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5-Substituted Derivatives of the Tricyclic (+)-Sparteine Surrogate in the Enantioselective Lithiation/Stannylation of an *O*-Alkyl Carbamate

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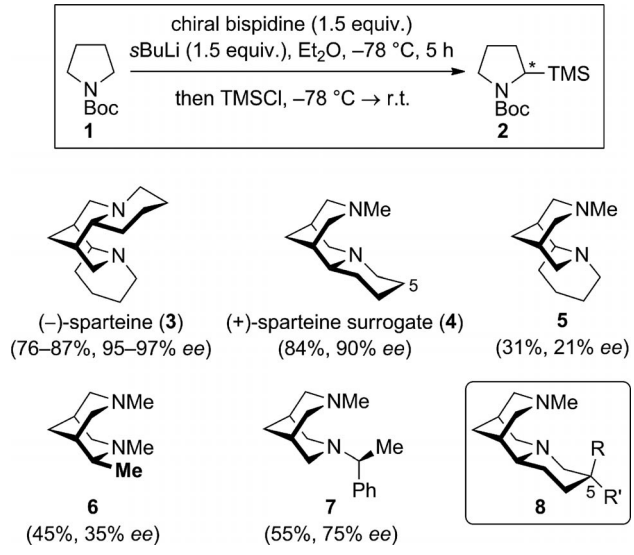
5-Mono- and 5,5-disubstituted tricyclic bispidines, derivatives of the known (+)-sparteine surrogate, have been synthesized in four-to-six steps from the natural alkaloid (–)-cytisine and evaluated as chiral ligands in the enantioselective lithiation/stannylation of an *O*-alkyl carbamate. Structure–selectivity studies revealed that a small 5-*endo* substituent is tolerated, whereas larger 5-*endo* substituents and even small 5-*exo* substituents lead to significantly reduced levels of chirality transfer.

Introduction

The natural tetracyclic bispidine (3,7-diazabicyclo[3.3.1]-nonane) (–)-sparteine (**3**, Scheme 1) is the ligand of choice for various asymmetric transformations,[1] in particular, for *s*BuLi-mediated enantioselective lithiation/electrophilic trapping reactions, including the recently developed enantioselective homologation of boronic esters.[2] The broad success of **3**, however, has been hampered by the restricted accessibility of its enantiomer, (+)-sparteine (*ent*-**3**),[3] which has triggered an intense search for modified and simplified derivatives,[4–14] finally culminating in the development of the tricyclic (+)-sparteine surrogate **4** by O'Brien and coworkers.[5,6,15,16] The stereodiscriminating power of bispidines has largely been investigated through studies of the enantioselective lithiation/silylation of *N*-Boc-pyrrolidine (**1**) discovered by Kerrick and Beak.[17] They revealed that the bispidine framework is superior to all other diamine structures tested,[7–10,18,19] and that the excellent 95–97% *ee* values obtained with (–)-sparteine (**3**) are still unrivalled.[10–13,17,20] In addition, these studies also provided some important information about the minimum structural requirements of a highly stereoselective bispidine, which showed that 1) the *endo*-fused piperidine ring of **3** plays a decisive role in chirality transfer, as is evident from the high asymmetric induction achieved with the (+)-sparteine surrogate **4** (90% *ee*)[6,9,13] and as supported by DFT calculations,[12,13] 2) the *exo*-fused ring of **3** is only of minor importance for chirality transfer (cf. **5**: 21% *ee*),[11] but it reduces the reactivity of **3** relative to that of **4**,[21] 3) substituents larger than the *N*-methyl group in **4** result in lower yields and enantioselectivities,[13] and 4) the rigidity of the 2-*endo*,3*N*-fused piperidine ring seems to be beneficial because none of the bicyclic bispidines tested so far, for example, **6** (35% *ee*)[12] and **7** (75% *ee*),[7] reached the excellent asymmetric inductions achieved with **3** and **4**.



Scheme 1. Chiral bispidines **3**–**7** in the enantioselective lithiation/silylation of *N*-Boc-pyrrolidine (**1**) and the targeted, modified (+)-sparteine surrogates **8**.

Surprisingly, the *endo*-fused piperidine ring in the (+)-sparteine surrogate **4** has not yet been modified,[22] despite its obviously decisive role in chirality transfer. In particular, substitutions at C-5 should be rewarding because they will significantly enhance the steric demand at the outermost carbon atom, which might exert a strong effect on the asymmetric induction. In this full paper we present the synthesis of the novel 5-mono- and 5,5-disubstituted deriva-

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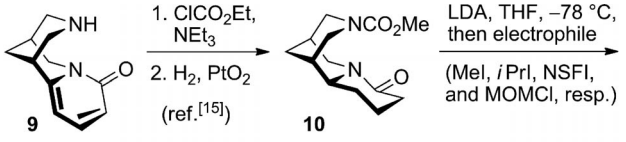
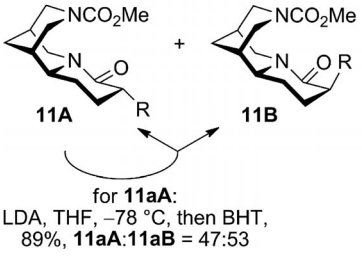
tives **8** of the tricyclic bispidine **4** and their application as chiral ligands in the enantioselective lithiation/stannylation of an *O*-alkyl carbamate.

Results and Discussion

Synthesis of the Bispidines 8

The synthesis of the 5-substituted bispidines **8** was straightforward from the natural alkaloid (–)-cytisine (**9**, Scheme 2), which can be isolated in good quantities from the seeds of the Golden Rain tree, *Laburnum anagyroides*.[15] Protection of the secondary amino group and hydrogenation of the annulated pyridone according to a known protocol[15] afforded the key intermediate, the lactam **10**. The required substituents at the 5-position were introduced by deprotonation of **10** with LDA and subsequent electrophilic trapping of the amide enolate with MeI, *i*PrI, NSFI [*N*-fluorobis(phenylsulfonyl)amide], or MOMCl (methoxymethyl chloride). The attack occurred preferentially from the sterically less hindered *exo* side, thus leading to diastereomeric mixtures with the *exo* isomer **11A**[23] prevailing over the *endo* isomer **11B** (**11A**:**11B** > 90:10, except for **11a**: **11aA**/**11aB** = 75:25). The major diastereomers **11A** were obtained in analytically pure form by column chromatography; in the case of **11aA**/**11aB**, both diamines could be isolated. Larger quantities of **11aB**, the minor *endo* product of the methylation of **10**, were accessible by epimerization of **11aA** by deprotonation and reprotonation with BHT (2,6-di-*tert*-butyl-4-methylphenol) as a sterically demanding proton source, giving a 47:53 mixture of **11aA** and **11aB**.



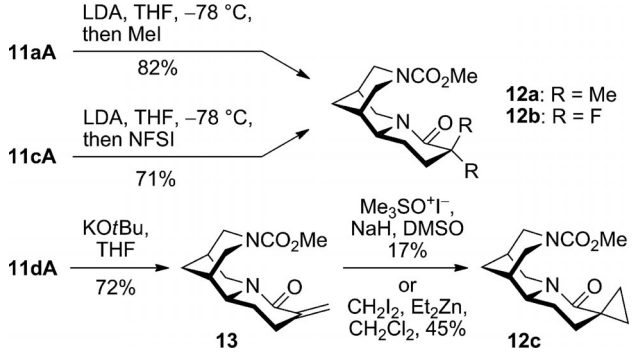


11	R	Yield 11A [%][a]
a	Me	59[b]
b	*i*Pr	51
c	F	77
d	CH_2OMe	73

[a] Isolated yield of the diastereomerically pure compound. [b] Isolated yield of **11aB**: 14%.

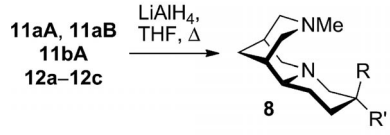
Scheme 2. Synthesis of the 5-monosubstituted tricyclic bispidinones **11a**–**11d** [NSFI = *N*-fluorobis(phenylsulfonyl)amide, MOMCl = methoxymethyl chloride, BHT = 2,6-di-*tert*-butyl-4-methylphenol].

The 5,5-disubstituted bispidine lactams **12a** (R = Me) and **12b** (R = F) were prepared from the corresponding 5-monosubstituted derivatives **11aA** and **11cA** by a subsequent deprotonation/electrophilic trapping sequence (Scheme 3). Transformation of **11dA** into the tetracyclic spiro compound **12c** required two steps, base-induced elimination of methanol to give the alkene **13** and cyclopropanation of the double bond. Under Corey–Chaykovsky conditions with $Me_3SO^+I^-$/NaH in DMSO, the product **12c** was obtained in a low yield of 17% as a result of decomposition of the starting material. Simmons–Smith cyclopropanation of **13** with CH_2I_2/Et_2Zn provided only partial conversion to **12c**, even in the presence of a large excess of CH_2I_2/Et_2Zn. Because all attempts to separate **12c** from **13** were unsuccessful, the resulting mixture of **12c**/**13** was twice re-subjected to these cyclopropanation conditions. This procedure ensured complete consumption of **13**, although the isolated yield of 45% was **12c** was low.



Scheme 3. Synthesis of the 5,5-disubstituted tricyclic bispidine lactams **12a**–**c**.

Final reduction of the bispidine lactams **11aA**, **11aB**, **11bA**, and **12a**–**c** with $LiAlH_4$ in THF at reflux afforded the target bispidines **8a**–**8f** in good-to-high yields (Scheme 4).



8	R	R'	Yield [%][a]
a	H	Me	70
b	H	*i*Pr	93
c	Me	H	79
d	Me	Me	90
e	F	F	71
f	$-CH_2-CH_2-$		84

[a] Isolated yield.

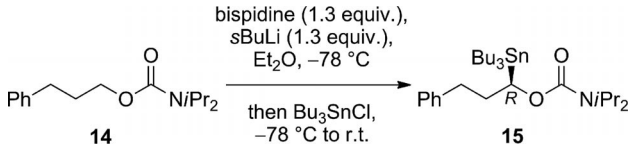
Scheme 4. Reduction of the bispidine lactams to the bispidines **8a**–**f**.

Enantioselective Deprotonation Reactions

Among the enantioselective deprotonation/electrophilic trapping reactions of *O*-alkyl carbamates, which were pioneered and developed by Hoppe and co-workers,[1,24] the lithiation/stannylation of **14** (Table 1) serves as a model reaction for the evaluation of new chiral diamines. This reaction is known to proceed under virtually complete stereocontrol (97–98% *ee*) in the presence of (–)-sparteine (**3**),[10,16,25,26] and provides high *ee* values of 90–92% with the (+)-sparteine surrogate **4**.[6,25] Typically, the chiral bispidine–*s*BuLi adduct is formed first by mixing equimolar amounts of the bispidine and *s*BuLi at –78 °C in Et_2O, then the substrate

14 is added and, after 4 h, the electrophile Bu_3SnCl, which traps the generated chiral α-lithio-carbamate.

Table 1. Lithiation/stannylation of the carbamate **14** in the presence of chiral bispidines.



Entry	Bispidine	Yield [%][a]	*ee* [%][b]	Configuration
1[c]	**3**	68–73	97–98	*S*
2[d]	**4**	84	90–92	*R*
3	**8a**	66	92	*R*
4	**8b**	64	51	*R*
5	**8c**	70	79	*R*
6	**8d**	71	34	*R*
7	**8e**	66	40	*R*
8	**8f**	68	65	*R*

[a] Isolated yields. [b] Determined by HPLC analysis on a chiral phase. [c] Data from ref.[6,14,25,26] [d] Data from ref.[6,25]

We tested our modified tricyclic bispidines first by using the 5-*exo*-methyl derivative **8a**,[23] which afforded (*R*)-**15** with an excellent 92% *ee* and good 66% yield. Because the stereodiscrimination is identical to that obtained with the known (+)-sparteine surrogate **4**, we initially assumed that a 5-*exo* substituent exerts only a minor effect on chirality transfer because it points away from the active *s*BuLi binding site between the two nitrogen atoms. The mediocre 51% *ee* reached with the 5-*exo*-isopropyl derivative **8b**,[23] however, contradicts this; a bulkier substituent at the 5-*exo*-position does have a significant and negative impact on the *ee*. A clear trend can be seen for the 5-*endo*-substituted bispidines **8c**–**f**: The enantiomeric excess of **15** rapidly drops with increasing size of the substituent and even small atoms such as fluorine in **8e** or the spiro-fused cyclopropyl group in **8f** result in significantly lower enantioselectivities (40 and 65% *ee*, respectively). Thus, the sterically least demanding CH_2 group as found in the (+)-sparteine surrogate (**4**) seems to be optimal; any substitution at this position is unfavorable with respect to chirality transfer.

The large difference in the asymmetric inductions achieved with the 5,5-dimethylated bispidine **8d** (34% *ee*) and the 5-*endo*-monomethylated derivative **8c** (79% *ee*) is surprising because both bispidines carry the same methyl substituent at the 5-*endo* position. However, it might be explained by the conformation of the fused piperidine ring in the pre-lithiation complex **16** (bispidine·*s*BuLi·complex, Figure 1),[27,28] which precedes the decisive lithiation step. For **8d** (and also for all other 5,5-di- and 5-*exo*-monosubstituted bispidines), it is very likely that this ring adopts the usual chair conformation (or a slightly distorted one) as shown in **16A**, whereas a twist-boat geometry of the fused piperidine ring as in **16B** might be energetically favorable in the case of the 5-*endo*-methyl-substituted bispidine **8c** (R = Me, R′ = H in **16**)[29] because this conformation allows the otherwise axially oriented methyl group to slip into a pseudo-equatorial position, which also reduces its steric demand at the active site. Thus, the real steric requisite of the methyl group in **8c** would lie in between that of an equatorial one (as in **8a**) and a truly axially one (as in **8d**), which is in good agreement with the experimentally observed decrease in the asymmetric inductions.

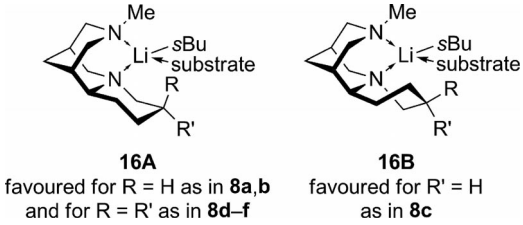


Figure 1. Proposed conformations of the fused piperidine ring in the prelithiation complexes **16A** and **16B**.

Conclusions

The novel 5-mono- and 5,5-disubstituted tricyclic bispidines **8a**–**f**, derivatives of the well-known (+)-sparteine surrogate **4**, have been prepared in four-to-six simple steps from the natural product (–)-cytisine (**9**) and their potential as chiral diamines evaluated in the enantioselective lithiation/stannylation of *O*-alkyl carbamate **14**. An excellent 92% *ee* was reached with the 5-*exo*-methyl-substituted bispidine **8a**, but larger 5-*exo* substituents, as in **8b**, and even small 5-*endo* substituents, as in **8c**–**f**, cause a strong decrease in enantioselectivity. Consequently, the unsubstituted methylene group, as present in the (+)-sparteine surrogate **4**, is confirmed as being crucial for high asymmetric inductions.

Experimental Section

General: All reactions with moisture-sensitive reagents and dry solvents were performed under argon in flame-dried glassware. Anhydrous THF, Et_2O, CH_2Cl_2, and DMSO were prepared by using standard procedures.[30] Commercially available reagents (highest quality available) were used as received. The bispidine lactam **10** was prepared according to ref.[15] from the natural alkaloid (–)-cytisine (**9**), which was isolated from the seeds of *Laburnum anagyroides*.[15] All reactions were monitored by TLC on precoated silica gel (Merck F254); spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$. Silica gel (Merck, particle size 63–200 μm) was used for column chromatography.

Melting points were measured with a Reichert–Kofler Heiztisch microscope. Optical rotations ($[\alpha]_D^T$) were recorded with a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were recorded with a Bruker Avance 400 instrument and calibrated by using residual non-deuteriated solvent as internal reference. The peak assignments in the ^1H and ^{13}C NMR spectra were made on the basis of 2D NMR experiments (COSY, HSQC, HMBC). IR spectra were recorded with a Jasco FT-IR-3410 spectrometer and HRMS with a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization).

General Procedure (GP1) for the Substitution of the Bispidine Lactams at the 5-Position: LDA (2.3 equiv.) was freshly prepared by deprotonation of iPr_2NH (2.5 equiv.) in dry THF (1 mL/mmol iPr_2NH) with *n*BuLi (2.3 equiv.) at –78 °C and room temp.

(30 min each). A solution of the lactam (1.0 equiv.) in dry THF (10 mL/mmol lactam) was added at –78 °C and, after 1–2 h of stirring, the electrophile (2.0–3.0 equiv.). The reaction mixture was warmed to room temp. over 16 h, quenched with water (25 mL/mmol lactam), and extracted with EtOAc (5× 25 mL/mmol lactam). The combined organic layers were washed with brine (25 mL/mmol lactam), dried with $MgSO_4$, and the solvents evaporated. Column chromatography (silica gel, EtOAc/MeOH, 100:0→ 90:10) delivered the 5-substituted bispidine lactam.

Methyl (1*R*,2*S*,5*R*,9*R*)-5-Methyl-6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]-tridecane-11-carboxylate (11aA) and Methyl (1*R*,2*S*,5*S*,9*R*)-5-Methyl-6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane-11-carboxylate (11aB): According to the general procedure GP1, bispidine lactam **10** (3.08 g, 12.2 mmol) was methylated with MeI (2.29 mL, 5.20 g, 36.6 mmol) to give the 5-*endo*-methylated bispidine **11aB** (faster eluting, 455 mg, 1.71 mmol, 14%) and the 5-*exo*-methylated bispidine **11aA** (slower eluting, 1.92 g, 7.20 mmol, 59%) as yellowish solids. The initial *dr* **11aA/11aB**, determined by ^{1}H NMR of the crude product, was 75:25.

11aA: M.p. 69 °C. $[\alpha]_D^{21}$ = –114.2 (MeOH, *c* = 0.27). IR (ATR): $\tilde{\nu}$ = 2933, 2856, 1687, 1631, 1434, 1411, 1227, 1011, 764, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 83:17 mixture of rotamers): δ = 4.67 (d, *J* = 13.8 Hz, 1 H, 8-H), 4.53 (d, *J* = 13.9 Hz, 0.83 H, 12-H_{rot1}), 4.30 (br. d, *J* = 13.8 Hz, 0.17 H, 12-H_{rot2}), 4.18 (br. d, *J* = 12.8 Hz, 0.17 H, 10-H_{rot2}), 4.10 (d, *J* = 13.3 Hz, 0.83 H, 10-H_{rot1}), 3.58 (s, 0.5 H, OMe_{rot2}), 3.50 (s, 2.5 H, OMe_{rot1}), 3.40 (br. d, *J* = 11.8 Hz, 1 H, 2-H), 2.99 (d, *J* = 13.4 Hz, 0.83 H, 10-H), 2.96–2.81 (m, 0.34 H, 10-H_{rot2}, 12-H_{rot2}), 2.78 (dd, *J* = 13.9, 2.0 Hz, 0.83 H, 12-H_{rot1}), 2.70 (d, *J* = 13.7 Hz, 1 H, 8-H), 2.31 (m, 1 H, 5-H_{ax}), 2.15 (qd, *J* = 12.8, 2.9 Hz, 1 H, 3-H), 1.90–1.65 (m, 5 H, 3-H, 4-H, 9-H, 13-H_2), 1.55 (br. s, 1 H, 1-H), 1.33 (qd, *J* = 13.0, 2.6 Hz, 1 H, 4-H_{ax}), 1.06 (d, *J* = 7.0 Hz, 3 H, 5-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, only signals of the major rotamer given): δ = 172.8 (C-6), 155.9 (CO_2), 59.9 (C-2), 52.4 (OMe), 48.9 (C-10), 46.0 (C-8), 44.1 (C-12), 36.6 (C-5), 33.05 (C-1), 33.03 (C-13), 28.8 (C-4), 27.7 (C-9), 27.5 (C-3), 17.0 (5-Me) ppm. HRMS (ESI): calcd. for $C_{14}H_{22}N_2NaO_3$ [M + Na]$^+$ 289.1523; found 289.1523.

The ^{1}H NMR splitting pattern of the proton 4-H_{ax} includes a large quartet (*J* = 13.0 Hz), which must originate from a geminal coupling with 4-H_{eq}, a 1,3-diaxial coupling with 3-H_{ax}, and a 1,3-diaxial coupling with 5-H_{ax}. The latter relation proves the equatorial and thus *exo* orientation of the 5-methyl group.

11aB: M.p. 73 °C. $[\alpha]_D^{21}$ = –96.9 (MeOH, *c* = 0.26). IR (ATR): $\tilde{\nu}$ = 2862, 1689, 1608, 1429, 1231, 935, 762 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 79:21 mixture of rotamers): δ = 4.64 (br. d, *J* = 13.7 Hz, 1 H, 8-H), 4.53 (d, *J* = 14.0 Hz, 0.79 H, 12-H_{rot1}), 4.33 (d, *J* = 14.0 Hz, 0.21 H, 12-H_{rot2}), 4.11 (d, *J* = 13.4 Hz, 1 H, 10-H), 3.61 (s, 0.63 H, OMe_{rot2}), 3.57 (s, 2.37 H, OMe_{rot1}), 3.40 (br. d, *J* = 10.1 Hz, 1 H, 2-H), 3.02 (d, *J* = 13.1 Hz, 1 H, 10-H), 2.80 (m, 1 H, 12-H), 2.77 (dt, *J* = 13.7, 2.7 Hz, 1 H, 8-H), 2.45 (m, 1 H, 5-H), 2.16 (m, 1 H, 3-H), 1.93–1.72 (m, 4 H, 4-H, 9-H, 13-H_2), 1.69–1.56 (m, 3 H, 1-H, 3-H, 4-H), 1.20 (d, *J* = 7.4 Hz, 3 H, 5-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, only signals of the major rotamer given): δ = 173.8 (C-6), 155.4 (CO_2), 59.3 (C-2), 52.4 (OMe), 48.6 (C-10), 46.2 (C-8), 44.1 (C-12), 36.1 (C-5), 33.1 (C-1), 32.7 (C-13), 27.7 (C-9), 26.6 (C-4), 23.5 (C-3), 18.7 (5-Me) ppm. HRMS (ESI): calcd. for $C_{14}H_{22}N_2NaO_3$ [M + Na]$^+$ 289.1523; found 289.1521.

Methyl (1*R*,2*S*,5*S*,9*R*)-5-Isopropyl-6-oxo-7,11-diazatricyclo-[7.3.1.0^{2,7}]tridecane-11-carboxylate (11bA): Bispidine lactam **10** (500 mg, 1.98 mmol) was treated with *i*PrI (594 µL, 1.01 g, 5.94 mmol) according to the general procedure GP1, yielding bispidine **11bA** (297 mg, 1.01 mmol, 51%) as a colorless oil. $[\alpha]_D^{21}$ = –124.0 (MeOH, *c* = 0.52). IR (ATR): $\tilde{\nu}$ = 2952, 2866, 1691, 1628, 1443, 1234, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 83:17 mixture of rotamers): δ = 4.79 (d, *J* = 14.0 Hz, 1 H, 8-H), 4.59 (d, *J* = 14.0 Hz, 0.83 H, 12-H_{rot1}), 4.38–4.22 (m, 0.34 H, 10-H_{rot2}, 12-H_{rot2}), 4.19 (d, *J* = 13.4 Hz, 0.83 H, 10-H_{rot1}), 3.66 (s, 0.51 H, OMe_{rot2}), 3.59 (s, 2.49 H, OMe_{rot1}), 3.44 (dt, *J* = 11.2, 3.2 Hz, 1 H, 2-H), 3.07 (br. d, *J* = 13.4 Hz, 0.83 H, 10-H_{rot1}), 3.02–2.88 (m, 0.34 H, 10-H_{rot2}, 12-H_{rot2}), 2.85 (dd, *J* = 14.0, 1.9 Hz, 0.83 H, 12-H_{rot1}), 2.78 (d, *J* = 13.8 Hz, 1 H, 8-H), 2.55 (m, 1 H, C*H*Me_2), 2.26 (m, 1 H, 5-H_{ax}), 2.16 (m, 1 H, 3-H), 1.76 (m, 5 H, 3-H, 4-H, 9-H, 13-H_2), 1.64 (br. s, 1 H, 1-H), 1.42 (br. q, *J* ≈ 13 Hz, 1 H, 4-H_{ax}), 0.92 (d, *J* = 7.1 Hz, 3 H, CH*Me*), 0.75 (d, *J* = 6.8 Hz, 3 H, CH*Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, only signals of the major rotamer given): δ = 171.6 (C-6), 156.0 (CO_2), 59.4 (C-2), 52.6 (OMe), 49.1 (C-10), 47.3 (C-5), 45.8 (C-8), 44.3 (C-12), 33.3 (C-1), 33.1 (C-13), 27.84 (C-9), 27.80 (*C*HMe_2), 27.4 (C-3), 20.3 (CH*Me*), 19.7 (C-4), 17.8 (CH*Me*) ppm. HRMS (ESI): calcd. for $C_{16}H_{26}N_2NaO_3$ [M + Na]$^+$ 317.1836; found 317.1835.

The ^{1}H NMR splitting pattern of the proton 4-H_{ax} includes a large quartet (*J* ≈ 13 Hz), which must originate from a geminal coupling with 4-H_{eq}, a 1,3-diaxial coupling with 3-H_{ax}, and a 1,3-diaxial coupling with 5-H_{ax}. The latter relation proves the equatorial and thus *exo* orientation of the 5-isopropyl group.

Methyl (1*R*,2*S*,5*R*,9*R*)-5-Fluoro-6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]-tridecane-11-carboxylate (11cA): According to the general procedure GP1, bispidine lactam **10** (1.00 g, 3.96 mmol) was fluorinated with NFSI (2.50 g, 7.92 mmol) to give bispidine **11cA** (824 mg, 3.05 mmol, 77%) as a yellowish solid, m.p. 132 °C. $[\alpha]_D^{21}$ = –103.6 (MeOH, *c* = 0.25). IR (ATR): $\tilde{\nu}$ = 2928, 2863, 1679, 1643, 1443, 1238, 1074, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 88:12 mixture of rotamers): δ = 4.86 (ddd, *J* = 47.9, 11.6, 5.9 Hz, 0.88 H, 5-$H_{ax,rot1}$), 4.58 (d, *J* = 13.9 Hz, 1 H, 8-H), 4.70–4.53 (m, 0.12 H, 5-$H_{ax,rot2}$), 4.51 (d, *J* = 14.1 Hz, 0.88 H, 12-H_{rot1}), 4.38–4.19 (m, 0.24 H, 10-H_{rot2}, 12-H_{rot2}), 4.14 (d, *J* = 12.4 Hz, 0.88 H, 10-H_{rot1}), 3.59 (s, 0.36 H, OMe_{rot2}), 3.54 (s, 2.64 H, OMe_{rot1}), 3.45 (br. d, *J* = 10.9 Hz, 1 H, 2-H), 3.03 (d, *J* = 13.5 Hz, 1 H, 10-H), 2.95–2.75 (m, 2 H, 8-H, 12-H), 2.38–2.10 (m, 2 H, 3-H, 4-H), 1.99–1.66 (m, 5 H, 3-H, 4-H, 9-H, 13-H_2), 1.59 (s, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, only signals of the major rotamer given): δ = 166.9 (d, *J* = 20.0 Hz, C-6), 156.1 (CO_2), 85.8 (d, *J* = 180 Hz, C-5), 59.2 (C-2), 52.6 (OMe), 49.1 (C-10), 46.0 (C-8), 44.1 (C-12), 32.9 (C-13), 32.8 (C-1), 27.3 (C-9), 26.8 (d, *J* = 20.0 Hz, 4-C), 23.8 (d, *J* = 11.9 Hz, 3-C) ppm. HRMS (ESI): calcd. for $C_{13}H_{19}FN_2NaO_3$ [M + Na]$^+$ 293.1272; found 293.1272.

The ^{1}H NMR splitting pattern of the proton 5-$H_{ax,rot1}$ includes a doublet with *J* = 11.6 Hz, which must originate from a 1,3-diaxial coupling with 4-H_{ax}. This relation proves the equatorial and thus *exo* orientation of the 5-fluoride substituent.

Methyl (1*R*,2*S*,5*S*,9*R*)-5-(Methoxymethyl)-6-oxo-7,11-diazatricyclo-[7.3.1.0^{2,7}]tridecane-11-carboxylate (11dA): Bispidine lactam **10** (1.50 g, 5.94 mmol) was treated with MOMCl (1.3 mL, 1.20 g, 14.9 mmol) according to the general procedure GP1, affording bispidine **11dA** (1.28 g, 4.32 mmol, 73%) as a yellowish oil. $[\alpha]_D^{21}$ = –108.7 (MeOH, *c* = 0.26). IR (ATR): $\tilde{\nu}$ = 2862, 1689, 1622, 1443, 1235, 1103, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 76:24 mixture of rotamers): δ = 4.76 (d, *J* = 13.9 Hz, 0.76 H, 8-H_{rot1}), 4.69 (br. d, *J* = 13.2 Hz, 0.24 H, 8-H_{rot2}), 4.60 (d, *J* = 14.0 Hz, 0.76 H, 12-H_{rot1}), 4.54 (br. d, *J* = 14.5 Hz, 0.24 H, 12-H_{rot2}), 4.19 (br. d, *J* = 14.7 Hz, 1 H, 10-H), 3.71 (dd, *J* = 8.9, 6.3 Hz, 1 H, CH*H*OMe), 3.68–3.54 (m, 4 H, C*H*HOMe, CO_2Me), 3.48 (m, 1 H, 2-H), 3.36 (s, 0.72 H, CH_2OMe_{rot2}), 3.32 (s, 2.28 H, CH_2OMe_{rot1}), 3.06 (m, 1 H, 10-H), 2.97–2.76 (m, 2 H, 8-H, 12-H), 2.70 (m, 0.24 H, 5-

$H_{ax,rot2}$), 2.53 (m, 0.76 H, 5-$H_{ax,rot1}$), 2.22 (m, 1 H, 3-H), 2.09–1.78 (m, 5 H, 3-H, 4-H, 9-H, 13-H_2), 1.75–1.57 (m, 2 H, 1-H, 4-H_{ax}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, only signals of the major rotamer given): δ = 170.0 (C-6), 156.1 (CO_2), 73.0 (OCH_2), 59.6 (C-2), 58.9 (CH_2O*Me*), 52.6 (CO_2*Me*), 49.2 (C-10), 45.9 (C-8), 44.3 (C-12), 42.3 (C-5), 33.3 (C-1), 33.2 (C-13), 27.9 (C-9), 27.3 (C-3), 23.7 (C-4) ppm. HRMS (ESI): calcd. for $C_{15}H_{24}N_2NaO_4$ [M + Na]$^+$ 319.1628; found 319.1628.

In the ^{1}H–^{1}H COSY NMR spectrum, the cross peak 4-H_{ax}/5-H_{ax} shows a quartet with a coupling constant of J = 13.1 Hz for 4-H_{ax}. This quartet must originate from a geminal coupling with 4-H_{eq}, a 1,3-diaxial coupling with 3-H_{ax}, and a 1,3-diaxial coupling with 5-H_{ax}. The latter relation proves the equatorial and thus *exo* orientation of the 5-methoxymethyl group.

Epimerization of 11aA: According to the general procedure GP1, bispidine lactam **11aA** (1.80 g, 6.76 mmol) was deprotonated and re-protonated with BHT (3.72 g, 16.9 mmol) to give the 5-*endo*-methylated bispidine **11aB** (faster eluting, 756 mg, 2.84 mmol, 42%) and the 5-*exo*-methylated bispidine **11aA** (slower eluting, 846 mg, 3.18 mmol, 47%) as slightly brownish solids. The initial *dr* **11aA/11aB**, determined by ^{1}H NMR of the crude product, was 47:53.

Methyl (1*R*,2*S*,9*R*)-5,5-Dimethyl-6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane-11-carboxylate (12a): Bispidine lactam **11aA** (900 mg, 3.38 mmol) was methylated with MeI (633 μL, 1.44 g, 10.1 mmol) according to the general procedure GP1, delivering bispidine **12a** (777 mg, 2.77 mmol, 82%) as a yellowish oil. $[\alpha]_D^{21}$ = –77.3 (MeOH, *c* = 0.60). IR (ATR): $\tilde{\nu}$ = 2921, 2860, 1691, 1626, 1445, 1235, 1141, 766 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 80:20 mixture of rotamers): δ = 4.63 (d, J = 13.7 Hz, 1 H, 8-H), 4.56 (br. d, J = 14.0 Hz, 0.80 H, 12-H_{rot1}), 4.56 (br. d, J = 12.8 Hz, 0.20 H, 12-H_{rot2}), 4.17 (m, 0.20 H, 10-H_{rot2}), 4.11 (d, J = 13.1 Hz, 0.80 H, 10-H_{rot1}), 3.62 (s, 0.60 H, OMe_{rot2}), 3.58 (s, 2.40 H, OMe_{rot1}), 3.43 (br. d, J = 11.3 Hz, 1 H, 2-H), 3.03 (br. d, J = 13.1 Hz, 1 H, 10-H), 2.84 (d, J = 13.9 Hz, 1 H, 12-H), 2.78 (dm, J = 13.8 Hz, 1 H, 8-H), 2.20 (m, 1 H, 3-H), 2.04–1.78 (m, 3 H, 9-H, 13-H_2), 1.72–1.56 (m, 4 H, 1-H, 3-H, 4-H_2), 1.17 (s, 2.4 H, 5-Me_{rot1}), 1.14 (s, 3 H, 5-Me), 1.12 (s, 0.6 H, 5-Me_{rot2}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, only signals of the major rotamer given): δ = 176.3 (C-6), 155.6 (CO_2), 59.8 (C-2), 52.5 (OMe), 48.8 (C-10), 46.6 (C-8), 44.2 (C-12), 38.4 (C-5), 35.0 (C-4), 33.3 (C-1), 32.5 (C-13), 28.3 (5-Me), 27.9 (C-9), 27.3 (5-Me), 24.4 (C-3) ppm. HRMS (ESI): calcd. for $C_{15}H_{25}N_2O_3$ [M + H]$^+$ 281.1860; found 281.1860.

Methyl (1*R*,2*S*,9*R*)-5,5-Difluoro-6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]-tridecane-11-carboxylate (12b): According to the general procedure GP1, bispidine lactam **11cA** (750 mg, 2.77 mmol) was fluorinated with NFSI (1.75 g, 5.55 mmol) to give bispidine **12b** (567 mg, 1.97 mmol, 71%) as a yellowish solid, m.p. 105 °C. $[\alpha]_D^{21}$ = –83.6 (MeOH, *c* = 0.25). IR (ATR): $\tilde{\nu}$ = 2923, 2865, 1692, 1660, 1445, 1236, 1125, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 68:32 mixture of rotamers): δ = 4.61 (d, J = 13.8 Hz, 1 H, 8-H), 4.55 (d, J = 14.0 Hz, 0.68 H, 12-H_{rot1}), 4.37 (d, J = 14.2 Hz, 0.32 H, 12-H_{rot2}), 4.32 (d, J = 13.9 Hz, 0.32 H, 10-H_{rot2}), 4.17 (d, J = 13.3 Hz, 0.68 H, 10-H_{rot1}), 3.63 (s, 0.96 H, OMe_{rot2}), 3.60 (s, 2.04 H, OMe_{rot1}), 3.55 (m, 1 H, 2-H), 3.08 (d, J = 13.2 Hz, 1 H, 10-H_{rot1}), 2.93 (d, J = 13.7 Hz, 1 H, 8-H_{rot1}), 3.03–2.89 (m, 0.64 H, 8-H_{rot2}, 10-H_{rot2}), 2.87 (d, J = 13.9 Hz, 1 H, 12-H), 2.54–2.18 (m, 2 H, 3-H, 4-H), 2.14–1.80 (m, 5 H, 3-H, 4-H, 9-H, 13-H_2), 1.74 (m, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, only signals of the major rotamer given): δ = 161.7 (t, J = 29.7 Hz, C-6), 155.5 (CO_2), 112.2 (t, J = 244 Hz, C-5), 58.8 (C-2), 52.7 (OMe), 48.6 (C-10), 46.8 (C-8), 44.2 (C-12), 33.1 (C-1), 32.3 (C-13), 30.7 (t, J = 23.0 Hz, C-4), 27.4 (C-9), 23.3 (d, J = 9.3 Hz, C-3) ppm. HRMS (ESI): calcd. for $C_{13}H_{18}F_2N_2NaO_3$ [M + Na]$^+$ 311.1178; found 311.1178.

Methyl (1*R*,2*S*,9*R*)-5-Methylene-6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane-11-carboxylate (13): A solution of lactam **11dA** (600 mg, 2.02 mmol) in dry THF (8 mL) was treated with KO*t*Bu (274 mg, 2.43 mmol) at –78 °C. The reaction mixture was warmed to room temp. over 16 h and the solvents evaporated. Colum chromatography (silica gel, EtOAc/MeOH, 100:0→ 90:10) delivered alkene **13** (385 mg, 1.46 mmol, 72%) as a yellowish solid, m.p. 100 °C. $[\alpha]_D^{23}$ = –103.6 (MeOH, *c* = 0.29). IR (ATR): $\tilde{\nu}$ = 2911, 2855, 1690, 1605, 1429, 1310, 1231, 934, 761 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 75:25 mixture of rotamers): δ = 6.05 (s, 1 H, C=CH), 5.20 (s, 1 H, C=CH), 4.80 (d, J = 13.8 Hz, 1 H, 8-H), 4.53 (d, J = 13.9 Hz, 0.75 H, 12-H_{rot1}), 4.33 (br. d, J = 13.8 Hz, 0.5 H, 10-H_{rot2} 12-H_{rot2}), 4.18 (d, J = 13.4 Hz, 0.75 H, 10-H_{rot1}), 3.56 (s, 3 H, OMe), 3.55 (m, 1 H, 2-H), 3.06 (br. d, J = 13.3 Hz, 0.75 H, 10-H_{rot1}), 2.99 (br. d, J = 13.9 Hz, 0.25 H, 10-H_{rot2}), 2.89 (br. d, J = 14.0 Hz, 1 H, 8-H), 2.83 (dd, J = 14.0, 2.0 Hz, 1 H, 12-H), 2.63 (dt, J = 14.1, 3.2 Hz, 1 H, 4-H), 2.36 (m, 1 H, 4-H), 2.22 (m, 1 H, 3-H), 2.09–1.77 (m, 4 H, 3-H, 9-H, 13-H_2), 1.68 (br. s, 0.75 H, 1-H_{rot1}), 1.63 (br. s, 0.25 H, 1-H_{rot2}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, only signals of the major rotamer given): δ = 164.2 (C-6), 155.9 (CO_2), 138.2 (*C*=CH_2), 120.5 (C=*C*H_2), 59.4 (C-2), 52.6 (OMe), 49.0 (C-10), 46.3 (C-8), 44.4 (C-12), 33.5 (C-1), 32.8 (C-13), 29.0 (C-4), 27.9 (C-9), 27.7 (C-3) ppm. HRMS (ESI): calcd. for $C_{14}H_{20}N_2NaO_3$ [M + Na]$^+$ 287.1366; found 287.1366.

Methyl (1*R*,2*S*,9*R*)-6-Oxo-7,11-diazaspiro[tricyclo[7.3.1.0^{2,7}]tridecane-5,1′-cyclopropane]-11-carboxylate (12c)

Method A – Corey–Chaykovsky Cyclopropanation: $Me_3SO^+I^-$ (83.3 mg, 378 μmol) in dry DMSO (500 μL) was deprotonated with NaH (9.0 mg, 378 μmol) at room temp. for 1 h. Alkene **13** (50 mg, 189 μmol) was added and stirring at room temp. was continued for 15 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (4× 15 mL). Drying with $MgSO_4$ and column chromatography (silica gel, EtOAc/MeOH, 100:0→ 90:10) afforded the spirocyclic product **12c** (9.0 mg, 32.3 μmol, 17%) as a yellowish oil.

Method B – Simmons–Smith Cyclopropanation: Alkene **13** (195 mg, 738 μmol) was dissolved in dry CH_2Cl_2 (10 mL) and $ZnEt_2$ (1.0 M in *n*-hexane, 2.21 mL, 2.21 mmol) and CH_2I_2 (298 μL, 988 mg, 3.69 mmol) were added at 0 °C. After 16 h at room temp., a further batch of $ZnEt_2$ (1.0 M in *n*-hexane, 2.21 mL, 2.21 mmol) and CH_2I_2 (298 μL, 988 mg, 3.69 mmol) was added at 0 °C. The reaction mixture was stirred for 16 h at room temp., quenched with HCl (1 N, 20 mL), basified with NaOH (1 N), and extracted with CH_2Cl_2 (3× 30 mL). The combined organic layers were washed with brine (20 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure to give a mixture of alkene **13** and product **12c**, which was purified by column chromatography (silica gel, EtOAc/MeOH, 100:0→ 90:10). Because **13** and **12c** could not be separated by chromatography, the cyclopropanation procedure described above was repeated twice, until no more alkene **13** was left. The pure product **12c** (92.4 mg, 332 μmol, 45%) was obtained as a slightly yellowish oil. $[\alpha]_D^{21}$ = –31.1 (MeOH, *c* = 0.25). IR (ATR): $\tilde{\nu}$ = 2930, 2862, 1694, 1626, 1444, 1236, 766 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 76:24 mixture of rotamers): δ = 4.78 (dt, J = 13.6, 2.0 Hz, 1 H, 8-H), 4.61 (br. d, J = 13.7 Hz, 0.76 H, 12-H_{rot1}), 4.61 (br. d, J = 14.9 Hz, 0.24 H, 12-H_{rot2}), 4.19 (br. d, J = 12.4 Hz, 1 H, 10-H), 3.69 (s, 0.72 H, OMe_{rot2}), 3.58 (s, 3.28 H, 2-H, OMe_{rot1}), 3.07 (br. d, J = 13.2 Hz, 1 H, 10-H), 2.96–2.78 (m, 2 H, 8-H, 12-H), 2.37 (m, 1 H, 4-H), 2.07 (m, 1 H, 3-H), 1.99–1.84 (m, 3 H, 9-H, 13-H_2), 1.79 (m, 1 H, 4-H), 1.70 (br. s, 1 H, 1-H), 1.43

(m, 1 H, $H_{cyclopropyl}$), 1.25 (m, 1 H, 3-H), 0.94 (m, 1 H, $H_{cyclopropyl}$), 0.57 (m, 1 H, $H_{cyclopropyl}$), 0.49 (m, 1 H, $H_{cyclopropyl}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, only signals of the major rotamer given): δ = 172.4 (C-6), 155.6 (CO_2), 59.9 (C-2), 52.5 (OMe), 48.9 (C-10), 46.4 (C-8), 44.3 (C-12), 33.4 (C-1), 33.0 (C-13), 30.2 (C-4), 27.9 (C-9), 27.4 (C-3), 21.3 (C-5), 18.6 ($C_{cyclopropyl}$), 13.6 ($C_{cyclopropyl}$) ppm. HRMS (ESI): calcd. for $C_{15}H_{23}N_2O_3$ $[M + H]^+$ 279.1703; found 279.1703.

General Procedure (GP2) for the Reduction of the Bispidine Lactams: The lactam (1.0 equiv.) was dissolved in dry THF (7–9 mL/mmol lactam) and slowly added at 0 °C to a suspension of $LiAlH_4$ (6 equiv.) in dry THF (4–7 mL/mmol lactam). The reaction mixture was allowed to slowly warm to room temp., heated at reflux overnight, cooled to 0 °C, and diluted with Et_2O. Saturated aqueous Na_2SO_4 was added dropwise until effervescence ceased. The solids were removed by filtration through a small pad of Celite and the filter cake was exhaustively washed with CH_2Cl_2/MeOH (90:10). The filtrate was dried with $MgSO_4$ and evaporated under reduced pressure to give bispidine **8**.

(1*R*,2*S*,5*R*,9*S*)-5,11-Dimethyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane (8a): Reduction of **11aA** (1.20 g, 4.51 mmol) according to the general procedure GP2 delivered bispidine **8a** (657 mg, 3.16 mmol, 70%) as a colorless oil. $[\alpha]_D^{23}$ = +10.6 (MeOH, *c* = 0.21). IR (ATR): $\tilde{\nu}$ = 2917, 1659, 1443, 1266, 1142, 1047, 891, 785, 743 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 3.04 (d, *J* = 11.4 Hz, 1 H, 12-H), 2.93 (d, *J* = 11.1 Hz, 1 H, 10-H), 2.87 (dt, *J* = 11.2, 2.0 Hz, 1 H, 8-H), 2.73 (ddd, *J* = 11.1, 3.7, 2.0 Hz, 1 H, 6-H), 2.27 (m, 2 H, 8-H, 10-H), 2.14 (s, 3 H, 11-Me), 2.09 (dd, *J* = 11.5, 2.6 Hz, 1 H, 12-H), 1.97 (d, *J* = 11.3 Hz, 1 H, 2-H), 1.88–1.73 (m, 3 H, 4-H, 5-H_{ax}, 9-H), 1.67–1.54 (m, 4 H, 1-H, 3-H, 13-H_2), 1.47 (t, *J* = 11.1 Hz, 1 H, 6-H_{ax}), 1.42 (m, 1 H, 3-H), 0.99 (qd, *J* = 13.0, 3.8 Hz, 1 H, 4-H_{ax}), 0.84 (d, *J* = 6.4 Hz, 3 H, 5-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 66.9 (C-2), 66.3 (C-6), 61.6 (C-8), 61.5 (C-10), 57.1 (C-12), 47.4 (11-Me), 36.1 (C-1), 34.9 (C-4 or C-13), 34.8 (C-4 or C-13), 31.9 (C-5), 31.50 (C-3), 31.48 (C-9), 20.0 (5-Me) ppm. HRMS (ESI): calcd. for $C_{13}H_{25}N_2$ $[M + H]^+$ 209.2012; found 209.2012.

In the ^1H NMR spectrum, the proton 6-H_{ax} appears as a large triplet (*J* = 11.1 Hz), which must originate from a geminal coupling with 6-H_{eq} and a 1,3-diaxial coupling with 5-H_{ax}. Furthermore, the large quartet of the proton 4-H_{ax} (*J* = 13.0 Hz) must originate from a geminal coupling with 4-H_{eq}, a 1,3-diaxial coupling with 3-H_{ax}, and a 1,3-diaxial coupling with 5-H_{ax}. Both relations prove the equatorial and thus *exo* orientation of the 5-methyl group.

(1*R*,2*S*,5*S*,9*S*)-5-Isopropyl-11-methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]-tridecane (8b): According to the general procedure GP2, lactam **11bA** (260 mg, 883 μmol) was reduced to give bispidine **8b** (194 mg, 821 μmol, 93%) as a colorless oil. $[\alpha]_D^{22}$ = +13.7 (MeOH, *c* = 0.23). IR (ATR): $\tilde{\nu}$ = 2930, 2871, 1660, 1465, 1443, 1065, 1039, 740 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 3.05 (d, *J* = 11.6 Hz, 1 H, 12-H), 2.94 (d, *J* = 11.2 Hz, 1 H, 10-H), 2.90 (dt, *J* = 11.2, 2 Hz, 1 H, 8-H), 2.85 (ddd, *J* = 10.6, 3.2, 2.0 Hz, 1 H, 6-H), 2.34 (ddd, *J* = 11.2, 3.2, 1.9 Hz, 1 H, 8-H), 2.26 (ddd, *J* = 11.1, 3.5, 1.9 Hz, 1 H, 10-H), 2.14 (s, 3 H, 11-Me), 2.11 (dd, *J* = 11.6, 2.7 Hz, 1 H, 12-H), 2.00 (d, *J* = 11.3 Hz, 1 H, 2-H), 1.86 (m, 2 H, 4-H, 9-H), 1.67–1.44 (m, 7 H, 1-H, 3-H_2, 5-H_{ax}, 6-H, 13-H_2), 1.38 (oct., *J* = 6.7 Hz, 1 H, C*H*Me$_2$), 1.05 (qd, *J* = 12.7, 4.0 Hz, 1 H, 4-H_{ax}), 0.90 (d, *J* = 6.8 Hz, 6 H, CH*Me*$_2$) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 67.3 (C-2), 62.2 (C-6), 61.8 (C-8), 61.5 (C-10), 57.1 (C-12), 47.2 (11-Me), 42.8 (C-5), 36.0 (C-1), 34.7 (C-13), 32.6 (*C*HMe$_2$), 31.8 (C-9), 31.4 (C-3), 29.5 (C-4), 20.6 (CH*Me*), 20.3 (CH*Me*) ppm. HRMS (ESI): calcd. for $C_{15}H_{29}N_2$ $[M + H]^+$ 237.2325; found 237.2326.

The ^1H NMR splitting pattern of the proton 4-H_{ax} includes a large quartet (*J* = 12.7 Hz), which must originate from a geminal coupling with 4-H_{eq}, a 1,3-diaxial coupling with 3-H_{ax}, and a 1,3-diaxial coupling with 5-H_{ax}. The latter relation proves the equatorial and thus *exo* orientation of the 5-isopropyl group.

(1*R*,2*S*,5*S*,9*S*)-5,11-Dimethyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane (8c): Reduction of **11aB** (1.20 g, 4.51 mmol) according to the general procedure GP2 afforded bispidine **8c** (741 mg, 3.56 mmol, 79%) as a slightly yellowish oil. $[\alpha]_D^{23}$ = –4.7 (MeOH, *c* = 0.59). IR (ATR): $\tilde{\nu}$ = 2935, 1654, 1447, 1039, 739 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 2.94 (br. d, *J* = 11.6 Hz, 1 H, 12-H), 2.78 (br. d, *J* = 11.0 Hz, 1 H, 10-H), 2.74 (dt, *J* = 11.2, 2.3 Hz, 1 H, 8-H), 2.57 (dt, *J* = 11.2, 1.8 Hz, 1 H, 6-H), 2.42 (dd, *J* = 11.1, 5.1 Hz, 1 H, 10-H), 2.28 (dd, *J* = 11.5, 5.2 Hz, 1 H, 12-H), 2.18 (s, 3 H, 11-Me), 2.16 (m, 1 H, 8-H), 2.06 (dd, *J* = 11.2, 3.6 Hz, 1 H, 6-H), 1.92 (m, 2 H, 2-H, 9-H), 1.85 (m, 1 H, 5-H_{eq}), 1.78 (m, 1 H, 3-H), 1.72 (m, 1 H, 13-H), 1.66–1.51 (m, 3 H, 1-H, 4-H_2), 1.48 (m, 1 H, 13-H), 1.16 (d, *J* = 7.1 Hz, 3 H, 5-Me), 1.14 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 68.3 (C-2), 63.3 (C-6), 62.3 (C-8), 60.8 (C-10), 56.6 (C-12), 47.0 (11-Me), 35.9 (C-1), 33.4 (C-13), 31.6 (C-4), 31.4 (C-9), 29.8 (C-5), 26.1 (C-3), 18.7 (5-Me) ppm. HRMS (ESI): calcd. for $C_{13}H_{25}N_2$ $[M + H]^+$ 209.2012; found 209.2012.

In the ^1H NMR spectrum, the two protons 6-H_{ax} and 6-H_{eq} possess, in addition to their large geminal coupling with *J* = 11.2 Hz, only a small doublet (*J* < 4 Hz), which excludes a 1,3-diaxial relationship between 6-H and 5-H. Therefore 5-H must be equatorial, which proves an axial and thus *endo* orientation of the 5-methyl group.

(1*R*,2*S*,9*S*)-5,5,11-Trimethyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane (8d): According to the general procedure GP2, lactam **12a** (640 mg, 2.28 mmol) was reduced to give bispidine **8d** (457 mg, 2.05 mmol, 90%) as a yellowish oil. $[\alpha]_D^{21}$ = –12.8 (MeOH, *c* = 0.46). IR (ATR): $\tilde{\nu}$ = 2930, 2777, 1654, 1445, 1032 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 2.96 (d, *J* = 11.6 Hz, 1 H, 12-H), 2.79 (m, 1 H, 8-H, 10-H), 2.47 (dd, *J* = 11.1, 5.1 Hz, 1 H, 10-H), 2.39 (dd, *J* = 11.1, 2.3 Hz, 1 H, 6-H), 2.34 (dd, *J* = 11.5, 5.2 Hz, 1 H, 12-H), 2.20 (s, 3 H, 11-Me), 2.19 (m, 1 H, 8-H), 1.91 (m, 2 H, 2-H, 9-H), 1.76 (m, 2 H, 3-H, 13-H), 1.68 (m, 2 H, 1-H, 6-H), 1.52–1.41 (m, 2 H, 4-H, 13-H), 1.22 (m, 2 H, 3-H, 4-H), 1.08 (s, 3 H, 5-Me), 0.86 (s, 3 H, 5-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 69.6 (C-6), 67.9 (C-2), 62.2 (C-8), 60.8 (C-10), 56.7 (C-12), 46.8 (11-Me), 39.0 (C-4), 35.5 (C-1), 33.2 (C-13), 31.6 (C-5), 31.2 (C-9), 30.5 (5-Me), 27.7 (C-3), 25.5 (5-Me) ppm. HRMS (ESI): calcd. for $C_{14}H_{27}N_2$ $[M + H]^+$ 223.2169; found 223.2173.

(1*R*,2*S*,9*S*)-5,5-Difluoro-11-methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane (8e): Reduction of **12b** (342 mg, 1.19 mmol) according to the general procedure GP2 delivered bispidine **8e** (195 mg, 847 μmol, 71%) as a slightly yellowish oil. $[\alpha]_D^{22}$ = –17.9 (MeOH, *c* = 0.10). IR (ATR): $\tilde{\nu}$ = 2917, 1660, 1442, 1284, 1099, 1052, 1000 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 3.01 (m, 2 H, 6-H, 12-H), 2.86 (m, 2 H, 8-H, 10-H), 2.37–2.25 (m, 2 H, 8-H, 10-H), 2.15 (s, 3 H, 11-Me), 2.20–2.02 (m, 4 H, 2-H, 4-H, 6-H, 12-H), 1.89 (m, 2 H, 9-H), 1.84–1.63 (m, 4 H, 1-H, 3-H, 4-H, 13-H), 1.55 (m, 2 H, 3-H, 13-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 121.1 (dd, *J* = 244, 237 Hz, C-5), 65.5 (C-2), 62.2 (dd, *J* = 31.2, 24.6 Hz, C-6), 61.0 (C-8), 60.8 (C-10), 56.8 (C-12), 47.1 (11-Me), 35.3 (C-1), 34.1 (C-13), 33.7 (dd, *J* = 25.1, 21.5 Hz, 3-C), 31.3 (C-9), 28.0 (d, *J* = 10.7 Hz, 4-C) ppm. HRMS (ESI): calcd. for $C_{12}H_{21}F_2N_2$ $[M + H]^+$: 231.1667; found 231.1667.

(1*R*,2*S*,9*S*)-11-Methyl-7,11-diazaspiro[tricyclo[7.3.1.0^{2,7}]tridecane-5,1′-cyclopropane] (8f): According to the general procedure GP2, lactam **12c** (205 mg, 736 μmol) was reduced to give bispidine **8f** (137 mg, 622 μmol, 84%) as a yellowish oil. $[\alpha]_D^{22}$ = +8.3 (MeOH, *c* = 0.25). IR (ATR): $\tilde{\nu}$ = 2923, 2820, 2770, 1441, 1110, 1038, 859 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 3.12 (d, *J* = 10.8 Hz, 1 H, 14-H), 2.96 (d, *J* = 11.0 Hz, 1 H, 12-H), 2.88 (br. d, *J* = 11.1 Hz, 1 H, 10-H), 2.34 (m, 3 H, 6-H, 8-H, 12-H), 2.21 (s, 3 H, 13-Me), 2.26–2.16 (m, 2 H, 2-H, 10-H), 2.02 (br. d, *J* = 11.5 Hz, 1 H, 6-H), 1.95–1.75 (m, 3 H, 1-H, 3-H, 4-H), 1.74–1.54 (m, 3 H, 9-H, 13-H$_2$), 1.49 (m, 1 H, 3-H), 1.00 (m, 1 H, 4-H), 0.67 (m, 1 H, $H_{cyclopropyl}$), 0.37 (m, 1 H, $H_{cyclopropyl}$), 0.27 (m, 2 H, $H_{cyclopropyl}$) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 67.4 (C-2), 66.0 (C-6), 61.4 (C-8), 61.2 (C-12), 57.2 (C-10), 47.0 (11-Me), 36.0 (C-9), 35.2 (C-4), 34.3 (C-13), 31.5 (C-1), 30.8 (C-3), 18.6 (C-5), 14.8 ($C_{cyclopropyl}$), 9.9 ($C_{cyclopropyl}$) ppm. HRMS (ESI): calcd. for $C_{14}H_{25}N_2$ [M + H]$^+$ 221.2012; found 221.2014.

General Procedure for the Lithiation/Stannylation of the *O*-Alkyl Carbamate 14: All reactions were performed as described in ref.[6], with carbamate **14** (400–700 μmol). The bispidines **8** were bulb-to-bulb distilled (0.8 mbar, 100–150 °C) from CaH_2 prior to use. A solution of bispidine **8** (1.3 equiv.) in dry Et_2O (2 mL/mmol **14**) was added dropwise to a solution of *s*BuLi (1.4 M in cyclohexane, 1.3 equiv.) in dry Et_2O (2 mL/mmol **14**) at –78 °C. After 30 min, carbamate **14** (1.0 equiv.) was added dropwise through a cannula over 10 min and stirring was continued for 4–6 h. Bu_3SnCl (1.5 equiv.) was added dropwise and the reaction mixture was warmed to room temp. over 16 h. The reaction mixture was quenched with HCl (1 N, 40 mL/mmol **14**) and extracted with Et_2O (3× 40 mL/mmol **14**). The combined organic layers were washed with saturated aqueous KF (40 mL/mmol **14**), dried with $MgSO_4$, and the solvents evaporated. Column chromatography (silica gel, *n*-pentane/EtOAc, 100:0→ 97:3) afforded carbamate **15** in analytically pure form. The spectroscopic data of **15** are consistent with those reported in ref.[26] The enantiomeric excess of product **15** was determined in accord with ref.[6] by HPLC: Daicel Chiralcel OD-H, *n*-hexane/*i*PrOH, 600:1, 0.5 mL/min, 226 nm, retention times: 9.1 min [(*S*)-**15**] and 10.7 min [(*R*)-**15**]. The chiral bispidine **8** was recovered from the acidic aqueous phase by addition of NaOH (80 mL/mmol **14**) and extraction with $CHCl_3$ (5× 40 mL/mmol **14**). The combined organic layers were dried with $MgSO_4$ and the solvent removed under reduced pressure. Bulb-to-bulb distillation (0.8 mbar, 100–150 °C) delivered the pure bispidine **8** (>50% recovery).

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all intermediates and final products.

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