Thieme Chemistry Journal Awardees – Where Are They Now? Bridgehead Lithiated 9-Oxabispidines

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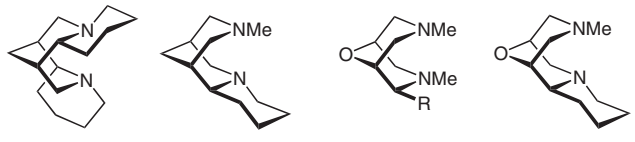
Abstract: Bi- and tricyclic 9-oxabispidines are smoothly deprotonated at –78 °C by *s*-BuLi at one of the bridgehead carbon atoms to give α-lithio ethers, which were trapped with electrophiles in good yields. Rearrangements to ring-contracted *N*,*O*-acetals occurred upon warming in the absence of an electrophile. The α-lithio ether intermediates are presumably stabilized by negative hyperconjugation.

Key words: 9-oxabispidines, carbanions, rearrangements, lithiation, bicyclic compounds

Matthias Breuning studied chemistry at the University of Würzburg, Germany, and obtained his PhD degree in 1999 under the guidance of Prof. G. Bringmann working on the atroposelective synthesis of axially chiral biaryls. After postdoctoral studies on enantioselective quinone Diels–Alder reactions with Prof. E. J. Corey at Harvard University in Cambridge, MA, USA, he joined the Bayer HealthCare AG in Wuppertal, Germany, as a senior research scientist in medicinal chemistry. His independent career began in 2002 as a group leader at the Institute of Organic Chemistry at the University of Würzburg. Dr. Breuning's main research interests include the development of novel chiral catalysts and auxiliaries, with particular emphasis on bicyclic diamines and organocatalysts, and their application in natural product synthesis. His research activities were recognized with the Emmy-Noether young investigator award (2002) and the Thieme Journal Award (2004).

The natural alkaloid (–)-sparteine (**1**, Figure 1)[1] and the (–)-cytisine derived (+)-sparteine surrogate **2**[2] are the auxiliaries of choice for almost all *s*-BuLi-mediated asymmetric deprotonation–electrophilic trapping reactions.[3] The enantioselective total synthesis of such chiral bispidines {3,7-diazabicyclo[3.3.1]nonanes}, however, is still a time-consuming challenge severely hampering an efficient design of derivatives.[3] We therefore investigated the closely related bi- and tricyclic 9-oxabispidines of types **3** and **4**, which are more easily accessible due to the ether bridge.[4–6] These diamines, in particular **4**, possess high potential as chiral ligands in transition-metal-catalyzed transformations: The complex [(**4**)$PdBr_2$] was successfully used in the oxidative kinetic resolution of secondary alcohols,[5] and [(**4**)$CuCl_2$] provided up to 98% ee in enantioselective Henry reactions.[6] Deprotonations with *s*-BuLi in the presence of **3** or **4**, however, failed, probably because the 9-oxabispidines are lithiated at one of the bridgehead carbon atoms.



(–)-sparteine (**1**) **2** **3** (R = H, alkyl, Ph) **4**

Figure 1

The stability of nonactivated[7] ethers against strong organolithium bases such as *s*-BuLi widely differs. Et_2O, for example, is relatively inert ($t_{1/2,\ 35\ °C}$ = 31 h)[8,9] and therefore it is often used as the solvent for deprotonation reactions, whereas THF gets readily deprotonated ($t_{1/2,\ 35\ °C}$ = 10 min).[8,10] The resulting α-lithio ethers are usually highly reactive intermediates[11] that undergo fast consecutive reactions like fragmentations,[12] [1,2]-alkyl shifts,[11a,13] or [2,3]-sigmatropic Wittig rearrangements.[11a,13a,b,14]

The intermolecular trapping of nonstabilized α-lithio ethers was as yet only realized with epoxides.[15,16] Well studied is the enantioselective deprotonation of cyclooctene oxide (**5**, Scheme 1) with *s*-BuLi at –90 °C in the presence of the chiral auxiliary (–)-sparteine (**1**).[15] Quench of the resulting anion with electrophiles delivered the α-substituted derivatives **6** in good yields and enantioselectivities. The lithiation of 9-oxabicyclo[3.3.1]nona-2,6-diene (**7**) with *t*-BuLi–TMEDA is the only example for a deprotonation of an oxygen-bridged bicyclic compound.[17,18] This process, however, is facilitated by the formation of a stabilized allyl anion intermediate, as obvious from the regioisomeric products **8A** and **8B** obtained upon addition of an electrophile.[17]

In this letter we report on the deprotonation of the 9-oxabispidines **3** and **4** with *s*-BuLi at –78 °C leading to stable α-lithio ethers that were trapped with electrophiles in

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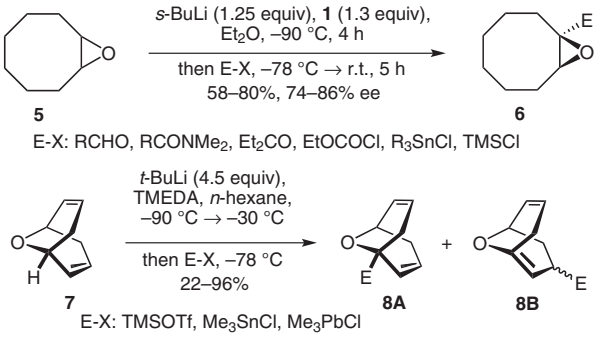


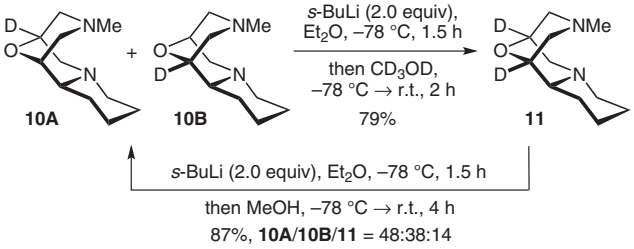
Scheme 1

good yields. At higher temperatures, rearrangements occurred.

In order to prove the instability of the 9-oxabispidines towards strong organolithium bases we used a deprotonation–deuteration sequence (Table 1). And indeed, treatment of **3a–c** and **4** with an excess of *s*-BuLi at –78 °C in Et_2O followed by quench with CD_3OD delivered the monodeuterated derivatives **9A/B** and **10A/B** in good isolated yields (75–89%) and with high deuterium incorporation (73–100%).[19] Thus, these 9-oxabispidines are the first examples of nonstabilized[7] and nonoxiranyl-derived ethers that undergo smooth deprotonation at low temperatures to give α-lithio ether intermediates which can be trapped by external electrophiles.

The exclusive formation of the regioisomers **9bA** and **9cA** from the unsymmetric bicyclic 9-oxabispidines **3b** and **3c** indicates a strong steric shielding of the bridgehead proton at C1 by the substituents R. In contrast to that, no significant differentiation was observed in the deprotonation–deuteration of the tricyclic diamine **4** possessing the annelated piperidine ring. The regioisomeric products **10A** and **10B** were obtained in a 55:45 ratio. It should be noted that the use of *s*-BuLi is essential since no reaction occurred at –78 °C with the weaker base *n*-BuLi; an external activation of *s*-BuLi by chelating ligands such as **1**, **2**, or TMEDA is not required. It is very likely that the 9-oxabispidines themselves autocatalytically activate the organolithium base by complexation, thus facilitating an intermolecular proton abstraction (vide supra).

The further lithiation–CD_3OD-trapping of **10A/B** solely afforded the dideuterated 9-oxabispidine **11** in 79% yield (Scheme 2).[19] The observed quantitative H/D exchange implies a highly selective deprotonation–deuteration sequence, since any competing dedeuteration–redeuteration processes would lead to the recovery of formally unchanged starting material. Consequently, the kinetic isotope effect causing this selectivity must be large;[20,21] a k_H/k_D value of >94:6 = 15.7 was calculated under the assumption that the lower detection limits of **10A** and **10B** in the ^1H NMR spectrum of **11** are <3%. If no bridgehead proton was available, dedeuteration occurred, as found in the lithiation–protonation of **11** giving a 48:38:14 mixture of **10A**, **10B**, and **11** in 87% yield.

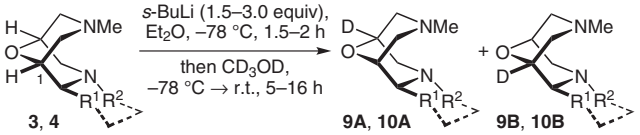


Scheme 2

Other electrophiles such as MeI, TMSCl, and BzCl were also suited for trapping the α-lithiated 9-oxabispidines, as demonstrated on **4** as the model substrate (Table 2). The products **12A/B**, **13A/B**, and **14A/B** were obtained in 43–78% yield and with an improved regioselectivity of up to 73:27 for the sterically more demanding electrophiles TMSCl and BzCl.[19]

The attempted further methylation of **12A/B** to give the 9-oxabispidine **15**, however, failed (Scheme 3). After deprotonation with *s*-BuLi, no reaction was observed with MeI as the electrophile, while stronger methylating agents

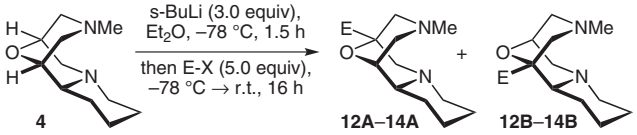
Table 1 Deprotonation–Deuteration of the 9-Oxabispidines **3a–c** and **4**



Entry	Starting material	R^1	R^2	Product	Isolated yield (%)	D incorporation (%)[a]	**A/B**[a]
1	**3a**	H	Me	**9a**	89	100	–[b]
2	**3b**	Et	Me	**9b**	86	85	100:0
3	**3c**	Ph	Me	**9c**[c]	75	73	100:0
4[d]	**4**	-$(CH_2)_4$-		**10**	85	100	55:45

[a] Determined by ^1H NMR.
[b] **9aA = 9aB**.
[c] According to ^1H NMR spectroscopy and mass spectrometry, some deuteration at the phenyl group had occurred, too.
[d] No reaction was observed with *n*-BuLi as the base.

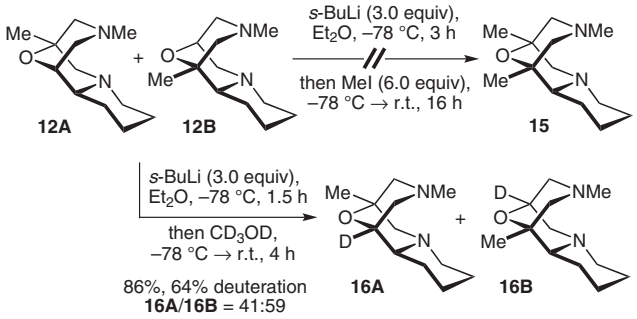
Table 2 Deprotonation–Electrophilic Trapping of **4**



Entry	EX	Product	E	Yield (%)	**A/B**[a]
1	MeI	**12**	Me	78	56:44
2	TMSCl	**13**	TMS	52 (65)[b]	64:36
3	BzCl	**14**	Bz	43 (56)[b]	73:27

[a] Determined by ^{1}H NMR.
[b] Based on recovered starting material.

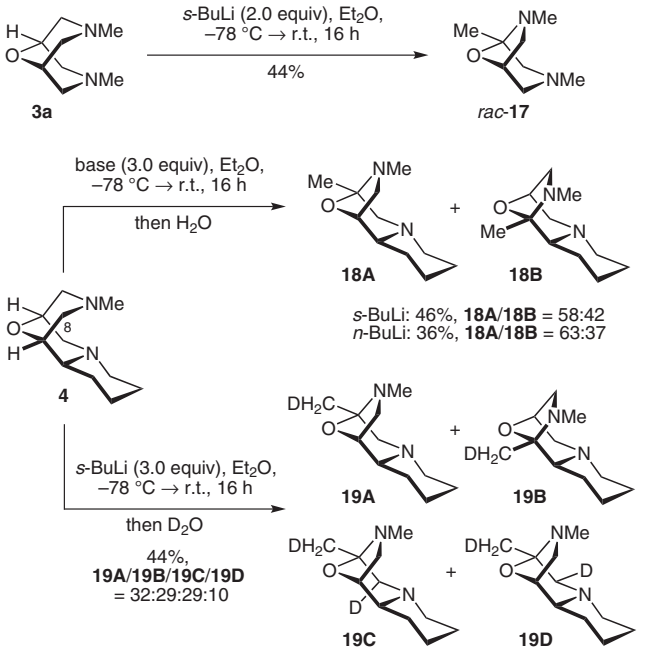
such as MeOTf afforded complex product mixtures hinting at *N*-methylated oxabispidinium salts. With the deprotonation–deuteration of **12A/B** resulting in a 64:36 mixture of the deuterated 9-oxabispidines **16A/B** (ratio 41:59) and **12A/B**, the electrophilic trapping of the α-lithio ethers of **12A/B** with MeI and MeOTf must have failed for unknown reasons.



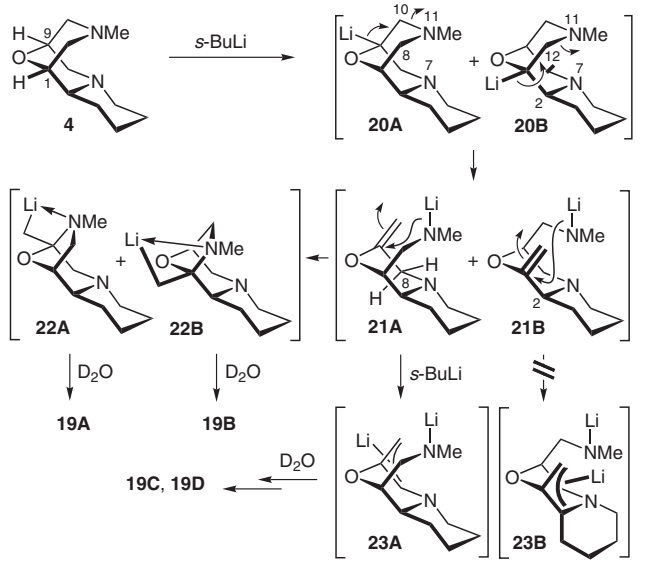
Scheme 3

If the unsubstituted 9-oxabispidine **3a** was lithiated at –78 °C and slowly warmed to room temperature in the absence of an electrophile, a rearrangement to the ring-contracted *N*,*O*-acetal *rac*-**17** occurred (44% yield, Scheme 4).[19] The analogous deprotonation–rearrangement of the unsymmetric tricyclic 9-oxabispidine **4** delivered the regioisomers **18A/B** in a 58:42 ratio and 46% yield.[22] A similar result (**18A/18B** = 63:37, 36% yield) was obtained by using *n*-BuLi as the base, which is apparently capable of lithiating **4** at higher temperatures, but not at –78 °C (cf. Table 1, footnote d). Quenching the crude reaction mixture with D_2O instead of water furnished, according to in-depth NMR and HRMS investigations, a 32:29:29:10 mixture of four compounds, the two expected monodeuterated *N*,*O*-acetals **19A** and **19B**, and, in addition, the two **19A**-derived dideuterated species **19C** and **19D**, in which a further H–D exchange at C8 had occurred.[23]

The latter result can be explained by the following mechanism (Scheme 5): Initial unselective deprotonation of **4** at one of the bridgehead carbon atoms C9 and C1 afforded the α-lithio ethers **20A/B**, which underwent β-elimination



Scheme 4

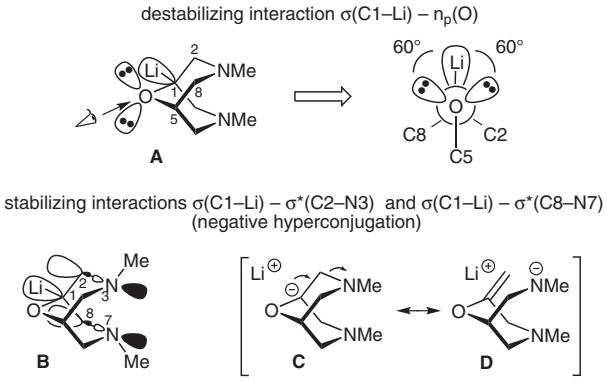


Scheme 5

upon warming to give the lithium amides **21A/B** under cleavage of the C10–N11 and the C12–N11 bond, respectively.[24] Products arising from a competing breakage of the C8–N7 or C2–N7 bond in the southern morpholine moiety were not detected. Intramolecular addition of the amide group in **21A/B** to the enol ether furnished the intermediates **22A/B**,[25] which were deuterated upon workup to give **19A/B**. The latter cyclization, in which a lithium amide is converted into a primary carbanion, is probably facilitated by an intramolecular chelation of the lithium atom with the nitrogen atom in β-position. In contrast to **21B**, which seems to be resistant towards further lithiation, the intermediate **21A** was again partly deprotonated at C8 giving the stabilized allylic anion **23A**. Twofold

deuteration and ring closure of **23A** finally led to the diastereomers **19C** and **19D**.

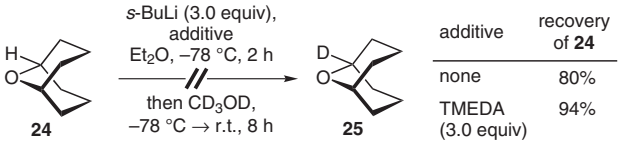
The unexpected stability of the bridgehead lithiated 9-oxabispidines at –78 °C is supposedly a consequence of two effects (Scheme 6): Firstly, the destabilizing interaction between the σ-orbital of the electron-rich C–Li bond and the free electron pair of the neighboring oxygen atom, which causes the high reactivity of 'normal' α-lithio ethers,[11] should be less pronounced. Assuming that the lithiated 9-oxabispidines preferentially adopt a double chair conformation, as known from their nonlithiated counterparts and from the structurally closely related bispidines,[26] the orbitals should be locked in an unfavorable gauche orientation which minimizes the destabilizing interaction (illustration **A**). Secondly, the nitrogen atoms in β-position probably exert a strong stabilizing effect by a twofold negative hyperconjugation.[27] As depicted in illustration **B**, the required overlap between the electron-rich σ-orbital of the C–Li bond and the two energetically low-lying σ*-orbitals of the two adjacent C–N bonds should be optimal due to the antiparallel orientation of these orbitals in the double chair conformation.[26] The resulting reduction of electron density in the C–Li bond in combination with the addition of some π-character to the σ(C–C)-bonds can also be expressed by the mesomeric structures **C** and **D**.



Scheme 6

The close structural relationship between **D** and the proposed intermediates **21A/B** in the rearrangements of **3a** (see Scheme 5) strongly implies that negative hyperconjugation also plays an important role in initiating the latter process.

In order to prove the pivotal role of the nitrogen atoms of the 9-oxabispidines in the deprotonation reactions, two control experiments were done with the ether **24**,[28] which possesses the same bicyclic skeleton, but lacks the two nitrogen atoms (Scheme 7): Treatment of **24** with *s*-BuLi and, subsequently, with CD_3OD did not lead to the monodeuterated ether **25** or any decomposition products; even in the presence of activating diamine TMEDA, only unchanged starting material was recovered in 94% yield. The reluctance of **24** towards lithiation clearly shows that the nitrogen atoms of the 9-oxabispidines not only activate *s*-BuLi by complexation, but also facilitate the deprotonation due to the formation of α-lithio ethers which are stabilized by negative hyperconjugation.



Scheme 7

In conclusion, the deprotonation of the 9-oxabispidines **3** and **4** with *s*-BuLi at –78 °C afforded α-lithio ethers, which are presumably stabilized by negative hyperconjugation. Trapping of these intermediates at –78 °C with electrophiles afforded bridgehead-substituted 9-oxabispidines in good yields, while rearrangements to ring-contracted *N*,*O*-acetals occurred in the absence of an electrophile upon warming.

Acknowledgment

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(19) All new compounds have been characterized by ^{1}H NMR and ^{13}C NMR spectroscopy as well as HRMS spectrometry. Compounds **9b**, **9c**, and **13A/B** could not be separated from the starting materials.

Spectroscopic Data for Selected Compounds

Compound **9a**: mp 70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 6 H, 3-Me, 6-Me), 2.41 (d, *J* = 11.1 Hz, 2 H, 6-H, 8-H), 2.42 (dd, *J* = 11.1, 4.4 Hz, 2 H, 4-H, 6-H), 2.89 (d, *J* = 11.1 Hz, 4 H, 2-H′, 4-H′, 6-H′, 8-H′), 3.85 (t, *J* = 4.3 Hz, 1 H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.8 (3-Me, 6-Me), 58.4 (NCH_2), 58.5 (NCH_2), 68.0 (t, *J* = 21.8 Hz, C-1), 68.4 (C-5). HRMS (ESI+): *m/z* calcd for $C_8H_{16}DN_2O$ [M + H]$^+$: 158.1398; found: 158.1398.

Compound **10A/B** (ratio **A/B** = 55:45): mp 35 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (m, 3 H **A**, 3 H **B**, CH_2), 1.56 (m, 1 H **A**, 1 H **B**, CH_2), 1.70–1.87 (m, 3 H **A**, 3 H **B**, CH_2, 6-H), 2.19 (s, 3 H **A**, 3 H **B**, 11-Me), 2.25 (m, 2 H **A**, 2 H **B**, 2-H, 12-H), 2.39 (dd, *J* = 11.7, 1.3 Hz, 1 H, 10-H **A**), 2.40 (ddd, *J* = 11.6, 4.2, 1.6 Hz, 1 H, 10-H **B**), 2.55 (dd, *J* = 11.6, 1.5 Hz, 1 H, 8-H **A**), 2.56 (ddd, *J* = 11.6, 4.5, 1.7 Hz, 1 H, 8-H **B**), 2.78–2.95 (m, 4 H **A**, 4-H **B**, 6-H′, 8-H′, 10-H′, 12-H′), 3.47 (t, *J* = 3.5 Hz, 1 H, 1-H **A**), 3.85 (t, *J* = 4.1 Hz, 1 H, 9-H **B**). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (CH_2 **A**, **B**), 25.1 (CH_2 **A**, **B**), 28.2 (CH_2 **A**, **B**), 47.4 (11-Me **A**, **B**), 54.4 (C-12), 54.5 (C-12), 57.2 (C-6 **A**, **B**), 57.8 (C-8), 57.9 (C-8), 58.2 (C-10), 58.3 (C-10), 64.9 (C-2), 65.0 (C-2), 68.3 (t, *J* = 19.8 Hz, C-9 **A**), 68.7 (C-9 **B**), 71.4 (t, *J* = 21.6 Hz, C-1 **B**), 71.8 (C-1 **A**). IR (ATR): ν = 2929, 2853, 2784, 1458, 1354, 1283, 1199, 1161, 1119, 1069, 973, 815, 722 cm^{-1}. HRMS (ESI+): *m/z* calcd for $C_{11}H_{19}DN_2O$ [M + H]$^+$: 198.1711; found: 198.1711.

Compound **11**: $[\alpha]_D^{22}$ +14.9 (*c* 0.22, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (m, 3 H, CH_2), 1.56 (m, 1 H, CH_2), 1.77 (m, 3 H, CH_2, 6-H), 2.19 (s, 3 H, 11-Me), 2.24 (d, *J* = 11.6 Hz, 1 H, 12-H), 2.26 (m, 1 H, 2-H), 2.39 (dd, *J* = 11.4, 1.3 Hz, 1 H, 10-H), 2.55 (dd, *J* = 11.6, 1.4 Hz, 1 H, 8-H), 2.81 (d, *J* = 11.6 Hz, 1 H, 8-H′), 2.89 (m, 1 H, 6-H′), 2.91 (d, *J* = 11.7 Hz, 1 H, 10-H′), 2.92 (m, 1 H, 12-H′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (CH_2), 25.3 (CH_2), 28.3 (CH_2), 47.5 (11-Me), 54.5 (C-12), 57.3 (C-6), 57.9 (C-8), 58.4 (C-10), 64.9 (C-2), 68.4 (t, *J* = 22.1 Hz, C-9), 71.6 (t, *J* = 22.2 Hz, C-1). IR (ATR): ν = 2931, 2754, 1438, 1352, 1288, 1276, 1176, 1135, 1076, 1056, 1023, 788, 752, 721, 699 cm^{-1} HRMS (ESI+): *m/z* calcd for $C_{11}H_{18}D_2N_2O$ [M + H]$^+$: 199.1774; found: 199.1774.

Compound **12A/B** (ratio **A/B** = 56:44): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 3 H **B**, 1-Me), 1.10 (s, 3 H **A**, 9-Me), 1.27–1.86 (m, 7 H **A**, 8 H **B**, CH_2, 12-H **B**), 1.91 (br d, *J* = 10.5 Hz, 1 H, 2-H **B**), 2.00 (dd, *J* = 11.4, 2.4 Hz, 1 H, 10-H **A**), 2.11–2.18 (m, 3 H, 2-H **A**, 8-H **A**, 12-H **A**), 2.15 (s, 3 H, 11-Me), 2.16 (s, 3 H, 11-Me), 2.29 (ddd, *J* = 11.5, 4.1, 1.7 Hz, 1 H, 10-H **B**), 2.55 (ddd, *J* = 11.5, 4.3, 1.8 Hz, 1 H, 8-H **B**), 2.80 (m, 2 H, 8-H′ **A**, 8-H′ **B**), 2.84–2.93 (m, 3 H **A**, 3 H **B**, 6-H′, 10-H′, 12-H′), 3.54 (t, *J* = 3.7 Hz, 1 H, 1-H **A**), 3.88 (t, *J* = 4.3 Hz, 1 H, 9-H **B**). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (CH_2), 25.16 (CH_2), 25.24 (2 × CH_2), 25.7 (1-Me **B**), 26.2 (1-Me **A**), 27.2 (CH_2), 28.1 (CH_2), 47.32 (11-Me), 47.34 (11-Me), 53.8 (C-12 **A**), 57.3 (C-6 **A**), 57.58 (C-6 **B** or C-10 **B**), 57.62 (C-6 **B** or C-10 **B**), 58.0 (C-8 **B**), 60.6 (C-12 **B**), 63.9 (C-8 **A**), 64.2 (C-2 **A**), 64.3 (C-10 **A**), 69.1 (C-9 **B**), 70.1 (C-9 **A**), 70.8 (C-2 **B**), 72.0 (C-1 **B**), 73.1 (C-1 **A**). IR (ATR): ν = 2930, 2854, 2758, 1457, 1357, 1286, 1260, 1102, 1055, 812 cm^{-1}. HRMS (ESI+): *m/z* calcd for $C_{12}H_{22}N_2O$ [M + H]$^+$: 211.1805; found: 211.1805.

Compound **14A/B** (ratio **A/B** = 73:27): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.65 (m, 4 H **A**, 4 H **B**, CH_2), 1.70–1.95 (m, 3 H **A**, 3 H **B**, CH_2, 6-H), 2.10–2.45 (m, 5 H, 2-H **A**, 10-H **A**, 12-H **A**, 10-H **B**, 12-H **B**,), 2.25 (s, 3 H, 11-Me **A**), 2.27 (s, 3 H, 11-Me **B**), 2.56 (dd, *J* = 11.7, 2.0 Hz, 1 H, 8-H **A**), 2.59 (br d, *J* = 10.7 Hz, 1 H, 2-H **B**), 2.82 (ddd, *J* = 11.7, 4.3, 1.6 Hz, 1 H, 8-H **B**), 2.95 (m, 5 H, 6-H′ **A**, 12-H′ **A**, 6-H′ **B**, 8-H′ **B**, 10-H **B**), 3.20 (d, *J* = 11.7 Hz, 1 H, 8-H′ **A**), 3.30 (d, *J* = 11.5 Hz, 1 H, 10-H′ **A**), 3.46 (d, *J* = 12.2 Hz, 1 H, 12-H′ **B**), 3.79 (t, *J* = 4.1 Hz, 1 H, 1-H **A**), 4.14 (t, *J* = 4.2 Hz, 1 H, 9-H **B**), 7.43 (m, 2 H **A**, 2 H **B**, PhH), 7.55 (m, 1 H **A**, 1 H **B**, PhH), 8.17 (m, 2 H **A**, PhH), 8.25 (m, 2 H **B**, PhH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.67 (CH_2 **B**), 24.70 (CH_2 **A**), 25.1 (CH_2 **B**), 25.2 (CH_2 **A**), 26.5 (CH_2 **B**), 27.8 (CH_2 **A**), 47.2 (11-Me **A**), 47.3 (11-Me **B**), 53.6 (C-12 **A**), 56.6 (C-12 **B**), 57.1 (C-6 **A**), 57.4 (C-10 **B**), 57.7 (C-8 **B**), 57.9 (C-6 **B**), 59.6 (C-8 **A**), 59.8 (C-10 **A**), 64.0 (C-2 **A**), 65.5 (C-2 **B**), 69.3 (C-9 **B**), 72.9 (C-1 **A**), 80.5 (C-9 **A**), 81.9 (C-1 **B**), 127.9 (PhH **A**), 128.0 (PhH **B**), 130.3 (PhH **A**), 130.6 (PhH **B**), 132.7 (PhH **A**), 132.8 (PhH **B**), 135.2 (PhH **A**), 135.5 (PhH **B**), 199.1 (C=O **B**), 200.7 (C=O **A**). IR (ATR): ν = 2934, 2852, 2763, 1674, 1446, 1266, 1099, 1054, 708, 689, 665 cm^{-1}. HRMS (ESI+): *m/z* calcd for $C_{18}H_{25}N_2O_2$ [M + H]$^+$: 301.1911; found: 301.1910.

Compound *rac*-**17**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3 H, 5-Me), 2.06 (d, *J* = 11.1 Hz, 1 H, 4-H), 2.21 (s, 3 H, 3-Me), 2.25 (dd, *J* = 11.0, 1.8 Hz, 1 H, 2-H), 2.42 (s, 3 H, 6-Me), 2.54 (dd, *J* = 11.1, 1.8 Hz, 1 H, 2-H′), 2.76 (d, *J* = 11.1 Hz, 1 H, 4-H′), 3.03 (dd, *J* = 8.3, 1.7 Hz, 1 H, 7-H), 3.05 (dd, *J* = 8.3, 5.4 Hz, 1 H, 7-H′), 4.32 (dq, *J* = 5.4, 1.8 Hz, 1 H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (5-Me), 37.1 (6-Me), 45.0 (3-Me), 57.8 (C-7), 58.2 (C-2), 62.3 (C-4), 73.0 (C-1), 92.7 (C-5). IR (ATR): ν = 2925, 2853, 1662, 1456, 1258, 1015, 854, 793 cm^{-1}. HRMS (ESI+): *m/z* calcd for $C_8H_{17}N_2O$ [M + H]$^+$: 157.1335; found: 157.1335.

(20) A dilithiation of **10A/B** followed by dideuteration, which would also explain the quantitative formation of **11**, but without relying on a high kinetic isotope effect, can be excluded since otherwise **11** should also had been formed in the lithiation–deuteration of **4**.

(21) For high kinetic isotope effects in (–)-sparteine(**1**)-mediated asymmetric deprotonations, see for example: (a) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. (b) Gallager, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092.

(22) **The Following Procedure is Representative: Rearrangement of Compound 4**
s-BuLi (3.30 mL, 4.59 mmol, 1.39 M in cyclohexane) was added at –78 °C to a solution of **4** (300 mg, 1.52 mmol) in anhyd Et_2O (10 mL). The reaction mixture was warmed to r.t. within 16 h, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (10 × 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Column chromatography (basic alumina, activity V, *n*-pentane–EtOAc = 6:1) delivered an inseparable 58:42 mixture of **18A** and **18B** (137 mg, 698 μmol, 46%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (m, 1 H, 3-H **A**), 1.18–1.40 (m, 4 H, 3-H′ **A**, 3-H **B**, 4-H **A**, 4-H **B**), 1.26 (s, 3 H, 1-Me **B**), 1.29 (s, 3 H, 9-Me **A**), 1.46–1.60 (m, 4 H, 3-H′ **B**, 5-H **A**, 5-H′ **A**, 5-H **B**), 1.66 (m, 1 H, 5-H′ **B**), 1.77 (m, 2 H, 4-H′ **A**, 4-H′ **B**), 1.88 (dd, *J* = 10.9, 2.3 Hz, 1 H, 2-H **B**), 2.03 (m, 1 H, 6-H **A**, 6-H **B**), 2.11 (dt, *J* = 11.7, 2.0 Hz, 1 H, 2-H **A**), 2.17 (d, *J* = 11.2 Hz, 1 H, 8-H **A**), 2.38 (dd, *J* = 11.4, 1.8 Hz, 1 H, 8-H **B**), 2.40 (s, 3 H, 11-Me **B**), 2.44 (s, 3 H, 10-Me **A**), 2.53 (dd, *J* = 11.1, 2.0 Hz, 1 H, 8-H′ **B**), 2.62 (dd, *J* = 8.9, 6.5 Hz, 1 H, 10-H **B**), 2.68 (d, *J* = 11.2 Hz, 1 H, 8-H′ **A**), 2.70 (m, 2 H, 6-H′ **A**, 6-H′ **B**), 2.91 (dd, *J* = 8.7, 6.4 Hz, 1 H, 11-H **A**), 3.15 (d, *J* = 8.8 Hz, 1 H, 11-H′ **A**), 3.41 (d, *J* = 9.0 Hz, 1 H, 10-H′ **B**), 3.97 (d, *J* = 6.5 Hz, 1 H, 1-H **A**), 4.27 (dt, *J* = 6.5, 2.0 Hz, 1 H, 9-H **B**). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3 (1-Me **B**), 19.8 (9-Me **A**), 24.1 (C-4 **A**), 24.2 (C-4 **B**), 24.9 (C-5 **B**), 25.4 (C-5 **A**), 26.3 (C-3 **B**), 26.7 (C-3 **A**), 37.5 (10-Me **A**), 40.7 (11-Me **B**), 54.3 (C-6 **A**), 55.16 (C-6 **B**, C-11 **A**), 58.8 (C-8 **B**), 60.1 (C-10 **B**), 62.3 (C-8 **A**), 63.3 (C-2 **A**), 71.4 (C-2 **B**), 72.2 (C-9 **B**), 76.9 (C-1 **A**), 93.5 (C-9 **A**), 96.0 (C-1 **B**). IR (ATR): ν = 2925, 2852, 2793, 1730, 1442, 1377, 1331, 1258, 1181, 1132, 823, 719, 607 cm^{-1} HRMS (ESI+): *m/z* calcd for $C_{11}H_{21}N_2O$ [M + H]$^+$: 197.1648; found: 197.1648.

(23) ^{13}C NMR and HRMS also indicate the formation of a small amount of a trideuterated species, the structure of which is unknown.

(24) The proposed β-elimination of **20A/B** to **21A/B** is comparable to the fragmentation of lithiated TMEDA, which provides $LiNMe_2$ and *N*,*N*-dimethylaminoethylene as intermediates, see: Köhler, F. H.; Hertkorn, N.; Blümel, J. *Chem. Ber.* **1987**, *120*, 2081.

(25) The proposed cyclization of **21A/B** to **22A/B** is similar to the LiHMDS/TMEDA-catalyzed hydroamination of electron-rich C–C double bonds, see: Horillo-Martinez, P.; Hultsch, K. C.; Gil, A.; Branchadell, V. *Eur. J. Org. Chem.* **2007**, 3311.

(26) According to preliminary quantum chemical calculations, the double chair conformation is highly favored for 2-*endo*-substituted 9-oxabispidines such as **3** and **4**. The same preference was found for the bispidines, see: (a) Galasso, V.; Goto, K.; Miyahara, Y.; Kovač, B.; Klasinc, L. *Chem. Phys.* **2002**, *277*, 229. (b) Galasso, V.; Asaro, F.; Berti, F.; Kovač, B.; Habuš, I.; Sacchetti, A. *Chem. Phys.* **2003**, *294*, 155.

(27) (a) Hoffmann, R.; Radom, L.; Pople, J. A.; Schleyer, P.v.R.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1972**, *94*, 6221. (b) Schleyer, P.v.R.; Kos, A. J. *Tetrahedron* **1983**, *39*, 1141. (c) Petillo, P. A.; Lerner, L. E. *ACS Symp. Ser.* **1993**, *539*, 156. (d) Lill, S. O. N.; Rauhaut, G.; Anders, E. *Chem. Eur. J.* **2003**, *9*, 3143; and references cited therein. (e) Karni, M.; Bernaconi, C. F.; Rappoport, Z. *J. Org. Chem.* **2008**, *73*, 2980; and references cited therein.

(28) Compound **24** was prepared from cycloocta-1,5-diene according to: Bordwell, F. G.; Douglass, M. L. *J. Am. Chem. Soc.* **1966**, *88*, 993.