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

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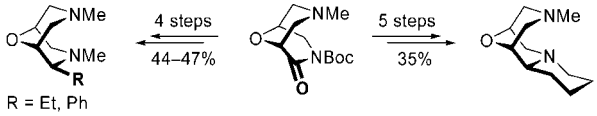

A new and flexible route to enantiomerically pure bi- and tricyclic 9-oxabispidines has been developed with use of (1*R*,5*S*)-7-methyl-2-oxo-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester as the common late-stage intermediate. The 9-oxabispidines synthesized were evaluated 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.[1] 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.[2] Particular attention was attributed to the (−)-sparteine/Pd(II)-catalyzed oxidative kinetic resolution of secondary alcohols developed by Stoltz and Sigman.[3−6]

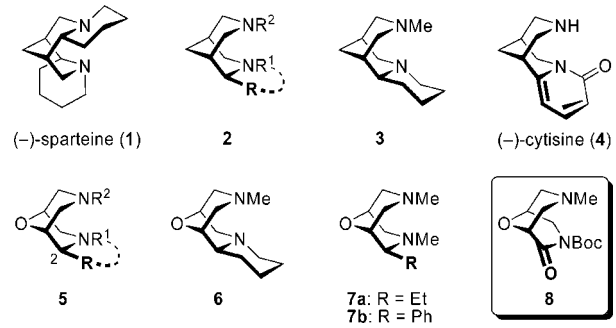

FIGURE 1. Chiral (9-oxa)bispidines and the key intermediate **8**.

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.[7−9] The only exception is given by the tricyclic bispidine **3**, which is available in 3 steps from the natural product (−)-cytisine (**4**).[10,11] Diamine **3** found application as a surrogate for the less readily available (+)-sparteine enantiomer, *ent*-**1**.[10,12]

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

(1) (a) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewksi, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (c) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: New York, 2002. (d) Hodgson, D. M. *Topics in Organometallic Chemistry*; Springer: Berlin, Germany, 2003; Vol. 5. (e) Gawley, R. E.; Coldham, I. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, UK, 2004; p 997. (f) Hoppe, D.; Christoph, G. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, UK, 2004; p 1055. (g) Chuzel, O.; Riant, O. In *Topics in Organometallic Chemistry*; Lemaire, M., Mangeney, P., Eds.; Springer: Berlin, Germany, 2005; Vol. 15, p 59.

(2) For some examples, see: (a) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1057. (b) Sorger, K.; Petersen, H.; Stohrer, J. U.S. Patent 6924386, 2005. (c) Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Ravikumar, K.; Sridhar, B.; Kantam, M. L. *Chem. Commun.* **2006**, 4066.

(3) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725. (b) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835. (c) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 353. (d) Caspi, D. D.; Ebner, D. C.; Bagdanoff, J. T.; Stoltz, B. M. *Adv. Synth. Catal.* **2004**, *346*, 185.

(4) (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475. (b) Mandal, S. K.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 7535.

(5) Nielsen, R. J.; Keith, J. M.; Stoltz, B. M.; Goddard, W. A., III *J. Am. Chem. Soc.* **2004**, *126*, 7967.

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(7) Enantioselective synthesis of **3**: (a) Danieli, B.; Lesma, G.; Passarella, D.; Piacenti, P.; Sacchetti, A.; Silvani, A.; Virdis, A. *Tetrahedron Lett.* **2002**, *43*, 7155. (b) Danieli, B.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A. *Tetrahedron Lett.* **2005**, *46*, 7121. (c) Hermet, J.-P. R.; Viterisi, A.; Wright, J. M.; McGrath, M. J.; O'Brien, P.; Whitwood, A. C.; Gilday, J. *Org. Biomol. Chem.* **2007**, *5*, 3614.

(8) Enantioselective synthesis of **1** or *ent*-**1**: (a) Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577. (b) Hermet, J.-P. R.; McGrath, M. J.; O'Brien, P.; Porter, D. W.; Gilday, J. *Chem. Commun.* **2004**, 1830.

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(10) (a) Dixon, A. J.; McGrath, M. J.; O'Brien, P. *Org. Synth.* **2006**, *83*, 141. (b) O'Brien, P. *Chem. Commun.* **2008**, 655.

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(12) *ent*-**1** is accessible from the naturally occurring alkaloid *rac*-lupanine (*rac*-10-oxosparteine) by reduction and resolution: Ebner, T.; Eichelbaum, M.; Fischer, P.; Meese, C. O. *Arch. Pharm. (Weinheim)* **1989**, *322*, 399.

(13) There is a single lecture abstract, in which an enantioselective route to **6** and some other bicyclic 9-oxabispidines of type **5** is sketched. However, no yields or characterization data are given, see: Gill, D. M.; Holness, H.; Keegan, P. S. *Abstracts of Papers*, 232nd ACS National Meeting, San Francisco, CA; American Chemical Society: Washington, DC, 2006.

(14) Comba, P.; Kerscher, M.; Schiek, W. *Prog. Inorg. Chem.* **2007**, *55*, 613.

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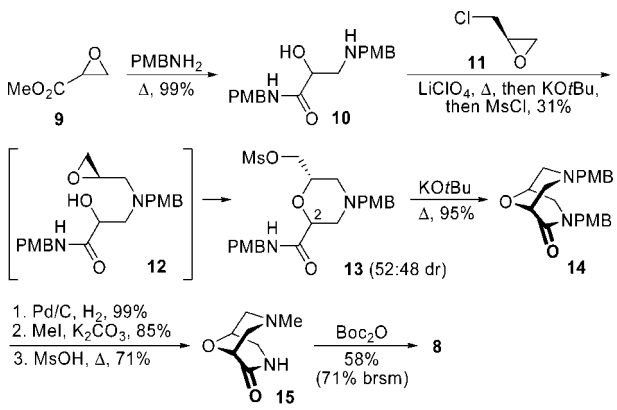
SCHEME 1. Synthesis of the Key Intermediate 8 from 9 and 11



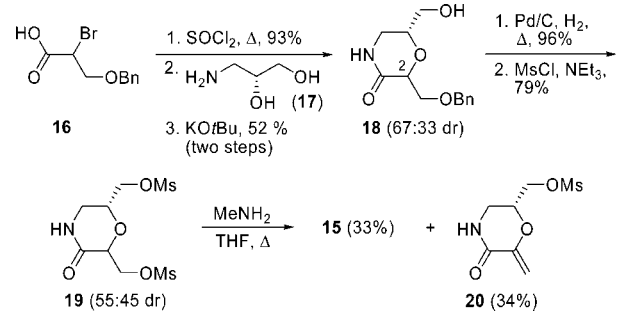
synthesis. With the methylene bridge in **2** being replaced by an ether function, the 9-oxabispidines **5** are often more easily accessible than the corresponding bispidines. This has recently been demonstrated in our group by the enantioselective preparation of a set of bicyclic 2-*endo*-phenyl-substituted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

One major problem, inherent to all known syntheses of bispidines and 9-oxabispidines, 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.[7−9] 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.

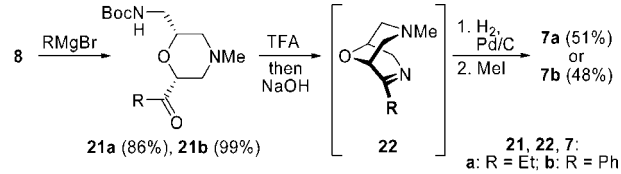
Herein we disclose a first solution to this problem by using the *N*-Boc-9-oxabispidin-2-one **8** as a common, late-stage intermediate. This imide, available in 7 steps by two different routes, was converted in just 4−5 steps and 35−47% yield into the bicyclic, 2-*endo*-substituted 9-oxabispidines **7a** 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[17] and 3-amino-1,2-diols.[15,16] Heating of **10** with (*R*)-epichlorohydrin (**11**) in the presence of $LiClO_4$ induced a highly regioselective ring opening of the epoxide at C-3 to give a chlorohydrin intermediate, which, upon addition of KO*t*Bu, 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. KO*t*Bu-induced ring closure of **13**, which involved an isomerization of the trans-epimer to the cis-configured derivative, gave the chiral 9-oxabispidine **14** in excellent 95% yield.[18] 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_2O 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.

SCHEME 2. Synthesis of 15 from 16 and 17



SCHEME 3. Preparation of the Bicyclic 9-Oxabispidines 7a,b from 8

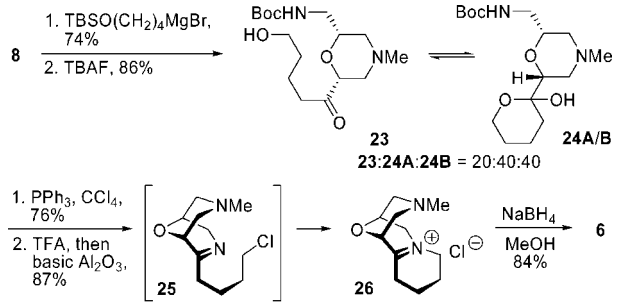


The second approach (Scheme 2) started with the known acid **16**, available in a single step from ethyl 2,3-dibromopropanoate.[19] Activation of **16** as the acid chloride, amide formation with (*R*)-3-aminopropane-1,2-diol (**17**), and ring closure under basic conditions afforded the morpholin-3-one **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-oxabispidin-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-oxabispidines was straightforward (Scheme 3). The bicyclic ethyl derivative **7a** was obtained in 44% yield by using a 4-step protocol:[20] Treatment of **8** with EtMgBr resulted in a clean monoaddition at the *N*-acyl moiety of the unsymmetric imide function,[21] delivering, after ring-opening of the initially formed semiaminal, the ketone **21a** in good 86% yield. Acidic

(15) Breuning, M.; Steiner, M. *Synthesis* **2007**, 1702.
(16) Breuning, M.; Steiner, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1978.
(17) Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem.* **2007**, 2100.
(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 bispidin-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.
(20) For a related protocol starting from achiral 2,4,6,8-tetraoxobispidine, see: (a) Blakemore, P. R.; Kilner, C.; Norcross, N. R.; Astles, P. C. *Org. Lett.* **2005**, *7*, 4721. (b) Norcross, N. R.; Melbardis, J. P.; Solera, M. F.; Sephton, M. A.; Kilner, C.; Zakharov, L. N.; Astles, P. C.; Warriner, S. L.; Blakemore, P. R. *J. Org. Chem.* **2008**, *73*, 7939.
(21) For additions of organometallic reagents to *N*-Boc-activated piperidines, see: (a) Williams, G. D.; Pike, R. A. *Org. Lett.* **2003**, *5*, 4227. (b) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228. (c) Wei, B.-G.; Chen, J.; Huang, P.-Q. *Tetrahedron* **2006**, *62*, 190. (d) Harrison, T. J.; Kozak, J. A.; Corbella-Pane, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525. (e) Williams, G. D.; Wade, C. E.; Wills, M. *Chem. Commun.* **2005**, 4735.

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



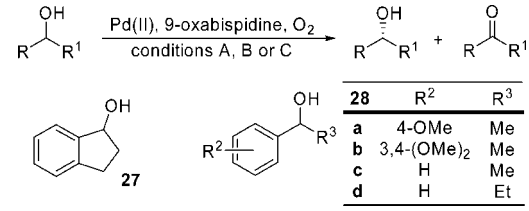
cleavage of the *N*-Boc group followed by base-induced cyclization gave the imine **22a**, which was hydrogenated and *N*-methylated to provide the target diamine **7a**. In agreement with known reductions and nucleophilic alkylations of bispidine-derived imines,[22] the hydrogenation of **22a** occurred 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**[15] was prepared analogously in 47% overall yield from **8**.

The tricyclic 9-oxabispidine **6**[16] was accessed by using a slightly modified sequence (Scheme 4). Reaction of **8** with $TBSO(CH_2)_4MgBr$ 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 $NaBH_4$ 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.[3,6] for the analogous (−)-sparteine-catalyzed reactions.[23] 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**.[24] Good to excellent selectivity factors *s*[25] of up to 19 were achieved applying conditions C, in which the preformed Pd(II)-complex **29** (Figure 2), prepared from **6** and $[Pd(MeCN)_2Br_2]$, 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 (−)-sparteine (**1**, $s = 17$)[6] and the bispidine **3** ($s = 19$)[6] as the chiral ligands. Lower differentiations were observed for **27** and **28b**−**d** ($s = 6.4$−12).

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



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

[a] Conditions A: $Pd(nbd)Cl_2$ (5 mol %), **6** or **7** (20 mol %), O_2 (1 bar), mol sieves 3 Å, toluene, 60−80 °C. Conditions B: $Pd(nbd)Cl_2$ (5 mol %), **6** (12 mol %), O_2 (1 bar), Cs_2CO_3, mol sieves 3 Å, $CHCl_3$, rt. Conditions C: **29** (5 mol %), **6** (7 mol %), O_2 (1 bar), Cs_2CO_3, mol sieves 3 Å, $CHCl_3$, rt. [b] Determined by ^1H NMR. [c] Determined by HPLC on the chiral phase. [d] Reference selectivity factors (ligand, conditions):[3,6,26] **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).

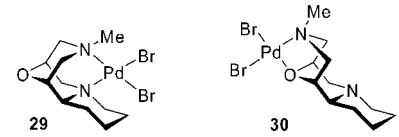


FIGURE 2. The chiral $PdBr_2$ complex **29** and the isomer **30**.

According to quantum chemical studies,[5] 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[27] basicity of **6** ($pK_{a,calcd} = 19.5$), which is more than two pK_a units lower than these of **1** ($pK_{a,calcd} = 21.7$, $pK_{a,exp.,MeCN} = 22.1$) and **3** ($pK_{a,calcd} = 21.9$).[28]

The coupling constants found in the ^1H 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. *Hetreocycles* **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-R2 = Me) in asymmetric synthesis was reported by Kozlowski et al.[9a] Low 33% ee was achieved in the enantioselective deprotonation of *N*-Boc pyrrolidine.

(25) The selectivity factor *s* is defined as $s = k_{fast}/k_{slow} = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$, 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 ($\epsilon = 36.64$). For details, see the Supporting Information.

(28) pK_a 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[27] heats of formation [$\Delta H_f = H_f(\mathbf{29}) - H_f(\mathbf{30}) = -43.9$ 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.

(2*R*,6*R*)-6-*tert*-Butoxycarbonylaminomethyl-4-methyl-2-propionylmorpholine (21a). EtMgBr (466 μL, 1.4 mmol, 3.0 M in Et_2O) was added at −78 °C to a solution of **8** (300 mg, 1.17 mmol) in anhydrous THF (20 mL). After 12 h at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and water (80 mL) and extracted with EtOAc (4 × 60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (silica gel, Et_2O/MeOH 1:0 → 9:1) delivered **21a** (288 mg, 1.01 mmol, 86%) as a yellowish oil. $[\alpha]^{22}_D$ +41.4 (*c* 0.15 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, 3H, J = 7.3 Hz, CH_2*Me*), 1.44 (s, 9H, CMe_3), 1.79 (td, J = 11.0, 3.7 Hz, 2H, 3-H_{ax}, 5-H_{ax}), 2.29 (s, 3H, NMe), 2.60 (q, J = 7.3 Hz, 2H, C*H*$_2$Me), 2.70 (d, J = 11.3 Hz, 1H, 5-H_{eq}), 2.98 (br d, J = 11.3 Hz, 1H, 3-H_{eq}), 3.16 (m, 1H, 6-C*H*H), 3.34 (m, 1H, 6-CH*H*), 3.65 (m, 1H, 6-H), 4.04 (dd, J = 11.0, 2.7 Hz, 1H, 2-H), 4.88 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9 (CH_2*Me*), 28.4 (C*Me*$_3$), 31.8 (*C*H$_2$Me), 43.0 (6-CH_2), 46.0 (NMe_3), 55.7 (C-3), 56.9 (C-5), 75.3 (C-6), 79.5 (*C*Me$_3$), 80.8 (C-2), 155.9 (CO_2), 209.5 (COEt). IR (film) 3361, 2978, 2939, 2800, 1715, 1523, 1467, 1366, 1252, 1173, 1117 cm^{-1}. HRMS (ESI) calcd for $[C_{14}H_{26}N_2O_4 + H]^+$ 287.1965, found 287.1966.

(1*R*,2*S*,5*S*)-2-Ethyl-3,7-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]-nonane (7a). A solution of the morpholine **21a** (260 mg, 908 μmol) in TFA (2 mL) was stirred for 4.5 h at 0 °C. NaOH (11 N, 50 mL) was added and the reaction was warmed to rt within 15 min. After extraction with Et_2O (3 × 100 mL), the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and evaporated. Concentrated HCl (3 mL) and $Pd(OH)_2$/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_2 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_2O (30 mL) and the pH was adjusted to 11 with 1 N NaOH (ca. 40 mL). After extraction with $CHCl_3$ (5 × 60 mL), the combined organic layers were dried over Na_2SO_4. Removal of the solvent in vacuo yielded the *N*-demethylated precursor of **7a** (122 mg, 717 μmol, 79%) as a brownish oil. $[\alpha]^{22}_D$ −1.4 (*c* 0.27 in MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 0.97 (t, J = 7.5 Hz, 3H, CH_2*Me*), 1.41 (m, 2H, C*H*$_2$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). ^{13}C NMR (100 MHz, CD_3OD) δ 10.9 (CH_2*Me*), 27.0 (*C*H$_2$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^{-1}. HRMS (ESI) calcd for $[C_9H_{18}N_2O + H]^+$ 171.1492, found 171.1494.

The 9-oxabispidine prepared above (100 mg, 587 μmol) was dissolved in CH_2Cl_2 (10 mL) and treated at rt with K_2CO_3 (162 mg, 1.17 mmol) and MeI (36.5 μL, 83.3 mg, 587 μmol). After 6 h at rt, 1 N NaOH (50 mL) and brine (50 mL) were added and the reaction mixture was extracted with $CHCl_3$ (3 × 75 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Column chromatography (basic Al_2O_3, activity V, EtOAc/MeOH 1:0 → 0:1) gave **7a** (69.1 mg, 375 μmol, 64%) as a colorless oil. $[\alpha]^{22}_D$ +32.1 (*c* 0.27 in MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (t, J = 7.6 Hz, 3H, CH_2*Me*), 1.28 (m, 1H, C*H*HMe), 1.91 (m, 1H, CH*H*Me), 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). ^{13}C NMR (100 MHz, CD_3OD) δ 10.6 (CH_2*Me*), 23.3 (*C*H$_2$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^{-1}. HRMS (ESI) calcd for $[C_{10}H_{20}N_2O + H]^+$ 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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