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Catalytic Asymmetric Hydrogenation of α-Arylcyclohexanones and Total Synthesis of (−)-α-Lycorane

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Abstract: An efficient catalytic asymmetric hydrogenation of racemic α-arylcyclohexanones with an ethylene ketal group at the 5-position of the cyclohexane ring *via* dynamic kinetic resolution has been developed, giving chiral α-arylcyclohexanols with two contiguous stereocenters with up to 99% *ee* and >99:1 *cis*/*trans*-selectivity. Using this highly efficient asymmetric hydrogenation reaction as a key step, (−)-α-lycorane was synthesized in 19.6% overall yield over 13 steps from commercially available starting material.

Keywords: Amarylliaceae alkaloids; asymmetric catalysis; chiral spiro catalyst; dynamic kinetic resolution; hydrogenation; lycorane

Introduction

The transition metal-catalyzed asymmetric hydrogenation of ketones is a powerful and useful methodology for the preparation of optically active chiral alcohols, which are very important building blocks in the synthesis of natural products and pharmaceuticals.[1] In the last decades, remarkable progress has been achieved in the asymmetric hydrogenation of ketones with special focus on the development of efficient chiral catalysts and the exploration of new types of ketone substrates.[2] However, the studies on the asymmetric hydrogenations of ketones directed towards the synthesis of natural products and pharmaceuticals are limited.[3] Recently, we developed several highly efficient hydrogenations of ketones with chiral spiro ruthenium and iridium catalysts,[4] which have been used for the total synthesis of natural products such as galanthamine,[5] mesembrine,[6] tetrahedrocannabinols,[7] and centrolobine.[8] In particular, the ruthenium-catalyzed enantioselective hydrogenation of racemic α,α′-disubstituted cycloalkanones has been developed for the synthesis of chiral diols with three contiguous stereocenters in one step, and was applied to the enantioselective total synthesis of alkaloid (+)-γ-lycorane.[9] However, this synthetic strategy is unsuitable for the synthesis of other lycorine-type Amaryllidaceae alkaloids such as (−)-α-lycorane, (−)-lycorine, and (−)-zephyranthine because they contain a *trans*-fused octahydroquinoline skeleton which are difficult to construct by the previous method (Figure 1).

To develop a new strategy for the enantioselective construction of chiral *trans*-fused octahydroquinoline skeleton, we studied the ruthenium-catalyzed asymmetric hydrogenation of racemic α-arylcyclohexanones **1** containing an ethylene ketal group at the 5-position *via* dynamic kinetic resolution.[10] Although the α-arylcyclohexanones **1** were base sensitive substrates, the chiral spiro ruthenium diphosphine/diamine catalysts **3** showed high efficiency for the hydrogenation of **1** and provided the chiral cyclohexanols **2** in high

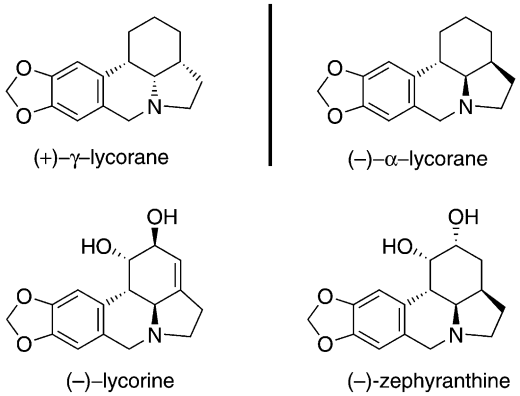
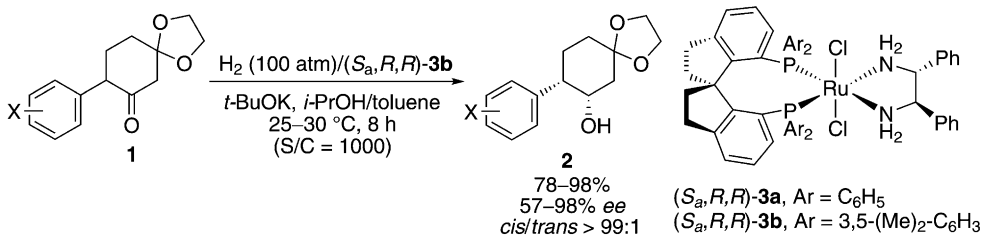


Figure 1. Selected lycorine-type Amarylliaceae alkaloids.



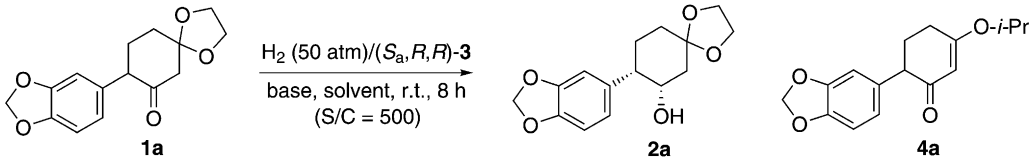
Scheme 1. Asymmetric hydrogenation of racemic α-arylcyclohexanones **1**.

yields with excellent enantioselectivities (up to 98% *ee*) and *cis*-selectivities (*cis*/*trans* >99:1) (Scheme 1). Herein, we report our results on the studies of the asymmetric hydrogenation of racemic α-arylcyclohexanones **1** with chiral spiro ruthenium catalysts and the application of this new strategy to the enantioselective total synthesis of (−)-α-lycorane.

Results and Discussion

The racemic α-arylcyclohexanone **1a** with a 3,4-methylenedioxy group was prepared from commercially available 1,4-dioxaspiro[4.5]decan-8-one in 4 steps in 62% yield (see the Supporting Information) and was studied for an optimization of the hydrogenation conditions. The hydrogenation was firstly performed in *i*-PrOH with (S_a,*R*,*R*)-**3a** as catalyst (S/C = 500) and *t*-BuOK as base (0.033 M) under 50 atm of H_2. However, this base-sensitive substrate gave as by-product 3-isopropoxycyclohex-2-enone **4a**, instead of the desired hydrogenation product **2a** (Table 1, entry 1).[11] When a mixed solvent (*i*-PrOH/toluene = 4:1 v/v) was used, **2a** was produced in 75% yield with 93% *ee* and excellent *cis*-selectivity (*cis*/*trans* >99:1, Table 1, entry 2). Better yield (81%) and enantioselectivity (94% *ee*) were obtained by using catalyst (S_a,*R*,*R*)-**3b** (entry 3). Increasing the ratio of toluene in the mixed solvent to

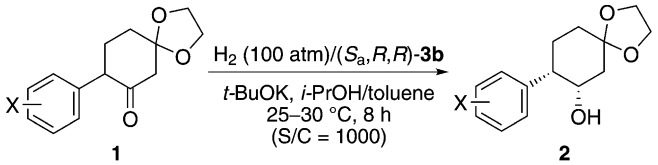
Table 1. Asymmetric hydrogenation of racemic α-arylcyclohexanone **1a**.[a]



Entry	**3**	Solvent	Base	**2a**/**4a**[b]	Yield [%][c]	*ee* [%][d]
1	**3a**	*i*-PrOH	*t*-BuOK	–/100	–	–
2	**3a**	*i*-PrOH/toluene (4:1)	*t*-BuOK	84/16	75	93
3	**3b**	*i*-PrOH/toluene (4:1)	*t*-BuOK	87/13	81	94
4	**3b**	*i*-PrOH/toluene (2:1)	*t*-BuOK	88/12	84	94
5	**3b**	*i*-PrOH/toluene (1:1)	*t*-BuOK	91/9	87	94
6	**3b**	*i*-PrOH/toluene (1:2)	*t*-BuOK	91/9	86	92
7	**3b**	*i*-PrOH/toluene (1:1)	*t*-BuONa	82/18	78	96
8	**3b**	*i*-PrOH/toluene (1:1)	*t*-BuOLi	32/68	29	94
9[e]	**3b**	*i*-PrOH/toluene (1:1)	*t*-BuOK	93/7	89	96
10[f]	**3b**	*i*-PrOH/toluene (1:1)	*t*-BuOK	94/6	90	96
11[g]	**3b**	*i*-PrOH/toluene (1:1)	*t*-BuOK	94/6	90	96
12[h]	**3b**	*i*-PrOH/toluene (1:1)	*t*-BuOK	82/18	81	95

[a] *Reaction conditions:* 1.0 mmol scale, [substrate] = 0.17 M, 0.2 mol% of catalyst, [base] = 0.033 M, solvent (6.0 mL), 50 atm of H_2, room temperature (25–30 °C), 8 h. The *cis*/*trans* selectivity of the product **2a** for all reactions was >99:1 as determined by GC.
[b] Determined by ^{1}H NMR.
[c] Isolated yield.
[d] The *ee* values of *cis*-isomers were determined by HPLC, the absolute configuration was (*S*,*S*) determined by X-ray analyses of the single crystal of **2a** (see the Supporting Information).
[e] 100 atm of H_2.
[f] [base] = 0.017 M, 100 atm of H_2.
[g] 2.0 mmol scale, 0.1 mol% of catalyst, [base] = 0.017 M, 100 atm of H_2.
[h] 20.0 mmol scale, 0.01 mol% of catalyst, [substrate] = 0.33 M, [base] = 0.042 M, 100 atm of H_2, 20 h.

Table 2. Asymmetric hydrogenation of racemic α-arylcyclohexanone **1**.[a]



Entry	X	2	*cis/trans*[b]	Yield [%][c]	*ee* [%][d]
1	3,4-O(CH_2)O	**2a**	>99:1	90	96
2	H	**2b**	>99:1	90	97
3	4-Me	**2c**	>99:1	94	99
4	4-MeO	**2d**	>99:1	98	98
5	4-CF_3	**2e**	>99:1	91	94
6	3-Me	**2f**	>99:1	89	94
7	3-MeO	**2g**	>99:1	92	98
8	2-Me	**2h**	>99:1	68	81
9	2-MeO	**2i**	>99:1	78	57
10	3,4-$(MeO)_2$	**2j**	>99:1	96	96
11	3,4-O(CH_2)O-5-MeO	**2k**	>99:1	87	96

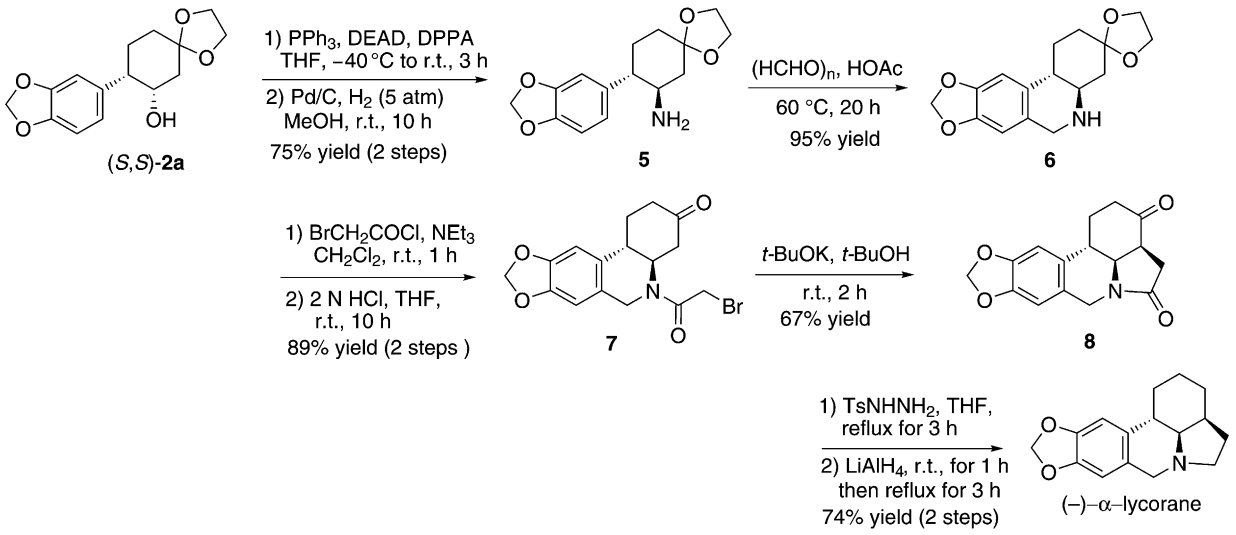
[a] *Reaction conditions:* 2.0 mmol scale, [substrate] = 0.33 M, 0.1 mol% of catalyst, [*t*-BuOK] = 0.017 M, solvent (3.0 mL *i*-PrOH and 3.0 mL toluene), 100 atm of H_2, room temperature (25–30 °C), 8 h.
[b] Determined by GC.
[c] Isolated yield. The major by-products are **4** for all reactions.
[d] The *ee* value of *cis*-isomer was determined by HPLC.

1:1 (v/v) slightly improved the yield (87% yield, entry 5). The base *t*-BuONa gave a higher enantioselectivity (96% *ee*) albeit with somewhat lower yield (78%) (entry 7); however, *t*-BuOLi was not a suitable base for the reaction because of poor solubility in the mixed solvent (entry 8). When the reaction was carried out at 100 atm of H_2, the yield was slightly increased (89%, entry 9). Furthermore, reducing the amount of base from 0.033 to 0.017 M gave no distinct effect on the yield of reaction (entries 9 and 10). The hydrogenation can also be performed smoothly at 0.1 mol% (S/C = 1000) of catalyst loading without diminishing the yield and selectivities (entries 10 and 11). However, when the catalyst loading was further reduced to 0.01 mol% (S/C = 10000), the yield decreased although the enantioselectivity was maintained (entry 12).[12]

Under the optimal reaction conditions, a series of racemic α-arylcyclohexanones **1** was hydrogenated and the results are summarized in Table 2. The electronic property of the substitute on the phenyl ring of the substrate has a distinct effect on both yield and *ee* value of the product (Table 2, entries 1–5). Generally, an electron-donating substituent at the 3- or 4-position gave a higher yield and *ee* value, whereby the substrate **1d** with a 4-OMe gave the highest yield (98%) and the substrate **1c** with a 4-Me gave the highest enantioselectivity (99% *ee*) (entries 3 and 4). The substrates bearing *ortho*-substituents afforded lower yields and *ee* values (entries 8 and 9). It is gratifying that the substrates with multiple oxo-substituents such as **1j** and **1k** also gave the corresponding alcohols **2j** and **2k**, the potential chiral materials for the synthesis of Amarylliaceae alkaloids, in high yields with excellent enantioselectivities (entries 10 and 11).

Subsequently, we studied the enantioselective synthesis of lycorine-type Amarylliaceae alkaloids by the Ru-catalyzed asymmetric hydrogenation of racemic α-arylcyclohexanones **1**. The lycorine-type Amarylliaceae alkaloids possess a vast array of biological properties.[13] For example, lycorine, a representative of this family, exhibits antineoplastic, antiviral, anti-inflammatory activities, as well as an inhibitory effect on cell apoptosis and DNA binding activity.[14] The major challenge in the synthesis of these alkaloids is to construct the intriguing chiral tetracyclic core structure. We selected α-lycorane, one of the degradation products of lycorine,[15] as a model molecule for synthesis by using asymmetric hydrogenation as a key step. Although several methods have been developed for the total synthesis of α-lycorane,[16] examples using a catalytic enantioselective strategy are scarce. Xu et al. reported a synthesis of (−)-α-lycorane by using an asymmetric bifunctional thiourea-catalyzed cascade reaction.[17]

Our synthetic route is outlined in Scheme 2. The hydroxy group of optically active alcohol (*S*,*S*)-**2a** (> 99% *ee*, after recrystallization) was substituted with diphenylphosphoryl azide (DPPA) under Mitsunobu reaction conditions (PPh_3/DEAD, THF, −40 °C to room temperature for 3 h), followed by hydrogenation with H_2/Pd-C in MeOH to yield chiral cyclohex-



Scheme 2. Enantioselective total synthesis of (−)-α-lycorane.

anamine **5** in 75% yield (2 steps). Pictet–Spengler cyclization of cyclohexanamine **5** with paraformadehyde in AcOH at 60 °C for 20 h furnished the tricyclic compound **6** with a six-membered aza-ring in 95% yield. The compound **6** was reacted with bromoacetyl chloride in the presence of triethylamine, followed by treatment with hydrochloric acid in THF to offer α-bromoacetamide derivative **7** in 89% yield (2 steps). According to the modified Umezawa's intramolecular nucleophilic cyclization method,[16g] the tetracyclic compound **8** was produced as a single isomer with 67% yield from intermediate **7** by using *t*-BuOK as a base in *t*-BuOH at room temperature for 2 h. Finally, one-pot reduction of both ketone group and amide group of tetracyclic compound **8** under modified Wolff–Kishner reduction conditions[18] gave the target molecule (−)-α-lycorane in 74% yield with 99% *ee* (determined by HPLC). The optical rotation of our synthetic (−)-α-lycorane is consistent with the reported data in the literature {$[\alpha]_D^{22}$: −29.8 (*c* 1.0, EtOH); lit.[16a] $[\alpha]_D^{22}$: −31.0 (*c* 0.99, EtOH)}. Thus, using a ruthenium-catalyzed asymmetric hydrogenation as a key step, the optically active (−)-α-lycorane was synthesized in 19.6% overall yield over 13 steps from the commercially available 1,4-dioxaspiro-[4.5]decan-8-one.

Conclusions

In conclusion, an efficient catalytic asymmetric hydrogenation of racemic α-arylcyclohexanones with an ethylene ketal group at the 5-position of the cyclohexane ring *via* dynamic kinetic resolution has been developed. With this highly efficient reaction (−)-α-lycorane was synthesized conveniently. Further applications of this strategy to the synthesis of other Amaryllidaceae alkaloids are in progress in our laboratory.

Experimental Section

General Remarks

All reactions and manipulations which are sensitive to moisture and/or air were performed in an argon-filled glovebox (VAC DRI-LAB HE 493) or by using standard Schlenk techniques. Hydrogen gas (99.999%) was purchased from Boc Gas Inc., Tianjin. Anhydrous THF and toluene were distilled from sodium benzophenone ketyl. Anhydrous CH_2Cl_2, NEt_3, *t*-BuOH and *i*-PrOH were freshly distilled from calcium hydride. *t*-BuOK was purchased from Acros Chemical Company. Chiral spiro diphosphine ligands (*S*)-SDP and (*S*)-Xyl-SDP are available from Strem Chemicals Co. and Zhejiang Jiuzhou Pharmaceutical Co. Melting points were measured on a RY-I apparatus and uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AMX-300 or Bruker AMX-400 spectrometers. Chemical shifts were reported in ppm downfield from internal $Si(CH_3)_4$ and external 85% H_3PO_4, respectively. Optical rotations were determined using a Perkin–Elmer 341 polarimeter and an Autopol-VI automatic polarimeter. GC analyses were performed using a Hewlett–Packard Model HP 6890 Series. HPLC analyses were performed using an Agilent Technologies 1260 Infinity. HR-MS were recorded on APEXII and ZAB-HS spectrometers. IR spectra were recorded on a Bruker TENSOR 27 spectrometer.

Asymmetric Hydrogenation of Racemic α-Arylcyclohexanones 1; General Procedure

The catalyst [$RuCl_2$-(S_a)-Xyl-SDP/(*R*,*R*)-DPEN] [(S_a,*R*,*R*)-**3b**] (2.2 mg, 0.002 mmol) and anhydrous *i*-PrOH (2.5 mL) were placed in a hydrogenation vessel. The vessel was placed in an autoclave and purged with hydrogen by pressurizing to 50 atm and releasing the pressure. The procedure

was repeated three times and then the solution was stirred under 50 atm of H_2 for 5 min. After releasing the pressure, α-arylcyclohexanones **1** (2.0 mmol in 3 mL toluene) and a solution of *t*-BuOK in *i*-PrOH (0.2 mmol mL^{-1}, 0.5 mL, 0.1 mmol) were added. The autoclave was purged with hydrogen and pressurized to 100 atm. The reaction mixture was stirred at room temperature (25–30 °C) until no obvious hydrogen pressure drop was observed (8 h). After the hydrogen pressure was released, the solution was concentrated under vacuum. The residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as the eluent to provide the product. The enantioselectivity of the product was determined by HPLC with a chiral column.

(7*S*,8*S*)-8-(Benzo[*d*][1,3]dioxol-5-yl)-1,4-dioxaspiro[4.5]-decan-7-ol (2a): White solid; mp 147–149 °C; yield: 90%; 96% *ee*; $[\alpha]_D^{20}$: +54.0 (*c* 1.0, $CHCl_3$); R_f = 0.5 (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 1H), 6.81–6.62 (m, 2H), 6.03–5.77 (m, 2H), 4.12–3.86 (m, 5H), 3.35 (d, *J* = 9.2 Hz, 1H), 2.62 (dt, *J* = 13.2, 2.8 Hz, 1H), 2.25–2.01 (m, 2H), 1.98–1.84 (m, 2H), 1.80–1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 145.9, 137.4, 120.9, 108.7, 108.6, 107.9, 100.8, 71.5, 64.7, 64.1, 47.2, 40.3, 35.1, 23.7; IR (KBr): ν = 3480, 2889, 2942, 1490, 1438, 1255, 1125, 1087, 1033, 930, 849, 808 cm^{-1}; HR-MS (ESI): *m/z* = 301.1040, calcd. for $C_{15}H_{18}O_5Na$ ([M+Na]$^+$): 301.1046; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 75:25; pressure, 51 bar; flow rate, 1.0 mL min^{-1}; detection, 205 nm light): t_R = 10.50 min (7*S*,8*S*), t_R = 12.04 min (7*R*,8*R*).

(7*S*,8*S*)-8-Phenyl-1,4-dioxaspiro[4.5]decan-7-ol (2b): White solid; mp 78–80 °C; yield: 90%; 97% *ee*; $[\alpha]_D^{20}$: +70.2 (*c* 0.9, $CHCl_3$); R_f = 0.5 (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 4.0 Hz, 4H), 7.25–7.16 (m, 1H), 4.17–3.92 (m, 5H), 3.35 (d, *J* = 9.2 Hz, 1H), 2.71 (dt, *J* = 12.8, 2.8 Hz, 1H), 2.28 (qd, *J* = 13.2, 3.4 Hz, 1H), 2.11 (dt, *J* = 14.0, 2.8 Hz, 1H), 2.02–1.88 (m, 2H), 1.85–1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 128.3, 128.2, 126.5, 108.9, 71.4, 64.8, 64.2, 47.6, 40.5, 35.3, 23.4; IR (KBr): ν = 3494, 2917, 2887, 1496, 1168, 1123, 1091, 852, 747, 698 cm^{-1}; HR-MS (ESI): *m/z* = 257.1150, calcd. for $C_{14}H_{18}O_3Na$ ([M+Na]$^+$): 257.1148; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 85:15; pressure, 47 bar; flow rate, 1.0 mL min^{-1}; detection, 210 nm light): t_R = 7.18 min (7*S*,8*S*), t_R = 8.81 min (7*R*,8*R*).

(7*S*,8*S*)-8-(4-Methylphenyl)-1,4-dioxaspiro[4.5]decan-7-ol (2c): White solid; mp 114–116 °C; yield: 94%; 99% *ee*; $[\alpha]_D^{20}$: +66.0 (*c* 1.0, $CHCl_3$); R_f = 0.5 (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 7.2 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 4.25–3.84 (m, 5H), 3.31 (s, 1H), 2.69 (d, *J* = 12.8 Hz, 1H), 2.33 (s, 3H), 2.41–2.18 (m, 1H), 2.11 (d, *J* = 13.6 Hz, 1H), 2.02–1.87 (m, 2H), 1.84–1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.3, 135.8, 129.0, 127.9, 108.9, 71.4, 64.8, 64.2, 47.1, 40.4, 35.2, 23.4, 21.1. IR (KBr): 3481, 2959, 1515, 1449, 1416, 1167, 1123, 1107, 850, 820 cm^{-1}; HR-MS (ESI): *m/z* = 249.1484, calcd. for $C_{15}H_{21}O_3$ ([M+H]$^+$): 249.1485; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 85:15; pressure, 46 bar; flow rate, 1.0 mL min^{-1}; detection, 220 nm light): t_R = 7.56 min (7*S*,8*S*), t_R = 9.60 min (7*R*,8*R*).

(7*S*,8*S*)-8-(4-Methoxyphenyl)-1,4-dioxaspiro[4.5]-decan-7-ol (2d): White solid; mp 120–122 °C; yield: 98%; 98% *ee*; $[\alpha]_D^{20}$: +67.2 (*c* 1.0, $CHCl_3$); R_f = 0.5 (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.11–3.92 (m, 5H), 3.78 (s, 3H), 3.31 (d, *J* = 8.8 Hz, 1H), 2.66 (dt, *J* = 13.2, 2.4 Hz, 1H), 2.23 (qd, *J* = 13.2, 3.6 Hz, 1H), 2.09 (dt, *J* = 14.0, 3.0 Hz, 1H), 1.98–1.87 (m, 2H), 1.81–1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 135.5, 129.0, 113.7, 108.9, 71.5, 64.8, 64.2, 55.3, 46.7, 40.4, 35.3, 23.6; IR (KBr): ν = 3486, 2905, 1514, 1246, 1086, 989, 814 cm^{-1}; HR-MS (ESI): *m/z* = 265.1435, calcd. for $C_{15}H_{21}O_4$([M+H]$^+$): 265.1434; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 85:15; pressure, 46 bar; flow rate, 1.0 mL min^{-1}; detection, 220 nm light): t_R = 13.56 min (7*S*,8*S*), t_R = 15.49 min (7*R*,8*R*).

(7*S*,8*S*)-8-[4-(Trifluoromethyl)phenyl]-1,4-dioxaspiro-[4.5]decan-7-ol (2e): White solid; mp 90–92 °C; yield: 91%; 94% *ee*; $[\alpha]_D^{20}$: +56.5 (*c* 1.0, $CHCl_3$); R_f = 0.5 (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 4.16–3.94 (m, 5H), 3.54 (d, *J* = 9.6 Hz, 1H), 2.75 (dt, *J* = 13.2, 2.0 Hz, 1H), 2.36–2.21 (m, 1H), 2.10 (dt, *J* = 14.0, 2.8 Hz, 1H), 2.00–1.88 (m, 2H), 1.84–1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 128.6 (q, *J* = 32 Hz), 128.5, 125.1 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 273 Hz), 108.7, 71.1, 64.8, 64.3, 47.5, 40.4, 35.1, 23.4; IR (KBr): ν = 3501, 2957, 2929, 1421, 1328, 1161, 1123, 849 cm^{-1}; HR-MS (ESI): *m/z* = 303.1205, calcd. for $C_{15}H_{18}F_3O_3$ ([M+H]$^+$): 303.1203; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 85:15; pressure, 46 bar; flow rate, 1.0 mL min^{-1}; detection, 220 nm light): t_R = 8.47 min (7*S*,8*S*), t_R = 9.71 min (7*R*,8*R*).

(7*S*,8*S*)-8-(3-Methylphenyl)-1,4-dioxaspiro[4.5]decan-7-ol (2f): Colorless oil; yield: 89%; 94% *ee*; $[\alpha]_D^{20}$: +65.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.15 (m, 1H), 7.14–7.06 (m, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 4.13–3.89 (m, 5H), 3.29 (d, *J* = 9.2 Hz, 1H), 2.66 (dt, *J* = 12.8, 2.8 Hz, 1H), 2.33(s, 3H), 2.35–2.19 (m, 1H), 2.08 (dt, *J* = 14.0, 2.8 Hz, 1H), 1.97–1.85 (m, 2H), 1.82–1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 137.6, 128.8, 128.1, 127.1, 125.1, 108.8, 71.3, 64.7, 64.1, 47.4, 40.4, 35.2, 23.2, 21.6; IR (KBr): ν = 3522, 2930, 2882, 1122, 1091, 703 cm^{-1}; HR-MS (ESI): *m/z* = 249.1490, calcd. for $C_{15}H_{21}O_3$ ([M+H]$^+$): 249.1485; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 85:15; pressure, 44 bar; flow rate, 1.0 mL min^{-1}; detection, 220 nm light): t_R = 6.46 min (7*S*,8*S*), t_R = 8.84 min (7*R*,8*R*).

(7*S*,8*S*)-8-(3-Methoxyphenyl)-1,4-dioxaspiro[4.5]decan-7-ol (2g): White solid; mp 114–116 °C; yield: 92%; 98% *ee*; $[\alpha]_D^{20}$: +64.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 7.8 Hz, 1H), 6.93–6.84 (m, 2H), 6.76 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.17–3.93 (m, 5H), 3.79 (s, 3H), 3.32 (d, *J* = 8.8 Hz, 1H), 2.68 (dt, *J* = 13.2, 2.4 Hz, 1H), 2.25 (qd, *J* = 13.2, 3.6 Hz, 1H), 2.10 (dt, *J* = 14.0, 3.0 Hz, 1H), 2.00–1.88 (m, 2H), 1.83–1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 145.0, 129.1, 120.5, 114.0, 111.6, 108.8, 71.3, 64.8, 64.2, 55.2, 47.5, 40.4, 35.2, 23.3; IR (KBr): ν = 3309, 2938, 2882, 1600, 1540, 1489, 1263, 1122, 1091, 1040, 699 cm^{-1}; HR-MS (ESI): *m/z* = 265.1437, calcd for $C_{15}H_{21}O_4$ ([M+H]$^+$): 265.1434; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 80:20; pressure, 50 bar; flow rate, 1.0 mL min^{-1}; detection, 220 nm light): t_R = 7.66 min (7*S*,8*S*), t_R = 10.42 min (7*R*,8*R*).

(7*S*,8*S*)-8-(2-Methylphenyl)-1,4-dioxaspiro[4.5]decan-7-ol (2h): White solid; mp 99–101 °C; yield: 68%; 81% *ee*; $[\alpha]_D^{20}$: +67.0 (*c* 1.0, $CHCl_3$); R_f = 0.5 (PE:EA = 1:1). ^{1}H NMR

(400 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J = 7.6$ Hz, 1H), 7.24–7.08 (m, 3H), 4.12–3.93 (m, 5H), 3.30 (d, $J = 8.8$ Hz, 1H), 2.95 (dt, $J = 12.8$, 2.8 Hz, 1H), 2.44–2.28 (m, 1H), 2.33(s, 3H), 2.12 (dt, $J = 14.0$, 3.0 Hz, 1H), 2.01–1.90 (m, 2H), 1.82–1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 141.0$, 135.3, 130.3, 127.8, 126.3, 125.9, 108.9, 69.3, 64.8, 64.2, 43.2, 40.7, 35.6, 23.3, 19.7; IR (KBr): $\nu = 3519$, 2930, 2886, 1445, 1125, 1081, 748 cm^{-1}; HR-MS (ESI): $m/z = 249.1487$, calcd. for $C_{15}H_{21}O_3$ ($[M+H]^+$): 249.1485; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 90:10; pressure, 42 bar; flow rate, 1.0 mL min^{-1}; detection, 220 nm light): $t_R = 7.56$ min (7*S*,8*S*), $t_R = 10.15$ min (7*R*,8*R*).

(7*S*,8*S*)-8-(2-Methoxyphenyl)-1,4-dioxaspiro[4.5]decan-7-ol (2i): White solid; mp 90–92 °C; yield: 78%; 57% *ee*; $[\alpha]_D^{20}$: +52.0 (*c* 0.9, $CHCl_3$); $R_f = 0.5$ (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$ (d, $J = 7.6$ Hz, 1H), 7.20 (t, $J = 7.4$ Hz, 1H), 6.94 (t, $J = 7.6$ Hz, 1H), 6.85 (d, $J = 8.0$ Hz, 1H), 4.17 (d, $J = 9.2$ Hz, 1H), 4.09–3.94 (m, 4H), 3.82 (s, 3H), 3.28–3.12 (m, 2H), 2.28 (qd, $J = 13.2$, 3.6 Hz, 1H), 2.08 (dt, $J = 14.0$, 2.8 Hz, 1H), 2.03–1.88 (m, 2H), 1.81–1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.7$, 131.3, 128.4, 127.3, 120.4, 110.0, 109.1, 69.3, 64.8, 64.2, 55.3, 40.4, 39.8, 35.5, 22.6; IR (KBr): $\nu = 3525$, 2945, 2886, 1600, 1492, 1238, 1126, 1082, 1029, 753 cm^{-1}; HR-MS (ESI): m/z = 265.1434, calcd. for $C_{15}H_{21}O_4$ ($[M+H]^+$): 265.1434; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 90:10; pressure, 46 bar; flow rate, 1.0 mL min^{-1}; detection, 220 nm light): $t_R =$ 8.82 min (7*S*,8*S*), $t_R = 12.49$ min (7*R*,8*R*).

(7*S*,8*S*)-8-(3,4-Dimethoxyphenyl)-1,4-dioxaspiro[4.5]-decan-7-ol (2j): White solid; mp 134–136 °C; yield: 95%; 96% *ee*; $[\alpha]_D^{20}$: +55.6 (*c* 0.9, $CHCl_3$); $R_f = 0.5$ (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.91$–6.77 (m, 3H), 4.15–3.93 (m, 5H), 3.87 (s, 3H), 3.85 (s, 3H), 3.29 (d, $J = 8.8$ Hz, 1H), 2.65 (dt, $J = 13.2$, 2.8 Hz, 1H), 2.22 (qd, $J = 13.2$, 4.0 Hz, 1H), 2.10 (dt, $J = 14.0$, 3.0 Hz, 1H), 2.00–1.86 (m, 2H), 1.83–1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 148.7, 147.6, 136.1, 119.9, 111.5, 111.1, 108.9, 71.5, 64.8, 64.2, 56.0, 55.9, 47.1, 40.4, 35.3, 23.8; IR (KBr): $\nu = 3523$, 2933, 2834, 1517, 1456, 1263, 1141, 1119, 1087, 1028, 845 cm^{-1}; HR-MS (ESI): $m/z = 317.1363$, calcd. for $C_{16}H_{22}O_5Na$ ($[M+Na]^+$): 317.1359; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 75:25; pressure, 54 bar; flow rate, 1.0 mL min^{-1}; detection, 210 nm light): $t_R = 11.54$ min (7*S*,8*S*), $t_R =$ 13.95 min (7*R*,8*R*).

(7*S*,8*S*)-8-(7-Methoxybenzo[*d*][1,3]dioxol-5-yl)-1,4-dioxaspiro[4.5]decan-7-ol (2k): White solid; mp 145–147 °C; yield: 87%; 96% *ee*; $[\alpha]_D^{20}$: +54.5 (*c* 1.0, $CHCl_3$); $R_f = 0.5$ (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.53$ (d, $J =$ 0.9 Hz, 1H), 6.47 (d, $J = 0.9$ Hz, 1H), 5.99–5.87 (m, 2H), 4.11–3.93 (m, 5H), 3.89 (s, 3H), 3.32 (d, $J = 9.2$ Hz, 1H), 2.61 (dt, $J = 13.2$, 2.4 Hz, 1H), 2.24–2.04 (m, 2H), 1.97–1.86 (m, 2H), 1.80–1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.7$, 143.3, 138.2, 133.8, 108.8, 107.5, 102.4, 101.3, 71.5, 64.8, 64.2, 56.7, 47.6, 40.5, 35.3, 23.8; IR (KBr): $\nu = 3502$, 2942, 2888, 1633, 1509, 1428, 1125, 1089, 1044, 825 cm^{-1}; HR-MS (ESI): $m/z = 331.1151$, calcd. for $C_{16}H_{20}O_6Na$ ($[M+Na]^+$): 331.1152; HPLC (Chiralcel AD-H; eluent, *n*-hexane/2-propanol = 75:25; pressure, 51 bar; flow rate, 1.0 mL min^{-1}; detection, 220 nm light): $t_R = 12.26$ min (7*S*,8*S*), $t_R =$ 14.39 min (7*R*,8*R*)

Enantioselective Synthesis of (−)-α-Lycorane

Compound 5: Diethyl azodicarboxylate (3.1 mL, 20 mmol) was added dropwise *via* syringe to a solution of **2a** (2.78 g, 10 mmol) and triphenylphosphine (5.24 g, 20 mmol) in THF (100 mL) under nitrogen atmosphere at −40 °C. After stirring for 5 min, diphenyl phosphorazidate (2.2 mL, 10 mmol) was slowly added. The mixture was allowed to warm to room temperature and stirred for additional 3 h to complete the reaction (TLC detected, EtOAc/petroleum ether = 1:4). The reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (10:1) as the eluent to provide a mixture of products including the desired azide product and the hydroxy group eliminated product; yield: 2.8 g (white solid; the azide and eliminated products were difficult to separate by column chromatography).

The mixture was dissolved in methanol (50 mL).To the solution was added 10% Pd/C (0.28 g, 10 wt%), and the mixture was stirred under 5 atm of hydrogen at room temperature for 10 h to complete the hydrogenation. The Pd catalyst was removed by filtration, washed with methanol (2× 20 mL), and the filtrate was concentrated under vacuum. The residue was purified by a column chromatography on silica gel with ethyl acetate/triethylamine (10:1) as the eluent to provide the product **5** as a white solid; yield: 2.1 g (75% for two steps); mp 102–104 °C; $[\alpha]_D^{20}$: −17.0 (*c* 1.0, $CHCl_3$); $R_f = 0.2$ (EA:Et_3N = 50:1). ^{1}H NMR (400 MHz, D_2O): $\delta = 7.03$–6.72 (m, 3H), 5.98 (s, 2H), 4.22–3.95 (m, 4H), 3.43 (td, $J = 12.0$, 4.0 Hz, 1H), 2.67 (td, $J = 11.2$, 3.6 Hz, 1H), 2.28 (dt, $J = 12.4$, 3.2 Hz, 1H), 2.01–1.70 (m, 5H); ^{13}C NMR (100 MHz, D_2O): $\delta = 147.8$, 146.6, 133.9, 121.3, 109.0, 108.1, 107.7, 101.2, 64.3, 64.2, 52.8, 46.9, 38.5, 33.4, 29.5; IR (KBr): $\nu = 2942$, 2883, 1504, 1487, 1439, 1247, 1122, 1038, 934, 808 cm^{-1}; HR-MS (ESI): $m/z = 278.1393$, calcd. for $C_{15}H_{20}NO_4$ ($[M+H]^+$): 278.1387.

Compound 6: A mixture of **5** (1.9 g, 7.0 mmol) and paraformaldehyde (210 mg, 7.0 mmol) dissolved in acetic acid (70 mL) was heating at 60 °C for 20 h. Then the reaction mixture was poured into ice water, basified with K_2CO_3 (powder). The mixture was extracted with CH_2Cl_2 (5× 40 mL). The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by a column chromatography on silica gel with ethyl acetate/triethylamine (20:1) as the eluent to provide the product **6** as a white solid; yield: 1.9 g (95%); mp 148–150 °C; $[\alpha]_D^{20}$: −135 (*c* 1.0, $CHCl_3$); $R_f = 0.3$ (EA:NEt_3 = 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.77$ (s, 1H), 6.47 (s, 1H), 5.97–5.81 (m, 2H), 4.11 (d, $J = 16.0$ Hz, 1H), 4.06–3.83 (m, 5H), 2.71 (td, $J = 11.0$, 3.2 Hz, 1H), 2.36–2.19 (m, 2H), 2.00 (dt, $J = 12.4$, 2.8 Hz, 1H), 1.95–1.84 (m, 1H), 1.71 (td, $J = 13.6$, 4.4 Hz, 1H), 1.59 (t, $J = 12.4$ Hz, 1H), 1.51–1.33 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 146.2$, 145.8, 130.8, 128.9, 108.9, 106.1, 106.0, 100.7, 64.5, 64.4, 56.6, 49.3, 43.0, 42.4, 35.2, 26.6; IR (KBr): $\nu = 3468$, 2924, 1711, 1503, 1227, 1038, 741 cm^{-1}; HR-MS (ESI): $m/z = 290.1391$, calcd. for $C_{16}H_{20}NO_4$ ($[M+H]^+$): 290.1387.

Compound 7: To the stirred solution of **6** (1.9 g, 6.7 mmol) in CH_2Cl_2 (50 mL), triethylamine (1.4 mL, 10.0 mmol) and 2-bromoacetyl chloride (0.7 mL, 8.0 mmol) were added and the mixture was stirred at room temperature for 1 h. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench the reaction and the aqueous phase was extracted with CH_2Cl_2

(3×20 mL). The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was dissolved in THF (50 mL) and cooled to 0 °C by ice-water bath, and 2 N HCl (60 mL) was added over a period of 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 10 h. Then the mixture was extracted with ethyl acetate (3×40 mL). The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (2:1 to 1:2) as the eluent to provide product **7** as a white solid; yield: 2.2 g (89% for two steps); mp 218–220 °C (decomposed); $[\alpha]_D^{20}$: −39.8 (*c* 1.0, $CHCl_3$); R_f = 0.4 (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88–6.71 (m, 2H), 5.97 (d, *J* = 4.8 Hz, 2H), 4.53 (d, *J* = 14.8 Hz, 1H), 4.33 (d, *J* = 14.4 Hz, 1H), 4.17–3.80 (m, 2H), 3.69 (t, *J* = 10.6 Hz, 1H), 3.31 (d, *J* = 13.6 Hz, 1H), 2.90 (t, *J* = 10.8 Hz, 1H), 2.75–2.57 (m, 2H), 2.57–2.31 (m, 2H), 1.87 (qd, *J* = 12.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.4, 165.6, 147.8, 146.4, 131.2, 128.6, 107.0, 104.9, 101.3, 56.6, 47.4, 45.0, 40.3, 40.0, 26.8, 24.9; IR (KBr): ν = 3291, 2890, 1715, 1646, 1505, 1485, 1419, 1276, 1036, 931, 733 cm^{-1}; HR-MS (ESI): *m/z* = 388.0153, calcd. for $C_{16}H_{16}BrNNaO_4$ ($[M+Na]^+$): 388.0155.

Compound 8: A mixture of **7** (730 mg, 2.0 mmol) and *t*-BuOK (448 mg, 4.0 mmol) in *t*-BuOH (20 mL) was stirred at room temperature under a nitrogen atmosphere for 2 h. The reaction was quenched with 1 N HCl (40 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by a column chromatography on silica gel with petroleum ether/ethyl acetate (3:1 to 1:1) as the eluent to provide the product **8** as a white solid; yield: 380 mg (67%); mp 195–197 °C (decomposed); $[\alpha]_D^{20}$: −47.8 (*c* 1.0, $CHCl_3$); R_f = 0.3 (PE:EA = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.73 (s, 1H), 6.62 (s, 1H), 6.02–5.88 (m, 2H), 4.97 (d, *J* = 17.2 Hz, 1H), 4.25 (d, *J* = 17.2 Hz, 1H), 3.85 (dd, *J* = 10.4, 9.2 Hz, 1H), 3.33 (q, *J* = 9.6 Hz, 1H), 2.82–2.42 (m, 6H), 1.94–1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 171.9, 147.1, 147.0, 129.4, 125.4, 106.7, 105.3, 101.4, 59.9, 43.6, 43.3, 38.9, 37.5, 31.8, 22.8; IR (KBr): ν = 3290, 3212, 1710, 1682, 1557, 1540, 1506, 1120, 1036, 668 cm^{-1}; HR-MS (ESI): *m/z* = 308.0895, calcd. for $C_{16}H_{15}NO_4Na$ ($[M+Na]^+$): 308.0893.

(−)-α-Lycorane: A stirred mixture of **8** (142 mg, 0.5 mmol) and tosylhydrazone (130 mg, 0.7 mmol) in THF (5 mL) was refluxed for 4 h under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and $LiAlH_4$ (38 mg, 1.0 mmol) was added. The mixture was stirred for 1 h at room temperature and then refluxed for 3 h. The reaction mixture was cooled to 0 °C and quenched with water (0.5 mL) carefully. The mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3×20 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography on silica gel with ethyl acetate/triethylamine (50:1) as the eluent to provide the (−)-α-lycorane as a white solid; yield: 97 mg (74%); mp 89–91 °C; 99% *ee*; $[\alpha]_D^{20}$: −29.8 (*c* 1.0, EtOH) {lit.[16a] $[\alpha]_D^{22}$: −31.0 (*c* 0.99, EtOH)}; R_f = 0.2 (EA:Et_3N = 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (s, 1H), 6.58 (s, 1H), 5.88 (s, 2H), 4.09 (d, *J* = 15.2 Hz, 1H), 3.76 (d, *J* = 15.2 Hz, 1H), 3.10 (q, *J* = 8.4 Hz, 1H), 2.81 (dt, *J* = 9.2, 2.8 Hz, 1H), 2.53–2.30 (m, 3H), 2.28–2.15 (m, 1H), 1.94–1.51 (m, 6H), 1.24–1.07 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 146.2, 145.5, 135.1, 128.9, 107.0, 104.6, 100.8, 64.6, 54.7, 54.3, 37.0, 34.0, 28.0, 26.2, 25.0, 21.0; IR (KBr): ν = 2921, 2872, 1504, 1481, 1239, 1039, 935, 847 cm^{-1}; HR-MS (ESI): *m/z* = 258.1489, calcd. for $C_{16}H_{20}NO_2$ ($[M+H]^+$): 258.1489; HPLC (Chiralcel OJ-H; eluent, *n*-hexane/2-propanol = 70:30; pressure, 60 bar; flow rate, 1.0 mL min^{-1}; detection, 220 nm light): t_R = 6.35 min (minor), t_R = 7.33 min (major).

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