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Synthesis of enantiopure diamine ligands related to sparteine, via scandium triflate-catalyzed imino Diels–Alder reactions

Bruno Danieli, Giordano Lesma,* Daniele Passarella, Paola Piacenti, Alessandro Sacchetti, Alessandra Silvani* and Andrea Virdis

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via Venezian 21, I-20133 Milano, Italy

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Abstract—Imino Diels–Alder reactions have been investigated as a new route to sparteine analogues. The first enantioselective synthesis of two diastereoisomeric tricyclic diamines, structurally equivalent to the ABC and BCD rings of the naturally occurring alkaloid, is reported, starting from enantiopure intermediates. The effectiveness of the diamines in the lithiation of *N*-Boc-pyrrolidine is discussed. © 2002 Elsevier Science Ltd. All rights reserved.

The development of efficient stereodirecting ligands readily available in both enantiomeric forms is nowadays of paramount importance to the field of enantioselective catalysis. Particularly interesting is the complex of *sec*-butyllithium and (−)-sparteine (**1**) (Fig. 1), which Hoppe[1] first showed could induce high enantioenrichments in lithiation–electrophilic quench reactions.[2] (−)-Sparteine is a lupine alkaloid extracted from papilionaceous plants such as *Scotch Broom*. It bears a bis-quinolizidine skeleton, with *trans*- and *cis*-quinolizidine moieties joined through a common bridge. With regard to the origin of enantioselectivity during the deprotonation process, steric effects in the diamine/organolithium complex have been proved to be important. For instance, the use of isosparteine, the C_2-symmetric structural analogue of sparteine consisting of two *trans*-quinolizidine moieties, appears to slow down the deprotonation reaction significantly and provides low enantioselectivity.

Since (+)-sparteine is also naturally occurring, but far less easily obtained,[3] this alkaloid is only commercially available as its (−)-antipode. This limitation on the use of sparteine as a chiral ligand prompts to find other chiral diamines capable of matching the enantioselectivity of sparteine and preparable in both enantiomeric forms.[4] Within our long-term program of enantioselective synthesis of some quinolizidine alkaloids, we attempted to address the need of sparteine analogues. In particular, we focused our attention to find out an original, stereoselective synthetic methodology for the preparation of chiral diamines, such as **2** and **3**, which embody, respectively, two different portions (ABC and BCD rings) of the sparteine framework. Being aware of difficulties in the synthesis of sparteine itself encountered by previous workers in the field,[5] we thought that these simplified structures would have been more easily achievable, moreover in both the enantiomeric forms, than the natural alkaloid. Most of the chiral architecture of sparteine is retained in diamines **2** and **3**, but, at the same time, the lack of A or D ring, respectively, significantly modifies their steric hindrances. So, the efficacy of these diamines appears to be hardly predictable as sparteine surrogates. Some preparations of racemic **2** and **3** have been previously reported, based on different synthetic strategies. For instance, the complete control of the ABC and BCD ring relative stereochemistry in the synthesis of sparteine analogues has been achieved by O'Brien.[6] Quite recently, the same

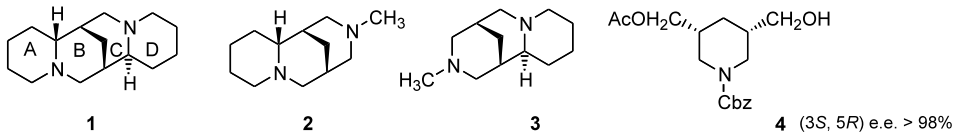

Figure 1.

* Corresponding authors. Tel.: +39 2 50314080; fax: +39 2 50314078; e-mail: alessandra.silvani@unimi.it

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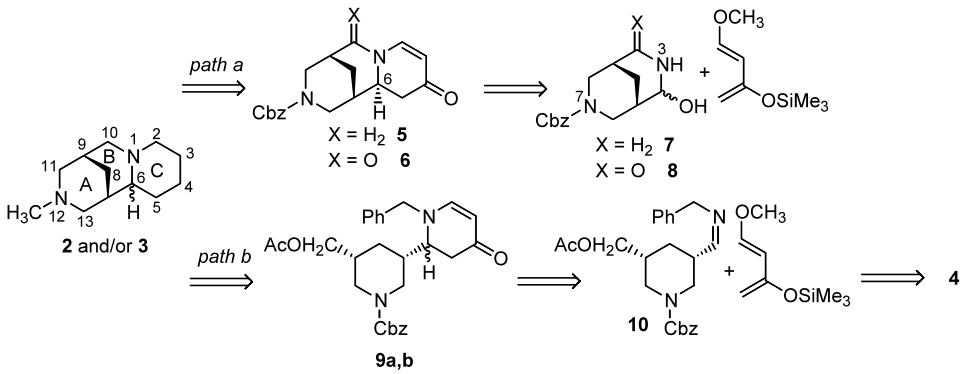
author developed a resolution protocol which furnishes chiral **2** with moderate yield and 60% enantiomeric eccess.[7] In this paper, we report the application of an original, imino Diels–Alder[8]-based methodology to the first enantioselective synthesis of tricyclic diamines **2** and **3**, preparable in both the enantiomeric forms starting from the chiral *cis*-piperidine-3,5-dimethanol monoacetate **4**. This precursor is readily available, together with its enantiomer, by mean of biocatalytic asymmetrization of the corresponding C_S-symmetric diols or diacetates.[9] Recently, we succeeded in developing some convenient enantioselective entries to highly functionalized 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives,[10] which allowed us to set up an original route to chiral, non-racemic functionalized piperido–quinolizidine ring systems.[11] Along the line of our previous results, we devised an innovative strategy for the preparation of **2** and **3**, relied on the application of imino-Diels–Alder reactions as the key step. In Scheme 1, two different paths are outlined, both of them based on an imino-Diels–Alder route, but differing in the order of construction of rings B and C. As a consequence of our previous work on the enantiosynthesis of 3,7-diazabicyclo[3.3.1]nonane derivatives,[10] the path a involves the cycloaddition between the Danishefsky' diene and the chiral bicyclic hydroxyamine **7** or hydroxylactam **8**, from which an imine or acylimine functionality can be generated, respectively, by Lewis acid-catalyzed elimination. In path b, the dissection of ring B in compounds **2** and **3** yields to the 2-piperidinyl-2,3-dihydropyridin-4-one **9**, which in turn could be accessed by cycloaddition of imine **10** with the same diene. For the preparation of imine **10**, the chiral *cis*-piperidine-3,5-dimethanol monoacetate **4**, which was already described by us,[9] can be employed.

In path a, the stereochemical outcome of the cycloaddition should be easily predictable, since imino dienophiles in which configuration is fixed by virtue of ring restraints (such as those derivable from **7** and **8**) usually give stereochemically defined adducts resulting from *endo* addition. Moreover, we expected the cycloaddition to occur predominantly from the less-hindered, convex, methylene bridgehead face of the bispidine nucleus to give ultimately a (6*S*) configuration (lupine alkaloids numbering) as indicated in structures **5** and **6**. In path b, the question about the stereochemical consequences of addition remained to be addressed, due to the lack of information about the geometry of the reacting imine and the steric hindrance at the two faces of the imine moiety.

Our initial work was directed to study the feasibility of path a. Preliminary results have been obtained on the reactivity of **7** as a dienophile. By using the Danishefsky' diene under the catalysis of $TiCl_4$, the cycloaddition product **5** has been isolated, but only in traces. Many attempts to improve the yield, using a variety of Lewis acid catalysts, including lanthanide triflates, and different oxygenated dienes, were unsuccessful. In some cases, using the (1-*tert*-butoxy-buta-1,3-dienyloxy)-trimethylsilane as diene, we could only observe the competing vinilogue Mannich addition, also in this case in low yield. Because of the LUMO-dienophile control to which the imino Diels–Alder reactions are subjected, we expected an enhanced reactivity for the acylimine derived from the 2-oxo analogue **8**. We found that on $TiCl_4$-catalyzed treatment with Danishefsky' diene, **8** gave the cycloadduct **6**, still in very low yield. A possible explanation of the scarce reactivity of **7** and **8** as dienophiles in the Lewis acid-catalyzed reactions is that the cation of the Lewis acid might give a bidentate binding through N3 and N7 of the diazabicycle, thus preventing the formation of the planar reactive imine or acylimine moiety. Actually, when **8** was refluxed with Danishefsky' diene in toluene for two days, without any acidic catalysis, the tricycle **6** was formed in some higher yield (35%). Longer reaction times, higher temperatures and larger excesses of diene had little effect upon the amount of adduct formed.

The structure of **6** was established by NMR spectroscopic analysis[12] which demonstrated, to the limits of detection by ^{1}H NMR, that the reaction is highly stereoselective, affording only the (6*S*) stereoisomer, derived from an *endo* attack on the *si*-face of the imino moiety. The stereochemistry of **6** was deduced from the observation of an almost negligible coupling (ca. 0.5 Hz) between 6-H (at $\delta = 3.93$) and 7-H (at $\delta = 1.92$) and then supported by NOE interactions of 6-H at $\delta = 3.93$ with 13e-H at $\delta = 4.16$, with 5e-H at $\delta = 2.30$ and with 7-H at $\delta = 1.92$ (Fig. 2).



Scheme 1.

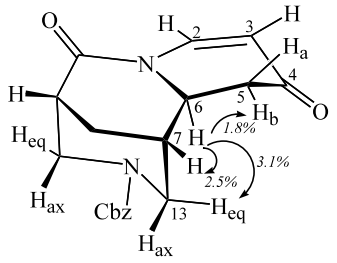


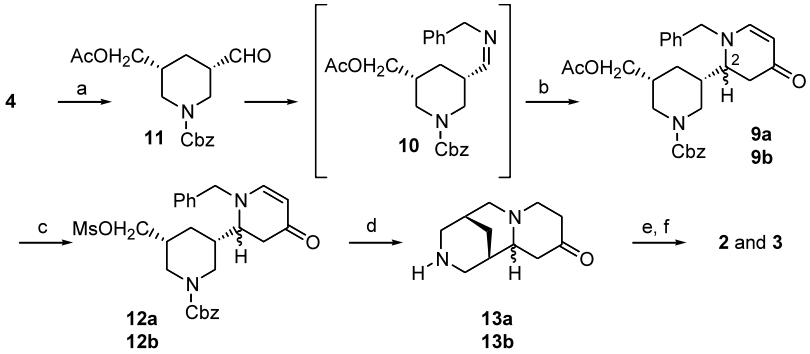
Figure 2. Selected NOE interactions detected by NOE difference studies (300 MHz, $CDCl_3$, 50°C) of **6**.

As a consequence of these unsatisfactory results, which did not allow to complete the synthesis efficiently, we considered the alternative strategy (path b) depicted in Scheme 1, based on the construction of the ring B in the last steps of the synthetic sequence, by formation of the N1–C10 bond.

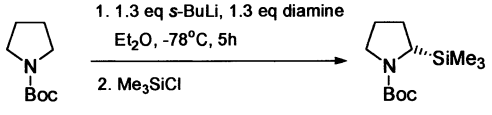
We hoped that carrying out the imino Diels–Alder cycloaddition before constructing the diazabicyclo[3.3.1] nonane framework would have been more effective, even if predictions on the stereochemical course of the reaction were more difficult to make in this case. The aldehyde **11** was converted to the required imine **10** by treatment with benzylamine in CH_2Cl_2 in the presence of $MgSO_4$ or, alternatively, of 4 Å molecular sieves (Scheme 2).

Due to its lability, this intermediate was not isolated. After exchange of the solvent, it was immediately subjected to the Lewis acid-mediated reaction with Danishefsky' diene. The cycloaddition reaction takes place from −80°C to room temperature, typically over a period of 16 h in the presence of 2 M equiv. of $ZnCl_2$ as Lewis acid in dry THF. The intermediate tetrahydropyridine derivative could not be isolated, as it underwent hydrolysis during the aqueous work up required to eliminate the Lewis acid catalyst. The dihydropyridone **9** was thus obtained directly in moderate yield, as a 1:1 mixture of *R* and *S* diastereoisomers at C2.[13] Bearing in mind that one synthetic problem in the imino Diels–Alder reactions is the imines' stability under the influence of Lewis acids more than stoichiometric, we also examined the one-pot procedure, reling on a three-component coupling reaction between aldehyde, amine and alkene via imine formation and imino Diels–Alder reaction by using lanthanide triflate as a catalyst.[14] In the presence of 10 mol% of $Sc(OTf)_3$ and $MgSO_4$, aldehyde **11** was treated with benzylamine and Danishefsky' diene in acetonitrile at room temperature. The reaction proceeded smoothly to afford **9** in very high yield. Also in this case, **9** was obtained as an inseparable mixture of adducts **9a** and **9b** in about a 1:1 ratio (estimated by ^1H NMR). Evidently, the chiral nature of aldehyde **11** does not play a crucial role in the stereochemical course of the reaction, since there is not any facial differentiation in the *endo* approach of the diene to the imine group. However, this result turned out to be favourable to us, in that it allows for a synthetic access to both the diastereoisomeric compounds **2** and **3**, at the same time. The mixture of adducts **9a** and **9b** was submitted to hydrolysis of the acetate group and then treated with MsCl to afford quantitatively the corresponding mesylates **12a** and **12b**. Finally, catalytic hydrogenation was performed, in order to remove the Cbz and benzyl protecting groups and at the same time to reduce the C5–C6 double bond. Subsequent heating in THF afforded tricycles **13a** and **13b** in high yield. Lastly, reduction of the carbonyl group followed by a reductive methylation at the N12 atom by means of $NaBH_3CN$ in the presence of formaldehyde yielded diastereoisomeric diamines **2** and **3**, at last separable by careful chromatography. Diamine (6*R*,7*S*,9*R*)-**2** and diamine (6*S*,7*S*,9*R*)-**3** show $[\alpha]_D = -20$ (*c* 1, $CHCl_3$) and $[\alpha]_D = -12$ (*c* 1, $CHCl_3$), respectively. Their NMR and MS spectral data resulted in full agreement with those published for the corresponding racemic compounds.[6b,c]

A preliminary study was performed, in which the *s*-BuLi complexes with **2** and **3** were tested for reactivity in the enantioselective deprotonation of *N*-Boc pyrrolidine **14** and subsequent trapping with Me_3SiCl (Fig. 3).[15] Since almost no lithiation occurs in the absence of a diamine, this case is especially significant for assaying the utility of new ligands. Using diamine **2**, we obtained a 63% isolated yield of silylated pyrrolidine (*S*)-**15** of 94% ee (by chiral GC), practically comparable to the



Scheme 2. *Reagents and conditions*: (a) DMSO, $(COCl)_2$, Et_3N, 90%; (b) benzylamine, Danishefsky' diene, $MgSO_4$, 10 mol% $Sc(OTf)_3$, CH_3CN, rt, 89%; (c) NaOH, MeOH, then MsCl, Et_3N, CH_2Cl_2, 76%; (d) Pd/C, H_2, EtOH, 2 equiv. HCl_{aq}, then Et_3N, THF, reflux, 65%; (e) $TsNHNH_2$, EtOH, reflux, then $NaBH_4$, THF/H_2O, reflux, 75%; (f) $NaBH_3CN$, CH_2O_{aq}, THF, 81%, then chromatographic separation (eluant: CH_2Cl_2/MeOH 95/5, NH_3 1%), 38% (**2**), 44% (**3**).



14 (S)-15

Diamine	Yield of (S)-15 (%)[a]	ee (%)[b]
(-)-sparteine **1**	76	97
(6*R*, 7*S*, 9*R*)-**2**	63	94
(6*S*, 7*S*, 9*R*)-**3**	31	21

[a] Isolated yield after column chromatography; [b] Enantiomeric excess determined by chiral GC on a 25 m × 0.25 mm id (β-cyclodextrin, dimethylpentyl derivative) column.

Figure 3.

76% yield and 97% ee which we achieved by (–)-sparteine. This good result entirely confirms the preliminary encouraging evidences provided by O'Brien et al.,[7] in their studies using a partially resolved diamine *rac*-**2** (55% ee).

Examination of diamine **3** in the same reaction led to a lower reactivity (31% yield of (*S*)-**15**) and to a disappointingly low enantioselectivity (21% ee), providing anyway insight into the important features relevant to the stereoselectivity in this deprotonation–substitution reaction. The ABC ring system of sparteine seems to be required in order to maintain the capacity of bidentate coordination of a cation, while the D ring not only appears unnecessary, but even it works against the favourable conformation for coordination in the BCD ring system. More interestingly, it has to be noted that the tricyclic diamine *ent*-**2**, easily accessible from *ent*-**4**[9] as described in Scheme 2, would represent a valuable surrogate of the commercially unavailable (+)-sparteine, for enantioselective lithiation–electrophilic quench reactions.

In summary, the first enantioselective synthesis of tricyclic diamines **2** and **3**, bearing the same absolute stereochemistry as the ABC and BCD rings of the naturally occurring alkaloid (–)-sparteine, has been reported. The key step of the route is a lanthanide triflate-catalyzed imino Diels–Alder reaction. The availability of both the enantiomeric forms (**4** and *ent*-**4**) of the chiral starting material would allow for an access to these diamine ligands as both antipodes. Work is now in progress in order to provide a totally stereoselective route to diamine **2** and to its enantiomer, in view of its high capacity of matching the enantioselectivity of sparteine.

Acknowledgements

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12. Selected data for **6**: $[\alpha]_D = -5$ (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, 1H, $J=8.1$ Hz), 7.32 (m, 5H), 5.52 (d, 1H, $J=8.1$ Hz), 5.07 (s, 2H), 4.43 (br d, 1H, $J=13.4$ Hz), 4.34 (br d, 1H, $J=13.4$ Hz), 3.93 (dd, 1H, $J=15.3$, 3.6 Hz), 3.01 (br d, 2H, $J=13.8$ Hz), 2.70 (t, 1H, $J=15.5$ Hz), 2.30 (dd, 1H, $J=15.5$, 3.3 Hz), 2.12 (br d, $J=13.5$ Hz), 1.92 (m, 1H), 1.71 (br d, $J=13.5$ Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 205.7, 169.1, 156.0, 142.5, 136.0, 128.4, 128.0, 109.7, 62.2, 60.5, 58.9, 56.4, 43.7, 39.2, 33.1, 25.6; FAB$^+$MS *m*/*z*: 341 [MH$^+$].
13. Selected data for **9a**,**b**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.20 (m, 10H), 7.12 (d, 1H, $J=8.0$ Hz), 5.07 (s, 2H), 4.96 (d, 1H, $J=8.0$ Hz), 4.55–4.10 (m, 4H), 3.99 (dd, 1H, $J=11.4$, 5.1 Hz), 3.84 (dd, 1H, $J=11.4$, 6.8 Hz), 3.34 (m, 1H), 2.76–2.25 (m, 4H), 2.03 (s, 3H), 2.20–1.85 (m, 3H), 1.15 (q, 0.5H, $J=12.4$ Hz), 0.94 (q, 0.5H, $J=12.4$ Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz, signals in brackets refer to the same carbon in **a** and **b** diastereoisomers): δ (189.9, 189.8), 170.7, 155.0, (153.6, 152.8), (136.5, 136.2), 129.1, 128.4, 127.9, 127.7, 127.2, (98.0, 97.8), 67.2, 66.0, 59.3, 58.3, (47.1, 46.9), 45.8, 38.8, (37.0, 36.4), (36.0, 35.6), (30.4, 29.9), 20.6; FAB$^+$MS *m*/*z*: 477 [MH$^+$].
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