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A synthesis of (±)-sparteine

Thomas Buttler and Ian Fleming*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: if10000@cam.ac.uk; Fax: +44 (0)1223 336362; Tel: +44 (0)1223 336372

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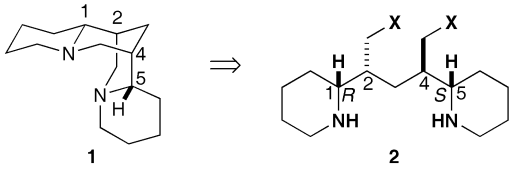
(±)-Sparteine has been synthesised with stereochemistry controlled in such a way as to make the route amenable to an efficient synthesis of either enantiomer.

(−)-Sparteine, **1**, has been used to induce absolute stereocontrol in a number of lithiations,[1] but is readily available only in one enantiomeric series. Its importance has excited much interest in its synthesis, first of the racemic alkaloid,[2,3] but only recently of the unnatural (+)-enantiomer.[4] Equally interesting has been the successful quest to find simpler analogues.[5] We report here a synthesis of the racemic alkaloid, which ought to be adaptable to the synthesis of either enantiomer.



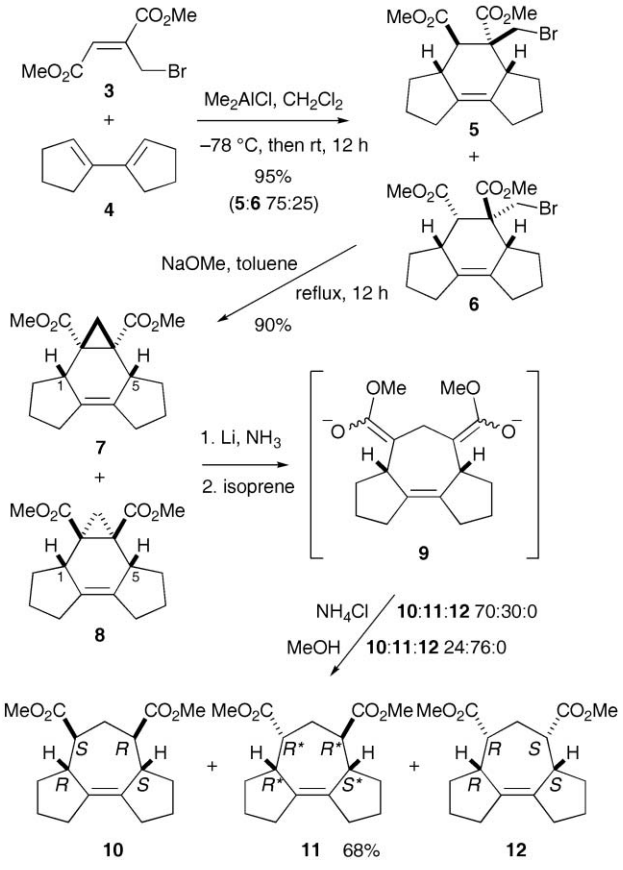
1 **2**

In our retrosynthetic analysis, the disconnection **1** ⇒ **2** is similar to that used in the earliest, but stereochemically random, synthesis of (±)-sparteine by Leonard and Beyler.[2] In particular, we sought to find an intermediate in which the two stereocentres numbered as C-1 and C-5 were firmly set up as *R* and *S*, respectively, in a *meso* intermediate, and later to set up the two stereocentres C-2 and C-4, either both *R* or both *S*, in such a way as to make either enantiomer equally easy to prepare. In the event we have synthesised racemic sparteine using this design, showing that the approach is workable. We have not had time to test its applicability to an enantiocontrolled synthesis, although there are many intriguing ways in which this might be achieved.

The first *meso* intermediates were the cyclopropanes **7** and **8**, prepared by Diels–Alder cycloaddition between dimethyl bromomesaconate **3**[6] and the diene **4**,[7] reliably setting up the stereochemical relationship between C-1 and C-5, followed by base-induced cyclopropane formation (Scheme 1).[8] The major isomer (75 : 25) was the cyclopropane **7** derived from the cycloadduct **5**, but the stereochemistry of the cyclopropanes was not of any importance, because the next step was to remove it in a reductive cleavage. Lithium in liquid ammonia reduced a mixture of the two cyclopropanes to give the bisenolate **9**, which can still be regarded as effectively *meso*, if one ignores the geometry of the enolates.

The interesting step, creating the stereochemistry at C-2 and C-4, was the protonation of the bisenolate. There are three possible diastereoisomeric products, two of which, the *R*,*S*,*R*,*S* and the *R*,*R*,*S*,*S* isomers **10** and **12**, respectively, are *meso*, and the third of which, the *R**,*R**,*R**,*S** **11**, the diastereoisomer required for the synthesis of sparteine, is not. The latter was identifiable because it had *two* methoxy singlets in the ^{1}H-NMR spectrum. In practice, we found no trace of isomer **12**, but the ratio in which the other two diastereoisomers were formed was affected by the nature of the acid used to protonate the bisenolate. Quenching the bisenolate in solution in liquid ammonia with ammonium chloride gave the esters **10**[9] and **11** in a ratio of 70 : 30. Quenching the solution with methanol, however, gave the esters **10** and **11** in a ratio of 24 : 76, acceptably favourable at this stage for the isomer that we wanted. Crystallisation followed by chromatography of the mother liquors gave a total yield of the diester **11** of 68% based on the cyclopropanes **7** and **8**.

With the relative stereochemistry set up, the remaining steps looked, and eventually were, straightforward. The next step, however, gave us some trouble, in spite of appearing to be uncomplicated. Ozonolysis in dichloromethane solution took place at low temperature as expected, but workup with dimethyl sulfide or triphenylphosphine gave us mixtures of isomeric diketones instead of a single diketone **15**. We deduced that one or more of the four stereocentres had to some extent lost its configuration. Although all four are in principle equilibratable, we did not at first see why any of them should have been so easily disturbed in essentially neutral conditions at low temperature. The explanation we offer is that the molozonide is formed as usual, but an intermediate ketone oxide **13** (Scheme 2) derived from it does not rapidly undergo the usual dipolar cycloaddition to give the ozonide, because the ring size for the intramolecular reaction is unfavourable—the smallest of the rings which would be formed is 8-membered. The ketone oxide group in the intermediate **13** is effectively an activated carbonyl group, and its unusually long life



Scheme 1

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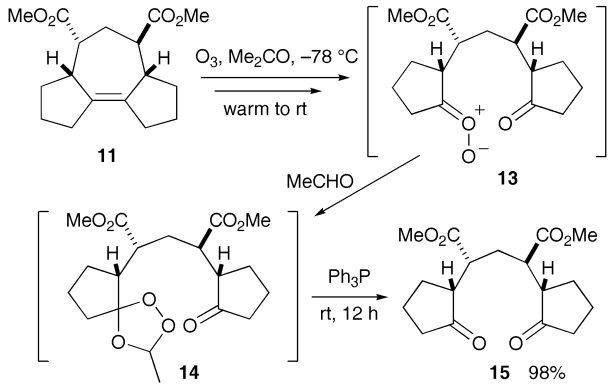
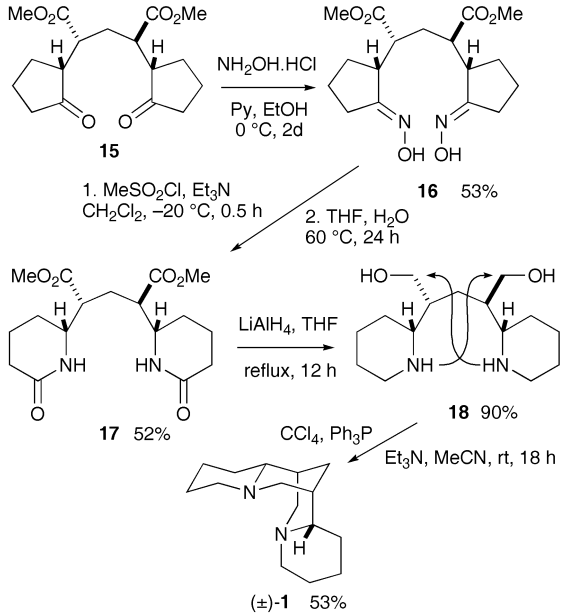


Scheme 2



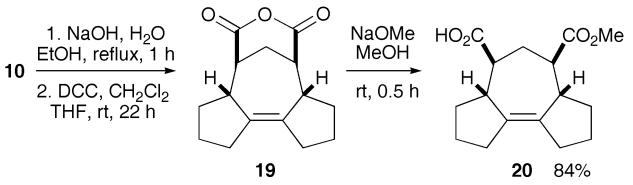
Scheme 3

allows epimerisation by the equivalent of enolisation. We do not, of course, know on which side of the molecule epimerisation occurs, and so the particular ketone oxide drawn as **13** is an arbitrary choice.

The solution to the problem, which also supports our analysis, was to carry out the ozonolysis in acetone, allowing the ketone oxide to be trapped by the solvent. Under these conditions we obtained the diketone **15** with 4% epimerisation. Better still was to add acetaldehyde to the acetone to trap the ketone oxide, even more efficiently, as the ozonide **14**. In this way we detected among the products only the diketone **15**, and isolated it in 98% yield.

The remaining steps (Scheme 3) were relatively uneventful, but have not been optimised. The bisoxime **16** was separable in 53% yield from the geometrically isomeric oximes by chromatography and crystallisation.[10] Beckmann rearrangement took place when the bisoxime methanesulfonate was warmed in aqueous tetrahydrofuran. The bislactam **17** gave the bispiperidine diol **18** on reduction with lithium aluminium hydride,[11] and the diol gave (±)-sparteine **1** when treated with carbon tetrachloride and triphenylphosphine, with the key bond-forming steps identified by the curly arrows.

Returning to the key protonation step **9** → **10** + **11**, we found that equilibration of the esters **10** and **11** using sodium methoxide in refluxing methanol, starting either from the isomer **10** or from the isomer **11**, gave, unhelpfully, an 84 : 16 ratio, which more or less matched a calculated difference in energy of 5.55 kJ mol^{-1} in



Scheme 4

favour of the *meso* isomer, with still no sign of the other *meso* isomer **12**, which was calculated to be higher again in energy by 6.46 kJ mol^{-1}.[12]

Looking ahead, we foresee that if the protonation step could be carried out with either an *R*- or an *S*-selective, enantiomerically enriched, chiral acid—if there were such a reagent—there would be an extraordinarily simple way to set up the stereochemistry at C-2 and C-4 in either sense. If an effective chiral acid cannot be found, there are still other pathways imaginable, of which one might use the *meso* anhydride **19** (Scheme 4), opening it with one of several methods for achieving enantiotopic selectivity.[13] Accordingly, we prepared for this work by making the anhydride **19** and opening it to give the racemic monomethyl ester **20** in an overall yield of 84%. Unfortunately, this ester was not epimerised by sodium methoxide in refluxing methanol over three days, and so more work needs to be done to find a route to the enantiomerically enriched natural or unnatural product.

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7 We thank StylaCats Limited for a gift of this diene, which we also prepared ourselves by the method of D. S. Greidinger and D. Ginsburg, *J. Org. Chem.*, 1957, **22**, 1406.

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9 Structure determined by X-ray crystallography.

10 The mixture of oxime byproducts—geometrical isomers and monoximes—can in principle be recycled, but we did not test this.

11 Separating the organic product from the inorganic byproducts proved to be difficult, but using sodium potassium tartrate in the workup solved the problem.

12 We thank Robert Richardson for the calculations, carried out using MacroModel (version 8.0) and the MM2 forcefield.

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