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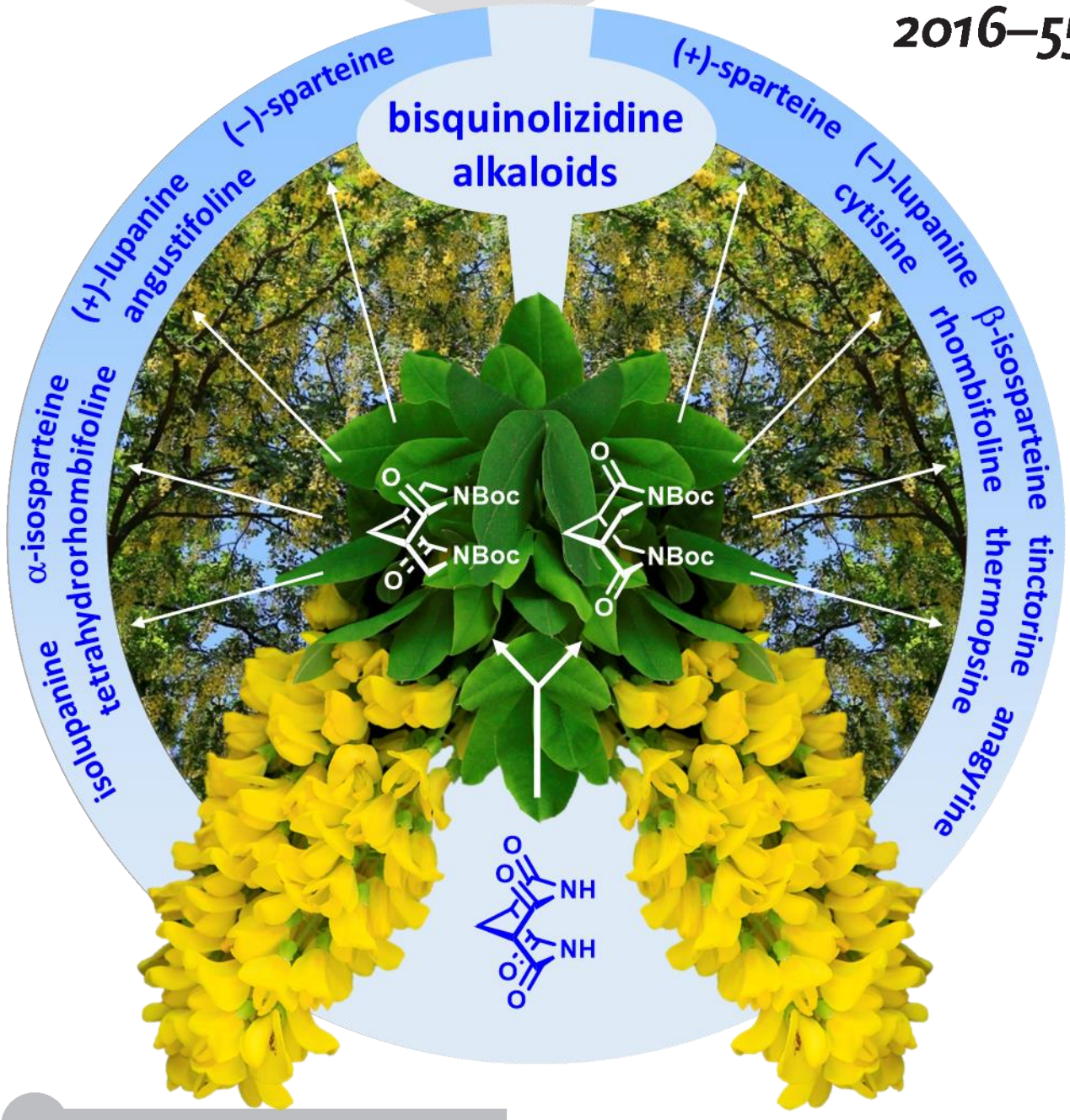

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The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular 'Inside-Out' Approach

Dagmar Scharnagel[+], Jessica Goller[+], Nicklas Deibl, Wolfgang Milius, and Matthias Breuning*

Abstract: Bisquinolizidine alkaloids are characterized by a chiral bispidine core (3,7-diazabicyclo[3.3.1]nonane) to which combinations of an α,*N*-fused 2-pyridone, an *endo*- or *exo*-α,*N*-annulated piperidin(on)e, and an *exo*-allyl substituent are attached. We developed a modular 'inside-out' approach that permits access to most members of this class. Its applicability was proven in the asymmetric synthesis of 21 natural bisquinolizidine alkaloids, among them more than ten first enantioselective total syntheses. Key steps are the first successful preparation of both enantiomers of C_2-symmetric 2,6-dioxobispidine by desymmetrization of a 2,4,6,8-tetraoxo precursor, the construction of the α,*N*-fused 2-pyridone by using an enamine–bromoacrylic acid strategy, and the installation of *endo*- or, optionally, *exo*-annulated piperidin(on)es.

(–)-Sparteine (**1**), (+)-lupanine (**2**), α-isosparteine (**3**), anagyrine (**4**), and cytisine (**5**) are the most prominent bisquinolizidine alkaloids, a class of secondary metabolites with about 50 members (Figure 1).[1] These natural products are produced by plants of the Faboideae subfamily, which includes the genera *Cytisus*, *Laburnum*, *Thermopsis*, and *Anagyris*. The biological activities of these diamines are widespread: (–)-Sparteine (**1**) possesses antiarrhythmic and oxytocic properties, (+)-lupanine (**2**) is moderately toxic, and anagyrine (**4**) is teratogenic.[1] Cytisine (**5**), a partial agonist of the nicotinic acetylcholine receptor, is pharmaceutically marketed for smoking cessation under the brand names Tabex® and Desmoxan® in Poland and Bulgaria.[2] In asymmetric synthesis, (–)-sparteine (**1**) and O'Brien's artificial (+)-sparteine surrogate (**6**),[3] prepared in a few steps from **5**,[4] received particular attention as the chiral ligands of choice in the deprotonation of weakly CH-acidic compounds,[5] the homologation of boronic esters,[6] and the Pd-catalyzed, oxidative kinetic resolution of secondary alcohols.[7,8]

Common structural feature of all bisquinolizidine alkaloids is a chiral bispidine core (3,7-diazabicyclo[3.3.1]nonane), which occurs in nature in both enantiomeric forms (**1**–**3** vs. **4**,**5**). Typically, combinations of an α,*N*-fused 2-pyridone, an *endo*- or *exo*- α,*N*-annulated piperidin(on)e, and an *exo*-allyl substituent are attached to the central core on opposite sites.

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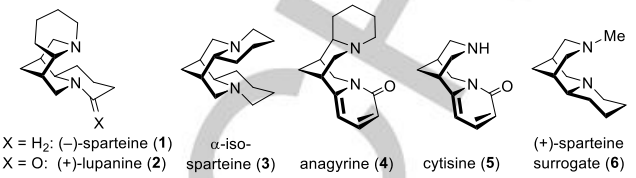
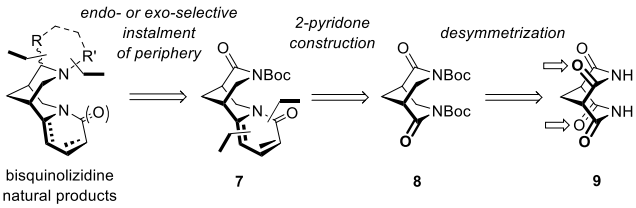


Figure 1. The most prominent bisquinolizidine alkaloids (**1**–**5**) and the artificial (+)-sparteine surrogate (**6**).

Several elegant, enantioselective syntheses of bisquinolizidine alkaloids have been reported so far.[9] However, these approaches are mostly limited to a particular target, mainly because 'outside-in' strategies were used that start with the periphery, which, however, is diverse in nature. A flexible route that permits access to a broad range is still missing. We developed such an approach and proved its applicability in the enantioselective total synthesis of 21 natural bisquinolizidine alkaloids. Key sequences are a desymmetrization permitting access to chiral, C_2-symmetric 2,6-dioxobispidine in both enantiomeric forms, a novel procedure for the annulation of an α,*N*-fused 2-pyridone, and robust methods for the *endo*- or, optionally, *exo*-selective attachment of fused piperidin(on)es and *exo*-allyl substituents to the bispidine core.

Our diversity-driven approach to bisquinolizidine alkaloids is based on a modular 'inside-out' strategy, in which the peripheral rings and substituents are installed on an adequately functionalized, chiral bispidine core (Scheme 1). With many of the bisquinolizidines possessing a fused 2-pyridone or a reduced form thereof, the tricyclic imide **7** was chosen as a late stage key intermediate. Further disconnection of the annulated pyridone led to the C_2-symmetric 2,6-dioxobispidine **8** as the second key intermediate, which we intended to prepare in either enantiomeric form by desymmetrization of achiral 2,4,6,8-tetraoxobispidine **9**.[10]



Scheme 1. Retrosynthetic analysis of the natural bisquinolizidine alkaloids. Only one of the two enantiomeric bispidine cores is shown.

The synthesis of the chiral 2,6-dioxobispidine **8** commenced with achiral 2,4,6,8-tetraoxobispidine **9** (Scheme 2), which is available from cheap malonic ester in just two steps.[11] For desymmetrization, one of the two enantiotopic pairs of carbonyl

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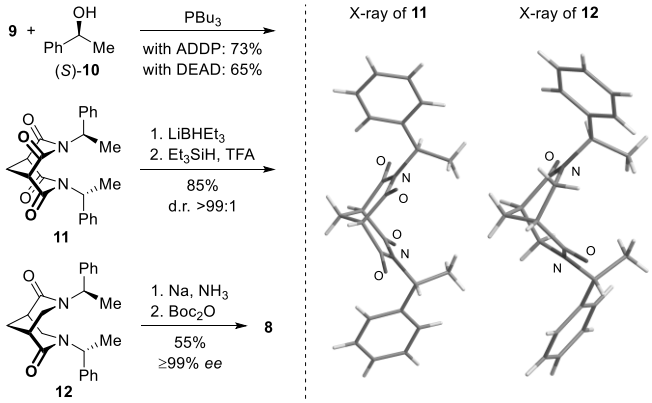
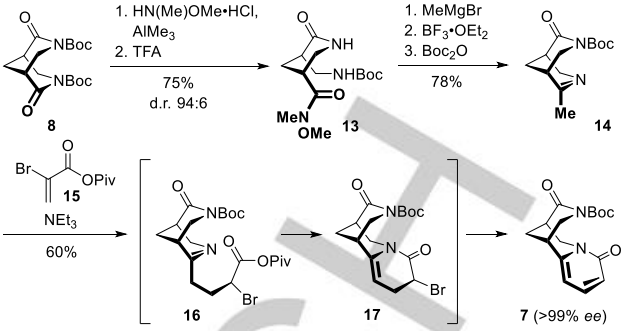
groups had to be deoxygenated. This was achieved by chiral modification of both nitrogen atoms in **9** with (*S*)-phenylethanol [(*S*)-**10**] under Mitsunobu conditions, followed by two-step diastereoselective reduction of resulting **11**. Pleasingly, the diamide **12** was obtained with virtually complete regio- and stereocontrol (d.r. >99:1).[12] Its absolute configuration was established by X-ray crystallography.[13] Reductive removal of the chiral auxiliary under Birch conditions and activation of the amide groups as *N*-Boc imides furnished the chiral key intermediate **8** in overall five steps, 30–34% yield, and ≥99% *ee* from **9**. The enantiomer, *ent*-**8**, was prepared analogously using (*R*)-**10**.



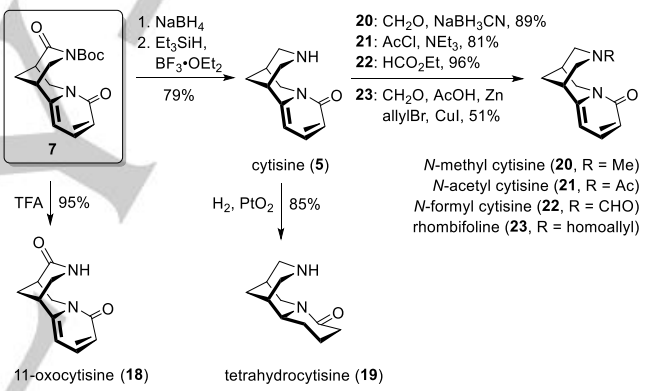
Scheme 2. Synthesis of the chiral key intermediate **8** and X-ray structures of **11** and **12**.[13] DEAD = diethylazodicarboxylate, ADDP = 1,1'-(azodicarbonyl)-dipiperidine, TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl.

Conversion of C_2-symmetric **8** into the tricyclic bispidine **7** required the α,*N*-annulation of a 2-pyridone (Scheme 3). Selective modification of just one of the two imide groups was achieved by Lewis acid-catalyzed ring opening with HN(OMe)Me·HCl/$AlMe_3$,[14] which provided, after *N*-Boc removal from the imide function, Weinreb amide **13** in 75% yield and with 94:6 dr. It is important to keep the temperature below –30 °C in the first step, in order to suppress isomerization at the former bridgehead carbon atoms. Annulation of the pyridone moiety was accomplished by using an enamine–Michael addition strategy.[15] Reaction of **13** with MeMgBr, *N*-Boc removal under Lewis-acidic conditions with concomitant imine formation, and *N*-Boc protection of the amide furnished bispidine **14**, which was treated with in-situ prepared α-bromoacrylic pivalic anhydride (**15**) and NEt_3 to give the desired pyridone fused bispidine **7** in >99% *ee* after crystallization.[16] For the latter sequence, we propose that the enamine tautomer of **14** undergoes Michael addition to the anhydride **15** generating intermediate **16**, which, after renewed enamine formation and lactamization to **17**, finally eliminates HBr.



Scheme 3. Annulation of **8** to the tricyclic key intermediate **7**. Piv = pivaloyl.

With key intermediate **7** in hand we synthesized a first set of natural tricyclic bisquinolizidine alkaloids (Scheme 4). Simple deprotection afforded 11-oxocytisine (**18**), reduction and *N*-Boc removal cytisine (**5**). The latter compound was hydrogenated or *N*-functionalized following literature protocols[17] to give tetrahydrocytisine (**19**), *N*-methyl cytisine (**20**), *N*-acetyl cytisine (**21**), *N*-formyl cytisine (**22**), and rhombifoline (**23**), respectively.



Scheme 4. Natural tricyclic bisquinolizidine alkaloids **18**–**23** prepared from **7**.

The installation of an *endo*-[8c,18] or *exo*-fused ring or substituent at the imide carbonyl group of **7** involves a hydride and an alkyl addition. Earlier investigations by us[8c,18,19] and others[10,11,20] on related systems revealed that an attack of a nucleophile on a bispidine imine or iminium salt occurs with high selectivity from the sterically less hindered *exo*-face (Scheme 5). Thus, reduction followed by addition will establish *exo*-orientation, whereas the reversed addition–reduction sequence will provide access to the *endo*-epimer. And indeed, treatment of **7** with 4-chlorobutyl magnesium bromide, *N*-deprotection, and reductive amination with concomitant nucleophilic substitution afforded the *endo*-piperidine fused alkaloid thermopsine (**24**) in just three steps and good 66% yield. *Exo*-substituents were introduced after reduction of **7** to the *N*,*O*-acetal **25**.[21] Sakurai allylation under loss of the *N*-Boc group delivered 11-allyl cytisine (**26**) and, after reductive *N*-methylation, tinctorine (**27**) in good 89% yield. *N*-Allylation of **26** followed by ring closing metathesis and hydrogenation gave access to the tetracyclic bispidine anagyrine (**4**), which was converted into (–)-lupanine (*ent*-**2**) by hydrogenation of the pyridone and, after reduction of the amide group, into (+)-sparteine (*ent*-**1**).

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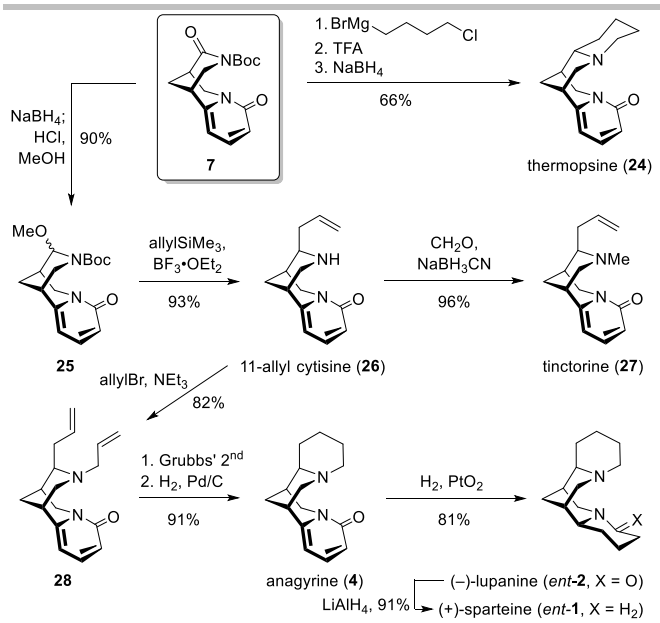
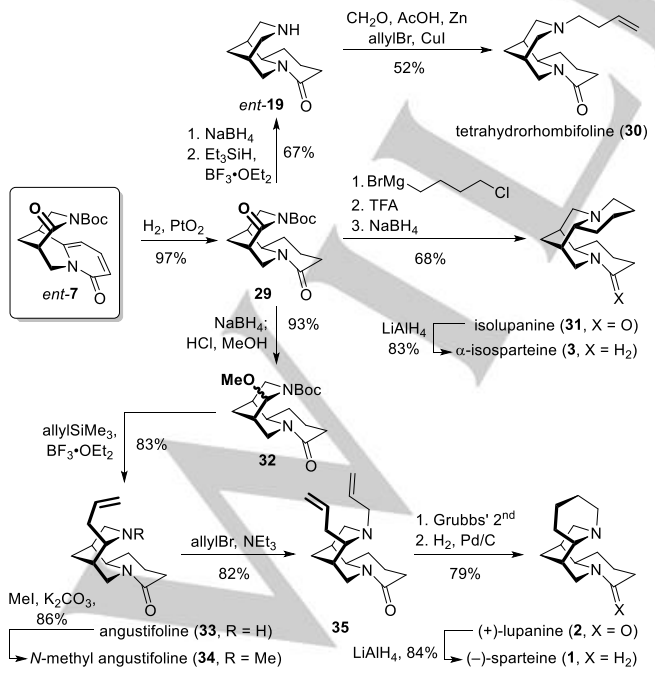


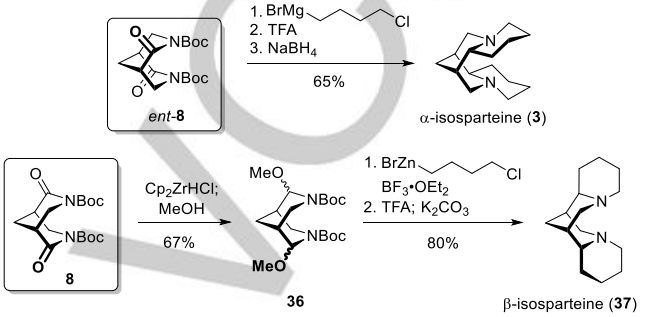
Scheme 5. Natural, core-disubstituted bisquinolizidine alkaloids from **7**.

Bisquinolizidine alkaloids possessing the enantiomeric bispidine core were synthesized from *ent*-**7** (Scheme 6), which was prepared from *ent*-**8** according to Scheme 3. Hydrogenation of *ent*-**7** provided the piperidone **29**, which was reduced and deprotected to give amine *ent*-**19** and, after Barbier-type *N*-homoallylation, tetrahydrorhombifoline (**30**).[22] Isolupanine (**31**) and its deoxygenated analog, α-isosparteine (**3**), were obtained by using the *endo*-piperidine annulation procedure described above. Reduction of imide **29** to the *N,O*-acetal **32**[21] set the stage for *exo*-functionalization (*vide supra*), finally leading to angustifoline (**33**), *N*-methyl angustifoline (**34**), (+)-lupanine (**2**), and (–)-sparteine (**1**).



Scheme 6. Natural tri- and tetracyclic bisquinolizidine alkaloids from *ent*-**7**.

The application of the *exo*- and *endo*-annulation procedures to both imide groups in the key intermediates *ent*-**8** and **8** also permitted a concise access to C_2-symmetric alkaloids (Scheme 7). Natural α-isosparteine (**3**) was thus available from *ent*-**8** in just three steps and good 65% overall yield. The *exo*-fused piperidine moieties in β-isosparteine (**37**) were constructed via the bis-*N,O*-acetal **36**,[21] which was available by reduction of **8** with the Schwartz reagent[23] and acetalization. Twofold Lewis acid assisted addition of 4-chlorobutylzinc bromide,[24] *N*-deprotection, and ring closure under basic conditions delivered **37** in 54% yield.



Scheme 7. Synthesis of the C_2-symmetric bisquinolizidine alkaloids α- and β-isosparteine (**3**, **37**) from *ent*-**8** and **8**.

In conclusion, we have developed a flexible and broadly applicable route to natural bisquinolizidines, the versatility of which was proven in the asymmetric synthesis of 21 alkaloids, including the first enantioselective total syntheses of (+)- and (–)-lupanine (**2** and *ent*-**2**), α-isosparteine (**3**), anagyrine (**4**), 11-oxocyctisine (**18**), thermopsine (**24**), 11-allyl cytisine (**26**), tinctorine (**27**), isolupanine (**31**), tetrahydrorhombifoline (**30**), angustifoline (**33**), and *N*-methyl angustifoline (**34**). Key was an 'inside-out' strategy based on the chiral 2,6-dioxobispidines **8** and *ent*-**8**, both available in enantiopure form by desymmetrization of the achiral tetraoxobispidine **9**. The α,*N*-fused 2-pyridone moiety in **7** was constructed by using a new enamine–Michael addition strategy. High diversity was reached by applying the *endo*- and *exo*-annulation protocols to the key intermediates **7**, *ent*-**7**, **8**, and *ent*-**8**.

Acknowledgements

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Keywords: total synthesis • natural products • bispidine • alkaloids • enantioselectivity

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[12] The sense and level of asymmetric induction is surprising and cannot be explained by simple steric effects. All preferred conformations, in which the phenyl group of the chiral auxiliary will occupy an *exo* position (cp. crystal structure of **11**), suggest a weak shielding of the attacked *pro-S* carbonyl groups, but not of the untouched *pro-R* carbonyl groups. For a related reduction of an *N*-phenylethyl substituted, norbornane fused succinimide giving the same unexpected stereochemical outcome, see: P. Rackler, C. Berthold, F. Voss, T. Bach, *J. Am. Chem. Soc.* **2010**, *132*, 15911.

[13] Crystals of **11** and **12** were obtained from Et_2O/CH_2Cl_2/pentane. CCDC 1815735 (**11**) and 1565771 (**12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures.

[14] All attempts to selectively modify just one carbonyl group in **8**, while keeping the bicyclic system intact (e.g., *N*-Boc deprotection or carbonyl reduction), mainly provided the undesired product of an attack on both imides. Ring opening reactions, by contrast, occurred with high mono-selectivity, presumably due to the release of conformational strain.

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[16] Crude **7** had just 94% *ee*. The loss of enantiopurity is most likely caused by the minor *trans*-diastereomer of **13**, which could not be removed. It had to be carried through the following steps, providing a mixture of **7** and *ent*-**7**. The enantiopurity of **7** was re-raised to >99% by simple fractional crystallization.

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[21] The ^1H and ^{13}C NMR spectra of **25** and **32** display two sets of signals, those of **36** three sets of signals. They probably result from *N*-Boc rotamers of the *exo*-configured diastereomer, but the existence of *endo*-diastereomers cannot be fully excluded.

[22] Note that tetrahydrorhombifoline (**30**) and rhombifoline (**23**) possess 'enantiomeric' bispidine cores.

[23] Twofold reduction of **8** with Cp_2ZrHCl was found to give higher yields, as compared to $NaBH_4$, $LiBHEt_3$, or iBu_2AlH.

[24] The Lewis acid assisted addition of 4-chlorobutylzinc bromide worked well on the bis-*N,O*-acetal **36** (Scheme 7), but failed for unknown reasons on **25** (Scheme 5) and **32** (Scheme 6).

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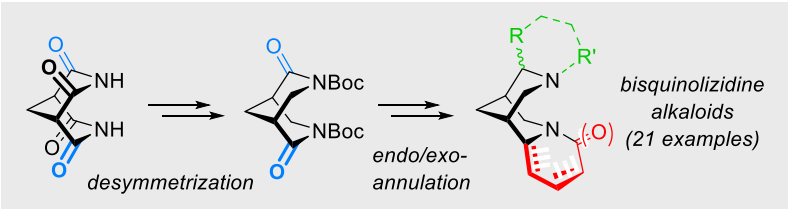

All in one sweep: A diversity-driven, modular 'inside-out' approach to natural bisquinolizidine alkaloids was developed. Its versatility was proven in the enantioselective total synthesis of 21 alkaloids of this class. Key steps are a desymmetrization, permitting access to C_2-symmetric 2,6-dioxobispidine in both enantiomeric forms, and the annulation of 2-pyridone and *endo*- or *exo*-fused piperidines to this chiral core building block.

*Dagmar Scharnagel, Jessica Goller, Nicklas Deibl, Wolfgang Milius, and Matthias Breuning**

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The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular 'Inside-Out'-Approach

10.1002/anie.201712852

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Text to the Cover Picture:

The Enantioselective Total Synthesis of Bisquinolizidine Alkaloids: A Modular 'Inside-Out' Approach…
to 21 natural bispidines, among them more than ten first enantioselective total syntheses, is reported by D. Scharnagel, J. Goller, M. Breuning et al. in their Communication on page xxxx ff. Key were the successful preparation of both enantiomers of C_2-symmetric 2,6-dioxobispidine by desymmetrization and the successive α,*N*-annulation of an 2-pyridone and *endo*- or *exo*-fused piperidin(on)es.