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Synthesis of the Enantiomers of Hexahydrodibenz[*d*,*f*]azecines

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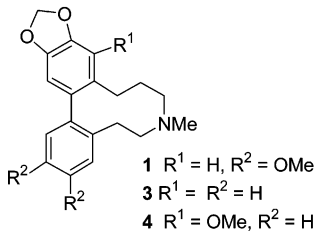
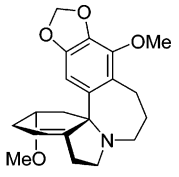
Suzuki coupling procedures were used to make appropriate 2-(3-aminopropyl)- 2′-(2-mesyloxy)-ethyl disubstituted biphenyl derivatives **19** and **20** from which the racemic hexahydrodibenz[*d*,*f*]-azecines **3** and **4** were produced following intramolecular mesyloxy displacement in dilute solution. The enantiomers of the former azecine were prepared by use of an analogue of the biphenyl aminomesylate **19** having a chiral auxiliary bound to the amino group during the closure of the 10-membered ring. Absolute configurations were assigned by X-ray diffraction analysis of compound **28**.

Introduction

Dysazecine (**1**) is the first alkaloid having the hexahydrodibenz[*d*,*f*]azecine structure to have been isolated from plants.[1] Members of this group are closely related to the widespread homoerythrinan alkaloids, for example, dyshomoerythrine (**2**),[2] which occurs as the major alkaloid of *Lagarostrobos colensoi* (New Zealand silver pine) and exhibits bioactivity against molluscs and agriculturally important insect pests.[3]



1 R^1 = H, R^2 = OMe
3 R^1 = R^2 = H
4 R^1 = OMe, R^2 = H



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Biosynthetically the homoerythrina alkaloids have been deemed to arise from hexahydrodibenzazecines,[4] and this transformation can be effected in vitro.[5] Conversely, the hexahydrodibenzazecines are obtainable from these alkaloids by acid-catalyzed cleavage of their benzylic C−N bond,[6] and in earlier work in this laboratory, dyshomoerythrine **2** was converted to the monomethoxy dibenzazecine **4** in 55% yield by application of the Hofmann elimination reaction (N-methylation followed by heating with sodium iodide in acetone).[3] Related transformations have been effected under a variety of conditions.[6,7] The object of the present work was to develop methods for the preparation of a range of enantiomerically pure hexahydrodibenzazecines required for biological testing.

Most reported syntheses of the hexahydrodibenzazecines are based on biphenyl coupling applied to *N*-2-phenylethyl-3-phenyl-propylamine[8] or -propanoamide[5,9] derivatives. Oxidation[8] and photochemical dehydrohalogenation[5,9] have been used to bring about coupling of the aromatic rings. Additionally, 1,2,3,4-tetrahydro-1-(2-phenylethyl)isoquinoline derivatives have been converted to hexahydrodibenzazecines through an oxidative biphenyl coupling.[10] Strategies based on hexahydroazecine ring formation from suitably 2,2′-substituted biphenyl derivatives appear not to have found much favor, although cyclization of 2-[(2-trifluoroacetylamino)ethyl]-2′-(2-formylethyl)biphenyl derivatives to give dibenzazecines has been reported.[11]

To develop a route to hexahydrodibenzazecines with a variety of substituents and substitution patterns, a general synthesis, based on biphenyl coupling by application of the Suzuki−Miyaura reaction,[12] followed by aza ring closure, has been developed. The syntheses of compound **3** and its methoxy derivative **4** are based on coupling of the bromobenzaldehydes **6** and **7** (Scheme 1)

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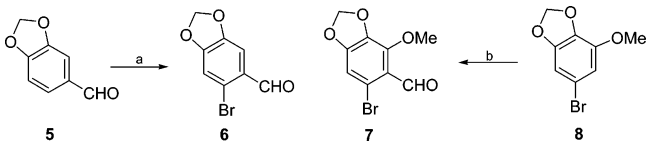
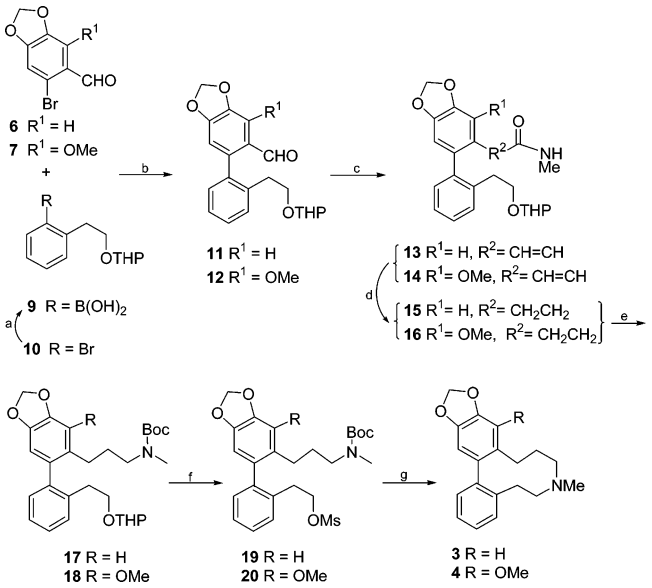
SCHEME 1[a]



[a] Reagents: (a) Br_2, $FeCl_3$, AcOH, 84%; (b) $MeOCHCl_2$, $SnCl_4$, then H_2O, 63%.

SCHEME 2[a]



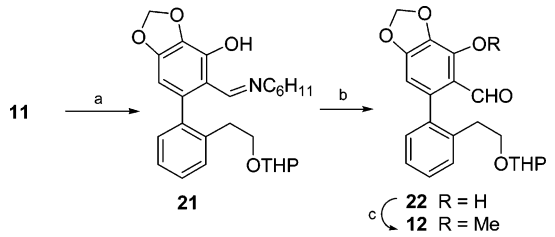
[a] Reagents: (a) *n*-BuLi, then $(MeO)_3B$, then H_2O; (b) $Pd(OAc)_2$, Ph_3P, $NaHCO_3$, 60−80% from **10**; (c) $(EtO)_2POCH_2CONHMe$, NaOH, $(C_6H_{13})_4NI$, 79−98%; (d) H_2, Raney Ni, 100%; (e) $LiAlH_4$ then $(t\text{-}BuOCO)_2CO$, Et_3N, 38−48%; (f) AcOH, H_2O then MsCl, Et_3N, 61−80%; (g) CF_3CO_2H then *i*-Pr_2EtN, MeCN, reflux, 57−77%.

with the substituted phenylboronic acid **9** to give biphenyls **11** and **12**, respectively, followed by the elaboration of the 10-membered rings (Scheme 2). Compounds **1**, **3**, and **4** are chiral (atropisomeric) as a result of inhibition of rotation about the biphenyl axis,[13] and all of the aforementioned synthetic procedures yielded racemates. A suitable method for obtaining pure enantiomers of compounds of this series involves the use of biphenyls having chiral groups attached to the amino functions employed in the aza ring formation. By this approach a method for preparing the enantiomers of compound **3** was developed (Scheme 4).

Results and Discussion

Bromination of piperonal (**5**) gives 84% of aldehyde **6**[14] (Scheme 1) which was coupled with boronic acid **9**, made from the tetrahydropyranyl acetal **10** of 2-(2-bromophenyl)ethanol. The Suzuki coupled biphenyl **11** was thus obtained in 59% yield based on the bromo-intermediate **10** (Scheme 2). Similarly, compound **12** was made by use of the same boronic acid **9** and aldehyde **7**, derived in 63% yield together with the regioisomer (17%) by formylation of the anisole derivative **8**[15] (Scheme 1). The relative positions of the methoxy and formyl groups of compound **7** were confirmed by its reduction with hydrogen over Raney nickel to the known (4-methoxybenzo-[1,3]dioxol-5-yl)-methanol (2-methoxypiperonol).[16]

SCHEME 3[a]



[a] Reagents: (a) $C_6H_{11}NH_2$, then *n*-BuLi, then $(MeO)_3B$, then H_2O_2, AcOH, 27%; (b) HCl, H_2O, 54%; (c) Me_2SO_4, K_2CO_3, 88%.

In an attempt to find another route to compound **12** the hydroxy derivative **21** was made from aldehyde **11** by boronation of the cyclohexylimino-protected aldehyde followed by oxidative cleavage of the C−B bond with hydrogen peroxide and acetic acid (Scheme 3). However, this process proved to be capricious, with 27% of the phenol **21** being the best yield obtained. Nevertheless, selective hydrolysis of this product afforded aldehyde **22** from which aldehyde **12** was synthesized. Overall, this approach was less satisfactory than that illustrated in Scheme 2.

Further elaboration of biphenyls **11** and **12** to the target compounds **3** and **4** is also illustrated in Scheme 2. Chain extension by use of the Horner−Emmons reagent, diethyl *N*-methylphosphonoacetamide,[17] gave compounds **13** and **14** in 98 and 79% yields, respectively, and hydrogenation of these enamides over Raney nickel afforded the dihydro adducts **15** and **16** quantitatively. Reaction of these amides with lithium aluminum hydride in dry THF gave the corresponding amines, which were treated with di-*tert*-butyl dicarbonate and triethylamine to yield the N-protected amines **17** and **18** with modest efficiency (38% and 48%, respectively). From these, the mesylates **19** and **20**, required for amine ring closure, were produced by acid hydrolytic removal of the tetrahydropyranyl group and O-mesylation. Cleavage of the *tert*-butoxycarbonyl group was effected by use of trifluoroacetic acid, and ring closure was carried out by treatment of the resulting secondary amines with diisopropylethylamine (Hunig's base) in dilute solution[18] in refluxing acetonitrile to give the racemic target dibenzazecines **3** and **4** in 77% and 57%, respectively, from compounds **19** and **20**. The yields from the parent biphenyls **11** and **12** were 22% and 13%, respectively.

There are no chiral centers in the compounds illustrated in Scheme 2 and no other elements of asymmetry until the ring-closing final step, assuming that the chiral rotamers of the biphenyls lacking the heterocyclic ring would readily racemize.[13] To obtain enantiomerically

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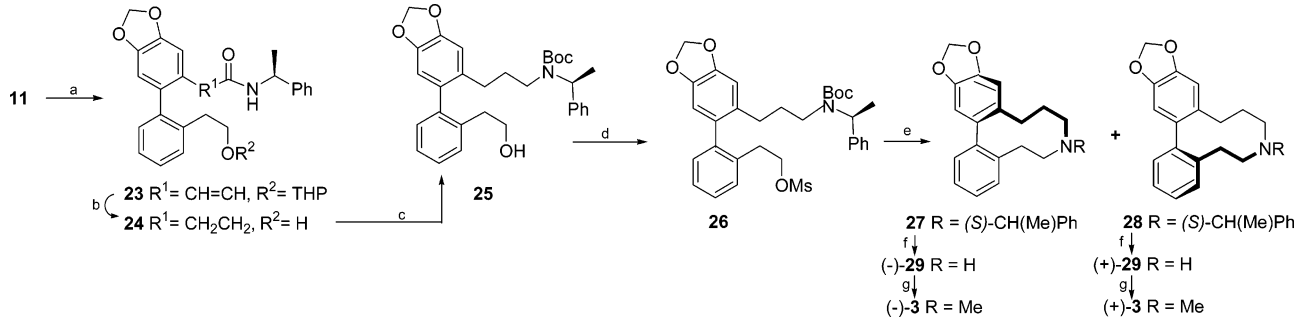
SCHEME 4[a]



[a] Reagents: (a) (*S*)-$(EtO)_2POCH_2CONHCH(Me)Ph$, 71%; (b) H_2, Pd/C, 88%; (c) $BH_3{\cdot}SMe_2$ then $(t\text{-}BuOCO)_2CO$, 65%; (d) MsCl, Et_3N, 99%; (e) CF_3CO_2H then $i\text{-}Pr_2EtN$, 84%; (f) H_2, Pd/C, 94%; (g) HCHO, $Na(AcO)_3BH$, 79−93%.

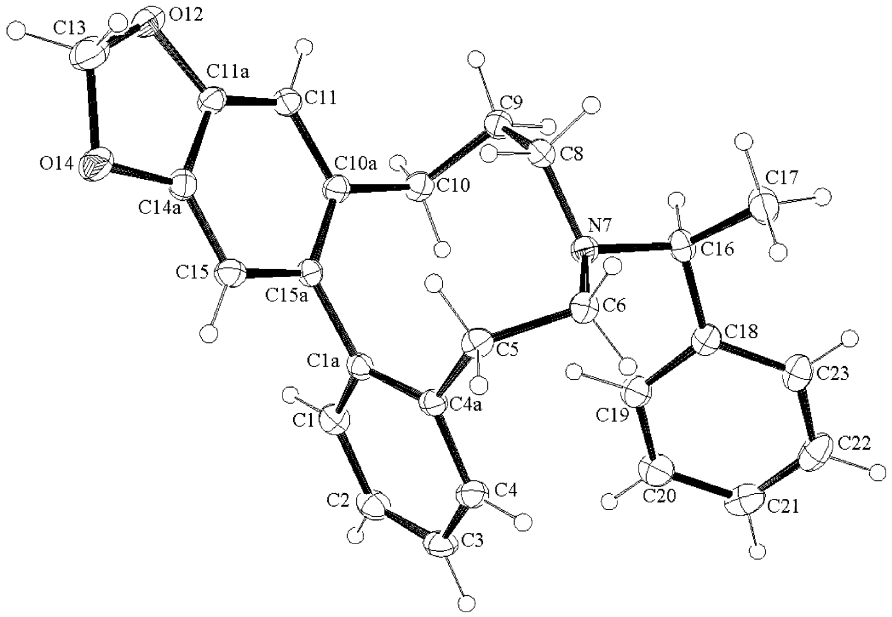


FIGURE 1. ORTEP diagram of compound **28**. Ellipsoids are drawn at 30% probability, $R = 0.030$; Space group orthorhombic, $P2_12_12_1$; cell dimensions $a = 9.345(7)$ Å, $b = 11.304(8)$ Å, $c = 14.799(11)$ Å; cell volume 1563(2) Å^3.

pure forms of the hexahydrodibenzazecines by the approach adopted in the present work it was necessary to introduce a chiral component into the precursors prior to ring closure, and for this reason analogues of the aminomesylates **19** and **20** bearing a chiral substituent on the nitrogen atom were sought.

The chiral Horner−Emmons reagent diethyl (*S*)-*N*-(1-phenylethyl)phosphonoacetamide was made from (*S*)-1-phenylethylamine[19] and used to synthesize enamide **23** from aldehyde **11** (Scheme 4) in a manner analogous to that used to prepare enamides **13** and **14** from aldehydes **11** and **12**. (Scheme 2). On hydrogenation to saturate the double bond compound **23** surprisingly also underwent cleavage of the tetrahydropyranyl group, and the isolated product was the amido alcohol **24**. Reduction of the amide moiety with borane−methyl sulfide gave an amino alcohol that was N-protected to give carbamate **25**. The derived *N*-*tert*-butoxycarbonyl *O*-mesylate **26** was subjected to the previously described cyclization to give a mixture of levo- and dextrorotatory diastereomers **27** and **28** in equal proportions and in 84% yield. Chromatographic separation gave these products in 97% and 98% purity, respectively (NMR evidence). The latter was recrystallized to >99% purity, and X-ray diffraction analysis (Figure 1) revealed it to be the S_a,S_c isomer, the biphenyl having the S_a configuration and the auxiliary being S_c. Compound **28** and the R_a,S_c diastereomer **27** were separately hydrogenolyzed, and the products, (+)-**29** and (−)-**29**, were N-methylated[20] to give the dextro- and levorotatory S_a and R_a enantiomers of compound **3**, respectively (Scheme 4). The crystal structure of (−)-**3** is shown in Figure 2. The configuration shown is derived from the method of synthesis as the crystallographic methods used were not enantio-discriminating.

Experimental Section

2-(2-Bromophenyl)ethyl Tetrahydro-2-*H*-pyran-2-yl Ether (10). A solution of 2-(2-bromophenyl)ethanol [21] (19.6 g, 92.5 mmol), 3,4-dihydro-2*H*-pyran (13 mL, 142 mmol) and

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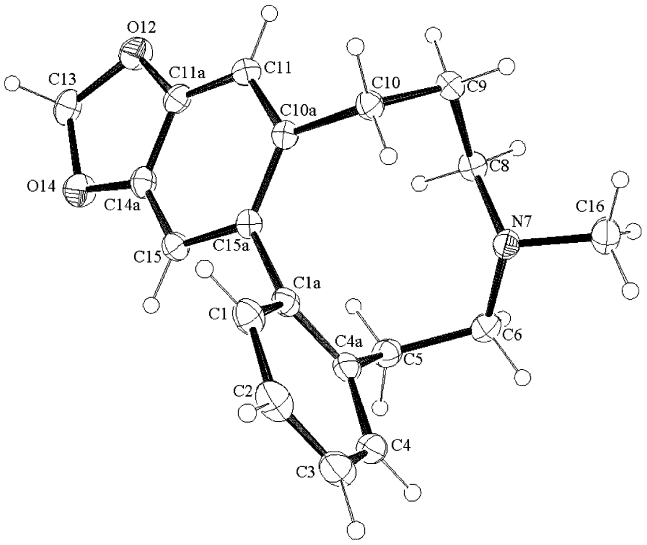

FIGURE 2. ORTEP diagram of (−)-**3**. Ellipsoids are drawn at 30% probability, $R = 0.037$; space group tetragonal, $P4_32_12$; cell dimensions $a = 11.0639(12)$ Å, $c = 33.688(7)$ Å; cell volume 4123.7(11) Å^3.

camphorsulfonic acid monohydrate (5 mg) in dry CH_2Cl_2 (100 mL) was stirred overnight at 20 °C. The reaction mixture was concentrated under reduced pressure, and the residue was column chromatographed with hexanes−ethyl acetate (19:1 and 9:1) as eluant to give the title compound as a light brown oil (19.0 g, 72%): ^{1}H NMR δ 7.52 (m, 1H), 7.20 (m, 2H), 7.06 (m, 1H), 4.61 (m, 1H), 3.94 (m, 1H), 3.76 (m, 1H), 3.65 (m, 1H), 3.48 (m, 1H), 3.16 (m, 2H), 1.86−1.47 (m, 6H); ^{13}C NMR δ 138.5, 132.7, 131.3, 128.0, 127.3, 124.8, 98.7, 66.5, 62.2, 36.6, 30.7, 25.5 19.5; HRMS (EI) *m*/*z* calcd for $C_{13}H_{17}BrO_2$ $(M)^+$ 284.0412, found 284.0413.

Biphenylaldehyde 11. A solution of the bromoacetal **10** (21.4 g, 75.1 mmol) in dry THF (160 mL) was cooled under argon to −78 °C. *n*-Butyllithium (1.1 M in hexanes, 82 mL, 90.0 mmol) was added with stirring over 15 min with the temperature kept below −50 °C, and trimethyl borate (16.6 mL, 160 mmol) was added over 15 min at this temperature. After a further 15 min with stirring the solution was transferred to an ice−water bath for 1 h and then quenched with aqueous NH_4Cl (saturated). The mixture, containing boronic acid **9**, was extracted twice with diethyl ether, and the extracts were washed with brine, dried, and concentrated under reduced pressure. The residue was taken up in dioxane (150 mL) containing 6-bromopiperonal (**6**, 13 g, 58 mmol), made according to the literature method[14] except that $FeCl_3$ was used instead of $FeBr_3$. Palladium acetate (0.235 g, 1.05 mmol) and Ph_3P (1.1 g, 4.2 mmol) were dissolved with heating in aqueous $NaHCO_3$ (50 mL, saturated), and the two solutions were mixed. The resulting pale yellow solution was heated at reflux under argon for 12 h. After it had been cooled, the mixture was extracted twice with diethyl ether, and the combined extracts were washed with aqueous NaOH (10%), HCl (2 M) and brine, dried, and concentrated under reduced pressure. The residue was column chromatographed with hexanes−ethyl acetate (6:1 and 4:1) as eluant to give **11** as a light brown oil (15.8 g, 77% based on compound **6**): ^{1}H NMR δ 9.43 (s, 1H), 7.37 (s, 1H), 7.29 (m, 2H) 7.18 (m, 1H), 7.08 (m, 1H), 6.67 (s, 1H), 6.01 (s, 2H), 4.37 (br s, 1H) 3.73 (m, 1H), 3.57 (m, 1H), 3.41−3.30 (m, 2H), 2.68 (m, 2H), 1.68−1.35 (m, 6H); ^{13}C NMR δ 190.1, 151.8, 147.6, 142.4, 137.4, 137.1, 130.5, 129.5, 129.0, 128.6, 125.7, 110.4, 105.6, 101.8, 98.5, 67.2, 61.9, 33.1, 30.2, 25.1,19.2; HRMS (EI) *m*/*z* calcd for $C_{21}H_{22}O_5$ (M^+) 354.1467, found 354.1469.

Biphenylaldehyde 12. (i) By Methoxylation of Aldehyde 11 via 21 and 22. A solution of aldehyde **11** (4.46 g, 12.6 mmol) and cyclohexylamine (1.73 mL, 15.1 mmol) in toluene (35 mL) was heated at reflux temperature for 2 h under a Dean−Stark distillation head to remove the water produced. The mixture was cooled and concentrated under reduced pressure to give the imine as a clear oil that was taken up in dry THF (60 mL), and the solution was cooled under an argon atmosphere in a CO_2−acetone bath. *n*-Butyllithium (1.7 M in hexanes, 12 mL, 20.4 mmol) was added slowly, and the mixture was stirred for 15 min. Trimethyl borate (3.4 mL, 30 mmol) was added, and the solution stirred for a further 15 min and transferred to an ice−water bath for 1 h. Acetic acid (2 mL) and hydrogen peroxide (30%, 5 mL, 45 mmol) were added, and stirring was continued at 20 °C for 16 h. The reaction mixture was then diluted with diethyl ether and washed with aqueous NH_4Cl (saturated), aqueous $NaHSO_3$ (5%), and brine, dried, and concentrated under reduced pressure. The residue was chromatographed using hexanes−ethyl acetate (6:1 and 3:1) as eluant to give the biphenylimine (**21**) as a light-brown-colored oil (1.70 g, 27%): ^{1}H NMR δ 9.35 (s, 1H), 7.66 (s, 1H), 7.37 (m, 2H), 7.28 (m, 1H), 7.14 (m, 1H), 6.19 (s, 1H), 6.03 (s, 2H), 4.47 (br s, 1H), 3.74 (m, 1H), 3.68 (m, 1H), 3.43 (m, 2H), 3.09 (br s, 1H), 2.74 (m, 2H), 1.79−1.25 (m, 16H); ^{13}C NMR δ 161.5, 155.9, 151.7, 140.2, 139.1, 138.0, 134.9, 130.9, 130.2, 128.3, 126.3, 113.1, 102.0, 102.0, 101.8, 67.9, 63.2, 62.5, 34.1, 34.0, 33.7, 30.9, 25.8, 25.5, 24.4, 19.9; HRMS (EI) *m*/*z* calcd for $C_{27}H_{33}NO_5$ (M^+) 451.2359, found 451.2353.

Biphenylimine **21** (1.3 g, 2.8 mmol) was dissolved in THF (10 mL), HCl (3 mL, 1 M) was added, and the mixture was heated under reflux for 15 min. After being cooled, it was diluted with ether, washed with water and brine, dried, and concentrated under reduced pressure. The residue was column chromatographed using hexanes−ethyl acetate (4:1) as eluant to give the hydroxybiphenyl aldehyde (**22**) as a light brown oil (0.54 g, 54%): ^{1}H NMR δ 11.85 (s, 1H), 9.35 (s, 1H), 7.37 (m, 2H), 7.24 (m, 1H), 7.16 (m, 1H), 6.41 (s, 1H), 6.12 (s, 2H), 4.47 (br s, 1H), 3.83 (m, 1H), 3.66 (m, 1H), 3.52−3.38 (m, 2H), 2.75 (m, 2H), 1.79−1.47 (m, 6H); ^{13}C NMR δ 196.3, 154.5, 146.8, 143.8, 138.1, 137.3, 133.6, 131.0, 130.0, 128.9, 126.3, 116.3, 104.4, 103.1, 99.2, 67.9, 62.6, 33.7, 30.9, 25.7, 19.9; HRMS (EI) *m*/*z* calcd for $C_{21}H_{22}O_6$ (M^+) 370.1416, found 370.1431.

Dimethyl sulfate (0.47 mL, 5.7 mmol) and K_2CO_3 (0.90 g, 6.5 mmol) were added to a stirred solution of phenol **22** (1.2 g, 3.2 mmol) in dry THF (50 mL). The mixture was heated under reflux for 3 h, cooled, diluted with ether, washed with water and brine, dried, and concentrated under reduced pressure. The residue was column chromatographed using hexanes−ethyl acetate (3:1) as eluant to give the title compound **12** as a light brown oil (1.10 g, 88%): ^{1}H NMR δ 9.79 (1H, s), 7.34−7.18 (m, 3H), 7.06 (m, 1H), 6.44 (s, 1H), 6.06 (s, 2H), 4.48 (br s, 1H), 4.13 (s, 3H), 3.80 (m, 1H), 3.70 (m, 1H), 3.48 (m, 2H), 2.72 (m, 2H), 1.75−1.50 (m, 6H); ^{13}C NMR δ 189.9, 153.1, 145.1, 142.5, 139.4, 137.3, 136.5, 130.1, 129.8, 128.3, 126.3, 121.9, 106.4, 102.3, 99.1, 67.9, 62.6, 60.8, 33.7, 31.0, 25.8, 19.9; HRMS (EI) *m*/*z* calcd for $C_{22}H_{24}O_6$ (M^+) 384.1573, found 384.1568.

(ii) By Suzuki Coupling of Compound 7 (Derived from Compound 8) and Boronic Acid 9. A stirred solution of 6-bromo-4-methoxybenzodioxole **8**[15] (4.6 g, 20 mmol) in CH_2Cl_2 (80 mL) was cooled under argon in a CO_2−acetone bath. Dichloromethyl methyl ether (1.9 mL, 20.1 mmol) and $SnCl_4$ (4.2 mL, 35 mmol) were added, and the mixture was brought to room temperature over 6 h. The mixture was washed with water, HCl (2 M), and aqueous $NaHCO_3$ (saturated), dried, and concentrated under reduced pressure. The residue was eluted through a plug of silica gel with hexanes−ethyl acetate (4:1) to give a two-component mixture of aldehyde **7** and its regioisomer in the ratio 3.7:1. The mixture was column chromatographed using hexanes−ethyl acetate (6:1) as eluant to give 6-bromo-4-methoxybenzo[1,3]dioxole-5-carbaldehyde (**7**) (2.70 g, 52%), mp 120−122 °C (dec) (from EtOH): ^{1}H NMR δ

10.23 (s, 1H), 6.86 (s, 1H), 6.04 (s, 2H), 4.08 (s, 3H); ^{13}C NMR δ 189.5, 154.8, 146.2, 137.1, 121.1, 118.9, 109.5, 102.8, 61.0; HRMS (EI) *m/z* calcd for $C_9H_7BrO_4$ (M^+) 259.9507, found 259.9505. Anal. Calcd for $C_9H_7BrO_4$: C 41.73, H 2.72. Found: C 42.02, H 2.56. Eluted second was 5-bromo-7-methoxybenzo-[1,3]dioxole-4-carbaldehyde as a colorless oil (0.73 g, 14%): ^{1}H NMR δ 10.17 (s, 1H), 6.81 (s, 1H), 6.15 (s, 2H), 3.98 (s, 3H); ^{13}C NMR δ 189.6, 150.8, 148.0, 136.2, 118.3, 113.3, 113.1, 103.9, 57.5; HRMS (EI) *m/z* found 259.9496.

Aldehyde **7** (50 mg, 0.19 mmol), boronic acid **9** (52 mg, 0.21 mmol), and Ph_3P (11 mg, 0.04 mmol) were dissolved in 1,4-dioxane (1.5 mL), and $Pd(OAc)_2$ (2 mg, 0.01 mmol) in hot aqueous $NaHCO_3$ (0.5 mL, saturated) was added. The mixture and the product formed were treated as described for compound **11** to give biphenylaldehyde **12** (60 mg, 80%), which gave ^{1}H and ^{13}C NMR spectra identical to those obtained from a sample made by route **i**.

(4-Methoxybenzo[1,3]dioxol-5-yl) Methanol. A solution of aldehyde **7** (10 mg) in methanol (1 mL) was stirred over Raney nickel (10 mg added in a MeOH suspension, 100 mL) under hydrogen for 18 h. The catalyst was removed by filtration through Celite, and concentration of the filtrate under reduced pressure gave the known title compound (5 mg): [16] ^{1}H NMR identical to the published data;[16] ^{13}C NMR δ 149.7, 142.1, 136.4, 126.5, 122.4, 102.6, 101.4, 62.2, 60.1.

Enamide 13. Diethyl-*N*-methylphosphonoacetamide was made according to literature procedures[17] and was used without purification: ^{1}H NMR δ 6.76 (br s, 1H), 4.14 (m, 4H), 2.83 (m, 5H), 1.34 (t, J = Hz, 6H); ^{13}C NMR δ 164.9, 63.1, 35.2 (d, $J_{C,P}$ = 125 Hz), 27.0, 16.7. A solution of aldehyde **11** (0.67 g, 1.9 mmol), the phosphonate (1.0 g, 4.8 mmol), and tetrahexylammonium iodide (5 mg) in CH_2Cl_2 (8 mL) was added to aqueous sodium hydroxide (50%, 3 mL) with rapid stirring, which was continued overnight. Dichloromethane was added; the solution was washed with water, aqueous NH_4Cl (saturated), and brine and dried; and the volatiles were removed under reduced pressure. The residue was column chromatographed using ethyl acetate as eluant to give **13** (0.77 g, 98%) as a light brown oil: ^{1}H NMR δ 7.35−7.04 (m, 6H), 6.69 (s, 1H), 6.07 (m, 1H), 6.02 (s, 2H), 5.79 (br s, 1H), 4.43 (m, 1H), 3.74 (m, 2H), 3.43 (m, 2H), 2.78 (m, 3H), 2.68 (m, 2H), 1.74−1.40 (6H, m); ^{13}C NMR δ 167.1, 148.8, 147.8, 140.0, 138.5, 137.5, 130.8, 130.3, 128.3, 127.8, 126.6, 120.5, 111.0, 105.6, 101.9, 99.1, 67.9, 62.5, 33.8, 31.0, 26.7, 25.8, 19.9. HRMS (EI) *m/z* calcd for $C_{24}H_{27}NO_5$ (M^+) 409.1889, found 409.1887.

Enamide 14. A solution of aldehyde **12** (1.0 g, 2.6 mmol) and diethyl-*N*-methylphosphonoacetamide (1.5 g, 7.2 mmol) was treated by the method described for the preparation of **13**. The yield of light brown oil was 0.90 g (79%): ^{1}H NMR δ 7.34−7.18 (m, 4H), 7.06 (m, 1H), 6.44 (s, 1H), 6.16 (dd, 1H, J = 15.9, 3.3 Hz), 6.00 (s, 2H), 5.42 (br s, 1H), 4.45 (m, 1H), 4.04 (s, 3H), 3.74 (m, 2H), 3.43 (m, 2H), 2.78 (m, 3H), 2.68 (m, 2H), 1.74−1.40 (m, 6H); ^{13}C NMR δ 167.8, 149.4, 143.3, 140.9, 138.3, 137.2, 136.7, 135.2, 130.5, 130.2, 128.1, 126.6, 123.6, 120.3, 106.0, 101.7, 99.1, 67.7, 62.6, 60.1, 33.6, 31.0, 26.6, 25.8, 19.9; HRMS (EI) *m/z* calcd for $C_{25}H_{29}NO_6$ (M^+) 439.1995, found 439.2004.

Amide 15. Compound **13** (0.77 g, 1.88 mmol) was dissolved in methanol (30 mL) and stirred with Raney nickel (0.7 g) under hydrogen at atmospheric pressure. After 24 h the mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to give amide **15** as a tan-colored oil (0.75 g, 97%): ^{1}H NMR δ 7.36−7.19 (br m, 3H), 7.09 (m, 1H), 6.79 (s, 1H), 6.60 (s, 1H), 5.95 (s, 2H), 5.47 (br s, 1H), 4.48 (m, 1H), 3.80 (m, 1H), 3.67 (m, 1H), 3.45 (m, 2H), 2.67 (m, 7H), 2.17 (m, 2H), 1.74−1.40 (m, 6H); ^{13}C NMR δ 173.0, 147.3, 146.0, 141.2, 137.4, 134.5, 132.1, 130.6, 129.9, 127.9, 126.4, 110.6, 109.4, 101.4, 99.2, 67.7, 62.7, 37.9, 33.6, 31.0, 29.5, 26.7, 25.8, 19.9; HRMS (EI) *m/z* calcd for $C_{24}H_{29}NO_5$ (M^+) 411.2046, found 411.2038.

Amide 16. Unsaturated amide **14** (0.93 g, 2.1 mmol) was hydrogenated as described for compound **13** to give the dihydro compound **16** as a tan-colored oil (0.92 g, 99%): ^{1}H NMR δ 7.28−7.12 (m, 3H), 7.00 (m, 1H), 6.27 (s, 1H), 5.87 (s, 2H), 5.16 (br s, 1H), 4.42 (br s, 1H), 3.98 (s, 3H), 3.74−3.60 (m, 2H), 3.43−3.34 (m, 2H), 2.60 (m, 6H), 2.35 (m, 1H), 2.08 (m, 2H), 1.71−1.27 (m, 6H); ^{13}C NMR δ 173.0, 147.6, 142.0, 141.2, 137.3, 135.9, 135.1, 130.4, 130.0, 127.9, 126.3, 124.5, 104.8, 101.2, 99.1, 67.8, 62.6, 60.1, 37.3, 33.6, 31.0, 26.5, 25.8, 24.3, 19.9; HRMS (EI) *m/z* calcd for $C_{25}H_{31}NO_6$ (M^+) 441.2151, found 441.2152.

Carbamate 17. Lithium aluminum hydride (0.17 g, 4.5 mmol) was added to a solution of amide **15** (0.75 g, 1.87 mmol) in dry THF (17 mL), and the suspension was heated under reflux for 2 h. Water (0.5 mL) and $MgSO_4$ (excess) were added in rapid succession to the cooled mixture, which was filtered through Celite. The filter cake was stirred for 10 min with CH_2Cl_2 (5 × 17 mL), and the extracts were dried and taken to dryness under reduced pressure. The resulting amine was taken up in CH_2Cl_2 and treated with di-*tert*-butyl dicarbonate (4.1 g, 2.3 mmol) and triethylamine (0.2 mL). After 1 h the reaction mixture was washed with HCl (2 M), aqueous K_2CO_3 (10%), and brine, dried, and concentrated under reduced pressure. The residue was column chromatographed with hexanes−ethyl acetate (5:1) as eluant to give carbamate **17** as a light brown oil (0.34 g, 37%): ^{1}H NMR δ 7.34−7.18 (br m, 3H), 7.07 (m, 1H), 6.75 (s, 1H), 6.60 (s, 1H), 5.95 (s, 2H), 4.47 (m, 1H), 3.74 (m, 2H), 3.44 (m, 2H), 3.03 (m, 2H), 2.67 (m, 5H), 2.21 (m, 2H), 1.74−1.40 (m, 8H), 1.38 (s, 9H); ^{13}C NMR δ 156.0, 147.3, 145.7, 141.4, 137.4, 134.0, 133.4, 130.6, 129.9, 127.7, 126.3, 110.5, 109.1, 101.3, 99.0, 79.4, 67.9, 62.5, 48.9, 34.1, 33.7, 31.0, 30.6, 29.6, 28.8, 25.8, 19.9; HRMS (FAB) *m/z* calcd for $C_{29}H_{39}NO_6$ (M^+) 497.2777, found 497.2772.

Carbamate 18. Amide **16** (0.87 g, 1.97 mmol) was treated as described for compound **15** to give carbamate **18** as a light-brown-colored oil (0.50 g, 48%): ^{1}H NMR δ 7.47−7.09 (m, 3H), 7.00 (m, 1H), 6.27 (s, 1H), 5.87 (s, 2H), 4.42 (br s, 1H), 3.96 (s, 3H), 3.74−3.60 (m, 2H), 3.39−3.32 (m, 2H), 2.91 (br s, 2H), 2.60 (m, 5H), 2.33 (m, 1H), 1.94 (m, 1H), 1.72−1.32 (m, 17H); ^{13}C NMR δ 156.1, 147.2, 142.0, 141.5, 137.2, 136.0, 134.9, 130.4, 129.9, 127.7, 126.2, 125.8, 104.8, 101.1, 99.0, 79.2, 68.0, 62.5, 59.9, 49.1, 33.9, 33.8, 31.0, 28.8, 28.8, 25.8, 25.2, 19.9; HRMS (EI) *m/z* calcd for $C_{30}H_{41}NO_7$ (M^+) 527.2885, found 527.2885.

Mesylate 19. A solution of tetrahydropyranyl ether **17** (0.32 g, 0.64 mmol) in acetic acid−THF−water (4:2:1, 10 mL) was heated at 50 °C for 5 h. The solvents were removed under reduced pressure, and the residue was chromatographed on a column of silica gel using hexanes−ethyl acetate (2:1) as eluant. The product, after evaporation of the solvent, was taken up in CH_2Cl_2 (10 mL) and treated with methanesulfonyl chloride (0.10 mL, 0.7 mmol) and triethylamine (0.25 mL, 1.5 mmol). After being stirred for 2 h the reaction mixture was extracted with HCl (2 M) and brine, dried, and concentrated under reduced pressure. The residue was column chromatographed using CH_2Cl_2−ethyl acetate (9:1 and 6:1) as eluant to give the title mesylate **19** as a light brown oil (0.25 g, 80%): ^{1}H NMR δ 7.23 (br m, 3H), 7.05 (m, 1H), 6.71 (s, 1H), 6.51 (s, 1H), 5.90 (m, 2H), 4.13 (m, 2H), 2.98 (m, 2H), 2.77 (m, 5H), 2.57 (m, 3H), 2.11 (m, 2H), 1.50 (m, 2H), 1.32 (s, 9H); ^{13}C NMR δ 156.0, 147.6, 146.0, 141.6, 134.6, 133.4, 133.2, 130.9, 130.6, 128.1, 127.4, 110.2, 109.2, 101.4, 79.5, 69.7, 48.8, 37.7, 34.1, 33.2, 30.6, 29.6, 28.8; HRMS (EI) *m/z* calcd for $C_{25}H_{33}NO_7S$ (M^+) 491.1978, found 491.1976.

Mesylate 20. By application of the method used to prepare mesylate **19**, tetrahydropyranyl ether **18** (0.45 g, 0.85 mmol) was converted to the mesylate **20** as a light-colored oil (0.27 g, 61%): ^{1}H NMR δ 7.61−7.23 (m, 3H), 7.12 (m, 1H), 6.32 (s, 1H), 5.95 (m, 2H), 4.20 (t, J = 7.2 Hz, 3H), 4.04 (s, 3H), 3.01 (br s, 2H), 2.84 (m, 5H), 2.61 (br s, 3H), 2.42 (m, 1H), 1.94 (m, 1H), 1.53 (m, 1H), 1.38 (m, 9H); ^{13}C NMR δ 156.1, 147.5, 142.2, 141.7, 136.2, 134.5, 134.1, 130.8, 130.0, 128.1, 127.2, 125.8, 104.4, 101.2, 79.2, 69.8, 60.0, 49.1, 37.7, 33.9, 33.3, 28.8, 28.8,

25.2; HRMS (EI) *m/z* calcd for $C_{26}H_{35}NO_8S$ (M^+) 521.2090, found 521.2090.

Hexahydrodibenzazecine (±)-3. A solution of compound **19** (0.15 g, 0.31 mmol) in trifluoroacetic acid (1 mL) was stirred at room temperature for 1 h. The acid was removed under reduced pressure, the residue was taken up in acetonitrile (175 mL) containing diisopropylethylamine (0.6 mL, 3.4 mmol), and the solution was heated under reflux for 16 h. After being cooled, it was taken to dryness under reduced pressure, and the residue was dissolved in CH_2Cl_2, washed with water, dried, and concentrated under reduced pressure. The new residue was column chromatographed using CH_2Cl_2−ethyl acetate (19:1 and 9:1) as eluant and then on a short column of neutral alumina using $CHCl_3$ as eluant to give the racemic title compound **3** as a light yellow oil that solidified on standing (0.070 g, 77%). Recrystallization from hexanes−ethyl acetate gave white prisms, mp 138−142 °C: ^{1}H NMR δ 7.18 (m, 2H), 7.05 (m, 1H), 6.92 (m, 1H), 6.66 (s, 1H), 6.42 (s, 1H), 5.84 (m, 2H), 2.54 (m, 3H), 2.27 (m, 2H), 2.18 (m, 2H), 1.97 (s, 3H), 1.62 (m, 2H), 1.37 (m, 1H); ^{13}C NMR δ 147.4, 145.3, 143.1, 141.1, 136.3, 134.6, 130.1, 128.3, 127.7, 125.3, 110.0, 108.4, 101.2, 59.7, 50.0, 44.8, 31.0, 29.0, 28.6; HRMS (EI) *m/z* calcd for $C_{19}H_{21}NO_2$ (M^+) 295.1572, found 295.1573. Anal. Calcd for $C_{19}H_{21}NO_2$: C 77.26, H 7.17, N 4.74. Found: C 77.14, H 7.16, N 4.70.

Hexahydrodibenzazecine (±)-4. Mesylate **20** (0.18 g, 0.35 mmol) was treated as described for compound **19** to give the title product as a light yellow oil that solidified on standing (0.064 g, 57%). A sample was recrystallized from ethyl acetate−hexanes to give colorless needles, mp 146−149 °C: ^{1}H and ^{13}C NMR spectral data identical to those already reported;[3] HRMS (EI) *m/z* calcd for $C_{20}H_{23}NO_3$ (M^+) 325.1682, found 325.1682. Anal. Calcd for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30. Found: C 74.10, H 7.04, N 4.59.

Enamide 23. Diethyl (*S*)-*N*-(1-phenylethyl)phosphonoacetamide was made by use of literature procedures[17] with (*S*)-1-phenylethylamine and was used without purification: ^{1}H NMR δ 7.33 (m, 5H), 7.11 (br s, 1H), 5.12 (m, 1H), 4.63 (m, 2H), 4.61 (m, 2H), 2.84 (dd, J = 5.1, 20.4 Hz, 2H), 1.49 (d, J = 6.9 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 163.3, 143.5, 129.0, 127.7, 126.5, 63.1, 63.0, 49.7, 35.5 (d, J_{CP} = 130 Hz), 22.4, 16.7, 16.6. Aldehyde **11** (10 g, 28.2 mmol) was treated with the phosphonate (10 g, 33.4 mmol) by the method described for making compound **13**. The crude reaction product was column chromatographed using hexanes−ethyl acetate (4:1−1:1) as eluant to give enamide **23** (10.0 g, 71%) as a light yellow oil: $[\alpha]_D$ −15.8 (*c* 1.1, CH_2Cl_2); ^{1}H NMR δ 7.28 (m, 9H), 7.08 (m, 2H), 6.68 (s, 1H), 6.15 (d, J = 15.5 Hz, 1H), 6.00 (s, 2H), 5.83 (br s, 1H), 5.12 (m, 1H), 4.44 (m, 1H), 3.70 (m, 2H), 3.40 (m, 2H), 2.67 (m, 2H), 1.47 (br m, 9H); ^{13}C NMR δ 165.4, 148.9, 147.8, 143.7, 139.9, 139.3, 137.8, 137.6, 130.8, 130.3, 130.2, 129.0, 128.3, 127.7, 126.6, 120.0, 111.0, 105.4, 101.9, 99.0, 67.8, 62.5, 49.2, 33.7, 31.0, 25.8, 19.9, 14.6; HRMS (FAB) *m/z* calcd for $C_{31}H_{34}NO_5$ (MH^+) 500.2437, found 500.2424.

Amide 24. Acrylamide **23** (10.0 g, 20.0 mmol) was dissolved in methanol (100 mL) and stirred with palladium on carbon (10%, 0.5 g) under hydrogen (1 atm) overnight. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. Column chromatography of the residue eluted with hexanes−ethyl acetate (1:1) and ethyl acetate gave the title compound (7.4 g, 88%) as a light yellow oil, $[\alpha]_D$ −24.5 (*c* 1.0, CH_2Cl_2): ^{1}H NMR δ 7.3−7.1 (m, 9H), 6.78 (s, 1H), 6.57 (s, 1H), 5.94 (m, 2H), 5.79 (br s, 1H), 4.98 (m, 1H), 4.46 (m, 1H), 3.66 (m, 2H), 2.67 (m, 2H), 2.56 (m, 2H), 2.17 (m, 2H), 1.34 (m, 3H); ^{13}C NMR δ 171.5, 147.4, 146.1, 143.6, 141.4, 137.0, 134.1, 132.2, 130.8, 129.6, 128.9, 128.1, 127.6, 126.5, 120.0, 110.6, 109.6, 101.4, 62.7, 48.8, 37.8, 36.4, 29.5, 22.0; HRMS (FAB) *m/z* calcd for $C_{26}H_{28}NO_4$ (MH^+) 418.2018, found 418.1996.

Carbamate 25. Amide **24** (1.0 g, 2.4 mmol) was dissolved in dry THF (20 mL) and cooled in an ice−water bath. Borane−methyl sulfide (0.34 mL, 3.6 mmol) was added by syringe, and the mixture was heated slowly to reflux temperature by which time the amide had reacted (TLC observation). The solution was cooled to room temperature, HCl (0.75 mL, 6M, 4.5 mmol) was added slowly, and the mixture was briefly heated under reflux. After cooling, neutralization was effected with aqueous K_2CO_3 (10%), and the mixture was extracted with CH_2Cl_2 (20 mL × 3), the combined extracts were washed with water (× 3) and dried, and the solvents were removed under reduced pressure. The residue was taken up in CH_2Cl_2 and treated with di-*tert*-butyl dicarbonate (0.70 g, 3.2 mmol). This solution was stirred overnight, concentrated under reduced pressure, and column chromatographed using hexanes−ethyl acetate (2:1) as eluant to give the protected amine **25** as a pale brown oil (0.79 g, 65%), $[\alpha]_D$ −47.0 (*c* 1, CH_2Cl_2): ^{1}H NMR δ 7.3 (m, 8H), 6.96 (m, 1H), 6.61 (s, 1H), 6.54 (s, 1H), 5.91 (m, 2H), 5.25 (m, 1H), 3.60 (m, 2H), 2.83 (br s, 1H), 2.61 (m, 3H), 2.17 (m, 2H), 1.83 (br s, 1H), 1.51 (m, 2H), 1.40 (m, 12H); ^{13}C NMR δ 156.1, 147.3, 145.7, 142.3, 141.6, 137.0, 133.8, 133.4, 130.8, 129.9, 128.7, 127.8, 127.4, 126.5, 110.6, 109.6, 101.3, 79.9, 63.2, 53.8, 43.8, 36.8, 31.6, 30.8, 28.9, 17.8; HRMS (FAB) *m/z* calcd for $C_{31}H_{38}NO_5$ (MH^+) 504.2750, found 504.2739.

Mesylate 26. Methanesulfonyl chloride (0.23 mL, 2.9 mmol) and triethylamine (0.46 mL, excess) were added to an ice-cold solution of hydroxyamine **25** (0.74 g, 1.47 mmol) in CH_2Cl_2 (5 mL). The mixture was brought to room temperature and stirred for 3 h. Extractive isolation and chromatography as for compound **19** gave the mesylate **26** as a pale brown oil (0.85 g, 99%), $[\alpha]_D$ −41.8 (*c* 1.1, CH_2Cl_2): ^{1}H NMR δ 7.3 (m, 8H), 6.99 (m, 1H), 6.62 (s, 1H), 6.53 (s, 1H), 5.96 (m, 2H), 5.35 (br s, 1H), 4.16 (m, 2H), 2.81 (s, 3H), 2.75 (m, 3H), 2.68 (m, 1H), 2.15 (m, 2H), 1.51 (m, 2H), 1.40 (m, 12H); ^{13}C NMR δ 156.0, 147.6, 145.9, 142.3, 141.6, 134.6, 133.4, 133.1, 130.9, 130.0, 128.6, 128.0, 127.4, 127.3, 110.0, 109.1, 101.4, 79.8, 69.8, 53.4, 43.8, 37.6, 33.2, 31.8, 30.8, 28.9, 17.8; HRMS (FAB) *m/z* calcd for $C_{32}H_{40}NO_7S$ (MH^+) 582.2526, found 582.2471.

Diastereomeric Hexahydrodibenzazecines 27 and 28. Compound **26** (1.8 g, 3.1 mmol) was stirred with trifluoroacetic acid (10 mL) at 20 °C for 1.5 h. The acid was evaporated under reduced pressure, the residue was taken up in acetonitrile (420 mL) containing diisopropylethylamine (7.2 mL, 75.4 mmol), and the solution was heated under reflux for 48 h. After cooling of the solution, the volatiles were removed under reduced pressure, and the residue was column chromatographed using hexanes−ethyl acetate (9:1) as eluant to give a 1:1 mixture of the cyclized diastereomers **27** and **28** (1.0 g, 84%) as a white solid. Further column chromatography with hexanes−ethyl acetate−CH_2Cl_2, (190:5:5) as eluant afforded the separated diastereomers in quantitative yields, containing 3% and 2%, respectively, of the other isomers (NMR evidence). Compound **28** was further purified by crystallization from ethanol.

(R_a,S_c) Isomer **27** was obtained as a white amorphous solid, mp 45−55 °C; $[\alpha]_D$ −60.7 (*c* 1, CH_2Cl_2): ^{1}H NMR δ 7.4−7.0 (m, 9H), 6.76 (s, 1H), 6.49 (s, 1H), 5.94 (m, 2H), 3.53 (m, 1H), 2.96 (m, 1H), 2.71 (m, 1H), 2.57 (m, 1H), 2.4−2.2 (br m, 5H), 1.86 (m, 1H), 1.43 (m, 1H), 1.03 (m, 3H); ^{13}C NMR δ 147.4, 145.3, 143.3, 142.8, 140.8, 136.2, 134.5, 129.8, 128.8, 128.3, 127.4, 126.9, 125.1, 110.0, 108.3, 101.2, 59.0, 51.0, 45.3, 31.0, 29.2, 28.2, 20.2; HRMS (FAB) *m/z* calcd for $C_{26}H_{28}NO_2$ (MH^+) 386.2120, found 386.2113. Anal. Calcd for $C_{26}H_{27}NO_2$: C 81.00, H 7.06, N 3.64. Found: C 81.08, H 7.34, N 3.43.

(S_a,S_c) Isomer **28** was crystallized from ethanol as white needles, mp 170−172 °C; $[\alpha]_D$ + 206 (*c* 1, CH_2Cl_2): ^{1}H NMR δ 7.2−6.7 (m, 9H), 6.54 (m, 1H), 6.41 (s, 1H), 5.87 (m, 2H), 3.66 (m, 1H), 2.81 (m, 1H), 2.6−2.2 (br m, 5H), 2.13 (br m, 2H), 1.76 (m, 1H), 1.45 (m, 1H), 1.17 (m, 3H); ^{13}C NMR δ 147.4, 145.3, 144.5, 142.8, 140.2, 136.5, 134.5, 129.7, 129.0, 128.2, 127.7, 126.2, 124.9, 110.0, 108.3, 101.2, 55.9, 48.3, 44.5, 30.7, 29.1, 28.6, 9.4. HRMS (FAB) *m/z* calcd for $C_{26}H_{28}NO_2$ (MH^+) 386.2120, found 386.2120. Anal. Calcd for $C_{26}H_{27}NO_2$: C 81.00, H 7.06, N 3.64. Found: C 81.03, H 6.87, N 3.64.

Enantiomers of Hexahydrodibenzazecine 3. Separate solutions of diastereomers **28** and **27** (0.215 g, 0.54 mmol) in ethanol (300 mL) were stirred over palladium-on-charcoal (0.1 g, 10%) under an atmosphere of hydrogen (30 psi) for 20 h. The solutions were filtered through Celite, and the filtrates were taken to dryness under reduced pressure to give the (+)- and (−)-enantiomers of secondary amine **29** (each 0.15 g, 94%): ^{1}H NMR δ 7.32 (m, 2H), 7.21 (m, 1H), 7.06 (m, 1H), 6.73 (s, 1H), 6.50 (s, 1H), 5.92 (m, 2H), 2.87 (m, 3H), 2.47 (m, 4H), 2.08 (m, 1H), 1.74 (m, 1H), 1.64 (m, 2H); ^{13}C NMR δ 147.6, 145.6, 143.5, 139.2, 135.7, 132.9, 130.6, 129.4, 128.3, 126.1, 110.1, 108.5, 101.3, 49.4, 42.0, 30.0, 29.9, 28.0.

The crude amines (each 0.14 g, 0.47 mmol) were separately taken up in CH_2ClCH_2Cl (10 mL) and stirred with formalin (0.075 mL, 1 mmol) and sodium triacetoxyborohydride (0.16 g, 0.8 mmol) for 0.5 h at room temperature.[20] The solutions were washed with aqueous K_2CO_3 (10%) and brine, dried, and concentrated under reduced pressure, and the residues were column chromatographed with CH_2Cl_2−MeOH (19:1 and 9:1) as eluant to give the title *N*-methyl derivatives (+)-**3** (0.13 g, 93%) and (−)-**3** (0.11 g, 79%) as colorless needles.

(+)-Enantiomer, mp 120−124 °C (from hexanes−ethyl acetate); $[\alpha]_D$ +73 (*c* 0.47, CH_2Cl_2): ^{1}H and ^{13}C NMR data identical to data for the (−)-enantiomer and the racemate. Anal. Calcd for $C_{19}H_{21}NO_2$: C 77.26, H 7.17, N 4.74. Found: C 77.18, H 7.04, N 4.79.

(−)-Enantiomer, mp 122−124 °C (from ethanol); $[\alpha]_D$ −68 (*c* 0.48, CH_2Cl_2): ^{1}H and ^{13}C NMR data identical to data for the (+)-enantiomer and the racemate. Anal. Found: C 77.12, H 7.05, N 4.79.

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Supporting Information Available: ^{13}C NMR spectra of compounds **10**−**26** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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