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Enantioselective total synthesis of the tricyclic 9-oxabispidine (1*R*,2*S*,9*S*)-11-methyl-13-oxa-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane

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Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

ABSTRACT

The enantiomerically pure tricyclic 9-oxabispidine (1*R*,2*S*,9*S*)-11-methyl-13-oxa-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane, a potential substitute for (+)-sparteine in asymmetric synthesis, was prepared in 7 steps and in 11% overall yield from a chiral epoxy alcohol and (*S*)-epichlorohydrin. The key intermediate was a bicyclic 9-oxabispidine with an appropriately functionalized, *endo*-oriented side chain.

1. Introduction

In 1990, Hoppe et al. discovered the first highly enantioselective deprotonation/electrophilic trapping reactions of prochiral *O*-alkyl carbamates with *s*-BuLi in the presence of a stoichiometric amount of the chiral lupine alkaloid,[1] (−)-sparteine (−)-**1** (Fig. 1).[2] This pioneering work opened up a new era in the asymmetric organolithium chemistry, leading to hundreds of successful applications, which are documented in a number of reviews.[3] In tandem with other metals such as Mg, Zn, Cu, and Pd, highly enantioselective transformations have also been realized using (−)-**1** as the chiral ligand; for example, desymmetrizations of *meso*-anhydrides,[4] Reformatsky[5] and Henry[6] reactions, oxidative kinetic resolutions of secondary alcohols,[7] and dynamic thermodynamic resolutions of 1,1′-biaryl-2,2′-diols.[8]

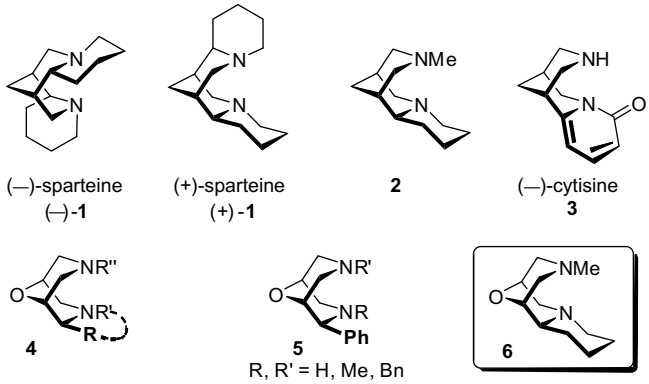

Figure 1.

Characteristic of the structure of (−)-sparteine (−)-**1** is the central bispidine (3,7-diazabicyclo[3.3.1]nonane) core. Of the two fused rings, the *endo*-positioned one plays the decisive role in chirality transfer,[9,10] as obvious from the tricyclic bispidine **2**, which was introduced by O'Brien et al. as an equally effective substitute for the less readily available enantiomer of (−)-**1**, (+)-sparteine[11] (+)-**1**.[12] Diamine **2** can be obtained in three steps by partial synthesis from the natural source (−)-cytisine;[10,12,13] its enantioselective total synthesis, however, is still a challenging and time-consuming task. Three approaches have been reported, two of which were developed by Lesma et al. Starting from a piperidine-3,5-dimethanol precursor, **2** was prepared in ⩾9 steps and in ⩽7% overall yield.[14] O'Brien et al. used a different strategy via a chiral homopipecolic ester, accessing **2** in 8 steps and in 15% overall yield.[15] Despite all these efforts, a generally applicable route that allows a flexible approach to a broad variety of tri- and tetracyclic bispidines in enantiomerically pure form is still missing.[16]

As yet, almost no attention has been paid to the closely related 9-oxabispidines of type **4**,[17] which, similar to the well-investigated bispidines, might possess a high potential as chiral ligands in asymmetric synthesis.[18] Replacement of the remote methylene bridge by an oxygen atom should not change the architecture, but the additional functionality offers new synthetic options, thus allowing a more convenient access. This advantage was previously demonstrated in the preparation of the bicyclic 2-*endo*-phenyl-substituted 9-oxabispidines **5**, which are available from (*R*,*R*)-3-phenylglycidol in just 3–5 steps and in 35–40% yield.[19] Herein, we report on an important extension of this method: the tricyclic 9-oxabispidine **6**,[17] the oxa analogue of the successful (+)-sparteine surrogate **2**, was synthesized in enantiomerically pure form from a known epoxy alcohol precursor and (*S*)-epichlorohydrin in 7 steps and in 11% overall yield.

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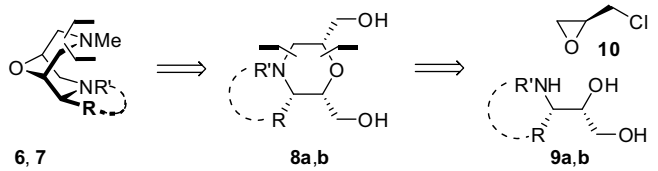
2. Results and discussion

2.1. Retrosynthetic analysis

The retrosynthetic analysis of the targeted tricyclic 9-oxabispidine **6** is depicted in Scheme 1. Disconnection of the methylamino function allows a first simplification of the molecule leading to the *cis*-configured morpholine-2,6-dimethanol **8** as the key intermediate. This compound should be accessible from the amino diol **9** by cyclization with a chiral 1,2,3-trifunctionalized three-carbon building block possessing two neighboring electrophilic positions. Previous investigations on the enantioselective synthesis of **5** (see Fig. 1)[19] and of morpholine-2-methanols from β-amino alcohols[20] revealed (*S*)-epichlorohydrin **10** to be well suited for this purpose.

The *endo*-fused piperidine ring in **6** can be implemented either after or before the construction of the bispidine core. In the first case, a bicyclic bispidine intermediate such as **7** with an appropriately functionalized side chain is required, which should be available via the morpholine **8a** from an acyclic amino diol such as **9a**. The tricyclic bispidine **6** might also be prepared via the morpholine **8b** from the piperidine-derived amino diol **9b**, in which the anellated ring is already incorporated. This route would allow a direct conversion of **8b** into the targeted bispidine **6**.

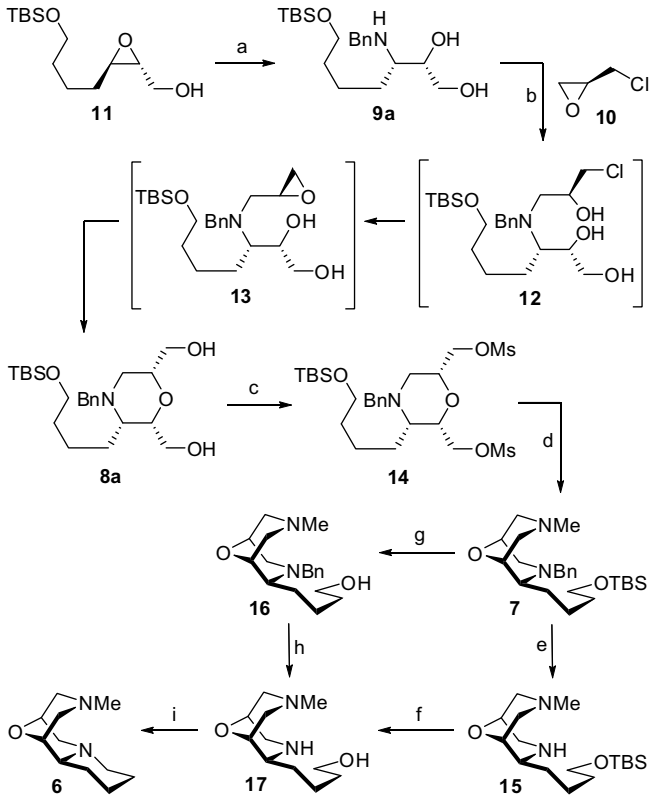


Scheme 1.

2.2. Enantioselective total synthesis of 6 via the bicyclic bispidine 7

The synthesis of **6** via the bicyclic bispidine intermediate **7** commenced with the known enantiomerically pure epoxy alcohol **11** (Scheme 2).[21] Ring opening of **11** with benzylamine in the presence of the Lewis acid $LiClO_4$ furnished an inseparable 85:15-mixture of the desired amino alcohol **9a** and a by-product, presumably the regioisomer of **9a**, resulting from the less favorable ring opening of **11** at C-2. This mixture was subjected to a one-pot multi-stage cyclization with (*S*)-epichlorohydrin **10** to give the all-*cis*-configured morpholine-2,6-dimethanol **8a**. In agreement with the mechanistic studies on related reactions,[20] heating of the two reactants with $LiClO_4$ in toluene induced a regioselective nucleophilic attack of the nitrogen atom at C-3 of the epoxide to give the chlorohydrin **12**. Upon addition of *t*BuOH and KO*t*Bu, this intermediate underwent a base-mediated domino reaction delivering **8a** via the epoxide **13**. After purification by fast column chromatography through deactivated silica gel, crude **8a** was bis-mesylated to set the stage for the ring closure to the bicyclic bispidine **7**, which occurred smoothly by heating **14** in ethanolic methylamine. The overall yield for this sequence was 19%.

The transformation of **7** into the N,O-unprotected derivative **17** was achieved either via **15** by using a debenzylation/desilylation procedure or in reverse order via the intermediate **16**. Even though the latter route delivered **17** in slightly lower yield (77% vs 83%), this sequence is advantageous since the latter dehydrogenation step gave the polar product **17** in >90% purity without the necessity of further purification. The final ring closure was realized under Mitsunobu conditions to afford the tricyclic target bispidine **6** in

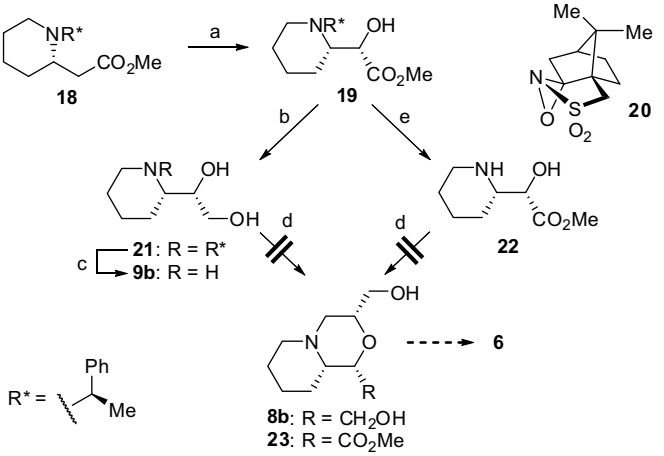


Scheme 2. Reagents and conditions: (a) $BnNH_2$, $LiClO_4$, MeCN, 65 °C, 16 h; (b) **10**, $LiClO_4$, toluene, 70 °C, 22 h, then KO*t*Bu, *t*BuOH, rt, 24 h; (c) MsCl, NEt_3, CH_2Cl_2, 0 °C→rt, 4 h, 25% from **11**; (d) $MeNH_2$, EtOH, 50 °C, 36 h, 75%; (e) H_2 (1 bar), $Pd(OH)_2$/C, EtOAc, rt, 5 h, 99%; (f) TBAF, THF, rt, 36 h, 84%; (g) TBAF, THF, rt, 48 h, 85%; (h) H_2 (1 bar), $Pd(OH)_2$/C, EtOAc, rt, 14 h, 90%; (i) PPh_3, DIAD, toluene, rt, 24 h, 80%.

3 steps and in 61% yield from **7**. The enantiomeric purity of **6** is ⩾98%, as deduced from the ^{19}F NMR spectra of the (*S*)- and (*R*)-Mosher amides of the precursor **15**.

2.3. Attempted synthesis of 6 from the homopipecolic ester 18

For an alternative approach, in which the *endo*-fused ring of **6** is already incorporated in the amino diol precursor, the



Scheme 3. Reagents and conditions: (a) LiHMDS, THF, 0 °C, 30 min, then **20**, −78 °C→rt, 16 h, 80%; (b) $LiAlH_4$, THF, −20 °C→rt, 4 h, 80%; (c) H_2 (3 bar), Pd/C, MeOH, 40 °C, 3 h, 76%; (d) **10**, $LiClO_4$, toluene, 70 °C, 16 h, then KO*t*Bu, *t*BuOH, rt, 23 h; (e) H_2 (3 bar), Pd/C, MeOH, 40 °C, 7 h, 98%.

N-(*R*)-phenylethyl-protected homopipecolic ester **18**, readily available in large quantities,[22] was chosen as the starting material (Scheme 3). Introduction of the required alcohol function next to the ester group was accomplished in 80% yield by α-hydroxylation of the lithium enolate of **18** with (1*R*)-(−)-(camphorylsulfonyl)oxaziridine **20**. In accordance with the related α-functionalizations of homopipecolic esters,[15,23] this reaction occurred highly diastereoselectively giving **19** as the sole product. The cyclization precursor **9b**[24] was prepared from **19** in two steps, by reduction and hydrogenolytic *N*-deprotection. In contrast to the successful morpholine syntheses from (*S*)-epichlorohydrin **10** and many other β-amino alcohols,[19,20] the cyclization of **9b** with **10** failed. The desired product **8b** (or any precursors to it, cf. Scheme 2) was not detected under a variety of reaction conditions. Apparently, the piperidine ring in **9b** impedes the attack of the nitrogen atom at the epoxide function of **10** for steric or electronic reasons. In addition, there was also no morpholine of type **23** formed in the analogous reaction of the α-hydroxy homopipecolic ester **22**, which was prepared from **19** by N-deprotection.

3. Conclusions

The tricyclic 9-oxabispidine **6**, which might possess a comparably high potential in asymmetric transformations as the well-known bispidines (−)-sparteine (−)-**1** and **2**, was prepared in 7 steps and in 11% overall yield starting from the enantiomerically pure epoxy alcohol **11**. The key step was a one-pot multi-stage cyclization of the amino diol **9a** with (*S*)-epichlorohydrin **10** delivering an *all-cis*-configured morpholine-2,6-dimethanol derivative. The related ring closure reaction of the piperidine-derived β-amino alcohols **9b** and **22** failed. Applications of **6** in enantioselective transformations are currently under investigation.

4. Experimental

Optical rotations (10 cm cell) were measured on a Jasco P-1020 polarimeter. All NMR spectra were acquired at 20 °C on a Bruker AV 400 instrument using $CDCl_3$ as the internal reference. IR spectra were recorded on a Jasco FT-IR-410 spectrometer. High resolution mass spectra were measured on a Bruker Daltonics micrOTOF focus. Column chromatography was done on silica gel (63–200 mesh). Microanalyses were performed at the Institute of Inorganic Chemistry, University of Würzburg. Anhydrous solvents were prepared using the standard procedures. The epoxy alcohol **11** (>95% ee) was synthesized according to Ref. 21, and the homopipecolic ester derivative **18** (>96% ee) was synthesized according to Ref. 22. All reactions with anhydrous solvents were performed under an argon atmosphere.

4.1. (2*S*,3*S*)-3-Benzylamino-7-*tert*-butyldimethylsiloxyheptane-1,2-diol 9a

$LiClO_4$ (7.18 g, 67.5 mmol) was added to a solution of **11** (2.24 g, 9.64 mmol) and $BnNH_2$ (7.37 mL, 7.23 g, 67.5 mmol) in MeCN (90 mL). After 16 h at 65 °C, water (100 mL) was added and the reaction mixture was extracted with Et_2O (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, and the solvent and excess $BnNH_2$ were removed under reduced pressure. Column chromatography [silica gel, deactivated with concd NH_3 (7.5 w/w %), CH_2Cl_2/MeOH 10:1] delivered a colorless foam (2.91 g) consisting of an inseparable 85:15-mixture of the desired amino diol **9a** and a by-product, presumably a regioisomer of **9a**. Compound **9a** was characterized in this mixture, and used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H, $SiMe_2$), 0.89 (s, 9H, CMe_3), 1.31–1.63 (m, 6H, 4-H, 5-H, 6-H), 2.60 (br s, 3H, OH, OH, NH), 2.85 (m, 1H, 3-H), 3.60 (t, *J* = 6.2 Hz, 2H, 7-H), 3.67 (m, 2H, 1-H, 2-H), 3.77 (m, 1H, 1-H), 3.82 (d, *J* = 12.8 Hz, 1H, NC*H*HPh), 3.90 (d, *J* = 12.8 Hz, 1H, NCH*H*Ph), 7.31 (m, 5H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3 ($SiMe_2$), 18.3 (*C*Me_3), 22.4 (C-5), 26.0 (C*Me*$_3$), 30.3 (C-4), 32.7 (C-6), 52.7 (N*C*H_2Ph), 60.9 (C-3), 62.7 (C-7), 64.1 (C-1), 71.3 (C-2), 127.5, 128.3, 128.6, 139.2 (C-Ph). IR (ATR): *ν* 3343, 2927, 2856, 1461, 1253, 1094, 1006, 833, 773, 698 cm^{-1}. HRMS (ESI, +) calcd for $[C_{20}H_{37}NO_3Si+H]^+$: 368.2616, found: 368.2618. Anal. Calcd for $C_{20}H_{37}NO_3Si$ (367.60): C, 65.35; H, 10.15; N, 3.81. Found: C, 65.27; H, 10.22; N, 4.07.

4.2. (2*S*,3*S*,6*R*)-4-Benzyl-3-(4-*tert*-butyldimethylsiloxybutyl)-2,6-di(methanesulfonyloxymethyl)morpholine 14

The crude mixture of **9a** (1.57 g) from the preceding experiment was dissolved in anhydrous toluene (45 mL) and treated at rt with (*S*)-epichlorohydrin (**10**, 412 μL, 474 mg, 5.12 mmol) and $LiClO_4$ (545 mg, 5.13 mmol). The reaction was stirred for 22 h at 70 °C. *t*BuOH (45 mL) and KO*t*Bu (2.16 g, 19.2 mmol) were introduced at rt, and stirring was continued for 24 h. After the addition of water (150 mL), the reaction mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The resulting morpholine **8a** was purified by fast column chromatography (silica gel, CH_2Cl_2/MeOH 100:0→95:5), and dissolved in CH_2Cl_2 (40 mL). NEt_3 (2.05 mL, 1.49 g, 14.7 mmol) and MsCl (759 μL, 1.12 g, 9.80 mmol) were slowly added at 0 °C. After 4 h at rt, the reaction mixture was diluted with water (200 mL) and extracted with Et_2O (3 × 200 mL). The organic layers were combined, washed with brine (200 mL), dried over Na_2SO_4, and evaporated. Column chromatography (1. silica gel, Et_2O/MeOH 100:0→10:1; 2. silica gel, CH_2Cl_2/MeOH 100:0→10:1) gave **14** (754 mg, 1.30 mmol, 30%) as a yellowish foam. $[\alpha]_D^{22} = -8.0$ (*c* 0.30, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 6H, $SiMe_2$), 0.90 (s, 9H, CMe_3), 1.21–1.46 (m, 2H, 2′-H), 1.47–1.54 (m, 2H, 3′-H), 1.65–1.72 (m, 2H, 1′-H), 2.44 (m, 1H, 5-H), 2.54 (m, 1H, 5-H), 2.95 (m, 1H, 3-H), 3.04 (s, 3H, SO_2Me), 3.05 (s, 3H, SO_2Me), 3.61 (m, 2H, 4′-H), 3.70 (d, *J* = 13.5 Hz, 1H, NC*H*HPh), 3.82 (d, *J* = 13.5 Hz, 1H, NCH*H*Ph), 3.98 (m, 1H, 6-H), 4.08–4.24 (m, 5H, 2-H, 2-CH_2, 6-CH_2), 7.24–7.35 (m, 5H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3 ($SiMe_2$), 18.3 (*C*Me_3), 22.2 (C-2′), 24.4 (C-1′), 26.0 (C*Me*$_3$), 33.0 (C-3′), 37.0 (SO_2Me), 37.8 (SO_2Me), 45.7 (C-5), 57.4 (C-3), 58.4 (4-CH_2), 62.8 (C-4′), 69.8 (2-CH_2 or 6-CH_2), 70.1 (2-CH_2 or 6-CH_2), 72.1 (C-6), 75.9 (C-2), 127.4, 128.4, 128.7, 138.1 (C-Ph). IR (KBr): *ν* 3029, 2934, 2857, 1463, 1357, 1255, 1176, 1098, 968, 836, 777, 738, 702, 661 cm^{-1}. HRMS (ESI, +) calcd for $[C_{25}H_{45}NO_8S_2Si+H]^+$: 580.2429, found: 580.2428.

4.3. (1*R*,2*S*,5*S*)-3-Benzyl-2-(4-*tert*-butyldimethylsiloxybutyl)-7-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 7

A solution of ethanolic $MeNH_2$ (33 w/w %, 50 mL) and **14** (649 mg, 1.12 mmol) in EtOH (100 mL) was stirred for 36 h at 50 °C. The reaction mixture was concentrated in vacuo and water (100 mL) was added. After extraction with Et_2O (4 × 100 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Column chromatography [silica gel, deactivated with conc. NH_3 (7.5 w/w %), Et_2O/MeOH 100:0→99:1] delivered **7** (350 mg, 836 μmol, 75%) as a colorless oil. $[\alpha]_D^{22} = +66.9$ (*c* 0.31, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H, $SiMe_2$), 0.89 (s, 9H, CMe_3), 1.29–1.61 (m, 5H, 1′-H, 2′-H, 3′-H), 1.94 (m, 1H, 1′-H), 2.22 (s, 3H, NMe), 2.30 (dd, *J* = 11.6, 4.4 Hz, 1H, 8-H_{exo}), 2.41 (ddd, *J* = 11.3, 4.5, 1.1 Hz, 1H, 6-H_{exo}), 2.58 (dd, *J* = 11.5, 4.2 Hz, 1H, 4-H_{exo}), 2.70 (m, 3H, 2-H, 4-H_{endo}, 6-H_{endo}), 2.96 (d, *J* = 11.6 Hz, 1H, 8-H_{endo}), 3.33 (d, *J* = 14.1 Hz, 1H, NC*H*HPh), 3.62 (t, *J* = 6.3 Hz, 2H, 4′-H), 3.74 (br t, *J* = 3.4 Hz, 1H, 1-H), 3.78 (br t,

J = 4.3 Hz, 1H, 5-H), 4.05 (d, J = 14.1 Hz, 1H, NCH*H*Ph), 7.25 (m, 1H, Ph-H), 7.28–7.35 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3 ($SiMe_2$), 18.3 (CMe_3), 22.1 (C-2′), 25.9 (CMe_3), 29.4 (C-1′), 33.2 (C-3′), 47.1 (NMe), 53.9 (C-8), 55.4 (C-4), 58.2 (C-6), 58.3 (NCH_2Ph), 61.6 (C-2), 62.7 (C-4′), 68.5 (C-5), 70.4 (C-1), 126.7, 128.1, 129.2, 138.0 (C-Ph). IR (film): ν 3061, 3026, 2931, 2785, 1494, 1461, 1360, 1254, 1094, 835, 775, 729, 698, 661 cm^{-1}. HRMS (ESI, +) calcd for $[C_{24}H_{42}N_2O_2Si+H]^+$: 419.3088, found: 419.3088.

4.4. (1*R*,2*S*,5*R*)-2-(4-*tert*-Butyldimethylsiloxybutyl)-7-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 15

The 9-oxabispidine **7** (100 mg, 239 μmol) was dissolved in EtOAc (6 mL) and hydrogenated over $Pd(OH)_2$/C (20 w/w %, 28.0 mg) under 1 bar H_2 pressure for 5 h at rt. The mixture was filtered through a pad of Celite and washed with MeOH (100 mL). Evaporation of the solvent delivered **15** (77.9 mg, 237 mmol, 99%) as a yellowish oil. $[\alpha]_D^{22} = +4.0$ (c 0.56, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 6H, $SiMe_2$), 0.88 (s, 9H, CMe_3), 1.25–1.56 (m, 6H, 1′-H, 2′-H, 3′-H), 2.11 (s, 3H, NMe), 2.38 (ddd, J = 11.7, 3.5, 1.0 Hz, 1H, 8-H$_{exo}$), 2.49 (dt, J = 11.3, 3.0 Hz, 1H, 6-H$_{exo}$), 2.70–3.00 (br s, 1H, NH), 2.81 (d, J = 11.2 Hz, 1H, 6-H$_{endo}$), 2.83 (br s, 1H, NH), 2.90 (d, J = 11.7 Hz, 1H, 8-H$_{endo}$), 2.98 (d, J = 13.7 Hz, 1H, 4-H$_{endo}$), 3.10 (m, 1H, 2-H), 3.27 (m, 1H, 4-H$_{exo}$), 3.47 (t, J = 3.0 Hz, 1-H), 3.60 (m, 3H, 5-H, 4′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3 ($SiMe_2$), 18.3 (CMe_3), 22.3 (CH_2), 25.9 (CMe_3), 32.9 (CH_2), 33.2 (CH_2), 47.0 (NMe), 50.4 (C-4), 55.2 (C-8), 57.9 (C-2), 59.6 (C-6), 62.9 (C-4′), 67.3 (C-5), 70.6 (C-1). IR (film): ν 3413, 2925, 2854, 2790, 1713, 1668, 1462, 1254, 1099, 837, 775 cm^{-1}. HRMS (ESI, +) calcd for $[C_{17}H_{36}N_2O_2Si+H]^+$: 329.2619, found: 329.2619.

4.5. (*R*)- and (*S*)-Mosher amides of 15

(*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionyl chloride [(*S*)-Mosher chloride, 99% ee, 12.5 μL, 16.9 mg, 67.0 μmol], NEt_3 (9.5 μL, 6.9 mg, 68 μmol) and a catalytic amount of DMAP were added at rt to a solution of **15** (11.0 mg, 33.5 μmol) in CH_2Cl_2 (1 mL). After 5 h, the reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (25 mL), dried over Na_2SO_4, and evaporated to give, after chromatographic purification (silica gel, *n*-pentane/Et_2O 5:1→0:1), the (*R*)-Mosher amide of **15** (12.0 mg, 22.0 μmol, 73%) as a yellowish oil. ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.08 (s, CF_3).

The (*S*)-Mosher amide of **15** (6.0 mg, 11.0 μmol, 37%) was analogously prepared from **15** (11.0 mg, 33.5 μmol) and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride [(*R*)-Mosher chloride, 99% ee, 12.5 μL, 16.9 mg, 67.0 μmol]. ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.30 (s, CF_3).

According to ^{19}F NMR, the diastereomeric purities of both Mosher amides of **15** were >98%.

4.6. (1*R*,2*S*,5*S*)-3-Benzyl-2-(4-hydroxybutyl)-7-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 16

A solution of **7** (168 mg, 401 μmol) in anhydrous THF (16 mL) was treated at rt with TBAF·H_2O (220 mg, 841 μmol) and stirred for 2 d. After dilution with water (40 mL) and extraction with EtOAc (4 × 40 mL), the combined organic layers were dried over Na_2SO_4. Removal of the solvent under reduced pressure and column chromatography (silica gel, CH_2Cl_2/MeOH 10:1→0:1) afforded **16** (104 mg, 342 μmol, 85%) as a yellowish oil. $[\alpha]_D^{22} = +62.2$ (c 0.20, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30–1.70 (m, 5H, 1′-H, 2′-H, 3′-H), 1.99 (m, 1H, 1′-H), 2.05–2.40 (br s, 1H, OH), 2.29 (s, 3H, NMe), 2.37 (dd, 1H, J = 11.6, 4.3 Hz, 8-H$_{exo}$), 2.46 (dd, J = 11.3, 3.6 Hz, 1H, 6-H$_{exo}$), 2.59 (ddd, J = 11.6, 4.2, 1.5 Hz, 1H, 4-H$_{exo}$), 2.70–2.81 (m, 3H, 2-H, 4-H$_{endo}$, 6-H$_{endo}$), 3.04 (d, J = 11.8 Hz, 1H, 8-H$_{endo}$), 3.33 (d, J = 14.0 Hz, 1H, NC*H*HPh), 3.67 (t, J = 6.4 Hz, 2H, 4′-H), 3.76 (t, J = 3.4 Hz, 1H, 1-H), 3.80 (t, J = 4.2 Hz, 5-H), 4.12 (d, J = 14.0 Hz, 1H, NCH*H*Ph), 7.24 (m, 1H, Ph-H), 7.29–7.36 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1 (C-2′), 29.4 (C-1′), 33.0 (C-3′), 47.1 (NMe), 53.8 (C-8), 55.3 (C-4), 58.1 (C-6), 58.2 (NCH_2), 61.8 (C-2), 62.4 (C-4′), 68.3 (C-5), 70.2 (C-1), 126.9, 128.2, 129.3, 137.6 (C-Ph). IR (film): ν 3387, 2985, 2793, 1495, 1453, 1377, 1278, 1093, 975, 911, 841, 730, 700 cm^{-1}. HRMS (ESI, +) calcd for $[C_{17}H_{28}N_2O_2+H]^+$: 305.2224, found: 305.2221.

4.7. (1*R*,2*S*,5*R*)-2-(4-Hydroxybutyl)-7-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane 17

4.7.1. Desilylation of 15

At first, TBAF·H_2O (75.0 mg, 287 μmol) was added at rt to a solution of the bispidine **15** (45.0 mg, 137 μmol) in anhydrous THF (5 mL). The reaction mixture was stirred for 36 h at rt, diluted with water (100 mL), and extracted with Et_2O (3 × 100 mL). The organic layers were discarded; the aqueous one was concentrated under reduced pressure to one-third of its volume and extracted with $CHCl_3$ (3 × 100 mL). The organic layers were combined and evaporated to give a 65:35-mixture of a tetrabutylammonium salt and **17** [75.0 mg, containing ca. 25 mg (115 μmol, 84%) of **17**]. Further attempts to purify **17** have not been undertaken.

4.7.2. Hydrogenolytic deprotection of 16

A solution of **16** (80.0 mg, 263 μmol) in EtOAc (4 mL) was hydrogenated over $Pd(OH)_2$/C (20 w/w %, 44.0 mg) under 1 bar H_2 pressure for 14 h at rt. The mixture was filtered through a pad of Celite and washed with MeOH (100 mL). Evaporation of the solvent delivered **17** (50.7 mg, 237 mmol, 90%) as a colorless oil. $[\alpha]_D^{22} = +3.7$ (c 0.15, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30–1.72 (m, 6H, 1′-H, 2′-H, 3′-H), 1.85–2.40 (br s, 2H, NH, OH), 2.19 (s, 3H, NMe), 2.48 (ddd, J = 12.0, 3.5, 1.2 Hz, 1H, 8-H$_{exo}$), 2.57 (dt, J = 11.7, 3.0 Hz, 1H, 6-H$_{exo}$), 2.90 (d, J = 11.4 Hz, 1H, 6-H$_{endo}$), 2.97 (d, J = 12.1 Hz, 1H, 8-H$_{endo}$), 3.24 (d, J = 13.6 Hz, 1H, 4-H$_{endo}$), 3.35 (m, 1H, 2-H), 3.38 (dm, J = 13.7 Hz, 1H, 4-H$_{exo}$), 3.69 (m, 1H, 1-H), 3.67 (t, J = 5.6 Hz, 2H, 4′-H), 3.83 (br t, J = 3.1 Hz, 1H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9 (CH_2), 31.4 (CH_2), 32.0 (CH_2), 46.5 (NMe), 49.3 (C-4), 55.0 (C-8), 58.1 (C-2), 59.2 (C-6), 61.9 (C-4′), 66.3 (C-5), 69.7 (C-1). IR (ATR): ν 3346, 2925, 2854, 1652, 1456, 1273, 1159, 1073, 1042, 862 cm^{-1}. HRMS (ESI, +) calcd for $[C_{11}H_{22}N_2O_2+H]^+$: 215.1754, found: 215.1754.

4.8. (1*R*,2*S*,9*S*)-11-Methyl-13-oxa-7,11-diazatricyclo-[7.3.1.0^{2,7}]tridecane 6

At first, PPh_3 (91.7 mg, 350 μmol) and DIAD (68.8 mL, 70.7 mg, 350 μmol) were added at rt to a solution of **17** (40.0 mg, 187 μmol) in anhydrous toluene (1 mL). After 24 h of stirring, the solvent was removed under reduced pressure and the residue was chromatographed (basic Al_2O_3, activity V, *n*-pentane/EtOAc 1:0→2:1) delivering **6** (29.4 mg, 150 μmol, 80%) as a colorless solid, mp 36–38 °C. $[\alpha]_D^{22} = +19.0$ (c 1.2, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): 1.36 (m, 3H, 3-H, 4-H), 1.56 (m, 1H, 5-H), 1.69–1.85 (m, 3H, 4-H, 5-H, 6-H), 2.19 (s, 3H, NMe), 2.25 (dd, J = 11.7, 4.3 Hz, 1H, 12-H$_{exo}$), 2.27 (m, 1H, 2-H), 2.40 (ddd, J = 11.5, 4.2, 1.7 Hz, 1H, 10-H$_{exo}$), 2.56 (ddd, J = 11.6, 4.4, 1.7 Hz, 1H, 8-H$_{exo}$), 2.82 (d, J = 11.7 Hz, 1H, 8-H$_{endo}$), 2.89 (m, 1H, 6-H), 2.92 (d, J = 12.0 Hz, 2H, 10-H$_{endo}$, 12-H$_{endo}$), 3.47 (t, J = 3.7 Hz, 1H, 1-H), 3.85 (t, J = 4.2 Hz, 1H, 9-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8 (C-4), 25.3 (C-5), 28.4 (C-3), 47.6 (NMe), 54.6 (C-12), 57.3 (C-6), 58.0 (C-8), 58.5 (C-10), 65.0 (C-2), 68.9 (C-9), 72.1 (C-1). IR (ATR): 2929, 2780, 2754, 1459, 1438, 1361,

1282, 1144, 1123, 1092, 1043, 979, 879, 816, 742, 721 cm^{-1}. HRMS (ESI, +) calcd for $[C_{11}H_{20}N_2O+H]^+$: 197.1648, found: 197.1650.

4.9. Methyl (α*S*,2*S*)-α-hydroxy-1-[(*R*)-1-phenylethyl]piperidine-2-acetate 19

A solution of the β-amino ester **18** (2.28 g, 8.72 mmol) in anhydrous THF (50 mL) was deprotonated at 0 °C for 30 min with LiHMDS (1.0 M in hexanes, 13.1 mL, 13.1 mmol). (1*R*)-(−)-(Camphorylsulfonyl)oxaziridine **20** (3.00 g, 13.1 mmol) was added at −78 °C. The mixture was warmed to rt overnight, quenched with satd aq NH_4Cl (200 mL), and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and evaporated. Column chromatography (silica gel, *n*-pentane/Et_2O 2:1→1:1) gave **19** (1.94 g, 6.98 mmol, 80%) as a yellowish oil. $[\alpha]_D^{20} = -2.0$ (*c* 0.20, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (m, 2H, 4-H, 5-H), 1.38 (d, *J* = 6.8 Hz, 3H, CH*Me*), 1.45 (m, 2H, 3-H, 4-H), 1.65 (m, 1H, 3-H), 1.76 (m, 1H, 5-H), 2.31 (td, *J* = 11.1, 2.8 Hz, 1H, 6-H), 2.58 (m, 1H, 6-H), 3.00 (dt, *J* = 9.7, 3.7 Hz, 1H, 2-H), 3.25 (br s, 1H, OH), 3.81 (s, 3H, OMe), 4.33 (q, *J* = 6.8 Hz, 1H, C*H*Me), 4.67 (d, *J* = 3.8 Hz, 1H, α-H), 7.23 (m, 1H, Ph-H), 7.32 (m, 2H, Ph-H), 7.39 (m, 2H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7 (CH*Me*), 23.5 (C-5), 24.9 (C-3 or C-4), 25.0 (C-3 or C-4), 44.2 (C-6), 52.2 (OMe), 55.0 (*C*HMe), 59.1 (C-2), 70.0 (C-α), 126.7, 127.7, 128.1, 143.5 (C-Ph), 173.7 (CO_2). IR (Film): *ν* 3400, 3059, 2936, 2857, 1739, 1625, 1494, 1449, 1267, 1224, 1136, 1086, 1034, 736, 701 cm^{-1}. HRMS (ESI, +) calcd for $[C_{16}H_{23}NO_3+H]^+$: 278.1751, found: 278.1747.

4.10. (β*S*,2*S*)-β-Hydroxy-1-[(*R*)-1-phenylethyl]piperidine-2-ethanol 21

At first, $LiAlH_4$ (384 mg, 10.1 mmol) was added at −20 °C to a solution of **19** (1.40 g, 5.05 mmol) in anhydrous THF (25 mL). The reaction mixture was warmed to rt within 4 h, quenched with saturated aq NH_4Cl (200 mL) and extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Evaporation of the solvent, purification of the residue by column chromatography (silica gel, *n*-pentane/EtOAc/NEt_3 33:65:2), and crystallization (CH_2Cl_2/*n*-pentane, −20 °C) afforded **21** (1.00 g, 4.04 mmol, 80%) as colorless crystals, mp 112–116 °C. $[\alpha]_D^{20} = +21.2$ (*c* 0.37, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (m, 1H, 3-H or 4-H or 5-H), 1.38 (d, *J* = 6.7 Hz, 3H, CH*Me*), 1.49–1.79 (m, 5H, 3-H, 4-H, 5-H), 2.60 (m, 1H, 2-H), 2.80–2.90 (m, 2H, 6-H), 3.45 (dd, *J* = 10.8, 6.3 Hz, 1H, α-H), 3.70 (dd, *J* = 10.8, 5.5 Hz, 1H, α-H), 4.16 (m, 1H, β-H), 4.30 (q, *J* = 6.7 Hz, 1H, C*H*Me), 7.27 (m, 1H, Ph-H), 7.39 (m, 4H, Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0 (CH*Me*), 20.8 (CH_2), 21.4 (CH_2), 21.5 (CH_2), 43.7 (C-6), 56.7 (*C*HMe), 59.3 (C-2), 66.6 (C-α), 67.7 (C-β), 127.2, 127.4, 128.6, 144.2 (C-Ph). IR (KBr): *ν* 3057, 2949, 2861, 1493, 1450, 1373, 1331, 1269, 1183, 1073, 1031, 937, 895, 833, 788, 757, 703 cm^{-1}. HRMS (ESI, +) calcd for $[C_{15}H_{23}NO_2+H]^+$: 250.1802, found: 250.1796.

4.11. (β*S*,2*S*)-β-Hydroxypiperidine-2-ethanol 9b

At first, Pd/C (10 w/w %, 90.0 mg) was added to a solution of **21** (400 mg, 1.60 mmol) in MeOH (50 mL). The reaction mixture was hydrogenated under 3 bar H_2 pressure for 3 h at 40 °C, filtered through a pad of Celite, and washed with MeOH (150 mL). After evaporation of the solvent, the residue was crystallized three times from warm Et_2O to give **9b**[24] (177 mg, 1.22 mmol, 76%) as a colorless solid, mp 82–84 °C. $[\alpha]_D^{22} = -17.7$ (*c* 0.15, MeOH). ^1H NMR (400 MHz, MeOD): δ 1.29–1.52 (m, 3H, 3-H, 4-H, 5-H), 1.65 (m, 1H, 5-H), 1.77 (m, 1H, 3-H), 1.86 (m, 1H, 4-H), 2.62–2.78 (m, 2H, 2-H, 6-H), 3.10 (m, 1H, 6-H), 3.54 (m, 3H, α-H, β-H). ^{13}C NMR (100 MHz, MeOD): δ 25.0 (C-4), 26.6 (C-5), 27.3 (C-3), 47.4 (C-6), 60.2 (C-2), 64.6 (C-α), 74.8 (C-β). IR (ATR): *ν* 3302, 2928, 1440, 1307, 1139, 1109, 1089, 1072, 1042, 1011, 958, 930, 874, 809 cm^{-1}. HRMS (ESI, +) calcd for $[C_7H_{15}NO_2+H]^+$: 146.1176, found: 146.1178.

4.12. Methyl (α*S*,2*S*)-α-hydroxypiperidine-2-acetate 22

The diol **19** (374 mg, 1.35 mmol) was dissolved in MeOH (10 mL) and hydrogenated over Pd/C (10 w/w %, 27.0 mg) under 3 bar H_2 pressure at 40 °C for 7 h. Removal of the catalyst by filtration through a pad of Celite, washing with MeOH (150 mL), and evaporation of the solvent afforded **22** (228 mg, 1.32 mmol, 98%) as a colorless solid, mp. 235–238 °C (dec). $[\alpha]_D^{22} = -21.2$ (*c* 0.40, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ 1.29–1.47 (m, 4H, CH), 1.57 (m, 1H, CH), 1.85 (m, 1H, CH), 2.64 (m, 1H, 6-H), 2.89 (m, 1H, 2-H), 3.12 (m, 1H, 6-H), 3.81 (s, 1H, OMe), 4.17 (d, *J* = 4.4 Hz, 1H, α-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3 (CH_2), 26.38 (CH_2), 26.44 (CH_2), 46.8 (C-6), 52.4 (OMe), 59.0 (C-2), 73.7 (C-α), 173.7 (CO_2). IR (Film): *ν* 3352, 2935, 2857, 1739, 1640, 1451, 1322, 1136, 809, 734 cm^{-1}. HRMS (ESI, +) calcd for $[C_8H_{15}NO_3+H]^+$: 174.1125, found: 174.1128.

4.13. Attempted cyclizations of 9b and 22 with 10

A suspension of **9b** (50.0 mg, 344 μmol) and $LiClO_4$ (44.0 g, 413 μmol) in anhydrous toluene (3.5 mL) was treated at rt with (*S*)-epichlorohydrin (**10**, 32.4 μL, 38.2 mg, 413 μmol) and stirred for 16 h at 70 °C. *t*BuOH (3.5 mL) and KO*t*Bu (97.0 mg, 864 μmol) were introduced at rt and stirring was continued for 23 h. The reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, washed with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo to give an inseparable mixture of compounds, in which neither the morpholine **8b** nor any other addition product of **9b** to **10** was detected by ^1H NMR spectroscopy.

The analogous cyclization of **22** (50.0 mg, 290 μmol) with **10** (27.3 μL, 32.2 mg, 348 μmol) also failed to produce the morpholine **23** or other addition products of **22** to **10**.

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