A Simple Total Synthesis of Viburtinal

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Viburtinal (**2**) has been synthesised from 2-cyclopentadienylpropanol (**3**) *via* the dihydrocyclopenta[*c*]pyran (**1c**), which was itself prepared *via* regioselective formylation.

A direct and efficient synthesis of the dihydrocyclopenta[*c*]-pyrans (**1a**) and (**1b**)[1] has been developed in our laboratory potentially providing access to three of the five families of cyclopentane monoterpenes: the iridoids, the secoiridoids, and the aminoterpene alkaloids.[2] All these products are known either for their role in the biogenesis of indole and Ipeca alkaloids[3] or for their interesting biological activities.[4]

To illustrate our approach to these interesting systems we report here the first synthesis of viburtinal (**2**),[5]† a non-glucosidic iridoid isolated from the leaves of *Viburnum tinus*[5] and *Viburnum opulus*[5] Caprifoliaceae.

The dihydrocyclopenta[*c*]pyran (**1c**) was prepared by a

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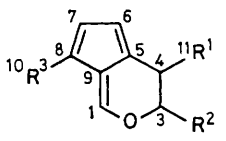
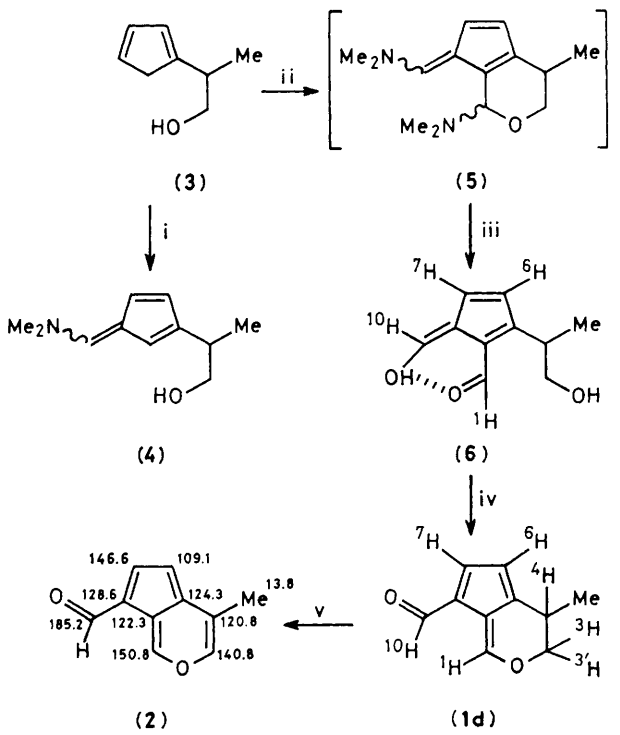
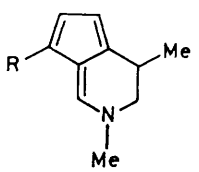


(1)

a; $R^1 = HC(OMe)_2$, $R^2 = Me$, $R^3 = H$
b; $R^1 = HC(OMe)_2$, $R^2 = Me$, $R^3 = CHO$
c; $R^1 = Me$, $R^2 = R^3 = H$
d; $R^1 = Me$, $R^2 = H$, $R^3 = CHO$



Compound (**3**) is a mixture of cyclopentadien-1-yl and -2-yl isomers. *Reagents:* i, $Me_2NCH(OMe)_2$ (1.1 equiv.), 1,2-dimethoxyethane (DME), 40 °C; ii, $Me_2NCH(OMe)_2$ (5 equiv.), DME, reflux, 24 h, concentration *in vacuo*; iii, 1 M-NaOH and $(CO_2H)_2$ in DME (pH 4); iv, anhydrous C_6H_6 and anhydrous $(CO_2H)_2$ catalyst, reflux, 1 h; v, DDQ (1.5 equiv.), anhydrous C_6H_6, reflux, 4 h.



(7) R = H
(8) R = CHO

short sequence of reactions from the cyclopentadienylpropanol (**3**) [itself prepared in two steps from sodium cyclopentadienide and ethyl 2-bromopropionate in tetrahydrofuran (THF) at −78 °C; $LiAlH_4$–THF, reflux]. Formylation of (**3**) with HCO_2Et–EtONa in THF at −20 °C[6] proved to be highly regioselective giving after cyclization (oxalic acid and benzene) the triene (**1c**) in good yield. When dimethylformamide (DMF) dimethyl acetal[7] [$Me_2NCH(OMe)_2$] was used however, regioselective β-formylation (*via* amino-formylation)[8] was observed leading to the aminofulvene (**4**). α-Regioselectivity possibly arises *via* prior *O*-formylation followed by rearrangement to carbon, whereas DMF dimethyl acetal probably reacts differently formylating first at the β-position for steric reasons. These hypotheses will be discussed elsewhere.[1c] Utilizing this interesting result, we found that when an excess of this reagent was used formylation at both the α- and β-positions occurred leading *via* the unstable intermediate (**5**) to the hydroxy-fulvene (**6**).‡ Subsequent cyclization of this compound gave the desired triene (**1d**)‡ [30% from (**3**)].

Dehydrogenation of the triene (**1d**) to the natural product viburtinal (**2**) was accomplished using dichlorodicyanobenzoquinone (DDQ) in refluxing benzene (55%). The physical constants observed for our synthetic product were identical with those published.§

Further applications of this transformation to the preparation of iridoids and secoiridoids will be published elsewhere,[1c] and its extension to the synthesis of monoterpene alkaloids (like tecomanine) and analogues (**7**) and (**8**) will also be presented.[9]†

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‡ ^1H N.m.r. δ ($CDCl_4$; $SiMe_4$; *J*-values in Hz): for (**6**), 1.30 (3H, d, Me), 2.89 (1H, s, OH), 3.08—3.76 (3H, m, CH_2 and 4-H), 6.45 (1H, AB, $J_{6,7}$ 4, 6-H), 7.33 (1H, AB × d, $J_{6,7}$ 4, $J_{7,10}$ *ca.* 1, 7-H), 8.49 (1H, s, 10-H), 8.81 (1H, s, 1-H), and 16.25 (1H, s, O–H · · · O); for (**1d**), 1.27 (3H, d, *J* 6.5, Me), 3.17 (1H, m, 4-H), 3.89 (1H, ABX, $J_{3,3'}$, 11, $J_{3',4}$ 11, 3-H'), 4.39 (1H, ABX, $J_{2,3'}$, 11, $J_{3,4}$ 5.25, 3-H), 6.15 (1H, AB × d × d, $J_{6,7}$ 2.6, $J_{6,4}$ 1.5, $J_{6,1}$ 1, 6-H), 7.15 (1H, AB, $J_{6,7}$ 2.6, 7-H), 8.21 (1H, s, $J_{1,6}$ *ca.* 1, 1-H), and 9.65 (1H, s, 10-H).

§ ^{13}C N.m.r. data (δ, $CDCl_3$) for viburtinal (**2**) are indicated on the formula. For other physical constants see ref. 5b.