Tetrahedron: *Asymmetry* 19 (2008) 2153–2158

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

The formal synthesis of isofebrifugine using stereoselective intramolecular Michael addition

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ARTICLE INFO

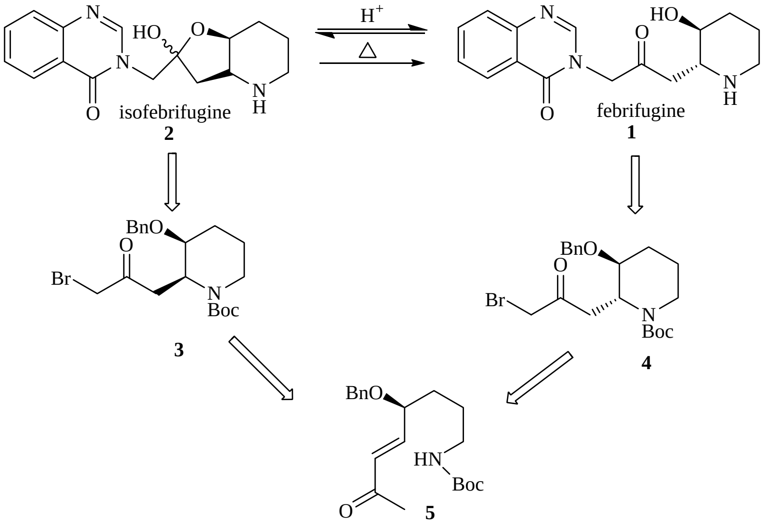
Article history:
Received 19 July 2008
Accepted 20 August 2008
Available online 1 October 2008

ABSTRACT

The formal synthesis of isofebrifugine, a bioactive alkaloid, was achieved via a stereoselective intramolecular Michael addition reaction from D-mannitol.

1. Introduction

Febrifugine **1** and isofebrifugine **2** are active principals against malaria,[1] occurring in the roots of *Dichroa febrifuga* (Chinese name: Chang Shan)[2] and related hydrangea plants.[3] These alkaloids are approximately 100 times as effective as quinine against *Plasmodia lophurae* in ducks.[2a] The absolute structures of these alkaloids were elucidated by the asymmetric total synthesis achieved by Kobayashi et al.[4] It is also known that there is a equilibrium between these alkaloids under acidic conditions.[5] Moreover, isofebrifugine **2** can be transformed into febrifugine **1** by heating (Scheme 1).[2a] The scarcity of these alkaloids from natural sources has spurred much research on the synthesis of febrifugine **1**, isofebrifugine **2**, and their analogues with the aim of developing new antimalarial drugs.[4,6] Kobayashi et al. synthesized isofebrifugine **2** and febrifugine **1** from **3** and **4**, respectively, in two-step reaction sequence.[4] Herein, we report the synthesis of **3** from D-mannitol via enone **5**, using base-induced intramolecular Michael addition reaction as the key step. The key aspect of the synthesis is to study the stereochemical outcome of the intramolecular Michael addition of **5** in the construction of the piperidine skeleton.



Scheme 1.

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doi:10.1016/j.tetasy.2008.08.021

2. Results and discussion

As shown in Scheme 2, enantiomerically pure (*R*)-2,3-*O*-isopropylidene glyceraldehyde **6** was prepared from D-mannitol in two steps as per the literature.[7] Compound **6** underwent a Wittig reaction with $PPh_3CHCOOEt$ in CH_2Cl_2 resulted in compound **7,** as mixture of *cis*- and *trans*-isomers (*Z*/*E* 2:8). Compound **7** upon hydrogenation using H_2–Pd/C in MeOH followed by reduction with $LiAlH_4$ in THF gave compound **8**. The alcohol functionality of compound **8** was converted into the corresponding mesylate, which afforded the azido compound **9,** on heating at 90 °C with sodium azide in DMF. Deprotection of the acetonide group in compound **9** was achieved using 80% aqueous acetic acid to give compound **10.** Selective protection of the primary hydroxyl group in compound **10** as its TBS ether yielded compound **11.** The secondary hydroxyl group in **11** was protected as its benzyl ether to give **12**. The silyl group in compound **12** was deprotected using TBAF in THF to give **13**. Azide **13** was reduced with triphenylphosphine to generate a primary amine, which was protected in situ with Boc_2O to provide the Boc-amide **14**. Compound **14** upon Swern oxidation followed by Wittig reaction with $PPh_3CHCOCH_3$ in toluene at reflux gave *trans* olefin **5** exclusively with 89% overall yield. In order to determine the stereochemical outcome of the intramolecular Michael addition, compound **5** was treated with NaH in THF at 0 °C to give compounds **16a** and **17a** as *cis*- and *trans*-isomers in 8:2 ratio in 98% yield. The confirmation of structures **16a** and **17a** was elucidated by detailed 1D and 2D NMR studies including DQFCOSY and NOESY experiments. For **16a**, NOE cross peaks were observed between the C_6Ha–C_7H, C_4Ha–C_7H, and C_3Ha–C_5Ha, whereas for **17a**, the NOE cross peaks were observed between the C_6Ha–C_7H, C_4Ha–C_7H and C_4Ha–C_6Ha (Fig. 1).

From the above results, it is clear that the 2-oxopropyl unit is oriented in an axial position in both compounds **16a** and **17a,** as shown in Figure 1.The axial orientation is because of the minimization of the $A^{(1,3)}$ strain between the *N*-acyl and the axial 2-oxopropyl units. It is well documented in the literature[10] that *N*-acylpiperidines are known to show significant $A^{(1,3)}$ strain between the *N*-acyl unit and a 2-equatorial substituent as shown in **16b** and **17b** (Fig. 1). This internal strain might have allowed the Michael addition to proceed to give the axial orientation of 2-oxopropyl units in **16a** and **17a** probably under thermodynamic control.[11] When the minimum energy conformation was generated in SYBYL 6.8 using the Tripose Force Field, the energy of the 2,3-diaxial conformation of **17a** was found to be 8.8 kcal/mol, whereas that for the 2,3-diequatorial conformation of **17b** was 12.224 kcal/mol (Fig. 2).

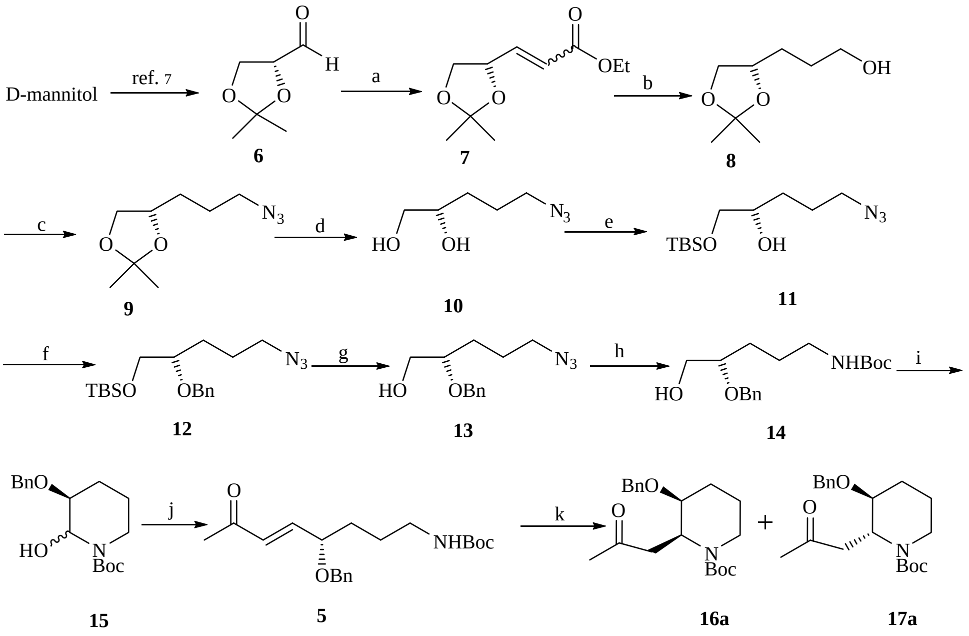
Compound **16a** was converted into silyl enol ether **18**, and treatment with NBS in CH_2Cl_2 afforded **3** in 70% overall yield (Scheme 3).[6n,8] Similarly, compound **17a** was also converted into brominated compound **4** in 72% overall yield (Scheme 4).[9] Isofebrifugine **2** and febrifugine **1** were synthesized from compounds **3** and **4** by Kobayashi et al. in a two-step reaction sequence.[4]

3. Conclusions

In conclusion, we have developed a strategy for the formal synthesis of isofebrifugine **2** and febrifugine **1** using a base-induced intramolecular Michael addition reaction**,** which is also useful to make febrifugine and isofebrifugine analogues and also differentially substituted piperidines for improved therapeutic activity.

4. Experimental

IR spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrometer. ESI mass spectra were recorded on an AUTO SPEC-M (Manchester, UK) mass spectrometer. ^1H NMR spectra were recorded at 200 MHz on a Varian Gemini, 300 MHz on a Bruker Avance, 400 MHz on a Varian Unity, and 500 MHz on a Varian Inova FT-NMR spectrometer. ^{13}C NMR spectra were recorded at 50 MHz on a Varian Gemini, 75 MHz on a Bruker Avance, 100 MHz on a Varian Unity, and 125 MHz on a Varian Inova FT-NMR spectrometer. Optical rotations were measured with a JASCO DIP-370 instrument. For column chromatography, silica gel 60–120 mesh was used. For TLC, Silica Gel 60 F_{254} (Merck) was used.



Scheme 2. Reagents and conditions: (a) $PPh_3CHCOOEt$, CH_2Cl_2, rt, 4 h, 87%; (b) (i) 10% Pd/C, H_2, MeOH, 6 h; (ii) $LiAlH_4$, THF, rt, 2 h (82% for two steps); (c) (i) MsCl, Et_3N, DMAP (cat), 0 °C–rt, 1 h; (ii) NaN_3, DMF, 90 °C, 8 h (93% for two steps); (d) 80% aq AcOH, rt, 8 h, 94%; (e) TBSCl, imidazole, DMAP (cat), CH_2Cl_2, rt, 12 h, 90%; (f) BnBr, THF, NaH (60% w/w), 0 °C–rt, 5 h, 92%; (g) TBAF, THF, rt, 3 h, 95%; (h) TPP, MeOH, rt, 4 h then $(Boc)_2O$, 6 h, 96%; (i) DMSO, $(COCl)_2$, DCM, −78 °C, 2 h then DIPEA; (j) $PPh_3CHCOCH_3$, toluene, reflux, 8 h (89% for two steps); (k) NaH, THF, 0.5 h, 0 °C, 98% (**16a**/**17a** = 8:2 ratio).

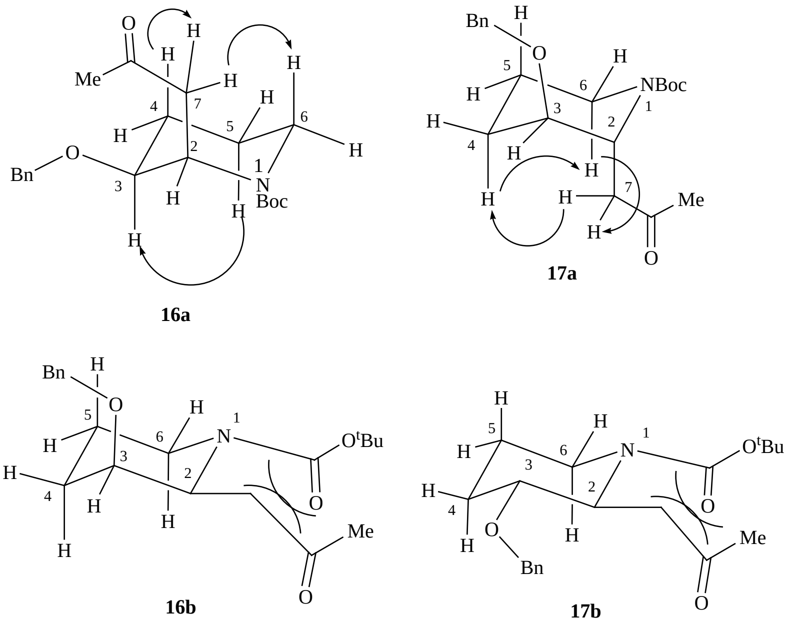


Figure 1.

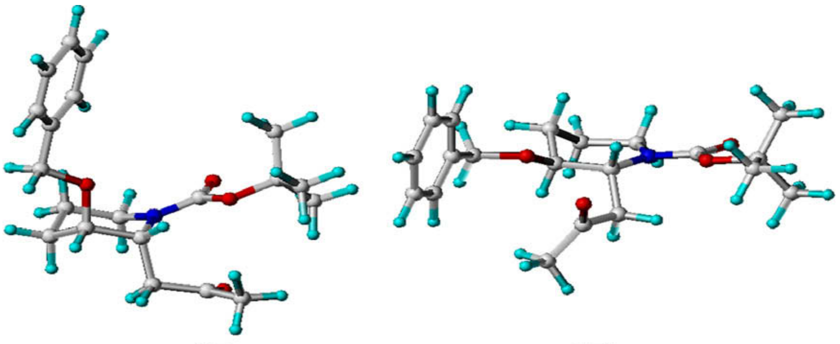
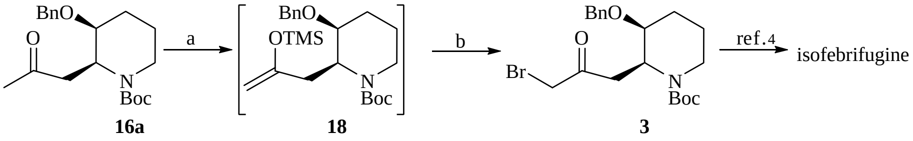
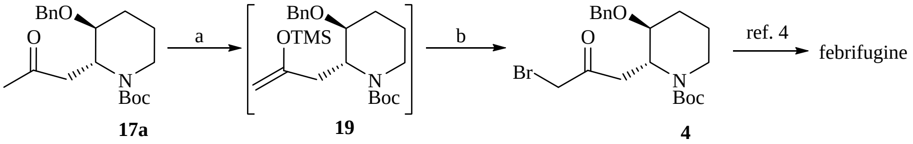


Figure 2.



Scheme 3. Reagents and conditions: (a) LHMDS, THF, −78 °C, 1 h, then TMSCl, 1 h; (b) NBS, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h (70% for two steps).



Scheme 4. Reagents and conditions: (a) LHMDS, THF, −78 °C, 1 h, then TMSCl, 1 h; (b) NBS, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h (72% for two steps).

4.1. (*S*,*E*/*Z*)-Methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl) acrylate 7

To an ice-cooled, stirred solution of aldehyde **6** (3 g, 23.07 mmol) in CH_2Cl_2 (40 mL), was added $PPh_3CHCOOEt$ (9.6 g, 27.69 mmol) and stirred at room temperature for 4 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (2 × 75 mL). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was then chromatographed on silica gel (ethyl acetate/hexane = 1:4) to give compounds *trans*-**7** and *cis*-**7** (4.0 g, 87% in 8:2 ratio) as colorless liquids. Data for *trans*-**7:** $[\alpha]_D^{25} = +4.3$ (*c* 1.8, CHCl$_3$); IR ν_{max} (neat, cm^{-1}): 2986, 1722, 1375, 1303, 1261, 1215, 1181, 1061; ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.83 (dd, 1H, *J* = 5.28, 15.48 Hz), 6.05 (dd, 1H, *J* = 1.13, 15.48 Hz), 4.62 (dt, 1H, *J* = 1.13, 6.79 Hz), 4.19 (q, 2H, *J* = 7.17 Hz), 4.15 (dd, 1H, *J* = 6.79, 8.31 Hz), 3.63 (t, 1H, *J* = 7.55 Hz), 1.43 (s, 3H), 1.38 (s, 3H), 1.30 (t, 3H, *J* = 7.17 Hz); MS (ESI): 223 [M+Na]$^+$. Data for *cis*-**7**: $[\alpha]_D^{25} = -48.0$ (*c* 1.1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.35 (dd, 1H, *J* = 6.42, 11.71 Hz), 5.82 (dd, 1H, *J* = 1.51, 11.71 Hz), 5.46 (ddd, 1H, *J* = 1.51, 6.79, 8.31 Hz), 4.36 (dd, 1H, *J* = 7.17, 8.31 Hz), 4.16 (q, 2H, *J* = 7.17 Hz), 3.58 (dd, 1H, *J* = 6.79, 8.30 Hz), 1.43 (s, 3H), 1.38 (s, 3H), 1.30 (t, 3H, *J* = 7.17 Hz); MS (LC): 223 [M+Na]$^+$.

4.2. (*S*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl) propan-1-ol 8

Hydrogenation of compound **7** (2.0 g, 10 mmol) was carried out with a catalytic amount of 10% Pd/C in MeOH (15 mL). After being stirred for 6 h at room temperature, the catalyst was removed by filtration. The filtrate was concentrated in vacuo to give the saturated ester.

To a suspension of LiAlH$_4$ (0.42 g, 11.0 mmol) in dry THF (10 mL) was added a solution of crude ester in THF (15 mL) at 0 °C. The reaction mixture was brought to room temperature and stirred for 2 h. The mixture was hydrolyzed by the cautious addition of water and 15% NaOH solution. The fine white precipitate which formed was washed with ethyl acetate and discarded. The filtrate was concentrated and purified by column chromatography (ethyl acetate/hexane = 1:3) to give alcoholic compound **8** (1.31 g, 82% for two steps) as a liquid. $[\alpha]_D^{25} = +7.4$ (*c* 1.3, CHCl$_3$); IR ν_{max} (neat, cm^{-1}): 3442, 2940, 1375, 1219, 1056; ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.09–4.21 (m, 1H), 4.06 (dd, 1H, *J* = 6.04, 7.55 Hz), 3.62–3.75 (m, 2H), 3.54 (dd, 1H, *J* = 7.55 Hz), 2.06 (br s, 1H), 1.60–1.74 (m, 4H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 108.97, 75.97, 69.47, 62.64, 30.27, 29.20, 26.89, 25.71; MS (ESI): 183 [M+Na]$^+$; HRMS (ESI) calcd for C$_8$H$_{16}$O$_3$ [M+Na]$^+$ = 183.0997, found: 183.0993.

4.3. (*S*)-4-(3-Azidopropyl)-2,2-dimethyl-1,3-dioxolane 9

Compound **8** (1.1 g, 6.87 mmol) was taken in dry CH$_2$Cl$_2$ (10 mL), cooled to 0 °C and treated with Et$_3$N (2.4 mL, 17.18 mmol), DMAP (3 mg), and mesyl chloride (0.65 mL, 8.25 mmol). The reaction mixture was then stirred at room temperature until consumption of the starting material (about 30–45 min). It was then poured into water (20 mL) and extracted with CH$_2$Cl$_2$ (2 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent provided the crude mesylate, which was directly used in the next step.

To a stirred solution of the crude mesylate obtained above in dry DMF (10 mL) was added NaN$_3$ (0.89 g, 13.69 mmol). The mixture was heated to 90 °C and stirred for approximately 8 h. The reaction was monitored by TLC until all starting material disappeared, then the mixture was diluted with water and extracted with EtOAc (3 × 40 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$ and concentrated. Purification of the residue by silica gel column chromatography (ethyl acetate/hexane = 1:6) gave pure azido compound **9** (1.18 g, 93% for two steps) as a liquid. $[\alpha]_D^{25} = +6.5$ (*c* 1.5, CHCl$_3$); IR (neat, cm^{-1}): 2987, 2931, 2097, 1375, 1250, 1220, 1064; ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.01–4.16 (m, 2H), 3.53 (dd, 1H, *J* = 6.79, 7.17 Hz), 3.33 (t, 2H, *J* = 5.66 Hz), 1.54–1.85 (m, 4H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 108.86, 75.34, 69.19, 51.18, 30.61, 26.79, 25.61, 25.27; MS (ESI): 208 [M+Na]$^+$; HRMS (ESI) calcd for C$_8$H$_{15}$N$_3$O$_2$ [M+Na]$^+$ = 208.1061, found: 208.1061.

4.4. (*S*)-5-Azidopentane-1,2-diol 10

A solution of compound **9** (1.1 g, 5.94 mmol) in 80% aqueous acetic acid (10 mL) was stirred for 8 h. The reaction mixture was neutralized by the cautious addition of saturated NaHCO$_3$ solution and extracted with EtOAc (2 × 40 mL). The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated. The residue was then chromatographed on silica gel (ethyl acetate/hexane = 1:2) to give diol compound **10** (0.81 g, 94%) as an oily liquid: $[\alpha]_D^{25} = -7.4$ (*c* 1.2, CHCl$_3$); IR ν_{max} (neat, cm^{-1}): 3372, 2938, 2874, 2100, 1258, 1061; ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.64 (dd, 1H, *J* = 2.64, 11.33 Hz), 3.50–3.76 (m, 2H), 3.43 (dd, 1H, *J* = 7.55, 10.95 Hz), 3.34 (t, 2H, *J* = 6.79 Hz), 1.56–1.87 (m, 2H), 1.42–1.55 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 71.68, 66.56, 51.41, 29.99, 25.05; MS (ESI): 168 [M+Na]$^+$; HRMS (ESI): calcd for C$_5$H$_{11}$N$_3$O$_2$ [M+Na]$^+$ = 168.0748, found: 168.0746.

4.5. (*S*)-5-Azido-1-(*tert*-butyldimethylsilyloxy) pentan-2-ol 11

To a stirred solution of **10** (0.70 g, 4.82 mmol) in CH$_2$Cl$_2$ (10 mL) were added imidazole (0.82 g, 12.06 mmol) and TBDMSCl (0.73 g, 4.82 mmol) and DMAP (5 mg) at room temperature and stirred for 12 h. The reaction mixture was then poured into water (20 mL) and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent followed by silica gel column chromatography of the crude residue (ethyl acetate/hexane = 1:5) afforded the silyl ether **11** (1.12 g, 90%) as a liquid. $[\alpha]_D^{25} = +1.1$ (*c* 1.0, CHCl$_3$); IR ν_{max} (neat, cm^{-1}): 3454, 2932, 2860, 2097, 1255, 1093, 838; ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.60–3.70 (m, 2H), 3.25–3.45 (m, 3H), 2.47 (d, 1H, *J* = 2.50 Hz), 1.58–1.92 (m, 2H), 1.43–1.56 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 71.25, 67.13, 51.46, 29.82, 25.85, 25.18, 18.26, −5.43; MS (ESI): 282 [M+Na]$^+$; HRMS (ESI): calcd for C$_{11}$H$_{25}$N$_3$O$_2$Si [M+Na]$^+$ = 282.1613, found: 282.1610.

4.6. (*S*)-(5-Azido-2-(benzyloxy) pentyloxy)(*tert*-butyl) dimethylsilane 12

To a suspension of NaH (0.31 g, 60% w/w, 7.72 mmol) in anhydrous THF (5 mL), alcohol **11** (1.0 g, 3.86 mmol) in anhydrous THF (10 mL) was slowly added at 0 °C, stirred for 15 min, followed by addition of benzyl bromide (0.50 mL, 4.63 mmol) and a catalytic amount of TBAI. The resulting mixture was stirred at room temperature for 5 h, quenched with saturated aqueous NH$_4$Cl solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified over silica gel column chromatography (ethyl acetate/hexane = 1:19) to give **12** (1.24 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = -21.6$ (*c* 2.1, CHCl$_3$); IR ν_{max} (neat, cm^{-1}): 2930, 2859, 2096, 1254, 1100, 837; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20–7.39 (m, 5H), 4.59 (ABq, 2H, *J* = 11.80 Hz), 3.12–3.91 (m, 5H), 1.42–1.83 (m, 4H), 0.90 (s, 9H, *J* = 5.53 Hz), 0.05 (s, 6H); MS (ESI): 372 [M+Na]$^+$; HRMS (ESI): calcd for C$_{18}$H$_{31}$N$_3$O$_2$Si [M+Na]$^+$ = 372.2083, found: 372.2073.

4.7. (*S*)-5-Azido-2-(benzyloxy) pentan-1-ol 13

To a solution of **12** (0.60 g, 1.72 mmol) in THF (8 mL) was added TBAF (3.4 mL of 1 M solution in THF, 3.43 mmol) at 0 °C and stirred at room temperature for 3 h. It was then poured into water (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. Evaporation of solvent followed by silica gel column chromatography of the crude residue (ethyl acetate/hexane = 1:4) afforded **13** (0.38 g, 95%) as a syrupy liquid. $[\alpha]_D^{25} = -5.0$ (*c* 0.9, CHCl$_3$); IR ν_{max} (neat,

cm^{-1}): 3425, 2927, 2870, 2096, 1455, 1065, 740; ^1H NMR (300 MHz, $CDCl_3$): δ 7.23–7.38 (m, 5H), 4.56 (s, 2H), 3.61–3.72 (m, 1H), 3.41–3.55 (m, 2H), 3.25 (t, 2H, $J = 6.42$ Hz), 1.89 (br s, 1H), 1.44–1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.15, 128.48, 127.83, 127.78, 78.88, 71.62, 63.89, 51.42, 28.05, 24.79; MS (ESI): 258 $[M+Na]^+$.

4.8. (*S*)-*tert*-Butyl 4-(benzyloxy)-5-hydroxypentylcarbamate 14

The azido compound **13** (0.25 g, 1.06 mmol) was dissolved in MeOH (5 mL), and triphenyl phosphine (0.55 g, 2.12 mmol) was added. The mixture was stirred for 4 h at ambient temperature, and then di-*tert*-butoxycarbonyl dicarbonate (0.5 mL, 2.12 mmol) was added. Stirring was continued for 6 h, after which the solvent was evaporated. Column chromatography of the residue over silica gel (ethyl acetate/hexane = 1:9) gave **14** (315 mg, 96%) as an oily liquid: $[\alpha]_D^{25} = -13.2$ (c 0.8, $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 3354, 2929, 1693, 1519, 1251, 1170; ^1H NMR (400 MHz, $CDCl_3$): δ 4.56 (ABq, 2H, $J = 11.72$ Hz), 4.47–4.54 (m, 1H), 3.61–3.73 (m, 1H), 3.42–3.58 (m, 2H), 2.94–3.26 (m, 2H), 1.99 (br s, 1H), 1.47–1.74 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.01, 138.29, 128.48, 127.79, 79.20, 71.63, 64.00, 40.47, 28.39, 28.04, 25.93; MS (ESI): 332 $[M+Na]^+$; HRMS (ESI): calcd for $C_{17}H_{27}NO_4$ $[M+Na]^+ = 332.1837$, found: 332.1831.

4.9. (*S*,*E*)-*tert*-Butyl 4-(benzyloxy)-7-oxooct-5-enylcarbamate 5

To a solution of $(COCl)_2$ (0.15 mL, 1.62 mmol) in CH_2Cl_2 (3 mL) was added DMSO (0.23 mL, 3.24 mmol) at −78 °C, and the mixture was stirred for 10 min. A solution of alcohol **14** (0.25 g, 0.81 mmol) in CH_2Cl_2 was added to the resulting mixture, and stirred it for 1 h at −78 °C. Then, DIPEA (0.55 mL, 3.24 mmol) was added at −78 °C and the reaction mixture was warmed to 0 °C for 20 min. Water (20 mL) was added to quench the reaction mixture, and the aqueous mixture was extracted with CH_2Cl_2 (2 × 20 mL), dried over anhydrous Na_2SO_4. Evaporation of solvent provided crude **15**, which was used directly in the next step.

To a solution of **15** in toluene (5 mL), $PPh_3CHCOCH_3$ (0.40 g, 1.21 mmol) was added. The mixture was heated at reflux with stirring for about 8 h, until TLC showed disappearance of **15**. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuo and column chromatography of the residue over silica gel (ethyl acetate/hexane = 1:5) gave **5** (0.25 g, 89% for two steps) as a syrupy liquid. $[\alpha]_D^{25} = -15.2$ (c 1.2, $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 2974, 2933, 1697, 1517, 1365, 1254, 1169; ^1H NMR (200 MHz, $CDCl_3$): δ 7.22–7.41 (m, 5H), 6.59 (dd, 1H, $J = 6.25$, 16.02 Hz), 6.19 (d, 1H, $J = 16.02$ Hz), 4.56 (d, 1H, $J = 11.72$ Hz), 4.35 (d, 1H, $J = 11.72$ Hz), 4.35–4.51 (m, 1H), 3.87–4.05 (m, 1 H), 2.97–3.24 (m, 2H), 2.25 (s, 3H), 1.45–1.71 (m, 4H), 1.43 (s, 9H); MS (ESI): 370 $[M+Na]^+$; HRMS (ESI): calcd for $C_{20}H_{29}NO_4$ $[M+Na]^+ =$ 370.1994, found: 370.1991.

4.10. (2*R*/*S*,3*S*)-*tert*-Butyl 3-(benzyloxy)-2-(2-oxopropyl) piperidine-1-carboxylate 16a/17a

To a suspension of NaH (46 mg, 60% w/w, 1.15 mmol) in anhydrous THF (4 mL), compound **5** (0.20 g, 0.57 mmol) in anhydrous THF (10.0 mL) was slowly added at 0 °C. The mixture was stirred at 0 °C for 30 min, quenched with saturated aqueous NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified over silica gel column chromatography (ethyl acetate/hexane = 1:7) to give pure compounds **16a** and **17a** in an 8:2 ratio (196 mg, 98%) as oily liquids. Data for **16a**: $[\alpha]_D^{25} = +22.0$ (c 1.7, $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 2934, 1692, 1412, 1365, 1256, 1154; ^1H NMR (500 MHz, DMSO at 50 °C): δ 7.25–7.37 (m, 5H, –Ph), 4.87 (br s, 1H, C_2H_e), 4.52 (d, 1H, $-CH_2Ph$, $J = 12.3$ Hz), 4.50 (d, 1H, $-CH_2Ph$, $J = 12.3$ Hz), 3.74 (dd, 1H, C_6H_e, $J = 5.1$, 14.0 Hz), 3.43 (td, 1H, C_3H_a, $J = 5.0$, 11.3 Hz), 2.73 (dd, 1H, C_7H, $J = 5.4$, 15.0 Hz), 2.70 (t, 1H, C_6H_a, $J = 14.0$ Hz), 2.50 (m, 1H, C_7H), 2.07 (s, 3H, $-COCH_3$), 1.82 (dq, 1H, C_4H_e, $J = 5.1$, 14.0 Hz), 1.62 (m, 1H, C_5H_e), 1.45 (dq, 1H, C_4H_a, $J = 5.1$, 14.0 Hz), 1.38 (s, 9H, $-Bu^t$), 1.30 (tq, 1H, C_5H_a, $J = 5.0$, 14.0 Hz); ^{13}C NMR (125 MHz, DMSO at 50 °C): δ 206.97, 154.55, 139.25, 128.91, 128.11, 79.86, 79.72, 75.87, 70.49, 55.50, 50.73, 38.56, 30.70, 28.69, 25.71, 24.34; MS (ESI): 370 $[M+Na]^+$; HRMS (ESI): calcd for $C_{20}H_{29}NO_4$ $[M+Na]^+ = 370.1994$, found: 370.2001. Data for **17a**: $[\alpha]_D^{25} = -42.3$ (c 1.1, $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 2934, 1690, 1419, 1366, 1271, 1167; ^1H NMR (500 MHz, CD_3OD at 45 °C): δ 7.21–7.40 (m, 5H, –Ph), 4.94 (dt, 1H, C_2H, $J = 1.5$, 7.5 Hz), 4.67 (d, 1H, $-CH_2Ph$, $J = 12.0$ Hz), 4.52 (d, 1H, $-CH_2Ph$, $J = 12.0$ Hz), 3.96 (dd, 1H, C_6H_e, $J = 4.3$, 13.0 Hz), 3.45 (q, 1H, C_3H, J = 3.0 Hz), 2.87 (td, 1H, C_6H_a, $J = 3.3$, 13.0 Hz), 2.72 (d, 2H, C_7H, $J = 7.5$ Hz), 2.17 (s, 3H, $-COCH_3$), 1.85 (m, 1H, C_5H_e), 1.82 (m, 1H, C_4H_e), 1.72 (m, 1H, C_4H_a), 1.42 (s, 9H, $-Bu^t$), 1.38 (m, 1H, C_5H_a); ^{13}C NMR (125 MHz, CD_3OD at 45 °C): δ 209.60, 157.97, 141.04, 130.09, 129.35, 82.04, 76.28, 72.16, 52.10, 50.49, 50.27, 44.80, 41.20, 29.59, 29.53, 26.12, 21.46; MS (ESI): 370 $[M+Na]^+$; HRMS (ESI): calcd for $C_{20}H_{29}NO_4$ $[M+Na]^+ = 70.1994$, found: 370.2000.

4.11. (2*S*/*R*,3*S*)-*tert*-Butyl 3-(benzyloxy)-2-(3-bromo-2-oxopropyl) piperidine-1-carboxylate 3/4

A solution of lithium hexamethyldisilazide (0.25 mL 1 M solution in toluene, 0.25 mmol) in dry THF (2.0 mL) was cooled to −78 °C, and to this solution was slowly added compound **16a** (70 mg, 0.20 mmol) in THF (2 mL). After 1 h, TMSCl (0.65 mL, 0.50 mmol) was added to the mixture, which was further stirred for 1 h. The reaction mixture was diluted with 10 mL of hexane at −78 °C and washed quickly with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure which gave silyl enol ether **18**. The crude silyl enol ether **18** was dissolved in CH_2Cl_2 (2 mL), and to this solution were added $NaHCO_3$ (68 mg, 0.80 mmol) and NBS (54 mg, 0.30 mmol) at 0 °C, and stirring was continued for 2 h at 0 °C. Then, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuo and column chromatography of the residue over silica gel (ethyl acetate/hexane = 1:14) gave **3** (60 mg, 70% for two steps) as a syrupy liquid. $[\alpha]_D^{25} = -19.3$ (c 0.7, $CHCl_3$) {lit.[4] (its enantiomer) $[\alpha]_D^{25} = +22.5$, (c 0.3, $CHCl_3$)}; IR ν_{max} (neat, cm^{-1}): 2935, 2865, 1687, 1410, 1364, 1152; ^1H NMR (300 MHz, DMSO at 50 °C): δ 7.20–7.47 (m, 5H), 4.88 (br, 1H), 4.37-4.60 (m, 2H), 4.32 (d, 1H, $J = 14.24$ Hz), 4.22 (d, 1H, $J = 14.24$ Hz), 3.65–3.85 (m, 1H), 3.35–3.52 (m, 1H), 2.99 (dd, 1H, $J = 5.08$, 15.26 Hz), 2.58–2.80 (m, 2H), 1.75–1.90 (m, 1H), 1.55–1.71 (m, 1H), 1.37 (s, 9H), 1.14–1.55 (m, 2H); ^{13}C NMR (75 MHz, DMSO at 50 °C): δ 198.76, 153.50, 138.08, 127.85, 127.11, 127.07, 78.85, 74.73, 69.51, 36.63, 35.16, 33.50, 27.64, 24.63, 23.17; MS (ESI): 448 $[M+Na]^+$; HRMS (ESI): calcd for $C_{20}H_{28}NO_4Br$ $[M+Na]^+ = 448.1099$, found: 448.1092.

Similarly, compound **4** was prepared from **17a** in 72% yield. $[\alpha]_D^{25} = -32.2$ (c 0.5, $CHCl_3$); {lit.[4] (its enantiomer) $[\alpha]_D^{25} = +28.4$ (c 0.2, $CHCl_3$)}; IR ν_{max} (neat, cm^{-1}): 2927, 2857, 1685, 1415, 1367, 1170; ^1H NMR (200 MHz, $CDCl_3$): δ 7.02–7.67 (m, 5H), 4.93 (t, 1H, $J = 7.05$ Hz), 4.68 (d, 1H, $J = 11.91$ Hz), 4.48 (d, 1H, $J = 11.91$ Hz), 3.85–4.16 (m, 2H), 3.79 (d, 1H, $J = 12.28$ Hz), 3.33–3.43 (m, 1H), 2.61–2.98 (m, 3H), 1.42 (s, 9H), 1.13–2.05 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 199.65, 155.27, 138.48, 128.28, 127.45, 80.03, 77.20, 73.48, 70.19, 49.49, 39.75, 34.04, 28.33, 24.63, 19.43; MS (ESI): 448 $[M+Na]^+$; HRMS (ESI): calcd for $C_{20}H_{28}NO_4Br$ $[M+Na]^+$ = 448.1099, found: 448.1092.

Acknowledgments

N.S. thanks UGC, New Delhi, G.S. and G.S.R. thank CSIR, New Delhi for fellowship. The authors thank Dr. A. C. Kunwar for his fruitful discussion and support. The authors also thank Dr. J. S. Yadhav and Dr. T. K. Chakraborthy for their support and encouragement.

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