic layers were washed with brine (10.0 mL), dried (Na_2SO_4), concentrated, and the residue purified by column chromatography (Silica gel 60–120, R_f 0.40, EtOAc/*n*-hexane, 2:8) to afford alcohol **13** (1.37 g, 76%) as a colorless syrup. $[\alpha]_D^{25} = +20.7$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.35 (m, 10H), 5.07 (s, 2H), 4.85 (d, *J* = 7.9 Hz, 1H), 4.43 (2 × d, AB pattern, *J* = 11.1 Hz, 2H), 3.66–3.76 (m, 1H), 3.60 (t, *J* = 5.9 Hz, 2H), 3.45 (qt, *J* = 5.7 Hz, 1H), 1.26–1.67 (m, 12H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.2, 138.5, 136.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.5, 70.6, 66.6, 62.7, 49.8, 39.3, 35.9, 35.7, 32.5, 21.8, 18.1, 14.2; IR (Neat) υ_{max} 3650, 3400, 2990, 1650, 1610 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{25}H_{36}NO_4$ $[M+H]^+$ 414.2639. Found: 414.2633.

4.1.13. Benzyl (4*S*,6*R*,*E*)-4-(benzyloxy)-12-oxotridec-10-en-6-ylcarbamate 14

To a stirred solution of alcohol **13** (0.5 g, 1.21 mmol), in CH_2Cl_2 (0.5 mL) and dimethyl sulfoxide (0.38 mL, 19.38 mmol), was added 2-iodoxybenzoic acid (0.41 g, 1.45 mmol) at 0 °C and stirred for 6 h. After completion of the reaction, the reaction mixture was filtered through a Celite pad and washed with CH_2Cl_2 (2 × 5.0 mL). The organic layer was washed with satd aq $NaHCO_3$ (1 × 5.0 mL). The organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude aldehyde was used for the next reaction without further purification.

To a stirred solution of the above obtained aldehyde (0.47 g, 1.14 mmol) in dry THF (6.0 mL), was added 1-(triphenylphosphoranylidene)-2-propanone ylide (0.47 g, 1.49 mmol) and stirred at reflux for 12 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.60, EtOAc/*n*-hexane, 2:8) to furnish compound **14** (0.40 g, 72%) as a colorless thick liquid. $[\alpha]_D^{25} = +13.6$ (*c* 1.0, $CHCl_3$); (two rotamers), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28–7.40 (m, 10H), 6.70–6.80 (m, 1H), 5.99–6.11 (m, 1H), 4.86–5.22 (m, 3H), 4.44 (2 × d, AB pattern, *J* = 11.3 Hz, 2H), 3.66–3.85 (m, 1H), 3.46 (t, *J* = 6.6 Hz, 1H), 2.10–2.28 (m, 5H), 1.25–1.88 (m, 10H), 0.92 (t, *J* = 7.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.7, 166.4, 156.1, 147.8, 147.6, 138.5, 136.4, 136.3, 133.3, 132.9, 131.5, 130.1, 129.5, 128.5, 128.3, 128.0, 127.9, 127.5, 127.4, 72.3, 70.6, 69.9, 66.8, 66.5, 53.4, 49.6, 48.6, 39.6, 39.3, 36.3, 35.9, 35.4, 35.1, 32.2, 32.1, 29.7, 26.8, 24.2, 18.5, 18.1, 14.2, 13.6; IR (Neat) υ_{max} 3680, 3040, 1740, 1660, 1620, 1070 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{28}H_{38}NO_4$ $[M+H]^+$ 452.2795. Found: 452.2795, Calcd for $C_{28}H_{41}N_2O_4$ $[M + NH_4]^+$ 469.3061. Found: 469.3059.

4.1.14. (2*R*,6*S*)-Benzyl 2-((*S*)-2-(benzyloxy)pentyl)-6-(2-oxopropyl) piperidine-1-carboxylate 15

To a stirred solution of compound **14** (0.20 g, 0.44 mmol) in isopropanol (2.0 mL) was added TFA (5.0 mL) and then heated at reflux for 6 h. at 65 °C. The solvent and TFA were then removed under reduced pressure, the crude TFA salt was used as such in the next step without further purification.

After 5 h, the reaction was brought to pH 8–9 using aq satd $NaHCO_3$ and the compound was extracted with CH_2Cl_2 (3 × 3.0 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to obtain a crude compound, which was used for the next step without further purification.

To the above obtained crude amine (0.095 g, 0.30 mmol) were added EtOAc/water (1:1, 2.0 mL), then Cbz-Cl (0.05 mL, 0.33 mmol) at 0 °C and stirred for 6 h at room temperature. After completion of the reaction, the reaction mixture was diluted with ethyl acetate and the combined organic layers were washed with brine (5.0 mL), dried (Na_2SO_4), and the organic solvent was evaporated under reduced pressure. The residue was purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.95, EtOAc/*n*-hexane, 1:9) to afford **15** (0.138 g, 69% over two steps) as a thick liquid {diastereoselectivity was measured by LCMS, Column: XDB-C18, acetonitrile/water (70:30)}. $[\alpha]_D^{25} = +6.3$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23–7.35 (m, 10H), 5.09 (s, 2H), 4.49 (2 × d, AB pattern, J = 11.6 Hz, 2H), 4.25–4.31 (br s, 1H), 4.06–4.13 (br s, 1H), 3.46 (qt, J = 6.1 Hz, 1H), 3.06–3.15 (m, 1H), 2.61 (dd, J = 7.9 Hz, 16.7, 1H), 2.35 (t, J = 7.2 Hz, 1H), 2.05–2.12 (m, 4H), 1.28–1.72 (m, 10H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 206.8, 155.6, 138.9, 136.7, 128.4, 128.2, 127.9, 127.8, 127.7, 127.3, 76.2, 70.3, 66.7, 50.1, 48.2, 48.0, 36.4, 35.9, 30.1, 27.9, 26.1, 18.4, 16.7, 14.2; IR (Neat) υ_{max} 3040, 2950, 1730, 1640, 1580 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{28}H_{38}NO_4$ $[M+H]^+$ 452.2795, found 452.2789. Calcd for $C_{28}H_{37}NO_4Na$ $[M+Na]^+$ 474.2615. Found: 474.2611.

4.1.15. (−)-Andrachcinidine 1

To a stirred solution of compound **15** (0.035 g, 0.07 mmol) in methanol (0.50 mL), 10.0 mg of 10% Pd/C was added and stirred under an H_2 atmosphere for 12 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure, adsorbed onto silica, and purified by column chromatography (Silica gel 60–120 mesh, R_f 0.40, MeOH: $CHCl_3$ 1:9, 5% NH_4OH) to obtain **1** (0.016 g, 89%) as a colorless liquid. $[\alpha]_D^{25} = -21.4$ (*c* 0.5, $CHCl_3$), lit.[4] $[\alpha]_D^{25} = -20.0$ (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80–3.83 (m, 1H), 3.10–3.18 (m, 2H), 2.99–3.07 (m, 1H), 2.66 (m, 1H), 2.19 (m, 4H), 1.10–1.89 (m, 13H), 0.92 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.0, 72.8, 58.9, 53.0, 49.1, 43.5, 39.7, 33.5, 32.2, 30.0, 24.0, 18.6, 14.1; IR (Neat) υ_{max} 3450, 3310, 2900, 1730, 1640 cm^{-1}; HRESIMS (*m*/*z*): Calcd for $C_{13}H_{26}NO_2$ $[M+H]^+$ 228.1963. Found: 228.1972.

Acknowledgments

One of the authors (B.K.R) thanks the CSIR, New Delhi, for financial support in the form of a fellowship.

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