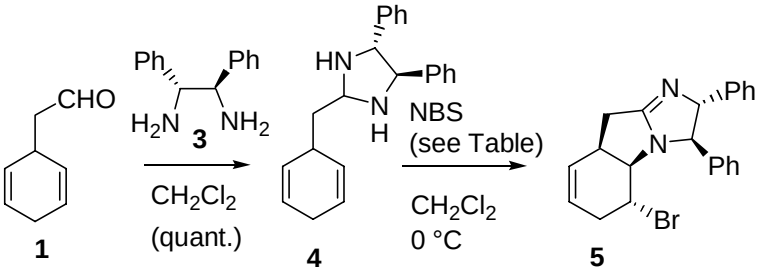
"Supporting Information"

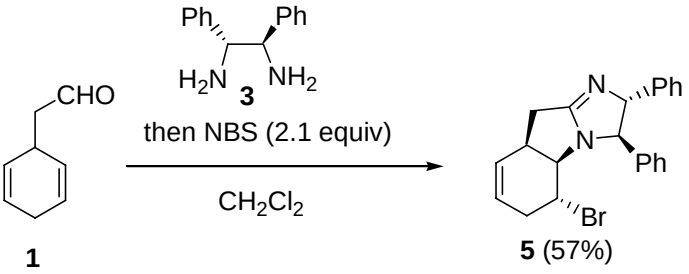
Intramolecular bromo-amination of 1,4-cyclohexadiene aminal: one-pot discrimination of two olefins and concise asymmetric synthesis of (–)-γ-lycorane

Hiromichi Fujioka,* Kenichi Murai, Yusuke Ohba, Hideki Hirose, and Yasuyuki Kita*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Osaka 565-0871, Osaka 565-0871, Japan



Scheme of Table 1.

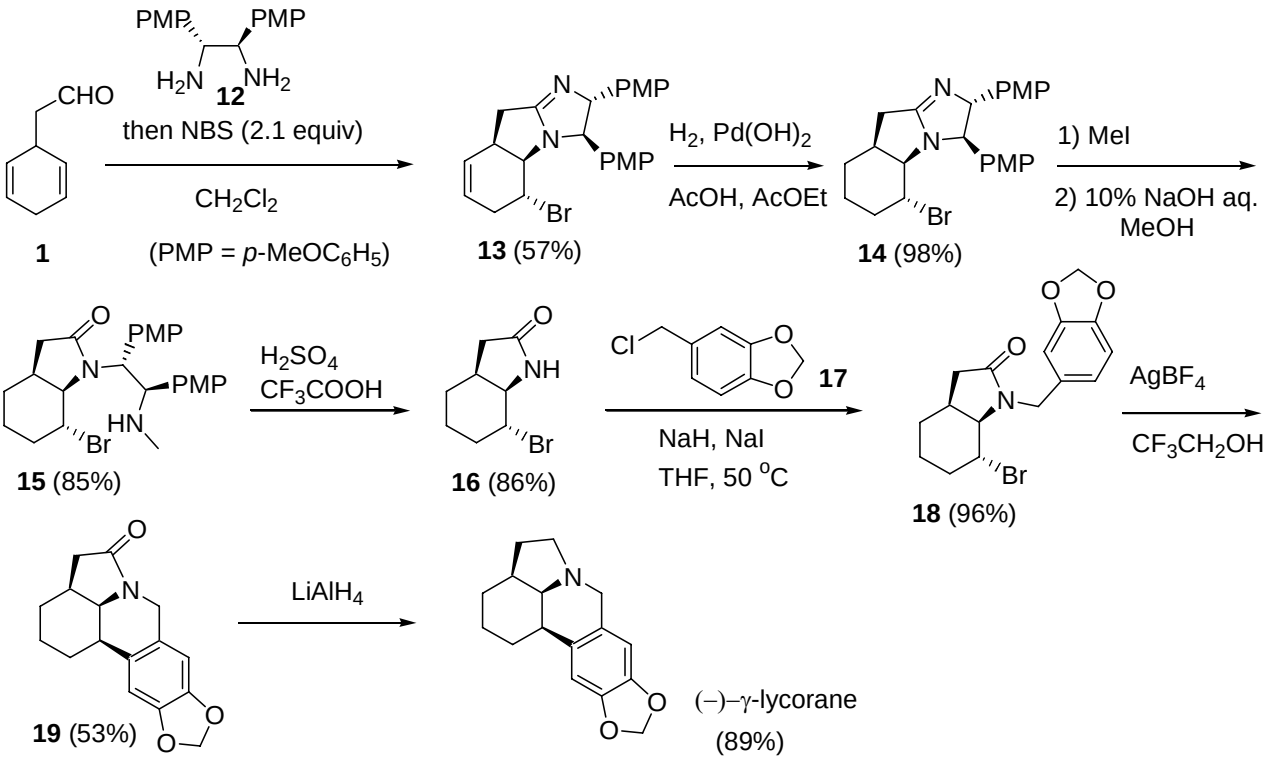


Scheme 5. One-pot operation

(4*R*S, 5*R*S**)-2-(2,5-Cyclohexadienylmethyl)-4,5-diphenylimidazolidine (4)**
3 (98.0 mg, 0.46 mmol) was added to a solution of **1**[1)] (56.4 mg, 0.46 mmol) in CH_2Cl_2 (30 ml) at 0 °C under N_2. The mixture was stirred for 30 min and then evaporated in vacuo. The obtained **4** was used in the next reaction without purification. **4**: Colorless oil; IR (KBr) cm^{-1}: 3309, 3026, 1454; ^1H NMR δ: 1.87 (2H, t, *J* = 12.0 Hz), 2.25 (2H, brs), 2.65—2.69 (2H, m), 3.00—3.07 (2H, m), 4.16 (1H, A in ABq, *J* = 7.5 Hz), 4.22 (1H, B in ABq, *J* = 7.5 Hz), 4.52 (1H, t, *J* = 6.0 Hz), 5.73—5.82 (4H, m), 7.20—7.37 (10H, m); ^{13}C NMR δ: 26.1, 33.0, 43.3, 68.9, 71.4, 73.3, 124.3, 126.4, 126.8, 127.2, 128.3, 128.3, 128.7, 128.7, 140.9, 142.8.

Compound 6
Synthesis from Diene Aminal 4 (entry 2 in the Table of Scheme 2): NBS (71 mg, 0.40 mmol) was added to a solution of **4** (60 mg, 0.19 mmol) in CH_2Cl_2 (3.7 ml) at 0 °C under N_2. The mixture was stirred for 15 min at the same temperature. The mixture was quenched by addition of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and evaporated in vauo. The residue was purified by SiO_2 column chromatography using (AcOEt-Et_3N (20/1) to AcOEt-MeOH-Et_3N (20/1/1)) as the eluent to give **5** (42.4 mg, 1.08 mmol) in 57%.
One-pot Synthesis: **3** (1.15 g, 5.43 mmol) was added to a solution of **1** (663 mg, 5.43 mmol) in

CH_2Cl_2 (110 ml) at 0 °C under N_2. The mixture was stirred for 1 h. NBS (2.03 g, 11.4 mmol) was added to the mixture, and the resulting solution was stirred for 15 min at the same temperature. The mixture was quenched by addition of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and evaporated in vauo. The residue was purified by SiO_2 column chromatography using (AcOEt-Et_3N (20/1) to AcOEt-MeOH-Et_3N (20/1/1)) as the eluent to give **5** (12.2 g, 1.08 mmol) in 57%.**5**: Colorless amorphous; IR (KBr) cm^{-1}: 1649, 912, 742; ^1H NMR δ: 2.37—2.46 (2H, m), 2.61 (1H, dt, *J* = 4.8, 17.4 Hz), 2.80 (1H, dd, *J* = 8.4, 16.2 Hz), 3.33—3.38 (1H, m), 3.52 (1H, dd, *J* = 7.5, 8.4 Hz), 4.11 (1H, ddd, *J* = 4.5, 8.4, 8.4 Hz), 4.86 (1H, d, *J* = 4.8 Hz), 5.31 (1H, d, *J* = 4.8 Hz), 5.60—5.67 (1H, m), 5.70—5.78 (1H, m), 7.25—7.40 (10H, m); ^{13}C NMR δ: 29.8, 33.2, 42.2, 50.0, 58.0, 69.8, 84.0, 124.6, 126.3, 126.8, 127.2, 128.0, 128.9, 140.6, 143.8, 170.1; FAB-MS *m/z*: 393 $(MH)^+$; FAB–HRMS m/z: calcd for $C_{22}H_{21}BrN_2$: 393.096 $(M+H^+)$; found: 393.0939.



Scheme 6. Asymmetric synthesis of (-)-γ-licorane

Compound 13

12 (4.39 g, 16.1 mmol) was added to a solution of **1** (1.97 g, 16.1 mmol) in CH_2Cl_2 (322 ml) at 0 °C under N_2. The mixture was stirred for 1 h. NBS (6.02 g, 33.8 mmol) was added to the mixture, and the resulting solution was stirred for 15 min at the same temperature. The mixture was quenched by addition of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and evaporated in vauo. The residue was purified by SiO_2 column chromatography using (AcOEt-Et_3N (20/1) to AcOEt-MeOH-Et_3N (20/1/1)) as the eluent to give **13** (4.15 g, 9.16 mmol) in 57%. **13**: Colorless amorphous; $[\alpha]_D^{26}$ –359.5 (c = 1.68, $CHCl_3$); IR (KBr) cm^{-1}: 1647, 1512, 1246, 741; ^1H NMR δ: 2.37—2.46 (2H, m), 2.62 (1H, dt, *J* = 4.8, 12.6 Hz), 2.79 (1H, dd, *J* = 8.1, 15.6 Hz), 3.24—3.36 (1H, m), 3.50 (1H, t, *J* = 8.1 Hz), 3.80 (3H, s), 3.82 (3H, s), 4.07—4.15 (1H, m), 4.77 (1H, d, J = 4.5 Hz), 5.24 (1H, d, J = 4.5 Hz),

5.62—5.79 (2H, m), 6.85—6.92 (4H, m), 7.17—7.26 (4H, m) ; ^{13}C NMR δ: 30.8, 34.1, 43.1, 51.0, 56.2, 58.9, 70.4, 85.1, 114.9, 115.2, 125.5, 128.3, 129.1, 133.6, 137.1, 159.7, 160.3, 170.8; FAB–HRMS m/z: calcd for $C_{24}H_{25}BrO_2N_2$: 453.1188 ($M+H^+$); found: 453.1178.

Compound 14

13 (1.27 g, 2.79 mmol) in AcOEt-AcOH (1/1) (32 ml) was hydrogenated in the presence of $Pd(OH)_2$ (100 mg) at rt for 12 h under H_2. The solution was filtered by celite pad. Thefiltrate was evaporated in vauo. The residue was purified by SiO_2 column chromatography using (AcOEt-MeOH-Et_3N (20/1/1)) as the eluent to give **14** (1.24 g, 2.72 mmol) in 98%. Colorless amorphous; $[\alpha]_D^{25}$ –220.2 (c = 0.617, $CHCl_3$); IR (KBr) cm^{-1}: 2934, 1643, 1612; ^{1}H NMR δ: 1.25—1.56 (1H, m), 1.63—1.78 (3H, m), 2.13—2.19 (1H, m), 2.43 (1H, m), 2.85—3.01 (1H, m), 3.42 (1H, t, *J* = 7.0 Hz), 3.80 (3H, s), 3.81 (3H, s), 3.93—4.01 (1H, m), 4.76 (1H, d, *J* = 7.3 Hz), 5.15 (1H, d, *J* = 7.3 Hz), 6.85—6.89 (4H, m), 7.13—7.26 (4H, m); ^{13}C NMR δ: 21.1, 26.6, 27.8, 34.1, 40.9, 52.3, 55.1, 55.1, 60.4, 69.6, 84.2, 113.6, 113.8, 127.5, 128.0, 132.3, 135.6, 158.4, 158.9, 170.3; FAB–HRMS m/z: calcd for $C_{24}H_{27}BrO_2N_2$: 454.1282 ($M+H^+$); found: 454.1256.

Compound 15

MeI (1 ml) was added to a solution of **14** (940 mg, 2.06 mmol) in CH_2Cl_2 (6 ml) at rt under N_2. The mixture was stirred overnight. The solution was evaporated in vacuo. The residue was dissolved with MeOH (12 ml) and CH_2Cl_2 (1 ml). 10% aq. NaOH was added slowly to the resulting solution at 0 °C. The mixture was stirred for 15 min at the same temperature. The resulting solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and evaporated in vauo. The residue was purified by SiO_2 column chromatography using hexane-AcOEt-Et_3N (5/10/1) as the eluent to give **15** (859 mg, 1.76 mmol) in 85%. Colorless amorphous; $[\alpha]_D^{27}$ –24.7 (c = 1.02, $CHCl_3$); IR (KBr) cm^{-1}: 2936, 2245, 1686, 1512, 1250; ^{1}H NMR δ: 1.35—1.90 (6H, m), 2.17—2.30 (5H, m), 2.45—2.53 (1H, m), 3.70—3.74 (7H, m), 4.57—4.90 (3H, m), 6.34—6.73 (4H, m), 7.03—7.11 (4H, m); ^{13}C NMR δ: 19.6, 26.9, 31.3, 32.3, 34.3, 37.9, 52.3, 55.0, 63.6, 64.9, 113.3, 113.4, 129.1, 129.5, 131.2, 132.9, 158.3, 158.3, 177.1; FAB–HRMS m/z: calcd for $C_{25}H_{31}BrO_3N_2$: 453.1188 ($M+H^+$); found: 452.1099.

(3a*S*, 7*R*, 7a*R*)-7-Bromo-octahydroindol-2-one (16)

Conc. H_2SO_4 (2 ml) was added to a solution of **15** (982.2 mg, 2.01 mmol) in CF_3COOH (20 ml) at rt. The mixture was stirred overnight under reflux. After being cooled to rt, the solution was evaporated in vacuo. The residue was neutralized by sat. aq. $NaHCO_3$, and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and evaporated in vauo. The residue was purified by SiO_2 column chromatography using AcOEt only as the eluent to give **16** (376 mg, 1.72 mmol) in 86%. Colorless crystals; $[\alpha]_D^{20}$ –32.3 (c = 1.83, $CHCl_3$); IR (KBr) cm^{-1}: 3209, 1690; ^{1}H NMR δ: 1.39—1.56(1H, m), 1.60—1.83(4H, m), 2.15—2.31(3H, m),2.66—2.81 (1H, m), 3.70 (1H, t, *J* = 7.7 Hz), 3.91 (1H, ddd, *J* = 4.3, 8.6, 11.3 Hz), 6.80 (1H, brs); ^{13}C NMR δ: 21.8, 25.9, 33.9, 34.3, 36.2, 56.1, 62.2, 177.7; *Anal*. Calcd for $C_8H_{12}BrNO$: C, 44.06; H, 5.55; N, 6.42; Br, 36.64. Found: C, 44.19; H, 5.44; N, 6.41; Br, 36.28.

(3aS, 7R, 7aR)-7-Bromo-1-(3,4-methylenedioxybenzyl)octahydroindol-2-one (18)

NaH (60% in oil, 28 mg, 0.70 mmol) was added to a solution of **16** (128.3 mg, 0.59 mmol) in THF (4 ml) at 0 °C under N_2. After being stirred for 5 min, a solution of **17** (186 mg, 1.09 mmol) in THF (2 ml) and NaI were added to the resulting mixture at 0 °C, successively. The solution was stirred at 50 °C for 2 h. The mixture was quenched with sat. aq. NH_4Cl, and was extracted with AcOEt. Organic layer was dried over Na_2SO_4, and evaporated in vauo. The residue was purified by SiO_2 column chromatography using hexane-AcOEt (20/1) as the eluent to give **18** as a mixture of *N*-

junction (199 mg, 0.565 mmol) in 96%. Colorless crystals; $[\alpha]_D^{19}$ –48.7 (c = 3.20, $CHCl_3$); IR (KBr) cm^{-1}: 2935, 1693, 1489, 1244; ^1H NMR δ: 1.44—1.98 (6H, m), 2.25—2.32 (2H, m), 2.47—2.52 (1H, m), 3.61 (3/4H, t, *J* = 6.6 Hz), 3.75 (1/4H, t, *J* = 5.4 Hz), 4.17—4.25 (3/4H, m), 4.30—4.37 (1H, m), 4.47—4.53 (1/4H, m), 5.95 (2H, s), 6.75 (3H,s); ^{13}C NMR δ: 20.2, 21.5, 26.5, 26.7, 29.9, 32.9, 33.3, 33.5, 34.2, 35.4, 36.6, 44.5, 44.8, 52.5, 62.5, 63.4, 100.8, 108.0, 108.1, 108.1 108.2, 121.1, 121.3, 130.2, 146.6, 147.6, 147.7, 174.7, 175.4; FAB–HRMS m/z: calcd for $C_{16}H_{18}BrO_3N$: 352.0548 ($M+H^+$); found: 352.0560.

(–)-γ-Lycorane-5-one (19)[2b)]

AgBF4 (100 mg, 0.514 mmol) was added to a solution of **18** (110 mg, 0.31 mmol) in CF_2CH_2OH (1 ml) at rt under N_2. The mixture was stirred overnight at the same temperature. The mixture was quenched by sat. aq. $NaHCO_3$, and was extracted with AcOEt. Organic layer was dried over Na_2SO_4, and evaporated in vauo. The residue was purified by SiO_2 column chromatography using hexane-AcOEt (1/3) as the eluent to give **19** (44.7 mg, 0.165 mmol) in 53%. Colorless crystals; $[\alpha]_D^{25}$ –96.0 (c = 1.00 ,$CHCl_3$); IR (KBr) cm^{-1}: 1691; ^1H NMR δ: 1.09—1.44 (3H, m), 1.71—1.75 (3H, m), 2.09 (1H, d, *J* = 16.2 Hz), 2.37—2.48 (1H, m), 2.58 (1H, dd, *J* = 7.0, 15.9 Hz), 2.72—2.79 (1H, m), 3.76 (1H, t, *J* = 4.3 Hz), 4.32 (1H, A in ABq, *J* = 17.5 Hz), 4.53 (1H, B in ABq, *J* = 17.5 Hz), 5.93 (2H, d, *J* = 3.2 Hz), 6.60 (2H, d, *J* = 7.6 Hz); ^{13}C NMR δ: 23.6, 27.8, 30.2, 32.9, 40.2, 42.6, 55.6, 100.9, 106.5, 108.3, 123.1, 131.4, 146.4, 146.4, 175.3.

(–)-γ-Lycorane[2)]

$LiAlH_4$ (25 mg, 0.66 mmol) was added to a solution of **19** (44.7 mg, 0.165 mmol) in THF (5 ml) at 0 °C. The mixture was stirred for 1.5 h under reflux. After being cooled to rt, H_2O, 10% aq. NaOH, AcOEt, and celite were added successively to the solution. The solution was stirred for 30 min to make precipitate, which was filtrated by short celite pad. The filtrate was evaporated in vacuo. The residue was purified by SiO_2 column chromatography using hexane-AcOEt-Et_3N (10/5/1) as the eluent to give **(–)-γ-lycorane** (38.0 mg, 0.148 mmol) in 89%. Colorless oil; $[\alpha]_D$ –19.5 (c = 0.65, $CHCl_3$) (lit.[7a)] $[\alpha]_D$ –17.1 (c = 0.25, EtOH); IR (KBr) cm^{-1}: 2925, 1483; ^1H NMR δ: 1.25—1.53 (4H, m), 1.60—1.78 (3H, m), 1.99—2.21 (3H, m), 2.36 (1H, t, *J* = 4.6 Hz), 2.69—2.75 (1H, m), 3.37 (1H, dt, *J* = 3.8, 9.2 Hz), 5.87 (2H, d, *J* = 1.4 Hz), 6.48 (1H, s), 6.61 (1H,s) ; ^{13}C NMR δ: 25.1, 29.2, 30.4, 31.6, 37.3, 39.4, 53.6, 57.0, 62.7, 100.4, 106.0, 108.1, 127.1, 132.9, 145.3, 145.7.

References

1) H. Bock and B. Solouki, *Chem. Ber*. 1974, **107**, 2295—2298.
2) (a) H. Yoshizaki, H. Satoh, Y. Sato, S. Nukui, M. Shibasaki and M.; Mori, *J. Org. Chem*. 1995, **60**, 2016—2021. (b) M. Ikeda, S. Ohtani, T. Sato and H. Ishibashi, *Synthesis* **1998**, 1803—1806. (c) M. G. Banwell, J. E. Harvey and D. C. R. Hockless, *J. Org. Chem*. 2000, **65**, 4241—4245.