Tetrahedron Letters 51 (2010) 1574–1577

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Total synthesis of (+)-pseudohygroline

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ARTICLE INFO

Article history:
Received 18 December 2009
Revised 9 January 2010
Accepted 17 January 2010
Available online 22 January 2010

Keywords:
(+)-Pseudohygroline
Prins cyclisation
Hydroboration
Pyrrolidine alkaloids

ABSTRACT

A simple and efficient total synthesis of five-membered pyrrolidine, (+)-pseudohygroline is described. The key steps involved in this synthesis are highly stereoselective Prins cyclisation followed by reductive ring opening and hydroboration.

Pyrrolidine ring is frequently found in a large number of natural products, many of which exhibit a wide range of biological and pharmacological activity, hence pyrrolidine alkaloids make them attractive targets to synthetic chemists.[1] (+)-Pseudohygroline and hygroline were isolated from *Carallia brachiata*,[2a] *Erythroxylon coca*[2b] and *Schizanthus hookeri*.[2c] Structurally, these natural products constitute 2-substituted pyrrolidine.[2] This small molecule occupies a significant place in alkaloid chemistry as it was prepared as part of the first chemical proof of the absolute stereochemistry of the biosynthetically important (+)-hygroline and (+)-hygrine.[3] (+)-Pseudohygroline and hygroline are found to exhibit a potent pharmacological activity.[4] Considering its potent biological activity and fascinating structural features, several approaches have been reported for the synthesis of (+)-pseudohygroline (Fig. 1).[5]

The Prins cyclisation is a powerful synthetic tool for the construction of multi-substituted tetrahydropyran systems and has been utilised in the synthesis of several natural products.[6] Our group has made a significant effort to explore the utility of Prins cyclisation in the synthesis of various polyketide intermediates and applied it to the total synthesis of some natural products.[7] As a part of our interest on the total synthesis of biologically active natural products, we herein report a total synthesis of (+)-pseudohygroline (**2**) by means of Prins cyclisation (Scheme 1).

Accordingly, the synthesis of (+)-pseudohygroline (**2**) began with a chiral homoallyl alcohol (**5**).[8] Prins cyclisation of **5** with acetaldehyde in the presence of TFA (10 equiv), followed by hydrolysis of the resulting trifluoroacetate gave the tetrahydropyranol **6** in 52% yield.[9] The stereochemistry of **6** was assumed to be in anticipated line with previous results.[6–8] It was later proved after elaborating the compound **6** to the target molecule which in all respects was identical with the reported one.[10] The chemoselective tosylation of primary alcohol **6** with 1.1 equiv of tosyl chloride in the presence of TEA in DCM gave the corresponding tosylate **7** in 96% yield.[11] Protection of secondary alcohol **7** with TBSCl, DMAP and imidazole gave the TBS ether **8** in 91% yield. Treatment of tosylate **8** with NaI in refluxing acetone afforded iodo compound **9** in 94% yield, which on exposure to activated zinc in refluxing ethanol furnished the key intermediate **10** with a required anti-1,3-diol system in 96% yield. The newly created secondary alcohol **10** was protected as its MOM ether **11** in the presence of DIPEA and MOM chloride in dichloromethane in 98% yield. Hydroboration of compound **11** using BH_3·DMS in THF furnished the primary alcohol **12** in 80% yield.[12] Treatment of compound **12** with TBAF in THF produced the diol **13** in 85% yield. Mesylation of diol **13** with mesyl chloride in the presence of TEA gave the dimesylate, which was subsequently treated with 40% aqueous methylamine in DMF at 60 °C to afford the *N*-methyl pyrrolidine **14**.[13] Deprotection of MOM ether using TMS chloride in methanol gave the pure (+)-pseudohygroline (**2**) in 96% yield (Scheme 2), the data of which were in good agreement with the reported values.[5]

In conclusion, we have demonstrated a simple and concise total synthesis of (+)-pseudohygroline (**2**)[14] by stereoselective Prins cyclization, reductive ring opening of tetrahydropyran and sequential intermolecular and intramolecular substitution reactions. Further application of Prins cyclisation in the synthesis of natural products is in progress, and will be disclosed in due course.

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doi:10.1016/j.tetlet.2010.01.060

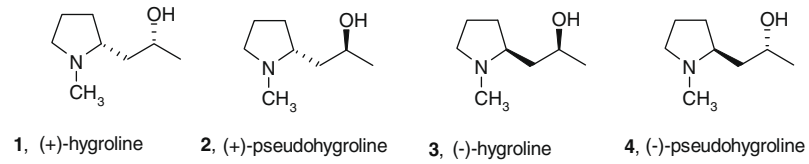
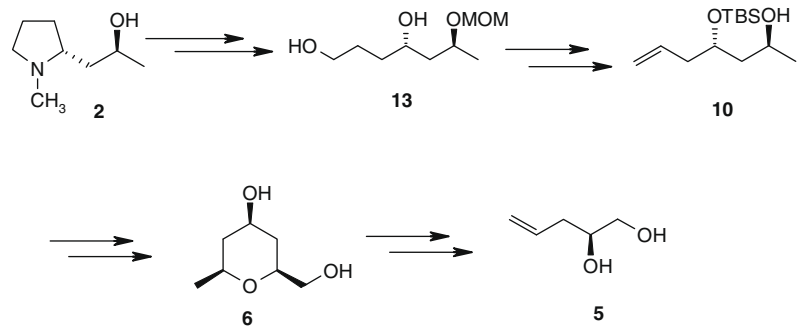
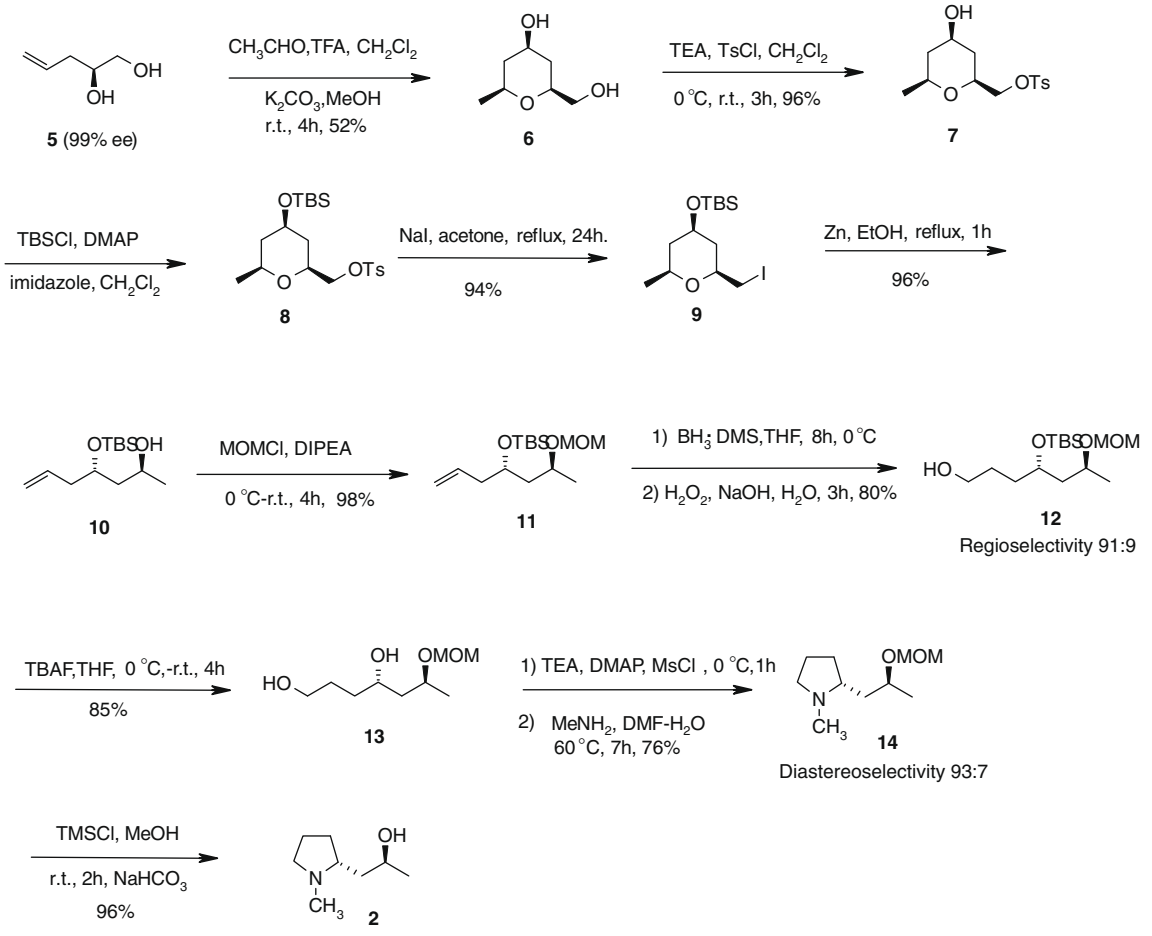


Figure 1. (+)-Hygroline (**1**), (+)-pseudohygroline (**2**), (−)-hygroline (**3**) and (−)-pseudohygroline (**4**).



Scheme 1. Retrosynthetic analysis of (+)-pseudohygroline.



Scheme 2. Synthetic sequence of pseudohygroline.

Acknowledgements

G.N.L. and N.M.R. thanks CSIR, New Delhi, for the award of fellowship and also we thank DST for the financial assistance under J. C. Bose fellowship scheme.

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14. *Experimental data*: IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C spectra were recorded on a Gemini-200 and a Varian Bruker-300 spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. (*2S,4R,6S)-2-(4Hydroxymethyl)-6-methyltetrahydro-2H-pyran-4-ol* (**6**): Trifluoroacetic acid (38.0 mL) was added slowly to a solution of the homoallylic alcohol **5** (2.5 g, 24.5 mmol) and acetaldehyde (3.2 g, 73.5 mmol) in CH_2Cl_2 (90 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h and then quenched with saturated sodium hydrogen carbonate solution (200 mL) and the pH was adjusted to >7 by addition of triethylamine. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 70 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The trifluoroacetate thus obtained in this reaction was directly used in the next reaction without purification. The residue was dissolved in methanol (40 mL) and stirred over potassium carbonate (6.77 g) for 0.5 h. Then methanol was removed under reduced pressure and water (30 mL) was added. The mixture was extracted with dichloromethane (3 × 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography on silica gel to give compound **6** (1.86 g, 52%) as a liquid. R_f = 0.2 (SiO_2, 60% EtOAc in hexane). $[\alpha]_D^{20}$ +9.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88–3.72 (m, 1H), 3.66–3.37 (m, 4H), 2.43–1.36 (m, 4H), 1.30–1.08 (m, 2H), 1.23 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.9, 71.7, 67.6, 65.7, 42.7, 36.4, 21.5 IR (neat): ν 3398, 2925, 2855, 1724, 1599, 1453, 1364, 1178, 1116, 1030, 976, 818, 668 cm^{-1}; ESI-MS: (*m/z*): 147 $(M+H)^+$, 129, 111, 102, 93, 67. HRMS calcd for $C_7H_{14}O_3Na$ 169.0840. Found: 169.0839. (*2S,4R,6S)-4-Hydroxy-6-methyltetrahydro-2H-pyran-2-yl)methyl-4-methylbenzenesulfonate* (**7**): To a solution of diol **6** (1.6 g, 10.95 mmol) in dry CH_2Cl_2 (15.0 mL), triethyl amine (3.04 mL, 21.9 mmol) was added at 0 °C. Then tosyl chloride (2.28 g, 12 mmol) was added over 2 h. The resulting mixture was allowed to warm to room temperature and stirred for 3 h. Then mixture was treated with aqueous 1 N HCl (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with $NaHCO_3$ (15 mL), and water (15 mL).The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the crude product afforded tosylate (3.12 g, 95%) as a gummy liquid. R_f = 0.4 (SiO2, 60% EtOAc in hexane). $[\alpha]_D^{25}$ +34.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 4.07–3.89 (m, 2H), 3.86–3.65 (m, 1H), 3.64–3.47 (m, 1H), 3.47–3.31 (m, 1H), 2.46 (s, 3H), 1.98–1.79 (m, 2H), 1.52–1.33 (m, 2H), 1.15 (d, 3H, *J* = 5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 132.8, 129.7, 127.9, 72.7, 71.9, 71.8, 67.4, 42.3, 36.6, 21.6, 21.3; IR (neat): ν 3399, 2923, 2853, 1723, 1598, 1453, 1358, 1177, 1096, 975, 816, 667 cm^{-1}; ESI-MS: 301 $[M+H]^+$; HRMS calcd for $C_{14}H_{21}O_5S$: 301.1104. Found: 301.1097. (*2S,4R,6S)-4-(tert-Butyldimethylsilyloxy)-6-methyltetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate* (**8**): To a solution of **7** (3.0 g, 10 mmol) in dry CH_2Cl_2 (30 mL) was added DMAP (5 mg) and imidazole (1.36 g, 20 mmol) in one portion followed by TBDMSCl (1.8 g, 12 mmol) in three portions. The reaction mixture was stirred for 3 h with the temperature slowly reaching to room temperature. It was quenched with the saturated NH_4Cl solution (30 mL), diluted with EtOAc (100 mL), washed with brine (25 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography afforded **8** (4.09 g, 99%) as a colourless liquid. R_f = 0.2 (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{20}$ +8.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.79 (d, 2H, *J* = 8.0 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 4.00–3.88 (m, 2H), 3.81–3.61 (m, 1H), 3.60–3.27 (m, 2H), 2.45 (s, 3H), 1.81–1.65 (m, 2H), 1.24–1.00 (m, 2H), 1.13 (d, 3H, *J* = 5.8 Hz), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.7, 127.9, 72.8, 72.1, 71.8, 68.0, 43.0, 37.1, 25.7, 21.5, 21.4, −4.6; IR (neat): ν 2931, 2856, 1598, 1465, 1363, 1254, 1181, 1073, 981, 836, 776 cm^{-1}; ESI-MS: 415 $[M+H]^+$; HRMS calcd for $C_{20}H_{35}O_5SSi$: 415.1969. Found: 415.1985. *tert-Butyl((2S,4R,6S)-2-(iodomethyl)-6-methyltetrahydro-2H-pyran-4-yloxy)dimethylsilane* (**9**): NaI (6.7 g, 45 mmol) was added to a solution of **8** (3.72 g, 9 mmol) in 60 mL of acetone and heated to reflux for 24 h. Acetone was removed under reduced pressure. To the residue was added water and EtOAc and the organic layer was separated, dried over Na_2SO_4, concentrated and chromatographed to afford **9** (3.23 g, 97%) as a colourless liquid. R_f = 0.7 (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{20}$ +15.6 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83–3.69 (m, 1H), 3.52–3.39 (m, 1H), 3.38–3.27 (m, 1H), 3.23–3.10 (m, 2H), 2.07–1.98 (m, 1H), 1.79–1.69 (m, 1H), 1.32–1.08 (m, 2H), 1.23 (d, 3H, *J* = 6.0 Hz), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 75.0, 72.0, 68.2, 42.9, 40.9, 21.7, 21.5, 18.0, 9.0, −4.5; IR (neat): ν 2951, 2932, 2856, 1466, 1383, 1253, 1157, 1120, 1071, 878, 836, 775 cm^{-1}; ESI-MS: 371 $[M+H]^+$. HRMS calcd for $C_{13}H_{28}O_2ISi$: 371.0898. Found: 371.0910. (*2S,4S)-4-(tert-Butyldimethylsilyloxy)hept-6-en-2-ol* (**10**): To the iodide **9** (3.0 g, 8.1 mmol) in ethanol (106 mL), commercial zinc dust (7.89 g, 121.5 mmol) was added. The resulting mixture was refluxed for 1 h, and then cooled to 25 °C. Addition of solid ammonium chloride (11.0 g) and ether (160 mL) followed by stirring for 5 min gave a grey suspension. The suspension was filtered through Celite and the filtrate was concentrated in vacuo. Purification by flash chromatography gave **10** (1.84 g, 93%) as a colourless liquid. R_f = 0.45 (SiO_2, 20% EtOAc in hexane). $[\alpha]_D^{25}$ +39.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83–5.65 (m, 1H), 5.14–4.99 (m, 2H), 4.19–3.85 (m, 2H), 3.04–2.70 (br s, 1H), 2.40–2.30 (m, 2H), 1.62–1.52 (m, 2H), 1.16 (d, 3H, *J* = 6.0 Hz), 0.92 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.6, 117.3, 71.1, 64.3, 43.0, 41.0, 25.7, 23.8, −4.5, −4.8; IR (neat): ν 3443, 2957, 2932, 2858, 1640, 1466, 1371, 1254, 1063, 1001, 912, 834, 775 cm^{-1}; ESI-MS: 245 $(M+H)^+$; HRMS calcd for $C_{13}H_{29}O_2Si$: 245.1931. Found: 245.1941. (*5S,7S)-7-Allyl-5,9,9,10,10-pentamethyl-2,4,8-trioxa-9-silaundecane* (**11**): To alcohol **10** (1.6 g, 6.55 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C were added diisopropylethylamine (3.4 mL, 19.65 mmol) and MOMCl (1.04 g, 13 mmol) successively and the mixture was stirred for 3 h at room temperature and then quenched by adding water (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to remove the solvent and the crude was purified by column chromatography to afford the pure product **11** (1.85 g, 98%). R_f = 0.8 (SiO_2, 20% EtOAc in hexane). $[\alpha]_D^{20}$ +69.4 (*c* 2.1, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90–5.72 (m, 1H), 5.10–4.99 (m, 2H), 4.63 (ddd, 2H, *J* = 6.7, 5.2, 12 Hz), 3.95–3.70 (m, 2H), 3.36 (s, 3H), 2.24 (t, 2H, *J* = 6.7, 5.2 Hz), 1.81–1.60 (m, 1H), 1.50–1.40 (m, 1H), 1.20 (d, 3H, *J* = 6.0 Hz), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.7, 117.0, 95.5, 71.4, 68.9, 55.3, 44.8, 42.4, 25.8, 21.5, −4.0, −4.5; IR (neat): ν 3076, 2931, 2890, 2858, 2361, 1641, 1467, 1378, 1253, 1215, 1100, 1042, 1001, 915, 834, 772 cm^{-1}; ESI-MS: 311 $(M+Na)^+$; HRMS calcd for $C_{15}H_{32}O_3SiNa$: 311.2013. Found: 311.2027. (*4S,6S)-4-(tert-Butyldimethylsilyoxy)-6-(methoxymethoxy)heptan-1-ol* **(12)**: To a stirred solution of **11** (1.5 g, 5.2 mmol) in dry THF (15 mL) was added BH_3·DMS (0.592 g, 7.8 mmol) for over a period of 15 min while maintaining the temperature at 0 °C. The reaction mixture was brought to room temperature and stirred for a period of 8 h. This was then treated with the very slow addition of 3 M NaOH until the reaction mixture was basic while maintaining the temperature at 0 °C. To this was added H_2O_2 (30%, 1.17 mL, 10.4 mmol) and the reaction mixture stirred over a period of 3 h, and then extracted with ethyl acetate (6 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford **12** (1.27 g, 80%) as a colourless liquid. R_f = 0.35 (SiO_2, 20% EtOAc in hexane). $[\alpha]_D^{20}$ +7.2 (*c* 2.0, $CHCl_3$); ^{1}H NMR

(300 MHz, $CDCl_3$): δ 4.67–4.58 (ddd, 2H, J = 6.7, 5.2, 12.0 Hz), 3.94–3.85 (m, 1H), 3.78–3.66 (m, 1H), 3.66–3.54 (m, 2H), 3.34 (s, 3H), 1.73–1.45 (m, 7H), 1.18 (d, 3H, J = 6.0 Hz), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.3, 71.3, 69.1, 62.9, 55.2, 44.6, 34.0, 27.7, 25.8, 21.2, −4.2, −4.6; IR (KBr): ν 3401, 2932, 2857, 1461, 1377, 1253, 1040, 917, 835, 774, 664 cm^{-1}; ESI-MS: 307 $[M+H]^+$. HRMS calcd for $C_{15}H_{35}O_4Si$: 307.2299. Found: 307.2313. (*4S,6S*)-*6*-(*Methoxymethoxy*)*heptane-1,4-diol* (**13**): To an ice cold solution of silyl ether **12** (1 g, 3.26 mmol) in dry THF (20 mL) was added TBAF (3.91 mL, 1 M in THF, 3.91 mmol). After 15 min of stirring, the reaction mixture was brought to room temperature and stirred for another 4 h. The reaction mixture was cooled and quenched with saturated NH_4Cl solution (5 mL), extracted with ethyl acetate (2 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford the alcohol **13** (0.596 g, 95% yield) as a colourless liquid. R_f = 0.2 (SiO_2, 40% EtOAc in hexane). $[\alpha]_D^{25}$ +51.2 (*c* 2.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.63 (dd, 2H, J = 6.2, 7.0 Hz), 4.04–3.82 (m, 2H), 3.69–3.56 (m, 2H), 3.38 (s, 3H), 3.24–2.50 (br s, 1H), 1.79–1.39 (m, 6H), 1.21 (d, 3H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.3, 71.4, 67.8, 62.7, 55.5, 43.6, 34.5, 29.2, 20.2; IR (KBr): ν 3389, 2938, 1655, 1448, 1378, 1211, 1145, 1037, 917, 853, 793, 754 cm^{-1}; ESI-MS: 215 $(M+Na)^+$; HRMS calcd for $C_9H_{20}O_4Na$: 215.1254. Found: 215.1263. (*R*)-*2*-((*S*)-*2*-(*Methoxymethoxy*)*propyl*)-*1-methylpyrrolidine* (**14**): To a solution of diol **13** (500 mg, 2.6 mmol) and triethylamine (1.08 mL, 7.81 mmol) in CH_2Cl_2 (42 mL) at 0 °C was added methanesulfonyl chloride (715 mg, 6.51 mmol). After 1 h, the mixture was poured into ice-water (35 mL). The layers were separated and the organic phase was washed with aqueous HCl (1 M, 20 mL), saturated $NaHCO_3$ solution (20 mL) and water (20 mL). The dried organic layer was evaporated and the crude dimesylate was used in the next step without further purification. A mixture of dimesylate and methylamine (4.04 mL, 40% solution in H_2O, 52 mmol) in DMF (17 mL) were maintained at 60 °C for 6 h. After dilution with ethyl acetate (50 mL), the mixture was washed with brine (20 mL) and water (20 mL), dried and evaporated. Chromatography on silica afforded pyrrolidine derivative **14** (370 mg, 76%) as a colourless oil. R_f = 0.4 (SiO_2, 10% MeOH in CH_2Cl_2). $[\alpha]_D^{25}$ +69.4 (*c* 2.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.62 (d, 1H, J = 6.7 Hz), 4.50 (d, 1H, J = 6.7 Hz), 3.71–3.59 (m, 1H), 3.30 (s, 3H), 3.07–2.98 (m, 1H), 2.27 (s, 3H), 2.29–2.17 (m, 1H), 2.15–2.04 (m, 1H), 2.01–1.82 (m, 2H), 1.80–1.56 (m, 2H), 1.53–1.33 (m, H),1.29–1.18 (m, 1H), 1.14 (d, 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 94.8, 71.6, 62.8, 57.0, 55.3, 41.7, 40.1, 30.8, 21.7, 21.2; IR (neat): ν 2917, 2849, 1595, 1462, 1383, 1350, 1260, 1216, 1033, 766 cm^{-1}; ESI-MS: 188 $(M+H)^+$; HRMS calcd for $C_{10}H_{22}NO_2$: 188.1650.; found: 188.1646. (*S*)-*1*-(*R*)-*1-Methylpyrrolidin-2-yl*)*propan-2-ol* (**2**): A solution of pyrrolidine **14** (200 mg, 1.06 mmol) in methanol (10 mL) was treated with TMS chloride (68 mg, 0.636 mmol). After being stirred at room temperature for 2 h, the solution was diluted with EtOAc (50 mL) and basified with aqueous $NaHCO_3$ solution until pH 9–10. The aqueous layer was extracted with ethyl acetate (2x10 mL). The organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified on silica gel to afford **2** (146 mg, 96%). R_f = 0.4 (SiO_2, 20% MeOH in CH_2Cl_2); $[\alpha]_D^{26}$ +53.8 (*c* 3.0, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93–3.81 (m, 1H), 3.11–2.97 (m, 1H), 2.79–2.66 (m, 1H), 2.39–2.30 (m, 1H), 2.34 (s, 3H), 2.03–1.90 (m, 1H), 1.83–1.61 (m, 2H), 1.45–1.29 (m, 3H), 1.11 (d, 3H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.2, 65.9, 55.4, 42.5, 42.3, 30.4, 24.2, 22.6; IR (KBr): ν 3422, 2921, 2851, 1557, 1413, 1075, 617 cm^{-1}; ESI-MS: 144 $(M+H)^+$; HRMS calcd for $C_8H_{18}ON$: 144.1388. Found: 144.1391.