Tetrahedron
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A short synthesis of (+)-β-lycorane by asymmetric conjugate addition cascade

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
chiral ligand
asymmetric synthesis
organolithiums
conjugate addition
lycorane

ABSTRACT

The chiral diether ligand-controlled asymmetric conjugate addition of organolithiums to nona-2,7-dienedioate and subsequent intramolecular conjugate addition of the enolate intermediate gave all-*trans* trisubstituted cyclohexanes with high ee and yields. Using this methodology, an efficient short asymmetric total synthesis of (+)-β-lycorane was accomplished in 33% overall yield through five steps from the dienedioate.

1. Introduction

The Amaryllidaceae alkaloids have attracted much attention due to their rich bioactivities, such as anti-Alzheimer, antifungal, antibacterial, and antineoplastic activities.[1] Among these alkaloids, lycorine (**1**)[1,2] and its deoxygenated derivatives lycoranes (**2a** and **b**)[3] possess the characteristic pyrrolophenanthridine skeleton (Figure 1). We have previously reported the asymmetric total synthesis of (–)-lycorine (**1**) using a chiral ligand-controlled asymmetric conjugate addition cascade.[4,5] As a continuation of this study to show the utility of this cascade reaction, here we report a short asymmetric total synthesis of (+)-β-lycorane (**2b**).[6,7,8]

Our strategy starts from the asymmetric conjugate addition[9,10] of aryllithium **4** to nona-2,7-dienedioate **3**[11,12] mediated by chiral ligand **5** (Scheme 1). The subsequent intramolecular Michael reaction of the resulting enolate **6** would afford trisubstituted cyclohexane **7a** with three contiguous stereogenic centers.[4] The nitrogen functionality could be introduced by Curtius rearrangement, and the subsequent cyclization gives (+)-β-lycorane (**2b**).

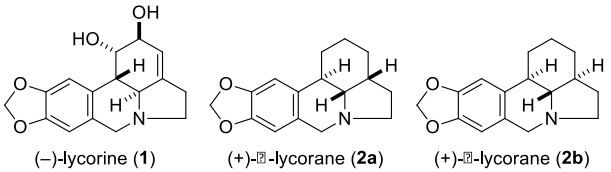
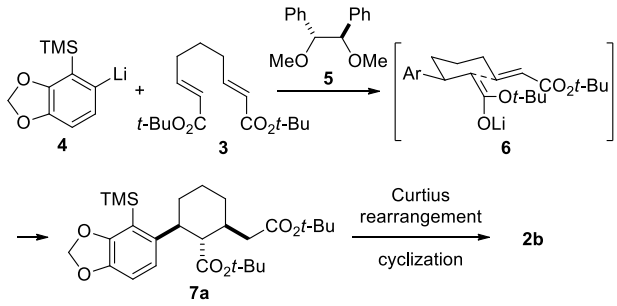


Figure 1. Structures of lycorine and lycoranes.



Scheme 1. Synthetic strategy to (+)-β-lycorane.

2. Results and discussion

First, the reaction of dienedioate **3** and phenyllithium was investigated as a model reaction. The reaction of PhLi (3 equiv) in the presence of **5** (4.2 equiv) was complete within 0.5 h to give *trans*,*trans*-cyclohexane ***tt*-7b** with 71% ee and *trans*,*cis*-cyclohexane ***tc*-7b** with 3% ee in 50% and 9% yields, respectively (Table 1, entry 1). The relative configuration of ***tt*-7b** was assigned based on the *trans*-diaxial coupling between the two pairs of the adjacent methine protons (J = 11.2 Hz each). The absolute configuration of ***tt*-7b** was determined by conversion to a known compound with established stereochemistry (see Supplementary Material).

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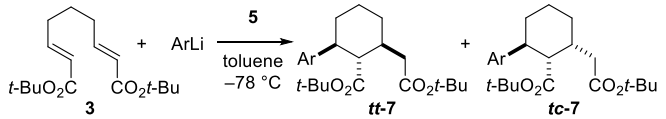
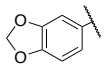
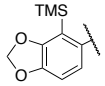
Table 1. Asymmetric conjugate addition cascade.[a]

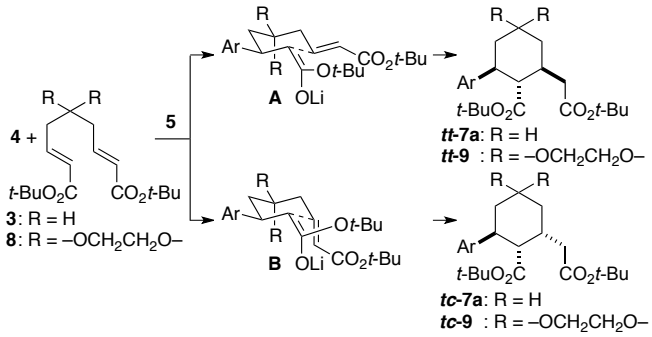


entry	Ar	7	*tt*-7		*tc*-7	
			yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	**7b**	50	71[b]	9	3[b]
2	2-MeC_6H_4	**7c**	63	68	7	42
3	2-*i*-PrC_6H_4	**7d**	72	67[b]	16	61
4	1-naphthyl	**7e**	79	81[b]	4	39[b]
5		**7f**	40	74	10	72
6		**7a**	68	99	18	88

[a] All reactions were carried out using ArLi (3 equiv) and **5** (4.2 equiv). [b] The ee was determined after derivatization (see Supplementary Material).

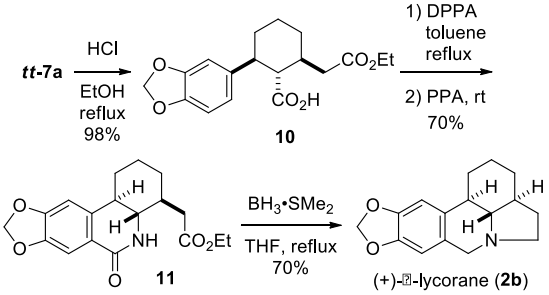
Toward the synthesis of (+)-β-lycorane, benzodioxol-5-yllithium was employed in the cascade reaction. The reaction proceeded with comparable enantioselectivity, and ***tt*-7f** with 74% ee was obtained in 40% yield along with ***tc*-7f** with 72% ee in 10% yield (entry 5). Although ***tt*-7c** and **7d** were obtained with the same level of enantioselectivity (67–68% ee) in the reactions with 2-methyl- and 2-isopropylphenyllithiums (entries 2 and 3), the enantioselectivity was improved in the reaction with 1-naphthyllithium to give ***tt*-7e** with 81% ee in 79% yield along with ***tc*-7e** with 39% ee in 4% yield (entry 4). Encouraged by this result, we utilized aryllithium **4**, bearing a bulky TMS group at the *ortho*-position, in the reaction. To our delight, ***tt*-7a**, which has all the carbon atoms and stereochemistry required for the total synthesis, was obtained in 68% yield with almost perfect enantioselectivity (99% ee; entry 6). Interestingly, the products were obtained in higher yields with the more bulky aryllithiums (entries 1 and 5 vs 2–4 and 6). This is explainable by decreased order of aggregation of the organolithium compounds in solution by the steric hindrance.[13] Unfortunately, lowering the amount of the aryllithium, the enantiomeric excesses of ***tt*-7a** and ***tc*-7a** were decreased to 85% and 54% (2 equiv), or to 50% and 27% (1.2 equiv), respectively, although the yield and the diastereoselectivity were unchanged. These results indicate that the lithium enolate that was generated by the conjugate addition cascade would form a ternary complex with the aryllithium and chiral ligand, which undergoes less enantioselective conjugate addition.[14] Importantly, chiral ligand **5** was quantitatively recovered without any loss of optical purity, and was reusable.

The diastereoselectivity of the cascade reaction is explainable as shown in Scheme 2. The lithium enolate intermediate, which results from the conjugate addition of **4** to **3**, would undergo the intramolecular Michael reaction preferentially via conformer **A** and lead to ***tt*-7a**, due to the absence of the 1,3-diaxial repulsion of the alkenoate moiety, which exists in conformer **B**. Therefore, the lower diastereoselectivity (4:1, Table 1, entry 6) than that in the previously reported reaction of **4** and **8** to give **9** (9:1)[4] could be attributed to the decreased 1,3-diaxial repulsion in conformer **B** (R = H vs ethylenedioxy).



Scheme 2. Rationale for observed diastereoselectivity.

The asymmetric total synthesis of (+)-β-lycorane (**2b**) was accomplished starting from ***tt*-7a** as shown in Scheme 3. Treatment of ***tt*-7a** with HCl for 0.5 h in refluxing ethanol gave protodesilylated half ester **10** in 98% yield. Interestingly and usefully, the carboxylic acid at the C-2 position was not esterified, probably due to steric hindrance.[15] Curtius rearrangement using diphenylphosphoryl azide (DPPA)[16] followed by Bischler–Napieralski-type cyclization with polyphosphoric acid (PPA)[17] converted **10** into lactam **11** via an isocyanate intermediate in 70% yield. Finally, treatment of **11** with borane–dimethyl sulfide complex[18] in refluxing THF induced three sequential transformations: reduction of the lactam, lactam formation between the resulting amine and the ester moiety, and reduction of the resulting lactam to directly give (+)-β-lycorane (**2b**) in 70% yield. ^{1}H and ^{13}C NMR,[6c,d] and the specific rotation[6d] were in good agreement with those reported. Notably, the asymmetric total synthesis was accomplished through only five steps from **3** in high overall yield (33%).



Scheme 3. Asymmetric total synthesis of (+)-β-lycorane (**2b**)

3. Conclusion

This study revealed that the bulky TMS group at the *ortho*-position of aryllithium is effective to improve the enantioselectivity of the chiral ligand-mediated asymmetric conjugate addition cascade of nonadienedioate. Cyclohexanes bearing three contiguous substituents with *trans*,*trans*-configuration were obtained in high optical purity. It was suggested that the 1,3-diaxial interaction would play an important role in determining the diastereoselectivity. This methodology enables the formation of two C–C bonds and three stereogenic centers in one pot to give synthetically useful chiral cyclohexane derivatives. The utility of this methodology was clearly demonstrated by the achievement of the shortest asymmetric total synthesis of (+)-β-lycorane. Importantly, the chiral ligand could be recycled, and the one-pot reactions are economically and ecologically beneficial.

4. Experimental section

4.1. General

All melting points are uncorrected. Silica gel was used for column chromatography. ^{1}H and ^{13}C NMR (500 and 125 MHz, respectively) were measured in $CDCl_3$ unless otherwise mentioned. Chemical shifts and coupling constants are presented in ppm δ relative to tetramethylsilane and Hz, respectively. The wavenumbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. Chiral ligand **5** was prepared as previously described.[19]

4.1.1. Di-*tert*-butyl (2*E*,7*E*)-nona-2,7-dienedioate (3):[20] To a stirred suspension of *tert*-butyl triphenylphosphoranylideneacetate (161 g, 0.43 mol) in toluene (0.26 L) was added a solution of glutaraldehyde (17.2 g, 0.17 mol) in toluene (80 mL) at rt. After 21 h, the mixture was filtered, and the residue was washed with hexane. The combined filtrate and washings were concentrated and purified by column chromatography (hexane/EtOAc = 20/1) to give the title compound (53 g, 90%) as a colorless oil of bp 135–140 °C/0.2 mmHg: R_f = 0.4 (hexane/EtOAc = 9/1). ^{1}H NMR: 1.48 (18H, s), 1.62 (2H, quintet, *J* = 7.3), 2.20 (4H, ddt, *J* = 1.5, 7.0, 7.3), 5.75 (2H, dt, *J* = 15.6, 1.5), 6.83 (2H, dt, *J* = 15.6, 7.0). ^{13}C NMR: 26.4 (CH_2), 28.1 (CH_3), 31.2 (CH_2), 80.1 (C), 123.6 (CH), 146.8 (CH), 165.9 (C). IR (neat): 1710, 1650. EIMS *m*/*z*: 223 (M – *t*-BuO). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.87; H, 9.57. ^{1}H NMR and IR spectra were in agreement with those reported,[20] while ^{13}C NMR had slight difference; 26.4 (CH_2) instead of reported 29.7 (CH_2).

4.2. Asymmetric Conjugate Addition Cascade (Table 1)

4.2.1. General Procedure. (1*S*,2*S*,3*S*)- and (1*R*,2*S*,3*S*)-*tert*-Butyl 2-*tert*-butoxycarbonyl-3-(4-trimethylsilylbenzo[1,3]dioxol-5-yl)cyclohexaneacetate (*tt*-7a and *tc*-7a) (Table 1, entry 3): To a solution of **5** (10.2 g, 42 mmol) and 3,4-methylenedioxy-2-trimethylsilylbromobenzene[21] (8.19 g, 30 mmol) in toluene (280 mL) was added a solution of *t*-BuLi (1.69 M; 16.6 mL, 28 mmol) in pentane at –78 °C, and the resulting solution was stirred for 1 h at the same temperature. A solution of **3** (2.96 g, 10 mmol) in toluene (20 mL) was added at –78 °C, and the mixture was stirred for 10 min at the same temperature. The reaction was quenched by the addition of saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were successively washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Column chromatography (hexane/Et_2O = 30/1) gave ***tt*-7a** (3.31 g, 68%) with 99% ee and ***tc*-7a** (860 mg, 18%) with 88% ee as colorless oils, and **5** (10.2 g, quantitative recovery) as a colorless solid.

***tt*-7a**: R_f = 0.4 (hexane/Et_2O = 9/1, developed twice). $[\alpha]_D^{25}$ +16.8 (*c* 1.26, $CHCl_3$). ^{1}H NMR: 0.35 (9H, s), 1.07 (9H, s), 1.07–1.20 (1H, m), 1.20–1.34 (2H, m), 1.42 (9H, s), 1.72–1.82 (2H, m), 1.89 (1H, m), 2.01 (1H, dd, *J* = 9.8, 14.4), 2.05 (1H, m), 2.27 (1H, dd, *J* = 2.4, 14.4), 2.33 (1H, t, *J* = 11.0), 2.97 (1H, dt, *J* = 1.8, 11.0), 5.78 (2H, m), 6.68–6.76 (2H, m). ^{13}C NMR: 1.5 (CH_3), 25.5 (CH_2), 27.6 (CH_3), 28.0 (CH_3), 30.6 (CH_2), 36.1 (CH_2), 37.6 (CH), 40.2 (CH_2), 45.4 (CH), 55.4 (CH), 79.6 (C), 80.1 (C), 99.4 (CH_2), 108.5 (CH), 119.0 (C), 120.1 (CH), 142.5 (C), 144.0 (C), 152.2 (C), 171.4 (C), 173.3 (C). IR (neat): 1728. EIMS *m*/*z*: 490 (M^+). Anal. Calcd for $C_{27}H_{42}O_6Si$: C, 66.09; H, 8.63. Found: C, 65.92; H, 8.70. The ee was determined by HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 1000/1, 1 mL/min, 250 nm; major 9.5 min, minor 7.5 min).

***tc*-7a:** R_f = 0.5 (hexane/Et_2O = 9/1, developed twice). $[\alpha]_D^{25}$ +11.7 (*c* 1.32, $CHCl_3$). ^{1}H NMR: 0.41 (9H, s), 1.18 (9H, s), 1.1–1.3 (2H. m), 1.44 (9H, s), 1.52–1.62 (2H, m), 1.72–1.84 (2H, m), 2.38 (1H, dd, *J* = 4.6, 15.2), 2.53 (1H, dd, *J* = 3.7, 15.2), 2.71 (1H, m), 2.84 (1H, dd, *J* = 4.0, 11.8), 3.00 (1H, dt, *J* = 3.1, 11.8), 5.83 (2H, m), 6.66 (1H, d, *J* = 8.2), 6.71 (1H, d, *J* = 8.2). ^{13}C NMR: 1.6 (CH_3), 20.5 (CH_2), 27.8 (CH_3), 28.1 (CH_3), 29.4 (CH_2), 33.3 (CH), 34.2 (CH_2), 37.0 (CH_2), 38.5 (CH), 53.0 (CH), 79.7 (C), 80.0 (C), 99.6 (CH_2), 108.6 (CH), 118.0 (CH), 118.9 (C), 143.9 (C), 144.4 (C), 152.5 (C), 172.4 (C), 172.6 (C). IR (neat): 1728. EIMS *m*/*z*: 490 (M^+). Anal. Calcd for $C_{27}H_{42}O_6Si$: C, 66.09; H, 8.63. Found: C, 66.17; H, 8.70. The ee was determined by HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 1000/1, 1 mL/min, 250 nm; major 8.9 min, minor 7.5 min).

4.2.2. *tert*-Butyl (1*S*,2*S*,3*S*)-2-(*tert*-butoxycarbonyl)-3-phenylcyclohexaneacetate (*tt*-7b) (Table 1, entry 1): R_f = 0.5 (hexane/EtOAc = 9/1). A white solid of mp 70–72 °C. 71% ee. $[\alpha]_D^{25}$ +14.0 (*c* 5.00, $CHCl_3$). ^{1}H NMR (C_6D_6): 1.12 (9H, s), 1.22–1.38 (3H, m), 1.41 (9H, s), 1.60 (1H, m), 1.70 (1H, m), 2.02 (1H, m), 2.24 (1H, dd, *J* = 9.5, 15.0), 2.34 (1H, t, *J* = 11.2), 2.40 (1H, m), 2.60 (1H, dd, *J* = 3.1, 15.0), 2.81 (1H, dt, *J* = 3.4, 11.2), 7.05–7.20 (5H, m). ^{13}C NMR (C_6D_6): 26.0 (CH_2), 27.2 (CH_3), 28.1 (CH_3), 31.2 (CH_2), 34.4 (CH_2), 37.9 (CH), 40.7 (CH_2), 48.3 (CH), 56.1 (CH), 79.5 (C), 79.8 (C), 126.6 (CH), 128.3 (CH), 128.3 (CH), 144.6 (C), 171.2 (C), 173.1 (C). IR ($CHCl_3$): 1710. EIMS *m*/*z*: 374 (M^+), 318, 262. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.75; H, 9.33. The ee was determined after reduction with $LiAlH_4$. The absolute configuration was determined after conversion into a known compound (see Supplementary Material).

4.2.3. *tert*-Butyl (1*R*,2*S*,3*S*)-2-(*tert*-butoxycarbonyl)-3-phenylcyclohexaneacetate (*tc*-7b) (Table 1, entry 1): R_f = 0.6 (hexane/EtOAc = 9/1). A white solid of mp 90–95 °C. 3% ee. $[\alpha]_D^{25}$ –19.8 (*c* 2.04, $CHCl_3$). ^{1}H NMR: 1.15 (9H, s), 1.34–1.40 (1H, m), 1.45 (9H, s), 1.58–1.62 (3H, m), 1.79 (1H, m), 1.87 (1H, m), 2.45 (1H, dd, *J* = 9.8, 15.6), 2.50 (1H, dd, *J* = 4.9, 15.6), 2.73 (1H, m), 2.82 (2H, m), 7.15–7.25 (5H, m). ^{13}C NMR: 20.6 (CH_2), 27.7 (CH_3), 28.1 (CH_3), 29.5 (CH_2), 32.8 (CH), 34.2 (CH_2), 35.0 (CH_2), 40.9 (CH), 52.6 (CH), 80.1 (C), 80.2 (C), 126.1 (CH), 127.4 (CH), 128.1 (CH), 145.2 (C), 172.4 (C), 172.9 (C). IR ($CHCl_3$): 1710. EIMS *m*/*z*: 374 (M^+), 318, 262. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.89; H, 9.00. The ee was determined after conversion to the corresponding dimethyl ester (see Supplementary Material).

4.2.4. (1*S*,2*S*,3*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonyl)-3-(2-methylphenyl)cyclohexanacetate (*tt*-7c) (Table 1, entry 2): R_f = 0.5 (hexane/Et_2O = 9/1, developed twice). A colorless oil. 68% ee (HPLC: Daicel Chiralcel OD-H × 2 were connected, hexane/*i*-PrOH = 100/1, 1 mL/min, 254 nm; major 37.5 min, minor 33.2 min). $[\alpha]_D^{25}$ +13.4 (*c* 2.16, $CHCl_3$). ^{1}H NMR: 1.07 (9H, s), 1.17 (1H, m), 1.33 (1H, m), 1.46 (9H, s), 1.56 (1H, m), 1.81 (2H, m), 1.94 (1H, m), 2.05 (1H, dd, *J* = 10.1, 14.7), 2.15 (1H, m), 2.32 (1H, dd, *J* = 3.4, 14.7), 2.32 (3H, s), 2.36 (1H, t, *J* = 10.7), 3.06 (1H, dt, *J* = 3.4, 11.9), 7.04–7.22 (4H, m). ^{13}C NMR: 19.6 (CH_3), 25.9 (CH_2), 27.5 (CH_3), 28.1 (CH_3), 31.0 (CH_2), 33.7 (CH_2), 37.5 (CH), 40.5 (CH_2), 42.1 (CH), 55.5 (CH), 79.9 (C), 80.2 (C), 125.8 (CH), 125.9 (CH), 126.4 (CH), 130.0 (CH), 135.5 (C), 142.1 (C), 171.7 (C), 173.6 (C). IR (neat): 1720. EIMS *m*/*z*: 388 (M^+), 332, 276. Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.91; H, 9.47.

4.2.5. (1*R*,2*S*,3*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonyl)-3-(2-methylphenyl)cyclohexanacetate (*tc*-7c) (Table 1, entry 2): R_f = 0.6 (hexane/Et_2O = 9/1, developed twice). A colorless solid of mp 60–75 °C. 42% ee (HPLC: Daicel Chiralcel OG, hexane/*i*-PrOH = 500/1, 0.5 mL/min, 254 nm; major 10.8 min, minor 15.8 min). $[\alpha]_D^{25}$ –8.28 (*c* 0.79, $CHCl_3$). ^{1}H NMR: 1.12 (9H, s), 1.19–1.27 (2H, m), 1.46 (9H, s), 1.59–1.63 (2H, m), 1.79–1.81 (2H, m),

2.36 (3H, s), 2.47 (1H, dd, *J* = 4.9, 15.3), 2.52 (1H, dd, *J* = 3.4, 14.7), 2.76 (1H, m), 2.92 (1H, dd, *J* = 4.0, 12.2), 3.05 (1H, dt, *J* = 3.7, 12.2), 7.02–7.15 (4H, m). ^{13}C NMR: 19.6 (CH_3), 20.8 (CH_2), 27.6 (CH_3), 28.1 (CH_3), 29.5 (CH_2), 33.1 (CH), 34.0 (CH_2), 34.1 (CH_2), 35.3 (CH), 52.5 (CH), 80.0 (C), 80.2 (C), 124.8 (CH), 125.6 (CH), 126.0 (CH), 130.1 (CH), 135.6 (C), 143.5 (C), 172.4 (C), 172.9 (C). IR (Nujol): 1730, 1710. EIMS *m/z*: 388 (M^+), 332, 276. Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.96; H, 9.38.

4.2.6. (1*S*,2*S*,3*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonyl)-3-(2-isopropylphenyl)cyclohexanacetate (*tt*-7d) (Table 1, entry 3): R_f = 0.4 (hexane/EtOAc = 9/1). A colorless oil. 67% ee. $[\alpha]_D^{25}$ +17.9 (*c* 5.11, $CHCl_3$). ^{1}H NMR: 1.05 (9H, s), 1.17 (3H, d, *J* = 6.7), 1.25 (3H, d, *J* = 6.7), 1.27–1.52 (3H, m), 1.46 (9H, s), 1.82 (1H, m), 1.95 (1H, m), 2.05 (1H, dd, *J* = 9.8, 14.7), 2.16 (1H, m), 2.31 (1H, dd, *J* = 3.1, 14.7), 2.41 (1H, t, *J* = 11.0), 3.17 (1H, dt, *J* = 3.1, 11.0), 3.29 (1H, septet, *J* = 6.7), 7.10–7.26 (4H, m). ^{13}C NMR: 23.2 (CH_3), 24.6 (CH_3), 26.0 (CH_2), 27.5 (CH_3), 28.12 (CH), 28.14 (CH_3), 30.9 (CH_2), 35.0 (CH_2), 37.7 (CH), 40.5 (CH_2), 41.3 (CH), 55.5 (CH), 79.9 (C), 80.2 (C), 124.8 (CH), 125.3 (CH), 126.2 (CH), 126.9 (CH), 140.7 (C), 146.0 (C), 171.6 (C), 173.7 (C). IR (neat): 1720. EIMS *m/z*: 416 (M^+), 360, 304. Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 75.17; H, 9.83. The ee was determined after reduction with $LiAlH_4$ (see Supplementary Material).

4.2.7. (1*R*,2*S*,3*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonyl)-3-(2-isopropylphenyl)cyclohexanacetate (*tc*-7d) (Table 1, entry 3): R_f = 0.5 (hexane/EtOAc = 9/1). A colorless solid of mp 79–81 °C. 61% ee (HPLC: Daicel Chiralcel AD, hexane/*i*-PrOH = 100/1, 0.5 mL/min, 254 nm; major 9.3 min, minor 8.2 min). $[\alpha]_D^{25}$ –15.1 (*c* 0.56, $CHCl_3$). ^{1}H NMR: 1.13 (9H, s), 1.20 (3H, d, *J* = 6.7), 1.29 (3H, d, *J* = 6.7), 1.46 (9H, s), 1.59–1.67 (4H, m), 1.79–1.82 (2H, m), 2.52 (1H, dd, *J* = 10.4, 15.6), 2.57 (1H, dd, *J* = 4.3, 15.6), 2.76 (1H, m), 2.92 (1H, dd, *J* = 4.3, 11.9), 3.17 (1H, dt, *J* = 3.4, 11.9), 3.32 (1H, septet, *J* = 6.7), 7.08–7.25 (4H, m). ^{13}C NMR: 20.7 (CH_2), 23.6 (CH_3), 24.3 (CH_3), 27.7 (CH_3), 28.0 (CH), 28.1 (CH_3), 29.5 (CH_2), 33.0 (CH), 33.9 (CH_2), 34.5 (CH), 35.4 (CH_2), 52.5 (CH), 79.8 (C), 80.1 (C), 125.0 (CH), 125.2 (CH), 125.4 (CH), 126.0 (CH), 141.7 (C), 146.1 (C), 172.5 (C), 172.8 (C). IR (Nujol): 1710. EIMS *m/z*: 416 (M^+), 360, 304. Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.69; H, 9.66.

4.2.8. (1*S*,2*S*,3*S*)- and (1*R*,2*S*,3*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonyl)-3-(naphthalen-1-yl)cyclohexanacetate (*tt*-7e and *tc*-7e) (Table 1, entry 4): R_f = 0.6 (hexane/EtOAc = 9/1, developed twice). A colorless oil. A 79:4 mixture of ***tt*-7e** with 81% ee and ***tc*-7e** with 39% ee. $[\alpha]_D^{25}$ –16.3 (*c* 5.00, $CHCl_3$). ^{1}H NMR: 0.88 (9H, s), 0.98 (1.8H, s), 1.21–1.50 (3H, m), 1.21–2.10 (1.4H, m), 1.48 (9H, s), 1.59 (1.8H, s), 1.66 (1H, m), 1.89 (1H, m), 2.01 (1H, m), 2.12 (1H, dd, *J* = 10.0, 15.0), 2.27 (1H, m), 2.38 (1H, dd, *J* = 3.4, 15.0), 2.51 (0.2H, dd, *J* = 4.0, 15.3), 2.55 (1H, t, *J* = 11.0), 2.65 (0.2H, dd, *J* = 11.0, 15.3), 2.86 (0.2H, m), 3.14 (0.2H, dd, *J* = 4.3, 11.9), 3.74 (1H, dt, *J* = 3.4, 11.0), 7.41–7.51 (4H, m), 7.30–7.50 (1H, m), 7.67 (0.2H, d, *J* = 7.9), 7.68 (1H, d, *J* = 7.9), 7.81 (1H, d, *J* = 8.1), 7.82 (0.2H, d, *J* = 8.0), 8.16 (1H, d, *J* = 8.6). ^{13}C NMR: (***tt*-7e**) 26.0 (CH_2), 27.3 (CH_3), 28.1 (CH_3), 31.2 (CH_2), 34.5 (CH_2), 37.9 (CH), 40.5 (CH_2), 40.9 (CH), 56.0 (CH), 80.0 (C), 80.2 (C), 123.1 (CH), 123.7 (CH), 125.2 (CH), 125.3 (CH), 125.7 (CH), 126.6 (CH), 128.6 (CH), 131.5 (C), 133.8 (C), 140.4 (C), 171.7 (C), 173.1 (C); (***tc*-7e**) 20.9 (CH_2), 27.5 (CH_3), 29.5 (CH_2), 33.4 (CH), 34.3 (CH_2), 34.9 (CH_2), 52.5 (CH), 80.1 (C), 123.0 (CH), 125.3 (CH), 126.4 (CH), 128.8 (CH), 131.6 (C), 133.8 (C), 141.8 (C), 172.3 (C), 172.8 (C). IR (neat): 1720. EIMS *m/z*: 424 (M^+), 368, 312. Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.61; H, 8.64. The ee was determined after reduction with $LiAlH_4$ (see Supplementary Material).

4.2.9. (1*S*,2*S*,3*S*)-*tert*-Butyl 2-*tert*-butoxycarbonyl-3-(benzo[1,3]dioxol-5-yl)cyclohexaneacetate (*tt*-7f) (Table 1, entry 5): R_f = 0.5 (hexane/Et_2O = 4/1). A colorless oil. 74% ee (HPLC: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 100/1, 1 mL/min, 250 nm; major 6.3 min, minor 7.0 min). $[\alpha]_D^{25}$ +15.2 (*c* 1.24, $CHCl_3$). ^{1}H NMR: 1.10 (9H, s), 1.0–1.4 (3H, m), 1.38 (9H, s), 1.70–1.78 (2H, m), 1.84 (1H, m), 1.95 (1H, dd, *J* = 9.8, 14.6), 2.03 (1H, m), 2.11 (1H, t, *J* = 11.0), 2.22 (1H, dd, *J* = 2.7, 14.6), 2.60 (1H, dt, *J* = 2.4, 11.0), 5.81 (2H, m), 6.55 (1H, m), 6.60–6.63 (2H, m). ^{13}C NMR: 25.5 (CH_2), 27.6 (CH_3), 28.0 (CH_3), 30.7 (CH_2), 34.1 (CH_2), 37.3 (CH), 40.3 (CH_2), 47.3 (CH), 56.3 (CH), 79.8 (C), 80.0 (C), 100.5 (CH_2), 107.7 (CH), 107.9 (CH), 120.7 (CH), 137.9 (C), 145.8 (C), 147.2 (C), 171.4 (C), 173.1 (C). IR (neat): 1728. EIMS *m/z*: 418 (M^+). Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.01; H, 8.40.

4.2.10. (1*R*,2*S*,3*S*)-*tert*-Butyl 2-*tert*-butoxycarbonyl-3-(benzo[1,3]dioxol-5-yl)cyclohexaneacetate (*tc*-7f) (Table 1, entry 5): R_f = 0.6 (hexane/Et_2O = 4/1). A colorless oil. 72% ee (HPLC: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 100/1, 1 mL/min, 250 nm; major 6.2 min, minor 7.1 min). $[\alpha]_D^{25}$ –20.1 (*c* 1.78, $CHCl_3$). ^{1}H NMR: 1.21 (9H, s), 1.2–1.4 (2H, m), 1.44 (9H, s), 1.5–1.7 (2H, m), 1.76 (1H, m), 1.84 (1H, m), 2.42 (1H, dd, *J*= 9.5, 15.6), 2.48 (1H, dd, *J* = 4.3, 15.6), 2.68–2.78 (3H, m), 5.89 (2H, m), 6.64 (1H, m), 6.69–6.71 (2H, m). ^{13}C NMR: 20.5 (CH_2), 27.8 (CH_3), 28.1 (CH_3), 29.5 (CH_2), 32.8 (CH), 34.2 (CH_2), 35.2 (CH_2), 40.5 (CH), 52.8 (CH), 80.10 (C), 80.12 (C), 100.7 (CH_2), 107.8 (CH), 107.9 (CH), 120.2 (CH), 139.3 (C), 145.6 (C), 147.3 (C), 172.4 (C), 172.7 (C). IR (neat): 1728. EIMS *m/z*: 418 (M^+). Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.66; H, 8.22.

4.3. Asymmetric total synthesis of (+)-β-lycorane (Scheme 3)

4.3.1. (1*S*,2*S*,6*S*)-2-(Benzo[1,3]dioxol-5-yl)-6-ethoxycarbonylmethylcyclohexanecarboxylic acid (10): To a solution of ***tt*-7a** (2.94 g, 6.0 mmol) in EtOH (2 mL) was added anhydrous 35% HCl in EtOH (20 mL) at rt, and the mixture was heated under reflux for 0.5 h. Water was added at 0 °C, and the whole was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (hexane/EtOAc = 4/1) gave the title compound (2.03 g, 98%) as colorless needles of mp 90–91 °C: R_f = 0.4 (hexane/EtOAc = 4/1). $[\alpha]_D^{25}$ +39.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR: 1.11 (1H, m), 1.23 (3H, t, *J* = 7.0), 1.36–1.51 (2H, m), 1.82–1.90 (3H, m), 2.11–2.19 (2H, m), 2.26 (1H, t, *J* = 11.0), 2.36 (1H, m), 2.71 (1H, dt, *J* = 2.8, 11.0), 4.09 (2H, q, *J* = 7.0), 5.89 (2H, s), 6.59 (1H, dd, *J* = 1.5, 7.9), 6.64–6.68 (2H, m). ^{13}C NMR: 14.1 (CH_3), 25.4 (CH_2), 30.9 (CH_2), 33.7 (CH_2), 37.0 (CH), 39.4 (CH_2), 46.6 (CH), 55.7 (CH), 60.4 (CH_2), 100.7 (CH_2), 107.4 (CH), 108.0 (CH), 120.4 (CH), 137.4 (C), 146.1 (C), 147.5 (C), 172.1 (C), 179.6 (C). IR (Nujol): 2800–3300, 1720, 1685. EIMS *m/z*: 334 (M^+), 288, 201, 135. Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.61; H, 6.55.

4.3.2. (4*S*,4a*R*,11b*R*)-Ethyl (6-oxo-1,2,3,4,4a,5,6,11b-octahydro[1,3]dioxolo[4,5-j]phenanthridin-4-yl)acetate (11): To a solution of **10** (1.84 g, 5.5 mmol) in toluene (16 mL) were added diphenylphosphoryl azide (1.3 mL, 6 mmol) and Et_3N (0.92 mL, 6.6 mmol) at 0 °C. The whole was heated under reflux for 0.5 h. After cooled to rt, the mixture was concentrated *in vacuo* to give colorless oil, which indicated the absorbance at 2250 cm^{-1} in the IR spectrum. To the above oil was added PPA (10 mL) at 0 °C, and the whole was stirred for 0.5 h at rt. Water was added, and the mixture was extracted with $CHCl_3$. The organic layer was successively washed with water, saturated $NaHCO_3$, and brine,

dried over Na_2SO_4, and concentrated. Column chromatography ($CHCl_3$/EtOAc = 4/1), followed by recrystallization from EtOH gave the title compound (1.28 g, 70%) as colorless needles of mp 205–206 °C: R_f = 0.3 ($CHCl_3$/EtOAc = 4/1). $[\alpha]_D^{25}$ +72.7 (*c* 1.06, $CHCl_3$). ^{1}H NMR: 1.17–1.36 (2H, m), 1.29 (3H, t, *J* = 7.0), 1.52 (1H, m), 1.90–1.94 (2H, m), 2.05 (1H, m), 2.27 (1H, dd, *J* = 7.0, 15.9), 2.34 (1H, m), 2.60 (1H, dd, *J* = 5.0, 15.9), 2.71 (1H, dt, *J* = 3.7, 11.6), 3.03 (1H, t, *J* = 11.6), 4.19 (2H, q, *J* = 7.0), 6.00 (2H, m), 6.73 (1H, brs), 6.76 (1H, s), 7.51 (1H, s). ^{13}C NMR: 14.1 (CH_3), 24.5 (CH_2), 26.9 (CH_2), 31.3 (CH_2), 37.7 (CH), 37.8 (CH_2), 41.6 (CH), 59.6 (CH), 60.7 (CH_2), 101.4 (CH_2), 103.9 (CH), 107.9 (CH), 123.2 (C), 138.0 (C), 146.4 (C), 151.0 (C), 165.8 (C), 172.6 (C). IR (Nujol): 3200, 1735, 1660. EIMS *m/z*: 331 (M^+), 243, 216, 202. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.02; H, 6.34; N, 4.25.

4.3.3. (+)-β-Lycorane (2b): To a solution of **11** (662 mg, 2.0 mmol) in THF (100 mL) was added $BH_3{\cdot}SMe_2$ (10 M; 1.0 mL, 10 mmol) at 0 °C, and the mixture was heated under reflux for 3 d. To the mixture was added 10% NaOH at 0 °C, and the whole was extracted with toluene. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (EtOAc/EtOH = 4/1) gave the title compound (442 mg, 70%) as colorless plates of mp 72–73 °C (lit.[3,22] mp 72–73 °C): R_f = 0.4 (EtOAc/EtOH = 4/1). $[\alpha]_D^{20}$ +153 (*c* 1.02, EtOH); lit. $[\alpha]_D^{20}$ –143.3 (*c* 1.04, EtOH) for the enantiomer,[3] $[\alpha]_D^{20}$ +142.5 (*c* 0.17, EtOH).[22] ^{1}H NMR: 1.1–1.2 (2H, m), 1.35–1.55 (2H, m), 1.51 (1H, t, *J* = 10.5), 1.65 (1H, m), 1.9–2.05 (3H, m), 2.26–2.35 (2H, m), 2.50 (1H, t, *J* = 10.5), 3.33 (1H, d, *J* = 14.3), 3.38 (1H, dt, *J* = 5.5, 9.0), 4.06 (1H, d, *J* = 14.3), 5.87 (1H, brs), 5.88 (1H, brs), 6.50 (1H, s), 6.71 (1H, s). ^{13}C NMR: 26.4 (CH_2), 28.2 (CH_2), 28.8 (CH_2), 30.0 (CH_2), 41.7 (CH), 42.9 (CH), 53.8 (CH_2), 57.2 (CH_2), 71.8 (CH), 100.6 (CH_2), 105.3 (CH), 106.8 (CH), 128.4 (C), 131.2 (C), 145.6 (C), 146.1 (C). IR ($CHCl_3$): 2928, 1593, 1485. EIMS *m/z*: 257 (M^+). ^{1}H NMR and ^{13}C NMR are in good agreement with those reported in ref 6c and 6b, respectively, while there are slight differences in ^{1}H NMR and IR from those reported in ref 6d, probably due to a misprint; ours 1.9–2.05 (3H, m) instead of reported 1.93–1.98 (2H, m) and 3.23 (1H, m), and ours 1593 cm^{-1} instead of reported 1724 cm^{-1}, respectively.

Acknowledgment

We thank JSPS and MEXT for financial support.

Supplementary Material

Determination of enantiomeric excess, and relative and absolute configuration, and characterization data of the products (PDF).

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