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Chiral diamines for asymmetric synthesis: an efficient RCM construction of the ligand core of (−)- and (+)-sparteine

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Abstract—An efficient RCM-based approach was applied to the total asymmetric synthesis of a tricyclic diamine and, formally, of its enantiomer, widely known as efficient and versatile chiral ligands of the sparteine-like type.

The quinolizidine alkaloid (−)-sparteine **1**[1] (Fig. 1) is a chiral bidentate ligand with broad applicability. Of particular interest has been its complex with *sec*-butyllithium, which Hoppe and Hense[2] first showed could induce high enantioenrichments in lithiation–electrophilic quench reactions.[3] After pioneering applications in very effective asymmetric deprotonation of *N*-Boc pyrrolidine,[4] this diamine was used for dynamic resolutions[5] and deprotonations[6] of phosphine–boranes, asymmetric additions of alkyllithiums to imines,[7] asymmetric carbometallations[8] and enantioselective α-lithiations of achiral epoxides.[9]

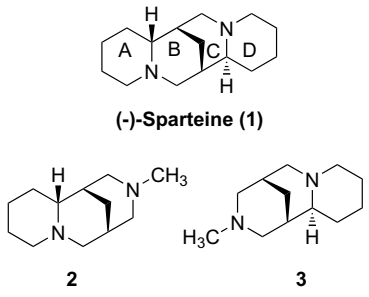

Figure 1.

The impact of sparteine as a chiral ligand in organolithium chemistry has been incredible and, more recently, the use has been extended to magnesium, for desymmetrization of anhydrides with carbon nucleophiles such as Grignard reagents,[10] and to palladium, for palladium-catalyzed oxidative kinetic resolutions of secondary alcohols.[11]

Due to the lack of ready availability of (+)-sparteine from natural sources, there is a need to develop ligands that behave in an enantiocomplementary fashion to (−)-sparteine. Our efforts in this field allowed to achieve the synthesis of various chiral bicyclic and tricyclic diamines embodying the bispidine (3,7-diazabicyclo[3.3.1]nonane) framework.[12] In particular, in a previous report,[13] we recently described the synthesis of enantiopure diamine ligands **2** and **3**, which constitute the ABC and BCD tricyclic portions of (−)-sparteine, via imino Diels–Alder reactions mediated by a catalytic amount of scandium triflate. The synthesis of **2** and **3** and their examination as ligands in the enantioselective deprotonation of *N*-Boc pyrrolidine provided insight into the important features relevant to the stereoselectivity by means of sparteine surrogates. The capacity of bidentate coordination of a cation is retained in the ABC ring system of **2**, while ring D does not allow a favourable conformation for coordination in the BCD ring system of **3**.

After these preliminary results, O'Brien et al. fully demonstrated the efficiency of diamine *ent*-**2** as a (+)-sparteine equivalent in a wide range of test reactions and provided a rapid access to this ligand from the natural

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occurring alkaloid (−)-cytisine.[14] Quite recently, Kann et al. still further expanded the field of applicability of *ent*-**2** to the desymmetrization of prochiral phosphine boranes.[15]

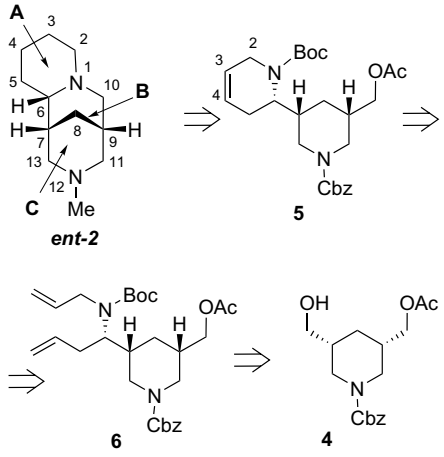
In connection with our recent results on the asymmetric synthesis of quinolizidine alkaloids,[16] we devised an innovative strategy for the preparation of **2** in both enantiomeric forms, relied on a RCM reaction as the key step. We report here our approach to *ent*-**2**.

In order to ensure a formal access to both the enantiomers of the target compound, our retrosynthetic plan (Scheme 1) features the chiral *cis*-piperidine-3,5-dimethanol monoacetate **4** as a suitable starting material. In fact, this compound, together with its enantiomer, is readily available by means of biocatalytic asymmetrization of appropriate C_S-symmetric forms.[17] The first dissection of ring B (N1–C10 bond) in *ent*-**2** yields to the decahydro-[2,3′]-bipyridine derivative **5**, which in turn could be accessed from the key intermediate **6**. In fact, the cleavage of the C3–C4 bond (dissection of ring A) in the retrosynthetic pathway reveals that **5** would in principle be obtained by a ring closing metathesis reaction on the *N*-allyl-(but-3-enyl)-carbamate moiety of **6**. Finally, intermediate **6** could in turn be fashioned by selective functional group modification of the chiral *cis*-piperidine-3,5-dimethanol monoacetate **4**.

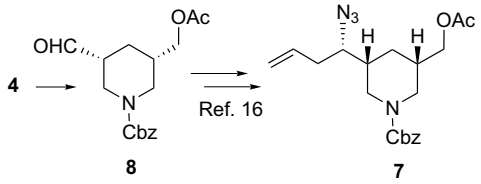
It should be noted that slight modifications of the synthetic sequence affording the precursor of RCM key step, would make this approach amenable for the synthesis of related compounds differing for the size of ring A.

We recently reported[16] a concise entry to azide **7**, starting from **4**, by means of an highly diastereoselective allylation of intermediate aldehyde **8** with (+)-allyldiisopinocampheylborane, as the key step (Scheme 2).

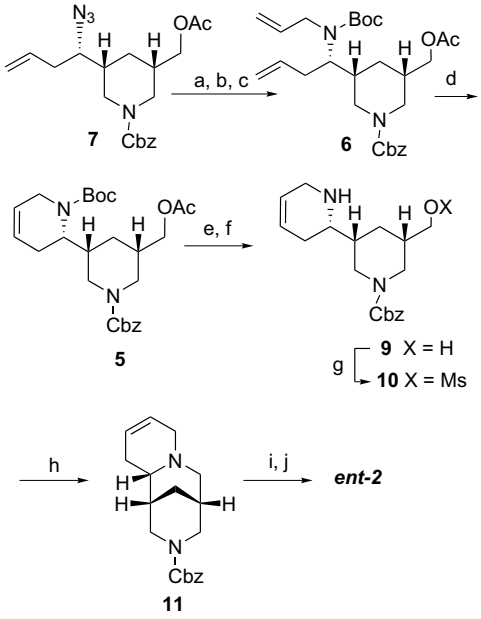
Conversion of azide **7** to *ent*-**2** was straightforward (Scheme 3). Reduction of azide with PPh_3–H_2O afforded the corresponding amine, which was directly protected as Boc carbamate and allowed to react with NaH and allyl bromide, to afford **6** in 47% overall yield from **7**. Ring closing metathesis on **6** was performed with first-generation Grubbs' ruthenium catalyst (benzylidene-bis(tricyclohexylphosphine)dichlororuthenium) and gave the decahydro-[2,3′]-bipyridine derivative **5** almost quantitatively.



Scheme 1. Retrosynthetic pathway.



Scheme 2.



Scheme 3. Reagents and conditions: (a) Ph_3P, THF, then H_2O (75%); (b) $(Boc)_2O$, TEA, CH_2Cl_2 (78%); (c) 80% NaH, allyl bromide, DMF (66%); (d) first generation Grubbs' catalyst, CH_2Cl_2, rt (89%); (e) 10% TFA, CH_2Cl_2 (98%); (f) NaOH 0.5 M, THF (98%); (g) mesyl chloride, TEA, CH_2Cl_2 (62%); (h) TEA, CH_2Cl_2, reflux (67%); (i) H_2, Pd/C, 10%, AcOEt (96%); (j) $NaCNBH_3$, CH_2O_{aq}, THF (66%).

Closure of ring B was performed by a standard three steps sequence, involving Boc deprotection, hydrolysis of acetate (**5** → **9**) and cyclization upon mesylate activation (**9** → **10** → **11**). Finally, *ent*-**2** was achieved from **11**, by means of hydrogenation of the C3–C4 double bond with concomitant Cbz deprotection, followed by a reductive methylation at the N12 atom, in the presence of $NaBH_3CN$ and formaldehyde.[18] Pure *ent*-**2** was found to have identical physical and spectroscopic properties to those reported in the literature.[14] {$[\alpha]_D$ +25.4 (*c* 0.5, EtOH), lit. $[\alpha]_D$ +26.5 (*c* 1, EtOH)}.

The efficiency of diamine *ent*-**2** as chiral ligand is by now quite established for many different kinds of reactions. Since the recovery and reuse of a chiral ligand or catalyst is an important feature in asymmetric reactions,

studies are in progress towards the synthesis of a polymer anchored version of **2** and *ent*-**2** and the evaluation of the supported ligands' retained activity.

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18. In this first preparation, 120 mg of pure *ent*-**2** were obtained. However, the synthetic sequence would be fully suitable in order to prepare larger amounts of the ligand, to be evaluated as reagent for asymmetric reactions.