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Concise asymmetric synthesis of (−)-sparteine†

Jean-Paul R. Hermet,[a] Matthew J. McGrath,[a] Peter O'Brien,*[a] David W. Porter[a] and John Gilday[b]

[a] *Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: paob1@york.ac.uk; Fax: +44 (0)1904 432516; Tel: +44 (0)1904 432535*

[b] *AstraZeneca, Process R & D, Avlon Works, Severn Road, Hallen, Bristol, UK BS10 7ZE*

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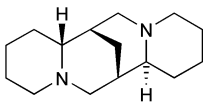
A six-step asymmetric synthesis of natural (−)-sparteine from ethyl 7-iodohept-2-enoate is reported, involving a connective Michael addition of an amino ester-derived enolate to an α,β-unsaturated amino ester.

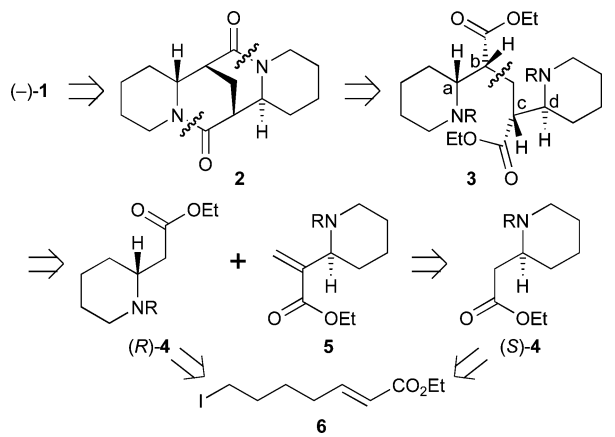
(−)-Sparteine **1**, a cardiovascular agent,[1] is the most well-known of the naturally occurring lupin alkaloids[2] due to its widespread use as a chiral ligand in asymmetric synthesis.[3] Following on from our recent work on the synthesis of sparteine analogues[4] (culminating in the introduction of a (+)-sparteine surrogate[5]), we became intrigued by (−)-sparteine as a target molecule in its own right. In particular, we envisaged developing a general, concise and connective methodology for the preparation of lupin alkaloids; the total asymmetric synthesis of (−)-sparteine was seen as a challenging test-bed of the new methodology. The route should also be adaptable to the synthesis of new "designer" sparteine analogues for use as chiral ligands.



(–)-sparteine **1**

Although seven different approaches to *racemic* sparteine (albeit with little or no control of relative stereochemistry) have been described over the last fifty years,[6] only one asymmetric synthesis is known. In 2002, Aubé and co-workers reported an elegant synthetic sequence that delivered (+)-sparteine in an efficient, 15-step route.[7] Herein, we report a new approach to the lupin alkaloids: natural (−)-sparteine **1** was prepared in just six steps from ethyl 7-iodohept-2-enoate. The key feature of the route is a connective, Michael reaction between an amino ester-derived enolate and an α,β-unsaturated amino ester.

Our retrosynthetic analysis of (−)-sparteine **1** is shown in Scheme 1. The direct precursor to (−)-**1** is tetracyclic bislactam **2**

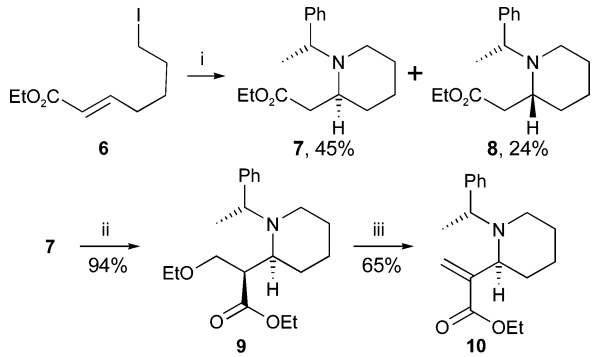


Scheme 1 Retrosynthetic analysis of (−)-sparteine **1**.

† Electronic supplementary information (ESI) available: full experimental procedures/data for **7**, **8**, *ent*-**7**, *ent*-**8**, **9**, **10**, **2** and (−)-**1**. See http://www.rsc.org/suppdata/cc/b4/b406632d/

which we imagined would be prepared from bicyclic amino ester **3**. Amino ester **3** is a 1,5-dicarbonyl compound which would be constructed from the union of the enolate of amino ester (*R*)-**4** with Michael acceptor **5** (itself prepared from amino ester (*S*)-**4**). An important design feature in this route to (−)-sparteine **1** was the anticipated stereocontrol in the Michael reaction. Alkylations of enolates of cyclic β-amino esters **4** (R = Boc[8] and R = α-methylbenzyl[9]) are known to give the required C_a–C_b relative stereochemistry (*syn* stereochemistry of C_a and C_b hydrogens as drawn—see **3**) and enolate reaction with an α,β-unsaturated ester was expected to proceed with similar C_a–C_b stereocontrol. Furthermore, stereoselective *protonation* of the Michael adduct enolate should proceed under analogous stereocontrol to furnish the desired C_c–C_d stereochemistry (*anti* stereochemistry of C_c and C_d hydrogens—see **3**). At the outset, we imagined preparing β-amino esters (*R*)- and (*S*)-**4** (R = α-methylbenzyl) using our previously published three-step route from ethyl 7-chlorohept-2-enoate, based on Davies-style lithium amide conjugate addition.[10] However, in the end, we developed a stereoselective version of a reaction introduced by Bunce *et al*.[11] in which ethyl 7-iodohept-2-enoate **6** was converted into β-amino ester **4** (R = α-methylbenzyl) in one step.

The three-step synthesis of Michael acceptor **10** is shown in Scheme 2. First of all, reaction of known[12] ethyl 7-iodohept-2-enoate **6** with (*R*)-α-methylbenzylamine (EtOH, Et_3N, reflux, 16 h) gave cyclic β-amino esters **7** and **8** directly, presumably *via* substitution and subsequent intramolecular conjugate addition of the amine (as proposed by Bunce *et al.* for the benzylamine reaction[11]). The stereochemistry of **7** and **8** was assigned as shown since we had previously prepared *ent*-**8** *via* a different route.[10] Although the stereocontrol in this reaction (~2 : 1 from the ^{1}H NMR spectrum of the crude product) was moderate,[13] amino esters **7** and **8** were readily separable by column chromatography and this allowed us to easily progress gram quantities of the major product **7** (45% isolated yield) for our synthetic endeavours. Attempts to improve the yield of **7** *via* acid- or base-mediated epimerisation of **8** have so far proved fruitless. Nonetheless, cyclic amino esters such as **7** are well established synthetic building blocks[8,9] and the *one*-



Scheme 2 *Reagents and conditions*: (i) (*R*)-α-methylbenzylamine, Et_3N, EtOH, reflux, 16 h. (ii) (a) 1.5 equiv. LHMDS, THF, −78 °C, 1 h; (b) $EtOCH_2Cl$, −78 °C → rt over 4 h; (c) rt, 12 h. (iii) 1.2 equiv. KO^{t}Bu, THF, −78 °C, 8.5 h.

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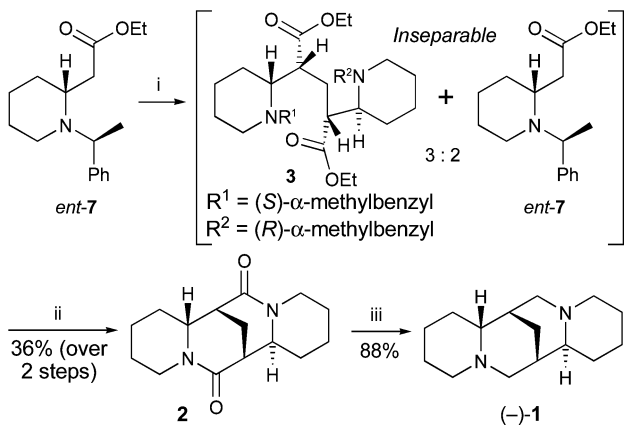
step direct asymmetric synthesis of amino ester **7** could prove to be a useful methodology for alkaloid natural product synthesis.

Next, amino ester **7** was alkylated using LHMDS and $EtOCH_2Cl$ to give a 94% yield of adduct **9**. Adduct **9** was obtained as a single diastereomer and, although of no consequence to the present work (as this stereochemical feature would subsequently be removed), the stereochemistry was assigned by analogy with other alkylations of *ent*-**7** reported by Lhommet *et al*.[9] Elimination of ethoxide from **9** using a procedure slightly modified from that reported by Sworin and Lin[14] (KO^tBu, THF, −78 °C) then gave Michael acceptor **10** (65% yield) (Scheme 2).

For the key Michael reaction, we proposed to combine the enolate of amino ester *ent*-**7** (prepared in 46% yield from (*S*)-α-methylbenzylamine and iodo ester **6** according to the method described above) with α,β-unsaturated amino ester **10**. Surprisingly, we were unable to find many examples of the Michael addition of monoester-derived enolates to α,β-unsaturated esters.[15–18] Adaptation of two of these protocols[15,16] led to a successful reaction with our system (Scheme 3).

Amino ester *ent*-**7** was deprotonated using LDA and the resulting enolate was allowed to react with Michael acceptor **10** at −78 °C → −30 °C for 8.5 hours in total before quenching with 1 M $HCl_{(aq)}$ at 0 °C.[16] After work-up and purification by column chromatography, we isolated an inseparable mixture (~3 : 2) of adduct **3** and amino ester *ent*-**7**. From close inspection of the ^1H and ^{13}C NMR spectra of this mixture, adduct **3** appears to be generated as a single diastereomer (stereochemistry assigned based on our earlier analysis of the expected stereocontrol[19] and on subsequent conversion into (−)-sparteine **1**). As it was not possible to obtain a pure sample of **3**, all of the ~3 : 2 mixture of **3** and *ent*-**7** was subjected to transfer hydrogenation ($Pd(OH)_2$/C, $NH_4^+HCO_2^-$, EtOH, reflux, 14 h). Under these conditions, hydrogenolysis of the α-methylbenzyl groups followed by cyclisation occurred to give bislactam **2** (single diastereomer) in 36% yield over the two steps from *ent*-**7** (isolated by crystallisation from Et_2O). Finally, lithium aluminium hydride reduction of bislactam **2** gave (−)-sparteine **1** {$[\alpha]_D$ −18.1 (*c* 1.3 in EtOH); $[\alpha]_D$ −18.0 (*c* 1.3 in EtOH) recorded for an authentic sample} in 88% yield after distillation, identical by ^1H and ^{13}C NMR spectroscopy to an authentic sample (Scheme 3).

In summary, a concise, six-step asymmetric synthesis of (−)-sparteine has been completed. This methodology represents a new approach to the lupin alkaloid family and could be adapted to complete total syntheses of other lupin alkaloids (*e.g.* lupanine and multiflorine[2]). Of note, our chiral auxiliary-based approach is also suitable for the synthesis of (+)-sparteine and for the synthesis of either enantiomer of novel sparteine analogues (for evaluation as chiral ligands for asymmetric synthesis).



Scheme 3 *Reagents and conditions*: (i) (a) 1.05 equiv. LDA, THF, −78 °C for 20 min, 0 °C for 5 min then to −78 °C for 30 min; (b) 1.0 equiv. Michael acceptor **10**; (c) −78 °C → −30 °C over 5.5 h then −30 °C for 3 h; (d) 1 M $HCl_{(aq)}$; (ii) (a) $Pd(OH)_2$/C, $NH_4^+HCO_2^-$, EtOH, reflux, 14 h; (b) crystallise from Et_2O; (iii) $LiAlH_4$, THF, reflux, 16 h.

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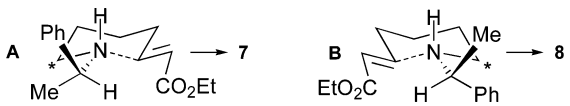

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