Tetrahedron 69 (2013) 1369–1377

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Asymmetric synthesis of (−)-(1*R*,7a*S*)-absouline

Stephen G. Davies *, Ai M. Fletcher, Clément Lebée, Paul M. Roberts, James E. Thomson, Jingda Yin

*Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK*

ARTICLE INFO

*Article history:*
Received 17 September 2012
Received in revised form 26 October 2012
Accepted 13 November 2012
Available online 29 November 2012

*Keywords:*
(−)-(1*R*,7a*S*)-Absouline
Lithium amide
Conjugate addition
Asymmetric synthesis

ABSTRACT

The most efficient and concise asymmetric synthesis of (−)-(1*R*,7a*S*)-absouline to date, which was accomplished in eight steps and 20% overall yield from commercially available starting materials, is described. The doubly diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)-amide to an enantiopure α,β-unsaturated ester derived from L-proline was employed as the key step. Subsequent hydrogenolytic N-debenzylation and acid-promoted cyclisation of the resultant β-amino ester produced the 1-aminopyrrolizidin-3-one scaffold, then reduction with DIBAL-H was followed by DCC-mediated coupling with (*E*)-*p*-methoxycinnamic acid to complete the synthesis of (−)-(1*R*,7a*S*)-absouline.



## 1. Introduction

The pyrrolizidine ring, which consists of two fused five-membered rings with a nitrogen atom at the bridge head, is a common unit within alkaloids, which have been shown to possess various biological activities.[1] For example, SC-53116 **1**[2] was reported to be the first selective agonist at the 5-$HT_4$ receptor, which has shown promise in the treatment of irritable bowel syndrome, atrial arrhythma, urinary incontinence and gastrointestinal motility disorders; other examples of naturally occurring pyrrolizidines include the glycosidase inhibitors (+)-hyacinthacine A1 **2**[3] and (+)-broussonetine N **3**.[4] The 1-aminopyrrolizidine (+)-absouline **4**, its (*Z*)-stereoisomer isoabsouline **5** and their corresponding *N*-oxide derivatives were isolated from the Caledonian plants *Hugonia oregana* and *Hugonia penicillanthemum* in 1987.[5] Since their isolation, two racemic[6,7] and three asymmetric[8–10] syntheses of absouline **4** have been reported. For example, Huang and co-workers applied a diastereoselective carbanionic approach to form a *trans*-2-subsituted-3-aminopyrrolidine in their asymmetric synthesis of (+)-absouline **4**, in 14 steps and 0.8% overall yield from *N*-Cbz-protected (*S*)-aspartic anhydride.[8,11] Couty and co-workers showcased the boron trifluouride-mediated rearrangement of an enantiopure 2-cyanoazetidine to give the corresponding enantiopure 3-aminopyrrolidine in their asymmetric synthesis of (−)-absouline **4**, which was accomplished in 12 steps and 6.3% overall yield from (*S*)-α-methylbenzylamine.[9] More recently, Scheerer and co-workers have reported the synthesis of (−)-absouline **4** in eight steps and 10% overall yield from *N*-Boc protected L-proline methyl ester, employing the conjugate addition of benzylamine to a (*Z*)-α,β-unsaturated ester[10] (Fig. 1).

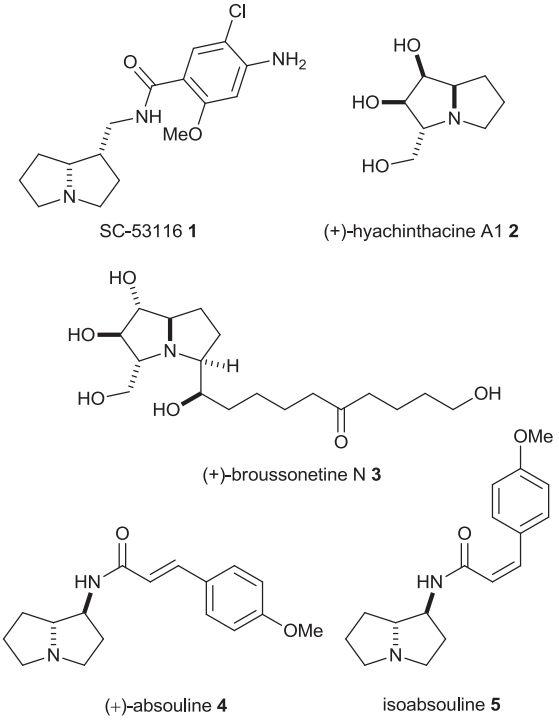
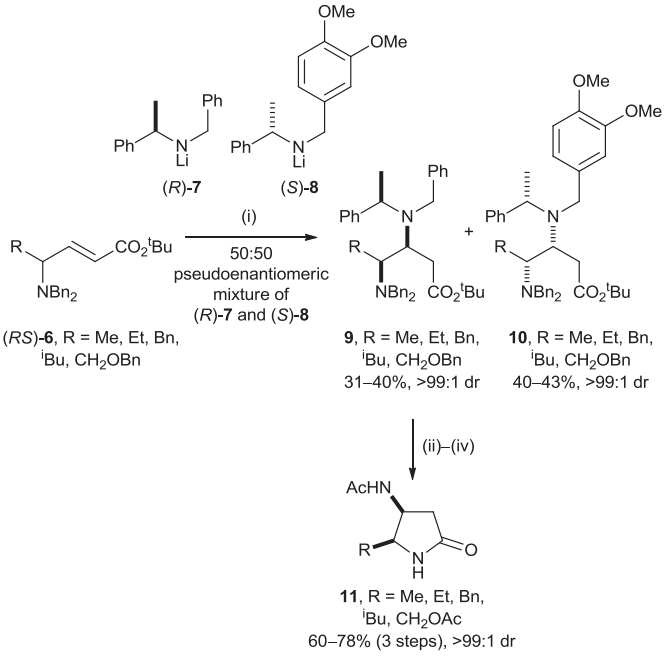



**Fig. 1.** Pyrrolizidine alkaloids **1**–**3**, (+)-absouline **4** and isoabsouline **5**.

* Corresponding author. E-mail address: steve.davies@chem.ox.ac.uk (S.G. Davies).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.11.080

We have recently developed a protocol for the efficient parallel kinetic resolution (PKR) of a range of racemic, acyclic *N*-protected γ-amino-α,β-unsaturated esters.[12] In this procedure, the conjugate addition of a 50:50 pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**7** and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*S*)-**8** to racemic γ-amino-α,β-unsaturated esters (*RS*)-**6** (derived from the corresponding racemic α-amino acids) furnished, in each case, a 50:50 mixture of enantiopure β-amino esters **9** and **10** as single diastereoisomers (>99:1 dr). The resultant β,γ-diamino esters **9** were then elaborated by hydrogenolytic N-debenzylation followed by acid-promoted cyclisation to enantiopure 5-substituted-4-aminopyrrolidin-2-ones, which were isolated as the corresponding acetate derivatives **11** (Scheme 1).




**Scheme 1.** Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**7**, lithium (*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(α-methylbenzyl)amide (*S*)-**8** (50:50 mixture), THF, −78 °C, 2 h; (ii) $H_2$ (5 atm), $Pd(OH)_2$/C, HCl (1.25 M in MeOH), rt, 48 h; (iii) HCl (3.0 M aq), 90 °C, 18 h; (iv) $Ac_2O$, pyridine, rt, 12 h.

As an extension of this methodology, we became interested in the introduction of a cyclic constraint within the γ-amino-α,β-unsaturated ester and therefore proposed to investigate the compatibility of DL-proline derived α,β-unsaturated ester (*RS*)-**12** within the PKR protocol. It was envisaged that this methodology would provide access to the 1-aminopyrrolizidin-3-one scaffold **15** via sequential N-deprotection and acid-promoted cyclisation. Further elaboration of **15** would then give the corresponding enantiopure 1-aminopyrrolizidine **16**, a precursor to absouline **4** (Fig. 2).

## 2. Results and discussion

### 2.1. Evaluation of *tert*-butyl (*RS*,*E*)-3-[*N*(1′)-benzylpyrrolidin-2′-yl]propenoate in the proposed PKR protocol

α,β-Unsaturated ester (*RS*)-**12** was prepared in three steps from racemic proline DL-**17**. Treatment of DL-**17** with benzoyl chloride, followed by global reduction with $LiAlH_4$ afforded *N*-benzyl protected α-amino alcohol (*RS*)-**19** in 81% yield. Swern oxidation of (*RS*)-**19** and in situ Wittig olefination of the resultant aldehyde gave racemic α,β-unsaturated ester (*RS*,*E*)-**12**[13] in >95:5 dr, and 42% yield and >99:1 dr after purification (Scheme 2).

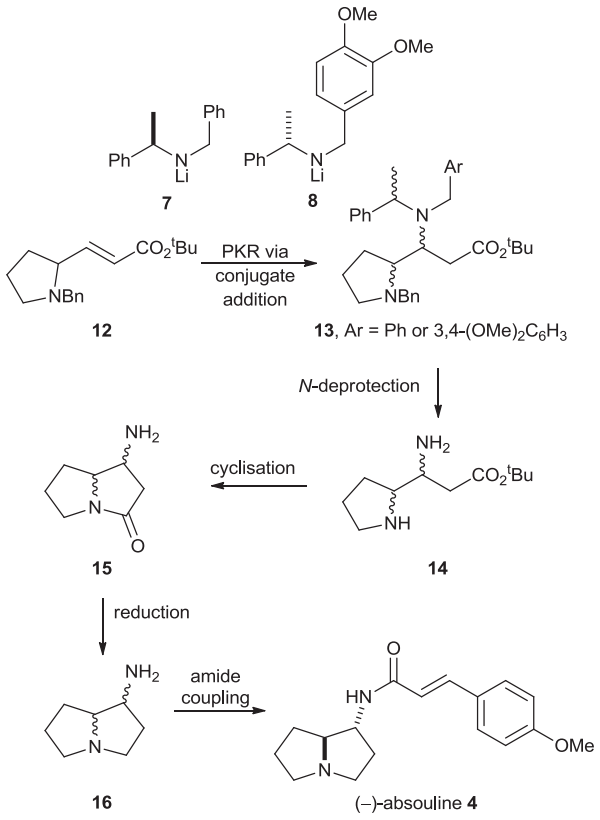
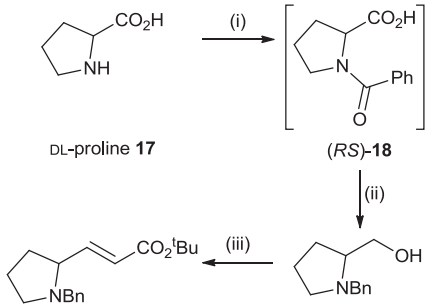



**Fig. 2.** Proposed asymmetric synthesis of absouline **4**.




**Scheme 2.** Reagents and conditions: (i) PhCOCl, NaOH, $H_2O$, 0 °C, 2 h; (ii) $LiAlH_4$, THF, reflux, 18 h; (iii) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 °C, 1 h, then $Ph_3P{=}CHCO_2{}^tBu$, $CH_2Cl_2$, rt, 18 h.

When investigating PKR,[14] we have found that it is prudent to follow a strategy of first evaluating the level of substrate control offered by the chiral α,β-unsaturated ester upon conjugate addition of achiral lithium *N*-benzyl-*N*-isopropylamide **20**.[15] In cases where high levels of substrate control are observed, the conjugate addition of lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**7** to the racemic α,β-unsaturated ester [i.e., a mutual kinetic resolution (MKR)] is then performed, allowing the maximum levels of enantiodiscrimination (as quantified by the stereoselectivity factor, *E*)[16] to be determined by analysis of the product distribution by $^1$H NMR spectroscopy. For those substrates with high levels of enantiorecognition (*E*>10), PKR employing a 50:50 pseudoenantiomeric mixture of enantiopure lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)-amide (*R*)-**7** and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*S*)-**8** may be performed. This approach was adopted to investigate whether α,β-unsaturated ester **12** would be