Anionic Oxy-Cope Rearrangement of 2-*endo*-Vinylbicyclo[2.2.1]hept-5-en-2-ol. A Facile Route towards *cis*-Hydrindanone Derivatives

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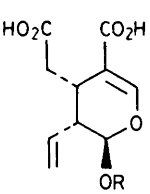
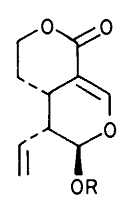
Efficient syntheses of the *cis*-hydrindanones (**10**) and (**14**), which are useful as iridoid precursors, are described.

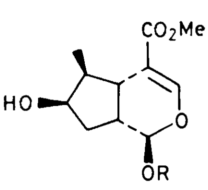
The broad diversity of biological activity exhibited by the iridoids has generated much interest in methods for their synthesis. We here report a synthesis of compounds (**10**) and (**14**), potential intermediates for the ready preparation of a variety of iridoids, such as secologanoside (**1**),[1] sweroside (**2**),[2] loganin (**3**),[3] and specionin (**4**).[4]



(**1**)

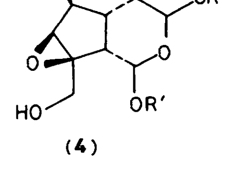


(**2**)



(**3**)

R = Glu
R′ = Et



(**4**)

Our starting material was Brown's aldehyde (**5**), which was made by the Diels–Alder reaction of 6-acetoxyfulvene with chloroacrylonitrile, and hydrolysis of the enol acetate.[5] Treatment of (**5**) with methanol in the presence of a catalytic amount of toluene-*p*-sulphonic acid provided the dimethyl acetal (**6**) in 95% yield. Hydrolysis of the chloronitrile (**6**) with sodium hydroxide in dimethyl sulphoxide gave a single ketone (**7**)† (73% yield), the structural assignment of which was based

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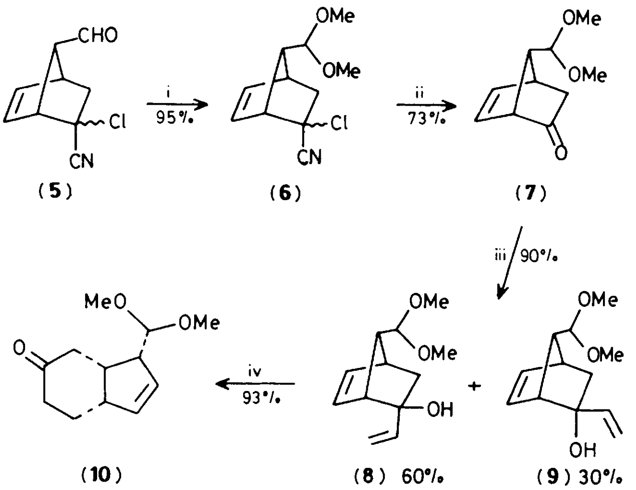
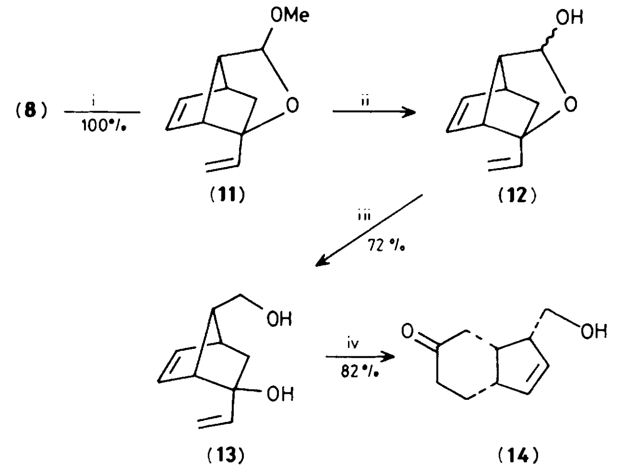
† *Spectroscopic data*: (**7**), $\nu_{max.}$ ($CHCl_3$) 1737 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.82 (dd, 1H, *J* 16.5, 2.0 Hz), 2.10 (dd, 1H, *J* 16.5, 3.0 Hz), 2.71 (m, 1H), 2.93 (m, 1H), 3.11 (m, 1H), 3.33 (s, 6H), 4.22 (d, 1H, *J* 8.3 Hz), 6.17 (m, 1H), 6.63 (dd, *J* 6.0, 3.0 Hz); ^{13}C n.m.r. ($CDCl_3$) δ 33.45, 40.78, 52.54, 54.13, 56.78, 63.44, 102.35, 131.08, 144.05, 214.01; (**10**), $\nu_{max.}$ ($CHCl_3$) 1710 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.60—3.30 (m, 9H), 3.33 (s, 6H), 4.28 (d, 1H, *J* 8.00 Hz), 4.72 (m, 2H); ^{13}C n.m.r. ($CDCl_3$) 25.3, 37.1, 37.2, 37.9, 43.9, 51.2, 52.7, 53.5, 104.1, 130.3, 135.0, 214.0; (**11**), ^1H n.m.r. ($CDCl_3$; 400 MHz) δ 1.15 (dd, 1H, *J* 11.88, 1.44 Hz), 1.67 (dd, 1H, *J* 11.88, 4.64 Hz), 2.61 (m, 1H), 2.75 (m, 1H), 2.86 (m, 1H), 3.35 (s, 3H), 4.52 (s, 1H), 5.09 (dd, 1H, *J* 10.90, 1.40 Hz), 5.22 (dd, 1H, *J* 1.40, 17.60 Hz), 5.85 (dd, 1H, *J* 5.40, 3.0 Hz), 5.92 (dd, 1H, *J* 10.90, 17.60 Hz), 6.26 (dd, 1H, *J* 5.40, 3.0 Hz); ^{13}C ($CDCl_3$) δ 40.45, 41.39, 54.64, 54.76, 69.19, 85.98, 100.90, 114.75, 128.68, 136.91, 140.94; (**14**), $\nu_{max.}$ ($CHCl_3$) 3200—3700 (OH), 1710 (C=O) cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1.50—3.30 (m, 9H), 3.63 (d, 2H, *J* 6.0 Hz), 5.57—5.83 (m, 2H); ^{13}C n.m.r. ($CDCl_3$) δ 25.66, 36.85, 37.44, 38.14, 44.33, 51.17, 62.01, 75.89, 77.16, 78.44, 131.17, 134.79, 215.14.



Scheme 1. *Reagents and conditions*: i, p-$MeC_6H_4SO_3H$, MeOH, reflux, 20 h; ii, EtOH, Me_2SO, NaOH, reflux, 20 h; iii, CH_2=CHMgBr, tetrahydrofuran (THF), reflux, 2 h; iv, NaH, benzene, reflux, 4.5 h.

on its ^{13}C and ^{1}H n.m.r. spectra. There was no evidence that the 7-epimer was formed. Vinylmagnesium bromide attacked the ketone (**7**) predominantly from the less hindered *endo*-direction to give the allylic alcohol (**8**) in 60% yield, with 30% of the diastereoisomer (**9**). When (**8**) was treated with sodium hydride in boiling benzene,[‡] it underwent an anionic oxy-Cope rearrangement,[6,7] to give the desired ketone (**10**)[†] in 93% yield. It is not surprising that (**9**) was recovered unchanged under the same conditions.

Passing (**8**) through a silica gel column yielded a nonpolar product, which was assigned the structure (**11**)[†] (100%). Hydrolysis of (**11**) with 1 M hydrochloric acid provided the hemiacetal (**12**). The crude (**12**) thus obtained on treatment with lithium aluminium hydride in tetrahydrofuran afforded the diol (**13**) [72% from (**12**)]. The formation of (**11**) implied that the dimethyl acetal group in (**7**) is '*anti*' to the double bond. Treatment of (**13**) with potassium hydride in tetrahydrofuran (25 °C) gave the rearranged product (**14**)[†] in 82% yield.



Scheme 2. *Reagents and conditions:* i, silica gel; ii, THF, 1 M HCl, reflux 3 h; iii, $LiAlH_4$, THF, reflux 2 h; iv, KH, THF, 25 °C, 3 h.

The sequential Grignard reaction of the norbornene (**7**) and anionic oxy-Cope rearrangement thus provides a new method for construction of the carbon skeleton and chiral centres necessary in synthesising various iridoids and analogues.

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References

1 I. Calis and O. Sticher, *Phytochemistry*, 1984, **23**, 2593.
2 H. Inouye, S. Uesa, and Y. Nakamura, *Chem. Pharm. Bull.*, 1970, **18**, 1856.
3 G. Buchi, J. A. Carlson, J. F. Powell, Jr., and L. F. Tietze, *J. Am. Chem. Soc.*, 1973, **95**, 540.
4 E. Van Der Eycken, P. Callant, and M. Vandewalle, *Tetrahedron Lett.*, 1985, **26**, 367.
5 E. D. Brown, R. Clarkson, T. J. Leeney, and G. E. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1507.
6 D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, 1975, **97**, 4765.
7 I. Fleming and N. K. Terrett, *Tetrahedron Lett.*, 1984, 5103.

[‡] Treatment of (**8**) with potassium hydride in boiling tetrahydrofuran gave only starting material.