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Towards the total synthesis of tangutorine by intramolecular Diels–Alder reaction

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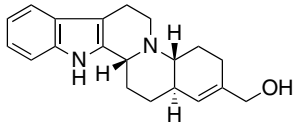
Abstract—The syntheses of 3,5-disubstituted-2-sulfolenes, and their participation in Pictet–Spengler reactions to give precursors of tangutorine, are described.

Tangutorine is an alkaloid isolated from the leaves of *Nitraria tangutorum*, a Chinese plant with some importance in local medicine.[1] Significant biological activity has recently been reported.[2] It has been the subject of some synthetic attention including total synthesis.[3]



Tangutorine

Here, we report progress towards achieving a total synthesis of this molecule via an inverse electron demand intramolecular Diels–Alder (IMDA) protocol. A retrosynthetic analysis is shown (Scheme 1). After a trivial functional group interconversion to an ester and reconnection of the tryptophan-derived carboxylate, the six-membered carbocycle disconnects by the key IMDA step to give an electron-deficient diene and an enamine in **1**. It was felt that a direct Pictet–Spengler disconnection of **1** would lead to a diene aldehyde, which would be difficult to synthesise and work with and hence the next retrosynthetic step gives a sulfolene (**2** or **3**). 3-Carbomethoxy-3-sulfolenes are known to extrude sulfur dioxide giving a geometrically predictable diene on heating while 3-carbomethoxy-2-sulfolenes can be isomerised and made to extrude SO_2 in one pot.[4] Pictet–Spengler disconnection of **2**/**3** gives a tryptophan ester and either aldehyde **4** or **5**. The stereochemistry of the Diels–Alder reaction was difficult to predict with any degree of confidence as literature precedent is in short supply and simple models were inconclusive. It is well known that the stereochemistry of the carboline 1-position can be adjusted if necessary and it was felt that the first-formed product, an unsaturated ester would also allow epimerisation of the γ-hydrogen with base to give the desired *trans* ring junction.[5]

Our route for the synthesis of **2**/**3** involved forming a tryptophan derivative bearing a masked enamine substituent and using this in the Pictet–Spengler reaction. We chose a sulfoxide as a leaving group since this could be eliminated with base to give an enamine, as has been demonstrated by Ishibashi's group, but is not so reactive as to cause problems in earlier steps.[6]

Reaction of tryptophan methyl ester with (2-chloroethyl)-phenyl sulfide[7] provided **6** in poor yield (Scheme 2).[8] Conditions were found, which gave a 45% yield of recovered starting material and virtually no doubly alkylated product. We first carried out a model study using benzaldehyde in order to test the feasibility of carrying out the Pictet–Spengler reaction followed by enamine formation. Recent work by the groups of Bailey and Cook has allowed the Pictet–Spengler reaction to be carried out with high degrees of stereoselectivity.[9] Reaction of **6** with benzaldehyde gave a single diastereomer **7** in 75% yield. The product was assigned as **7** by literature precedent, since the conditions used were

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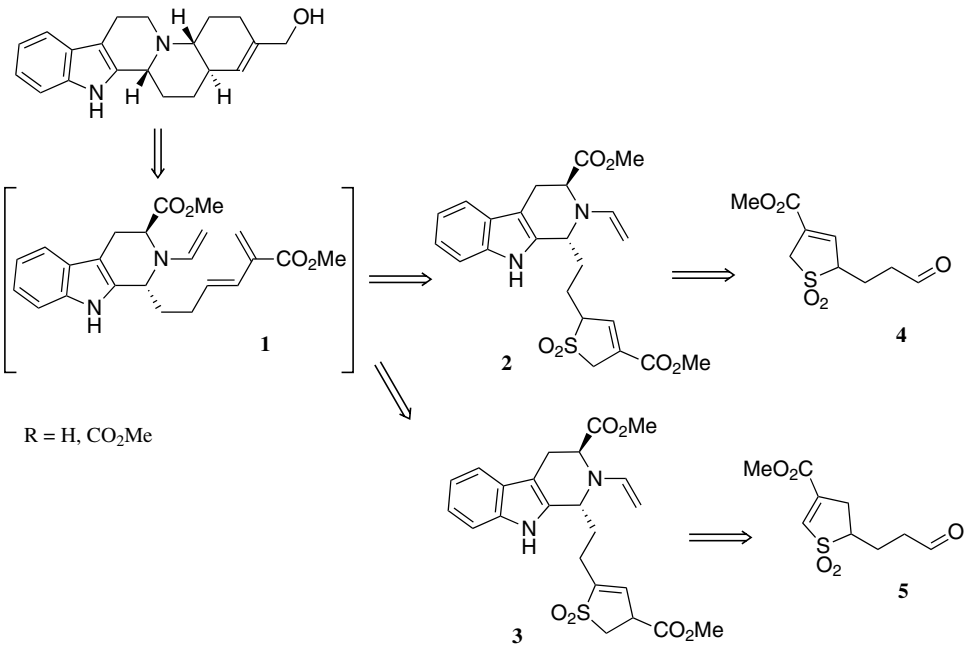
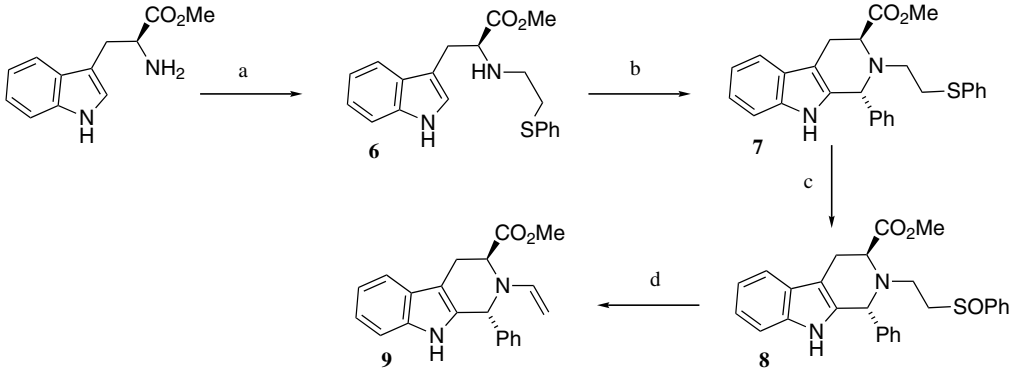


Scheme 1.

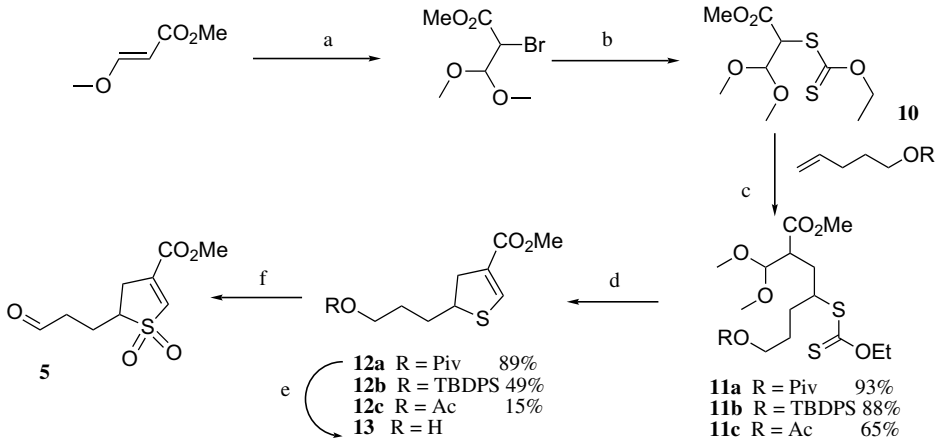


Scheme 2. Reagents and conditions: (a) $NaHCO_3$, (2-chloroethyl)-phenyl sulfide, MeOH, rt, 18 h, 26%; (b) PhCHO, $CHCl_3$/AcOH 5:1, reflux, 18 h, 75%; (c) *m*-CPBA, CH_2Cl_2, 0 °C, 1 h, 66%; (d) $NaHCO_3$, toluene, reflux, 45% conversion after 24 h.

those of Cook, which are known to give high stereoselectivity for *trans*-products when N_b is substituted, though this particular substituent has not previously been investigated.[10] This compound was oxidised with *m*-CPBA in reasonable yield to give a mixture of sulfoxides **8**. The ratio was approximately 1.25:1 but no attempt has been made to identify the diastereomers. On treatment with $NaHCO_3$ in refluxing toluene, proton and carbon, NMR studies indicated clean conversion of the sulfoxides to the enamine **9**. The enamine was not purified.

Our efforts towards the synthesis of compound **4** will be detailed in a full paper. The methodology adopted for the synthesis of **5** was Zard's xanthate radical transfer protocol.[11] This has been shown to be an excellent method for the preparation of xanthate-substituted acetals, themselves good precursors for 3,4-dihydrothiophenes.

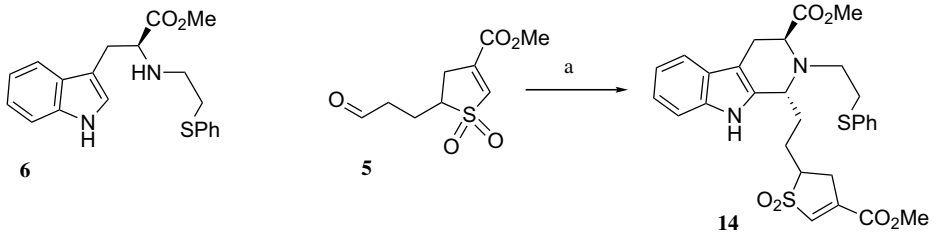
The xanthate precursor **10** was prepared from methyl methoxyacrylate in 37% overall yield (Scheme 3). Purification of **10** proved difficult, accounting for the low yield. A number of alkenes were used for the addition step with the aldehyde masked as a hydroxy group, variously protected. Generally the radical addition, under Zard's standard conditions, proceeded well with good yields of products **11a** and **11b** obtained and a reasonable yield of the acetate **11c**. The products were then subjected to cleavage of the xanthate and acid-catalyzed cyclisation, which provided the dihydrothiophenes **12a**–**c**. As might have been expected, the acetate group performed poorly in this sequence but we were slightly surprised to obtain only 49% of **12b**. It appeared that the silyl protection was largely lost after cyclisation had occurred since an 18% yield of alcohol **13** was also recovered. With our best protecting group established as pivaloyl, we took **12a** and gently cleaved with methoxide to give **13**, oxidised to the sulfolene and performed a Swern oxidation to obtain our target aldehyde **5**, in just under 25% yield from the starting olefin.



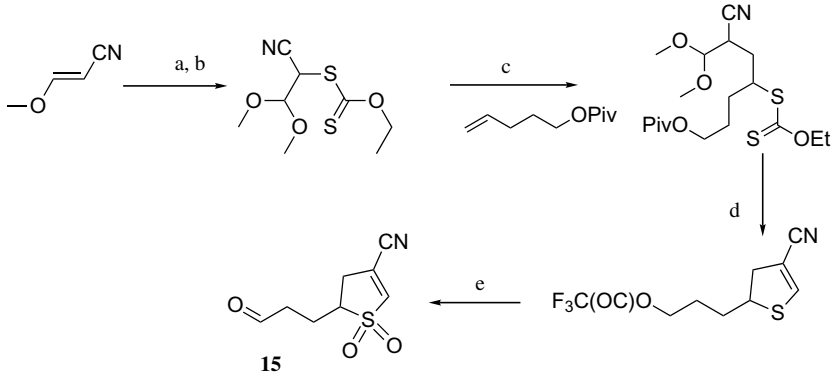
Scheme 3. Reagents and conditions: (a) NBS, MeOH, 0 °C; (b) (i) NaI, Et_2O, rt, 1 h; (ii) KSC(S)OEt, Et_2O, 0 °C to rt, 18 h, 37% for three steps; (c) dilauryl peroxide (16 mol %), 1,2-DCE, reflux, 2 h; (d) (i) ethylenediamine, EtOH, rt, 1 h; (ii) TFA, CH_2Cl_2, rt, 1 h; (e) NaOMe, MeOH, 0 °C to rt, 20 h, 70%; (f) (i) oxone, MeOH, H_2O, 0 °C, 15 min, 55%; (ii) oxalyl chloride, DMSO, CH_2Cl_2, triethylamine, −78 °C to rt, 90%.

Pictet–Spengler reaction of **6** with aldehyde **5** gave a very poor yield of **14** (a single diastereomer was obtained), one problem being that the methyl ester in **5** was cleaved under the reaction conditions (Scheme 4). The methyl ester would also have been problematic for the later stages of the proposed synthesis, since it would have had to be differentiated from the tryptophan-derived ester.

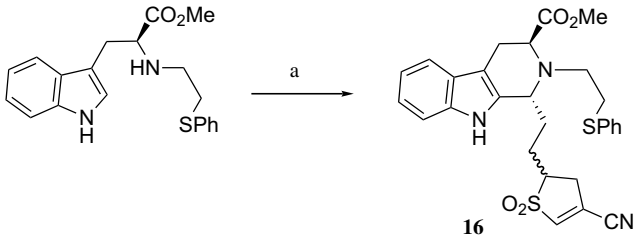
To avoid using the ester, we prepared the 3-cyano-2-sulfolene derivative **15** (Scheme 5). The Zard chemistry followed much the same route as for the preparation of **5** but there were some idiosyncracies. While the radical addition of the xanthate took place in very high yield, the cleavage/cyclisation protocol was much more difficult to achieve. Conditions were found, which cleaved the xanthate and the pivaloyl protecting group, giving the trifluoroacetate ester of the desired product in moderate yield after cyclisation. Cleavage of the trifluoroacetate, and oxidation to a sulfolene were straightforward but Swern oxidation gave only a 37% isolated yield of the aldehyde **15**, which was found to be a fairly unstable compound and had to be used immediately.



Scheme 4. Reagents and conditions: (a) AcOH, 70 °C, 24 h, 7%.



Scheme 5. Reagents and conditions: (a) NIS, MeOH, 0 °C to rt, 3 h, 88%; (b) KSC(S)OEt, Et_2O, 0 °C to rt, 22 h, 47%; (c) dilaurylperoxide (16 mol %), 1,2-DCE, reflux, 6 h, 90%; (d) (i) NaOMe, MeOH, 0 °C to rt, 24 h; (ii) Amberlite-H 120; (iii) TFA, CH_2Cl_2, rt, 1 h, 41% over three steps; (e) (i) KOH, MeOH/H_2O, 0 °C, 1 h, 63%; (ii) oxone, MeOH/H_2O, 0 °C, 1 h, 65%; (iii) oxalyl chloride, DMSO, CH_2Cl_2, triethylamine, −78 °C to rt, 37%.



Scheme 6. Reagents and conditions: (a) **15**, $CHCl_3$/AcOH, 5:1, reflux, 18 h, 78%.

In contrast to ester **5** the use of **15** in the Pictet–Spengler reaction (Scheme 6) gave a 78% yield of the desired products **16** (1.1:1 ratio of diastereomers, again a *trans* stereochemistry at the carboline ring has been assumed with a mixture of epimers at the sulfolene 5-position).

Work is ongoing to complete the synthesis via the IMDA reaction.

Acknowledgements

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