# ASYMMETRIC TOTAL SYNTHESIS FROM CYCLOPENTENE-1,2-DIONES: CHARACTERISATION OF A DIASTEREOMERICALLY PURE MICHAEL ADDUCT

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Abstract *A key cyclopentenolone intermediate in the asymmetric synthesis of alkaloids and seco-iridoids has been prepared from reaction of a chiral 5,7-dioxoperhydro-1,4-oxazepine with a cyclopentene-1,2-dione dimer; the absolute configuration at the induced chiral centres has been assigned from n.O.e. experiments.*

The iridoid glucoside secologanin **1** is the key biological precursor for virtually all monoterpenoid indole and related alkaloids. In its transformations *in vivo* and *in vitro* it behaves as the trisaldehyde **2** for which we have devised a synthetic equivalent in the lactol **3**. The latter was prepared[1] in racemic form from the novel dimer **6** *via* the cyclopentenolone **4**, and converted into representative alkaloids: (±)-hirsutine, protoemetine and related bases[2,3]. Racemic dihydrosecologanin aglucone, *E*-secologanin aglucone and elenolide have also been obtained from **4** using a novel decarbomethoxylation procedure[4].
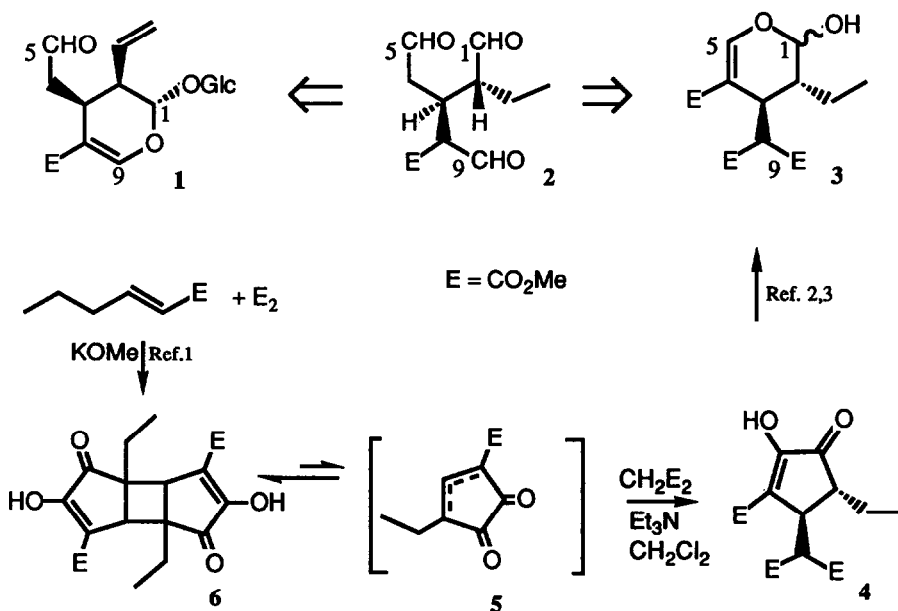
Both chiral centres in the crucial cyclopentenolone **4** are introduced in a thermodynamically controlled, reversible, stereospecifically *trans* Michael addition to an achiral intermediate cyclopentenedione **5** in equilibrium with dimer **6**. We envisaged that use of a *chiral* base

and / or a *chiral* malonate derivative might induce an enantiomeric or diastereomeric excess in the addition and thus afford an asymmetric total synthesis of the above alkaloids and seco-iridoids. After examining various chiral bases to little avail, several chiral malonate derivatives were prepared and tested in the Michael reaction, the best being the oxazepine **7**, for which, incidentally, an improved synthesis[5] from (–)-ephedrine was devised since the original procedure by Mukaiyama and co-workers[6] gave a rather low overall yield. Not only was a good diastereomeric excess of >70% obtained but, since the reaction is reversible, at least as important was the ready separation of the diastereoisomers. Thus, heating dimer **6** and oxazepine **7** (1:2 molar ratio) with triethylamine in dichloromethane under reflux for 48 hours followed by work-up and column chromatography (silica, dichloromethane/triethylamine 40:1 l) gave one pure stereoisomer of the 2,7-*trans* Michael adduct **8** in 60% yield, m.p. 184-6°C, $[\alpha]_D$ +25° (0.1, MeOH). The minor isomers, unreacted dimer and oxazepine could be re-equilibrated to afford more of the desired adduct. On treatment with diazomethane the methyl ether **9** was readily formed. By an analogous procedure the enantiomeric adduct $[\alpha]_D$ –25° (0.1, MeOH) derived from (+)-ephedrine was also obtained.

8 R = H
9 R = Me

7

7a
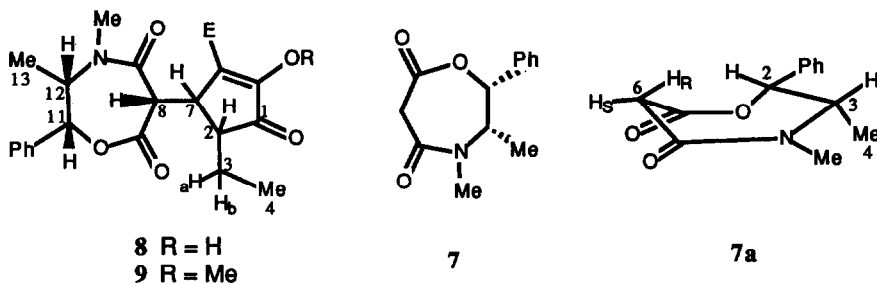
It was now essential to establish the absolute configuration of the induced chiral centres at C-2 and 7 in the cyclopentenolone ring of the adduct. One possible method would be to correlate with the (–)-ephedrine moiety by n.O.e. experiments, but these are only usually effective where the relative positions of the interacting centres do not vary too much, *i.e.* in systems where there is no or restricted rotation. The oxazepine and cyclopentenolone rings are joined by a single 7 - 8 bond around which in principle there should be free rotation; however, if the rotation were sufficiently restricted, as seemed possible from models, then the n.O.e. method might be useful.

Initial n.O.e. studies on **7** showed that although a chair-like conformer might be expected, the twist-boat **7a** is in fact the major conformer, as indicated *inter alia* by enhancements between the benzylic proton and H_R and H_S-6 of +27 and –10% respectively, and $J_{2,3}$ ~0 Hz. Hence a reasonable extrapolation would be for a substituent at C-6 to replace the pseudo-equatorial H_S-6, locking the ring even more into this conformation. It was obvious from n.O.e. experiments (25°C/CDCl$_3$) on the methyl ether **9**, that this was indeed the case with a 35% enhancement of H-8 on irradiation of H-11 (see Figure) but none observable between H-12 and H-8. More importantly, there was a negative n.O.e. between H-11 and H-7 of –3.3% (and an inverse enhancement of –1.2%) implying that H-11, H-8 and H-7 are on average approximately collinear[7]. This and other pieces of evidence lead us to believe that C-7, C-8 bond rotation must

be restricted. Thus the coupling constant $J_{7,8}$ = 2.7 Hz is consistent with a dihedral angle between H-7 and H-8 of ~60° (*i.e.* a staggered rotamer), whereas a completely free rotation would have given a considerably larger coupling, and when the n.m.r. spectrum is run at –60°C there is no indication of the broadening or splitting of signals which might well be expected to occur if rotation were only slightly hindered.These spectroscopic indications were corroborated by rationalisation of stereochemical aspects of reactions of **9** and related compounds (the *relative* stereochemistry in the cyclopentenolone ring is indicated by part-structures **9a, 10** and **11**). Where the malonate/malonamide groups are free to rotate as in **10** and **11**, the stereochemical course of reduction with the bulky lithium tri-tert.-butoxyaluminium hydride reagent at 25°C is controlled by the ethyl group to give the 1,2-*cis* products **12**. However, in **9a** no reduction occurs at 25°C, and even at 45°C it proceeds sluggishly to give the alternative 1,2-*trans* derivative **13**, *i.e.* the hydride is delivered *cis* to the ethyl group, implying that the oxazepine

9a R-R' = -OCH(Ph)CH(Me)NMe- ⟶ 1,2 *trans* **13**
10 R = R' = OMe
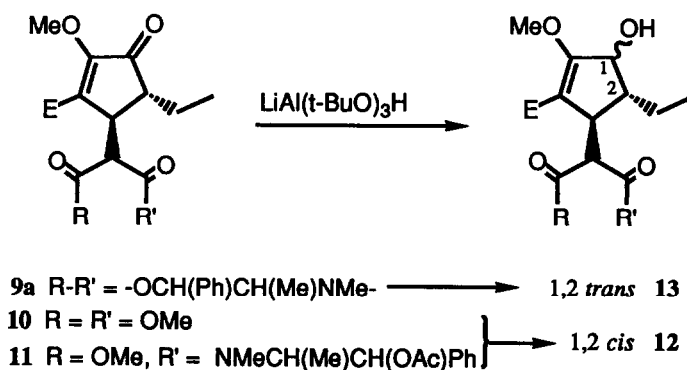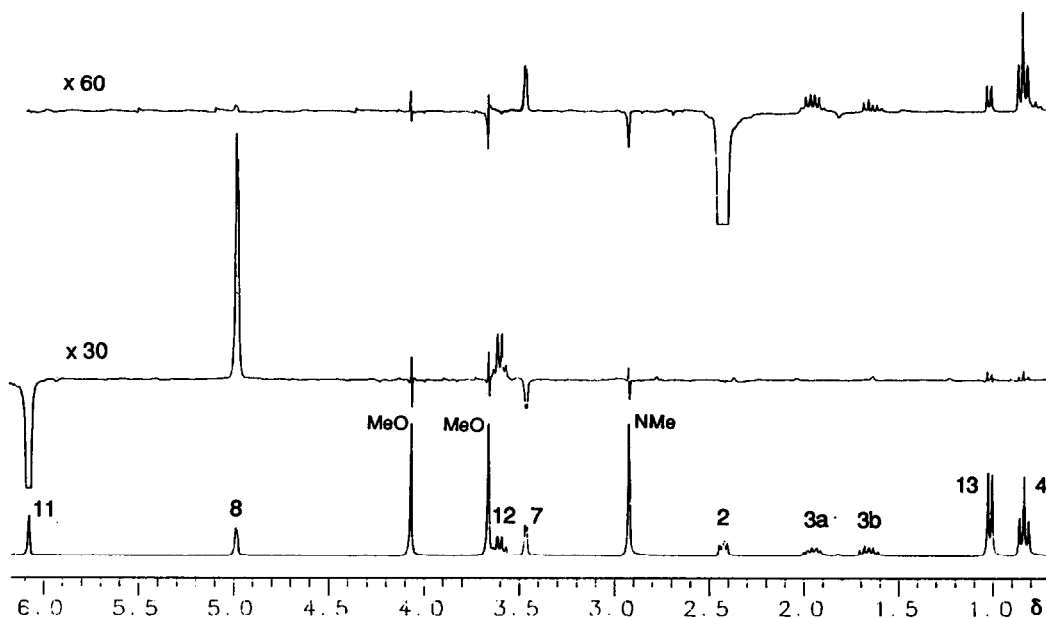**11** R = OMe, R' = NMeCH(Me)CH(OAc)Ph ⟶ 1,2 *cis* **12**

Figure : Selected n.O.e. spectra of methyl ether **9**.

does not rotate away from the top face of the cyclopentenolone, because this would require deformation of the oxazepine ring and result in the methyl and phenyl substituents being pushed together.

We are thus reasonably confident that at 25°C there is one dominant rotamer of the enol ether **9**. Consequently, the long-range n.O.e. between H-2 and Me-13 of 0.6% shown in the Figure (and the inverse enhancement of 1.0%) indicates that they are on the same side of the molecule, which, in conjunction with the negative n.O.e.'s between H-11 and H-7 previously mentioned, is consistent with the conformation **14** of the 2R,7S isomer rather than the 2S,7R alternative. On this basis the absolute stereochemistry of the major adduct derived from (–)-ephedrine is represented by structure **15**. The possibility that any of these n.O.e's might arise from *intermolecular* head-to-tail interactions between pairs of molecules was eliminated when an osmometric molecular weight determination in CDCl$_3$ on **9** showed that only monomeric species exist in solution.

14 View along C-7, C-8
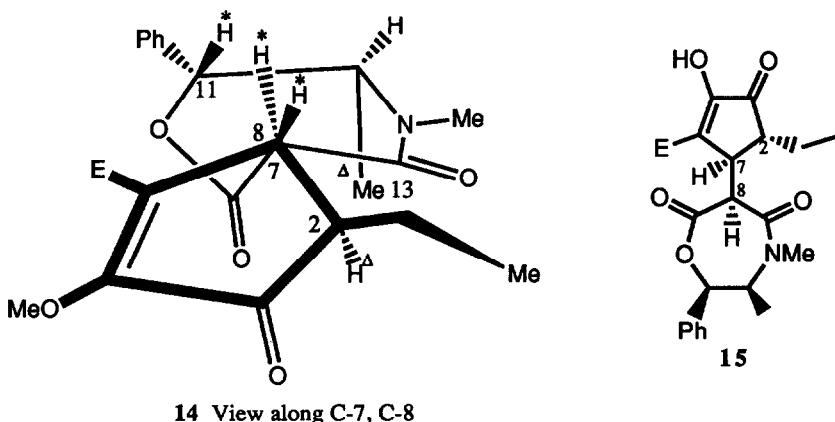
Subsequent confirmation of these deductions has been obtained by a single crystal X-ray structural determination on the methyl ether of the enantiomeric (–)-adduct derived from (+)-ephedrine, which, significantly, exhibits a C-7, C-8 conformation analogous to **14**[8].

References

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