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THE SYNTHESIS OF HOMOISOTWISTANES BY THE TANDEM WESSELY OXIDATION - DIELS-ALDER REACTION SEQUENCE

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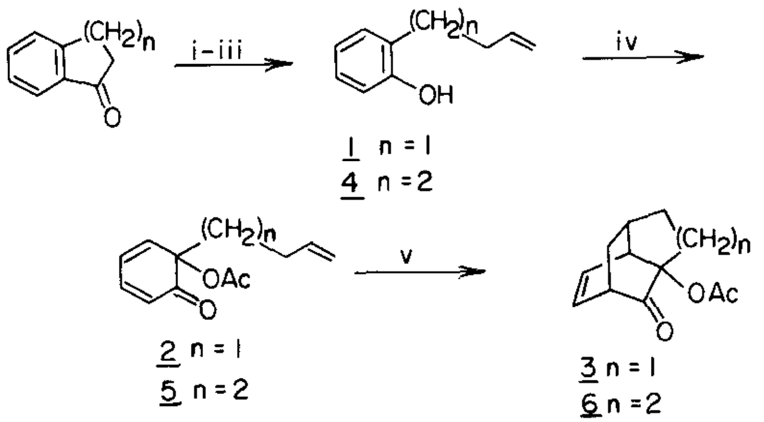
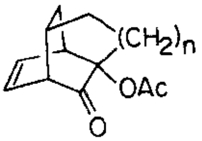
Summary. Wessely oxidation of 5-(2-hydroxyphenyl)-1-pentene and -1-penten-3-ones followed by intramolecular Diels-Alder reactions gave homoisotwistanes; similar treatment of 5-(2-hydroxyphenyl)-3-methylene-1-pentene gave twistane and isotwistane derivatives.

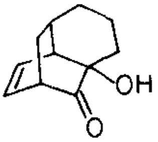
We have shown[1] that a tandem Wessely oxidtion - Diels-Alder reaction sequence can be used for the synthesis of isotwistanes of type 3 from 4-(2-hydroxyphenyl)-1-butenes (1) via 2,4-cyclohexadienones of type 2 (Scheme 1), and have recently applied this sequence in a synthesis of (±)-coronafacic acid.[2] We now report on the extension of this method to the synthesis of homoisotwistane derivatives of type 6 from 5-(2-hydroxyphenyl)-1-pentenes (4) via 2,4-cyclohexadienones of type 5.



Scheme 1. Reagents and conditions: i, m-$ClC_6H_4CO_3H$, CH_2Cl_2; ii, $(i\text{-}Bu)_2AlH$, C_6H_5Me; iii, $Ph_3P{=}CH_2$, DMSO;; iv, $Pb(OAc)_4$, AcOH; v, $C_6H_4Me_2$, Δ.

Although two regioisomers, 3 and 7, could be formed in the intramolecular Diels-Alder reaction of 2, only the so-called 'ortho' product[3] 3 was obtained. However, the formation of the 'meta' product[3] 8 as the major product from 5 could not be discounted, owing to the greater flexibility of its side chain.[4] Preliminary work on the application of this reaction sequence to 5-(2-hydroxyphenyl)-1-pentene (4) led to the isolation of the homoisotwistane derivative 6 (Scheme 1). This was obtained as colorless crystals, m.p. 62-63°C, and identified by its spectra,[5] ν_{max} 1760, 1748 cm^{-1}, δ_H 1.2-2.3 (m, 9H),


7 n = 1
8 n = 2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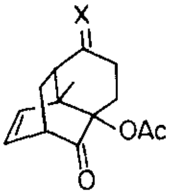
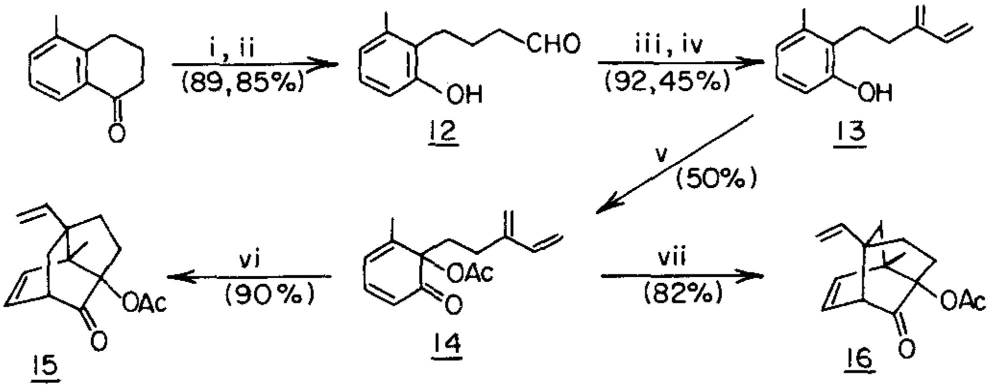

10 X = CH_2
11 X = O

1.21 (s, 3H), 3.15 (m, 1H), 3.6 (m, 1H), 6.25 (m, 2H), and comparison with those of its hydrolysis product 9, ν_{max} 3635, 1742 cm^{-1}, δ_H 1.2-2.2 (m, 9H), 2.23 (br s, 1H), 2.55 (m, 1H), 3.1 (m, 1H), 6.2 (m, 1H), 6.4-6.5 (m, 1H). Although none of 8 was isolated, this did not exclude the possibility of its formation, because the yield of 6 was low (16% ex 4). Nevertheless, the formation of the latter encouraged us to pursue this route. This was done with phenols of type 4 that incorporated additional substituents that could provide homoisotwistanes with substitution patterns, *e.g.*, 10 and 11, that would make them attractive intermediates for the synthesis of terpenes.

The first such compound investigated was the diene 13, prepared from 5-methyl-1-tetralone via 12 (Scheme 2). Here questions of both chemoselectivity and regioselectivity are involved, in that Diels-Alder reaction of either double bond is possible.[4] Wessely oxidation of 13 gave the 2,4-dienone 14, which on being heated gave the isotwistane 15,

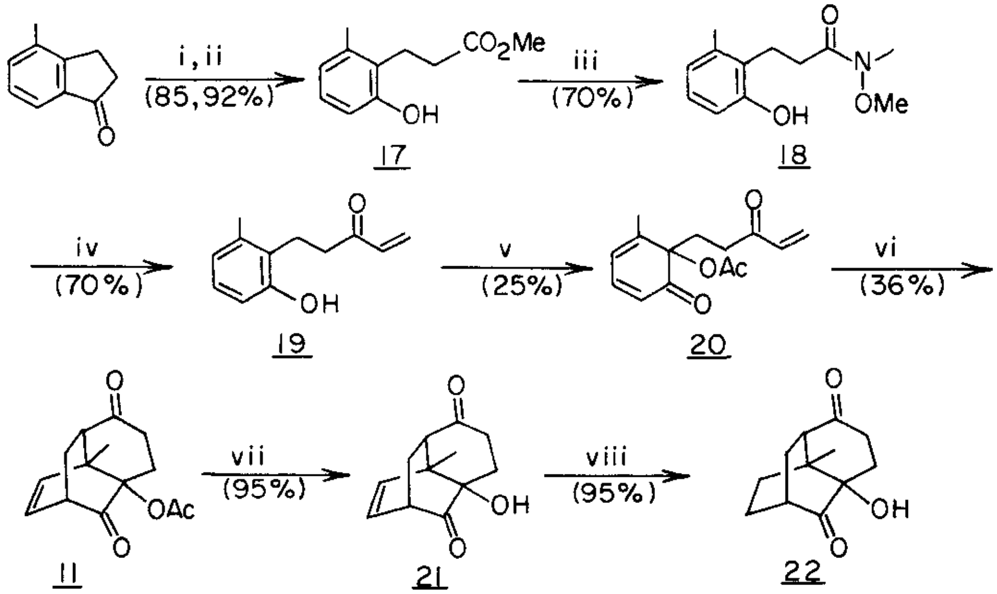


Scheme 2. Reagents and conditions: i, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2; ii, $(i\text{-}Bu)_2AlH$, C_6H_5Me; iii, $(CH_2O)_n$, Et_2NH_2Cl, THF, Δ; iv, $Ph_3P{=}CH_2$, DMSO; v, $Pb(OAc)_4$, AcOH; vi, C_6H_5Me, Δ; vii, Et_2AlCl, CH_2Cl_2.

ν_{max} 1757, 1730, 1634 cm^{-1}, δ_H 1.03 (s, 3H), 1.68 (d, *J* 2.6 Hz, 2H), 1.9-2.3 (m, 4H), 2.00 (s, 3H), 3.16 (m, 1H), 4.97 (dd, *J* 17.5, 1.3 Hz, 1H), 5.04 (dd, *J* 10.7, 1.3 Hz, 1H), 5.64 (dd, *J* 17.5, 10.7 Hz, 1H), 5.72 (dd, *J* 7.9, 1.2 Hz, 1H), 6.28 (dd, *J* 7.8, 6.9 Hz, 1H). When 14 was treated with diethylaluminum chloride at room temperature, it gave the twistane 16, the regioisomer of 15, ν_{max} 1757, 1742, 1631 cm^{-1}, δ_H 1.14 (s, 3H), 1.4-2.3 (m, 6H), 2.08 (s, 3H), 3.05 (d, *J* 6.8 Hz, 1H), 4.92 (d, *J* 17.4 Hz, 1H), 4.95 (d, *J* 10.8 Hz, 1H), 5.72 (dd, *J* 17.4, 10.8 Hz, 1H), 5.81 (dd, *J* 7.6, 6.9 Hz, 1H), 6.37 (d, *J* 7.6 Hz, 1H). Although the regioselectivity of the Diels-Alder reaction could be controlled, the chemoselectivity could not, and the desired homotwistane 10 was not obtained.

In the expectation that we could overcome the problems of both chemoselectivity and regiochemistry we turned to the synthesis of 11 via the phenol 19. It was anticipated that Diels-Alder addition would occur at the ethylenic double bond and that formation of the 'ortho' product 11 would be favored by the polarization of the α,β-unsaturated carbonyl system. Compound 19 was prepared from the amide 18,[6] which was obtained from the ester 17, which itself was prepared from 4-methyl-1-indanone (Scheme 3). Wessely oxidation of 19 gave the 2,4-cyclohexadienone 20, which was heated in boiling xylenes in the presence of Amberlyst ion-exchange resin to give a mixture of 11 and its hydrolysis product 21, m.p. 208-209°C. This hydrolysis is very ready and a sample of 11 was completely converted to 21 on exposure to the atmosphere for 10 days. The homoisotwistane structures of these products were assigned on the basis of comparison of the spectra of 11, and 21 and 22, the hydrogenation product of 21, m.p. 224-225°C (11: ν_{max} 1742, 1730, 1715 cm^{-1}, δ_H 1.28 (s, 3H), 1.96 (s, 3H), 1.65-2.5 (m, 7H), 3.5 (m, 1H), 5.85 (d, *J* 8.3 Hz, 1H), 6.48 (dd, *J* 8.3, 7.5 Hz, 1H); 21: ν_{max} 3470, 1730, 1697 cm^{-1}, δ_H 1.28 (s, 3H), 1.8-2.5 (m, 8H), 3.3 (m, 1H), 6.10 (dd, *J* 7.9, 1.0 Hz, 1H), 6.39 (dd, *J* 7.9, 7.0 Hz, 1H); 22: ν_{max} 3450, 1721, 1715 cm^{-1}; δ_H 0.96 (s, 3H), 1.2-2.5 (m, 12H), 2.6 (br s, 1H, absent after D_2O treatment).

This work shows that the Wessely oxidation can be effected in the presence of a side-chain with an α,β-enone system, albeit in modest yield, and that the regiochemistry of the intramolecular Diels-Alder reaction can be controlled, which augurs well for the general utility of this reaction sequence.



Scheme 3. Reagents and conditions: i, m-$ClC_6H_4CO_3H$, CH_2Cl_2; ii, MeoNa, MeOH; iii, Me_3Al, $Me(MeO)NH_2Cl$, CH_2Cl_2; iv, CH_2=CHMgBr, THF, -23-0°C; v, $Pb(OAc)_4$, AcOH; vi, $C_6H_4Me_2$, Amberlyst 15 (wet), Δ; vii, H_2O; viii, H_2, Pd/C, EtOAc.

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5. Ir spectra were taken in $CHCl_3$ and ^1H nmr spectra (400 MHz) in $CDCl_3$.
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