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Asymmetric synthesis of (*S*)-(−)-*N*-acetylcolchinol via Ullmann biaryl coupling

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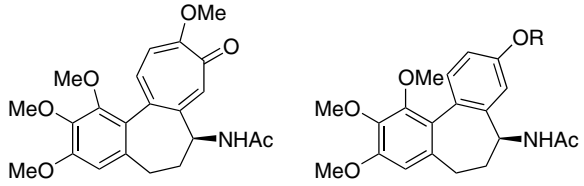
Abstract—A modified Ziegler Ullmann coupling process has been developed as the key step in an effective synthesis of (*S*)-(−)-*N*-acetylcolchinol, analogues of which are selective vascular targeting agents with potential importance in cancer chemotherapy. Asymmetric induction is achieved by enamide hydrogenation using FerroTANE catalysts.

The anti-tumour properties of colchicine **1** have been known for several decades.[1,2] It has also been established that the biological activity stems from strong tubulin binding, which leads to selective disruption of tumour vasculature with consequent tumour necrosis. Colchicine itself is much too toxic to have any therapeutic value in this regard, but it has recently been recognised that derivatives of *N*-acetylcolchinol **2** could be of value in cancer therapy. A particular compound that has been in clinical development at AstraZeneca is the phosphate pro-drug of *N*-acetylcolchinol, known as ZD6126 **3**[3] (Fig. 1).



Colchicine, **1**

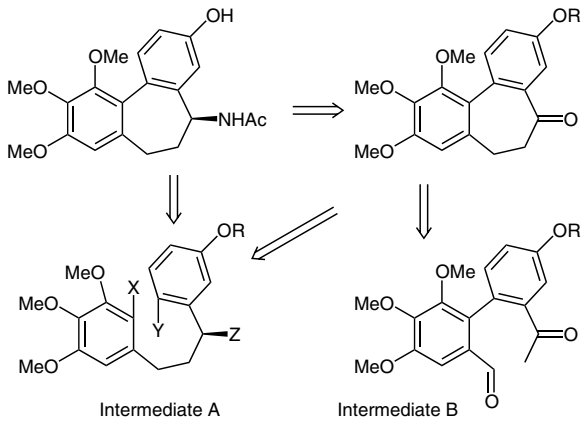
R = H, *N*-Acetylcolchinol, **2**
R = $P(O)OH_2$, ZD6126, **3**

Figure 1.

We have been investigating a number of synthetic approaches to *N*-acetylcolchinol as a key precursor to ZD6126. In the first instance we needed a route that could supply material for clinical trials, but ultimately we were looking for a route that had the potential to be developed for commercial manufacture of the drug.[4]

N-Acetylcolchinol was originally prepared in low yield as a derivative of colchicine.[5] The natural product is extracted commercially, predominantly for the treatment of gout, from the lily *Gloriosa superba*, a native flower of Northern India. However, reported yields of colchinol derivatives from colchicine are low and the development of an effective total synthesis was considered to be a better option. In this communication we report an efficient total synthesis of *N*-acetylcolchinol, which utilises low temperature Ullmann coupling chemistry for the construction of the core ring system.

For construction of the colchinol ring system, two strategies were considered as shown in Figure 2. In both



Intermediate A

Intermediate B

Figure 2.

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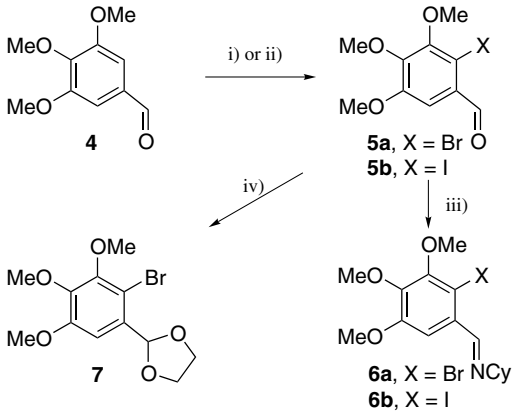
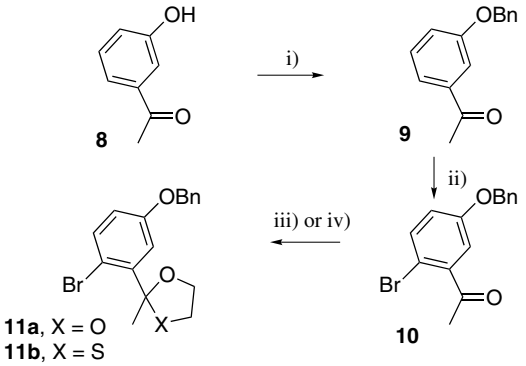
approaches, the key step is formation of the bond between the aromatic rings and a range of appropriately substituted aromatic building blocks were required to evaluate the routes. 3,4,5-Trimethoxybenzaldehyde **4** was selectively brominated or iodinated to provide **5a/b**, which were functionalised, as shown in Scheme 1, to provide a range of potential A-ring synthons **6a/b** and **7**.

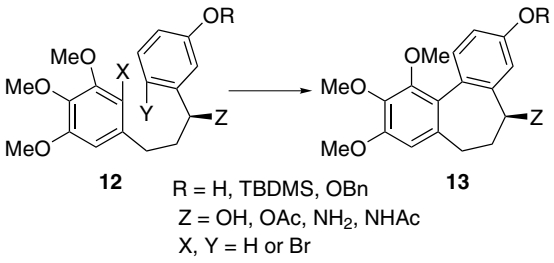


Scheme 1. (i) NBS/MeCN/96%; (ii) NIS/MeCN/88%; (iii) cyclohexylamine/toluene/88%, X = Br, 98% X = I; (iv) ethylene glycol/TsOH/90%.

3-Hydroxyacetophenone was readily converted into a range of C-ring precursors as shown in Scheme 2. Several approaches were explored that involved cyclising intermediates of type A, in Figure 2, to give the core tricyclic ring system. Such strategies have literature precedent,[6–8] and the required precursors, such as **12**, were readily prepared from chalcone derivatives, formed by reaction of aldehydes **4** or **5a** with ketones **9** or **10**.[9] One report suggested that such compounds (where X = Y = H) can be cyclised efficiently using thallium trifluoroacetate,[6] but we were unable to carry out such a reaction in anything other than very low yields.[7,8] Modest yields (34–60%) of a tricyclic product **13** were provided when intermediate **12** (Y = Br, X = H, Z = OAc) was treated with a catalytic amount of $Pd(OAc)_2$ (up to 1 equiv required) but the process was not considered to be of practical utility (Scheme 3).[9]

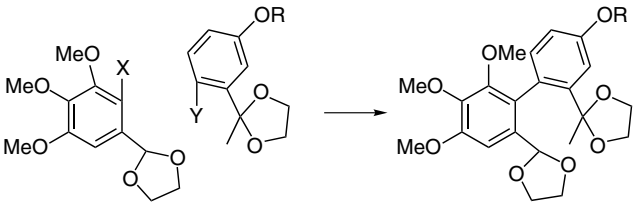


Scheme 2. (i) BnCl/DMF/K_2CO_3, 90%; (ii) NBS/MeCN/70%; (iii) $HO(CH_2)_2OH$/TsOH/Tol/93%; (iv) $HS(CH_2)_2OH$/TsOH/Tol/66%.



Scheme 3.

Faced with the inefficiency of routes involving intramolecular biaryl cyclisation of intermediates of type A, we turned our attention to the alternative approach, starting with an intermolecular biaryl coupling, to provide intermediates of type B (Fig. 1), followed by subsequent aldol cyclisation. The Suzuki reaction is perhaps the most obvious choice for preparing biaryl systems and we therefore prepared a broad range of boronic acid and boronate derivatives from bromides **7** and **11**. However, although we expended considerable efforts to find palladium catalysts and procedures for coupling the components, yields were always disappointing, Scheme 4.[10]

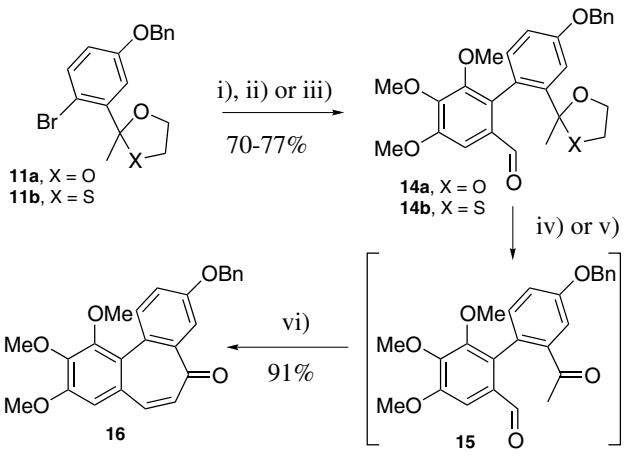


Scheme 4.

The Ullmann reaction is an alternative biaryl coupling reaction and Ziegler et al. devised an ambient temperature procedure that is useful for cross-coupling of aromatics with certain substitution patterns.[11] The aromatic systems that they were able to couple were electron-rich iodides and bromides bearing *ortho*-substituents that are capable of co-ordinating to copper. We therefore devised coupling components bearing substituents that would, in the first instance, be suitable for co-ordinating to copper during an Ullmann reaction, and could then be converted into residues that would cyclise to form the central 7-membered colchinol ring.

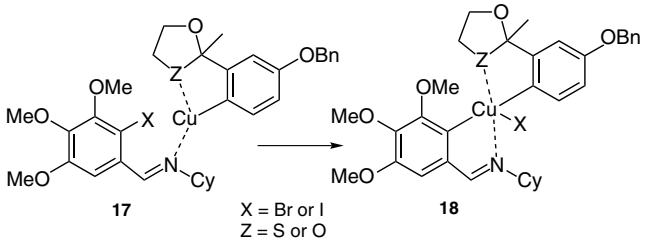
Ziegler found that a thioacetal sulfur atom could be used to co-ordinate the cuprate intermediate and in our initial study we used thioacetal **11b** as the key intermediate. This was lithiated with *n*-BuLi in THF at −78 °C, then treated with 1.5 equiv of CuI·P(OEt)$_3$ complex, followed by 1.1 equiv of iodide **6b** (X = I). The mixture was then allowed to stir at room temperature for 18 h. During work-up with aqueous AcOH the cyclohexylimine was hydrolysed and aldehyde **14b** was isolated by chromatography in 70% yield. Unfortu-

nately, the thioacetal protecting group proved difficult to remove and heating in acetone with MeI (40 equiv) was required. This did provide keto-aldehyde **15** in almost quantitative yield, which was efficiently cyclised under basic conditions to give enone **16** (Scheme 5).



Scheme 5. (i) (a) *n*-BuLi/THF/−78 °C, (b) CuI·P(OEt)$_3$ (1.5 equiv), (c) **6b** (1.1 equiv), (d) 18 h, rt, (e) aq AcOH (70%); (ii) (a) *n*-BuLi/THF/−78 °C, (b) CuBr·P(OEt)$_3$ (1.5 equiv), (c) **6b** (1.1 equiv), (d) 18 h, rt, (e) aq AcOH (76%); (iii) (a) *n*-BuLi/THF/−78 °C, (b) CuBr·P(OEt)$_3$ (1.5 equiv), (c) **6a** (1.1 equiv), (d) 18 h, rt, then 48 h, 45 °C (77%), (e) 10% aq AcOH (76%); (iv) MeI (40 equiv); (v) 10% HCl/EtOH; (vi) K_2CO_3/90 °C/5 h (91% over two steps).

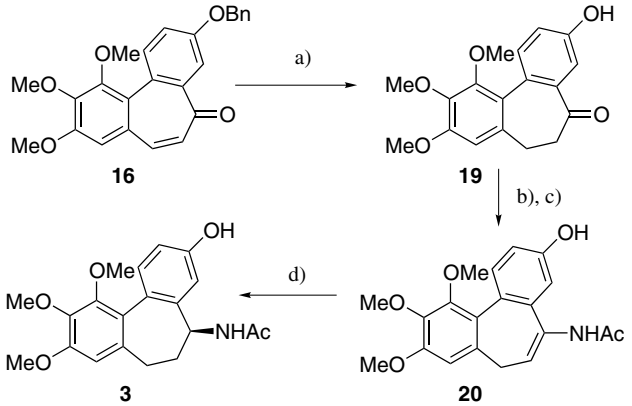
This was the first high-yielding preparation of a colchinol tricyclic unit that we achieved and as such the result was very encouraging. However, two major issues compromised the efficiency of the route and challenged its viability as a large scale manufacturing process. Firstly, removal of the thioacetal unit was difficult and required a large excess of methyl iodide. Secondly, the iodide residues generated by the reaction are highly undesirable in manufacturing waste streams. We therefore wanted to establish whether or not this type of Ullmann coupling could be effected with alternative functionalities, that would greatly enhance the general synthetic utility of this type of reaction. A crucial step in the mechanism is thought to be the oxidative insertion of Cu into the Ar–I bond in co-ordinated intermediate **17** (Scheme 6). The key questions we had regarding the reaction intermediates were: (i) would oxidative insertion into an Ar–Br bond be effective, and (ii) could an acetal oxygen co-ordinate effectively with the copper in place of the thioacetal sulfur atom?



Scheme 6.

In the first instance the viability of replacing the iodides with bromides was tested by repeating the procedure, but with aryl bromide **6a** as a reactant and CuBr·(OEt)$_3$ as the copper source. Significantly, we observed very little difference in the reaction profile and the yield of **14b** was unchanged. Next, using acetal **11a** as the reaction substrate instead of the thioacetal **11b** tested the effect of oxygen versus sulfur co-ordination. In this case the rate of conversion to biaryl product **14a** was considerably reduced and we observed an increase in the level of by-products formed. However, this problem was resolved by raising the reaction temperature slightly. Thus, when the reaction was held at ambient temperature for 16 h, followed by 48 h at 45 °C the desired reaction pathway was favoured and, following hydrolytic work-up with 10% AcOH, the aldehyde product **14a** was isolated by crystallisation from ethanol in 77% yield. The major advantages of using the acetal could now be realised. Simple and quantitative hydrolysis of **14a** was achieved using dil. HCl/EtOH, for 2 h at 65 °C and the resultant solution of aldehyde **15** was then basified with K_2CO_3 and heated at 90 °C for 5 h, during which time the enone **16** precipitated as yellow crystals, which were isolated by filtration in 91% yield from **14a**.

With the core ring system complete, asymmetric introduction of the acetamide was the major remaining hurdle. Firstly, simultaneous hydrogenation of the enone and hydrogenolysis of the benzyl ether, using Pd(OH)$_2$, was effected in THF containing 1% AcOH. Following filtration of the mixture and evaporation of the solvent, the ketone **19** was isolated by crystallisation from methanol in 79% yield. This was converted into enamide **20** in a two-step procedure: the oxime of **19** was obtained in 93% yield by treatment with hydroxylamine.HCl in EtOH/pyridine, followed by filtration of the crystalline product; this was converted into enamide **20**, in 63% yield, by treatment with Ac_2O and Fe (powder) in AcOH, followed by basic work-up and crystallisation (Scheme 7).



Scheme 7. (i) Pd(OH)$_2$/THF/AcOH (79%); (ii) NH$_2$OH·HCl/pyridine/EtOH (93%); (iii) Fe (powder)/Ac_2O/AcOH (63%); (iv) (*S*)-*i*PrFerroTANE Ru(methallyl)$_2$/H$_2$/MeOH (~100%).

For the hydrogenation of enamide **20**, a systematic study of a wide variety of asymmetric rhodium, ruthenium

and iridium hydrogenation catalysts was carried out and a full report of that study is presented in the accompanying paper.[12] FerroTANE derivatives were the most effective catalysts screened. Reactions were carried out in MeOH, with a 500–1000:1 substrate: catalyst mole ratio, and were essentially quantitative. (*S*)-*i*PrFerroTANE Ru(methallyl)$_2$ gave (*S*)-(−)-*N*-acetylcolchinol **3** with an ee of 92% and [(*S*)-*t*BuFerroTANE Rh(COD)]BF_4 gave (*R*)-(−)-*N*-acetylcolchinol with an ee of 94%. The hydrogenations were not fully optimised and no attempt was made to enhance the enantiomeric purity further.

Conversion of (*S*)-(−)-*N*-acetylcolchinol into the drug substance, ZD6126, was easily carried out by treatment with excess $POCl_3$ in THF/NEt_3.[13] The work described here provides access to (*S*)-(−)-*N*-acetylcolchinol in a short sequence of synthetic steps, starting from readily available, simple aromatic precursors. All intermediates were isolated by crystallisation and no chromatography was required, making the route amenable to scale-up. We have also demonstrated that low temperature Zeigler–Ullmann couplings can be carried out using substrates containing bromides instead of iodides and acetals rather than thioacetals, which will increase their synthetic utility.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.103.

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13. The details of the isolation and purification of ZD6126 will be reported in a subsequent publication.