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Formal total synthesis of (−)- and (+)-balanol: two complementary enantiodivergent routes from vinyloxiranes and vinylaziridines☆

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ABSTRACT

Formal total syntheses of both enantiomers of balanol have been achieved by the preparation of the protected hexahydroazepine core **2**. Two complementary routes have been investigated. The first relied on the regioselective opening of 1,2-epoxycyclohex-3-ene with a chiral-auxiliary version of the Burgess reagent to provide a diastereomeric pair of cis-fused cyclic sulfamidates. The sulfamidates were transformed to *trans*-amino benzoates with ammonium benzoate and, after separation, converted to (−)-**2** and (+)-**2** by oxidative cleavage and reductive amination. The second approach utilized vinylaziridines derived from 1-bromo-2,3-dihydroxycyclohexa-4,6-diene obtained by the whole-cell fermentation of bromobenzene with *Escherichia coli* JM109(pDTG601). Stereoselective opening of the aziridines generated the requisite *trans*-amino alcohol derivatives, which after saturation of the vinyl bromide moieties were converted to (−)-**2** and (+)-**2** by oxidative cleavage of the *cis*-diol and reductive amination. Experimental and spectral data are provided for all new compounds.

1. Introduction

Following its isolation[2] in 1993 by a group at Sphinx Pharmaceuticals, balanol (**1**) attracted focused attention of the synthetic community, driven in no small part by the biological activity[3] of this interesting fungal metabolite as a potent inhibitor of protein kinase C. Its synthesis, as well as the preparation of unnatural derivatives, depends on efficient access to the hexahydroazepine core containing the 1,2-*trans*-amino alcohol functionality. Following the first published total syntheses by Nicolaou[4a] and the Sphinx Pharmaceutical group of Lampe and Hughes[4b] many creative approaches to balanol were reported; 11 total[4,5] and more than 20 formal[1,6] syntheses in either enantiomeric series are now available for comparison of strategy or practicality. The formal syntheses focus on the generation of the hexahydroazepine core, which usually contains the *p*-hydroxybenzamide moiety and a variety of oxygen and nitrogen protecting groups such as the Boc, Cbz, or benzyl functionalities. One intermediate frequently employed in these formal syntheses is alcohol **2**, which contains two benzyl protecting groups (Fig. 1).[7]

Our own strategy has focused on the generation of this hexahydroazepine core by the reductive amination of an appropriate dialdehyde provided by oxidative cleavage of the corresponding 1,2-diol. The 1,2-*trans*-amino alcohol moiety then becomes available via the nucleophilic opening of either an appropriate epoxide or an aziridine. We have used both approaches to **2**; both are designed to be enantiodivergent and are shown in an abbreviated form in Figure 2.

The first approach relies on the opening of vinyl oxirane **3** with a chiral version of the Burgess reagent that we have recently developed[8] to produce diastereomeric pairs of cyclic sulfamidates. These compounds resemble cyclic sulfates in their reactions with nucleophiles[9] and yield easily *trans*-amino alcohols **4a** and **4b**, whose separation provides, after the removal of the chiral auxiliary, enantiomerically pure intermediates for the reductive amination to (−)-**2** and (+)-**2**, respectively.

The second approach employs the single enantiomer of the *cis*-dihydrodiol **5**,[10] available from the whole-cell fermentation of bromobenzene with the recombinant strain *Escherichia coli* JM109(pDTG601),[11] which overexpresses toluene dioxygenase. Two diastereomeric vinylaziridines **6**[12] and **7**[13] are prepared from the acetonide-protected diol **5** and are transformed into the *trans*-amino alcohol derivatives **8** and **9**, respectively, by nucleophilic opening with acetic acid or water. Saturation and oxidative cleavage of the *cis*-diol then set the stage for the reductive amination to (−)-**2** and (+)-**2**, respectively.

☆ See Ref. 1.

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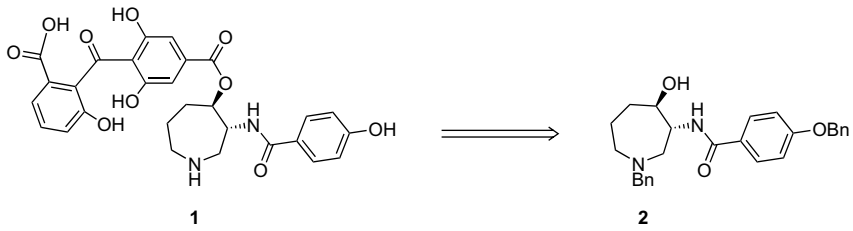


Figure 1. Balanol and the protected hexahydroazepine intermediate.

An obvious advantage of the chemoenzymatic strategy is in the transfer of asymmetry from the enzymatically generated *cis*-diol moiety to either the *syn* or the *anti* aziridines. The attainment of these intermediates defines the access to both enantiomers of balanol and allows, following the saturation of the vinyl bromide moiety, for the oxidative cleavage of the *cis*-diol and the subsequent reductive amination to each enantiomer of **2**. In addition, the two complementary routes allow for the comparison of optical purities of intermediates available from the Burgess-reagent route with those obtained from the enantiomerically pure diol **5**. In this paper, we provide the details of both approaches and furnish the experimental and spectral data for all compounds not reported previously.

2. Results and discussion

2.1. Diastereoselective Burgess-reagent-based strategy

The availability of the chiral version of the Burgess reagent (**10**)[8] has permitted the synthesis of the diastereomeric cis-fused sulfamidates **11a** and **11b** in 36% yield, Scheme 1. Treatment of these diastereomers with sodium benzoate provided a separable mixture of the trans-functionalized menthyl carbamates **4a** and **4b** in 76% yield, at which point the access to both enantiomers of balanol was defined. Conversion of benzoate **4a** to (−)-**2** constitutes a formal synthesis of the natural enantiomer of balanol, the details of which we have already reported.[1a] Similarly, the antipodal benzoate **4b** was converted to the cyclic carbamate **12b** and subjected to the same sequence of reactions leading to final reductive amination.[14] This sequence furnished the cyclic carbamate **14b**, whose mild hydrolysis (1 N NaOH, THF, −20 °C to rt) gave (+)-**2** ($[\alpha]_D^{23}$ +4.4 (*c* 0.2, $CHCl_3$)), thereby completing the formal synthesis of (+)-balanol.

The enantiomeric purity of the product was evaluated by ^{19}F NMR of the corresponding Mosher ester and judged to be approximately 96:4. As the separation of the diastereomeric benzoates was incomplete, the small amount of the minor diastereomer **4a** contributed to the lower optical purity of the final product. We have not been able to locate optical rotation data in the literature for either (−)-**2** or (+)-**2**; therefore, we embarked on the synthesis of both enantiomers of **2** in a manner that would guarantee absolute optical integrity of the final product (Scheme 2).

2.2. Enantioselective chemoenzymatic strategy

The optical purity of diol **5** obtained by the enzymatic dihydroxylation is absolute and has been amply demonstrated in many total syntheses of naturally occurring substances.[15] No diastereomeric impurities resulting from the antipodal diol have ever been detected in the final products of the many synthetic

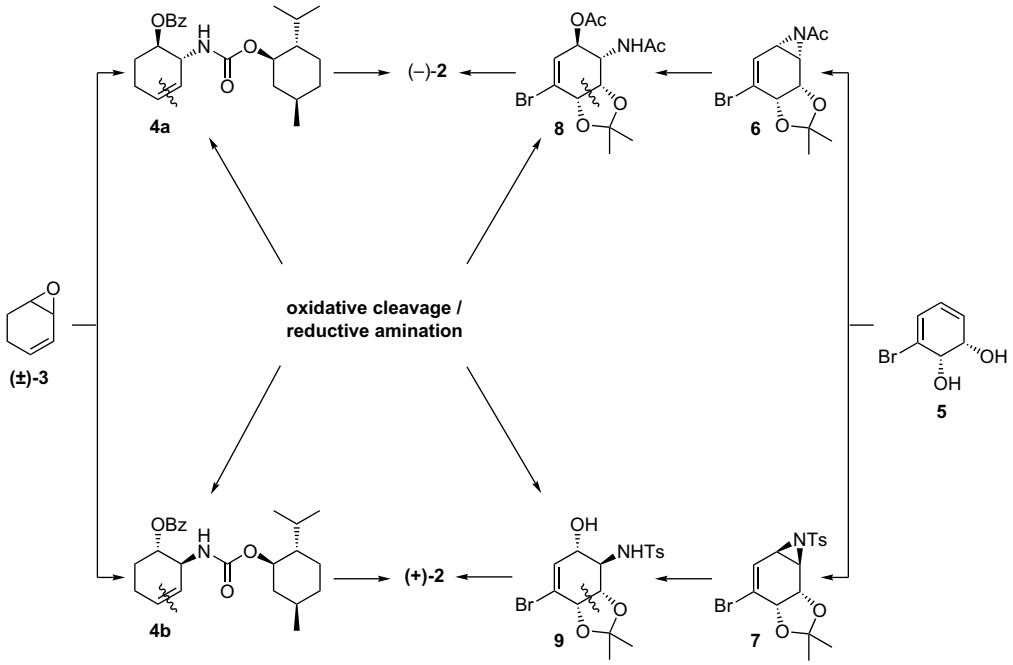
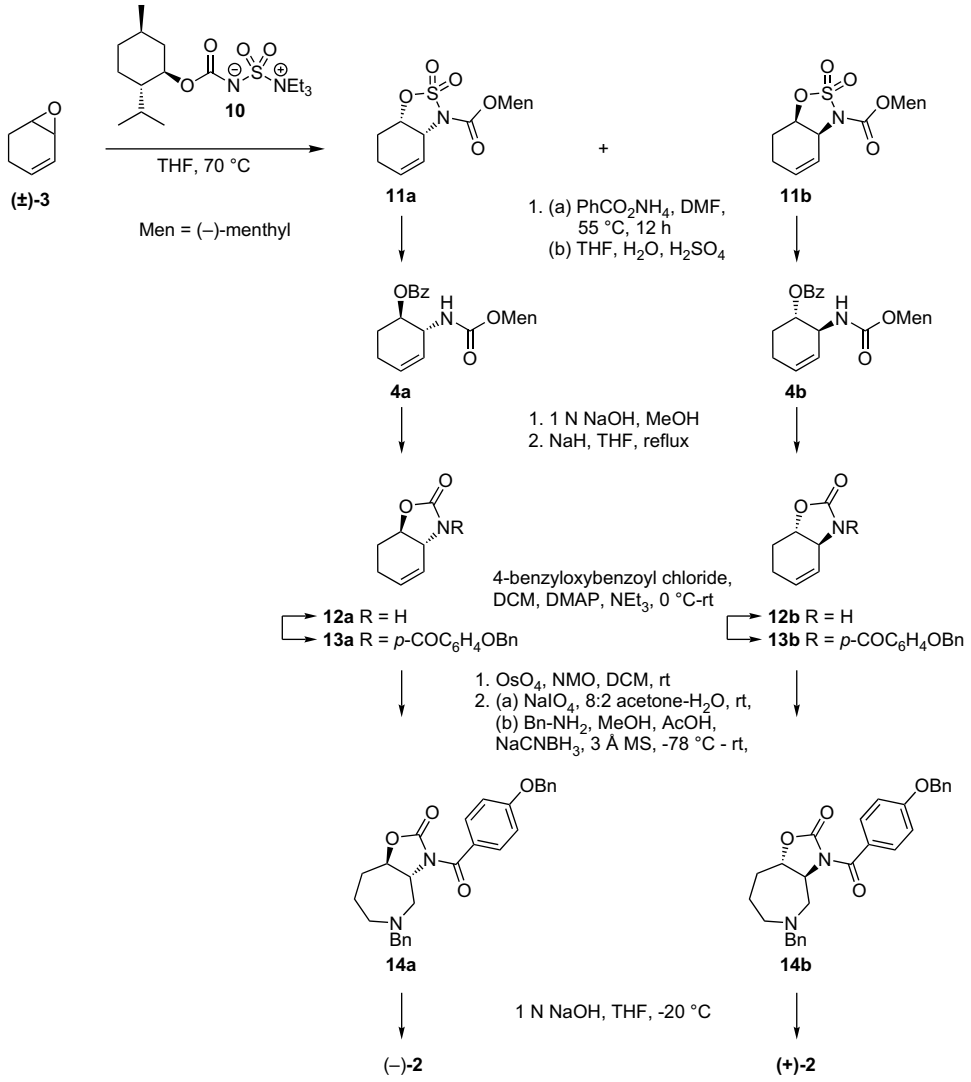


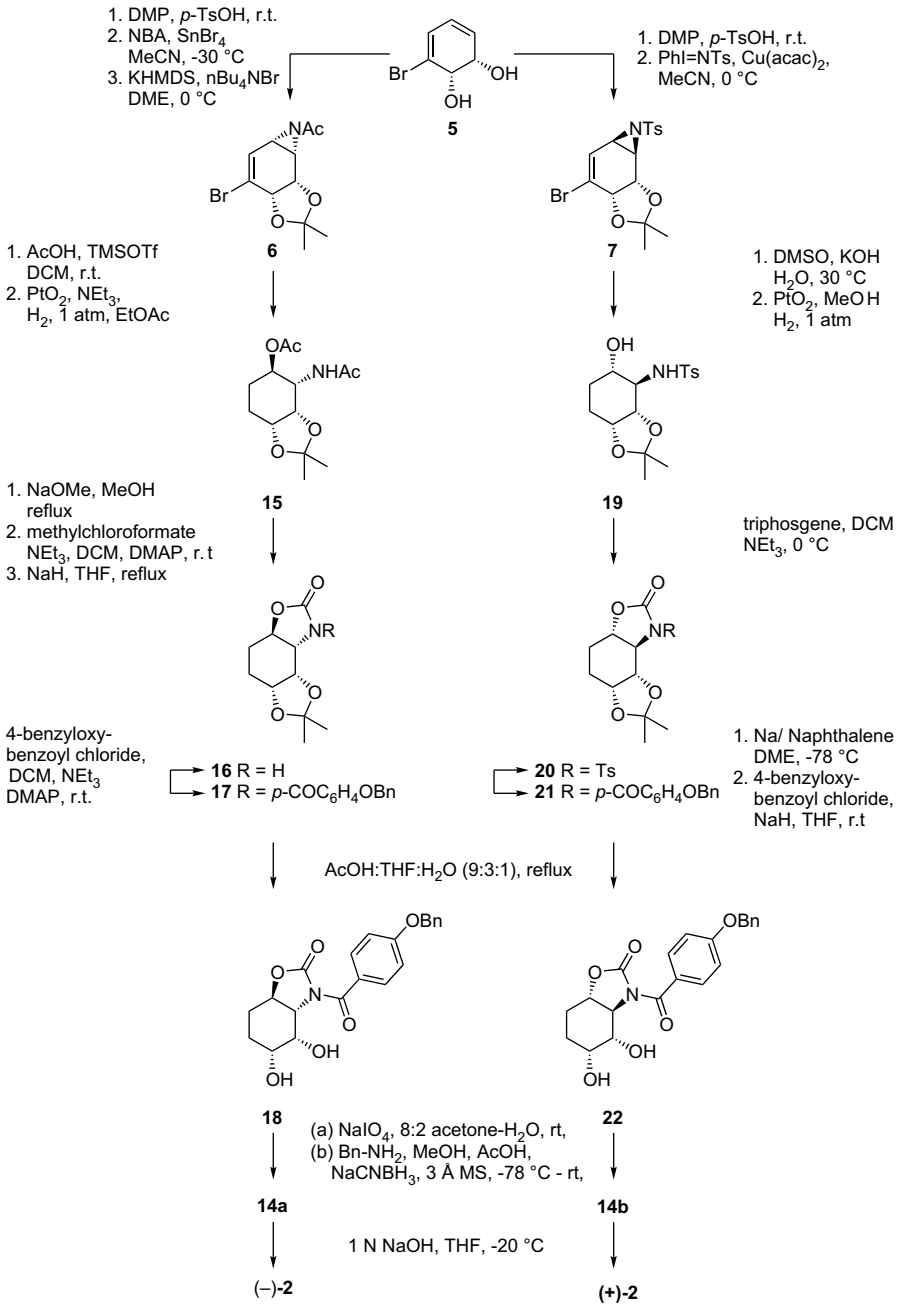
Figure 2. Complementary strategies for the synthesis of hexahydroazepine **2** from vinyloxiranes and vinylaziridines.



Scheme 1.

endeavors reported by our group and others.[16] The yield of diol **5** in whole-cell fermentations is very high (15–22 g/L) (it is also available commercially from Aldrich, sold as a suspension in phosphate buffer, catalog #48,949-2). Diols derived from chlorobenzene (cat. #48,950-6), naphthalene (cat. #49,032-6), and biphenyl (cat. #48,963-8) are also available.

We approached the synthesis of both enantiomers of hexahydroazepine derivative **2** by the general strategy depicted in Figure 2 with the preparation of two vinylaziridines that would yield, upon hydrolytic opening, the requisite *trans*-amino alcohols for both enantiomeric series. The stereochemical relationship of the amino alcohol functionality with the biochemically generated *cis*-diol is of no consequence because the diol unit itself is subjected to oxidative cleavage once its purpose in transferring asymmetry has been served. To this end diol **5** was converted to its acetonide, treated with *N*-bromoacetamide in the presence of $SnBr_4$ followed by a KHMDS-mediated elimination to furnish aziridine **6** in 68% yield over three steps. This procedure was adapted from the one reported in Corey's synthesis of oseltamivir.[12] Treatment of **6** with acetic acid in the presence of TMSOTf furnished a 4:1 mixture of *trans*- and *cis*-acetate with the minor cis isomer resulting from the S_N1 process operating in the aziridine ring opening. After separation by column chromatography, the trans isomer was subjected to hydrogenation to provide the fully saturated derivative **15** (84%). Removal of both acetyl groups was accomplished with NaOMe in MeOH, and the free amine was converted to its methyl carbamate by exposure to methyl chloroformate in 73% yield over the two steps. The hydroxy carbamate was then treated with sodium hydride in tetrahydrofuran to afford the cyclic carbamate **16**, which was acylated with 4-benzyloxybenzoyl chloride to give **17** (82%). Hydrolysis of the acetonide in aqueous acetic acid and tetrahydrofuran provided the free *cis*-diol **18** as a single isomer, which corresponded in all respects to the minor product obtained from OsO_4 treatment of the cyclic carbamate **13a**, the intermediate from the chiral Burgess-reagent route. Oxidative cleavage of the diol unit with sodium periodate provided the dialdehyde, which was subjected, without isolation or purification, to the reductive amination protocol with benzyl amine, adapted from a literature protocol.[14] The cyclic carbamate **14a** was converted to (−)-**2** ($[\alpha]_D^{23}$ −5.6 (*c* 0.2, $CHCl_3$)), by hydrolysis with aqueous sodium hydroxide and detailed analysis of optical purity was performed by ^{19}F NMR of its (*S*)-(+)-Mosher esters (δ −71.26, (*S*)-(+)-Mosher ester of (+/⁻)-**2** δ −71.26, δ −71.58). Optical rotation data (higher in value than that reported for the product of the Burgess route[1a] as a result of higher optical purity) was provided for this compound and reported in our preliminary disclosure earlier this year.[1b]



Scheme 2.

To provide accurate data for the (+)-enantiomer the anti-disposed *N*-tosylaziridine **7**, an intermediate that we have used in several syntheses of Amaryllidaceae alkaloids was utilized.[13] Protection of diol **5** as an acetonide followed by its reaction with the Yamada–Jacobsen reagent[17] furnished the aziridine in 63% yield over two steps. The aziridine **7** was treated with aqueous potassium hydroxide in DMSO followed by saturation of the vinyl bromide moiety under PtO_2-mediated hydrogenation to provide the *trans*-amino alcohol derivative **19** as a single isomer in 86% yield over two steps. After this material was converted to the cyclic *N*-tosyl carbamate **20** with triphosgene, the tosyl group was reductively removed with sodium naphthalide in DME to provide, after acylation with 4-benzyloxybenzoyl chloride, the fully saturated cyclic carbamate **21**. Hydrolysis of the acetonide gave the free diol **22**, which was subjected to the oxidative cleavage and reductive amination to furnish **14b** in 72% yield over three steps. Final hydrolysis provided (+)-**2**, identical in all respects but optical rotation ($[\alpha]_D^{23}$ +5.77 (*c* 0.75, $CHCl_3$)) to the −enantiomer obtained from either the *syn* aziridine **6** or sulfamidate **11a**.

3. Conclusion

Two complementary routes to (−)-**2** and (+)-**2** have been provided via reactions of a chiral Burgess reagent with vinyloxiranes and the regioselective opening of homochiral vinylaziridines derived from diene diol **5**. Detailed experimental procedures were reported for all new compounds. Most importantly, accurate optical data were provided for both enantiomers of **2**, as this data were

absent from the literature despite several reported syntheses. Our preparation of (−)-**2** and (+)-**2** is comparable in efficiency to previously published routes.

4. Experimental section

4.1. Preparation of (3a*S*,7a*S*)-3a,6,7,7a-tetrahydro-3*H*-benzoxazol-2-one (12b)

A round-bottomed flask was charged with **4b**[1a] (500 mg, 1.25 mmol) and 25 mL of 1 N NaOH in methanol. The reaction mixture was stirred at room temperature for 30 min before concentrating. The residue was dissolved in methylene chloride (5 mL) and water (2 mL) was added. The mixture was extracted into methylene chloride (3×2 mL). The combined organic layers were washed with brine (3 mL) and dried over Na_2SO_4. Recrystallization of the crude material from ethyl ether–hexanes afforded the free alcohol *(1R,6S)-(6-hydroxycyclohex-2-enyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester* as a white solid (367 mg, 94%): mp 134–135 °C (ethyl ether–hexanes); R_f 0.44 (2:1 hexanes–ethyl acetate); $[\alpha]_D^{23}$ −32.4 (*c* 0.78, $CHCl_3$); IR (film) ν 3435, 2955, 2869, 1645, 1529, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79–5.88 (m, 1H), 5.39 (d, *J*=9.7 Hz, 1H), 4.65–4.75 (m, 1H), 4.56 (td, *J*=4.1, 10.8 Hz, 1H), 4.06–4.15 (m, 1H), 3.61–3.70 (dq, *J*=3.6, 10.7 Hz, 1H), 2.01–2.14 (m, 1H), 1.95–2.09 (m, 2H), 1.84–1.99 (m, 2H), 1.58–1.71 (m, 4H) 1.40–1.54 (m, 1H), 1.26–1.40 (m, 1H), 1.07 (dq, *J*=1.8, 13.1 Hz, 1H), 0.98 (q, *J*=11.8 Hz, 1H), 0.89 (d, *J*=2.6 Hz, 3H), 0.86 (d, *J*=2.6 Hz, 3H), 0.77 (d, *J*=6.78 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 131.2, 125.2, 75.5, 73.6, 55.5, 47.5, 41.4, 34.2, 31.4, 29.1, 26.3, 24.0, 23.5, 22.0, 20.8, 16.5 ppm; MS (EI) *m*/*z* (%): 295(M), 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 68.96, H 9.89.

A suspension of NaH (60% in mineral oil, 24 mg, 0.99 mmol) was washed with hexanes (3×5 mL) and then dissolved in tetrahydrofuran (15 mL). A solution of *(1R,6S)-(6-hydroxycyclohex-2-enyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester* (175 mg, 0.590 mmol) in tetrahydrofuran (7 mL) was added dropwise at 0 °C. The reaction mixture was heated to reflux for 18 h. After the mixture was cooled to room temperature, the reaction mixture was quenched by the addition of satd NH_4Cl (10 mL). The mixture was concentrated before extracting the aqueous layer with methylene chloride (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give the crude product. Recrystallization of the crude material from diethyl ether–hexanes afforded **12b** (81 mg, 86%) as a white solid: mp 114–115 °C (diethyl ether–hexanes); R_f 0.36 (1:1 hexane–ethyl acetate); $[\alpha]_D^{23}$ +36.8 (*c* 1.25, $CHCl_3$); IR (film) ν 3854, 3435, 3020, 1751, 1644, 1216, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88–6.15 (br s, 1NH), 5.85 (dd, *J*=9.1, 0.77 Hz, 1H), 5.50–5.65 (m, 1H), 4.14 (td, *J*=12.3, 1.1 Hz, 1H), 4.07 (t, *J*=11.4 Hz, 1H), 2.29–2.50 (m, 2H), 2.21–2.28 (m, 1H), 1.92 (td, *J*=9.8, 0.94 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 128.4, 123.9, 81.3, 58.1, 25.3, 24.5 ppm; MS (EI) *m*/*z* (%): 139(M), 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.

Optical and analytical data for intermediates in the synthesis of (+)-**2**. For experimental details pertaining to the synthesis of (−)-**2** see Ref. 1a.

4.2. (3a*S*,7a*S*)-3-(4-Benzyloxybenzoyl)-3a,6,7,7a-tetrahydro-3*H*-benzoxazol-2-one (13b)

Yield 83%; $[\alpha]_D^{23}$ +98.2 (*c* 0.78, $CHCl_3$). Anal. Calcd: C 72.19, H 5.48; found: C 72.22, H 5.55.

4.3. Preparation of (3a*S*,7a*S*)-5-benzyl-3-(4-benzyloxybenzoyl)-octahydro-1-oxa-3,5-diaza-azulen-2-one (14b)

Yield 59%; $[\alpha]_D^{23}$ +25.8 (*c* 0.9, $CHCl_3$).

4.4. *N*-[(3*S*,4*S*)-Hexahydro-4-hydroxy-1-(phenylmethyl)-1*H*-azepin-3-yl]-4-(phenylmethoxy)-benzamide ((+)-2)

Yield 79%; $[\alpha]_D^{23}$ +4.4 (*c* 0.2, $CHCl_3$).

*4.4.1. Determination of enantiomeric excess in (+)-**2** by ^{19}F NMR of its Mosher ester*

To a stirred solution of (+)-**2** (4 mg, 0.009 mmol) in freshly distilled methylene chloride (0.5 mL) were added triethylamine (2.58 μL, 0.0185 mmol) and DMAP (catalytic amount). The reaction mixture was cooled to 0 °C and then (*S*)-(+)-Mosher's acid chloride (1.67 μL, 0.0092 mmol) was added. The reaction mixture was stirred for 12 h and then diluted with methylene chloride (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 (1×1 mL) and dried over Na_2SO_4. The crude product was subjected to flash column chromatography on silica gel (6:1 hexanes–ethyl acetate) to afford 5 mg (83%) of the (*S*)-(+)-Mosher ester: ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.58 ppm, ((*S*)-(+)-Mosher ester of (+/−)-**2** δ −71.26, −71.58 ppm).

4.5. Preparation of (1*S*,4*S*,5*S*,6*S*)-7-acetyl-3-bromo-4,5-isopropylidenedioxy-7-azabicyclo[4.1.0]hept-2-ene (6)

To a stirred solution of *N*-bromoacetamide (309 mg, 2.25 mmol) and $SnBr_4$ (0.28 mL of a 0.4 M solution in methylene chloride) in acetonitrile (40 mL) was added a solution of the acetonide-protected diol **5** (432 mg, 1.87 mmol) in acetonitrile (20 mL) dropwise over a period of 4 h at −40 °C in the dark. The reaction mixture was stirred for further 1 h at −40 °C before the slow addition of satd $NaHCO_3$ (10 mL) followed by satd Na_2SO_3 (10 mL). The phases were separated and the aqueous phase was extracted with methylene chloride (5×50 mL). The combined organic layers were washed with brine (1×100 mL), dried over Mg_2SO_4, and concentrated under reduced pressure. The crude material was subjected to flash column chromatography on neutral alumina with methylene chloride as the elution solvent to yield *N-[(1S,4S,5R,6R)-3,6-dibromo-4,5-(isopropylidenedioxy)cyclohex-2-en-1-yl]* (524 mg, 76%) as colorless crystals: R_f 0.71 (96:4 methylene chloride–methanol); mp 181–182 °C (methylene chloride); $[\alpha]_D^{23}$ +188.2 (*c* 0.50, $CHCl_3$); IR (film) ν 3684, 3019, 2400, 1675, 1498, 1424, 1216, 1063, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, *J*=9.0 Hz, 1H), 4.93 (m, 1H), 4.68 (d, *J*=5.1 Hz, 1H), 4.60 (t, *J*=4.5 Hz, 1H), 4.21 (t, *J*=3.6 Hz, 1H), 1.97 (s, 3H), 1.51 (s, 3H), 1.42 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 128.0, 124.7, 112.0, 77.8, 75.8, 50.3, 44.4, 27.8, 26.5, 23.3 ppm; MS (EI) *m*/*z* (%): 369 (M), 43 (100), 59 (10), 109 (21), 173 (10), 188 (11), 190 (11), 230 (34), 232 (33), 253 (11); HRMS (EI) calcd for $C_{11}H_{15}Br_2NO_3$ 366.9419, found 366.9380.

To a stirred solution of *N-[(1S,4S,5R,6R)-3,6-dibromo-4,5-(isopropylidenedioxy)cyclohex-2-en-1-yl]* (2.50 g, 6.77 mmol) and *n*-Bu_4NBr (2.40 g, 7.44 mmol) in DME (65 mL) at 0 °C was added KHMDS (15 mL of a 0.5 M solution in toluene) dropwise over a period of 2 h. The reaction mixture was allowed to stir for further 3 h at 0 °C before it was quenched by the addition of a pH 7 buffer solution (65 mL of potassium phosphate monobasic-sodium hydroxide buffer). The layers were separated and then the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (1×50 mL) and dried over Na_2SO_4. The crude material was subjected to flash column chromatography on silica gel (1:1 hexanes–ethyl acetate) to yield **6**

(1.17 g, 60%) as white crystals: mp 128 °C; R_f 0.44 (1:1 hexanes–ethyl acetate); $[\alpha]_D^{23}$ −57.6 (*c* 0.75, $CHCl_3$); IR (film) ν 3016, 2937, 1703, 1215, 1062, 894 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, *J*=4.8 Hz, 1H), 4.72 (dd, *J*=0.9, 6.9 Hz, 1H), 4.46 (dd, *J*=4.2, 6.9 Hz, 1H), 3.19 (dd, *J*=5.1, 6.0 Hz, 1H), 3.11 (dd, *J*=0.9, 6.0 Hz, 1H), 2.14 (s, 3H), 1.53 (s, 3H), 1.39 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 129.9, 122.8, 108.5, 76.6, 71.9, 39.6, 36.7, 27.0, 24.9, 23.2 ppm; MS (EI) *m*/*z* (%): 287 (M), 43 (100), 80 (16), 109 (18), 150 (17), 100 (22), 108 (44), 272 (13), 274 (12); HRMS (EI) calcd for $C_{11}H_{14}BrNO_3$ 287.0157, found 287.0162.

4.6. Preparation of (3a*S*,4*S*,5*R*,7a*R*)-4-acetylamino-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-5-yl ester acetic acid (15)

To a stirred solution of *(1S,4S,5S,6S)-7-acetyl-3-bromo-4,5-isopropylidenedioxy-7-azabicyclo[4.1.0]hept-2-ene* (***6***) (50 mg, 0.17 mmol) and acetic acid (0.19 mL, 3.5 mmol) in methylene chloride (0.5 mL) was added trimethylsilyl trifluoromethanesulfonate (3.1 μL, 0.017 mmol). The reaction mixture was allowed to stir at room temperature for 12 h and then filtered through a plug of SiO_2 and Na_2SO_4 before concentrating under reduced pressure. The crude material was subjected to flash column chromatography on silica gel with a solvent gradient of 3:1 and then 1:1 (hexanes–ethyl acetate) to yield the trans isomer (43 mg, 70%) and the cis isomer (11 mg, 18%) as white solids.

4.6.1. trans Isomer: (3aS,4S,5R,7aS)-4-acetylamino-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-5-yl ester, acetic acid

R_f 0.35 (1:3 hexanes–ethyl acetate); mp 168–169 °C (ethyl acetate–hexanes); $[\alpha]_D^{23}$ −111.4 (*c* 1.00, $CHCl_3$); IR (film) ν 3583, 3272, 1743, 1655, 1371, 1226, 1043 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.03 (d, *J*=9.85 Hz, 1H), 6.02 (d, *J*=2.0 Hz, 1H), 5.45 (dt, *J*=2.1, 9.3 Hz, 1H), 4.62 (dd, *J*=1.98, 5.04 Hz, 1H), 4.41 (td, *J*=2.3, 9.5 Hz, 1H), 4.39 (t, *J*=3.3 Hz, 1H), 2.05 (s, 3H), 1.97 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 170.1, 129.4, 124.7, 110.7, 77.3, 76.0, 69.4, 50.8, 27.4, 26.4, 23.3, 20.1 ppm; MS (EI) *m*/*z* (%): 347 (M), 43 (100), 84 (45), 142 (79); HRMS calcd for $C_{13}H_{18}BrNO_5$ 347.0368, found 347.0384. Anal. Calcd: C 44.84, H 5.21; found: C 44.60, H 5.24.

4.6.2. cis Isomer: (3aS,4S,5S,7aS)-4-acetylamino-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-5-yl ester, acetic acid

R_f 0.21 (1:3 hexane–ethyl acetate); mp 95–97 °C (ethyl acetate–hexanes); $[\alpha]_D^{23}$ +102.6 (*c* 1.28, $CHCl_3$); IR (film) ν 3391, 2947, 2835, 1731, 1653, 1375, 1250, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, *J*=5.7 Hz, 1H), 6.14 (d, *J*=9.0 Hz, 1H), 5.17 (t, *J*=5.1 Hz, 1H), 4.64 (d, *J*=6.0 Hz, 1H), 4.54–4.61 (m, 1H), 4.41–4.45 (m, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 169.9, 129.6, 127.2, 111.3, 76.9, 75.0, 67.3, 45.8, 27.3, 26.3, 23.2, 20.9 ppm; MS (EI) *m*/*z* (%): 347 (M), 43 (100), 56 (45), 57 (52); HRMS calcd for $C_{13}H_{18}BrNO_5$ 347.0368, found 347.0368.

To a stirred solution of *(3aS,4S,5R,7aS)-4-acetylamino-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-5-yl ester, acetic acid* (753 mg, 2.16 mmol) and triethylamine (2.10 mL, 15.1 mmol) in ethyl acetate (3 mL) was added platinum(IV)oxide (12 mg, 0.43 mmol) before purging the reaction flask with H_2. The reaction mixture was stirred at room temperature and 1 atm of H_2 for 36 h before filtering through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography on silica gel with a solvent gradient of 1:2 and then 1:5 (hexanes–ethyl acetate) to yield **15** (493 mg, 84%) as a clear oil: R_f 0.30 (1:5 hexanes–ethyl acetate); $[\alpha]_D^{23}$ −49.2 (*c* 1.24, $CHCl_3$); IR (film) ν 3286, 2939, 2988, 1735, 1657, 1547, 1374, 1243, 1041, 868, 755 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 7.99 (d, *J*=8.7 Hz, 1NH), 4.79 (dt, *J*=5.8, 11.1 Hz, 1H), 4.29 (dd, *J*=5.7, 11.0 Hz, 1H) 4.23 (dd, *J*=3.2, 5.9 Hz, 1H), 4.13 (td, *J*=2.4, 9.4 Hz, 1H), 1.96 (m, 1H), 1.94 (s, 3H), 1.82 (s, 3H), 1.73 (td, *J*=4.4, 9.3 Hz, 1H), 1.47 (td, *J*=4.4, 9.1 Hz, 1H), 1.42 (s, 3H), 1.33–1.39 (m, 1H), 1.24 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 170.0, 108.7, 75.7, 73.3, 70.0, 50.7, 27.3, 25.2, 25.1 (2×C), 23.3, 21.1 ppm; MS (EI) *m*/*z* (%): 256 ($M-CH_3^+$), 43 (100), 60 (32), 84 (43), 94 (45), 111 (48), 112 (36), 153 (57), 213 (31); HRMS calcd for $C_{12}H_{18}NO_5$ 256.1180, found 256.1187.

4.7. Preparation of (3a*R*,5a*R*,8a*S*,8b*S*)-2,2-dimethyl-hexahydro-[1,3]dioxolo[4′,5′:3,4]benzo[2,1-*d*]oxazol-7-one (16)

To a stirred solution of *(3aS,4S,5R,7aR)-4-acetylamino-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-5-yl ester acetic acid* (***15***) (300 mg, 1.11 mmol) in methanol (5 mL) was added Na (254 mg, 11.1 mmol) portionwise until completely dissolved (30 min). The reaction mixture was brought to reflux and stirred for 18 h, and then cooled to room temperature and quenched by the slow addition of H_2O (5 mL). The reaction mixture was concentrated under reduced pressure and then extracted into $CHCl_3$ (5×1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to yield the *(3aS,4S,5R,7aR)-4-amino-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-5-ol* as a pale yellow oil, which was used without further purification: ^1H NMR (300 MHz, CD_3OD) δ 4.33–4.39 (m, 1H), 4.22 (dt, *J*=5.6, 8.5 Hz, 1H), 3.54 (td, *J*=4.6, 9.5 Hz, 1H), 2.64 (dd, *J*=3.6, 9.6 Hz, 1H), 1.80–1.95 (m, 2H), 1.54–1.66 (m, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.30–1.33 (m, 1H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 108.4, 77.0, 74.2, 70.6, 55.6, 28.6, 27.0, 26.7, 24.5 ppm.

To a stirred solution of the *(3aS,4S,5R,7aR)-4-amino-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-5-ol* (178 mg, 0.951 mmol), triethylamine (0.26 mL, 1.9 mmol), and DMAP (catalytic amount) in methylene chloride (1 mL) was added methyl chloroformate (80.5 μL, 1.05 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 12 h and then diluted with methylene chloride (1 mL), washed with satd $NaHCO_3$ (1×1 mL) and brine (1 mL), and then dried over Na_2SO_4. The crude material was purified via flash column chromatography on silica gel (60:1 $CHCl_3$–MeOH) to yield *((3aS,4S,5R,7aR)-5-hydroxy-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-4-yl)-carbamic acid methyl ester* (197 mg, 73% over two steps) as a yellow oil: R_f 0.43 (10:1 $CHCl_3$–MeOH); $[\alpha]_D^{23}$ −24.7 (*c* 0.7, MeOH); IR (film) ν 3433, 2988, 2940, 1695, 1645, 1241, 1219, 1035, 1077 cm^{-1}; ^1H NMR (600 MHz, $CO(CD_3)_2$) δ 5.98 (br d, *J*=4.9 Hz, 1NH), 4.36 (dd, *J*=3.6, 5.5 Hz, 1H), 4.29 (dd, *J*=2.8, 5.6 Hz, 1H), 3.89 (br s, OH), 3.67–3.77 (m, 2H), 3.63 (s, 3H), 1.93–1.99 (m, 1H), 1.79–1.86 (m, 1H), 1.53–1.61 (m, 1H), 1.44 (s, 3H), 1.37–1.42 (m, 1H), 1.28 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CO(CD_3)_2$) δ 158.8, 107.9, 76.1, 73.8, 67.8, 55.9, 51.1, 28.6, 27.2, 26.1, 24.8 ppm; MS (EI) *m*/*z* (%): 230 ($M-CH_3^+$), 43 (34), 59 (43), 76 (38), 95 (31), 99 (34), 130 (100), 143 (33); HRMS calcd for $C_{10}H_{16}NO_5$ 230.1028, found 230.1028.

To a stirred suspension of NaH (128 mg, 5.34 mmol) in tetrahydrofuran (4 mL) was added a solution of *((3aS,4S,5R,7aR)-5-hydroxy-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-4-yl)-carbamic acid methyl ester* (131 mg, 0.534 mmol) in tetrahydrofuran (2.5 mL). The reaction mixture was brought to reflux and stirred for 24 h, and then cooled to room temperature and quenched by the addition of satd NH_4Cl (5 mL). The reaction mixture was extracted into EtOAc (5×2 mL), and the combined organic layers were washed with brine (2 mL) and dried over Na_2SO_4. Recrystallization of the crude materials from acetone yielded **16** (95 mg, 83%) as white needles: R_f 0.21 (1:3 hexanes–ethyl acetate); mp 179–181 °C (acetone); $[\alpha]_D^{23}$ −19.7 (*c* 0.75, $CHCl_3$); IR (film) ν 3459, 2983, 2925, 1733, 1639, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (br s, 1NH), 4.51–4.61 (m, 1H), 4.43–4.51 (m, 2H), 3.49 (dd, *J*=1.9, 12.1 Hz, 1H), 2.22–2.37 (m, 1H), 1.99–2.17 (m, 1H), 1.76–1.94 (m, 2H), 1.49 (s, 3H), 1.31 (s,

3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 109.5, 73.8, 73.5, 70.9, 58.3, 26.1, 23.8, 22.2, 21.9 ppm; MS (EI) *m*/*z* (%): 213 (M), 43 (92), 59 (41), 67 (45), 94 (42), 99 (100), 198 (64); HRMS calcd for $C_{10}H_{15}NO_4$ 213.1001, found 213.0998.

4.8. Preparation of (3a*R*,5a*R*,8a*S*,8b*S*)-8-(4-benzyloxybenzoyl)-2,2-dimethyl-hexahydro-[1,3]dioxolo-[4′,5′:3,4]benzo[2,1-*d*]oxazol-7-one (17)

To a stirred solution of *(3aR,5aR,8aS,8bS)-2,2-dimethyl-hexahydro-[1,3]dioxolo[4′,5′:3,4]benzo[2,1-d]oxazol-7-one (**16**)* (40 mg, 0.19 mmol), triethylamine (104 μL, 0.750 mmol), and DMAP (catalytic) in methylene chloride (0.25 mL) was added 4-benzyloxybenzoyl chloride (51 mg, 0.21 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature slowly over 16 h and then diluted with methylene chloride (0.5 mL), washed with cold 1 N NaOH (1×0.5 mL) and brine (1×0.5 mL), and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 6:1 and then 4:1 (hexanes–ethyl acetate) to yield **17** (65 mg, 82%) as a white solid: R_f 0.38 (2:1 hexanes–ethyl acetate); mp 153–154 °C (MeOH); $[\alpha]_D^{23}$ −163.8 (*c* 0.43, $CHCl_3$); IR (film) ν 3433, 1638, 1259, 1027 cm^{-1}; ^{1}H NMR (600 MHz, $CO(CD_3)_2$) δ 7.79 (d, *J*=8.7 Hz, 2H), 7.55 (d, *J*=7.6 Hz, 2H), 7.45 (t, *J*=7.6 Hz, 2H), 7.39 (t, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.7 Hz, 2H), 5.22 (s, 2H), 4.94 (dd, *J*=3.4, 7.2 Hz, 1H), 4.77 (ddd, *J*=7.7, 10.2, 12.1 Hz, 1H), 4.66 (dt, *J*=3.2, 7.2 Hz, 1H), 4.11 (dd, *J*=3.4, 12.1 Hz, 1H), 2.27–2.36 (m, 1H), 2.14–2.20 (m, 2H), 1.89–1.98 (m, 1H), 1.53 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CO(CD_3)_2$) δ 169.2, 162.6, 154.2, 136.9, 132.0 (2×C), 128.5, 128.0 (2×C), 127.7 (2×C), 125.8, 114.0 (2×C), 108.9, 73.9, 71.3, 70.1, 69.8, 60.2, 25.4, 23.2, 21.6, 20.9 ppm; MS (EI) *m*/*z* (%): 423 (M), 43 (24), 83 (23), 91 (100), 211 (26), 423 (21); HRMS calcd for $C_{24}H_{25}NO_6$ 423.1682, found 423.1662.

4.9. Preparation of (3a*R*,4*S*,5*R*,7a*R*)-3-(4-benzyloxybenzoyl)-4,5-dihydroxy-hexahydro-benzooxazol-2-one (18)

A stirred solution of *(3aR,5aR,8aS,8bS)-8-(4-benzyloxybenzoyl)-2,2-dimethyl-hexahydro-[1,3]dioxolo[4′,5′:3,4]benzo[2,1-d]oxazol-7-one (**17**)* (65 mg, 0.15 mmol) in 1 mL of 9:3:1 (AcOH–tetrahydrofuran–H_2O) was brought to reflux for 16 h and then cooled to room temperature and concentrated under reduced pressure. The resulting residue was triturated with benzene (2×1 mL) and $CHCl_3$ (2×1 mL), filtered through a plug of SiO_2, and then recrystallized from $CHCl_3$ to yield **18**(52 mg, 88%) as a white solid: R_f 0.33 (1:3 hexanes–ethyl acetate); mp 174–175 °C ($CHCl_3$); $[\alpha]_D^{23}$ −68.4 (*c* 0.5, MeOH); IR (film) ν 3435, 2918, 1786, 1660, 1604, 1220, 1036 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.7 Hz, 2H), 7.38–7.44 (m, 4H), 7.34 (t, *J*=7.1 Hz, 1H), 7.00 (d, *J*=8.7 Hz, 2H), 5.09 (s, 2H), 4.79–4.82 (m, 1H), 4.66 (td, *J*=3.5, 11.6 Hz, 1H), 3.86–3.91 (m, 1H), 3.78 (dd, *J*=1.5, 11.5 Hz, 1H), 2.24–2.29 (m, 1H (1OH)), 2.02–2.15 (m, 2H) 1.65–1.80 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 162.9, 154.7, 136.1, 132.4 (2×C), 128.7, 128.3 (2×C), 127.6, 127.5, 124.9, 114.3 (2×C), 73.6, 70.2, 69.6, 67.3, 64.3, 27.4, 25.4 ppm; MS (EI) *m*/*z* (%): 383 (M), 43 (15), 65 (10), 91 (100), 92 (25), 121 (13), 211 (19); HRMS calcd for $C_{21}H_{21}NO_6$ 383.1369, found 383.1372.

4.10. Preparation of (3a*R*,7a*R*)-5-benzyl-3-(4-benzyloxybenzoyl)-octahydro-1-oxa-3,5-diaza-azulen-2-one (14a)

To a stirred solution of *(3aR,4S,5R,7aR)-3-(4-benzyloxybenzoyl)-4,5-dihydroxy-hexahydro-benzooxazol-2-one (**18**)* (30 mg, 0.078 mmol) in 10:1 acetone–H_2O (1 mL) was added $NaIO_4$ (167 mg, 0.780 mmol). The resulting suspension was stirred at room temperature for 6 h, and then the solvent was removed and the crude residue was triturated with ethyl acetate (3×5 mL), and then washed with brine (2×5 mL). The resulting organic layers were filtered through a plug of silica gel and concentrated under reduced pressure to yield *(4S,5R)-3-(4-benzyloxybenzoyl)-2-oxo-5-(3-oxo-propyl)-oxazolidine-4-carbaldehyde*, which was used without further purification. The crude dialdehyde was dissolved in dry MeOH (2 mL) and cooled to −78 °C in an acetone and liquid N_2 bath. To this solution was added 3 Å molecular sieves (75 mg), followed by $NaCNBH_3$ (6 mg, 0.09 mmol) and then AcOH (8.9 μL, 0.156 mmol), and finally benzyl amine (9.4 μL, 0.086 mmol). The reaction mixture was warmed to room temperature slowly over 24 h before concentrating under reduced pressure. The resulting residue was triturated with ethyl acetate (3×2 mL) and washed with $NaHCO_3$ (1×1 mL). The organic layer was washed with brine (1 mL) and then dried over Na_2SO_4. The crude material was recrystallized from ethyl ether–hexanes to yield **14a** as a pale yellow solid (23 mg, 64% over two steps): mp 126–128 °C (ethyl ether–hexanes); R_f 0.68 (2:1 hexanes–ethyl acetate); $[\alpha]_D^{23}$ −29.9 (*c* 0.8, $CHCl_3$); IR (film) ν 3029, 2835, 1783, 1679, 1604, 1300, 1253, 1119 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J*=8.7 Hz, 2H), 7.29–7.37 (m, 10H), 6.98 (d, *J*=8.7 Hz, 2H), 5.10 (s, 2H), 4.90 (td, *J*=3.2, 10.5 Hz, 1H), 4.39 (td, *J*=7.1, 9.6 Hz, 1H), 3.71 (d, *J*=13.2 Hz, 1H), 3.64 (d, *J*=13.2 Hz, 1H), 3.44 (dd, *J*=6.6, 11.1 Hz, 1H), 2.50–2.73 (m, 3H), 2.35–2.45 (m, 1H), 1.66–1.78 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 162.8, 154.1, 138.9, 136.1, 132.3 (3×C), 128.7 (2×C), 128.4 (2×C), 128.2, 127.5 (3×C), 125.2, 114.1 (3×C), 78.0, 70.1, 63.0, 61.8, 55.3, 51.4, 31.2, 26.4 ppm; 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.

4.11. Preparation of benzamide, *N*-[(3*R*,4*R*)-hexahydro-4-hydroxy-1-(phenylmethyl)-1*H*-azepin-3-yl]-4-(phenylmethoxy)benzamide (−)-2

To a stirred solution of *(3aR,7aR)-5-benzyl-3-(4-benzyloxybenzoyl)-octahydro-1-oxa-3,5-diaza-azulen-2-one (**14a**)* (21 mg, 0.046 mmol) in tetrahydrofuran (0.3 mL) was added 1 N NaOH (1.5 mL) at −20 °C. The reaction mixture was warmed and allowed to warm to room temperature slowly over 12 h before concentrating under reduced pressure. The resulting residue was diluted with H_2O (1 mL) and extracted into EtOAc (5×1 mL), washed with brine (1 mL), and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent system of 3:1 (hexanes–ethyl acetate) to yield (−)-**2** (17 mg, 86%) as a pale yellow oil: R_f 0.31 (3:2 ethyl acetate–hexanes); $[\alpha]_D^{23}$ −5.6 (*c* 0.2, $CHCl_3$); IR (film) ν 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.39 (m, 4H), 7.39–7.31 (m, 7H), 7.31–7.23 (m, 1H), 6.99 (d, *J*=6.8 Hz, 2H), 6.54 (d, *J*=8.7 Hz, 1H), 5.15 (s, 2H), 3.88 (m, 1H), 3.69–3.78 (m, 1H), 3.63 (d, *J*=13.2 Hz, 1H), 3.42 (d, *J*=13.2 Hz, 1H), 3.00 (m, 1H), 2.93 (dd, *J*=2.0, 14.2 Hz, 1H), 2.73 (dd, *J*=1.9, 14.3 Hz, 1H), 2.50 (m, 1H), 1.85–1.95 (m, 2H), 1.60–1.85 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 161.4, 136.4 (2×C), 129.5 (2×C), 129.0, 128.9 (2×C), 128.7 (2×C), 128.2 (2×C), 127.5 (2×C), 127.4 (2×C), 126.4, 114.5 (2×C), 77.5, 70.1, 64.2, 59.9, 58.0, 54.4, 31.5, 29.7 ppm; 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.

*4.11.1. Determination of enantiomeric excess in (−)-**2** by ^{19}F NMR of its Mosher ester*

To a stirred solution of (−)-**2** (6 mg, 0.0139 mmol) in freshly distilled methylene chloride (0.3 mL) were added triethylamine (3.86 μL, 0.0279 mmol) and DMAP (catalytic amount). The reaction mixture was cooled to 0 °C and then (*S*)-(+)-Mosher's acid chloride (2.42 μL, 0.0139 mmol) was added in portions over a period of 5 min. The reaction mixture was stirred until the starting material had been completely consumed (12 h) and then diluted with methylene chloride (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 over Na_2SO_4, and evaporated. The crude product was subjected to flash column chromatography on silica gel (6:1 hexanes–ethyl acetate) to afford 7 mg (77%) of the (*S*)-(+)-Mosher ester: ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.26 ppm, ((*S*)-(+)-Mosher ester of (+/−)-**2** δ −71.26, −71.58 ppm).

4.12. Preparation of *N*-((3a*S*,4*R*,5*S*,7a*R*)-5-hydroxy-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide (19)

To a stirred solution of *(1R,4S,5S,6R)-3-bromo-4,5-(isopropylidenedioxy)-7-(4′-methylphenylsulfonyl)-7-azabicyclo[4.1.0]hept-2-ene* (***7***)[13c] (200 mg, 0.499 mmol) in dimethyl sulfoxide (1.5 mL) was added 10% KOH (1.5 mL). The reaction temperature was raised to 40 °C and stirred for 2 h before being cooled to room temperature. The reaction mixture was then neutralized with satd NH_4Cl and extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude material was recrystallized from hexane–ethyl acetate to yield *N-((3aS,4R,5S,7aS)-7-bromo-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide* (196 mg, 94%) as white crystals: mp 155–156 °C (hexanes–ethyl acetate); R_f 0.43 (1:1 hexanes–ethyl acetate); $[\alpha]_D^{23}$ −22.7 (*c* 0.7, $CHCl_3$); IR (film) ν 3445, 2993, 2087, 1646, 1216, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.1 Hz, 2H), 7.32 (d, *J*=8.1 Hz, 2H), 6.24 (d, *J*=3.1 Hz, 1H), 5.48 (br s, 1NH), 4.58 (d, *J*=5.6 Hz, 1H), 4.17 (t, *J*=6.7 Hz, 1H), 3.99 (br s, 1H (1OH)), 3.79 (d, *J*=4.7 Hz, 1H), 3.33 (t, *J*=6.8, 1H), 2.41 (s, 3H), 1.28 (s, 3H), 1.06 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 135.9, 134.1, 129.9, 127.6, 120.6, 111.4, 76.3, 75.9, 70.0, 56.7, 27.2, 25.9, 21.6 ppm; MS (EI) *m*/*z* (%): 402 ($M-CH_3^+$), 43 (40), 59 (32), 65 (30), 91 (85), 92 (16), 97 (15), 98 (48), 99 (68), 139 (30), 155 (26), 254 (100), 255 (15); HRMS calcd for $C_{15}H_{17}BrNO_5S$ 402.0011, found 402.0004.

To a stirred solution of *N-((3aS,4R,5S,7aS)-7-bromo-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide* (196 mg, 0.468 mmol), in MeOH (2 mL) were added K_2CO_3 (10 mg) and platinum(IV)oxide (catalytic amount) before purging the reaction flask with H_2. The reaction mixture was stirred at room temperature and 1 atm of H_2 for 36 h before filtering through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography with a solvent gradient of 1:1 and then 1:2 (hexanes–ethyl acetate) to yield **19** (123 mg, 77%) as a white solid: mp 155–156 °C (hexanes–ethyl acetate); R_f 0.30 (1:2 hexanes–ethyl acetate); $[\alpha]_D^{23}$ −105.2 (*c* 1.32, $CHCl_3$); IR (film) ν 3381, 3255, 2985, 2934, 2893, 2765, 1597, 1155, 1088, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=8.1 Hz, 2H), 5.48 (d, *J*=6.9 Hz, 1H), 4.17–4.10 (m, 1H), 3.72 (dd, *J*=8.4, 4.9 Hz, 1H), 3.51 (d, *J*=3.0 Hz, 1H), 3.50–3.35 (m, 1H), 2.97, (q, *J*=17.4, 8.3 Hz, 1H), 2.39 (s, 3H), 2.11–2.03 (m, 1H), 1.88–1.80 (m, 1H), 1.72–1.57 (m, 2H), 1.18 (s, 3H), 0.937 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.1, 129.7, 129.4, 127.8, 127.4, 108.9, 78.7, 73.6, 70.7, 63.0, 27.5, 27.4, 26.1, 23.2, 21.5 ppm; MS (EI) *m*/*z* (%): 341 (M), 43 (21), 59 (34), 65 (29), 82 (35), 83 (20), 91 (100), 100 (28), 128 (65), 155 (34); HRMS calcd for $C_{16}H_{23}NO_5S$ 341.1297, found 341.1297.

4.13. Preparation of *N*-[(3*S*,4*S*)-hexahydro-4-hydroxy-1-(phenylmethyl)-1*H*-azepin-3-yl]-4-(phenylmethoxy)-benzamide (+)-2

To a stirred solution of **14b** (12 mg, 0.026 mmol) in tetrahydrofuran (0.3 mL) was added 1 N NaOH (1.5 mL) at −20 °C. The reaction mixture was allowed to warm to room temperature slowly over 12 h before concentrating under reduced pressure. The resulting residue was diluted with H_2O (1 mL) and extracted into ethyl acetate (5×1 mL), and then the combined organic layers were washed with brine (1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent system of 3:1 (hexanes–ethyl acetate) to yield (+)-**2** (6.5 mg, 56%) as a pale yellow oil: R_f 0.31 (3:2 hexane–ethyl acetate); $[\alpha]_D^{23}$ +5.77 (*c* 0.75, $CHCl_3$), $[\alpha]_D^{23}$ +5.80 (*c* 0.20, $CHCl_3$); IR (film) ν 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.22–7.50 (m, 12H), 6.99 (d, *J*=6.8 Hz, 2H), 6.54 (d, *J*=8.7 Hz, 1NH), 5.11 (s, 2H), 3.88 (m, 1H), 3.69–3.78 (m, 1H), 3.63 (d, *J*=13.2 Hz, 1H), 3.42 (d, *J*=13.2 Hz, 1H), 3.00 (m, 1H), 2.93 (dd, *J*=2.0, 14.2 Hz, 1H), 2.73 (dd, *J*=1.9, 14.3 Hz, 1H), 2.50 (m, 1H), 1.85–1.95(m, 2H), 1.60–1.85 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 161.4, 136.4 (2×C), 129.5 (2×C), 129.0, 128.9 (2×C), 128.7 (2×C), 128.2 (2×C), 127.5 (2×C), 127.4 (2×C), 126.4, 114.5 (2×C), 77.5, 70.1, 64.2, 59.9, 58.0, 54.4, 31.5, 29.7 ppm; 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.

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Supplementary data

Experimental procedures for the preparation of **20**, **21**, **22**, and **14b** and ^1H and ^{13}C NMR spectra of compounds (−)-**2**, (+)-**2**, **6**, **12b**, **13b**, **14a**, **14b**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, and **22**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.070.

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