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A short formal route to (±)-lepadin B using a xanthate-mediated free radical cyclisation/vinylation sequence†

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A short route towards (±)-lepadin B has been developed starting from cyclohexenylamine, featuring a diastereoselective xanthate-mediated free radical cyclisation/vinylation sequence.

(−)-Lepadin B **1** is a decahydroquinoline alkaloid first isolated in 1995 from *Clavelina lepadiformis*;[1] it possesses significant *in vitro* cytotoxicity against human cancer cell lines,[1] and has been the subject of two recent total syntheses.[2,3] Our continuing interest in developing reactions using xanthates as free radical precursors has led to several recent applications in synthesis,[4] and here we present a new approach to (±)-**1** (Fig. 1) based on a xanthate-mediated radical cyclisation/vinylation sequence.

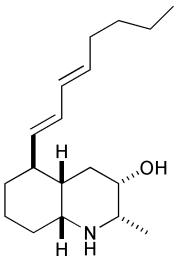
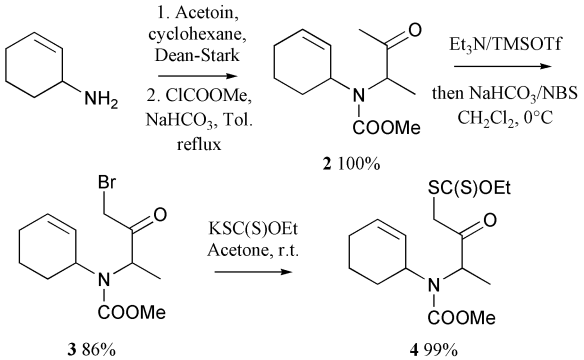


Fig. 1 (−)-Lepadin B **1**

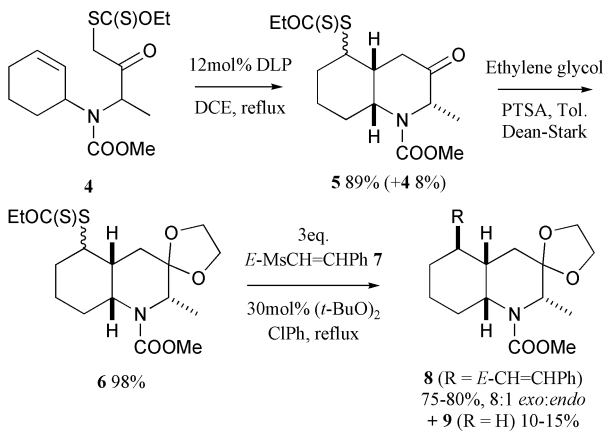
The xanthate radical cyclisation precursor **4** was prepared in four steps from readily available cyclohex-2-enylamine.[5] Thus condensation with acetoin and protection of the nitrogen with methylchloroformate gave methoxycarbamate **2** in quantitative yield (Scheme 1). One-pot bromination of crude **2** *via* formation of the trimethylsilyl (TMS) enol ether in dichloromethane followed by treatment with *N*-bromosuccinimide (NBS) led to α-bromo ketone **3** in 86% yield, and displacement of the bromine with potassium *O*-ethyldithiocarbonate afforded the desired xanthate **4** in 99% yield.

Initiation of the radical cyclisation was best performed using 12 mol% dilauroyl peroxide (DLP) in degassed refluxing dichloroethane (DCE), under which conditions the bicyclic xanthate **5** was formed in 89% yield over 2 hours, with **4** being recovered in 8% yield (Scheme 2).‡ The bicycle of **5** was formed exclusively *cis*,[6] and as an approximately 3:2 mixture of epimers at the carbon bearing the xanthate group; the lack of selectivity at this latter centre is of no consequence since it is subsequently regenerated as a secondary radical. The fortuitous concurrent epimerisation of the α-methyl group to the thermodynamically favoured *cis* isomer may be catalysed by the trace of lauric acid, known to form during the thermal homolytic fission of DLP.

We planned to introduce a carbon substituent at the xanthate-bearing carbon using radical vinylation methodology developed in our laboratories.[7] However, attempts to react xanthate **5** with ethyl styryl sulfone[8] under established conditions (chlorobenzene 1.5 M in **5**, 4.5 M in ethyl styryl sulfone, 30 mol% *tert*-butyl peroxide, reflux, 12 h) met with very low conversion to the desired styryl bicycle, accompanied by substantial reduction by hydrogen transfer. Such a reduction may be facilitated by the activated nature of the hydrogen lying between the carbamate and the ketone in **5**, which would generate a tertiary capto-dative radical upon abstraction. Following this hypothesis, we supposed that temporary protection of the ketone moiety with ethylene glycol (2 eq. ethylene glycol, 3 mol% *p*-toluene sulfonic acid (PTSA), toluene, Dean-Stark, 5 h, 98% yield) might alleviate this problem; in fact we found that ketone protection did indeed largely suppress reduction, and that complete conversion of **5** could be achieved if mesylstyrene **7**[9] was used as the vinylating reagent.[10] Thus treatment of a 1.5 M solution of the acetal **6** and a three-fold excess of **7** in refluxing chlorobenzene with 30 mol% *tert*-butyl peroxide for 12 h gave **8** in 75–80% yield as a 8:1 *exo*/*endo* mixture at the newly formed centre, along with a variable quantity (10–15%) of the corresponding reduced product **9**. The high concentration of **6** and **7** is key to obtaining high conversion. Both diastereoisomers of **8** and reduced product **9** proved inseparable by chromatography at this stage, though **9** was evident in the proton NMR and mass spectra by comparison to an authentic sample prepared *via* tributyltin hydride/AIBN reduction of **6**



Scheme 1



Scheme 2

† Electronic supplementary information (ESI) available: experimental and characterisation data for the transformation of **13** and **14**. See http://www.rsc.org/suppdata/cc/b2/b203604e/

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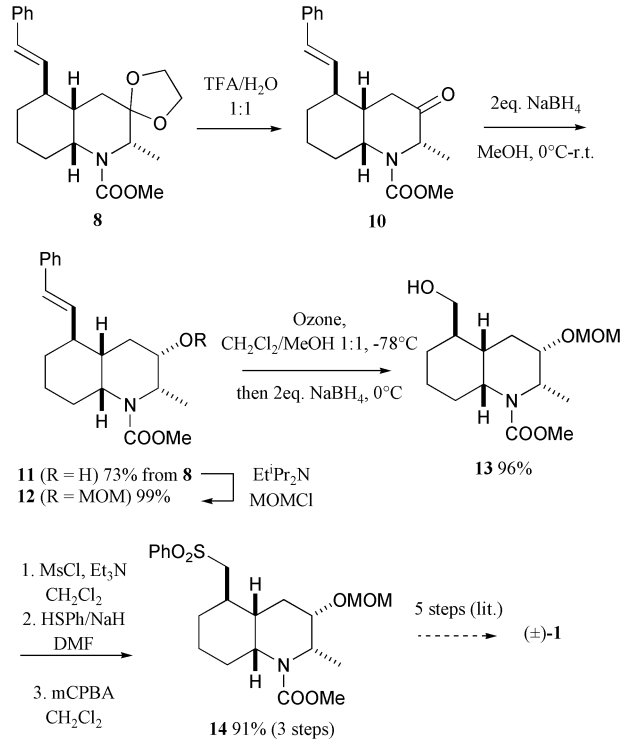
(1.2 eq. tributyltin hydride, 10 mol% AIBN, benzene, reflux 2h, 79% yield).

Treatment of acetal **8** with 50% aqueous trifluoroacetic acid gave crude ketone **10** which was reduced without further purification with $NaBH_4$ in methanol to give alcohol **11** (Scheme 3). It appears that a high degree of control is exerted by the convex bicycle of **10**, and no evidence of the epimeric alcohol was observed in the proton NMR of the crude alcohol. Furthermore, careful column chromatography of the crude product allowed removal of both the alcohol derived from the reduced compound **9** and the undesired *endo* isomer of **11**, affording alcohol **11** as a single isomer in 73% overall yield from acetal **8**. Protection of the alcohol with chloromethoxymethane gave MOM ether **12** in 99% yield. Introduction of the diene side chain in lepadin B was initiated by reductive ozonolysis of the styryl moiety to give alcohol **13** (96% yield). Conversion to the known sulfone 14[3] was performed *via* mesylation and displacement with sodium phenylthiolate, followed by oxidation with *meta*-chloroperbenzoic acid (mCPBA), in 91% yield over the 3 steps. This concludes our formal route towards lepadin B, as Toyooka *et al.* have shown that sulfone **14** may be converted to lepadin B in a five step sequence utilising a Julia coupling with commercially available 2-heptenal.[2]



Scheme 3

The short route towards (±)-lepadin B described here should prove amenable to the synthesis of related natural products lepadins A and C.[11] Furthermore, the ready availability of *S*-cyclohex-2-enylamine[12] suggests that an enantioselective total synthesis of (−)-lepadin B could be straightforwardly realised.

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Notes and references

‡ Interestingly, when cyclisation was performed on a tosyl protected analogue of **4**, the cyclisation proceeded with only 30% conversion, presumably for reasons of steric hindrance.

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