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Efficient construction of polycyclic alkaloid synthetic precursors by a xanthate free radical addition and Mannich cyclisation cascade

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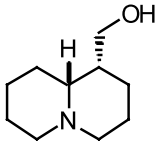
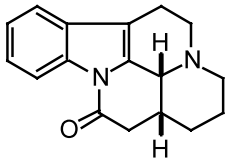
Abstract—Routes to synthetic precursors of Lupin and Eburna alkaloids have been developed, featuring the rapid construction of highly functionalised intermediates by the intermolecular radical coupling of xanthates and alkenes, followed by acid-mediated condensation–cyclisation. © 2002 Elsevier Science Ltd. All rights reserved.

Polycyclic alkaloids continue to be of widespread interest to both chemists and biologists. For example, the lupin-derived quinolizidine alkaloids such as (−)-lupinine **1**,[1] and the Eburna alkaloid *cis*-deethyleburnamine **2**, have been the subject of several total syntheses[2,3] and pharmacological studies.[4] We have long been interested in intermolecular tin-free radical addition of dithiocarbonates (xanthates) to alkenes as a powerful method for the rapid construction of highly functionalised synthetic intermediates, and have recently demonstrated their potential in several total syntheses.[5] Here we describe an approach towards polycyclic alkaloids using the radical chemistry of xanthates to rapidly build up advanced intermediates for a biomimetic acid-mediated cascade condensation–cyclisation.[6]

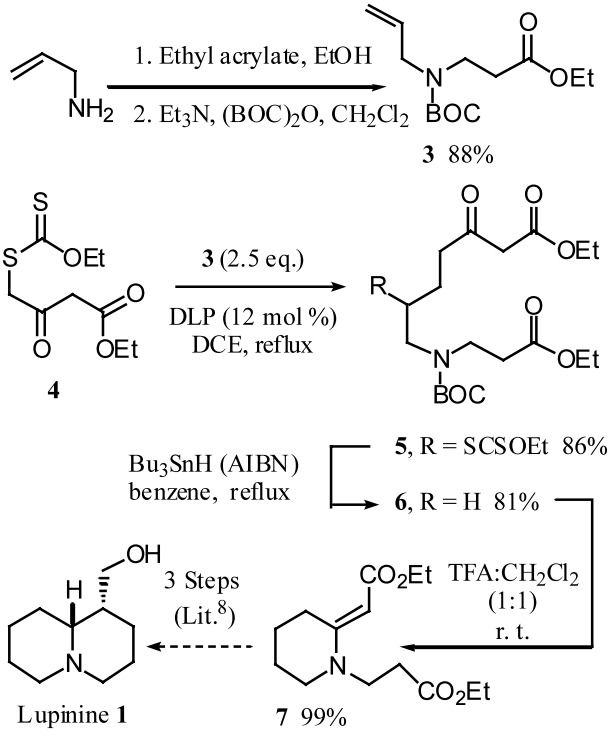


Lupinine **1**



cis-Deethyleburnamine **2**

We envisaged forming the bicycle of lupinine by the condensation–cyclisation of a secondary amine onto a pendant β-ketoester group. Thus, our route towards this key intermediate begins from readily available allylamine with conjugate addition to ethyl acrylate, followed by *t*-butyl-oxycarbonyl (BOC) protection of the amine to give the alkene radical coupling partner, carbamate **3** in 88% yield over the two steps (Scheme 1). The xanthate **4**, which is derived in one step from commercially available ethyl chloroacetoacetate (ethyl chloroacetoacetate, 2 equiv. potassium *O*-ethylxan-



Scheme 1. Formal synthesis of lupinine **1**.

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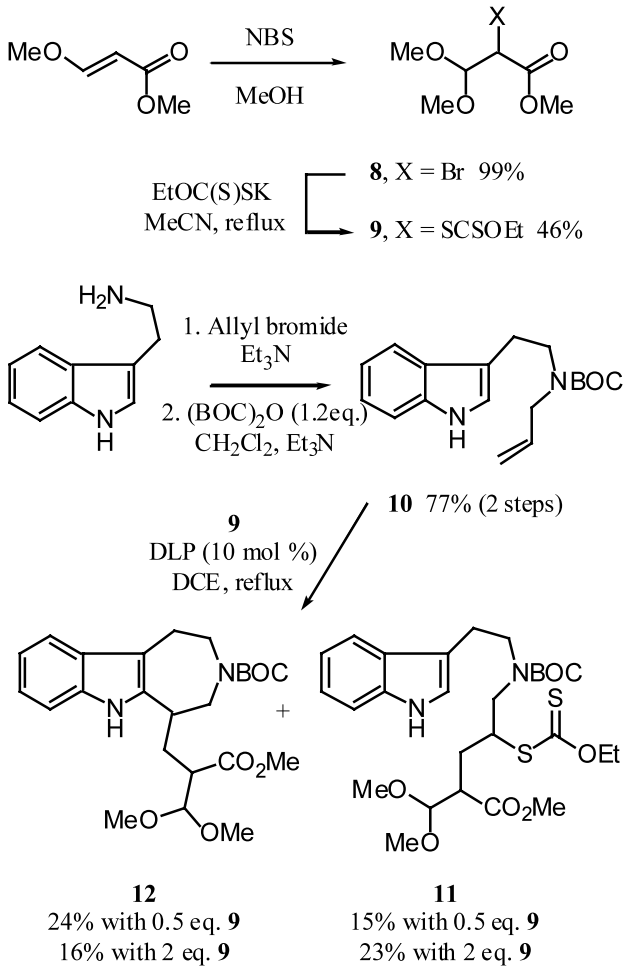
thate, acetone, rt, 2 h, 97% yield), is then reacted with a 2.5-fold excess of **3** and a small amount of the radical initiator dilauroyl peroxide (DLP) at high concentration (1.5 M in **4**) in refluxing dichloroethane (DCE), to give the addition product **5** in 86% yield. Transformation to the desired condensation precursor, aminoketodiester **6**, is performed in a single step by removal of the xanthate with tributyltin hydride and azoisobisbutyronitrile (AIBN), in 81% yield.[7] Under acidic conditions (trifluoroacetic acid (TFA)/dichloromethane 1:1) **6** rapidly undergoes a deprotection–cyclisation–condensation cascade to give monocyclic compound **7** in 99% yield, which constitutes a formal synthesis of (±)-lupinine.[8]

Inspired by the success of this approach, we turned our attention to the more complex skeleton of the indolic Eburna alkaloids. We supposed that an indole ring bearing a protected aminoaldehyde could be condensed in an acid-mediated Mannich-type cyclisation, to give an iminium ion, which would subsequently be trapped by the indole ring system to give four of the five rings present in the deethyleburnamine carbon skeleton; further elaboration, as reported in the literature,[3e] would then lead to deethyleburnamine itself. The key indole aminoaldehyde could in turn be prepared by the coupling of a highly functionalised xanthate with a tryptamine-derived alkene.

The required xanthate is formed from commercially available methoxy methacrylate by bromination with *N*-bromosuccinimide (NBS) in methanol to give bromoacetal ester **9** (99% yield), followed by displacement with the potassium salt of ethyl dithiocarbonate in acetonitrile at reflux (46% yield) (Scheme 2). This last reaction is atypical of such bromine displacements, which usually proceed in much higher yield; in the present case, elimination of methanol from product or starting material competes with the relatively slow displacement of a secondary somewhat hindered bromide. The alkene coupling partner **10** is available starting from tryptamine by a two-step allylation and protection sequence in 77% overall yield.

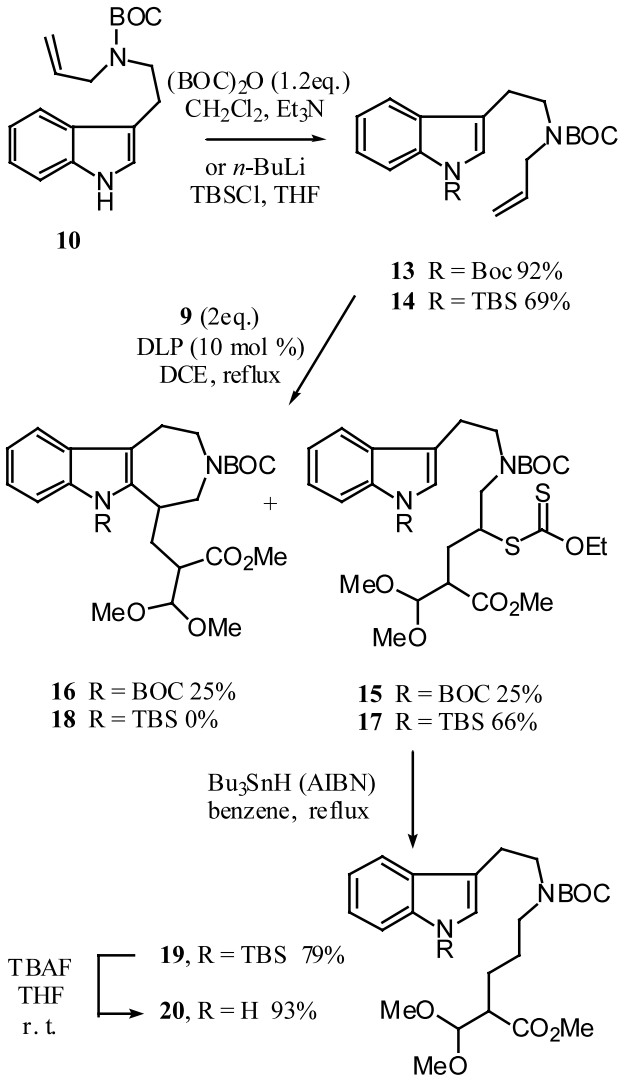
In contrast to the radical addition described above, reaction of xanthate **9** and 2 equiv. of alkene **10** with 10 mol% of DLP in refluxing DCE results in very low conversion to the desired addition product **11** (15% yield). Along with a substantial quantity of starting xanthate **9** (ca. 40%), a tricyclic product **12** was isolated in 24% yield, evidently resulting from radical cyclisation onto the 2-position of the indole, followed by rearomatisation. Cyclisations following xanthate addition on an alkenic chain bearing an appropriately placed aromatic substituent are well precedented, and indeed we have deliberately exploited them in synthesis.[9] As might be expected, addition of further initiator resulted in increased conversion to tricycle **12** (up to 55% with 2 equiv. of DLP), but changes in initiator, solvent and temperature failed to improve the yield of the desired intermediate **11**. However, use of a two-fold excess of xanthate over alkene provided a slightly more favourable 23% yield of **11**, with **12** being obtained in



Scheme 2. Attempted formation of **11**.

16% yield, possibly due to more efficient trapping of the transient secondary radical.

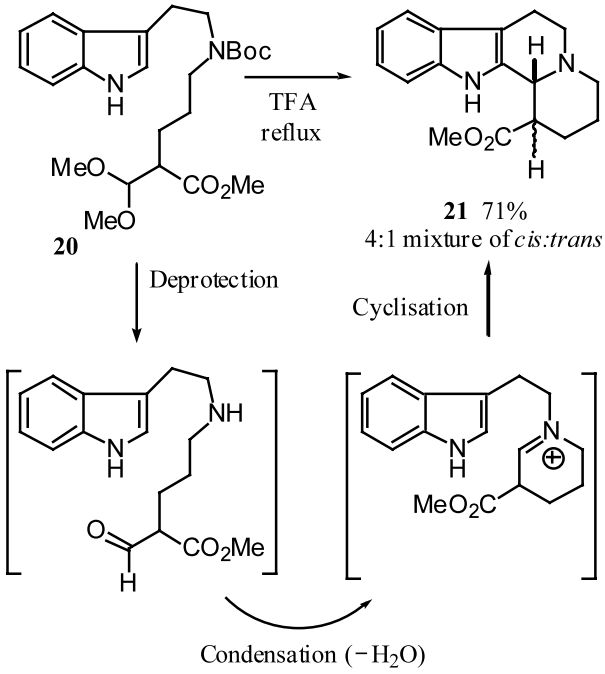
Whilst **12** itself represents an unusual synthesis of a 6/5/7 indolic tricycle, a method was sought for enabling selective formation of xanthate **11** by blocking access of the incipient secondary radical to the indole nucleus. Protection of the nitrogen in both indoles and pyrroles with a bulky group is a well-established method of directing attack in ionic reactions from the 2-position to the 3-position, and we wondered if analogous protection at the indole nitrogen might block the undesired radical cyclisation at the 2-position by steric hindrance. Di-BOC protected aminoindole **13** was duly prepared from **10** and treated under the conditions described above (200 mol% **9**, 10 mol% DLP, reflux DCE), but to our dismay we obtained di-BOC xanthate **15** in only 25% yield, with concurrent cyclisation also leading to tricycle **16** in 25% yield (Scheme 3). Supposing that the electron-withdrawing effect of the carbamate group was possibly counteracting its steric influence by accelerating cyclisation, we instead prepared the *tert*-butyldimethylsilyl (TBS) protected indole **14** in 69% yield from **10** (1.2 equiv. *n*-BuLi, 2 equiv. TBSCl),[10] and addition of this alkene to xanthate **9** under the usual conditions gave exclusively xanthate **17** in 66% yield, with the alkene returned in 23% yield. To our



Scheme 3. Synthesis of precursor **20**.

knowledge, this is the first extension of such a protecting group strategy to block an indole 2-position from radical attack. As a prelude to the condensation/cyclisation, the xanthate was efficiently reduced under the conditions described above for **5**, in 79% yield, without concurrent cyclisation, and the TBS group removed in 93% yield with tetra-*n*-butylammonium fluoride (TBAF) to give free indole **20**.[11]

The anticipated acid-mediated deprotection and cascade cyclisation proceeded smoothly upon treatment of **20** with TFA at reflux, to give the known quadricyclic amine **21** in 71% yield, as a 4:1 *cis*:*trans* mixture (Scheme 4).[12] The presumed mechanism for this step is initial deprotection of the (BOC)amine and acetal protected aldehyde, and subsequent condensation between these groups to give an iminium ion. This is followed by a Pictet–Spengler ring closure.[13] The somewhat lower yield observed here, compared to the cyclisation to form **7**, may be due to the well documented susceptibility of indole rings to attack by *tert*-butyl cation which is liberated during acidic BOC deprotection.[14] Lounasmaa et al. have reported that ester **21** may be



Scheme 4. Acid-mediated condensation/cyclisation.

further elaborated in a four-step sequence to (±)-*cis*-deethyleburnamine,[3e] and thus the formal synthesis of this molecule has been achieved.

In summary, a strategy for the synthesis of polycyclic alkaloids has been developed using the radical addition of xanthates to alkenes to give highly functionalised intermediates suitable for Mannich-type acid-mediated cyclisation. In this context, formal syntheses of (±)-lupinine and (±)-*cis*-deethyleburnamine have been realised. By virtue of the tolerance of the xanthate addition step for a variety of functional groups, we anticipate that this strategy may be applicable to a wide range of related polycyclic alkaloids.

Acknowledgements

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10. All attempts to triisopropylsilylate **10** resulted in substantial degradation.
11. TBS protected indoles are susceptible to deprotection by TFA, and thus the subsequent cyclisation reaction may be performed directly without this final deprotection, albeit in rather lower yield (49%).
12. Compound **21** has been shown to isomerise under acidic conditions, see: Ref. 3e.
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