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REGULAR ARTICLE

Efforts toward the synthesis of (+)-Lyconadin A

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Abstract. Synthetic efforts toward the synthesis of (+)-lyconadin A are described. B-Alkyl Suzuki coupling is utilized for combining 2-iodo cyclohexenone with the piperidine subunit. The piperidine subunit is derived from 5-bromo-3-nicotinic acid, and iodo cyclohexenone from commercially available (*R*)-pulegone. An intramolecular Michael reaction is employed for the creation of the C6-C7 bond.

Keywords. Lyconadin-A; 5-bromo-3-nicotinic acid; B-alkyl Suzuki coupling; intramolecular Michael reaction.

1. Introduction

A large number of alkaloids with structural diversity constitute the *Lycopodium* family.[1] (+)-Lyconadin A[2] (**1**: Figure 1), and (-)-Lyconadin B[3] (**2**) were isolated by Kobayashi and co-workers from the club moss *Lycopodium complanatum*. Lyconadin A exhibits moderate cytotoxicity against murine lymphoma L1210 cells and human epidermoid carcinoma KB cells. Lyconadin A also augments mRNA expression for nerve growth factor in 1321N1 human arystoma cells.[3] Lyconadin A possesses a pentacyclic ring system with an α-pyridinone ring united to a tetracyclic core.

The unique structural features and biological activities of lyconadin A has drawn the attention of synthetic chemists and four total syntheses have been reported to date. The first synthesis of lyconadin A was disclosed by Smith and co-workers, Scheme 1, wherein an intramolecular aldol/conjugate addition cascade and aminoiodination were utilized to construct the tetracyclic moiety.[4] Sarpong's group reported the synthesis of racemic and (+)-lyconadin A taking advantage of C-N bond formation to create the pentacyclic skeleton.[5] Fukuyama and co-workers accomplished the synthesis of (+)-lyconadin utilizing an aza-Prins reaction and electrocyclic ring-opening to construct a tetracyclic compound.[6] Dai and co-workers reported the synthesis of lyconadin A through a formal aza [4+2] cyclization.[7] Herein, we disclose our efforts, resulting in an advanced intermediate toward lyconadin A, using B-alkyl Suzuki reaction and intramolecular Michael reaction as key steps.

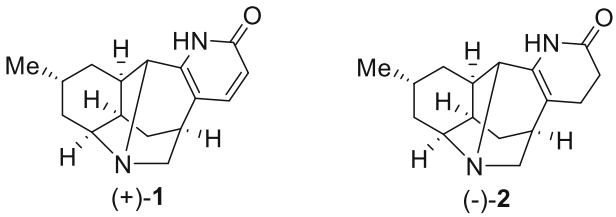

Figure 1. Lyconadin A and B.

2. Experimental

Methyl 5-aminonicotinate (23): The mixture of 5-bromonicotinic acid **21** (20.2 g, 100 mmol) and $CuSO_4.5H_2O$ (4.98 g, 20 mmol) in aq NH_3 (40 mL) was stirred at 170-180 °C for 19 h in an autoclave. The dark coloured solution after cooling was treated with aq Na_2S to remove copper ions and filtered. The filtrate was adjusted to

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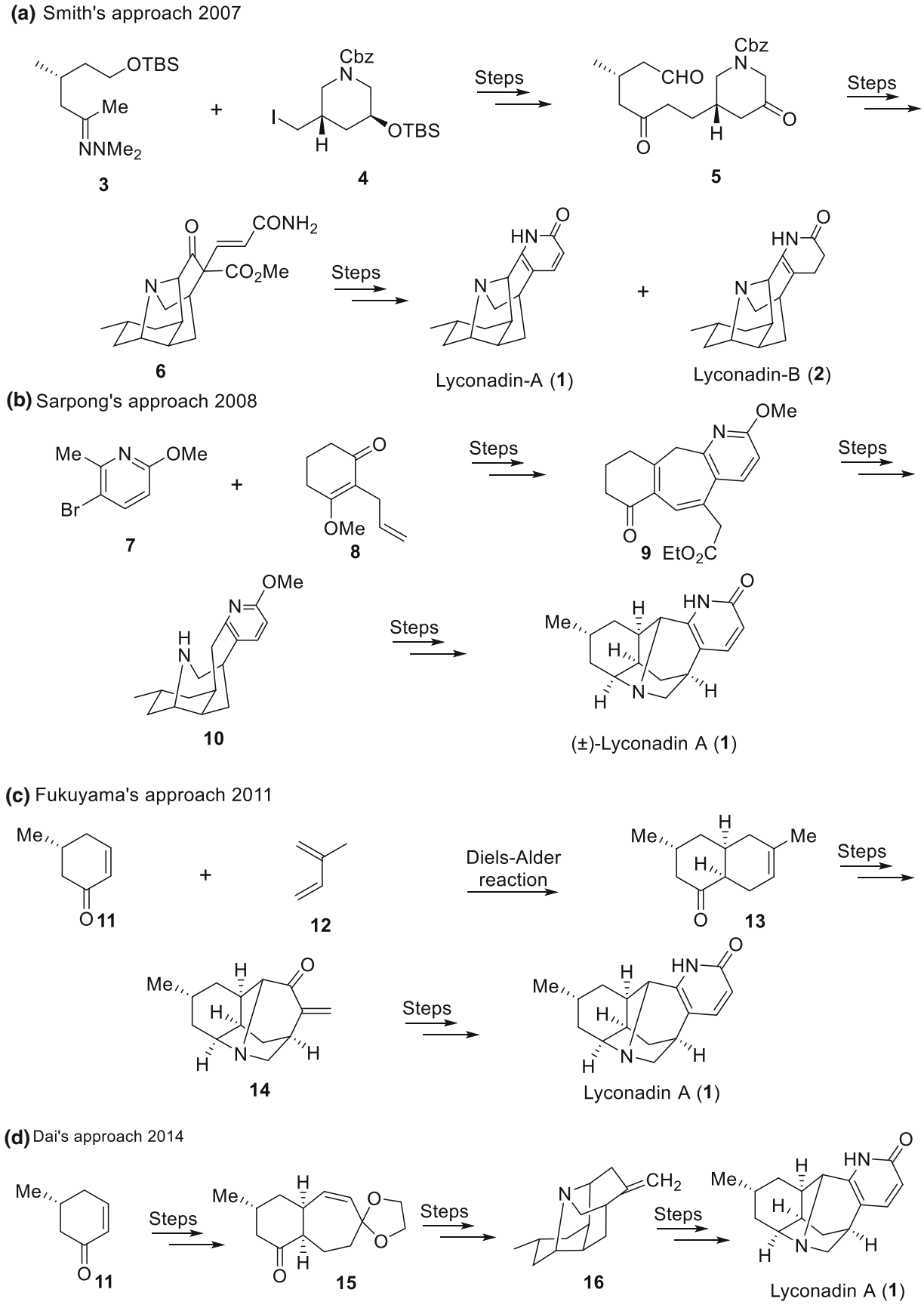


Scheme 1. Earlier approaches to Lyconadin-A.

pH 4-5 and concentrated. The brown coloured crude acid was taken to the next step without any further purification. To the crude compound in MeOH (500 mL) was added $SOCl_2$ (108 mL, 1500 mmol) at 0 °C and the mixture was stirred at reflux for 2 d. The solvent was removed under reduced pressure. The residue was dissolved in a minimum volume of water (20 mL) at 0 °C and a solution of sat. Na_2CO_3 (100 mL) was added until the product precipitated. The precipitate was collected by filtration to give the methyl ester **23** (13.2 g, 87 mmol) as a solid in 87% yield over two steps. TLC R_f: 0.2 (ethyl acetate:hexane, 1:1). M.p. 133-135 °C. IR (KBr): 3328, 3142, 1729, 1584, 1107, 766 cm^{-1}; ^1H NMR (300 MHz, Acetone-d_6) δ 8.38 (bs, 1H), 8.23 (bs, 1H), 7.54 (dd, J = 2.5, 1.9 Hz, 1H), 5.19 (bs, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, Acetone-d_6) δ 166.9, 145.5, 141.5, 139.4, 127, 120.9, 52.4. MS (ESI): m/z 153 $[M+H]^+$. HRMS (ESI): calcd. for $C_7H_9N_2O_2$: 153.0658; found: 153.0656.

5-Aminopyridin-3-yl)methanol (24): To the suspension of $LiAlH_4$ (13 g, 342 mmol) in anhydrous tetrahydrofuran (300 mL) was slowly added the solution of methyl ester **23** (13 g, 85.5 mmol) in anhydrous tetrahydrofuran (160 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 0.5 h, gradually warmed to rt and stirred further for a period of 24 h. The resulting mixture was cooled to 0 °C, carefully acidified with 2 N HCl to pH 3 and thereafter basified with solid Na_2CO_3 to pH 8. The mixture was filtered through a Celite pad. The filtrate was extracted with ethyl acetate (3 x 300 mL). The combined organic layers were washed successively with water (300 mL), brine (300 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (methanol/dichloromethane, 1:9) to afford compound **24** (9 g, 72.68 mmol) in 85% yield as an oil. IR (KBr): 3325, 2933, 1596, 1444, 1017, 544 cm^{-1}; ^1H NMR (300 MHz, Acetone-d_6) δ 7.92 (d, J = 1.7 Hz, 1H), 7.80 (bs, 1H), 7.01 (dd, J = 2.5, 1.7 Hz 1H), 4.81 (bs, 2H), 4.52 (s, 2H), 4.33 (bs, 1H); ^{13}C NMR (75 MHz, Acetone-d_6) δ 145.2, 138.6, 137.7, 136.5, 119.7, 62.5. MS (ESI): m/z 125 $[M+H]^+$. HRMS (ESI): calcd. for $C_6H_9N_2O$: 125.0709; found: 125.0707.

5-(Hydroxymethyl)pyridin-3-ol (25): The amino pyridine derivative **24** (6.2 g, 50.0 mmol) was dissolved in aq sulfuric acid (2.5 M, 75 mL) and cooled in an ice bath. Small portions of $NaNO_2$ (3.45 g, 50 mmol) were added over a 10 min period. The solution was stirred for a further period of 30 min where after aq sulfuric acid (1 M, 200 mL) was added and the mixture heated to 70 °C for 2 h. The reaction mixture was cooled to 0 °C and solid Na_2CO_3 added to adjust the pH to 8. Water was evaporated and the residue was extracted by washing with MeOH:DCM (1:1) (200 mL). The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (methanol:dichloromethane, 1:9) to afford the product **25** (5.8 g, 46.5 mmol) in 93% yield as a solid. M.p. 112-114 °C. TLC R_f: 0.2 (methanol:dichloromethane, 0.5:9.5). IR (KBr): 3319, 3192, 2815, 1593, 1443, 1018, 704 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.87 (d, J = 1.9, 1H), 7.84 (d, J = 2.5, 1H), 7.31 (dd, J = 2.5, 1.9 Hz, 1H), 4.59 (s, 2H); ^{13}C NMR (75 MHz, MeOD) δ 156.0, 140.3, 139.6, 137.2, 123.1, 62.5. MS (ESI): m/z 126 $[M+H]^+$. HRMS (ESI): calcd. for $C_6H_8NO_2$: 126.0549; found: 126.0546.

5-(Hydroxymethyl)piperidin-3-ol (26): To the solution of pyridine derivative **25** (5.25 g, 42 mmol) in ethanol (80 mL) in a pressure vessel, Rh/C (2.1 g, 40% w/w) was added. The above was subjected to hydrogenation under a pressure (1000 psi) while being heated at 80 °C for 24 h. The mixture was cooled and filtered through a Celite pad. The filtrate was evaporated under reduced pressure to furnish the product **26** (5.5 g, 42 mmol) in quantitative yield as a viscous oil. TLC R_f: 0.2 (methanol:dichloromethane:aq NH_3, 1:9:1). ^1H NMR (400 MHz, D_2O) δ 3.76–3.61 (m, 1H), 3.48 (d, J = 7.4 Hz, 2H), 3.11 (d, J = 11.0 Hz, 1H), 2.99 (d, J = 11.7 Hz, 1H), 2.25 (t, J = 11.0 Hz, 1H), 2.19–1.97 (m, 2H), 1.87–1.69 (m, 1H), 1.03 (q, J = 11.7, Hz 1H); ^{13}C NMR (100 MHz, D_2O) δ 67.2, 64.4, 51.4, 47.1, 38.1, 35.6. MS (ESI): m/z 132 $[M+H]^+$. HRMS (ESI): calcd for $C_6H_{14}NO_2$: 132.1019; found: 132.1016.

***tert*-Butyl 3-hydroxy-5-(hydroxymethyl)piperidine-1-carboxylate (27)**: To a stirred solution of piperidinol derivative **26** (5.12 g, 39.12 mmol) and TEA (11 mL, 78.24 mmol) in dichloromethane (80 mL) was added di-*tert*-butyl dicarbonate (9.2 mL, 40 mmol) in dropwise manner at 0 °C. The mixture was stirred at rt for 4 h. The reaction mixture was diluted with water (50 mL) and the phases were separated. The aq layer was extracted with dichloromethane (2 x 100 mL), the combined organic layers were washed with water (100 mL), brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (ethylacetate:hexanes, 8:2) to afford the product **27** (8.5 g, 36.8 mmol) in 94% yield as a solid. TLC R_f: 0.2 (ethyl acetate:hexane, 8:2). M.p. 93-95 °C. IR (neat): 3404, 2974, 2928, 1667, 1429, 1152, 1055, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88–3.77 (m, 1H), 3.76–3.64 (m, 1H), 3.64–3.47 (m, 2H), 3.03–2.63 (m, 3H), 2.06 (d, J = 12.6 Hz, 1H), 1.85–1.67 (m, 1H), 1.45 (s, 9H), 1.35–1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 80.1, 66.0, 64.8, 51.0, 46.5, 37.4, 36.3, 28.4. MS (ESI): m/z 254 $[M+Na]^+$. HRMS (ESI): calcd for $zC_{11}H_{21}NO_4Na$: 254.1368; found: 254.1368.

***tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-hydroxypiperidine-1-carboxylate (28)**: To a stirred solution of diol **27** (8.3 g, 35.9 mmol) in anhydrous dichloromethane (70 mL) was added imidazole (3.73 g, 54 mmol) followed by TBSCl (8.3 g, 61.3 mmol) at 25 °C. After 45 min, the reaction mixture was quenched with saturated aq NH_4Cl (25 mL) and the phases were separated. The aq layer was

extracted with dichloromethane (40 mL), the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 4:6) to afford the product **28** (12.0 g, 34.78 mmol) in 97% yield as a solid. TLC R_f: 0.2 (ethyl acetate:hexane, 4:6). M.p. 88-90 °C. IR (KBr): 3468, 2953, 2931, 2857, 1676, 1438, 1094, 841, 581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31–4.14 (m, 1H), 4.08 (dd, J = 13.2, 4.1 Hz, 1H), 3.71– 3.61 (m, 1H), 3.53 (dd, J = 10.0, 5.0 Hz, 1H), 3.40–3.40 (m, 1H), 2.52–2.36 (m, 2H), 2.09–1.93 (m, 1H), 1.79–1.59 (m, 1H), 1.44 (s, 9H), 1.18–1.05 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 79.7, 66.3, 65.3, 50.5, 47.3, 38.1, 36.1, 28.4, 25.8, 18.2, -5.5. MS (ESI): m/z 368 $[M+Na]^+$. HRMS (ESI): calcd for $C_{17}H_{35}NO_4NaSi$: 368.2233; found: 368.2233.

***tert*-Butyl 3-acetoxy-5-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine-1-carboxylate (29)**: To a stirred solution of secondary alcohol **28** (10.0 g, 29.0 mmol) in anhydrous dichloromethane (60 mL) was added Et_3N (8.1 mL, z58 mmol) followed by acetyl chloride (2.0 mL, 30 mmol) at 0 °C. After 1 h, the reaction mixture was quenched by adding saturated aq NH_4Cl (50 mL). Dichloromehtane was added (50 mL) and aq layer was separated. The organic layer was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc:hexane, 1:9) to afford the product **29** (10.4 g, 27.0 mmol) in 93% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 1:9). IR (KBr): 2954, 2858, 1743, 1698, 1421, 1235, 1106, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.78–4.63 (m, 1H), 4.28–4.11 (m, 1H), 4.07 (dd, J = 13.1, 4.0 Hz, 1H), 3.53 (dd, J = 10.0, 5.0 Hz, 1H), 3.50–3.38 (m, 1H), 2.67–2.58 (m, 1H), 2.49 (dd, J = 13.1, 10.8 Hz, 1H), 2.10–1.99 (m, 4H), 1.83–1.74 (m, 1H), 1.49–1.41 (m, 10H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 154.6, 79.8, 68.6, 64.9, 47.1, 45.9, 37.4, 32.8, 28.3, 25.8, 21.1, 18.2, -5.5. MS (ESI): m/z 410 $[M+Na]^+$. HRMS (ESI): calcd for $C_{20}H_{16}O_2Na$: 410.2339; found: 410.2339.

***tert*-Butyl 3-acetoxy-5-(hydroxymethyl)piperidine-1-carboxylate (30)**: To a solution of compound **29** (10.3 g, 26.6 mmol) in THF (25 mL) cooled to 0 °C, TBAF (1M in THF, 27 mL, 27 mmol) was added. The reaction mixture was allowed to warm to rt and stirred for 12 h. The solvent was evaporated under reduced pressure to afford the crude compound which was purified by column chromatography on silica gel (EtOAc:hexane, 1:9) to afford the product **30** (6.5 g, 23.9 mmol) in 90% yield as a solid. TLC R_f: 0.2 (ethyl acetate:hexane, 3.0:7.0). M.p. 96-98 °C. IR (KBr): 3489, 2950, 2863, 1741, 1671, 1433, 1155, 1070, 1029, 863, 570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.78–4.70 (m, 1H), 4.05–3.47 (m, 4H), 3.30–2.69 (m, 2H), 2.14–2.00 (m, 5H), 1.94–1.81 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.0, 80.0, 68.2, 63.8, 47.8, 45.2, 36.9, 32.1, 28.2, 21.1. MS (ESI): m/z 296 $[M+Na]^+$. HRMS (ESI): calcd for $C_{13}H_{23}O_5NNa$: 296.1474; found: 296.1461.

***tert*-Butyl-3-acetoxy-5-(iodomethyl)piperidine-1-carboxylate (31)**: To a stirred solution of primary alcohol **30** (6.4 g, 23.4 mmol) in anhydrous dichloromethane (50 mL) under nitrogen atmosphere at 0 °C, were added imidazole (5.26 g, 35.1 mmol), triphenylphosphine (9.2 g, 35.1 mmol) and iodine (8.98 g, 35.1 mmol). The reaction mixture was stirred at 0 °C for 1 h. After completion of the reaction, dilute the reaction mixture with dichloromethane (50 mL) and the excess iodine was removed by washing with sat. aq. $Na_2S_2O_3$ solution (50 mL) and the phases were separated. The aq layer was extracted with dichloromethane (50 mL), the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 0.2:9.8) to afford the product **31** (7.88 g, 20.6 mmol) in 88% yield as a viscous oil. TLC R_f: 0.2 (ethyl acetate:hexane, 0.2:9.8). IR (KBr): 2968, 2855, 1735, 1683, 1415, 1248, 1155, 1032, 879 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.84–4.66 (m, 1H), 4.08–3.79 (m, 2H), 3.15 (d, J = 6.3 Hz, 2H), 2.99–2.49 (m, 2H), 2.20 (dt, J = 12.7, 4.0 Hz, 1H), 2.06 (s, 3H), 1.86–1.69 (m, 1H), 1.47 (s, 9H), 1.40–1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 154.6, 80.3, 67.9, 48.5, 47.5, 36.7, 36.4, 28.4, 21.2, 8.7. MS(ESI): m/z 406 $[M+Na]^+$. HRMS (ESI): calcd for $C_{13}H_{22}O_4NNaI$: 406.0491; found: 406.0492.

***tert*-Butyl-3-acetoxy-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)piperidine-1-carboxylate (20)**: To a suspension of CuI (38 mg, 0.2 mmol), LiO^tBu (3.2 g, 40.2 mmol) and bis(pinacolato)diboron (10.15 g, 40.0 mmol) in tetrahydrofuran (40 mL) was added the solution of alkyl iodide **31** (7.7 g, 20.1 mmol) in tetrahydrofuran (30 mL). The resulting reaction mixture was stirred vigorously at 25 °C for 18 h. The reaction mixture was then diluted with ethyl acetate (1 mL) and filtered through a pad of Celite. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc:hexane, 0.5:9.5) to afford the product **20** (6.7 g, 17.68 mmol) in 88% yield as a viscous oil. TLC R_f: 0.2 (ethyl acetate:hexane, 0.2:9.8). IR (neat): 2977, 2931, 1741, 1696, 1418, 1371, 1237, 1150, 1034, 873 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.74–4.63 (m, 1H), 4.32–4.10 (m, 1H), 4.08–3.93 (m, 1H), 2.54 (t, J = 11.2 Hz, 1H), 2.31 (t, J = 11.2 Hz, 1H), 2.23–2.11 (m, 1H), 2.04 (s, 3H), 1.88–1.73 (m, 1H), 1.45 (s, 9H), 1.25 (s, 12H), 1.16–1.06 (m, 1H), 0.8–0.7 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 154.5, 83.2, 79.7, 68.6, 50.3, 46.5, 38.7, 31.1, 28.4, 24.8, 21.2, 15.9. MS (ESI): m/z 406 $[M+Na]^+$. HRMS (ESI): calcd for $C_{19}H_{34}BO_6NNa$: 406.2377; found: 406.2397.

(6*R*)-2,2,6-Trimethyl-1-oxaspiro[2.5]octan-4-one (34): To a mixture of (*R*)-pulegone **33** (15.22 g, 100 mmol) and aq H_2O_2 (30%, 56.7 mL, 500 mmol) in methanol (300 mL) cooled at 15 °C was added aq LiOH (0.5 M, 20 mL) in a dropwise manner over a period of 15 mins. Stirring was continued for 4 h at 20 °C. The reaction mixture was then poured into brine solution (150 mL) and the aq layer was extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with water (100 mL), brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 0.5:9.5) to afford the epoxide **34** as a 1:1 mixture of diasteromers (15.96 g, 95.0 mmol) in 95% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 1:9). IR (KBr): 2958, 2872, 1721, 1116, 1032, 881, 605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.57 (m, 1H), 2.41–2.36 (m, 3H), 2.19–2.12 (m, 1H), 2.04–1.93 (m, 5H), 1.79–1.68 (m, 2H), 1.45–1.39 (m, 8H), 1.18 (s, 3H), 1.17 (s, 3H), 1.04 (d, J = 6.3 Hz, 3H), 1.02 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 206.1, 69.9, 69.8, 63.0, 62.9, 51.0, 49.2, 33.7, 32.6, 30.3, 29.8, 29.6, 25.9, 21.7, 19.6, 19.4, 19.3, 19.0, 18.6. MS (ESI): m/z 191 $[M+Na]^+$. HRMS (ESI): calcd for $C_{20}H_{16}O_2Na$: 191.1048; found: 191.1049

(5*R*)-5-Methyl-2-(phenylthio)cyclohexanone (35): To a suspension of sodium hydride (60% in mineral oil, 5.7 g 142.5 mmol) in anhydrous THF (140 mL) cooled at 0 °C was added a solution of thiophenol (14.5 mL, 142.5 mmol) in anhydrous THF (140 mL). After the evolution of hydrogen had ceased, the mixture was stirred at room temperature for 0.5 h and a solution of diastereomeric mixture of pulegone epoxide **34** (15.86 g, 94.4 mmol) in anhydrous THF (95 mL) was added. The resulting mixture was then refluxed for 24 h, cooled to rt and quenched with saturated aq NH_4Cl (100 mL). The layers were separated and the aq layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 0.5:9.5) to afford the product **35** as an inseparable mixture of diasteromers in 1:3 ratio (17.65 g, 80.24 mmol) in 85% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 0.5:9.5). ^1H NMR (500 MHz, $CDCl_3$) (Asterisk mark indicates signals for the minor isomer) δ 7.42–7.37 (m, 4H), 7.31–7.22 (m, 6H), 3.86* (dd, J = 11.3, 5.8 Hz, 1H), 3.76–3.70 (m, 1H), 2.79 (dd, J = 13.7, 12.2 Hz, 1H), 2.71–2.67* (m, 2H), 2.37–2.28* (m, 1H), 2.28–2.20 (m, 2H), 2.18–2.09 (m, 2H), 2.05–1.99* (m, 1H), 1.95–1.87 (m, 1H), 1.80–1.76* (m, 1H), 1.72–1.65 (m, 2H), 1.22–1.13 (m, 1H), 1.06 (d, J = 6.5 Hz, 3H), 1.03* (d, J = 6.5 Hz, 3H). MS (ESI): m/z 221 $[M+H]^+$. HRMS (ESI): calcd for $C_{20}H_{16}O_2Na$: 221.1000; found: 221.0995.

(*R*)-5-Methylcyclohex-2-enone (11): To stirred solution of sulfide **35** (17.55 g, 79.8 mmol) in DCM (160 mL) cooled at -78 °C was added mCPBA (70 wt%, 19.6 g, 79.8 mmol). After 10 min the reaction mixture was diluted with saturated aq Na_2SO_3 (50 mL). The layers were separated and the aq layer was extracted with DCM (2 x 50 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (50 mL), water (50 mL), brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude sulfoxide. Which without further purification and characterization was taken ahead to the next step. The crude sulfoxide was dissolved in CCl_4 (800 mL) and $CaCO_3$ (790 mg, 7.9 mmol) was added and the mixture was refluxed for 24 h. The reaction mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure to afford the crude compound. Distillation under reduced pressure afforded enone **11** (b.p. 85–87 °C, 20-22 torr, 5.44 g, 49.45 mmol) in 62% yield as an oil. $[\alpha]_D^{20}$ = -89.5 (*c* 2.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (ddd, J = 10.1, 5.5, 2.6 Hz, 1H), 6.06–5.97 (m, 1H), 2.52–2.36 (m, 2H), 2.29–2.17 (m, 1H), 2.17–1.99 (m, 2H), 1.08 (d, J = 6.5 Hz, 3H). MS (ESI): m/z 111 $[M+H]^+$.

(*R*)-2-Iodo-5-methylcyclohex-2-enone (19): To a solution of I_2 (12.4 g, 48.54 mmol) and pyridine (3.9 mL, 48.54 mmol) in DCM (50 mL) cooled at 0 °C was added a solution of enone **11** (5.34 g, 48.54 mmol) in DCM (50 mL). The mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and stirred further for a period of 2 h. The reaction mixture was quenched with HCl (1 N, 50 mL). The layers were separated and the aq layer was extracted with DCM (2 x 50 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$ solution (50 mL), brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 0.3:9.7) to afford the product **19** (10.23 g, 43.69 mmol) in 90% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 0.3:9.7). $[\alpha]_D^{20}$ = -80.2 (*c* 1.0, $CHCl_3$); IR (KBr): 2919, 1678, 1587, 1450, 1408, 1117, 1016, 875, 546 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, J = 5.9, 3.0 Hz, 1H), 2.76 (dd, J = 12.1, 1.6 Hz, 1H), 2.50–2.41 (m, 1H), 2.34–2.25 (m, 2H), 2.21–2.11 (m, 1H), 1.07 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 158.5, 103.5, 45.1, 38.0, 30.4, 20.7. MS (ESI): m/z 258 $[M+Na]^+$. HRMS (ESI): calcd for $zC_{20}H_{16}O_2Na$: 236.9776; found: 236.9774.

(3*S*,5*R*)-*tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(((*S*)-2-(4-methylphenylsulfonamido)-3-phenylpropanoyl)oxy)piperidine—carboxylate (37) & (3*R*,5*S*)-*tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(((*S*)-2-(4-methylphenylsulfonamido)-3-phenylpropanoyl)oxy) piperidine—carboxylate (38): To a stirred solution of secondary alcohol **28** (1.77 g, 5.12 mmol) in anhydrous dichloromethane (10 mL) was added pyridine (0.8 mL, 10.25 mmol) followed by solution of acid chloride **36** (2.6 g, 7.68 mmol) in anhydrous dichloromethane (10 mL) at 0 °C. After 6 h, the reaction mixture was quenched

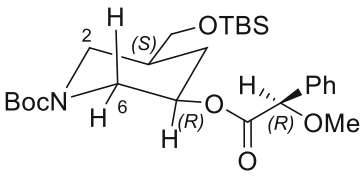
with saturated aq NH_4Cl (20 mL) and the phases were separated. The aq layer was extracted with dichloromethane (20 mL), the combined organic layers were washed with water (300 mL), brine (300 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to afford products **37** and **38** (3 g, 4.63 mmol) in 90% yield as a solid. TLC R_f: 0.2 (ethyl acetate:hexane, 1:9).

Compound 37: M.p. 90-92 °C. $[\alpha]_D^{20}$ = -9.3 (*c* 1.0, $CHCl_3$); IR (KBr): 3540, 2937, 2861, 1699, 1428, 1158, 1095, 840, 555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.31–7.19 (m, 5H), 7.12–7.05 (m, 2H), 5.06 (d, *J* = 9.3 Hz, 1H), 4.43–4.31 (m, 1H), 4.17 (q, *J* = 6.6 Hz, 1H), 4.06 (d, *J* = 11.0 Hz, 1H), 3.97 (bs, 1H), 3.46 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.37 (bs, 1H), 3.09–2.93 (m, 2H), 2.41 (s, 3H), 2.37–2.21 (m, 2H), 1.81–1.69 (m, 1H), 1.70–1.59 (m, 2H), 1.45 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 154.3, 143.9, 136.7, 134.8, 129.7, 129.5, 128.5, 127.2, 127.1, 80.0, 70.0, 64.8, 56.5, 46.9, 39.5, 37.4, 32.5, 28.3, 25.8, 21.4, 18.2, -5.5. MS (ESI): m/z 669 $[M+Na]^+$. HRMS (ESI): calcd for $C_{33}H_{50}N_2O_7NaSSi$: 669.3006; found: 669.2999.

Compound 38: M.p. 92-94 °C. $[\alpha]_D^{20}$ = +6.7 (*c* 1.0, $CHCl_3$); IR (KBr): 3327, 2933, 2857, 1726, 1700, 1424, 1260, 1085, 840,559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.25–7.21 (m, 5H), 7.12–7.04 (m, 2H), 5.05 (d, *J* = 9.4 Hz, 1H), 4.51–4.36 (m, 1H), 4.17 (dt, *J* = 9.3, 6.2 Hz, 1H), 4.05 (d, *J* = 12.7 Hz, 1H), 4.00–3.87 (m, 1H), 3.48 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.43–3.35 (m, 1H), 3.08–2.92 (m, 2H), 2.40 (s, 3H), 2.38–2.23 (m, 2H), 1.76–1.61 (m, 2H), 1.47–1.42 (m, 10H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 154.4, 143.5, 136.7, 134.8, 129.6, 129.4, 128.6, 127.3, 127.1, 80.0, 70.0, 64.9, 56.6, 47.2, 39.6, 37.4, 32.5, 28.3, 25.8, 25.6, 21.5, 18.2, -5.5. MS (ESI): m/z 669 $[M+Na]^+$. HRMS (ESI): calcd for $C_{33}H_{50}N_2O_7NaSSi$: 669.3006; found: 669.2990.

(3*S*,5*R*)-*tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-hydroxypiperidine-1-carboxylate (39): To a stirred solution of ester **37** (1.15 g, 1.78 mmol) in tetrahydrofuran (2 mL) was added aq NaOH solution (5N, 2 mL) at 25 °C. The mixture was stirred at rt for 4 h. The reaction mixture was diluted with water (10 mL) and the phases were separated. The aq layer was extracted with dichloromethane (20 mL), the combined organic layers were washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 4:6) to afford the product **39** (600 mg, 1.74 mmol) in 98% yield as a solid. TLC R_f: 0.2 (ethyl acetate:hexane, 4:6). $[\alpha]_D^{20}$ = +0.3 (*c* 1.0, $CHCl_3$); M.p. 88-90 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 4.31–4.14 (m, 1H), 4.08 (dd, *J* = 13.2, 4.3 Hz, 1H), 3.71–3.61 (m, 1H), 3.53 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.40–3.40 (m, 1H), 2.52– 2.36 (m, 2H), 2.09–1.93 (m, 1H), 1.79–1.59 (m, 2H), 1.44 (s, 9H), 1.18–1.05 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 79.7, 66.3, 65.3, 50.5, 47.3, 38.1, 36.1, 28.4, 25.8, 18.2, -5.5. MS (ESI): m/z 368 $[M+Na]^+$. HRMS (ESI): calcd for $C_{17}H_{35}NO_4NaSi$: 368.2233; found: 368.2233.

(*R*)-Mandelate ester of compound 39:



(3*S*,5*R*)-*tert*-butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((*R*)-2-methoxy-2-phenylacetoxy)piperidine-1-carboxylate: To a solution of alcohol **39** (15 mg, 0.043 mmol) in dichloromethane (0.5 mL) cooled at 0 °C was added (*R*)-methoxyphenylacetic acid (9 mg, 0.05 mmol), DMAP (2 mg, 20 mol%) and EDC.HCl (8 mg, 0.051 mmol). The reaction mixture was stirred at rt for 2 h. After complete consumption of starting material, the reaction mixture was diluted with dichloromethane (2 mL) and H_2O (2 mL). The layers were separated and the aq layer was extracted with dichloromethane (2x5 mL). The combined organic layers were sequentially washed with satd aq $NaHCO_3$ (5 mL), 1 N HCl (5 mL), H_2O (2x5 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the corresponding ester in 95% yield as a liquid. TLC R_f: 0.2 (ethyl acetate:hexane, 1:9).

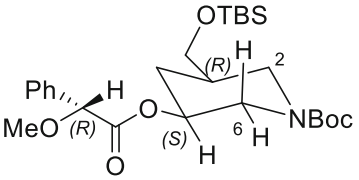
^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 2H), 7.38–7.30 (m, 3H), 4.83–4.66 (m, 2H), 4.13–3.94 (m, 2H), 3.51 dd, *J* = 10.0, 4.8 Hz, 1H), 3.47–3.34 (m, 4H), 2.56–2.36 (m, 2H), 2.12–2.00 (m, 1H), 1.83–1.68 (m, 1H), 1.42 (s, 9H), 1.33–1.28 (m, 1H), 0.88 (s, 9H), 0.03 (s, 6H).

NOTE: The absolute configuration of carbinol stereogenic center in compound **39** was established as '*R*'. The C-6 equatorial and axial protons of (*R*)-mandelate ester of **39** appear at upfield region at δ 4.05 (1H) and 2.47 (1H) respectively.

(3*R*,5*S*)-*tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-hydroxypiperidine-1-carboxylate (*epi*-39): Compound **38** (1.15 g, 1.78 mmol) was converted to the secondary alcohol ***epi*-39** (600 mg, 1.74 mmol) in 98% yield following the procedure detailed for the preparation of

alcohol **39**. TLC R_f: 0.2 (ethyl acetate:hexane, 4:6). $[\alpha]_D^{20}$ = -0.3 (*c* 1.0, $CHCl_3$); IR (KBr): 3473, 2985, 2857, 1676, 1437, 1157, 1092, 1041, 841, 591 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{35}NO_4NaSi$: 368.2233; found: 368.2237.

(*R*)-Mandelate ester of compound *epi*-39:



z(3*R*,5*S*)-*tert*-butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((*R*)-2-methoxy-2-phenylacetoxy)piperidine-1-carboxylate: Compound ***epi*-39** (15 mg, 0.043 mmol) was converted to the mandelate ester of ***epi*-39** in 95% yield following the procedure detailed for the preparation of mandelate ester **39**. TLC R_f: 0.2 (ethyl acetate:hexane, 1:9). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.38 (m, 2H), 7.38–7.30 (m, 3H), 4.84–4.68 (m, 2H), 4.27–4.11 (m, 1H), 4.10–3.97 (m, 1H), 3.47–3.33 (m, 5H), 2.63 (dd, *J* = 12.6, 10.3 Hz, 1H), 2.43 (t, *J* = 12.6 Hz, 1H), 1.96–1.83 (m, 1H), 1.81–1.65 (m, 1H), 1.44 (s, 9H), 1.33–1.27 (m, 1H), 0.86 (s, 9H), -0.01 (s, 6H).

NOTE: The absolute configuration of carbinol stereogenic center in compounds ***epi*-39** was established as '*S*'. The C-6 equatorial and axial protons of (*R*)-mandelate ester of ***epi*-39** appear at downfield region at δ 4.18 (m, 1H) and 2.63 (dd, 1H), respectively.

(3*S*,5*R*)-*tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((*tert*-butyldiphenylsilyl)oxy)piperidine-1-carboxylate (40): To a stirred solution of alcohol **39** (430 mg, 1.25 mmol) in anhydrous dichloromethane (24 mL) was added imidazole (2.6 g, 17.4 mmol) followed by TBDPSCl (3.6 mL, 13.9 mmol) at 25 °C. After 45 min, the reaction mixture was quenched with saturated aq NH_4Cl (15 mL) and the phases were separated. The aq layer was extracted with dichloromethane (25 mL), the combined organic layers were washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 0.2:9.8) to afford the product **40** (700 mg, 1.2 mmol) in 96% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 0.5:9.5). $[\alpha]_D^{20}$ = +2.8 (*c* 2.0, $CHCl_3$); IR (neat): 2931, 2857, 1696, 1467, 1156, 1106, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.62 (m, 4H), 7.45–7.34 (m, 6H), 4.02 (dd, *J* = 13.1, 3.6 Hz, 1H), 3.68–3.53 (m, 1H), 3.39 (d, *J* = 4.7 Hz, 2H), 2.56 (dd, *J* = 12.6, 10.1 Hz, 1H), 2.31 (dd, *J* = 12.6, 11.3 Hz, 1H), 2.00–1.65 (m, 1H), 1.56–1.44 (m, 1H), 1.37 (s, 9H), 1.06 (s, 9H), 0.92– 0.82 (m, 10H), -0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) (Asterisk mark indicates signals for the rotamer) δ 154.6, 135.7, 134.2, 133.9*, 129.7, 129.6*, 127.6, 127.5*, 79.4, 68.2, 65.3, 51.2, 50.3*, 47.1, 45.6*, 37.6, 37.1, 28.3, 26.9, 25.9, 19.2, 18.2, -5.5. MS (ESI): m/z 584 $[M+H]^+$. HRMS (ESI): calcd for $C_{33}H_{53}NO_4NaSi_2$: 606.3411; found: 606.3406.

(3*R*,5*S*)-*tert*-Butyl 3-((*tert*-butyldiphenylsilyl)oxy)-5-(hydroxymethyl)piperidine-1-carboxylate (41): To a stirred solution of silyl ether **40** (641 mg, 1.1 mmol) in methanol:tetrahydrofuran (9:1, 10 mL) was added PPTS (25 mg, 0.1 mmol) at rt. The reaction mixture was stirred overnight. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 3:7) to afford the product **41** (450 mg, 0.99 mmol) in 90% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 3:7). $[\alpha]_D^{20}$ = +5.3 (*c* 1.0, $CHCl_3$); IR (neat): 3447, 2932, 2858, 1692, 1426, 1156, 1108, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.61 (m, 4H), 7.46–7.33 (m, 6H), 4.05–3.78 (m, 2H), 3.71–3.62 (m, 1H), 3.57–3.43 (m, 2H), 2.78 (dd, *J* = 12.8, 9.0 Hz, 1H), 2.60 (dd, *J* = 12.8, 10.5 Hz, 1H), 1.92–1.77 (m, 1H), 1.45–1.18 (m, 11H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 135.7, 133.8, 129.7, 127.6, 79.6, 67.9, 64.9, 51.3, 45.7, 37.4, 36.5, 28.3, 26.9, 19.1. MS (ESI): m/z 492 $[M+Na]^+$. HRMS (ESI): calcd for $C_{27}H_{39}NO_4NaSi$: 492.2546; found: 492.2539.

(3*R*,5*S*)-*tert*-Butyl 3-((*tert*-butyldiphenylsilyl)oxy)-5-(iodomethyl)piperidine-1-carboxylate (42): Compound **41** (370 mg, 0.784 mmol) was converted to the alkyl iodide **42** (400 mg, 0.69 mmol) in 88% yield following the procedure detailed for the preparation of iodide **31**. TLC R_f: 0.2 (ethyl acetate:hexane, 0.2:9.8). $[\alpha]_D^{20}$ = -5.8 (*c* 1.0, $CHCl_3$); IR (neat): 2931, 2857, 1695, 1423, 1157, 1108, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4H), 7.46–7.34 (m, 6H), 4.16–3.90 (m, 2H), 3.72–3.56 (m, 1H), 3.03 (d, *J* = 6.3 Hz, 2H), 2.76–2.26 (m, 2H), 2.09–1.83 (m, 1H), 1.54–1.31 (m, 10H), 1.29–1.20 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 135.7, 133.9, 129.8, 127.7, 79.8, 67.7, 50.9, 48.7, 40.7, 36.3, 28.3, 26.9, 19.1, 8.9. MS (ESI): m/z 602 $[M+Na]^+$. HRMS (ESI): calcd for $C_{27}H_{38}NO_3INaSi$: 602.1563; found: 602.1570.

(*R*)-*tert*-Butyl 3-((*tert*-butyldiphenylsilyl)oxy)-5-methylenepiperidine-1-carboxylate (44): To the suspension of KO^tBu (56 mg, 0.5 mmol) at 25 °C was added a solution of iodo compound **42** (284 mg, 0.49 mmol) in anhydrous dimethoxyethane (2 mL). After 45 min, the reaction mixture was quenched with saturated aq NH_4Cl (10 mL) and the phases were separated. The aq layer was extracted with dichloromethane (10 mL), the combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 0.1:9.9) to afford the product **44** (200 mg, 0.45 mmol) in 92% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 0.1:9.9). $[\alpha]_D^{20}$ = +3.8 (*c* 2.0, $CHCl_3$); IR (neat): 2961, 2857, 1697, 1421, 1169, 1112, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.62 (m, 4H), 7.45–7.35 (m, 6H), 4.84 (s, 1H), 4.64 (s, 1H),

4.12–3.89 (m, 1H), 3.80–3.68 (m, 2H), 3.63 (d, J = 13.7 Hz, 1H), 3.23–3.07 (m, 1H), 2.41–2.24 (m, 1H), 2.19–2.11 (m, 1H), 1.39 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) (Asterisk mark indicates signals for the rotamer) δ 154.5, 139.7, 135.7, 134.1*, 133.7, 129.7, 127.6, 127.5*, 112.0, 79.5, 68.2, 50.4, 48.8, 41.9, 28.3, 26.9, 19.1. MS (ESI): m/z 474 $[M+Na]^+$. HRMS (ESI): calcd for $C_{27}H_{37}NO_3NaSi$: 474.2440; found: 474.2437.

(*R*)-*tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxopiperidine-1-carboxylate (45): To a solution of alcohol ***epi*-39** (550 mg, 1.59 mmol) in anhydrous dichloromethane (3 mL) was added Dess-Martin periodinane (1.02 g, 2.4 mmol) and the mixture was stirred at room temperature for 5 h. Diluted the reaction mixture with dichloromethane (10 mL), the reaction mixture was filtered, the filtrate was washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude diketone which was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to afford the product **45** (520 mg, 1.52 mmol) in 96% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 1:9). $[\alpha]_D^{20}$ = -3.5 (c 2.0, $CHCl_3$); IR (neat): 2937, 2860, 1706, 1468, 1160, 1004, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (d, J = 18.0 Hz, 1H), 3.96–3.76 (m, 2H), 3.65–3.50 (m, 2H), 3.22 (dd, J = 13.2, 9.0 Hz, 1H), 2.51 (dd, J = 16.0, 5.0 Hz, 1H), 2.41–2.28 (m, 1H), 2.27–2.19 (m, 1H), 1.46 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 154.4, 80.5, 64.5, 54.4, 44.1, 41.2, 36.6, 28.3, 25.8, 18.2, -5.6. MS (ESI): m/z 366 $[M+Na]^+$.

(3*R*,5*R*)-*tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-hydroxypiperidine-1-carboxylate (46): To a cooled (-78 °C) solution of compound **45** (480 mg, 1.4 mmol) in anhydrous tetrahydrofuran (3 mL) was added a solution of L-Selectride (1 M, 1.5 mL, 1.5 mmol) under nitrogen atmosphere and the mixture was gradually warmed to 0 °C and stirred for 1 h. The reaction mixture was further allowed to warm to rt and stirred for 1 h. The reaction mixture was quenched with a saturated aq NH_4Cl (5 mL). The layers were separated and the aq layer was extracted with ethyl acetate (10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc:hexane, 3:7) to afford the product **46** (439 mg, 1.27 mmol) in 91% yield as a solid. TLC R_f: 0.2 (ethyl acetate:hexane, 3:7). $[\alpha]_D^{20}$ = -4.7 (c 1.0, $CHCl_3$); M.p. 70-72 °C. IR (KBr): 3430, 2933, 2860, 1684, 1429, 1158, 1004, 840, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.05–3.79 (m, 3H), 3.48 (dd, J = 10.1, 4.9 Hz, 1H), 3.43–3.29 (m, 1H), 2.94 (d, J = 13.1 Hz, 1H), 2.60 (dd, J = 13.1, 10.1 Hz, 1H), 2.11–1.93 (m, 2H), 1.80–1.73 (m, 1H), 1.42 (s, 9H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 79.8, 65.3, 64.9, 50.0, 47.8, 33.6, 33.4, 28.4, 25.9, 18.2, -5.5. MS (ESI): m/z 368 $[M+Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{35}NO_4NaSi$: 368.2233; found: 368.2240

(3*R*,5*R*)-*tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((tert-butyldiphenylsilyl)oxy)piperidine-1-carboxylate (47): Compound **46** (400 mg, 1.16 mmol) converted to TBDPS ether **47** (640 mg, 1.1 mmol) in 96% yield following the procedure detailed for the preparation of **40**. TLC R_f: 0.2 (ethyl acetate:hexane, 0.5:9.5). $[\alpha]_D^{20}$ = +1.4 (c 2.0, $CHCl_3$); IR (KBr): 2956, 2856, 1696, 1427, 1111, 1021, 837, 609 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75–7.60 (m, 4H), 7.45–7.32 (m, 6H), 4.15–3.83 (m, 3H), 3.46–3.23 (m, 2H), 2.80 (d, J = 11.6 Hz, 1H), 2.65–2.48 (m, 1H), 2.25–2.16 (m, 1H), 1.71–1.58 (m, 1H), 1.43 (s, 9H), 1.31–1.19 (m, 1H), 1.07 (s, 9H), 0.86 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) (Asterisk mark denotes signals for the rotamer) δ 155.3, 155.0*, 136.0*, 135.7, 134.1, 134.0*, 129.6, 127.5, 79.3, 79.0*, 66.0, 65.4, 50.4, 49.6*, 47.2*, 45.7, 34.6, 33.7*, 33.2, 28.4, 27.0, 25.9, 19.3, 18.3, -5.4. MS (ESI): m/z 606 $[M+Na]^+$. HRMS (ESI): calcd for $C_{33}H_{53}NO_4NaSi_2$: 606.3411; found: 606.3395.

(3*R*,5*R*)-*tert*-Butyl 3-((*tert*-butyldiphenylsilyl)oxy)-5-(hydroxymethyl)piperidine-1-carboxylate (48): Silyl ether **47** (600 mg, 1.03 mmol) was deprotected to furnish primary alcohol **48** (435 mg, 0.927 mmol) in 90% yield following the procedure detailed for the preparation of **41**. TLC R_f: 0.2 (ethyl acetate:hexane, 3:7). $[\alpha]_D^{20}$ = +0.4 (c 1.0, $CHCl_3$); IR (neat): 3438, 2930, 2859, 1680, 1428, 1147, 1071, 704, 504 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.60 (m, 4H), 7.47–7.33 (m, 6H), 3.96–3.59 (m, 2H), 3.59–3.43 (m, 1H), 3.45–2.83 (m, 4H), 2.20–2.06 (m, 1H), 1.73–1.54 (m, 2H), 1.39 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 135.5, 133.9, 129.6, 127.5, 79.6, 65.5, 63.6, 50.9, 45.0, 34.7, 34.4, 28.2, 26.8, 19.1; MS (ESI): m/z 492 $[M+Na]^+$. HRMS (ESI): calcd for $C_{27}H_{39}NO_4NaSi$: 492.2546; found: 492.2550.

(3*R*,5*R*)-*tert*-Butyl 3-((*tert*-butyldiphenylsilyl)oxy)-5-(iodomethyl)piperidine-1-carboxylate (49): Primary alcohol **48** (400 mg, 0.85 mmol) was converted to the iodo compound **49** (434 mg, 0.75 mmol) in 88% yield following the procedure detailed for the preparation of **31**. TLC R_f: 0.2 (ethyl acetate:hexane, 0.2:9.8). $[\alpha]_D^{20}$ = -6.1 (c 1.0, $CHCl_3$); IR (neat): 2930, 2858, 2363, 1692, 1424, 1156, 1106, 702, 505 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.62 (m, 4H), 7.47–7.34 (m, 6H), 4.27–3.80 (m, 3H), 3.12–2.39 (m, 4H), 2.20–2.07 (m, 1H), 1.82–1.66 (m, 1H), 1.45 (s, 9H), 1.23–1.12 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 135.7, 133.8, 129.7, 127.6, 79.7, 65.8, 50.2, 48.6, 38.5, 32.6, 28.4, 26.9, 19.2, 10.2. MS (ESI): m/z 602 $[M+Na]^+$. HRMS (ESI): calcd for $C_{27}H_{38}NO_3INaSi$: 602.1563; found: 602.1569.

(3*R*,5*S*)-*tert*-Butyl 3-((*tert*-butyldiphenylsilyl)oxy)-5-(((*R*)-4-methyl-6-oxocyclohex-1-en-1-yl)methyl)piperidine-1-carboxylate (50): To a solution of 9-BBN dimer (40 mg, 0.153 mmol) in anhydrous tetrahydrofuran (0.5 mL) was added a solution of compound **44** (70 mg, 0.153 mmol) in anhydrous tetrahydrofuran (1 mL) at rt and the mixture was heated at

reflux for 2 h. In another flask alkenyl iodide **19** (36 mg, 0.153 mmol) and $PdCl_2(dppf).CH_2Cl_2$ (16 mg, 0.02 mmol) were dissolved in a mixture of tetrahydrofuran (2 mL) and aq. NaOH (15%, 2 mL) at rt. To this solution was added the above solution containing the boron reagent and the resultant mixture was stirred at the same temperature for 30 min. After dilution with EtOAc, the reaction mixture was quenched with aq. NH_4Cl (5 mL). The aq layer was extracted with ethyl acetate (5 mL), the combined organic layers were washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to afford the product **50** (70 mg, 0.13 mmol) in 85% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 1:9). $[\alpha]_D^{20}$ = -29.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.60 (m, 4H), 7.46–7.32 (m, 6H), 6.66–6.49 (m, 1H), 4.12–3.72 (m, 2H), 3.63–3.53 (m, 1H), 2.51 (t, *J* = 11.4 Hz 1H), 2.43 (dd, *J* = 15.8, 3.5 Hz, 1H), 2.39–2.20 (m, 2H), 2.19–1.91 (m, 6H), 1.51–1.41 (m, 2H), 1.36 (s, 9H), 1.05 (s, 9H), 1.02 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 154.3, 145.9, 136.6, 135.6, 133.9, 129.6, 127.6, 79.3, 68.2, 51.1, 48.1, 46.4, 40.8, 34.3, 33.6, 33.3, 30.5, 28.3, 26.9, 21.1, 19.1.

MS (ESI): m/z 584 $[M+Na]^+$. HRMS (ESI): calcd for $C_{34}H_{47}NO_4NaSi$: 584.3172; found: 584.3181.

(3*R*,5*S*)-*tert*-Butyl 3-hydroxy-5-(((*R*)-4-methyl-6-oxocyclohex-1-en-1-yl)methyl)piperidine-1-carboxylate (51): To a stirred solution of compound **50** (35 mg, 0.064 mmol) in anhydrous tetrahydrofuran (2 mL) was added TBAF (1 M, 0.1 mL) at rt. The reaction mixture was stirred for 45 min at the same temperature. The solvent was removed under reduced pressure and the residual mass was purified by column chromatography (EtOAc/hexane, 4:6) to afford compound **51** (20 mg, 0.06 mmol) in 93% yield as an oil. TLC R_f: 0.2 (ethyl acetate:hexane, 4:6). $[\alpha]_D^{20}$ = -26.2 (*c* 0.25, $CHCl_3$); IR (neat): 3423, 2927, 1670, 1424, 1148, 1071, 889 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74–6.69 (m, 1H), 4.31–4.06 (m, 1H), 4.06–3.66 (m, 1H), 3.66–3.51 (m, 1H), 2.50 (dd, *J* = 15.4, 3.3 Hz, 1H), 2.46–2.37 (m, 2H), 2.26–1.96 (m, 7H), 1.71–1.66 (m, 2H), 1.43 (s, 9H), 1.05 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 154.6, 146.4, 136.7, 79.7, 66.7, 50.9, 49.4, 46.5, 40.5, 34.4, 34.0, 33.6, 30.6, 28.4, 21.1. MS (ESI): m/z 346 $[M+Na]^+$. HRMS (ESI): calcd for $C_{18}H_{29}NO_4Na$: 346.1994; found: 346.1998.

(*S*)-*tert*-Butyl 3-(((*R*)-4-methyl-6-oxocyclohex-1-en-1-yl)methyl)-5-oxopiperidine-1-carboxylate (18): Alcohol **51** (17 mg, 0.0.54 mmol) was converted to the diketo compound **18** (15 mg, 0.05 mmol) in 92% yield following the procedure detailed for the preparation of **45**. TLC R_f: 0.2 (ethyl acetate:hexane, 1:9). $[\alpha]_D^{20}$ = -11.3 (*c* 0.9, $CHCl_3$); IR (KBr): 2958, 2927, 1627, 1417, 1164, 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75–6.69 (m, 1H), 4.0 (d, 18.0 Hz, 1H), 3.89 (d, *J* = 18.0 Hz, 1H), 3.74 (d, *J* = 11.7 Hz, 1H), 3.09 (dd, *J* = 11.7, 6.9 Hz, 1H), 2.55–2.38 (m, 3H), 2.28–2.04 (m, 7H), 1.46 (s, 9H), 1.06 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 199.4, 154.4, 147.4, 136.0, 80.5, 54.3, 46.5, 44.6, 34.4, 33.6, 30.6, 28.3, 28.1, 27.9, 21.1. MS (ESI): m/z 344 $[M+Na]^+$. HRMS (ESI): calcd for $C_{18}H_{27}NO_4Na$: 344.1838; found: 344.1845.

(3*R*,4a*R*,5*S*,8*R*,9a*S*)-*tert*-Butyl 3-methyl-1-oxodecahydro-1*H*-5,8-(epiminomethano)benzo[7]annulene-11-carboxylate (52) & (3*R*,4a*R*,5*R*,8*S*,9a*S*)-3-methyloctahydro-1*H*-5,8-(epiminomethano)benzo[7]annulene-1,6(2*H*)-dione (53): To a stirred solution of diketone **18** (10 mg, 0.03 mmol) in anhydrous DMSO (2 mL) was added aq HCl (35 wt%, 0.10 mL). The resulting mixture was heated at 60 °C for 4 h. After cooling, the reaction mixture was diluted with ether (10 mL), water (10 mL) and the layers were separated. The aq layer was extracted with ether (2 x 5 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc:hexane, 0.5:9.5) to afford the product **52** as rotamers in 1:1 ratio (4.4 mg, 0.0137 mmol) in 46% yield as a viscous oil. The aq layer was basified with aq $NaHCO_3$ (5 mL) and extracted with ether (2 x 5 mL) and the combined organic layers were washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the Boc deprotected compound **53** (1.6 mg, 0.0072 mmol) in 24% yield as a viscous oil.

Compound 52: TLC R_f: 0.2 (ethyl acetate:hexane, 1:9). ^{1}H NMR (500 MHz, $CDCl_3$) (Asterisk mark indicates signals for the minor rotamer) δ 4.57* (s, 1H), 4.40 (s, 1H), 3.56* (t, *J* = 1.7 Hz, 1H), 3.53 (t, *J* = 1.7, Hz, 1H), 3.47 (dd, *J* = 11.9, 4.0 Hz, 2H), 2.66–2.35 (m, 16H), 2.24–2.12 (m, 4H), 2.07–1.92 (m, 6H), 1.89–1.78 (m, 2H), 1.50 (s, 18H), 0.96–0.94 (m, 6H).

(3*R*,4a*R*,5*R*,8*S*,9a*S*)-3-methyloctahydro-1*H*-5,8-(epiminomethano)benzo[7]annulene-1,6(2*H*)-dione (53): To a stirred solution of tricyclic compound **52** (4.4 mg, 0.0137 mmol) in anhydrous DCM (0.3 mL) was added TFA (0.3 mL) at 0 °C and resultant reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by adding saturated aq $NaHCO_3$ (2 mL) and extracted with dichloromethane (2 x 5 mL). The combined organic layers were washed successively with water (2 mL), brine (2 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography on silica gel (EtOAc/hexane, 1:1) to afford the product **53** (2.6 mg, 0.0119 mmol) in 87% yield as gummy gel. TLC R_f: 0.2 (ethyl acetate:hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16 (d, *J* = 12.0 Hz, 1H), 3.08 (dd, *J* = 11.8, 4.7 Hz, 1H), 3.04 (s, 1H), 2.73 (td, *J* = 12.3, 4.0 Hz, 1H), 2.57 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.53–2.48 (m, 2H), 2.45–2.41 (m, 2H), 2.22–2.12 (m, 3H), 1.87 (td, *J* = 12.3, 3.8 Hz, 1H), 1.58 (d, *J* = 13.8 Hz, 1H), 1.50 (dd, *J* = 15.1, 12.3 Hz, 1H), 0.95 (d,

J = 7.2 Hz, 3H). MS (ESI): m/z 222 $[M+H]^+$. HRMS (ESI): calcd. for $C_{13}H_{20}O_2N$: 222.1495; found: 222.1489.

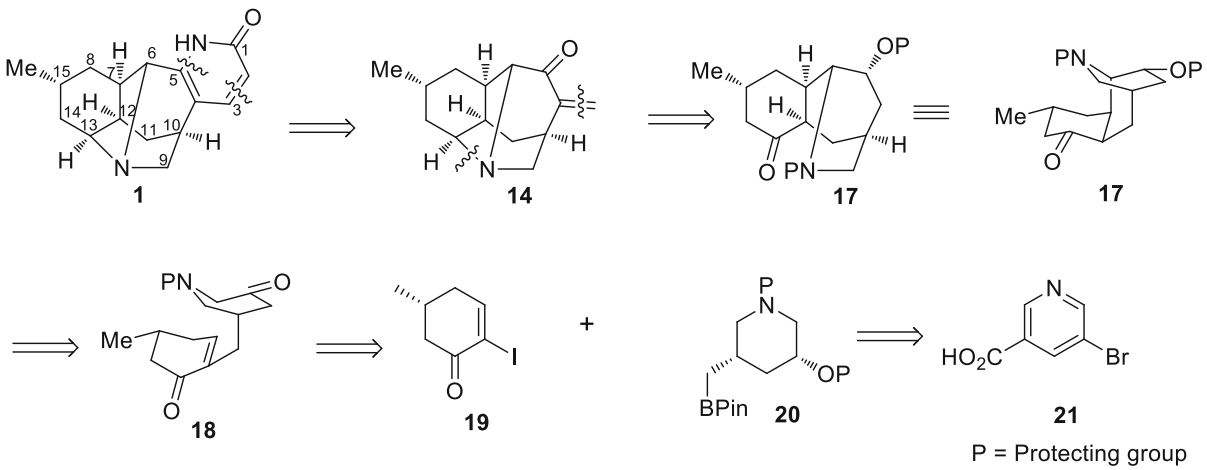
3. Results and Discussion

The retrosynthetic disconnection of lyconadin A is outlined in Scheme 2. The pyridone moiety of lyconadin A might be constructed from the unsaturated ketone **14** following Fukuyama's protocol.[8] We envisioned that ketone **14** might be obtained by C-N bond formation via stereoselective reduction of ketone **17** (C13 lyconadin numbering) to equatorial alcohol,[9] conversions to a nucleofuge, followed by intramolecular nucleophilic displacement and subsequent α-methylenation at C4. We proposed to synthesize keto alcohol derivative **17** from the unsaturated ketone **18** utilizing a Michael reaction. We surmised that the ketone **18** might be obtained from iodo cyclohexenone **19** and compound **20** using B-alkyl Suzuki coupling. We proposed to synthesize compound **20** from bromo pyridine derivative **21**.

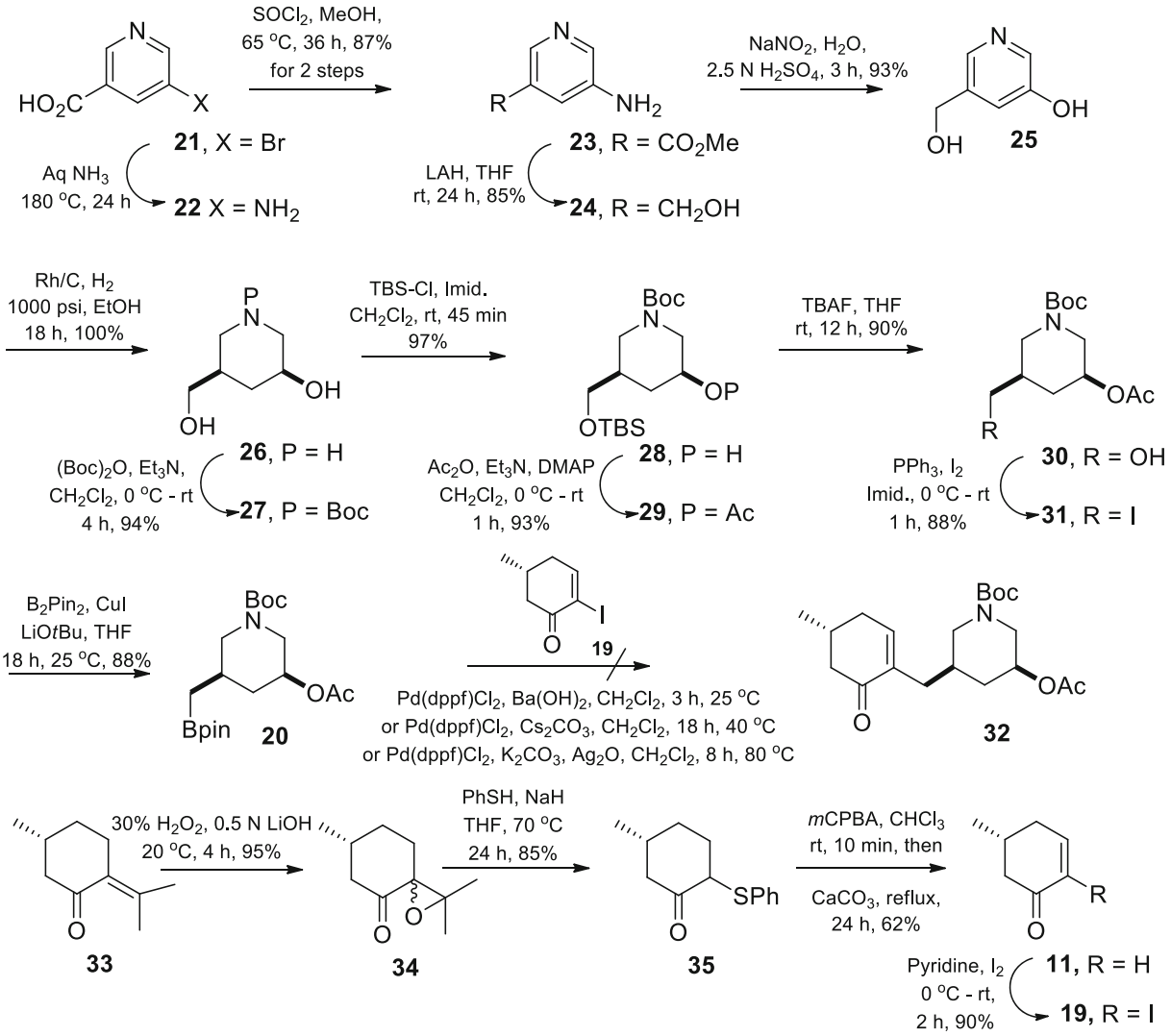
The synthesis of piperidine derivative **20** began from commercially available 5-bromo-nicotinic acid **21**, Scheme 3. Displacement of bromine by reaction with aq ammonia in a sealed vessel[10] afforded the amino compound **22** that was converted to the methyl ester **23**, using thionyl chloride and methanol. Reduction of the ester using LAH furnished the hydroxymethyl derivative **24**. Diazotization followed by hydrolysis furnished compound **25**, that on hydrogenation using Rh/C under high pressure, yielded racemic piperidine derivative **26**. Protection of the secondary amine as its carbamate **27**, followed by selective protection of the primary alcohol afforded alcohol **28**. The secondary carbinol was protected as its acetate **29**. Deprotection of the primary alcohol by cleavage of the silyl ether gave compound **30**. Iodo compound **31** was obtained straightforwardly by treatment of the alcohol with iodine, triphenylphosphine and imidazole.[11] Boronate **20** was obtained by a copper-catalyzed reaction of iodo compound **31** with B_2Pin_2.[12] Attempted coupling of boronate **20** with iodo compound **19**[13] however, failed to afford any of the desired product **32** (and its diastereoisomer) under a variety of reaction conditions. Probably, transmetalation of piperidinyl residue to alkenyl palladium did not occur. Iodo cyclohexenone **19** was prepared from (*R*)-pulegone **33** via intermediates **34**-**11**, following literature precedent.[14]

In parallel, the resolution of alcohol **28** was examined. Initial attempts at enzymatic resolution using *Daucus carota*[15] yielded a mixture of products, probably due to the instability of the substrate under the reaction conditions. Therefore, following Ikegami's protocol,[16] alcohol **28**, on treatment with acid chloride **36** in the presence of pyridine, furnished the two diastereomeric esters **37** and **38** that could be separated readily, Scheme 4. Hydrolysis of the esters afforded alcohols **39** and *epi*-**39**.[17]

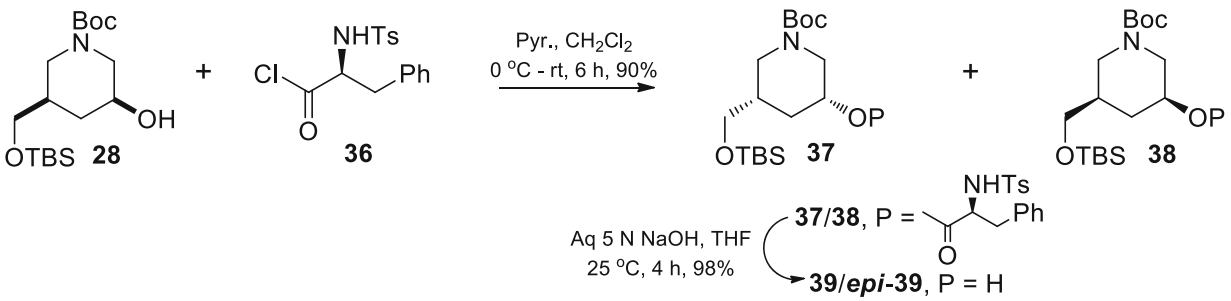
Alcohol **39** was converted to iodo compound **42** by a straightforward sequence of reactions. Thus the protection of the carbinol as its TBDPS ether **40**, followed by selective deprotection of the primary alcohol by cleavage of the TBS ether gave alcohol **41** that on treatment with iodine and triphenylphosphine furnished iodide **42**. With compound **42** being available, its alkylation[18] with



Scheme 2. Retrosynthetic disconnection of lyconadin A.



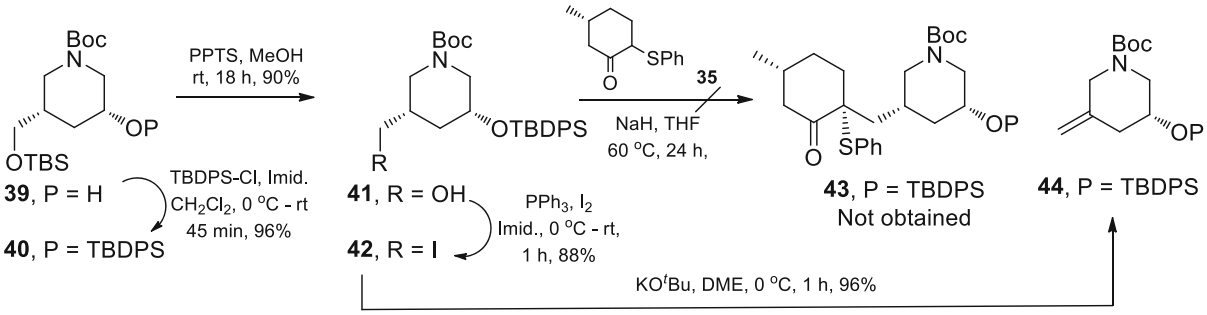
Scheme 3. Attempted coupling of iodo cyclohexenone **19** and boronate **20**.



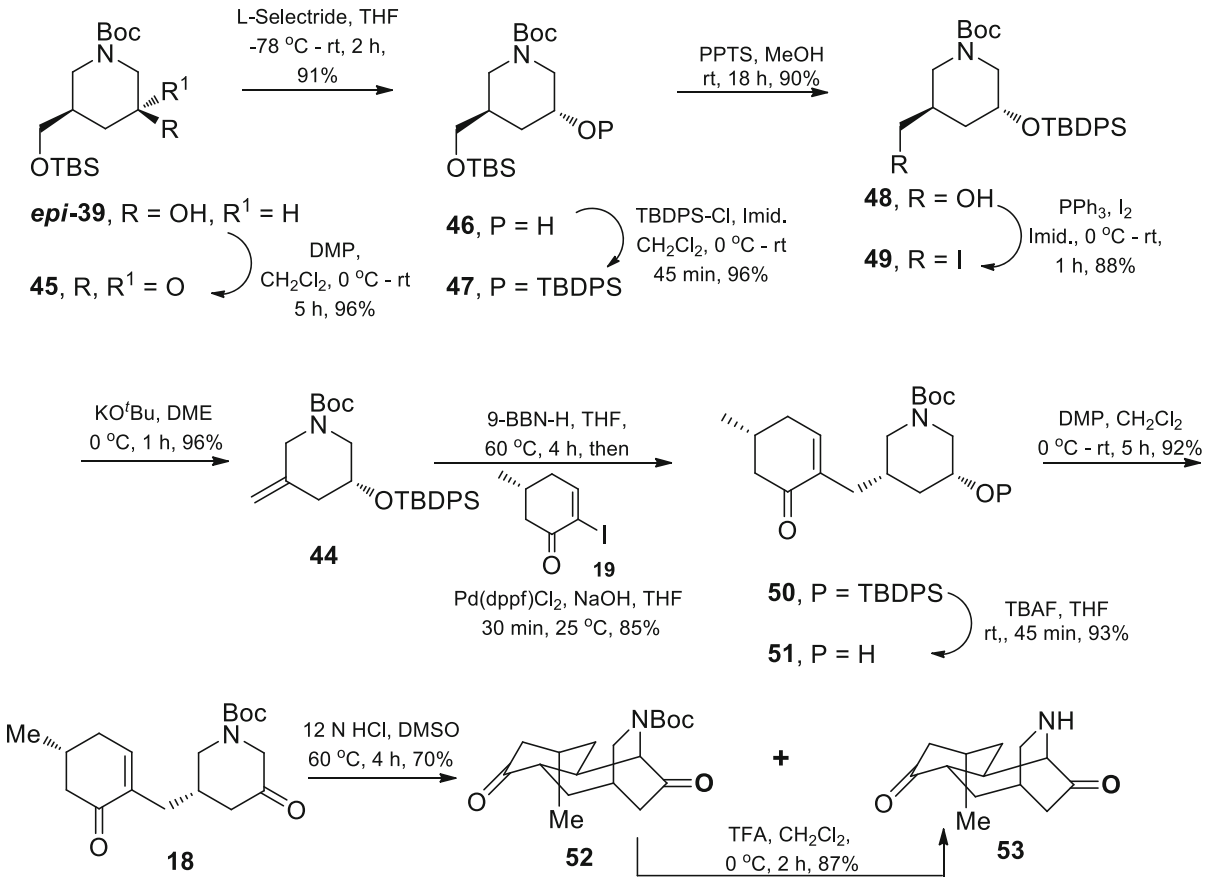
Scheme 4. Resolution of racemic alcohol **28**.

2-thiophenyl-5-methyl cyclohexanone **35**, an intermediate en route to alkenyl iodide **19**, from (*R*)-pulegone was investigated.

In the event, the reaction of sodium enolate of compound **35** with iodide **42** didn't afford any of the desired product **43** but the alkene **44**, Scheme 5. Though disappointing, the obtention of alkene **44** paved the way for attempting the Suzuki coupling utilizing the trialkyl boron derived from it and utilize alcohol *epi*-**39** as detailed below.



Scheme 5. Attempted alkylation of compound **35** with iodide **42**.



Scheme 6. Synthesis of the advanced intermediate **52**.

The alkene **44** was readily obtained by the treatment of iodide **42** with KO^{t}Bu in 96% yield. The alcohol *epi*-**39** was converted to alkene **44** following a straightforward sequence of reactions. Thus oxidation of the secondary alcohol afforded ketone **45**, that on reduction using L-selectride furnished alcohol **46**. Protection as its silyl ether **47**, selective deprotection of the primary alcohol to furnish compound **48**, followed by iodination yielded iodide **49**. Base promoted elimination gave alkene **44**. Hydroboration of alkene **44** with 9-BBN-H dimer gave the hydroboration product that on reaction with alkenyl iodide **19** cleanly afforded the coupling product **50**, Scheme 6.

Proceeding, the secondary alcohol **50** was deprotected by cleavage of the silyl ether to yield compound **51**, that on oxidation afforded ketone **18**. Ketone **18**, on treatment with aq HCl in DMSO underwent intramolecular Michael addition to yield carbamate **52** (46%) and the secondary amine **53** (24%) in a 2:1 ratio. Although axial protonation was expected,

probably due to thermodynamic stability, carbamate **52** was observed in agreement with the observations of Smith and co-workers.[4] Deprotection of the carbamate **52** afforded the compound **53**, with spectral characteristics in good agreement to the same compound synthesized by Smith's group. Thus a formal synthesis of lyconadin A is completed.

4. Conclusions

The synthesis of an advanced intermediate toward (+)-lyconadin A is disclosed. The iodo cyclohexenone subunit is readily obtained from (*R*)-pulegone. The piperidine subunit is synthesized from bromo nicotinic acid. Rhodium/C catalyzed high-pressure hydrogenation of a pyridine derivative afforded *cis*-3,5-disubstituted piperidine. The resolution was achieved by the formation of diastereomeric esters. The two subunits were coupled using B-alkyl Suzuki coupling reaction.

Supplementary Information (SI)

^{1}H NMR, ^{13}C NMR spectra data is available at www.ias.ac.in/chemsci.

Acknowledgements

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