Total Synthesis of a (±)-Secologanin Aglucone and (±)-Elenolide

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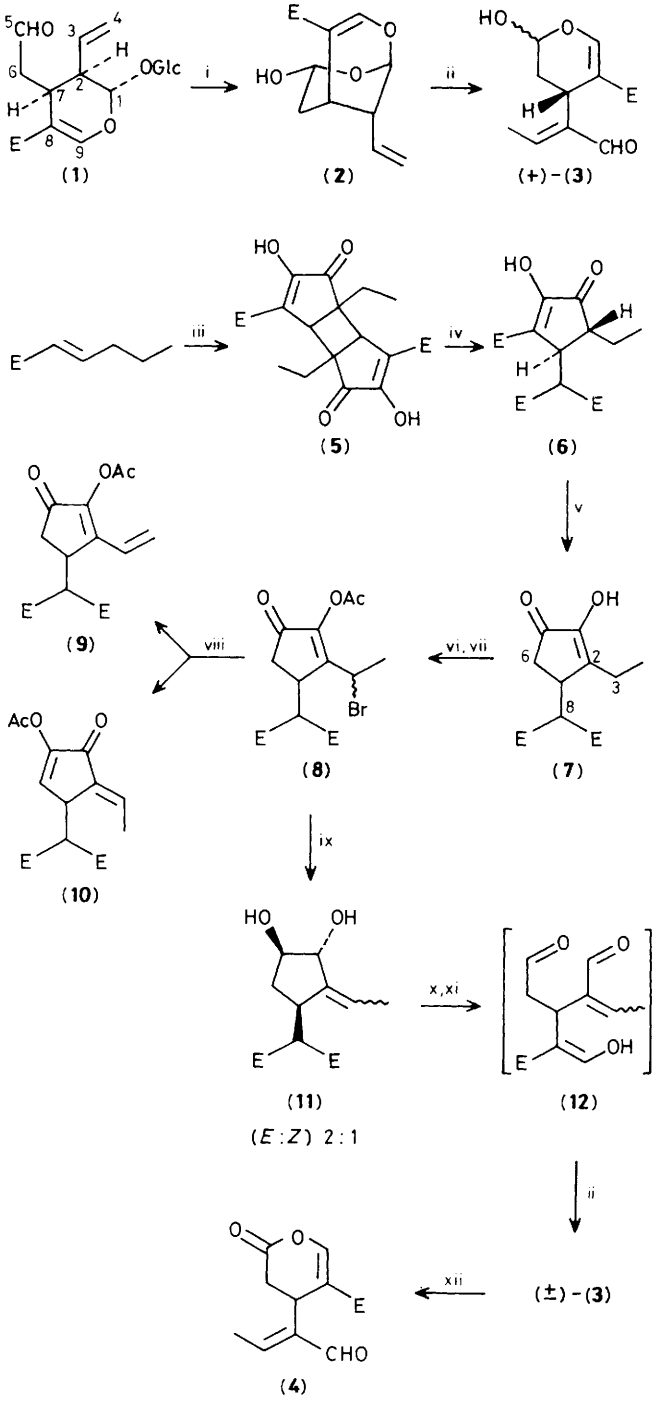
The rearranged (*E*)-aglucone of secologanin (**3**) and the related monoterpene elenolide (**4**) have been prepared *via* substituted hydroxycyclopentenones in a short reaction sequence involving chemoselective demethoxycarbonylation and regioselective allylic bromination.

The iridoid glucoside secologanin (**1**) is important as a key precursor in the biogenesis of the large class of monoterpenoid indole and isoquinoline alkaloids.[1] Treatment of (**1**) with β-glucosidase in pH 5 buffer results in the rapid formation of a bicyclic aglucone (**2**),[2] which on contact with mild base or prolonged standing rearranges yet again to the lactol structure (**3**).[3] Recently, we reported[4] the total synthesis of (±)-dihydrosecologanin aglucone (**2**, 3,4-dihydro) *via* novel hydroxycyclopentenones (**6**), (**7**), and we now describe how these have been used to prepare the rearranged lactol (**3**) and the related elenolide (**4**), a constituent of *Olea europa*.[5]

Double vinylogous Claisen condensation of methyl hex-2-enoate with dimethyl oxalate and potassium methoxide afforded the dimeric species (**5**), which with dimethyl malo-



Scheme 1. *Reagents:* i, β-glucosidase, pH 5; ii, Et_3N; iii, $(CO_2Me)_2$, KOMe; iv, $CH_2(CO_2Me)_2$, base; v, AcOH, heat, 24 h; vi, Ac_2O, py; vii, Br_2, peroxide, $NaHCO_3$, CH_2Cl_2, *hv*; viii, DBU; ix, $NaBH_4$, MeOH, pH 7 buffer; x, Bu^i_2AlH, PhMe, −78 °C; xi, HCl, $NaIO_4$; xii, PCC.

nate in the presence of base was converted into the hydroxycyclopentenone (**6**);[6] selective demethoxycarbonylation of (**6**) in refluxing acetic acid[7] then gave the α-diketone (**7**) in 40% overall yield. The crucial step was now to introduce 2,3-unsaturation into (**7**) by functionalising C-2 or C-3, and to this end a range of halogenating, hydroxylating, and selenating

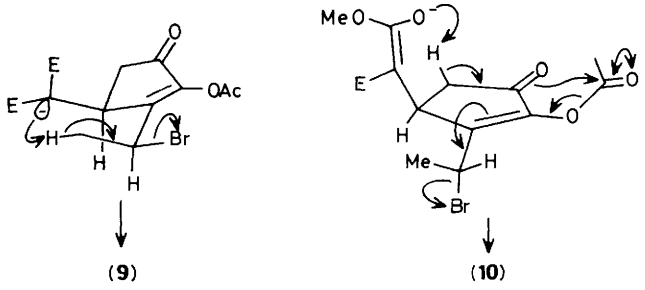


Figure 1. E = CO_2Me.

reagents were investigated. In the event, regioselective allylic bromination at C-3 of the enol acetate of (**7**) to give (**8**) was achieved (only a trace of the alternative C-7 bromide being detectable) under carefully controlled conditions using bromine in the presence of light, peroxide, and sodium hydrogen carbonate. The necessity for close definition of reagents and conditions is graphically demonstrated by the observation that the enol acetate of (**7**) gave an excellent yield of the 8-bromo derivative as the sole product when *N*-bromosuccinimide was used instead of bromine. Incidentally, (**7**) itself afforded a single 6-bromo derivative under a variety of conditions.

From the n.m.r. spectrum, the bromide (**8**) was evidently a 2:1 mixture of diastereoisomers. On elimination of hydrogen bromide with the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), two products (**10**) and (**9**) in the ratio 2:1 were obtained, which can be rationalised in terms of the stereoelectronic requirements for elimination. Loss of the most acidic proton gives a malonate anion where only the minor diastereoisomer can adopt a chair-like transition state with the necessary antiperiplanar conformation of hydrogen on C-4 and bromide on C-3 to lead to (**9**) (Figure 1). This is not possible for the major diastereoisomer, and an alternative pathway involving deprotonation at C-6, acyl transfer, and departure of the bromide from the less hindered side opposite to the malonate moiety results in stereospecific generation of the (*E*)-alkene (**10**) (Figure 1). Corroboration of these derivatives was afforded by cleavage of the enol acetate and elimination of bromide from (**8**) with methanolic potassium hydroxide, reacetylation yielding (**10**) and the corresponding (*Z*)-alkene in the same 2:1 ratio.

The next step in the synthesis was reduction of (**8**) with sodium borohydride in pH 7 buffer, conditions where deacylation and elimination of bromide also occurred to give the *trans* diol (**11**) as a 2:1 *E*:*Z* mixture, the stereochemical features being established by nuclear Overhauser enhancement (n.O.e.) difference spectra. In a 'one-pot' sequence, the malonate function in (**11**) was partially reduced with diisobutylaluminium hydride, and subsequent periodate cleavage of the diol afforded (±)-(**3**) *via* (**12**). As first formed the lactol was still a mixture of (*E*) and (*Z*) geometrical isomers, but *in situ* treatment with a tertiary amine (Et_3N or pyridine) at room temperature yielded the desired (*E*) isomer as the sole product [27% overall isolated yield from (**8**)]. Such an isomerisation had been expected, partly from the rearrangement of secologanin aglucone itself, and partly by analogy with the behaviour of other α,β-unsaturated aldehydes,[8] and was also achieved by acetylation of the crude product with acetic anhydride and pyridine (py). The synthetic racemate was identical by t.l.c. and spectroscopic (n.m.r., i.r., u.v., mass) comparison with the (+)-(*E*)-secologanin aglucone (**3**) from natural sources, consisting of the same pair of C-5 epimers. Finally, oxidation of (±)-(**3**) with pyridinium chlorochromate (PCC)[9] yielded (±)-elenolide (**4**), identical

by the same criteria with the natural material, and it was notable that the basic reagent again brought about (*Z*) to (*E*) isomerisation.

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