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Chiral Version of the Burgess Reagent and Its Reactions with Oxiranes: Application to the Formal Enantiodivergent Synthesis of Balanol†

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An efficient formal synthesis of a (−)-balanol intermediate (**25a**) from cyclohexadiene oxide was accomplished in eight steps. An asymmetric version of the Burgess reagent allows for an enantiodivergent approach to both enantiomers of balanol from a racemic starting material.

The reactivity of the Burgess reagent[1] has been the focus of several recent investigations. Originally designed to convert aliphatic alcohols to olefins by intramolecular elimination, the reagent has been employed in the preparation of urethanes from primary alcohols,[2] the synthesis of α- and β-glycosylamines,[3] dehydration of amides to nitriles,[4] and the synthesis of oxazolines.[5] It has been featured in several total syntheses of natural products, such as those of cedrene,[6] Taxol,[7] and narciclasine,[8] among others. The most recent application of the Burgess reagent allowed for the conversion of thiols to symmetrical disulfides.[9]

Until recently, it was widely believed that oxiranes and aziridines were inert[10] to the action of the Burgess reagent. In 2003 we published the first report on the conversion of epoxides to cyclic sulfamidates with the Burgess reagent.[11] These sulfamidates can also be prepared by reactions of diols[12] or epoxy alcohols[13] with the Burgess reagent. The two pathways share common mechanistic features; for example, it has been shown that the reaction with epoxides and diols requires 2 equiv of the Burgess reagent.[11,13] It seems likely that the formation of sulfamidates from certain diols may proceed via initially formed oxiranes, which then yield *cis*-fused sulfamidates according to the mechanistic rationale shown in Figure 1.[14] The corresponding *trans*-fused sulfamidates, not available from epoxides, are accessible from *cis* diols.[12,13]

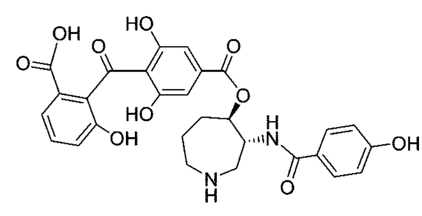
In 2006 we prepared the first asymmetric version of the Burgess reagent[14] and demonstrated its utility on the synthesis of both *cis* and *trans* amino alcohols, which are synthesized in either enantiomeric series by the reaction of the menthyl derivative of the Burgess reagent (**9**) with oxiranes, Figure 2. Diastereomeric sulfamidates of type **10** and **11** may be hydrolyzed to *cis* amino alcohols following their sometimes arduous separation. Because cyclic sulfamidates resemble cyclic sulfates in their reactivity with nucleophiles, they yield the corresponding *trans* derivatives of amino alcohols **13** and **14** via inversion with ammonium benzoate.[15,16] The benzoates are generally separated easily and yield the *trans* amino alcohols upon hydrolysis, as shown in Figure 2.[14] Thus both *cis* and *trans* derivatives of amino alcohols in both enantiomeric series may be attained.

Results and Discussion

An effective application of this methodology presented itself in the enantiodivergent synthesis of balanol,[17,18] a fungal metabolite with significant inhibitory activities against protein kinase C (PKC) isozymes.[19] The synthesis began with the reaction of Burgess reagent **9** with vinyl oxirane **16**, followed by regioselective opening at the allylic site to yield the two diasteromeric sulfamidates **17** and **18** in approximately 40% isolated yield.[20]

The mixture of sulfamidates was treated with ammonium benzoate to effect the inversion at the sulfamidate oxygen, and the resulting benzoates were separated. Benzoate **19a**, with the correct absolute configuration for natural balanol, was converted to cyclic carbamate **21** under basic conditions, as shown in Scheme 1. The absolute configurations of **17**, **18**, and **19a** and **19b** were established by hydrogenation, hydrolysis, and conversion to their cyclic carbamates, then comparison of the physical and spectroscopic properties with literature values of the saturated cyclic carbamate derivative of **21** ($[\alpha]^{22}_D$ +7.0 (*c* 1.0, EtOH), lit.[21] $[\alpha]^{22}_D$ +6.0 (*c* 1.0, EtOH)). Acylation of the cyclic carbamate **21**, now freed of the chiral auxiliary group, with *p*-benzyloxybenzoyl chloride furnished **22** in 83% yield. Osmium tetraoxide-mediated oxidation generated the *cis* diol **23** in a >95:5 ratio of diastereomers. Oxidative cleavage of **23** with sodium periodate generated a dialdehyde species that was immediately treated with benzylamine under reductive amination conditions to furnish the hexahydroazepine derivative **24**.[22] Mild base hydrolysis of the cyclic carbamate yielded the known hydroxy amide **25a** ($[\alpha]^{23}_D$ –4.7 (*c* 0.02, $CHCl_3$), which had been previously converted to (−)-balanol.[17f] The optical purity of **25a**, established by a complete conversion to its Mosher ester and ^{19}F NMR analysis, was shown to be greater than 95%. We could not locate optical rotation data for **25a** in the literature despite the fact that three preparations have been reported.[17f,18f,p] Optical rotation data has been reported for the unprotected hexahydroazepine amino alcohol (lit.[17f] $[\alpha]^{25}_D$ −19.3 (*c* 0.171, MeOH), lit.[18n] $[\alpha]^{23}_D$ −20.0 (*c* 0.5, MeOH)).

The attainment of **25a** in eight steps constitutes a formal total synthesis of (−)-balanol. The unnatural enantiomer may be obtained by an identical procedure from the *trans* benzoate **19b**. Future efforts in this area will focus on the synthesis of regioisomeric derivatives of balanol and improving the design of more thermally stable Burgess reagents.



(−)-Balanol

Experimental Section

General Experimental Procedures. All nonaqueous reactions were carried out in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. Methylene chloride was distilled from calcium hydride. THF and benzene were dried over potassium/benzophenone. Analytical thin-layer chromatography was performed on Silicycle 60 Å 250 μm TLC plates with F-254 indicator. Flash

† Dedicated to Dr. G. Robert Pettit of Arizona State University for his pioneering work on bioactive natural products.

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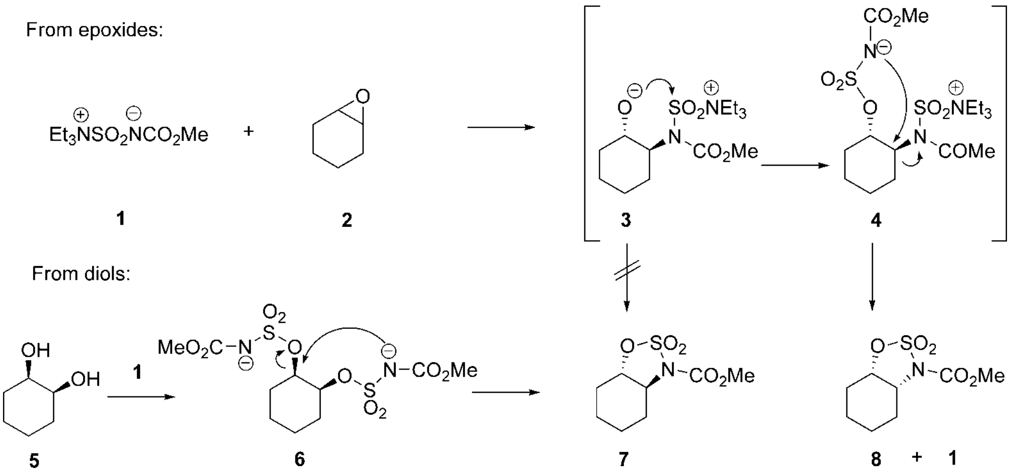


Figure 1. Proposed mechanism for the formation of cyclic sulfamidates from epoxides and diols.

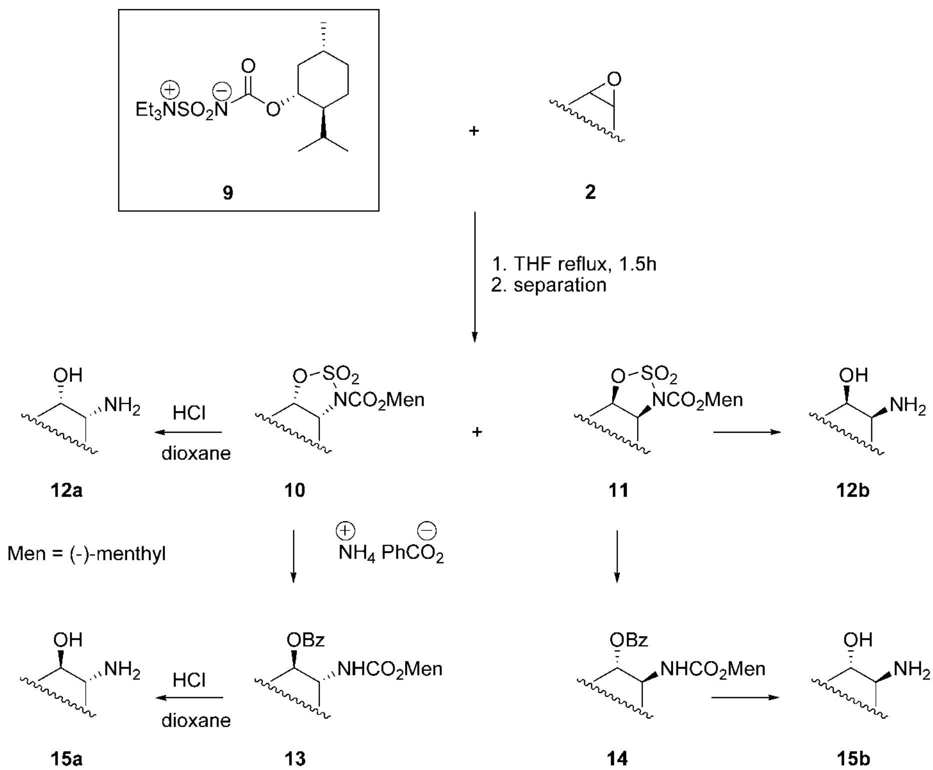
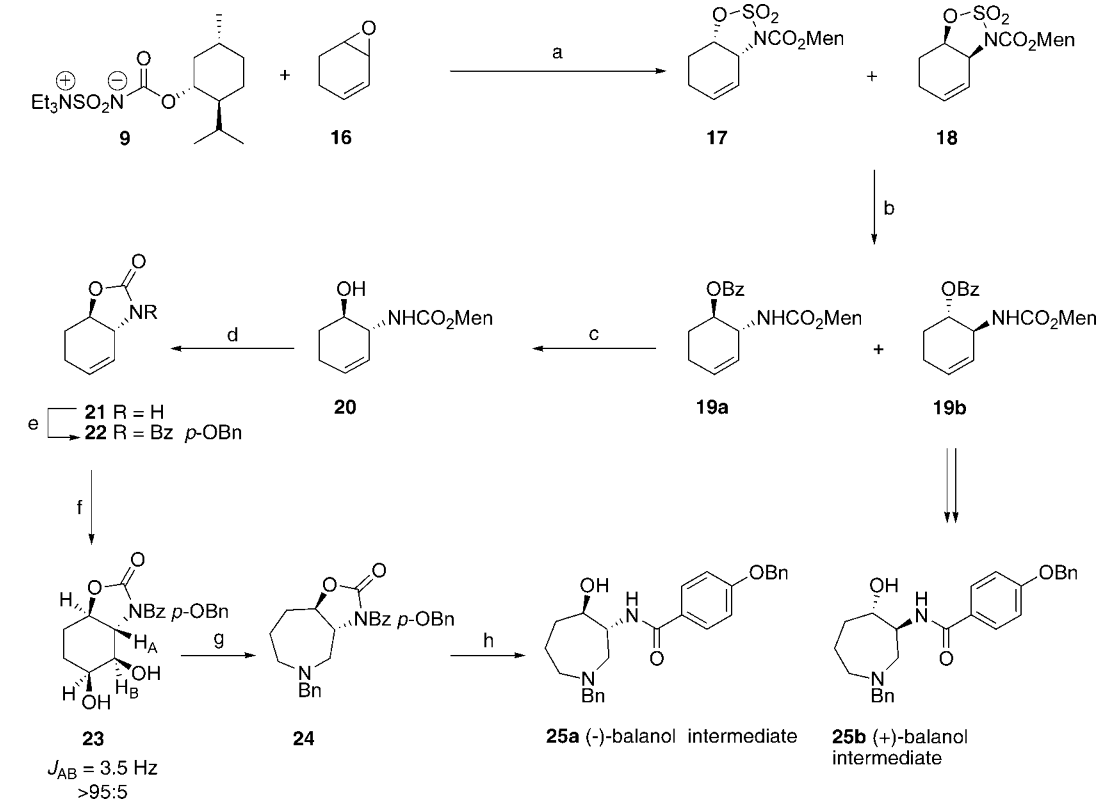


Figure 2. Synthesis of both enantiomers of *cis* and *trans* amino alcohols from epoxides with the Burgess reagent containing a menthyl chiral auxiliary group.

column chromatography was performed using Natland 200–400 mesh silica gel. Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer One FT-IR spectrometer. Optical rotation was measured on a Perkin-Elmer 341 polarimeter. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Brucker (300 or 600 MHz) spectrometer. All chemical shifts are referenced to TMS or residual undeuterated solvent ($CHCl_3$, CH_2Cl_2). Combustion analyses were performed by Atlantic Microlabs, Norcross, GA. Mass spectra were recorded on a Kreatus/MsI Concept 1S mass spectrometer at Brock University.

(3a*R*,7a*S*)-2,2-Dioxo-3a,6,7,7a-tetrahydro-2λ^6-1,2,3-benzoxathiazole-3-carboxylic acid-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl ester (17) and (3a*S*,7a*R*)-2,2-Dioxo-3a,6,7,7a-tetrahydro-2λ^6-1,2,3-benzoxathiazole-3-carboxylic acid-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl ester (18). To a solution of oxirane **16** (186 mg, 2.0 mmol) in THF (5 mL) was added menthol Burgess reagent **9** (1.668 g, 4.6 mmol). The resulting reaction mixture was stirred at 70 °C until complete consumption of the oxirane (TLC), then cooled to room temperature and filtered through a plug of silica to remove salts formed during the reaction. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (8:1 hexanes−ethyl acetate) to give 257 mg of diastereomers **17** and **18** (1:1) as colorless crystals in 36% yield: mp 115–118 °C (hexanes−ethyl acetate); R_f 0.55 (4:1 hexanes−ethyl acetate); $[\alpha]_D^{23}$ -54.5 (*c* 1.25, $CHCl_3$); IR (film) ν 3443, 3031, 2959, 2930, 2873, 1731, 1599, 1457, 1432, 1371, 1331, 1307, 1241, 1217, 1189, 1170, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 0.74–0.85 (m, 3H), 0.87–0.96 (m, 6H), 1.00–1.31 (m, 3H), 1.39–1.75 (m, 5H), 1.82–2.44 (m, 5H), 4.66–4.84 (m, 2H), 5.13–5.33 (m, 1H), 5.56–5.85 (m, 1H), 6.02–6.28 (m, 1H); ^{13}C NMR (rotamers) (75 MHz, $CDCl_3$) δ 18.7, 18.7, 18.8, 18.9, 19.9, 20.3, 21.2, 22.1, 22.6, 23.7, 23.9, 24.2, 29.3, 29.3, 29.5, 32.0, 37.7, 37.9, 38.6, 44.7, 44.8, 44.9, 45.2, 51.5, 53.2, 53.2, 72.8, 72.9, 74.6, 75.1, 75.3, 75.5, 79.2, 81.6, 81.7, 117.9, 119.0, 119.0, 129.5, 135.0, 147.9; MS (EI) *m*/*z* (%) 357 (M); 220(16), 140(14), 139(90), 137(33), 97(24), 95(24), 83(100), 81(36), 80(11), 79(47), 69(43), 67(19), 57(35), 55(49), 53(12); HRMS calcd for $C_{17}H_{27}NO_5S$ 357.1610, found 357.1593.

Scheme 1. Formal Enantiodivergent Synthesis of (−)- and (+)-Balanol[a]



[a] Reagents and conditions: (a) **9**, THF, reflux, 1.5 h, 36%; (b) (i) ammonium benzoate, DMF, 45 °C, 12 h; (ii) THF, H_2O, H_2SO_4, 76%; (c) 1 N NaOH, MeOH, 2 h, 94%; (d) NaH, THF, reflux, 86%; (e) 4-benzyloxybenzoyl chloride, DCM, DMAP, NEt_3, 0 °C−rt, 83%; (f) OsO_4, NMO, DCM, rt, 24 h, 83%; (g) (i) $NaIO_4$, 8:2 acetone−H_2O, rt, 6 h; (ii) Bn-NH_2, MeOH, AcOH, $NaCNBH_3$, 3 Å molecular sieves, −78 °C to rt, 16 h, 68%; (h) 1 N NaOH, −20 °C, 12 h, 81%.

(1*S*,2*R*)-Benzoic acid-2-(1*R*,2*S*,5*R*)-(2-isopropyl-5-methylcyclohexyloxycarbonylamino)cyclohex-3-enyl ester (19a) and (1*R*,2*S*)-Benzoic acid-2-(1*R*,2*S*,5*R*)-(2-isopropyl-5-methylcyclohexyloxycarbonylamino)cyclohex-3-enyl ester (19b). To a stirred solution of **17** and **18** (320 mg, 1.25 mmol) in dry DMF (5 mL) was added ammonium benzoate (346 mg, 2.49 mmol). The solution was heated to 55 °C and stirred for 18 h. The solvent was evaporated, and the residue was dissolved in freshly distilled THF (3 mL). Three drops of H_2O and three drops of concentrated H_2SO_4 were added, and the reaction mixture was stirred for 12 h. After the pH was adjusted to 9 (saturated $NaHCO_3$), the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated. The crude material was recrystallized from ethyl acetate–hexanes to afford a mixture of diastereomers (279 mg, 76%) as a white solid. The diastereomers were separated via flash column chromatography (400:1 CH_2Cl_2−MeOH) to afford **19a** and **19b** as a white solid.

19a: mp 103–105 °C (ethyl acetate–hexanes); R_f 0.67 (400:1 CH_2Cl_2−MeOH); $[\alpha]^{23}_D$ −100.8 (*c* 0.25, $CHCl_3$); IR (film) 3436, 3019, 2962, 1713, 1602, 1511, 1424, 1277, 1117, 1048, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, J = 5.8 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 7.1 Hz, 3H), 0.98–1.04 (m, 1H), 1.21–1.27 (m, 1H), 1.26–1.42 (m, 2H), 1.59–1.72 (m, 4H), 1.88–1.93 (m, 1H), 1.96–2.00 (m, 1H), 2.08–2.11 (m, 1H), 2.25–2.28 (m, 2H), 4.46 (dt, J = 10.7, 3.9 Hz, 1H), 4.52–4.62 (m, 1H), 4.66 (d, J = 9.2 Hz, 1H), 5.04–5.11 (m, 1H), 5.69 (dd, J = 9.5 Hz, 1.5, 1H), 5.85 (d, J = 10.2 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 8.07 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 20.8, 21.9, 23.5, 24.0, 26.3, 26.4, 31.2, 34.2, 41.0, 47.2, 51.7, 73.9, 74.8, 126.8, 128.3 (2×C), 129.5, 129.8 (2×C), 130.2, 133.0, 156.2, 166.5; MS (EI) *m/z* (%) 399; 41(18), 43(22), 44(15), 55(22), 47(18), 69(26), 71(21), 77(26), 81(15), 83(24), 95(18), 105(100), 112(12), 121(14), 123(8), 139(27), 294(6); HRMS calcd for $C_{24}H_{33}NO_4$ 399.2410, found 399.2403; *anal.* calcd C 72.15, H 8.33, found C 72.42, H 8.44.

19b: mp 107–109 °C (ethyl acetate–hexanes); R_f 0.62 (400:1 CH_2Cl_2−MeOH); $[\alpha]^{23}_D$ +16.2 (*c* 0.4, $CHCl_3$); IR (film) 3369, 3033, 2954, 2928, 2869, 1714, 1523, 1277, 1241, 1116, 1027 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.42 (d, J = 6.6 Hz, 3H), 0.65 (d, J = 6.6 Hz, 3H), 0.85–0.97 (m, 6H), 1.21 (t, J = 11.5 Hz), 1.41–1.49 (m, 1H), 1.54–1.71 (m, 3H), 1.91–2.03 (m, 2H), 2.06–2.13 (m, 1H), 2.23–2.29 (m, 2H), 4.49 (td, J = 10.8, 3.7 Hz, 1H), 4.55–4.61 (m, 1H), 4.70 (d, J = 9.5 Hz, 1H), 5.04–5.12 (m, 1H), 5.59 (dq J = 9.8, 2.2 Hz, 1 H), 5.84 (d, J = 8.6 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 8.06 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 20.5, 22.0, 23.5, 24.0, 26.2, 26.6, 31.3, 34.2, 41.4, 47.3, 51.7, 73.7, 74.5, 127.0, 128.3 (2×C), 129.3, 129.8 (2×C), 130.1, 132.9, 156.0, 166.5; MS (EI) *m/z* (%) 399; 41 (15), 43 (14), 55 (23), 57 (19), 69 (32), 71 (16), 77 (27), 79 (10), 81 (15), 83 (39), 95 (20) 105 (100), 112 (19), 113 (14), 121 (12), 123 (10), 138 (11), 139 (47), 156 (15), 251 (15), 294 (12); HRMS calcd for $C_{24}H_{33}NO_4$ 399.2410, found 399.2410.

(1*S*,6*R*)-(6-Hydroxycyclohex-2-enyl)carbamic acid (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl ester (20). A round-bottomed flask was charged with **19a** (122 mg, 0.305 mmol) and 1 N NaOH (12 mL) in methanol. The resulting solution was stirred at room temperature for 1 h and then concentrated before the residue was dissolved in 5 mL of water, and the aqueous layer was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and evaporated to give the crude product. Recrystallization of the crude material from ethyl ether−hexanes afforded 85 mg (94%) of the alcohol as a white solid: mp 115–116 °C (ethyl ether−hexanes); R_f 0.44 (2:1 hexanes−ethyl acetate); $[\alpha]^{23}_D$ −72.9 (*c* 0.775, $CHCl_3$); IR (film) 3435, 2955, 2869, 1645, 1529, 1455 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 2.2 Hz, 3H), 0.86 (d, J = 2.2 Hz, 3H), 0.89–1.07 (m, 2H), 1.21–1.32 (m, 1H), 1.36–1.48 (m, 1H), 1.54–1.63 (m, 2H), 1.63–1.69 (m, 1H), 1.82–1.96 (m, 2H), 1.96–2.02 (m, 1H), 2.03–2.13 (m, 2H), 3.01–3.18 (br s, 1H), 3.60 (dq, J = 10.7 Hz, 3.6, 1H), 3.96–4.16 (m, 1H), 4.51 (td, J = 9.9, 1.6 Hz, 1H), 4.73 (d, J = 6.4 Hz, 1H), 5.36 (d, J = 9.8 Hz, 1H), 5.77 (d, J = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 20.8, 22.0, 23.4, 23.9, 26.2, 28.9, 31.3, 34.2, 41.3, 47.3, 55.3, 73.2, 75.4, 125.4, 130.9, 157.8; MS (EI) *m/z* (%) 295; 41(58), 43(43), 54(29), 55(56), 56(21), 57(34), 67(67), 68(23), 69(70), 71(68), 81(61), 82(32), 83(66), 95(100), 96(31), 113(75), 123(28), 138(29); HRMS calcd for $C_{17}H_{29}NO_3$ 295.2147, found 295.2147; *anal.* calcd C 69.12, H 9.89, found C 68.86, H 9.89.

(3a*R*,7a*R*)-3a,6,7,7a-Tetrahydro-3*H*-benzoxazol-2-one (21). A suspension of NaH (60% in mineral oil, 33 mg, 1.35 mmol, prewashed with hexanes (5 mL × 3)) in THF (15 mL) at 0 °C was added dropwise to a solution of alcohol **20** (200 mg, 6.77 mmol) in freshly distilled THF (7 mL), then the reaction mixture was brought to reflux. After stirring for 12 h, the mixture was cooled to room temperature and the reaction was quenched by the addition of saturated NH_4Cl and then concentrated before extracting the aqueous layer with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and evaporated to give the crude product. Recrystallization of the crude material from ethyl ether−hexanes afforded 81 mg (86%) of the title compound as a white solid: mp 114–115 °C (ethyl ether−hexanes); R_f 0.36 (1:1 hexane−ethyl acetate); $[\alpha]^{23}_{D}$ −37.7 (*c* 1.37, $CHCl_3$); IR (film) 3854, 3435, 3020, 1751, 1644, 1216, 769 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (td, J = 9.8, 0.94 Hz, 1H), 2.21–2.28 (m, 1H), 2.29–2.50 (m, 2H), 4.07 (t, J = 11.4 Hz, 1H), 4.14 (td, J = 12.3, 1.1 Hz, 1H), 5.50–5.65 (m, 1H), 5.85 (dd, J = 9.1, 0.77 Hz, 1H), 5.88–6.15 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 25.3, 58.1, 81.3, 123.9, 128.4, 161.6; MS (EI) *m*/*z* (%) 139; 41(22), 54(100), 55(11), 67(55), 68(17), 95(13), 111(26); HRMS calcd for $C_7H_9NO_2$ 139.0633, found 139.0632.

(3a*R*,7a*R*)-3-(4-Benzyloxybenzoyl)-3a,6,7,7a-tetrahydro-3*H*-benzoxazol-2-one (22). To a stirred solution of **21** (57 mg, 0.409 mmol) in freshly distilled CH_2Cl_2 (7 mL) were added triethylamine (0.11 mL, 0.819 mmol) and DMAP (17 mg, 0.122 mmol). The reaction was cooled to 0 °C, then 4-benzyloxybenzoyl chloride (101 mg, 0.409 mmol) was added in portions over a period of 30 min. The reaction was stirred for 12 h and then diluted with CH_2Cl_2 (5 mL). The organic layer was washed with cold 1 N HCl (3 × 3 mL) and then with saturated $NaHCO_3$ (1 × 3 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and then evaporated. The crude product was subjected to flash column chromatography (6:1 hexanes−ethyl acetate), then recrystallized from ethyl ether−hexanes to afford 102 mg (72%) of the title compound as a white solid: mp 167–169 °C (ethyl ether−hexanes); R_f 0.47 (2:1 hexanes−ethyl acetate); $[\alpha]^{23}_{D}$ −104.6 (*c* 0.5, $CHCl_3$); IR (film) 2922, 1790, 1674, 1604, 1298, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97–2.07 (m, 1H), 2.27–2.45 (m, 2H), 2.45–2.55 (m, 1H), 4.24–4.38 (m, 1H), 4.50 (d, J = 8.6 Hz, 1H), 5.10 (s, 2H), 5.68 (dd, J = 6.6, 3.2 Hz, 1H), 6.13 (dd, J = 9.6, 1.3 Hz, 1H), 6.98 (d, J = 8.6 Hz, 2H), 7.31–7.45 (m, 5H), 7.77 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 25.3, 60.4, 70.2, 78.5, 114.3, 123.1, 125.1, 127.6, 128.3, 128.7, 128.8, 132.3, 136.2, 155.2, 162.9, 169.9; MS (EI) *m*/*z* (%) 349; 43(11), 83(10), 91(100), 113(10), 167(56), 168(16), 183(18), 184(15), 211(12), 226(27), 349(18); HRMS calcd for $C_{21}H_{19}NO_4$ 349.1314, found 349.1314; *anal.* calcd C 72.19, H 5.48, found C 72.22, H 5.55.

(3a*R*,7a*R*)-3-(4-Benzyloxybenzoyl)-4,5-dihydroxyhexahydrobenzoxazol-2-one (23). To a stirred solution of **22** (93 mg, 0.266 mmol) in freshly distilled CH_2Cl_2 (5 mL) were added *N*-methylmorpoline-*N*-oxide (47 mg, 3.99 mmol), one drop of distilled water, and a catalytic amount of OsO_4. The reaction was stirred at room temperature for 36 h before filtering through a plug of Celite and silica gel. The crude material was recrystallized from ethyl ether−hexanes and then dried over P_2O_5 to yield 84 mg (83%) of the title compound as a white solid: mp 178–180 °C (ethyl ether−hexanes); R_f 0.35 (1:3 hexanes−ethyl acetate); $[\alpha]^{23}_{D}$ −77.2 (*c* 0.5, $CHCl_3$); IR (film) 2922, 1790, 1674, 1604, 1298, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65–1.75 (m, 2H), 2.02–2.07 (m, 1H), 2.22–2.28 (m, 1H), 3.75 (dd, J = 11.1, 0.93 Hz, 1H), 3.81–3.91 (m, 1H), 4.60–4.68 (m, 1H), 4.75–4.80 (m, 1H), 5.10 (s, 2H), 6.98 (d, J = 7.9 Hz, 2H), 7.31–7.34 (m, 1H), 7.36–7.42 (m, 4H), 7.76 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 25.3, 60.4, 70.2, 78.5, 114.3, 123.1, 125.1, 127.6, 128.3, 128.7, 128.8, 132.3, 136.2, 155.2, 162.9, 169.9; MS (EI) *m*/*z* (%) 349; 43(11), 83(10), 91(100), 113(10), 167(56), 168(16), 183(18), 184(15), 211(12), 226(27), 349(18); HRMS calcd for $C_{21}H_{19}NO_4$ 349.1314, found 349.1314.

(3a*R*,7a*R*)-5-Benzyl-3-(4-benzyloxybenzoyl)octahydro-1-oxa-3,5-diaza-azulen-2-one (24). To a stirred solution of **23** (58 mg, 0.151 mmol) in acetone (3 mL) was added a suspension of $NaIO_4$ (322 mg, 1.51 mmol) in distilled water. The reaction was stirred at room temperature for 6 h, then the solvent was removed. The crude residue was triturated with ethyl acetate (3 × 5 mL), then washed with brine (2 × 5 mL). The resulting solution was filtered through a plug of silica gel and concentrated under reduced pressure to yield the dialdehyde, which was used without further purification. It was dissolved in dry MeOH (3 mL) and cooled to −78 °C in an acetone and liquid N_2 bath. To this solution was added 3 Å molecular sieves (150 mg), followed by $NaCNBH_3$ (10 mg, 0.166 mmol), then AcOH (17.3 μL, 0.302 mmol), and finally benzylamine (18.2 μL, 0.166 mmol). The reaction was warmed to room temperature slowly over 24 h before concentrating under reduced pressure. The resulting residue was triturated with ethyl acetate (3 × 5 mL) and washed with $NaHCO_3$ (1 × 3 mL). The organic layer was washed with brine (3 mL), then dried with Na_2SO_4 before concentrating. The crude material was recrystallized from ethyl ether−hexanes to yield 47 mg (68%) of the title compound as a pale yellow solid: mp 126–128 °C (ethyl ether−hexanes); R_f 0.68 (2:1 hexanes−ethyl acetate); $[\alpha]^{23}_{D}$ −27.9 (*c* 0.7, $CHCl_3$); IR (film) 3029, 2835, 1783, 1679, 1604, 1300, 1253, 1119 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69–1.78 (m, 3H), 2.33–2.45 (m, 1H), 2.50–2.73 (m, 1H), 3.40–3.47 (m, 1H), 3.68 (q, J = 18.6 Hz, 2H), 4.39 (q, J = 8.7 Hz, 2H), 4.90 (t, J = 8.5 Hz, 1H), 5.11 (s, 2H), 6.98 (d, J = 8.6 Hz, 2H), 7.28–7.44 (m, 10H), 7.74 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 31.2, 51.4, 55.3, 61.8, 63.0, 70.1, 78.0, 114.1, 125.2, 127.2, 127.5, 128.2, 128.4, 128.7, 132.3, 136.1, 138.9, 154.1, 162.8, 169.7; MS (EI) *m*/*z* (%): 412 (M – CO_2); 44(20), 91(100), 160(76), 161(10); HRMS (M – CO_2) calcd for $C_{27}H_{28}N_2O_2$ 412.2151, found 412.2151.

Benzamide, *N*-[(3*R*,4*R*)-hexahydro-4-hydroxy-1-(phenylmethyl)-1*H*-azepin-3-yl]-4-(phenylmethoxy)benzamide (25a). To a stirred solution of **24** (12 mg, 0.0263 mmol) in freshly distilled THF (0.2 mL) was added 1 N NaOH (1 mL) at −20 °C. The reaction was warmed to room temperature slowly over 12 h before concentrating under reduced pressure. The reaction was concentrated, extracted into ethyl ether (5 × 1 mL), washed with brine, and then dried over Na_2SO_4. The crude product was subjected to flash column chromatography (3:1 hexanes−ethyl acetate) to yield 9 mg (81%) of the title compound as a yellow oil: R_f 0.31 (3:2 ethyl acetate–hexanes); $[\alpha]^{23}_{D}$ −4.7 (*c* 0.2, $CHCl_3$); IR (film) 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55–1.99 (m, 4H), 2.50 (m, 1H), 2.73 (dd, J = 1.9, 14.3 Hz, 1H), 2.93 (dd, J = 2.0, 14.2 Hz, 1H), 3.00 (m, 1H), 3.42 (d, J = 13.2 Hz, 1H), 3.74–3.78 (m, 2H), 3.88 (m, 1H), 5.15 (s, 2H), 6.54 (d, J = 8.7 Hz, 1H), 6.99 (d, J = 6.8 Hz, 2H), 7.22–7.50 (m, 12H); MS (FAB) *m*/*z* (%) 431 (M + H$^+$); 41(34), 43(43), 57(51), 71(34), 91(71), 149(100); HRMS calcd for $C_{27}H_{31}N_2O_3$ 431.2310, found 431.2312.

Determination of Enantiomeric Excess in 25a by ^{19}F NMR of Its Mosher's Ester. To a stirred solution of **25a** (8 mg, 0.0185 mmol) in freshly distilled CH_2Cl_2 (0.5 mL) were added triethylamine (5.16 μL, 0.0370 mmol) and DMAP (catalytic amount). The reaction was cooled to 0 °C; then (*S*)-(+)-Mosher's acid chloride (3.34 μL, 0.0185 mmol) was added in portions over a period of 10 min. The reaction was stirred until the starting material had been completely consumed (12 h) and then diluted with CH_2Cl_2 (1 mL). The organic layer was washed with cold 1 N HCl (1 × 1 mL) and then with saturated $NaHCO_3$ (1 × 1 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and evaporated. The crude product was subjected to flash column chromatography (6:1 hexanes−ethyl acetate) to afford 9 mg (77%) of the Mosher's ester: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39–1.48 (m, 2H), 1.65–1.76 (m, 2H), 2.27–2.37 (m, 2H), 3.43 (s, 3H), 2.98–3.02 (m, 1H), 3.08–3.12 (m, 1H), 3.90–3.95 (m, 1H), 4.13 (q, J = 7.1, 2H), 4.26–4.29 (m, 1H), 5.15 (s, 2H), 6.35–6.40 (m, 1H), 6.89–6.96 (m, 2H), 7.41–7.64 (m, 15H), 7.96–8.06 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.26 (major isomer), −71.58 (minor isomer); MS (FAB) *m*/*z* (%) 647 (M + H$^+$); 41(34), 43(43), 57(51), 71(34), 91(71), 149(100); HRMS calcd for $C_{37}H_{37}F_3N_2O_5$ 647.2709, found 647.2711.

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