Regioselective Diels–Alder Addition to 2-Benzopyran-3-ones; a Route to Aromatic Steroids

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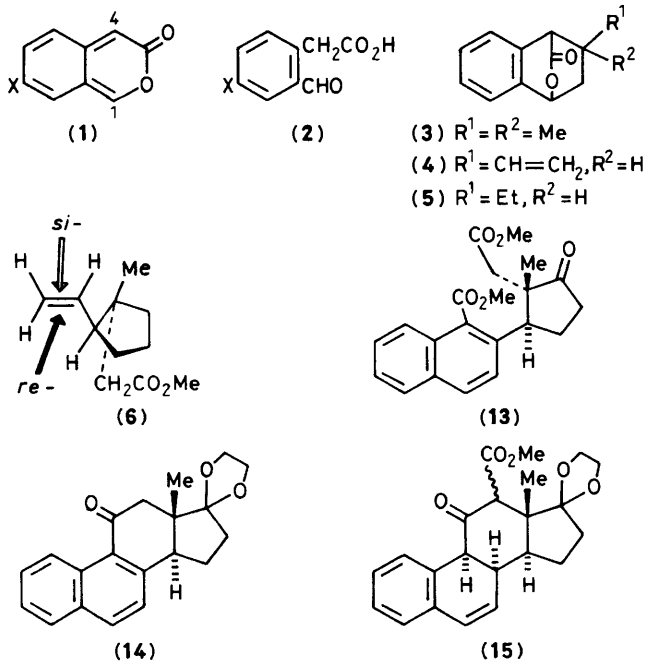
2-Benzopyran-3-one (**1**; X = H) undergoes strongly regioselective Diels–Alder additions to buta-1,3-diene, isobutene, but-1-ene, and the olefin (**6**); the adducts derived from (**6**) and either (**1**; X = H) or (**1**; X = OMe) are readily transformed into the aromatic steroids: (**9**), (**10**), (**17**), (**18**), 9-*epi*-(**10**), 9-*epi*-(**18**), the naphthalene (**14**), and the dihydronaphthalene (**15**).

2-Benzopyran-3-one (**1**; X = H) is a reactive intermediate responsible for the yellow colour of hot acetic anhydride solutions of *o*-formylphenylacetic acid (**2**; X = H).[1] Unlike many other *o*-quinonoid compounds (**1**; X = H) does not dimerise/oligomerise readily and is efficiently trapped not only by electron-deficient dienophiles[2] but also with simple olefins like *cis*-but-2-ene.[3] If its additions to unsymmetrical olefins were regioselective (**1**; X = H) should be a useful building block in synthesis. Simple Hückel calculations showed that the LUMO's of both (**1**; X = H) and (**1**; X = OMe) had much larger coefficients at C-1 than at C-4. Accordingly the inverse electron demand Diels–Alder additions of (**1**; X = H) to electron rich olefins would be expected to show strong regioselectivity. In agreement addition of simple olefins to (**1**; X = H), generated by acetic anhydride dehydration,[3] was found to be strongly regioselective; isobutene gave the adduct (**3**), and butadiene gave *endo*- and *exo*-(**4**) (ratio 5.5 : 1) as the only isolable products. But-1-ene gave a 3.5 : 1 mixture of regioisomers with *endo*- and *exo*-(**5**) predominating (*endo* : *exo* ratio 3.5 : 1).

The efficient and strongly regioselective trapping of (**1**; X = H) by simple olefins encouraged us to explore a synthetic approach to estrone derivatives based upon *intermolecular* Diels–Alder addition. Dehydration of (**2**; X = H)† in boiling acetic anhydride in the presence of the readily available Oppolzer olefin (**6**)[4] (2.2 equiv.) gave in 70% yield, a mixture of adducts in which the adducts of correct regiochemistry (**7**) for steroid synthesis (Scheme 1) predominated (ratio 5.1 : 1, 400 MHz ^{1}H n.m.r.). The four adducts of correct regiochemistry derive by *endo*- and *exo*-addition to the diastereotopic faces of the olefin (**6**). Subsequent transformation of the adducts shows that addition to the *re*-face of (**6**) leading to steroids of unnatural 8α-configuration is preferred (ratio 3.25 : 1). However epimerisation at C-8 is readily achieved

† Ozonolysis of the readily available enol ethyl ether of indan-2-one and acid hydrolysis (HCl–HOAc–H_2O) gives (**2**; X = H) in 54% yield based on indan-2-one. Ozonolysis of the related enol silyl ether has now been reported (ref. 8).



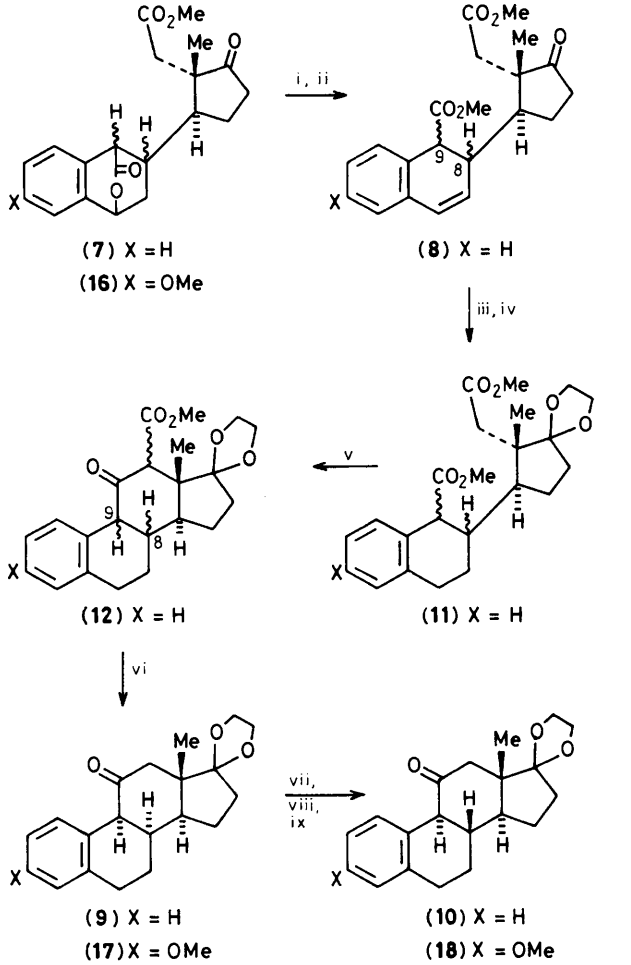
(see below). With boiling methanolic hydrogen chloride the adducts gave four 1,2-dihydronaphthalenes (**8**). Equilibration at the benzylic centre of (**8**) [reagent (ii), Scheme 1] gave two *trans*-1,2-dihydronaphthalenes (**8**; 8α,9β)‡ and (**8**; 8β,9α)‡ separated by short-column chromatography on silica in benzene–diethyl ether (9 : 1).

The major product (**8**; 8α,9β)‡ was smoothly converted into (**9**) (Scheme 1). Epimerisation at C-8 of (**9**) is achieved *via* the 9-ene-11-one in three steps in an overall yield of (40%) (Scheme 1).

Epimerisation at C-9 of (**10**) [reagent (ii), Scheme 1] gave the more stable 9β-isomer.[5] The Dieckmann cyclisation of (**11**; 8β,9α) gave both (**12**; 8β,9α) and (**12**; 8β,9β) (ratio 1 : 1). Removal of the CO_2Me group of the latter ($CaCl_2 \cdot 2H_2O$, Me_2SO, 150 °C) also gave both (**10**) and its C-9-epimer (ratio 3 : 1). The mixture of 1,2-dihydronaphthalenes (**8**) can be dehydrogenated [2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), PhCl, 132 °C] to the naphthalene (**13**) (50%) which after acetalisation [reagent (iii)], cyclisation [reagent (v)], and removal of CO_2Me ($CaCl_2 \cdot 2H_2O$, Me_2SO, 150 °C) gives the equilenin derivative (**14**). The ethylene acetals of the dihydronaphthalenes (**8**) can also be individually cyclised [reagent (v)] and the 8α,9α-isomer (**15**) smoothly dehydrogenated (DDQ, benzene, 80 °C) to the 12-methoxycarbonyl derivative of (**14**).

In a similar way 2-formyl-4-methoxyphenylacetic acid (**2**; X = OMe)§ was dehydrated in the presence of (**6**) to give a *ca.* 60% yield of adducts (**16**). These were transformed as described in Scheme 1 for the X = H series into the 11-oxo-ring-A-aromatic steroids (**17**), (**18**), and 9-*epi*-(**18**).

The regioselective Diels–Alder additions of (**1**; X = H) and (**1**; X = OMe) and the subsequent transformations of the



Scheme 1. *Reagents:* i, MeOH/HCl; ii, 1,5-diazabicyclo[3.4.0]non-5-ene, C_6H_6, 80 °C; iii, $(CH_2OSiMe_3)_2$, cat. trimethylsilyl triflate, CH_2Cl_2, −25 °C, 14 days; iv, H_2, cat. Pd–C, EtOAc; v, NaH, tetrahydrofuran (THF), cat. MeOH, reflux, 4 h; vi, $Ba(OH)_2$, H_2O, EtOH, reflux, 16 h; vii, Me_3SiCl, Et_3N, dimethylformamide; viii, $Pd(OAc)_2$, MeCN, 80 °C; ix, Li, NH_3, Bu^tOH, THF.

adducts described herein confirm the synthetic utility of *o*-quinonoid pyrones. Regioselective additions of (**1**; X = H) to vinyl ethers has recently been employed in the preparation of bicyclic AB-ring analogues of anthracyclinones.[8]

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‡ Steroid numbering and nomenclature. All compounds are racemates.

§ The readily available 2-acetyl-5-methoxybenzyl acetate (ref. 6) was oxidatively rearranged [$Tl(NO_3)_3 \cdot 3H_2O$, MeOH, $HClO_4$, 20 °C] (ref. 7) to the methyl ester and δ-lactone of 2-hydroxymethyl-4-methoxyphenylacetic acid. Hydrolysis of this mixture ($NaOH/H_2O$, EtOH, 100 °C, 4 h), acidification at 0—5 °C and immediate reaction with diazomethane gave the pure methyl ester which gave (**2**; X = OMe) after Swern oxidation, and hydrolysis (HCl, HOAc, H_2O) (34% yield over the four steps).