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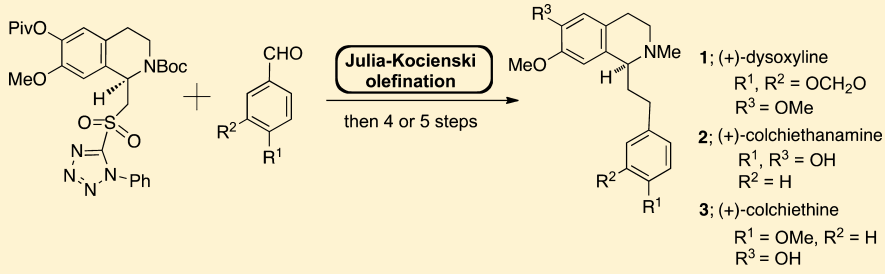
Synthesis of the 1-Phenethyltetrahydroisoquinoline Alkaloids (+)-Dysoxyline, (+)-Colchiethanamine, and (+)-Colchiethine

Raju Jannapu Reddy, Nobuyuki Kawai, and Jun'ichi Uenishi*

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan

Supporting Information



ABSTRACT: Asymmetric total syntheses of the 1-phenethyl-1,2,3,4-tetrahydroisoquinoline alkaloids (+)-dysoxyline (**1**), (+)-colchiethanamine (**2**), and (+)-colchiethine (**3**) are described. In the synthetic routes, coupling of a key, enatiomerically pure 1-(sulfonylmethyl)tetrahydroisoquinoline with aromatic aldehydes, performed by using the Julia–Kocienski reaction, afforded the corresponding 1-(*β*-styryl)-substituted tetrahydroisoquinolines with complete retention of the absolute configuration at the C1 carbon atom. Functionalization of the products generated in these processes by using four- or five-step sequences gave the target alkaloids **1**–**3**.

INTRODUCTION

Alkaloids possessing the 1,2,3,4-tetrahydroisoquinoline (THIQ) ring system are of great interest because of their unique and wide-ranging biological activities.[1] Numerous 1-substituted tetrahydroisoquinolines and related alkaloids are found in nature, as exemplified by 1-phenethyltetrahydroisoquinoline, which serves as a precursor of the homoaporphine, homoproaporphine, and homomorphinandione alkaloids[2] involved in the biosynthesis of colchicine.[3] Importantly, an intramolecular oxidative coupling reaction of 1-phenethyltetrahydroisoquinoline has been proposed to be the pivotal process in the colchicine biosynthetic pathway.

It is interesting that alkaloids conatining both (*S*)- and (*R*)-configurations at the C-1 positions of 1-substituted tetrahydroisoquinoline moieties are found in nature. For example, (+)-dysoxyline (**1**),[4] (+)-colchiethanamine (**2**),[5] (+)-colchiethine (**3**),[5] and (+)-homolaudanosine (**4**)[4] have an (*S*)-configuration at their C-1 centers, while (−)-autumnaline[6] and (−)-isoautumnaline[7] have the (*R*)-configuration at their C-1 positions (Figure 1). As a consequence of this feature, strategies to construct C-1-substituted members of the THIQ alkaloid family must pay attention to the control of the absolute stereochemistry at the C-1 center.[2] Although a number of synthetic methods have been developed to control the stereochemistry of the C-1 center in the 1-substituted THIQ,[8] only the synthesis of optically pure (+)-homolaudanosine has been reported thus far[9,10] for the synthesis of 1-phenethyl-THIQ alkaloids. In the studies described below, we have developed routes for the synthesis of (+)-dysoxyline (**1**), (+)-colchiethanamine (**2**), and (+)-colchiethine (**3**) that rely on key Julia–Kocienski olefination processes.

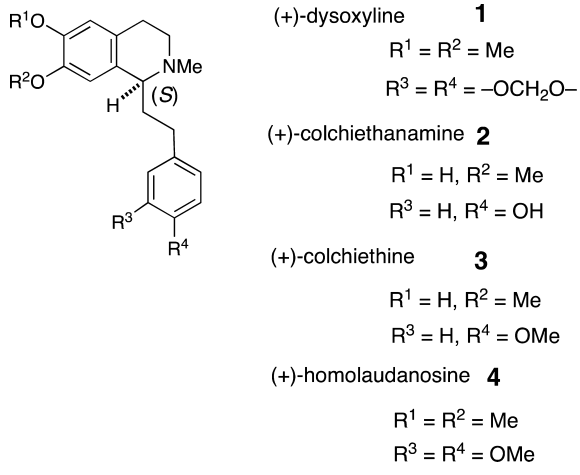


Figure 1. Structures of 1-phenethyltetrahydroisoquinoline natural products.

RESULTS AND DISCUSSION

We have recently described the employment of a $Bi(OTf)_3$-catalyzed dehydrative cyclization, which takes place with 1,3-chirality transfer,[11] to the preparation of the (*S*)- and (*R*)-

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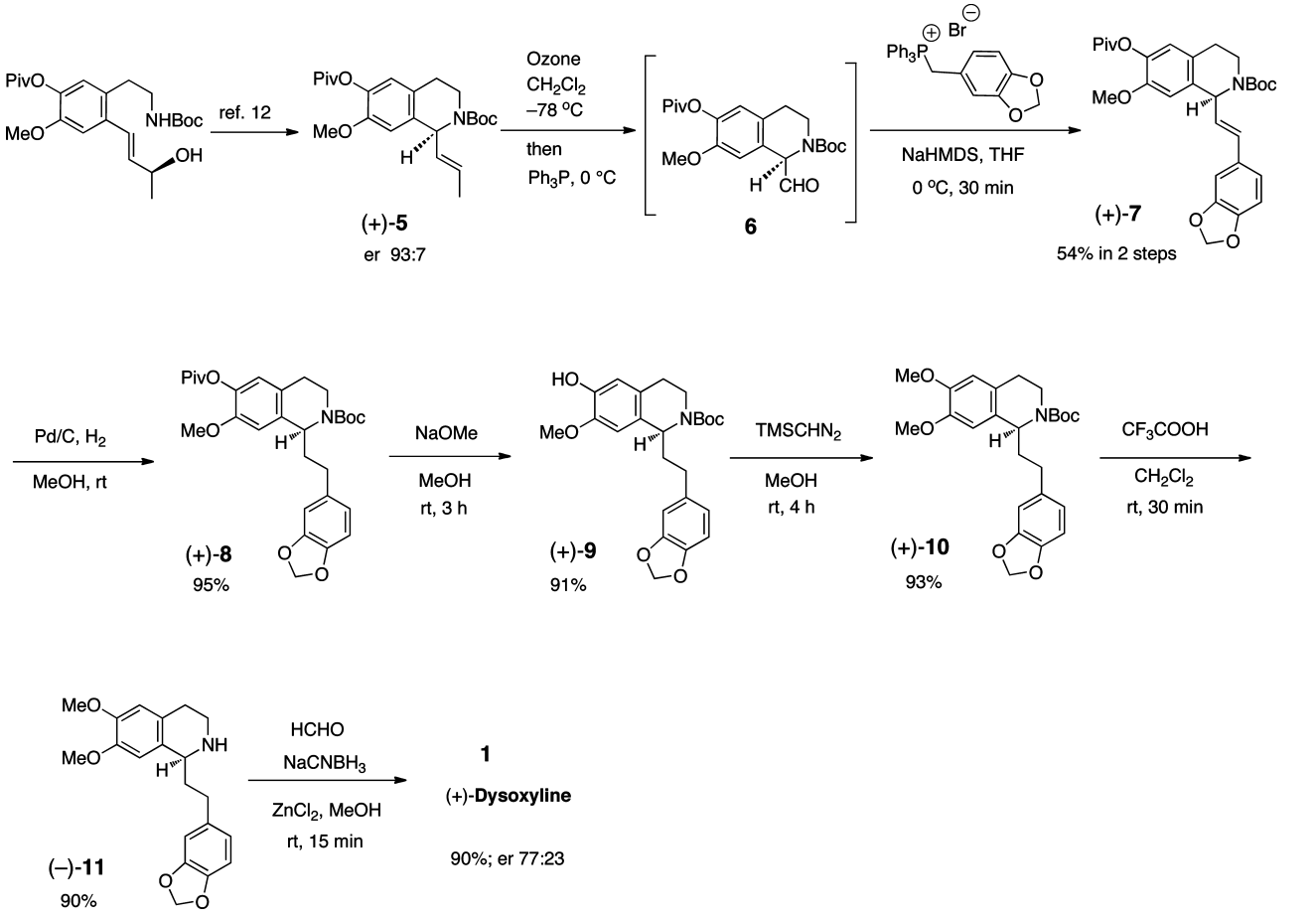
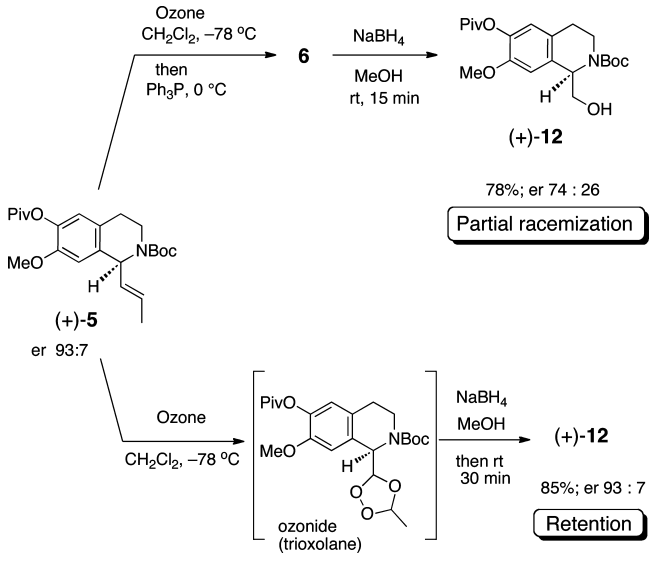
Scheme 1. Synthesis of (+)-Dysoxyline Using a Wittig Reaction Protocol



enantiomers of the 1-alkenyl-substituted THIQ **5** and its application to the synthesis of selected pyrrolotetrahydroisoquinoline alkaloids,[12] exemplified by the preparation of (+)-dysoxyline (**1**) (Scheme 1).

The route employed to prepare **1** began with ozonolysis of **5** followed by reduction of the ozonide with triphenylphosphine to give aldehyde **6**, which was immediately subjected to Wittig olefination, using the ylide generated from (benzo[*d*][1,3]-dioxol-5-ylmethyl)triphenylphosphonium bromide with NaHMDS, to afford alkenyl product **7** in 54% yield (two steps). Pd-catalyzed hydrogenation of the alkene moiety in **7** gave **8** in 95% yield. Replacement of the C-6 *O*-pivaloyl ester in **8** by an *O*-methyl ether was performed in two steps, involving sequential reaction with NaOMe and diazotrimethylsilylmethane to generate **10** in 84% yield (two steps). Removal of the *N*-Boc group in **10** with trifluoroacetic acid gave **11** (90%), which upon reductive methylation with formaldehyde and $NaB(CN)H_3$ in the presence of $ZnCl_2$ afforded (+)-dysoxyline **1** in 90% yield. Unfortunately, the specific rotation of the synthetic dysoxyline $\{[\alpha]_D^{25} = +5.2$ (*c* 0.4, EtOH)} was found to be considerably lower than that of the reported natural (+)-dysoxyline $\{[\alpha]_D^{25} = +22$ (*c* 0.34, EtOH)}.[4] Moreover, chiral HPLC analysis of the synthetic dysoxyline showed that it had a low 74:26 ratio of enantiomers (48% ee). Because the starting tetrahydroisoquinoline (+)-**5** had a high enantiomeric ratio of 93:7 (86% ee), we speculated that partial racemization at the C-1 center occurred during the conversion of **5** to aldehyde **6** and/or during the ensuing Wittig olefination reaction.[13] This expectation was confirmed by the results obtained from the following experiments (Scheme 2). Specifically, the ozonide intermediate produced by treatment of **5** with ozone was reduced by the addition of triphenylphosphine and immediately treated with $NaBH_4$ in methanol at room temperature to form alcohol **12** (78% yield). Analysis of the alcohol product **12** showed that it was comprised of a 74:26 mixture of enantiomers. In contrast,

Scheme 2. Ozonolysis and Reduction



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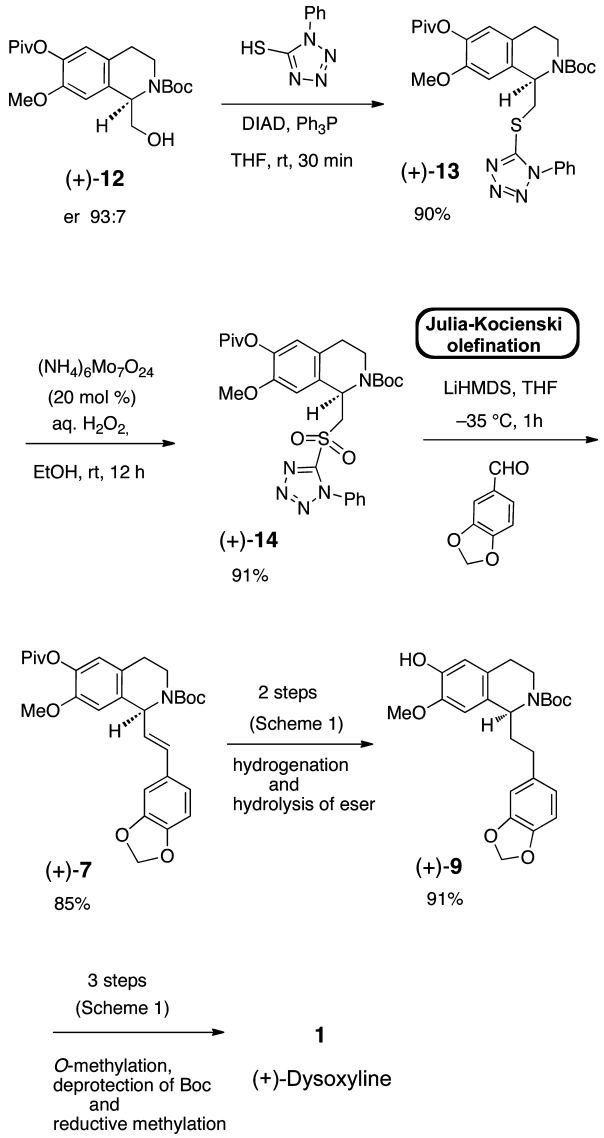
when the ozonide was directly reduced by addition of $NaBH_4$ at −78 °C, alcohol **12** was generated in an high 93:7 enantiomeric ratio (86% ee, determined by using chiral HPLC).[14]

Because the aldehyde **6** undergoes ready racemization, the synthetic route was modified by using the Julia−Kocienski reaction[15] instead of the Wittig reaction to prepare alkene **7** (Scheme 3). We believed that the alternative approach would

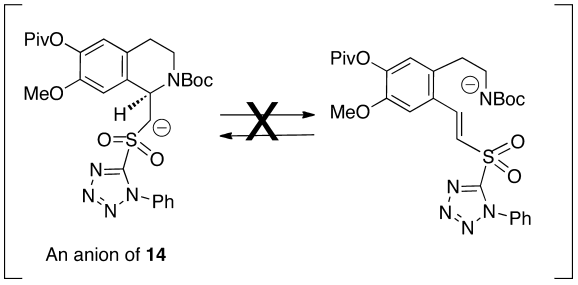
Scheme 3. Synthesis of (+)-Dysoxyline by Using the Julia−Kocienski Reaction Based Route



avoid racemization at the C-1 center. The sulfone precursor, required for the Julia−Kocienski reaction, was prepared by using a two-step procedure starting with alcohol **12** (86% ee).

Sulfenylation of **12** with 5-mercapto-1-phenyltetrazole under Mitsunobu reaction conditions gave the desired sulfide **13**, which was then oxidized by treatment with 30% hydrogen peroxide in the presence of catalytic $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ to give sulfone **14** in 82% yield (two steps). The anion of **14** generated by treatment with LiHMDS in THF was reacted with piperonal in THF at −35 °C to produce alkene **7** in 85% yield as a single (*E*)-isomer. Although concerned by the possibility, the Julia−Kocienski reaction was not complicated by competitive retro-Michael type C−N bond cleavage of the anion intermediate (Scheme 4). Conversion of **7** to

Scheme 4. Possible Retro-Michael Cleavage of Sulfonylmethyl Anion of 14



(+)-dysoxyline (**1**) was then achieved by utilizing the same five-step route outlined in Scheme 3. Importantly, the specific rotation of **1** generated by using the modified procedure was found to be +16.2, corresponding to a 94:6 enantiomer ratio (88% ee) by using chiral HPLC analysis.

The general strategy used to carry out the synthesis of (+)-dysoxyline was employed to prepare the enantiomerically enriched 6,7-dioxytetrahydroisoquinoline alkaloids (+)-colchiethanamine (**2**) and (+)-colchiethine (**3**) (Scheme 5). Julia−Kocienski olefination of **14** with the 4-(pivaloyloxy)-benzaldehyde in the presence of LiHMDS provided the desired **15a** as a single *E*-isomer in 79% yield. Hydrogenation of **15a** provided **16a** (94%), which was then subjected to sequential deprotection of the *N*-Boc group with TMSOTf in CH_2Cl_2 and reductive methylation to form **18a** in 70% overall yield in two steps. Finally, removal of the pivaloyl groups in **18a** by using NaOMe afforded (+)-colchiethanamine (**2**) in a 93:7 enantiomeric ratio (chiral HPLC analysis), the spectroscopic data of which matched those reported in the literature.[5] (+)-Colchiethine (**3**) was also synthesized in a similar manner starting with **14** by using anisaldehyde instead of 4-(pivaloyloxy)benzaldehyde in the Julia−Kocienski coupling step (five steps, 53% yield, Scheme 5).

In the study described above, we have demonstrated that the chiral tetrahydroisoquinoline (*S*)-**5** can be employed as a common starting material for the synthesis of enantiomerically enriched 1-phenethyltetrahydroisoquinoline alkaloids. Specifically, a strategy leading to the first asymmetric total syntheses of (+)-dysoxyline (**1**), (+)-colchiethanamine (**2**), and (+)-colchiethine (**3**) has been developed that relies on Julia−Kocienski olefination reactions as key steps. The sulfone **14** used in these approaches should serve as a versatile intermediate in the routes for the synthesis of other phenethyltetrahydroisoquinoline and related alkaloids.[2,3]

■ EXPERIMENTAL SECTION[16]

(*S*)-1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethenyl)-*N*-*tert*-butoxycarbonyl-7-methoxy-6-(pivaloyloxy)-3,4-dihydro-2(1*H*)-isoquinoline (7) Using a Wittig Olefination Strategy. To a stirred solution of **5** (50 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) was bubbled a stream of ozone at −78 °C until TLC analysis indicated complete consumption of the starting material (ca. 1 min). Argon gas was passed through the solution for an additional 1 min and then Ph_3P (84 mg, 0.32 mmol) was added. The mixture was stirred at 0 °C for 15 min and concentrated in vacuo, giving a residue that was dissolved in THF (1.5 mL). The solution was added immediately to a solution of Wittig reagent generated from (piperonyl)triphenylphosphonium bromide (190 mg, 0.4 mmol) and NaHMDS (1.9 M solution in THF, 0.17 mL,

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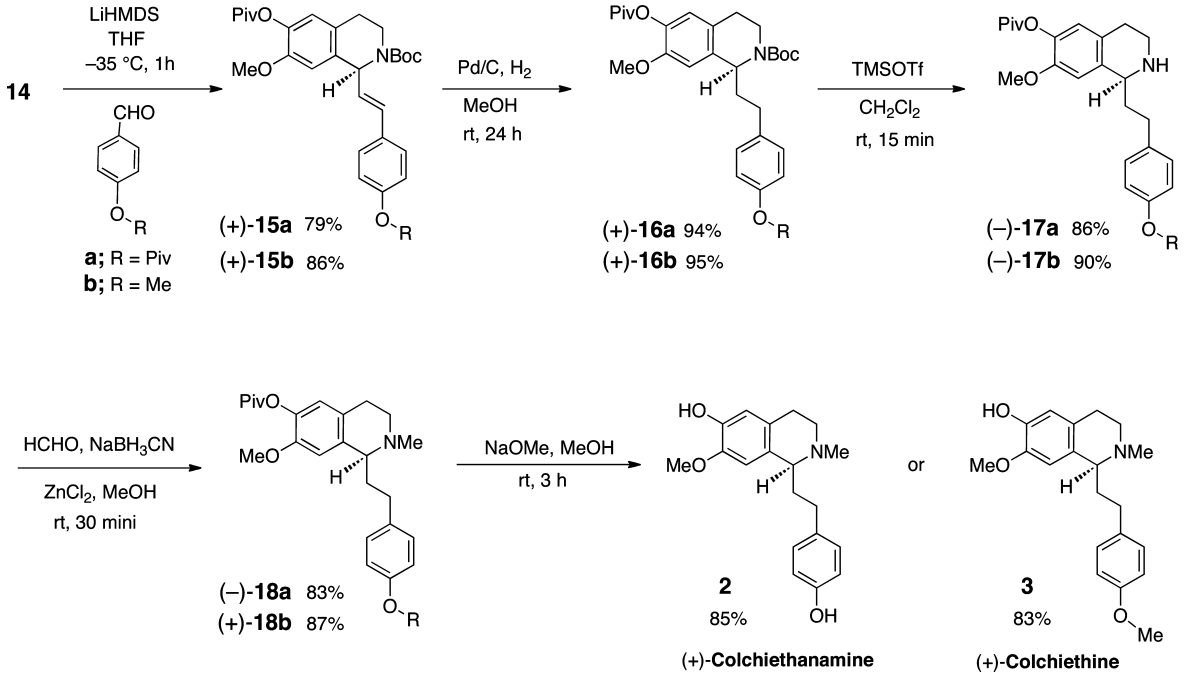
Scheme 5. Syntheses of (+)-Colchiethanamine (2) and (+)-Colchiethine (3)



0.32 mmol) in THF (1.5 mL) at 0 °C. After stirring for 30 min, saturated ammonium chloride was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residual product was purified by silica gel column chromatography (5% and then 10% EtOAc in hexane) to provide the alkene **7** (30 mg) as a colorless oil in 49% yield. $[\alpha]_D^{22}$ = +25.4 (*c* 0.1, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1752, 1691. ^1H NMR (500 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.86–6.66 (m, 4H), 6.32 (d, *J* = 15.0 Hz, 1H), 6.12 (d, *J* = 15.0 Hz, 1H), 5.93 (s, 2H), 5.65 (apparent bs, 1H), 4.20 (apparent bs, 1H), 3.75 (s, 3H), 3.15 (apparent bs, 1H), 2.85 (t, *J* = 15.0 Hz, 1H), 2.64 (d, *J* = 15.0 Hz, 1H), 1.49 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.8, 154.5, 149.5, 148.0, 147.2, 138.9, 131.2, 131.0, 127.3, 127.1, 122.7, 121.1, 111.8, 108.3, 108.2, 105.7, 101.0, 79.9, 56.0, 39.0, 29.6, 28.5, 27.8, 27.1. MS (EI): *m*/*z* 509 (M^+). HRMS (EI): calcd for $C_{29}H_{35}NO_7$ *m*/*z* 509.2413, found 509.2405.

(*R*)-*N*-*tert*-Butoxycarbonyl-1-(hydroxymethyl)-7-methoxy-6-(pivaloyloxy)-3,4-dihydro-2(1*H*)-isoquinoline (12). Stepwise Preparation by Ozonolysis of Alkene 5 and Reduction of Aldehyde 6. To a stirred solution of **5** (20 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was bubbled a stream of ozone at −78 °C (ca. 60 s). An argon gas was then passed through the solution for an additional 1 min and Ph_3P (26 mg, 0.1 mmol) was added. The mixture was stirred at 0 °C for 15 min and concentrated in vacuo at 0 °C, giving a residue that was dissolved in MeOH (2 mL). Then, to the MeOH solution was added sodium borohydride (9.6 mg, 0.25 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 15 min. Saturated ammonium chloride was slowly added to give a mixture that was extracted with dichloromethane. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual product was purified by silica gel column chromatography (50% EtOAc in hexane) to provide alcohol **12** (15.2 mg) in 78% yield. $[\alpha]_D^{22}$ = +40.4 (*c* 0.1, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 3434, 1749, 1680. ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.78:1 mixture of carbamate rotamers; δ 6.79 (s, 1H), 6.75 (s, 1H), 5.25 (apparent bs, 0.64H), 5.10 (apparent bs, 0.36H), 3.94–3.70 (m, 6H), 3.40 (apparent bs, 0.64H), 3.24 (apparent bs, 0.36H), 2.86–2.62 (m, 2H), 1.49 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): signals correspond to both rotamers; δ 176.8, 157.0, 154.0, 149.6, 139.1, 131.5, 127.6, 127.3, 123.0, 122.6, 111.3, 80.5, 67.3, 66.0, 56.9, 56.6, 56.1, 39.6, 39.0, 37.7, 28.4, 27.7, 27.2. MS (EI): *m*/*z* 393 (M^+). HRMS (EI): calcd for $C_{21}H_{31}NO_6$ *m*/*z* 393.2151, found 393.2147. Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.81; H, 7.84; N, 3.42. The enantiomeric ratio of the alcohol **12** was found to be 74:26 (48% ee) determined by chiral HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexane, flow rate = 0.5 mL/min, *T* = 20 °C, 254 nm): t_s = 13.8 (major; *S*-isomer), t_s = 18.3 (minor; *R*-isomer).

Preparation of 12 by Ozonolysis of 5 and Direct Reduction of the Ozonide. To a stirred solution of **5** (400 mg, 1 mmol) in CH_2Cl_2 (20 mL) cooled at −78 °C was bubbled a stream of ozone until TLC analysis indicated complete consumption of the starting material. An excess of ozone was removed by bubbling of Ar through the solution at the same temperature. Dilution of the solution with MeOH (10 mL) at −78 °C was followed by addition of sodium borohydride (190 mg, 5 mmol) in one portion at the same temperature. Following stirring at room temperature for 30 min, the mixture was diluted by slow addition of saturated ammonium chloride and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual product was purified by flash column chromatography (50% EtOAc in hexane) to provide the alcohol (334 mg, 85%) as a white amorphous powder. R_f = 0.5 (50% EtOAc in hexane). Mp: 57–59 °C. $[\alpha]_D^{20}$ = +53.9 (*c* 0.77, $CHCl_3$). The enantiomeric ratio (er: 93:7; 86% ee) was determined by chiral HPLC analysis under the conditions described in the proceeding experiment.

(*R*)-*N*-*tert*-Butoxycarbonyl-1-[(1-phenyl-1*H*-tetrazol-5-yl)-thiomethyl]-7-methoxy-6-(pivaloyloxy)-3,4-dihydro-2(1*H*)-isoquinoline (13). To a stirred solution of **12** (200 mg, 0.5 mmol), phenyl-1*H*-tetrazole-5-thiol (107 mg, 0.6 mmol), and triphenylphosphine (157 mg, 0.6 mmol) in THF (10 mL) was added diisopropyl azodicarboxylate (2.2 M solution in hexane, 280 μL, 0.6 mmol) dropwise at 0 °C. The solution was allowed to stir at room temperature for an additional 30 min and concentrated in vacuo. The residual product was purified by flash column chromatography (20%–30% EtOAc in hexane) to give **13** (250 mg, 90%) as a colorless viscous liquid. R_f = 0.35 (30% EtOAc in hexane). $[\alpha]_D^{20}$ = +82.5 (*c* 1.65, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1752, 1692. ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.5:1 mixture of carbamate rotamers; signals correspond to both rotamers; δ 7.62 (d, *J* = 7.0 Hz, 2H), 7.58–7.50 (m, 3H), 7.06 (s, 0.6H), 6.97 (s, 0.4H), 6.78 (s, 1H), 5.66 (apparent d, *J* = 10.0 Hz, 0.6H), 5.55 (apparent d, *J* = 10.0 Hz, 0.4H), 4.30 (apparent d, *J* = 14.0 Hz, 0.8H), 4.00 (apparent d, *J* = 14.0 Hz, 1.2H), 3.86 (s, 1.8H), 3.82 (s, 1.2H), 3.55 (apparent t, *J* = 12.0 Hz, 0.4H), 3.43 (apparent t, *J* = 12.0 Hz, 0.6H), 3.23 (apparent t, *J* = 12.0

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Hz, 0.4H), 3.04 (apparent t, J = 12.0 Hz, 0.6H), 3.00−2.78 (m, 1H), 2.64−2.58 (m, 1H), 1.39 (s, 3H), 1.35 (s, 9H), 1.20 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): signals correspond to both rotamers; δ 176.7, 154.5, 154.2, 149.8, 139.4, 133.6, 132.9, 130.0, 129.9, 129.8, 129.5, 126.5, 124.1, 123.3, 123.0, 122.8, 111.2, 80.3, 79.9, 56.1, 52.5, 39.0, 38.1, 36.1, 28.1, 27.2, 27.1. MS (EI): m/z 553 (M^+). HRMS (EI): calcd for $C_{28}H_{35}N_5O_5S$ m/z 553.2358, found 553.2366.

(*R*)-*N*-*tert*-Butoxycarbonyl-1-[(1-phenyl-1*H*-tetrazol-5-sulfonyl)methyl]-7-methoxy-6-(pivaloyloxy)-3,4-dihydro-2(1*H*)-isoquinoline (14). To a stirred solution of sulfide **13** (250 mg, 0.45 mmol) in ethanol (10 mL) were added ammonium paramolybdate tetrahydrate (111 mg, 0.09 mmol) and 30% hydrogen peroxide (0.5 mL, 5.4 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h, poured into saturated aqueous sodium thiosulfate, and extracted with ethyl acetate three times. The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residual product was purified by flash chromatography (30% EtOAc in hexane) to give **14** (240 mg, 91%) as a white amorphous solid. R_f = 0.38 (30% EtOAc in hexane). Mp: 70−71 °C. $[\alpha]_D^{20}$ = +73.8 (c 0.3, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1750, 1691, 1352, 1116. ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 2:1 mixture of carbamate rotamers; δ 7.72 (d, J = 7.0 Hz, 2H), 7.66−7.54 (m, 3H), 6.88 (s, 0.33H), 6.84 (s, 0.67H), 6.80 (s, 0.33H), 6.77 (s, 0.67H), 5.99 (apparent t, J = 6.0 Hz, 0.33H), 5.84 (apparent d, J = 6.0 Hz, 0.67H), 4.24−4.10 (m, 2H), 4.5 (m, 0.67H), 3.96 (m, 0.33H), 3.80 (m, 3H), 3.26 (m, 0.67H), 3.15 (m, 0.33H), 2.86 (m, 0.33H), 2.78 (m, 0.67H), 2.69−2.60 (m, 1H), 1.35 (s, 9H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): signals correspond to both rotamers; δ 176.6, 154.2, 153.8, 153.5, 153.2, 150.1, 149.9, 139.8, 139.7, 133.1, 132.8, 131.8, 131.4, 131.3, 131.2, 129.7, 129.3, 127.2, 126.7, 125.5, 124.8, 123.4, 123.1, 110.7, 110.5, 81.0, 80.6, 60.3, 59.8, 56.1, 49.6, 49.3, 39.0, 38.4, 36.7, 28.2, 28.0, 27.1. MS (EI): m/z 585 (M^+). HRMS (EI): calcd for $C_{28}H_{35}N_5O_7S$ m/z 585.2257, found 585.2251. Anal. Calcd for $C_{28}H_{35}N_5O_7S$: C, 57.42; H, 6.02; N, 11.96. Found: C, 57.63; H, 6.10; N, 11.69.

(*S*)-1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethenyl)-*N*-*tert*-butoxycarbonyl-7-methoxy-6-(pivaloyloxy)-3,4-dihydro-2(1*H*)-isoquinoline (7). To a stirred solution of **14** (117 mg, 0.2 mmol) and piperonal (164 mg, 1 mmol) in THF (5 mL) was added lithium bis(trimethylsilyl)amide (1.30 M in THF, 0.46 mL, 0.6 mmol) dropwise at −35 °C. The resulting pale-yellow solution was stirred vigorously for an additional 1 h and diluted with the sat. ammonium chloride, and the mixture was extracted with ethyl acetate. The organic extract was washed with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residual product was purified by silica gel column chromatography (5% and then 10% EtOAc in hexane) to provide **7** in 85% yield (86 mg) as a colorless solid. R_f = 0.40 (20% EtOAc in hexane). $[\alpha]_D^{20}$ = +37.3 (c 0.28, $CHCl_3$). Mp: 61−62 °C. IR ($CHCl_3$, cm^{-1}): 1752, 1691. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.86−6.66 (m, 4H), 6.32 (d, J = 15.0 Hz, 1H), 6.12 (d, J = 15.0 Hz, 1H), 5.93 (s, 2H), 5.65 (apparent bs, 1H), 4.20 (apparent bs, 1H), 3.75 (s, 3H), 3.15 (apparent bs, 1H), 2.85 (t, J = 15.0 Hz, 1H), 2.64 (d, J = 15.0 Hz, 1H), 1.49 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.8, 154.5, 149.5, 148.0, 147.2, 138.9, 131.2, 131.0, 127.3, 127.1, 122.7, 121.1, 111.8, 108.3, 108.2, 105.7, 101.0, 79.9, 56.0, 39.0, 29.6, 28.5, 27.8, 27.1. MS (EI): m/z 509 (M^+). HRMS (EI): calcd for $C_{29}H_{35}NO_7$ m/z 509.2413, found 509.2405. Anal. Calcd for $C_{29}H_{35}NO_7$: C, 68.35; H, 6.92; N, 2.75. Found: C, 68.05; H, 6.66; N, 2.99.

(*S*)-1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-*tert*-butoxycarbonyl-7-methoxy-6-(pivaloyloxy)-3,4-dihydro-2(1*H*)-isoquinoline (8). A mixture of **7** (76 mg, 0.15 mmol) and 5% Pd−charcoal (20 mg) was stirred in MeOH (5 mL) under a H_2 gas atmosphere at room temperature for 24 h. The mixture was diluted with $CHCl_3$ and filtered through a Celite pad. The filtrate was concentrated in vacuo, giving a residue that was subjected to silica gel column chromatography (20% EtOAc in hexane) to give **8** in 95% yield (73 mg) as a colorless solid. R_f = 0.42 (20% EtOAc in hexane). Mp: 50−52 °C. $[\alpha]_D^{22}$ = +41.1 (c 0.3, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1749, 1684. ^{1}H NMR (500 MHz, $CDCl_3$): the compound exits as a 1.13:1 mixture of carbamate rotamers; δ 6.79−6.60 (m, 5H), 5.91 (s, 2H), 5.20 (apparent bs, 0.47H), 5.05 (apparent bs, 0.53H), 4.23 (apparent d, J = 12.0 Hz, 0.53H), 3.97 (apparent d, J = 12.0 Hz, 0.47H), 3.76 (apparent d, J = 12.0 Hz, 3H), 3.26−3.12 (m, 1H), 2.90−2.70 (m, 1H), 2.69−2.58 (m, 3H), 2.14−1.94 (m, 2H), 1.48 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): signals correspond to both rotamers; δ 176.8, 155.0, 154.8, 149.3, 147.5, 147.4, 145.6, 145.4, 138.7, 138.6, 136.1, 135.8, 135.6, 135.5, 126.6, 126.2, 122.8, 122.6, 121.0, 120.9, 111.2, 110.9, 108.8, 108.7, 108.1, 100.7, 80.0, 79.6, 56.0, 54.6, 53.8, 39.0, 38.6, 38.1, 36.6, 32.6, 32.5, 28.4, 27.6, 27.4, 27.1. MS (EI): m/z 511 (M^+). HRMS (EI): calcd for $C_{29}H_{37}NO_7$ m/z 511.2570, found 511.2562. Anal. Calcd for $C_{29}H_{37}NO_7$: C, 68.08; H, 7.29; N, 2.74. Found: C, 67.68; H, 6.97; N, 2.75.

(*S*)-1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-*tert*-butoxycarbonyl-6-hydroxy-7-methoxy-3,4-dihydro-2(1*H*)-isoquinoline (9). A mixture of **8** (66 mg, 0.13 mmol) and NaOMe (70.0 mg, 1.3 mmol) in MeOH (4 mL) was stirred for 4 h at room temperature. The mixture was quenched with dilute HCl and extracted with ethyl acetate. The extract was dried over $MgSO_4$, and concentrated in vacuo, giving a residue that was subjected to silica gel column chromatography (30% EtOAc in hexane) to give **9** (50 mg, 90%) as a colorless solid. R_f = 0.31 (30% EtOAc in hexane). Mp: 129−131 °C. $[\alpha]_D^{22}$ = +51.4 (c 0.24, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 3365, 1683. ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1:1 mixture of carbamate rotamers; δ 6.76−6.64 (m, 4H), 6.53 (s, 1H), 5.90 (s, 2H), 5.52 (s, 1H), 5.13 (apparent bs, 0.5H), 4.99 (apparent bs, 0.5H), 4.18 (apparent d, J = 10.0 Hz, 0.5H), 3.94 (apparent d, J = 10.0 Hz, 0.5H), 3.85 (apparent d, J = 10.0 Hz, 3H), 3.28−3.15 (m, 1H), 2.84−2.70 (m, 1H), 2.68−2.56 (m, 3H), 2.10−1.92 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): signals correspond to both rotamers; δ 155.0, 154.8, 147.5, 147.4, 145.6, 145.4, 144.9, 144.2, 144.1, 136.0, 135.7, 129.4, 128.9, 127.1, 126.7, 120.9, 120.8, 114.4, 114.2, 109.5, 109.1, 108.8, 108.7, 108.1, 108.0 100.7, 79.9, 79.5, 56.0, 54.5, 53.7, 39.2, 38.8, 38.4, 36.9, 32.6, 32.5, 28.4, 27.8, 27.6. MS (EI): m/z 427 (M^+). HRMS (EI): calcd for $C_{24}H_{29}NO_6$ m/z 427.1995, found 427.1989. Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.11; H, 6.51; N, 3.22.

(*S*)-1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-*tert*-butoxycarbonyl-6,7-dimethoxy-3,4-dihydro-2(1*H*)-isoquinoline (10). To a solution of **9** (43 mg, 0.1 mmol) in MeOH (4 mL) was added $TMSCHN_2$ (0.6 M solution in hexane, 1.66 mL, 1 mmol) and the mixture was stirred at room temperature for 4 h. Water was added and the reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and concentrated in vacuo, giving a residue that was subjected to silica gel column chromatography (30% EtOAc in hexane) to give **10** (41 mg, 93%) as a pale yellow liquid. R_f = 0.3 (30% EtOAc in hexane). $[\alpha]_D^{22}$ = +56.2 (c 0.95, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1749, 1684. ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.13:1 mixture of carbamate rotamers; δ 6.75−6.57 (m, 3H), 6.56−6.50 (m, 2H), 5.90 (s, 2H), 5.15 (apparent bs, 0.47H), 5.00 (apparent bs, 0.53H), 4.25 (apparent d, J = 12.0 Hz, 0.53H), 4.00 (apparent d, J = 12.0 Hz, 0.47H), 3.84 (s, 6H), 3.22−3.10 (m, 1H), 2.90−2.63 (m, 1H), 2.62−2.58 (m, 3H), 2.10−1.94 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): signals correspond to both rotamers; δ 155.0, 154.8, 147.6, 147.5, 147.3, 145.6, 145.4, 144.9, 136.0, 135.7, 130.0, 129.5, 126.3, 125.9, 120.8, 111.5, 111.4, 110.1, 109.8, 108.7, 108.1, 100.7, 79.9, 79.5, 56.0, 55.8, 54.4, 53.1, 39.1, 38.7, 38.2, 36.8, 32.7, 32.6, 28.4, 28.0, 27.9. MS (EI): m/z 441 (M^+). HRMS (EI): calcd for $C_{25}H_{31}NO_6$ m/z 441.2151, found 441.2157.

(*S*)-1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (11). A solution of **10** (38 mg, 0.086 mmol) and trifluoroacetic acid (0.32 mL, 4.3 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 30 min. The reaction mixture was carefully poured into aq $NaHCO_3$ and extracted with CH_2Cl_2 three times. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residual product was purified by silica gel column chromatography (10% MeOH in $CHCl_3$) to provide **11** (26 mg, 90%) as a pale yellow liquid. R_f = 0.36 (10% MeOH in $CHCl_3$). $[\alpha]_D^{20}$ = −2.7 (c 0.56, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): 3346. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 8.0

Hz, 1H), 6.57 (s, 1H), 6.55 (s, 1H), 5.91 (s, 2H), 4.00 (d, J = 6.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.28 (m, 1H), 3.04 (m, 1H), 2.85−2.60 (m, 4H), 2.41 (bs, 1H), 2.14−1.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 147.5, 147.3, 145.6, 135.8, 130.1, 126.7, 121.0, 111.7, 109.1, 108.8, 108.2, 100.7, 56.0, 55.8, 54.8, 40.8, 38.2, 32.0, 28.8. MS (EI): m/z 341 (M^+). HRMS (EI): calcd for $C_{20}H_{23}NO_4$ m/z 341.1627, found 341.1636.

(+)-Dysoxyline (1). A mixture of **11** (24 mg, 0.07 mmol) and paraformaldehyde (6.3 mg, 0.21 mmol) in MeOH (1 mL) was added to a stirred solution of $ZnCl_2$ (4.7 mg, 0.035 mmol) and $NaBH_3CN$ (4.8 mg, 0.077 mmol) in MeOH (3 mL) at room temperature and the mixture was stirred for 15 min. Water was added and the mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$, filtered, and condensed. The residual product was purified by silica gel column chromatography (10% MeOH in $CHCl_3$) to provide (+)-dysoxyline **1** (26 mg, 90%) as a pale yellow liquid. R_f = 0.38 (10% MeOH in $CHCl_3$). $[\alpha]_D^{20}$ = +16.2 (c 0.35, EtOH); lit.[4] $[\alpha]_D^{25}$ = +22 (c 0.34, MeOH). IR ($CHCl_3$, cm^{-1}): 2933, 1608, 1515, 1440, 1372, 1246, 1104, 1038, 928, 808, 755. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.71 (d, J = 8.0 Hz, 1H), 6.67 (s, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.56 (s, 1H), 6.53 (s, 1H), 5.90 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.40 (t, J = 4.0 Hz, 1H), 3.15 (m, 1H), 2.82−2.60 (m, 4H), 2.49 (m, 1H), 2.46 (s, 3H), 2.06−1.94 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4, 147.27, 147.22, 145.3, 136.8, 129.7, 126.7, 121.0, 111.2, 110.0, 108.9, 108.0, 100.6, 62.6, 55.9, 55.7, 48.1, 42.6, 37.1, 31.3, 25.4. MS (EI): m/z 355 (M^+). HRMS (EI): calcd for $C_{21}H_{25}NO_4$ m/z 355.1783, found 355.1792. The enantiomeric ratio (er: 94:6; 88% ee) was determined by chiral HPLC analysis (Sumichiral OA-4700, hexane:2-propanol:TFA = 90:10:0.2, flow rate = 1.0 mL/min, T = 20 °C, 254 nm): t_s = 20.0 (minor; R-isomer), t_s = 20.8 (major; S-isomer).

Synthesis of 15a and 15b from 14. A stirred solution of sulfone **14** (117 mg, 0.2 mmol) and 4-(pivaloyloxy)benzaldehyde (206 mg, 1 mmol) or 4-methoxybenzaldehyde (136 mg, 1 mmol) was cooled to −35 °C in THF (5 mL). To this mixture was added dropwise a solution of lithium bis(trimethylsilyl)amide (1.30 M in THF, 0.46 mL, 0.6 mmol) at the same temperature. After following the experimental procedure described for the synthesis of **7**, compounds **15a** and **15b** were obtained in 79% and 86% yields, respectively.

15a. R_f = 0.30 (20% EtOAc in hexane); colorless solid. Mp: 82−84 °C. $[\alpha]_D^{20}$ = +54.9 (c 0.24, $CHCl_3$). IR ($CHCl_3$ film, cm^{-1}): 1751, 1696. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 6.81 (s, 1H), 6.71 (s, 1H), 6.40 (apparent d, J = 14.0 Hz, 1H), 6.25 (apparent d, J = 14.0 Hz, 1H), 5.63 (apparent bs, 1H), 4.16 (apparent bs, 1H), 3.75 (s, 3H), 3.20 (apparent bs, 1H), 2.86 (apparent t, J = 13.5 Hz, 1H), 2.65 (apparent d, J = 13.5 Hz, 1H), 1.49 (s, 9H), 1.36 (s, 9H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.9, 176.8, 154.5, 150.5, 149.5, 139.0, 134.1, 132.9, 130.6, 129.1, 127.3, 127.1, 122.7, 121.5, 111.7, 80.0, 56.6, 56.0, 39.0, 37.5, 28.4, 27.8, 27.1, 27.0. MS (EI): m/z 565 (M^+). HRMS (EI): calcd for $C_{33}H_{43}NO_7$ m/z 565.3039, found 565.3047. Anal. Calcd for $C_{33}H_{43}NO_7$: C, 70.06; H, 7.66; N, 2.48. Found: C, 69.89; H, 7.39; N, 2.35.

15b. R_f = 0.40 (20% EtOAc in hexane); colorless solid. Mp: 49−51 °C. $[\alpha]_D^{24}$ = +73.9 (c 0.5, $CHCl_3$). IR ($CHCl_3$ film, cm^{-1}): 1752, 1691, 1606. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.80 (s, 1H), 6.71 (s, 1H), 6.36 (apparent d, J = 16.0 Hz, 1H), 6.17 (apparent d, J = 16.0 Hz, 1H), 5.75 (apparent bs, 1H), 4.16 (apparent bs, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.20 (apparent bs, 1H), 2.85 (m, 1H), 2.63 (m, 1H), 1.49 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.8, 159.3, 154.6, 149.5, 139.0, 133.3, 131.1, 129.4, 127.7, 127.2, 126.9, 122.8, 114.0, 111.9, 79.9, 56.6, 56.1, 55.3, 39.0, 37.9, 29.7, 28.5, 27.9, 27.2. MS (EI): m/z 495 (M^+). HRMS (EI): calcd for $C_{29}H_{37}NO_6$ m/z 495.2621, found 495.2612. Anal. Calcd for $C_{29}H_{37}NO_6$: C, 70.28; H, 7.52; N, 2.83. Found: C, 70.48; H, 7.22; N, 3.01.

Synthesis of 16a and 16b from 15a and 15b. Compounds **15a** and **15b** (0.15 mmol) were hydrogenated in MeOH (5 mL) under the same conditions described for the synthesis of **8** to provide **16a** or **16b** in 94% and 95% yields, respectively.

16a. R_f = 0.32 (20% EtOAc in hexane); colorless solid. Mp: 68−70 °C. $[\alpha]_D^{20}$ = +42.1 (c 0.5, $CHCl_3$). IR ($CHCl_3$ film, cm^{-1}): 1752, 1691, 1508. ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.13:1 mixture of carbamate rotamers; δ 7.19 (d, J = 7.0 Hz, 2H), 6.96 (d, J = 7.0 Hz, 2H), 6.75 (s, 0.53H), 6.74 (s, 0.47H), 6.62 (s, 1H), 5.21 (apparent bs, 0.47H), 5.07 (apparent bs, 0.53H), 4.23 (apparent d, J = 8.4 Hz, 0.53H), 3.97 (apparent d, J = 5.5 Hz, 0.47H), 3.76 (apparent d, J = 10.5 Hz, 3H), 3.28−3.12 (m, 1H), 2.90−2.56 (m, 4H), 2.14−1.98 (m, 2H), 1.49 (s, 9H), 1.35 (s, 9H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): signals correspond to both rotamers; δ 177.1, 176.8, 155.0, 154.8, 149.4, 149.2, 139.2, 139.0, 138.7, 138.6, 136.0, 135.6, 129.0, 126.6, 126.2, 122.8, 122.6, 121.3, 121.2, 111.2, 110.9, 80.0, 79.6, 56.1, 54.7, 53.8, 39.02, 39.00, 38.6, 38.2, 36.7, 32.3, 32.2, 28.4, 27.6, 27.4, 27.18, 27.12. MS (EI): m/z 567 (M^+). HRMS (EI): calcd for $C_{33}H_{45}NO_7$ m/z 567.3196, found 567.3193. Anal. Calcd for $C_{33}H_{45}NO_7$: C, 69.82; H, 7.99; N, 2.47. Found: C, 69.53; H, 7.80; N, 2.42.

16b. R_f = 0.42 (20% EtOAc in hexane); colorless solid. Mp: 118−120 °C. $[\alpha]_D^{24}$ = +45.5 (c 1.0, $CHCl_3$). IR ($CHCl_3$ film, cm^{-1}): 1752, 1688, 1614. ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.13:1 mixture of carbamate rotamers; δ 7.10 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 6.78−6.72 (apparent m, 1H), 6.62 (s, 1H), 5.20 (apparent bs, 0.47H), 5.06 (apparent bs, 0.53H), 4.23 (apparent d, J = 14.5 Hz, 0.53H), 3.97 (apparent d, J = 14.5 Hz, 0.47H), 3.80−3.72 (m, 6H), 3.30−3.12 (m, 1H), 2.90−2.78 (m, 1H), 2.74−2.55 (m, 3H), 2.12−1.92 (m, 2H), 1.49 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): signals correspond to both rotamers; δ 176.8, 157.8, 157.7, 155.0, 154.8, 149.4, 138.7, 138.5, 135.7, 134.1, 129.1, 126.7, 126.2, 122.8, 122.6, 114.7, 113.8, 111.3, 111.0, 80.0, 79.5, 56.1, 55.2, 54.7, 53.9, 39.0, 38.6, 38.2, 36.7, 32.0. 31.8, 28.5, 27.7, 27.4, 27.2. MS (EI): m/z 497 (M^+). HRMS (EI): calcd for $C_{29}H_{39}NO_6$ m/z 497.2777, found 497.2779. Anal. Calcd for $C_{29}H_{39}NO_6$: C, 69.99; H, 7.90; N, 2.81. Found: C, 69.70; H, 7.98; N, 2.66.

Synthesis of 17a and 17b from 16a and 16b. Into a stirred solution of **16** (0.12 mmol) in CH_2Cl_2 (4 mL) was dropped TMSOTf (83 μL, 0.36 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 15 min. The mixture was poured into aq $NaHCO_3$, stirred for 10 min, and diluted with water. It was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residual product was purified by silica gel column chromatography (10% MeOH in $CHCl_3$) to provide the desired compound **17a** in 86% yield and **17b** in 90% yield, respectively.

17a. R_f = 0.40 (10% MeOH in $CHCl_3$); pale-yellow liquid. $[\alpha]_D^{20}$ = −15.4 (c 0.5, $CHCl_3$). IR ($CHCl_3$ film, cm^{-1}): 3420, 1749, 1508. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 6.72 (s, 1H), 6.62 (s, 1H), 3.97 (dd, J = 3.0 and 6.0 Hz, 1H), 3.74 (s, 3H), 3.22 (m, 1H), 2.99 (m, 1H), 2.83 (m, 1H), 2.80−2.60 (m, 3H), 2.20−1.98 (m, 2H), 1.35 (s, 9H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 176.8, 149.2, 149.1, 139.4, 138.4, 137.0, 129.2, 127.4, 122.9, 121.3, 110.1, 56.1, 55.1, 40.6, 39.0, 38.0, 31.7, 29.6, 28.8, 27.2, 27.1. MS (EI): m/z 467 (M^+). HRMS (EI): calcd for $C_{28}H_{37}NO_5$ m/z 467.2671, found 467.2663.

17b. R_f = 0.40 (10% MeOH in $CHCl_3$); pale-yellow liquid. $[\alpha]_D^{24}$ = −14.2 (c 0.75, $CHCl_3$). IR ($CHCl_3$ film, cm^{-1}): 3584, 1751. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 9.5 Hz, 2H), 6.83 (d, J = 9.5 Hz, 2H), 6.71 (s, 1H), 6.60 (s, 1H), 4.02 (m, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.24 (m, 1H), 3.03 (m, 1H), 2.95 (bs, 1H), 2.86−2.73 (m, 2H), 2.72−2.64 (m, 2H), 2.14−1.95 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.8, 157.8, 149.4, 138.6, 136.1, 133.8, 129.3, 126.8, 122.9, 113.9, 110.2, 56.1, 55.2, 55.0, 40.4, 39.0, 37.9, 31.3, 28.2, 27.2. MS (EI): m/z 397 (M^+). HRMS (EI): calcd for $C_{24}H_{31}NO_4$ m/z 397.2253, found 397.2259.

Synthesis of 18a and 18b from 17a and 17b. A mixture of compound **17** (0.1 mmol) and paraformaldehyde (9 mg, 0.3 mmol) in MeOH (1 mL) was added to a stirred solution of $ZnCl_2$ (6.8 mg, 0.05 mmol) and $NaCNBH_3$ (6.9 mg, 0.11 mmol) in MeOH (4 mL). The resulting mixture was stirred at room temperature for 20 min. Following a similar procedure, **18a** and **18b** were obtained in 83% and 87% yields, respectively.

18a. R_f = 0.5 (10% MeOH in $CHCl_3$); pale-yellow liquid. $[\alpha]_D^{20}$ = −2.2 (*c* 0.5, $CHCl_3$). IR ($CHCl_3$ film, cm^{-1}): 1750. ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.73 (s, 1H), 6.59 (s, 1H), 3.74 (s, 3H), 3.44 (t, *J* = 5.5 Hz, 1H), 3.12 (m, 1H), 2.84−2.61 (m, 4H), 2.56 (m, 1H), 2.45 (s, 3H), 2.08−1.96 (m, 2H), 1.35 (s, 9H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 176.9, 149.3, 149.0, 140.0, 138.3, 135.9, 129.2, 126.9, 122.5, 121.1, 111.1, 62.7, 56.1, 47.5, 42.5, 39.02, 39.01, 36.9, 30.9, 27.2, 27.1, 24.6. MS (EI): *m*/*z* 481 (M^+). HRMS (EI): calcd for $C_{29}H_{39}NO_5$ *m*/*z* 481.2828, found 481.2833.

18b. R_f = 0.42 (10% MeOH in $CHCl_3$); pale-yellow liquid. $[\alpha]_D^{24}$ = +0.42 (*c* 0.22, $CHCl_3$). IR ($CHCl_3$ film, cm^{-1}): 1748. ^1H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.72 (s, 1H), 6.58 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.44 (t, *J* = 5.6 Hz, 1H), 3.14 (m, 1H), 2.80−2.59 (m, 4H), 2.54 (m, 1H), 2.46 (s, 3H), 2.08−1.96 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 157.6, 149.2, 138.3, 136.0, 134.7, 129.3, 126.8, 122.4, 113.7, 111.1, 62.7, 56.0, 55.2, 47.4, 42.4, 39.0, 37.1, 30.8, 27.2, 24.6. MS (EI): *m*/*z* 411 (M^+). HRMS (EI): calcd for $C_{25}H_{33}NO_4$ *m*/*z* 411.2409, found 411.2406.

Synthesis of Compounds 2 and 3. Methanolysis of *O*-pivaloates **18a** and **18b** was carried out by the same method described for the methanolysis of **8**.

(+)-Colchiethanamine ***2***. Compound **2** was obtained from **18a** in 85% yield as a pale-yellow liquid using 20% MeOH in $CHCl_3$ as an eluent for column chromatography. R_f = 0.5 (20% MeOH in $CHCl_3$). $[\alpha]_D^{20}$ = +4.8 (*c* 0.3, MeOH). IR ($CHCl_3$, cm^{-1}): 3566, 3460, 3024, 2360, 1508, 1456. ^1H NMR (500 MHz, $CDCl_3$): δ 7.00 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.63 (s, 1H), 6.47 (s, 1H), 3.82 (s, 3H), 3.49 (t, *J* = 6.0 Hz, 1H), 3.20 (m, 1H), 2.84−2.73 (m, 2H), 2.72−2.62 (m, 2H), 2.55 (m, 1H), 2.48 (s, 3H), 2.11 (m, 1H), 1.97 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 145.0, 144.0, 134,0, 129.4, 128.3, 126.4, 115.3, 114.2, 109.4, 62.6, 56.0, 47.1, 42.0, 37.2, 30.9, 29.6. MS (EI): *m*/*z* 313 (M^+). HRMS (EI): calcd for $C_{19}H_{23}NO_3$ *m*/*z* 313.1678, found 313.1669. The enantiomeric ratio (er: 93:7; 86% ee) was determined by chiral HPLC analysis (Sumichiral OA-4700, hexane:2-propanol:TFA = 85:15:0.2, flow rate = 1.0 mL/min, *T* = 20 °C, 254 nm): t_s = 24.0 (minor; *R*-isomer), t_s = 25.2 (major; *S*-isomer).

(+)-Colchiethine ***3***. Compound **3** was obtained from **18b** in 83% yield as a yellow viscous liquid using 15% MeOH in $CHCl_3$ as an eluent for column chromatography. R_f = 0.38 (10% MeOH in $CHCl_3$). $[\alpha]_D^{24}$ = +1.9 (*c* 0.4, MeOH). IR ($CHCl_3$, cm^{-1}): 3544, 3018, 2936, 2360, 1611, 1509, 1464, 1371, 1339, 1245, 1215, 1178, 1105, 1034, 754, 668. ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (dd, *J* = 2.0 and 8.5 Hz, 2H), 6.83 (dd, *J* = 2.0 and 8.5 Hz, 2H), 6.65 (s, 1H), 6.50 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.47 (t, *J* = 6.4 Hz, 1H), 3.19 (m, 1H), 2.80−2.64 (m, 4H), 2.57 (m, 1H), 2.50 (s, 3H), 2.14−1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 145.0, 143.8, 134.6, 129.3, 114.1, 113.7, 109.3, 62.7, 56.0, 55.2, 47.5, 42.3, 37.1, 30.8, 24.7. MS (EI): *m*/*z* 327 (M^+). HRMS (EI): calcd for $C_{20}H_{25}NO_3$ *m*/*z* 327.1834, found 327.1837. The enantiomeric ratio (er: 93.5:6.5; 87% ee) was determined by chiral HPLC analysis (Sumichiral OA-4700, hexane:2-propanol:TFA = 85:15:0.2, flow rate = 0.5 mL/min, *T* = 24 °C, 254 nm): t_s = 28.1 (minor; *R*-isomer), t_s = 29.1 (major; *S*-isomer).

■ ASSOCIATED CONTENT

Supporting Information

HPLC chromatograms of **12** and **1**−**3** and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: juenishi@mb.kyoto-phu.ac.jp

Notes

The authors declare no competing financial interest.

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