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ASYMMETRIC TOTAL SYNTHESIS OF ALKALOIDS AND SECO-IRIDOIDS

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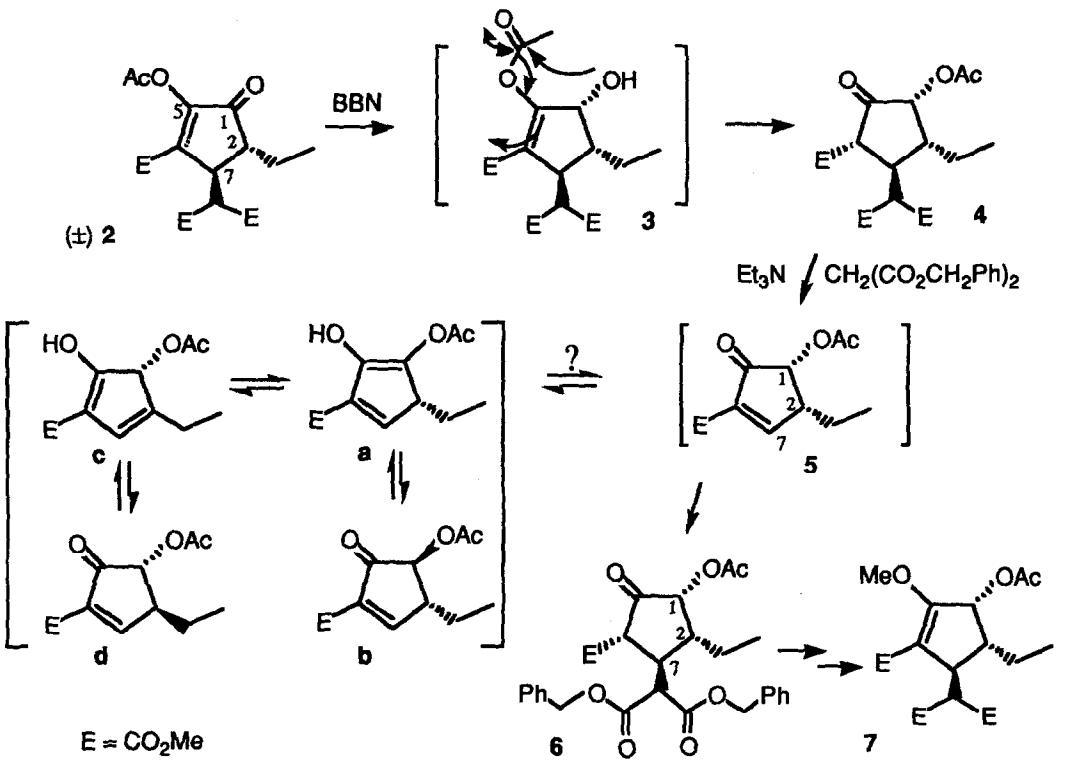
Abstract *A chiral cyclopentenolone from Michael addition of an oxazepine derived from ephedrine to a cyclopentene-1,2-dione has been converted into pure enantiomers of established synthetic precursors to alkaloids and seco-iridoids via a novel exchange which recovers the chiral auxiliary.*

In the preceding paper we reported the synthesis and characterisation of a single diastereomer (+)-**1** from the Michael addition of a chiral oxazepine to a cyclopentene-1,2-dione, and established that the chirality induced in the cyclopentenolone ring corresponded to the natural series of monoterpenoid indole alkaloids and secoiridoids. Subsequently we turned to finding procedures that would convert **1** into pure enantiomers of the key intermediates previously used in racemic syntheses[1-3] of these compounds, and, moreover, allow recycling of the chiral auxiliary. It should be noted that Mukaiyama and co-workers[4] had used this oxazepine for asymmetric synthesis of simple structures on several occasions, but in no case was recovery of the chiral auxiliary reported. This was not surprising in view of the rather drastic acid hydrolysis used which would lead to epimerisation and breakdown of the ephedrine. Such traditional hydrolytic and other methods for cleavage of the malonamide moiety proved particularly unsatisfactory with our polyfunctional substrate, and hence we sought to devise an alternative milder method that would also retain the stereochemical integrity of the ephedrine.

In this approach the chiral oxazepine moiety was to be exchanged for dimethyl malonate by taking advantage of the reversible nature of Michael addition, the essential requirement being that the induced chirality in the cyclopentenone ring should be conserved. We envisaged that this might be achieved by selectively reducing the C-1 ketone to a 1,2-*cis* alcohol, followed by acylation to prevent 1,5 tautomerism and 1,2 enolisation, and thus retain the C-2 configuration of the ethyl group in the intermediate **5**. In turn, any Michael addition would be stereospecifically *trans* to the ethyl group, ensuring retention of configuration at C-7, provided that no appreciable 2,7 dienolisation occurred in the intermediate *i.e.* **5c** ⇌ **5d**. A check on the extent of the latter (as well as any 1,5 enolisation) would be provided by the *cis* relationship of the C-1 and C-2 substituents which would promptly invert to the more stable *trans* geometry under such circumstances as well as *via* **5a** ⇌ **5b**.

To test the feasibility of this approach we carried out a trial reaction sequence on a racemic adduct where the C-5 enol was protected as the acetate **2** . As anticipated, chemo- and stereoselective reduction with 9-BBN gave a 1,2-*cis* alcohol **3**, but an additional bonus was that an intramolecular transacetylation occurred on work-up to afford in one step the acetoxy-ketone **4**. On heating with excess dibenzyl malonate and Et_3N in CH_2Cl_2 under reflux for 7 hours, the exchange product **6** was indeed obtained in an overall unoptimised yield of 66%. Importantly,

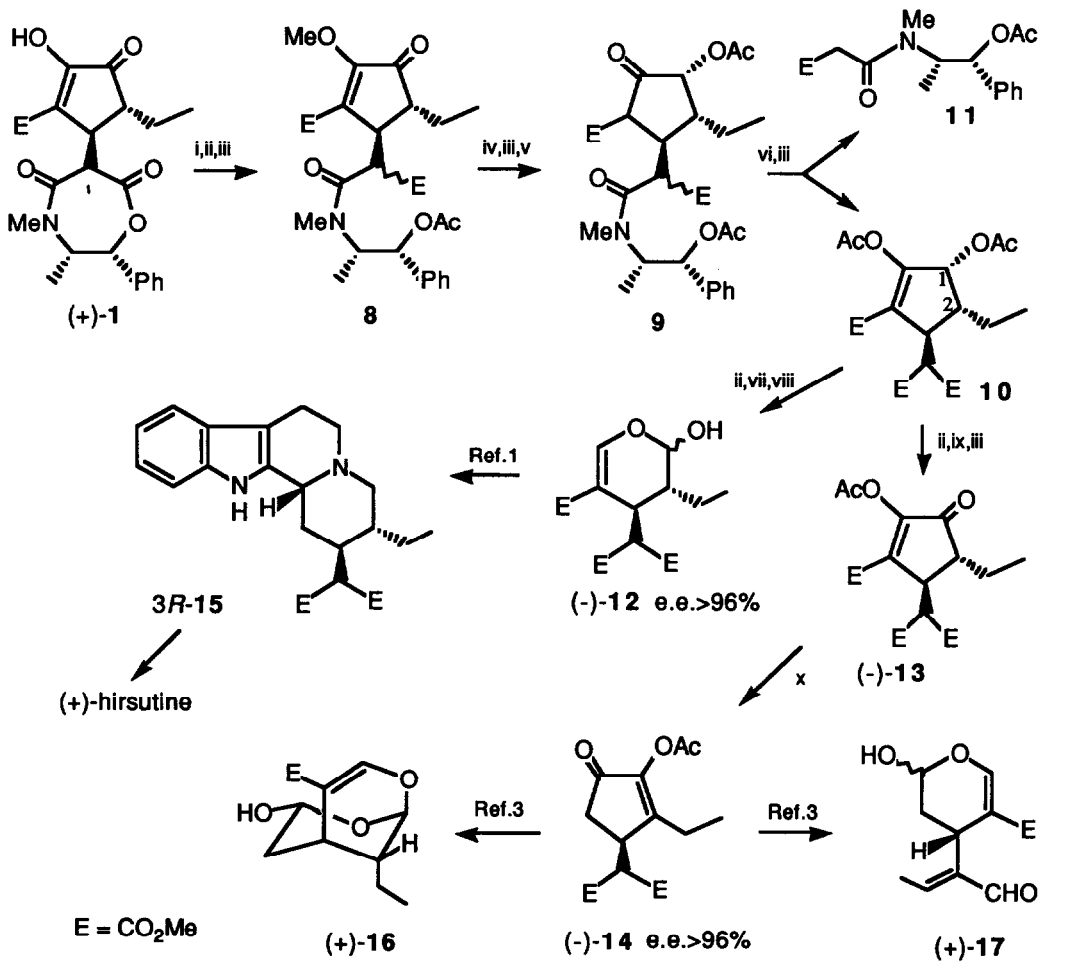


correlation with the known[5] compound (±)-**7** established that the C-1,2,7 relative stereochemistry had remained unchanged. Hence no enolisation could have taken place and our basic strategy of Michael exchange with retention of configuration was valid. In a second preliminary check, the oxazepine adduct (+)-**1** was exchanged with dimethyl malonate under the same conditions, when there was a quantitative recovery of the chiral oxazepine.

However, when a similar sequence was attempted on the enol acetate of the oxazepine adduct , we were disappointed to be unable to achieve reduction with BBN. Various other reducing reagents in combination with ester, alkyl or silyl protecting groups for the enol were equally unsuccessful. It became apparent that the problem lay with steric congestion by the oxazepine ring, which either prevented reduction of the C-1 ketone or led to a 1,2 *trans* alcohol which rapidly attacked the oxazepine to form a lactone that could not be exchanged.

Our solution was to open the oxazepine ring by methanolysis of the methyl ether of **1** to afford **8** where the C-1 ketone could be selectively reduced with $NaBH_4$ or $LiAl(OBu^t)_3H$ in the desired manner. After acetylation, cleavage of the enol ether was eventually achieved with trimethylsilyl iodide, but only in moderate yield (*ca.* 35%) which was attributed to the presence of an amide function since the corresponding malonate ester analogue **7** gave an excellent yield. Nevertheless, heating the crude product **9** with dimethyl malonate and Et_3N in CH_2Cl_2 for 7 hours gave a Michael exchange product, conveniently isolated as the diacetate **10** in an overall yield of 25% from **1**. The chiral auxiliary was recovered as **11**, which after saponification could be recyclised to the original oxazepine[6].

Crucially, that the absolute configuration at C-2 had been retained in the intermediate **5** with stereospecific *trans* addition of the malonate to C-7, was established by deacylation of **10** and methylation with diazomethane to give (+)-**7**, m.p.75° $[\alpha]_D$ +23° ($CHCl_3$), and determination of its e.e. with the chiral tris-3-trifluoroacetyl-D-camphorato-europium n.m.r. shift reagent. The e.e. was found to be >96% from comparison of the methyl ether signal with that of the racemate and corresponded to the enantiomeric purity of the starting (-)-ephedrine. A minor amount of C-1 epimerisation (*ca.* 15%) had occurred but was of no consequence in the overall synthesis. As a check , the reaction was repeated using $CD_2(CO_2Me)_2$ for a prolonged time (48 hours), when deuterium exchange *via* enolisation was found to occur only at C-1 (*ca.* 40%) and not at C-2.



Reagents: i CH_2N_2; ii NaOMe; iii Ac_2O/py; iv $LiAl(OBu^t)_3H$; v Me_3SiCl/NaI; vi $Et_3N/CH_2E_2/CH_2Cl_2/\Delta$; vii $NaBH_4$; viii HIO_4; ix PCC; x AcOH/Δ

Finally, **10** as the mixture of 1,2- *cis* and *trans* epimers was reduced with $NaBH_4$, deacetylated and the diols cleaved with periodate to afford in good yield the lactol **12** $[\alpha]_D$ -6° (CH_2Cl_2) which again had an e.e. of >96%. As with the racemate[2], (-)-**12** was reductively coupled with tryptamine to a dihydronicotinate which on subsequent selective decarbomethoxylation and stereoselective Pictet-Spengler condensation yielded the natural hirsutine precursor **15** with 3*R* configuration. This stereochemistry was established from the negative Cotton effect at 288 nm in its c.d. spectrum[7] and thus independently corroborated the absolute stereochemistry assigned to C-2 and C-7 .

By a simple deacetylation of **10** and oxidation with PCC, the pure enantiomer of the original racemic dimethyl malonate adduct[1,8] was obtained in good yield and characterised as its acetate **13** $[\alpha]_D$ -18° (CH_2Cl_2). Furthermore, selective decarbomethoxylation of **13** in refluxing acetic acid gave the enol acetate **14** $[\alpha]_D$ -35° (CH_2Cl_2) , which in racemic form had been the key precursor in the syntheses[3] of dihydrosecologanin aglucone **16** and *E* secologanin aglucone **17**. Again, this sequence had proceded with no loss of enantiomeric purity because (-)-**14** also had the same e.e. of >96% as its predecessors. Since the remaining steps to the alkaloids and other secologanin derivatives have already been carried out on the racemates, and, moreover, could not involve loss of absolute chirality at any stage, the above transformations constitute formal total asymmetric syntheses of the natural products with essentially complete stereoselectivity. Evidently , use of the oxazepine derived from (+)-ephedrine would lead to the antipodal unnatural series.

We have thus achieved our objective of a short, effective route to a key chiral synthetic precursor **10** from cheap, readily available starting materials. The current overall yield is reasonable at 25%, but even this is largely due to one rather unsatisfactory step, *i.e.* cleavage of the methyl ether, which could be rectified with a more labile protecting group. Again , the whole sequence could be dramatically improved if one of the many as yet untested reducing agents proves to be effective for an oxazepine adduct. We envisage that the chiral Michael exchange strategy will be more generally applicable in appropriate Michael acceptor systems and with other nucleophiles such as nitro-alkanes and β-keto-esters.

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