A Stereoselective Total Synthesis of (±)-Dihydrosecologanin Aglucone

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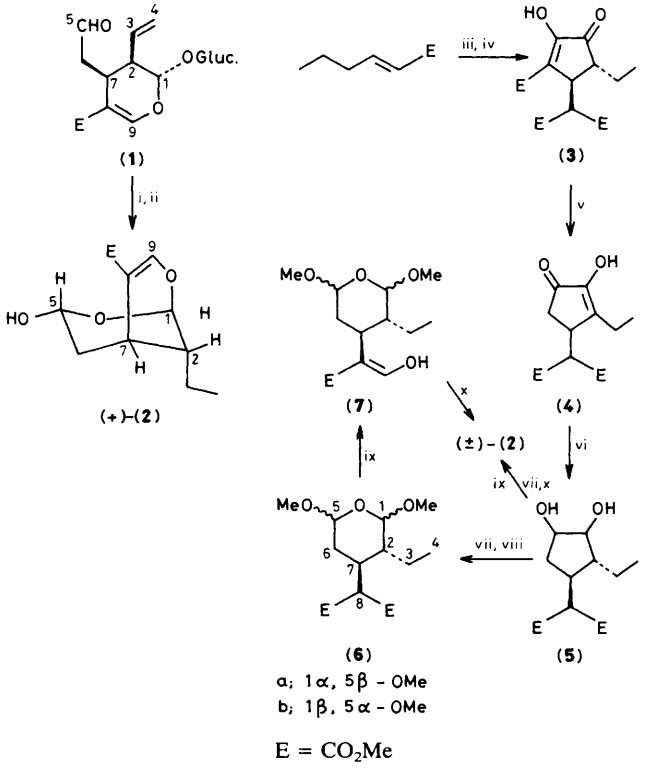
Racemic dihydrosecologanin aglucone (**2**) has been prepared *via* substituted cyclopentenolones in an efficient synthetic sequence involving a novel selective decarboalkoxylation of β-keto-esters as a key step.

The iridoid glucoside secologanin (**1**) is important as the key biogenetic precursor of all the monoterpenoid indole alkaloids.[1] Catalytic hydrogenation of (**1**) to 3,4-dihydrosecologanin and subsequent treatment with β-glucosidase in pH 5 buffer affords an aglucone as the bicyclic hemiacetal structure (**2**),[2] from which we have synthesised several indole and oxindole alkaloids of the natural enantiomeric series.[3—5] Recently, we reported the simple preparation of the novel cyclopentenolone (**3**) and its conversion into representative (racemic) indole and isoquinoline monoterpenoid alkaloids *via* a dihydrosecologanin equivalent.[6—8] During the course of this work we discovered that a smooth decarboalkoxylation of malonate esters occurred in refluxing alkanoic acids, a process which was also found to be applicable to β-keto-esters.[9] Since this reaction occurred more readily with the latter than the former, it seemed that a preferential mono-decarbomethoxylation of (**3**) might be possible to afford a 'C_{10} unit' (**4**) and hence a potential synthetic route to dihydrosecologanin aglucone itself.

In the event, decarbomethoxylation of (**3**) in refluxing acetic acid proved to be highly selective for the β-keto-ester, giving a virtually quantitative yield of the α-diketone (**4**). Sodium borohydride in pH 7 buffer reduced (**4**) to largely one diol (**5**), together with minor stereoisomers, all of which were cleaved by sodium periodate to a dialdehyde and converted by methanol and acid into the bis-acetal (**6**) in >90% overall yield from (**3**). Although the *trans* relative stereochemistry at C-2 and C-7 in (**3**) is lost in (**4**), we anticipated that ketonisation of the enol during the reduction process would regenerate a *trans* relationship because of steric interactions between the ethyl and malonate groups in the five-membered ring. Indeed, this proved to be the case as established by a complete 400 MHz ^{1}H n.m.r. analysis of (**6**), which consisted essentially of a 1:1 mixture of the two alternative *trans*-dimethyl acetals (**6a** and **b**). The former existed in a chair conformation with obvious *trans–trans* triaxial couplings of 11 Hz between H-2, H-7, and H-$6_{ax.}$, but with the latter the corresponding coupling constants of 7 Hz were not definitive of stereochemistry. However, the *trans* relationship of H-2 and H-7 in (**6b**) was consistent with nuclear Overhauser enhancement (n.O.e.) difference spectra which indicated a twist boat conformation



Scheme 1. *Reagents:* i, H_2–Pd; ii, β-glucosidase, pH 5 buffer; iii, $(CO_2Me)_2$, KOMe; iv, $CH_2(CO_2Me)_2$; v, AcOH, heat, 24 h; vi, $NaBH_4$, MeOH, pH 7 buffer; vii, $NaIO_4$; viii, MeOH/H^+; ix, $(Bu^i)_2AlH$, PhMe, −78 °C; x, tetrahydrofuran, H_3O^+.

with interactions between H-1 and H-6, and H-5 and H-8. In any case, (**6a** and **b**) must have the same 2,7 relative stereochemistry since both are derived from the same diol (**5**).

Partial reduction of the malonate function in (**6**) with di-isobutylaluminium hydride yielded the aldehydo-ester (**7**), which on treatment with acid underwent cleavage of the acetal functions and cyclisation to (±)-(**2**) in 40% overall yield. The synthetic racemate was identical by t.l.c. and spectroscopic (n.m.r., i.r., u.v., mass) comparison with the bicyclic aglucone from natural sources. An apparently shorter alternative route in which the diol (**5**) was reduced to an aldehydo-ester before periodate cleavage was also investigated, but although successful the overall yield was much lower (*ca.* 20%). Finally, corroboration that the configuration at C-2 in (**2**) had not been inverted at any stage was obtained when n.O.e. difference spectra displayed *inter alia* an enhancement of 5% between H-2 and H-9 in the acetate derivative.

This stereoselective synthesis of racemic dihydrosecologanin aglucone constitutes a formal total synthesis of the several alkaloids that have been prepared from the natural material.[3—5] We are currently extending the work towards a chiral synthesis of (**3**) and of secologanin itself.

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