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A FORMAL TOTAL SYNTHESIS OF (-)-LIMASPERMINE[#]

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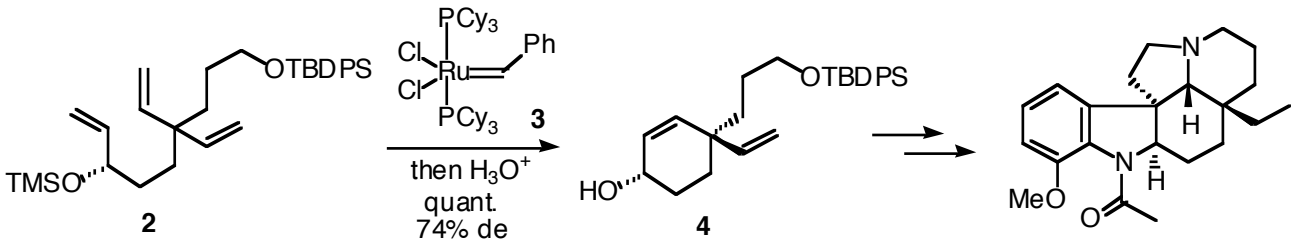
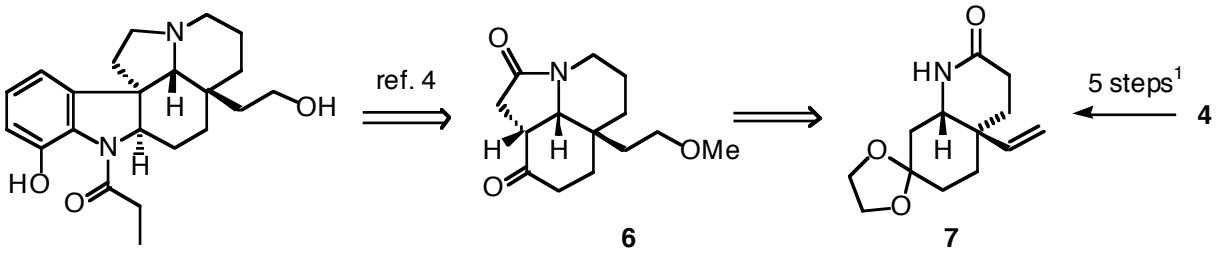
Abstract – An enantiocontrolled formal total synthesis of an aspidosperma indole alkaloid (-)-limaspermine has been accomplished using a diastereoselective ring-closing metathesis for formation of the quaternary stereogenic center.

In a previous paper, we reported an enantioselective total synthesis of (-)-aspidospermine (**1**)[1] using a methodology for assembling the quaternary stereogenic center *via* a diastereoselective ring-closing metathesis (RCM) reaction developed in our laboratory[2] (Scheme 1).



Scheme 1

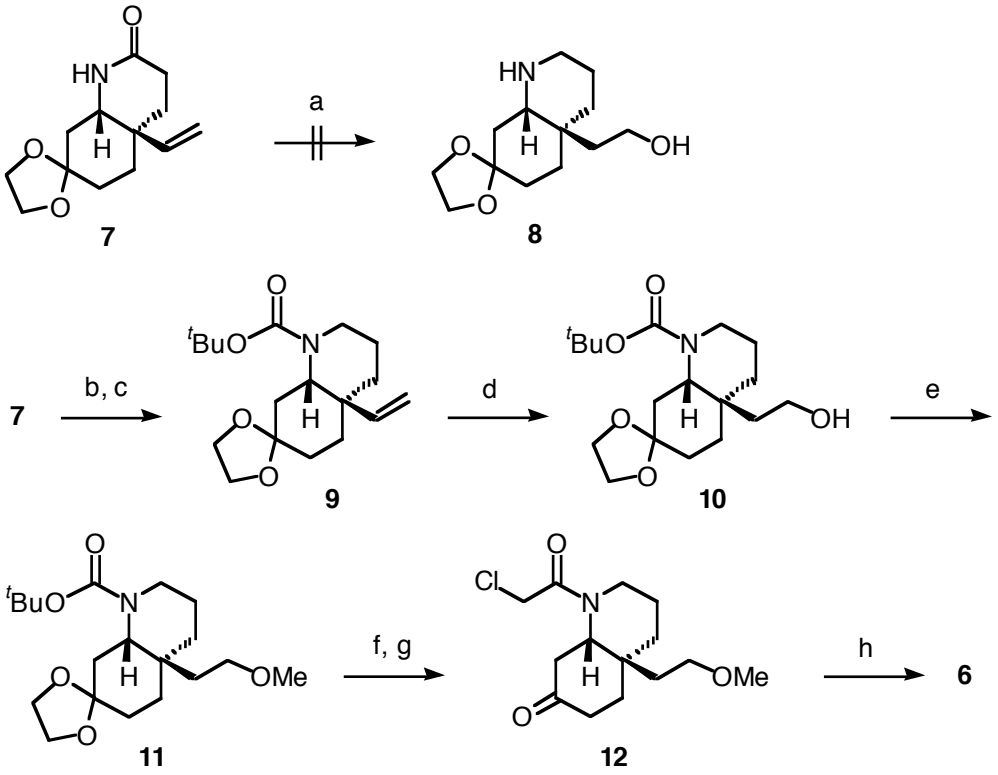
As a further application of the methodology, we wanted to synthesize a more oxygenated aspidosperma indole alkaloid (-)-limaspermine (**5**) by taking advantage of the vinyl substituent on the quaternary stereogenic center of the enantiomerically pure cyclohexenol (**4**), which was obtained in 87% yield by the Grubbs' ruthenium carbene complex (**3**)[3] catalyzed RCM reaction of the triene (**2**) and subsequent separation of diastereomers. Although the total synthesis of racemic limaspermine has been achieved by Pearson,[4] the enantioselective synthesis has never been reported. In this paper, we report an enantioselective formal synthesis of (-)-limaspermine (**5**) starting from the enantiomerically pure RCM product (**4**). Our synthetic plan is shown in Scheme 2. Since the tricyclic keto lactam (**6**) has been transformed successfully to limaspermine, we chose **6** as our synthetic target. The tricycle (**6**) would be elaborated from the bicyclic lactam (**7**), prepared *via* the 5-step sequence from **4** in our total synthesis of (-)-aspidospermine (Scheme 2). We first examined the conversion of **7** into the amino alcohol (**8**) to find



Scheme 2

the shortest route to **6**. We thought that the reaction of **7** with borane would give **8** *via* hydroboration and concomitant reduction of the lactam carbonyl. Treatment of **7** with borane-tetrahydrofuran (THF) complex followed by alkaline hydrogen peroxide treatment gave intractable mixtures. Therefore we chose the following stepwise sequence instead. Reduction of **7** with lithium aluminum hydride in refluxing THF provided the amine, which was protected as the *tert*-butyl carbamate (BOC) to give **9**.[5] Hydroboration of **9** using the above conditions produced the BOC-protected amino alcohol (**10**),[5] which was treated with sodium hydride and methyl iodide in the presence of the phase-transfer catalyst (n-$Bu_4N^+I^-$) to afford the methyl ether (**11**).[5] Removal of the *N*-BOC protecting group and concomitant hydrolysis of the acetal were realized by treatment of **11** with 1N HCl in refluxing THF to give the corresponding amino ketone, which was immediately acylated with chloroacetyl chloride and triethylamine to give the amide ketone (**12**).[5] Finally, cyclization of **12** with potassium *tert*-butoxide in a mixture of benzene and *tert*-butanol produced the tricyclic ketone (**6**), which was spectroscopically indistinguishable from the reported data for **6**[4] (^{1}H NMR spectrometry) (Scheme 3).

In summary, we have accomplished the first enantioselective formal total synthesis of (-)-limaspermine (**1**) by taking advantage of the presence of a vinyl group on the asymmetric quaternary stereogenic center of the optically pure **4**, which was obtained by a diastereoselective RCM reaction developed in our laboratory. The synthetic route shown here would be applicable not only to the synthesis of other highly oxygenated aspidosperma indole alkaloids but also to the synthesis of other biologically important natural products.



Scheme 3. *Reagents and Conditions*; (a) BH_3•THF, THF, rt then NaOH, H_2O_2, rt; (b) $LiAlH_4$, THF, reflux; (c) $(Boc)_2O$, Et_3N, 4-DMAP, CH_2Cl_2, rt, 81% (2 steps); (d) BH_3•THF, THF, rt then NaOH, H_2O_2, rt, 87%; (e) NaH, *n*-$Bu_4N^+I^-$, MeI, THF, rt, 81%; (f) 1N HCl, THF, reflux; (g) $ClCH_2COCl$, Et_3N, CH_2Cl_2, rt, 90% (2 steps); (h) *t*-BuOK, *t*-BuOH, benzene, rt, 72%.

EXPERIMENTAL

All reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of dry argon. Tetrahydrofuran (THF) and benzene were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride: Methanol (MeOH) and *tert*-butanol (*t*-BuOH) were distilled from sodium and kept over 3 Å molecular sieves. Melting points were measured with a Yanaco MP-500D apparatus and are uncorrected. Optical rotations were mesured with JASCO P-1010 with a ø3.5 x 50 mm quartz cell. ^1H NMR spectra were taken in $CDCl_3$ solution and referenced to TMS (0.00 ppm) and referenced to C_6H_6 (7.15 ppm) using JEOL JNM-AL-400 (400 MHz) spectrometer.^{13}C NMR spectra were taken in $CDCl_3$ solution and referenced to TMS (0.00 ppm) or $CDCl_3$ (77.0 ppm) using JEOL JNM-AL-400 (100 MHz) spectrometer. Chemical shifts are reported in □ (from TMS) with coupling constants reported in Hz. MS spectra were obtained on a JMS-SX102A mass spectrometers. Analytical thin layer chromatography (TLC) was performed on precoated plates (0.25 mm, silica gel Merck $60F_{245}$), and compounds were visualized with UV light and *p*-anisaldehyde stain. Column chromatography was performed on a silica gel, KANTO Silica Gel 60 N (63-210 mesh).

(4a*S*,8a*S*)-1-*tert*-Butyloxycarbonyl-7,7-ethylenedioxy-4a-vinyldecahydroquinoline (9).

A 200 mL flask was charged with $LiAlH_4$ (1.37 g, 36.0 mmol) and 70 mL of THF was added carefully. A solution of **7** (1.71 g, 7.21 mmol) in 30 mL of THF was added dropwise and the resulting suspension was refluxed for 2 h, then cooled to 0 ˚C. Water (1.37 mL), 15% NaOH (1.37 mL), and water (4.11 mL) were added sequentially with stirring and resulting mixture was stirred at rt for 1 h then filtered through a glass filter. The filtrate was dried over Na_2SO_4 and concentrated to afford 1.67 g of the crude amine as a colorless oil.

To the solution of the crude amine (1.67 g) in 30 mL of dichloromethane were added Et_3N (1.15 mL, 8.23 mmol), $(Boc)_2O$ (1.80 mL, 7.85 mmol), and 4-DMAP (45.7 mg, 0.73 mmol). The resulting solution was stirred at rt for 1 h, then treated with 20 mL saturated aqueous solution of $NaHCO_3$. The phases were separated and the aqueous phase was extracted three times with 20 mL portions of dichloromethane. The combined organic phases were dried over Na_2SO_4 and concentrated. Purification of the residue *via* silica gel column chromatography (hexane/AcOEt = 80/20 to 70/30) provided 1.89 g (81% for 2 steps) of **9** as a colorless solid; mp 113-116°C (hexane); $[\alpha]_D^{26}$ = -5.94° ($CHCl_3$, c = 1.22); IR ($CHCl_3$): 2935, 1676, 1418, 1163, 1098, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (br d, *J* = 12.8 Hz, 1H), 1.45-1.76 (m, 16H), 1.87-2.06 (m, 2H), 2.67-2.81 (m, 1H), 3.86-4.02 (m, 5H), 4.25 (dd, *J* = 4.4, 12.0 Hz, 0.6H), 4.42 (dd, *J* = 4.8, 12.8 Hz, 0.4H), 5.02-5.11 (m, 2H), 5.77 (dd, *J* = 10.8, 17.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.4, 26.6, 26.7, 28.4, 28.5, 30.3, 30.4, 33.2, 33.4, 34.6, 37.4, 38.4, 38.5, 38.6, 52.5, 53.8, 64.1, 64.2 (d), 64.3, 79.1, 79.2, 108.8, 112.6, 145.4, 145.5, 154.5, 154.7; MS (FAB) *m/z* 324 (M^++H); HRMS (FAB) Calcd for $C_{18}H_{30}NO_4$ (M^++H): 324.2175; found: 324.2184.

(4a*S*,8a*S*)-1-*tert*-Butyloxycarbonyl-7,7-ethylenedioxy-4a-(2-hydroxyethyl)decahydroquinoline (10). To a solution of **9** (1.78 g, 5.50 mmol) in 27 mL of THF was added BH_3•THF (9.17 mL of 0.9 M THF solution; 8.26 mmol) and the resulting solution was stirred at rt for 3 h, then cooled to 0 ˚C. Water (5 mL), 1 N NaOH (8.26 mL, 8.36 mmol), and 35% H_2O_2 (0.81 mL, 8.26 mmol) were added sequentially and the resulting mixture was stirred at rt for 30 min. The reaction mixture was diluted with 10 mL brine and extracted three times with 20 mL portions of dichloromethane. The combined organic phases were dried over Na_2SO_4 and concentrated. Purification of the residue *via* silica gel column chromatography (hexane/AcOEt = 70/30 to 0/100) provided 1.63 g (87%) of **10** as a colorless oil; $[\alpha]_D^{28}$ = +11.6° ($CHCl_3$, c = 1.13); IR (neat): 3439, 2935, 1683, 1418, 1163, 1098, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.10-1.18 (m, 1H), 1.38-2.06 (m, 21H), 2.69-2.85 (m, 1H), 3.62-3.77 (m, 2H), 3.91-4.07 (m, 5.5H), 4.26 (dd, *J* = 4.0, 12.4 Hz, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 20.8, 25.0, 25.9, 28.5, 30.0, 30.1, 32.6, 32.8, 33.2, 34.1, 34.2, 37.2, 38.3, 39.5, 39.6, 53.2, 55.4, 58.4, 58.6, 64.1, 64.2, 64.3, 79.4, 79.5, 108.8 (d), 155.1 (d); MS (FAB) *m/z* 342 (M^++H); HRMS (FAB) Calcd for $C_{18}H_{32}NO_5$ (M^++H): 342.2280; found: 342.2304.

(4a*S*,8a*S*)-1-*tert*-Butyloxycarbonyl-7,7-ethylenedioxy-4a-(2-methoxyethyl)decahydroquinoline (11). A flame dried 20 mL flask was charged with NaH (14.5 mg of 62.5% in mineral oil; 0.378 mmol) and 3

mL THF. The suspension was cooled to 0 ˚C and a solution of **10** (85.9 mg, 0.252 mmol) in 2 mL of THF was added slowly. After the mixture was stirred at 0 ˚C for 30 min, iodomethane (0.05 mL, 0.755 mmol) was added and the resulting mixture was stirred at rt for 14 h. The reaction mixture was diluted with 5 mL of saturated aqueous solution of NH_4Cl and extracted three times with 5 mL portions of ether. The combined organic phases were washed with 5 mL brine, dried over $MgSO_4$, and concentrated. Purification of the residue *via* silica gel column chromatography (hexane/AcOEt = 90/10 to 70/30) provided 73.0 mg (81%) of **11** as a colorless oil; $[\alpha]_D^{28}$ = +23.6° ($CHCl_3$, c = 1.04); IR (neat): 2933, 1689, 1551, 1415, 1164, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15-1.23 (m, 1H), 1.44-2.06 (m, 20H), 2.68-2.82 (m, 1H), 3.30 (s, 1.2H), 3.31 (s, 1.8H), 3.38-3.43 (m, 2H), 3.89-4.06 (m, 5.6H), 4.13 (dd, *J* = 4.8, 12.4 Hz, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 20.7, 24.9, 25.0, 28.4, 30.0, 30.2, 32.8, 32.9, 33.2, 34.0, 36.0, 36.2, 37.1, 38.3, 54.0, 55.3, 58.5, 64.1 64.2, 64.3, 68.8, 68.9, 79.1, 79.2, 108.8, 154.6, 155.0; MS (FAB) *m/z* 356 (M^++H); HRMS (FAB) Calcd for $C_{19}H_{34}NO_5$ (M^++H): 356.2437; found: 356.2429.

(4a*S*,8a*S*)-1-Chloroacetyl-7,7-ethylenedioxy-4a-(2-methoxyethyl)decahydroquinoline (12).

The carbamate (**11**) (64.9 mg, 0.183 mmol) was dissolved in 3 mL of THF and 1 mL 1 of N HCl was added. The resulting mixture was refluxed for 14 h, cooled to rt, basified with 2 N NaOH, and extracted three times with 5 mL portions of dichloromethane. The combined organic phases were dried over Na_2SO_4 and concentrated to afford 41.5 mg of the crude amino ketone as a colorless oil.

To the solution of the crude amino ketone (41.5 mg) in 2 mL of dichloromethane was added Et_3N (0.03 mL, 0.235 mmol) followed by chloroacetyl chloride (0.02 mL, 0.216 mmol). The resulting solution was stirred at room temperature for 30 min, then 5 mL of sat $NaHCO_3$ was added. The phases were separated and the aqueous phase was extracted three times with 5 mL portions of dichloromethane. The combined organic phases were dried over Na_2SO_4 and concentrated. Purification of the residue *via* silica gel column chromatography (hexane/AcOEt = 50/50 to 0/100) provided 47.5 mg (90% for 2 steps) of **12** as a colorless oil; $[\alpha]_D^{28}$ = +29.4° ($CHCl_3$, c = 0.60); IR (neat): 2933, 1689, 1551, 1415, 1164, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 0.4H), 1.40-2.05 (m, 7.6H), 2.28-2.52 (m, 3H), 2.73 (t, *J* = 13.2 Hz, 0.6H), 2.96 (t, *J* = 13.6 Hz, 0.4H), 3.12-3.25 (m, 1H), 3.30 (s, 3H), 3.42-3.50 (m, 2H), 3.74 (br d, *J* = 12.4 Hz, 0.6H), 4.00-4.23 (m, 2.4H), 4.58 (br d, *J* = 10.8 Hz, 0.4H), 4.71 (dd, *J* = 5.2, 12.4 Hz, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 20.9, 25.1, 26.4, 32.9, 33.8, 34.7, 35.1, 35.6, 35.7, 35.8, 36.6, 39.6, 40.4, 41.0, 41.4, 54.1, 58.6, 58.8, 59.4, 68.5, 165.6, 165.8, 207.9, 208.1; MS (FAB) *m/z* 288 (M^++H); HRMS (FAB) Calcd for $C_{14}H_{23}NO_3Cl$ (M^++H): 288.1366; found: 288.1338.

(6a*S*,9a*R*,9b*R*)-6a-(2-Methoxyethyl)octahydropyrrolo[3,2,1-*ij*]quinoline-2,9-dione (6).

The amide (**12**) (43.8 mg, 0.152 mmol) was dissolved in 1 mL of benzene and 1 mL *t*-BuOH. *t*-BuOK (25.6 mg, 0.228 mmol) was added portionwise and the resulting mixture was stirred at rt for 30 min, then

concentrated. The residue was diluted with 5 mL of water and extracted three times with 5 mL portions of dichloromethane. The combined organic phases were dried over Na_2SO_4 and concentrated. Purification of the residue *via* silica gel column chromatography (AcOEt/MeOH = 95/5) provided 27.6 mg (72%) of **6** as a colorless solid; mp 146-148°C (hexane); $[\alpha]_D^{24}$ = -56.9° ($CHCl_3$, c = 0.82); IR ($CHCl_3$): 3009, 1711, 1685, 1415, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42-1.71 (m, 5H), 1.86 (br d, *J* = 13.6 Hz, 1H), 2.01-2.14 (m, 2H), 2.29-2.41 (m, 2H), 2.50-2.62 (m, 2H), 2.89-2.93 (m, 1H), 2.98 (br d, *J* = 17.2 Hz, 1H), 3.35 (s, 3H), 3.49 (dd, *J* = 2.0, 6.4 Hz, 1H), 3.51-3.60 (m, 2H), 4.05 (br d, *J* = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 25.7, 32.6, 33.8, 33.9, 35.7, 36.2, 40.4, 42.6, 58.8, 65.4, 68.0, 174.3, 208.4; MS (FAB) *m/z* 252 (M^++H); HRMS (FAB) Calcd for $C_{14}H_{22}NO_3$ (M^++H): 252.1600; found: 252.1614.

REFERENCES AND NOTES

[#] Dedicated to Professor Leo A. Paquette on the occasion of his 70th birthday.

1. Y. Fukuda, M. Shindo, and K. Shishido, *Org. Lett.*, in press. Experimental details of the prepartation of compound (**7**) are described in the Supporting Information.
2. Y. Fukuda, H, Sasaki, M. Shindo, and K. Shishido, *Tetrahedron Lett.*, 2002, **43**, 2047.
3. P. Schweb, R. H. Grubbs, and J. W. Ziller, *J. Am, Chem., Soc.*, 1996, **118**, 100.
4. A. J. Pearson and D. C. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2467.
5. The ^1H and ^{13}C NMR spectra showed two set of signals arising from the rotational isomers.