

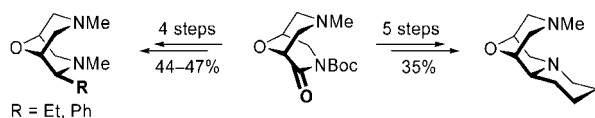
# A Flexible Route to Chiral 2-endo-Substituted 9-Oxabispidines and Their Application in the Enantioselective Oxidation of Secondary Alcohols

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A new and flexible route to enantiomerically pure bi- and tricyclic 9-oxabispidines has been developed with use of (1*R*,5*S*)-7-methyl-2-oxo-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester as the common late-stage intermediate. The 9-oxabispidines synthesized were evaluated as the chiral ligands in the Pd(II)-catalyzed oxidative kinetic resolution of secondary alcohols giving good to excellent selectivity factors of up to 19.

The lupine alkaloid (–)-sparteine (**1**, Figure 1) belongs to the privileged ligands in asymmetric synthesis. It is, for example, the unrivalled chiral auxiliary of choice in almost all enantioselective deprotonation/electrophilic trapping reactions of weakly C–H acidic compounds using strong organolithium bases such as *s*-BuLi.<sup>1</sup> The extraordinary complexation properties of **1** are, however, not restricted to lithium organyls; highly enantioselective transformations have also been realized in combination with other metals.<sup>2</sup> Particular attention was at-

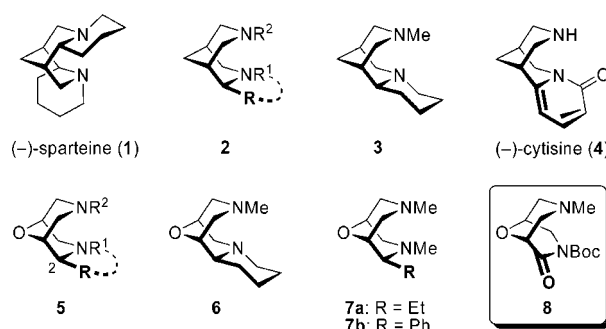


FIGURE 1. Chiral (9-oxa)bispidines and the key intermediate **8**.

tributed to the (–)-sparteine/Pd(II)-catalyzed oxidative kinetic resolution of secondary alcohols developed by Stoltz and Sigman.<sup>3–6</sup>

Structurally simpler derivatives of **1** that also possess a chirally modified bispidine (3,7-diazabicyclo[3.3.1]nonane) core of type **2** are rare since their total synthesis is still a challenging and laborious task.<sup>7–9</sup> The only exception is given by the tricyclic bispidine **3**, which is available in 3 steps from the natural product (–)-cytisine (**4**).<sup>10,11</sup> Diamine **3** found application as a surrogate for the less readily available (+)-sparteine enantiomer, *ent*-**1**.<sup>10,12</sup>

Our search for novel sparteine substitutes focuses on the structurally closely related, but only poorly investigated<sup>13</sup> 9-oxabispidines of type **5**. Their cage-like architectures are comparable to those of the well-known bispidines,<sup>14</sup> thus giving rise to excellent properties as chiral ligands in asymmetric

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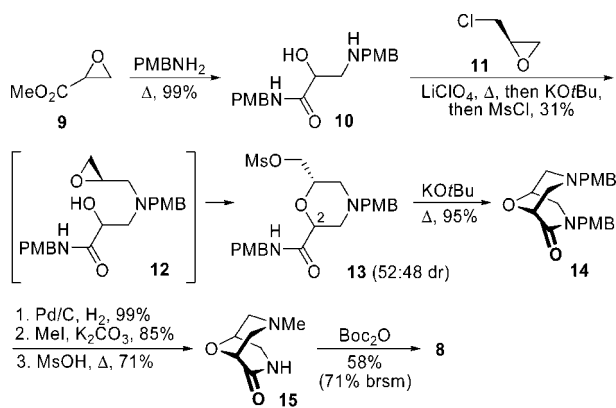
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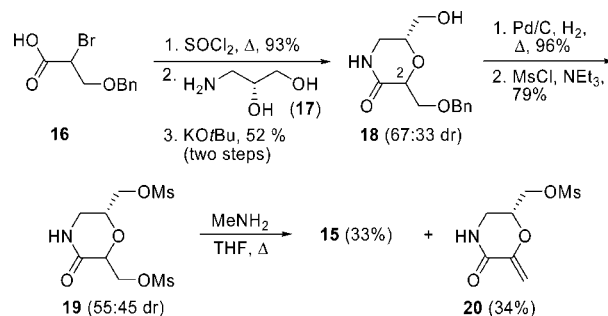
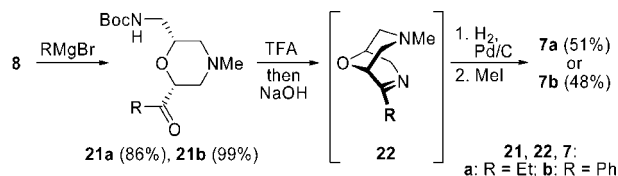
SCHEME 1. Synthesis of the Key Intermediate **8** from **9** and **11**

synthesis. With the methylene bridge in **2** being replaced by an ether function, the 9-oxabispindines **5** are often more easily accessible than the corresponding bispindines. This has recently been demonstrated in our group by the enantioselective preparation of a set of bicyclic 2-*endo*-phenyl-substituted derivatives (**5**, R = Ph; R<sup>1</sup>, R<sup>2</sup> = H, Me, Bn) from commercially available (*R,R*)-phenylglycidol (3–5 steps, 35–41% yield).<sup>15</sup> A first asymmetric synthesis of the tricyclic 9-oxabispindine **6** was successfully accomplished, too.<sup>16</sup>

One major problem, inherent to all known syntheses of bispindines and 9-oxabispindines, still remained unsolved: a late-stage variation of the appendage at C-2 is not possible since this part of the molecule (or a precursor to it) is usually constructed in the very beginning.<sup>7–9</sup> The missing synthetic flexibility in the southern hemisphere, which plays the decisive role in the chirality transfer, severely hampers more in-depth structure-selectivity investigations.

Herein we disclose a first solution to this problem by using the *N*-Boc-9-oxabispindin-2-one **8** as a common, late-stage intermediate. This imide, available in 7 steps by two different routes, was converted in just 4–5 steps and 35–47% yield into the bicyclic, 2-*endo*-substituted 9-oxabispindines **7a** and **7b** and the tricycle **6**. The potential of these diamines in the oxidative kinetic resolution of secondary alcohols was studied.

Two conceptually different approaches have been realized for the enantioselective synthesis of the key intermediate **8**. Route 1 (Scheme 1) commenced with methyl glycidate (**9**), which was treated with *p*-methoxybenzylamine to afford the amide **10** in 99% yield. The morpholine **13** was prepared following a multistep one-pot sequence developed earlier on related cyclizations of β-amino alcohols<sup>17</sup> and 3-amino-1,2-diols.<sup>15,16</sup> Heating of **10** with (*R*)-epichlorohydrin (**11**) in the presence of LiClO<sub>4</sub> induced a highly regioselective ring opening of the epoxide at C-3 to give a chlorohydrin intermediate, which, upon addition of KOtBu, underwent an intramolecular cyclization to provide **12**. Nucleophilic attack of the hydroxy group at the epoxide function and mesylation delivered **13** as a 52:48 mixture of epimers at C-2 in 31% yield. KOtBu-induced ring closure of **13**, which involved an isomerization of the trans-

SCHEME 2. Synthesis of **15** from **16** and **17**SCHEME 3. Preparation of the Bicyclic 9-Oxabispindines **7a,b** from **8**

epimer to the *cis*-configured derivative, gave the chiral 9-oxabispindine **14** in excellent 95% yield.<sup>18</sup> Hydrogenolytic removal of the northern PMB group, *N*-alkylation, and MsOH-induced cleavage of the amidic PMB substituent delivered the lactam **15**, which was converted into the key intermediate **8** by treatment with Boc<sub>2</sub>O in pyridine. This route, in which the chiral, 1,2-bis-electrophilic C-3 building block **11** was used, afforded **8** in overall 7 steps and 12% yield.

The second approach (Scheme 2) started with the known acid **16**, available in a single step from ethyl 2,3-dibromopropanoate.<sup>19</sup> Activation of **16** as the acid chloride, amide formation with (*R*)-3-aminopropane-1,2-diol (**17**), and ring closure under basic conditions afforded the morpholin-3-one **18** as a 67:33 mixture of the epimers at C-2 in 48% yield. *O*-Debenzylation and mesylation of the two hydroxy groups provided **19** in 76% yield and set the stage for the cyclization with methylamine, which delivered the desired 9-oxabispindin-2-one **15** in 33% yield. As a byproduct, the α,β-unsaturated morpholin-2-one **20** was obtained in 34% yield. The final conversion of **15** into **8** is shown in Scheme 1. Compared to route 1, this 7-step approach is based on the chiral, 1,2-bis-nucleophilic C-3 building block **17** giving **8** in slightly lower 9% overall yield, but offers the advantage of more convenient reaction procedures.

The transformation of the key intermediate **8** into the 2-*endo*-substituted 9-oxabispindines was straightforward (Scheme 3). The bicyclic ethyl derivative **7a** was obtained in 44% yield by using a 4-step protocol.<sup>20</sup> Treatment of **8** with EtMgBr resulted in a clean monoaddition at the *N*-acyl moiety of the unsymmetric imide function,<sup>21</sup> delivering, after ring-opening of the initially formed semiaminal, the ketone **21a** in good 86% yield. Acidic

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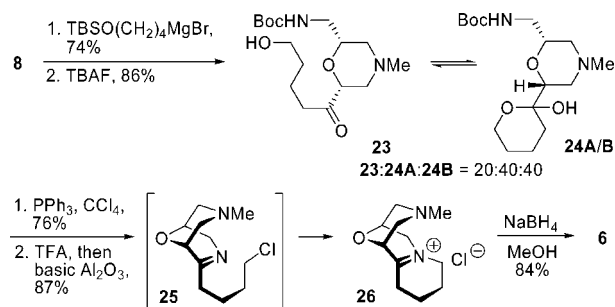
(18) The epimers of **13** are easily separable by column chromatography. Ring closure of the *cis*-configured derivative (2*R*,6*S*)-**13** to the bispindin-2-one **14** occurred at rt in 99% yield, the trans-isomer (2*S*,6*S*)-**13** cyclized in refluxing toluene (92% yield).

(19) Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C. *Tetrahedron: Asymmetry* **1995**, *6*, 469.

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SCHEME 4. Final Stages to the Tricyclic 9-Oxabispidine 6



cleavage of the *N*-Boc group followed by base-induced cyclization gave the imine **22a**, which was hydrogenated and *N*-methylated to provide the target diamine **7a**. In agreement with known reductions and nucleophilic alkylations of bispidine-derived imines,<sup>22</sup> the hydrogenation of **22a** occurred highly stereoselectively from the less hindered *exo*-face thus leading to the exclusive formation of the *endo*-substituted isomer **7a**. The 2-*endo*-phenyl derivative **7b**<sup>15</sup> was prepared analogously in 47% overall yield from **8**.

The tricyclic 9-oxabispidine **6**<sup>16</sup> was accessed by using a slightly modified sequence (Scheme 4). Reaction of **8** with TBSO(CH<sub>2</sub>)<sub>4</sub>MgBr and *O*-deprotection afforded the ketone **23**, which exists in a 20:40:40 ratio with its two diastereomeric lactol isomers **24A** and **24B**. Hydroxy/chlorine exchange, acidic removal of the *N*-Boc protective group, and filtration through basic aluminum oxide furnished, probably via the imine **25**, the iminium salt **26**, the structure of which was fully established by two-dimensional NMR measurements. Final reduction with NaBH<sub>4</sub> in methanol delivered **6** in 35% overall yield, again with full stereocontrol.

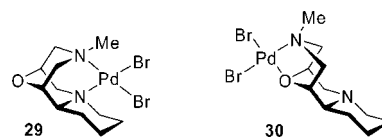
As exemplified by the preparations of **7a,b** and **6**, the imide **8** is well-suited as a late-stage intermediate, from which a variety of bi- and tricyclic 9-oxabispidines with different 2-*endo*-substituents or 2-*endo*-fused rings should be accessible.

The potential of the 9-oxabispidines as chiral ligands in asymmetric synthesis was studied on the Pd(II)-catalyzed oxidative kinetic resolution of the secondary alcohols **27** and **28** (Table 1) with conditions A–C developed by Stoltz et al.<sup>3,6</sup> for the analogous (–)-sparteine-catalyzed reactions.<sup>23</sup> Even though only low enantiomer differentiations were found under conditions A with 1-indanol (*rac*-**27**) and 1-(4-methoxyphenyl)ethanol (*rac*-**28a**) as the substrates, the results clearly showed that the tricyclic 9-oxabispidine **6** is superior to the bicyclic 9-oxabispidines **7a** and **7b**.<sup>24</sup> Good to excellent selectivity factors *s*<sup>25</sup> of up to 19 were achieved applying conditions C, in which the preformed Pd(II)-complex **29** (Figure 2), prepared from **6** and [Pd(MeCN)<sub>2</sub>Br<sub>2</sub>], in combination with some additional ligand **6** was used as the catalytic system. The enantioselective oxidation of *rac*-**28a**, for example, delivered the alcohol (*R*)-**28a** in 99.4:0.6 er after 20 h at 63% conversion and in 33% isolated yield. In this case, the high selectivity factor of *s* = 19 is fully in the range of those obtained with (–)-

TABLE 1. Oxidative Kinetic Resolution of the Alcohols **27** and **28** in the Presence of the 9-Oxabispidines **6** and **7**

| sm         | ligand    | cond. <sup>a</sup> | <i>t</i> (d) | conv. (%) <sup>b</sup> | yield (%) | er ( <i>R</i> : <i>S</i> ) <sup>c</sup> | <i>s</i> <sup>d</sup> |
|------------|-----------|--------------------|--------------|------------------------|-----------|-----------------------------------------|-----------------------|
| <b>27</b>  | <b>7a</b> | A                  | 17           | 31                     |           | 50:50                                   | 0.0                   |
| <b>27</b>  | <b>7b</b> | A                  | 17           | 25                     |           | 54:46                                   | 1.8                   |
| <b>27</b>  | <b>6</b>  | A                  | 30           | 54                     |           | 75:25                                   | 3.8                   |
| <b>28a</b> | <b>7a</b> | A                  | 17           | 47                     |           | 50:50                                   | 0.0                   |
| <b>28a</b> | <b>7b</b> | A                  | 17           | 41                     |           | 59:41                                   | 2.0                   |
| <b>28a</b> | <b>6</b>  | A                  | 17           | 61                     |           | 89:11                                   | 6.7                   |
| <b>27</b>  | <b>6</b>  | B                  | 4.5          | 62                     |           | 80:20                                   | 3.7                   |
| <b>28a</b> | <b>6</b>  | B                  | 4.5          | 53                     |           | 83:17                                   | 7.1                   |
| <b>27</b>  | <b>6</b>  | C                  | 0.75         | 67                     | 21        | 93:7                                    | 6.4                   |
| <b>28a</b> | <b>6</b>  | C                  | 0.8          | 63                     | 33        | 99.6:0.4                                | 19                    |
| <b>28b</b> | <b>6</b>  | C                  | 0.9          | 58                     | 35        | 94:6                                    | 12                    |
| <b>28c</b> | <b>6</b>  | C                  | 2.5          | 48                     | 39        | 83:17                                   | 12                    |
| <b>28d</b> | <b>6</b>  | C                  | 2.5          | 42                     | 48        | 76:24                                   | 10                    |

<sup>a</sup> Conditions A: Pd(nbd)Cl<sub>2</sub> (5 mol %), **6** or **7** (20 mol %), O<sub>2</sub> (1 bar), mol sieves 3 Å, toluene, 60–80 °C. Conditions B: Pd(nbd)Cl<sub>2</sub> (5 mol %), **6** (12 mol %), O<sub>2</sub> (1 bar), Cs<sub>2</sub>CO<sub>3</sub>, mol sieves 3 Å, CHCl<sub>3</sub>, rt. Conditions C: **29** (5 mol %), **6** (7 mol %), O<sub>2</sub> (1 bar), Cs<sub>2</sub>CO<sub>3</sub>, mol sieves 3 Å, CHCl<sub>3</sub>, rt. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Determined by HPLC on the chiral phase. <sup>d</sup> Reference selectivity factors (ligand, conditions):<sup>3,6,26</sup> **27**: *s* = 10 (**1**, B), *s* = 6.8 (**3**, A); **28a**: *s* = 17 (**1**, C), *s* = 19 (**3**, C); **28b**: *s* = 15 (**1**, B); **28c**: *s* = 28 (**1**, C), *s* = 25 (**3**, C); **28d**: *s* = 20 (**1**, C).

FIGURE 2. The chiral PdBr<sub>2</sub> complex **29** and the isomer **30**.

sparteine (**1**, *s* = 17)<sup>6</sup> and the bispidine **3** (*s* = 19)<sup>6</sup> as the chiral ligands. Lower differentiations were observed for **27** and **28b–d** (*s* = 6.4–12).

According to quantum chemical studies,<sup>5</sup> a cationic species is involved in the rate-limiting step of the catalytic cycle, the β-hydride shift from the complexed alcohol to the Pd-metal. Since this process is facilitated by a stronger electron-donating ligand, the lower reaction rates (factor 5–10), observed with **6** as compared to **1** and **3**, might be a consequence of a reduced basicity of the 9-oxabispidine, caused by the electron-withdrawing oxygen atom in the bridge. This assumption is supported by the calculated<sup>27</sup> basicity of **6** (p*K*<sub>a,calcd</sub> = 19.5), which is more than two p*K*<sub>a</sub> units lower than these of **1** (p*K*<sub>a,calcd</sub> = 21.7, p*K*<sub>a,exp,MeCN</sub> = 22.1) and **3** (p*K*<sub>a,calcd</sub> = 21.9).<sup>28</sup>

The coupling constants found in the <sup>1</sup>H NMR data of the catalyst **29** strongly support the desired *N,N*-complexation of the chiral ligand **6** (chair-chair conformation) to the Pd-metal,

(22) (a) Harrison, J. R.; O'Brien, P. *Tetrahedron Lett.* **2000**, *41*, 6167. (b) Blakemore, P. R.; Norcross, N. R.; Warriner, S. L.; Astles, P. C. *Heterocycles* **2006**, *70*, 609. (c) References 9b and 20.

(23) For a recent study on 9-bispidinones as the ligands, see: Lesma, G.; Pilati, T.; Sacchetti, A.; Silvani, A. *Tetrahedron: Asymmetry* **2008**, *19*, 1363.

(24) The only other application of a chiral bicyclic bispidine (**2**, R-R<sub>2</sub> = Me) in asymmetric synthesis was reported by Kozłowski et al.<sup>9a</sup> Low 33% ee was achieved in the enantioselective deprotonation of *N*-Boc pyrrolidine.

(25) The selectivity factor *s* is defined as *s* = *k*<sub>fast</sub>/*k*<sub>slow</sub> = ln[(1 - *C*)/(1 - ee)]/ln[(1 - *C*)/(1 + ee)], where *C* is the conversion.

(26) (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871. (b) Reference 11a.

(27) All calculated structures were optimized with the TURBOMOLE program package on the B3LYP/BLYP-RI level of theory, employing the TZVP basis set. Solvent effects were taken into account by using the COSMO solvent model (ε = 36.64). For details, see the Supporting Information.

(28) p*K*<sub>a</sub> values refer to the acidities of the protonated (9-oxa)bispidines. They were calculated by using a method established by Gogoll et al., see: Toom, L.; Kütt, A.; Kaljurand, I.; Leito, I.; Ottosson, H.; Grennberg, H.; Gogoll, A. *J. Org. Chem.* **2006**, *71*, 7155.

although, a priori, an *N,O*-ligation of **6** (boat-chair conformation) as in **30** cannot fully be excluded (Figure 2). The large difference in the calculated<sup>27</sup> heats of formation [ $\Delta H_f = H_f(\mathbf{29}) - H_f(\mathbf{30}) = -43.9 \text{ kJ mol}^{-1}$ ], however, makes a competing *N,O*-chelation as in **30** very unlikely.

In conclusion, a novel enantioselective approach to 9-oxabispidines has been developed. Using the *N*-Boc-activated 9-oxabispidin-2-one **8** as the key intermediate, a flexible introduction of substituents in the 2-*endo* position was possible via a 4–5 step sequence, as demonstrated in the preparation of the bicyclic derivatives **7a** and **7b** and the tricycle **6**. This route will permit efficient access to a broader variety of interesting derivatives for further structure-selectivity investigations. In the oxidative kinetic resolution of secondary alcohols, selectivity factors of up to 19 have been achieved with the tricyclic 9-oxabispidine **6**. The prolonged reaction times, as compared to **1** and **3** as the chiral ligands, are probably a consequence of the electron-withdrawing oxygen atom in **6**.

## Experimental Section

The following preparation of **7a** from **8** is representative.

**(2R,6R)-6-tert-Butoxycarbonylaminomethyl-4-methyl-2-propionylmorpholine (21a).** EtMgBr (466  $\mu\text{L}$ , 1.4 mmol, 3.0 M in Et<sub>2</sub>O) was added at  $-78^\circ\text{C}$  to a solution of **8** (300 mg, 1.17 mmol) in anhydrous THF (20 mL). After 12 h at  $-78^\circ\text{C}$ , the reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (20 mL) and water (80 mL) and extracted with EtOAc (4  $\times$  60 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo. Column chromatography (silica gel, Et<sub>2</sub>O/MeOH 1:0  $\rightarrow$  9:1) delivered **21a** (288 mg, 1.01 mmol, 86%) as a yellowish oil.  $[\alpha]_D^{22} +41.4$  (*c* 0.15 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.02 (t, 3H, *J* = 7.3 Hz, CH<sub>2</sub>Me), 1.44 (s, 9H, CMe<sub>3</sub>), 1.79 (td, *J* = 11.0, 3.7 Hz, 2H, 3-H<sub>ax</sub>, 5-H<sub>ax</sub>), 2.29 (s, 3H, NMe), 2.60 (q, *J* = 7.3 Hz, 2H, CH<sub>2</sub>Me), 2.70 (d, *J* = 11.3 Hz, 1H, 5-H<sub>eq</sub>), 2.98 (br d, *J* = 11.3 Hz, 1H, 3-H<sub>eq</sub>), 3.16 (m, 1H, 6-CHH), 3.34 (m, 1H, 6-CHH), 3.65 (m, 1H, 6-H), 4.04 (dd, *J* = 11.0, 2.7 Hz, 1H, 2-H), 4.88 (br s, 1H, NH). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  6.9 (CH<sub>2</sub>Me), 28.4 (CMe<sub>3</sub>), 31.8 (CH<sub>2</sub>Me), 43.0 (6-CH<sub>2</sub>), 46.0 (NMe<sub>3</sub>), 55.7 (C-3), 56.9 (C-5), 75.3 (C-6), 79.5 (CMe<sub>3</sub>), 80.8 (C-2), 155.9 (CO<sub>2</sub>), 209.5 (COEt). IR (film) 3361, 2978, 2939, 2800, 1715, 1523, 1467, 1366, 1252, 1173, 1117 cm<sup>-1</sup>. HRMS (ESI) calcd for [C<sub>14</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> + H]<sup>+</sup> 287.1965, found 287.1966.

**(1R,2S,5S)-2-Ethyl-3,7-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]-nonane (7a).** A solution of the morpholine **21a** (260 mg, 908  $\mu\text{mol}$ ) in TFA (2 mL) was stirred for 4.5 h at 0  $^\circ\text{C}$ . NaOH (11 N, 50 mL) was added and the reaction was warmed to rt within 15 min. After extraction with Et<sub>2</sub>O (3  $\times$  100 mL), the combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. Concentrated HCl (3 mL) and Pd(OH)<sub>2</sub>/C (20 w/w %,

120 mg) were added to the residue dissolved in EtOH (30 mL). The reaction mixture was hydrogenated for 20 h under 1 bar of H<sub>2</sub> pressure. The crude product was sucked through a pad of Celite, washed with MeOH (150 mL), and concentrated under reduced pressure. The residue was dissolved in H<sub>2</sub>O (30 mL) and the pH was adjusted to 11 with 1 N NaOH (ca. 40 mL). After extraction with CHCl<sub>3</sub> (5  $\times$  60 mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent in vacuo yielded the *N*-demethylated precursor of **7a** (122 mg, 717  $\mu\text{mol}$ , 79%) as a brownish oil.  $[\alpha]_D^{22} -1.4$  (*c* 0.27 in MeOH). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  0.97 (t, *J* = 7.5 Hz, 3H, CH<sub>2</sub>Me), 1.41 (m, 2H, CH<sub>2</sub>Me), 2.15 (s, 3H, NMe), 2.36 (ddd, *J* = 11.9, 3.6, 1.4 Hz, 1H, 8-H), 2.45 (m, 1H, 6-H), 2.95 (m, 4H, 2-H, 4-H, 6-H, 8-H), 3.15 (ddd, *J* = 13.8, 3.9, 2.5 Hz, 1H, 4-H), 3.56 (t, *J* = 3.3 Hz, 1H, 1H), 3.64 (t, *J* = 3.8 Hz, 1H, 5-H). <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD)  $\delta$  10.9 (CH<sub>2</sub>Me), 27.0 (CH<sub>2</sub>Me), 47.1 (NMe), 50.9 (C-4), 56.1 (C-8), 60.6 (C-6), 60.7 (C-2), 68.6 (C-5), 71.4 (C-1). IR (film) 3300, 2933, 2789, 1460, 1269, 1210, 1078, 846 cm<sup>-1</sup>. HRMS (ESI) calcd for [C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>O + H]<sup>+</sup> 171.1492, found 171.1494.

The 9-oxabispidine prepared above (100 mg, 587  $\mu\text{mol}$ ) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and treated at rt with K<sub>2</sub>CO<sub>3</sub> (162 mg, 1.17 mmol) and MeI (36.5  $\mu\text{L}$ , 83.3 mg, 587  $\mu\text{mol}$ ). After 6 h at rt, 1 N NaOH (50 mL) and brine (50 mL) were added and the reaction mixture was extracted with CHCl<sub>3</sub> (3  $\times$  75 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the solvent was removed in vacuo. Column chromatography (basic Al<sub>2</sub>O<sub>3</sub>, activity V, EtOAc/MeOH 1:0  $\rightarrow$  0:1) gave **7a** (69.1 mg, 375  $\mu\text{mol}$ , 64%) as a colorless oil.  $[\alpha]_D^{22} +32.1$  (*c* 0.27 in MeOH). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  0.90 (t, *J* = 7.6 Hz, 3H, CH<sub>2</sub>Me), 1.28 (m, 1H, CHHMe), 1.91 (m, 1H, CHHMe), 2.15 (s, 3H, NMe), 2.18 (s, 3H, NMe), 2.23 (m, 2H, 8-H, 2-H), 2.38 (dd, *J* = 11.4, 2.5 Hz, 1H, 6-H), 2.55 (dd, *J* = 11.8, 4.2 Hz, 1H, 4-H), 2.84 (d, *J* = 11.8 Hz, 2H, 4-H, 6-H), 2.95 (d, *J* = 12 Hz, 1H, 8-H), 3.72 (t, *J* = 3.7 Hz, 1H, 1-H), 3.82 (t, *J* = 4.0 Hz, 1H, 5-H). <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD)  $\delta$  10.6 (CH<sub>2</sub>Me), 23.3 (CH<sub>2</sub>Me), 44.4 (3-Me), 47.1 (7-Me), 54.8 (C-8), 59.5 (C-6), 60.4 (C-4), 68.5 (C-2), 69.7 (C-5), 71.1 (C-1). IR (ATR) 2940, 2800, 1676, 1460, 1176, 1130, 1092, 801 cm<sup>-1</sup>. HRMS (ESI) calcd for [C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O + H]<sup>+</sup> 185.1648, found 185.1648.

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**Supporting Information Available:** Experimental procedures and quantum chemical calculations, as well as characterization data and NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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