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INDENONE CHEMISTRY—II

SYNTHESIS AND REACTIONS OF 2,3-DIMETHYLENE-6-METHOXYINDANONE[1]

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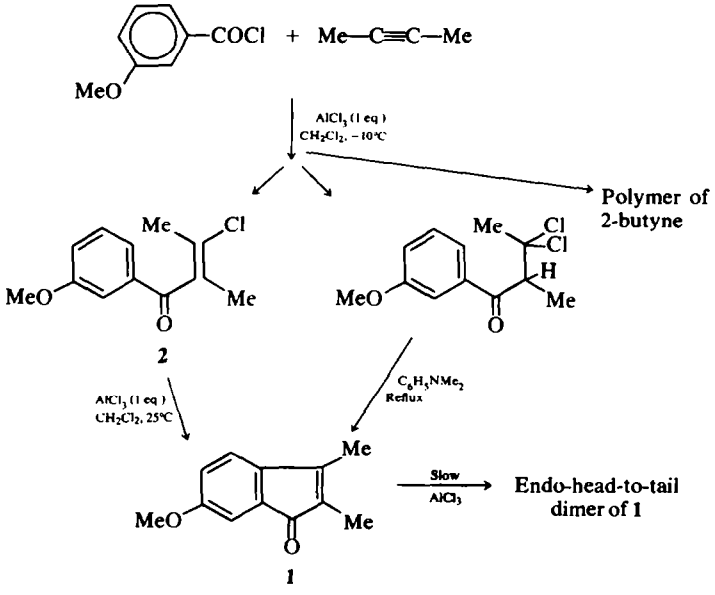
Abstract—Debromination of the dibromoindenone **5** affords the title compound **8**, which dimerizes immediately via a Diels–Alder reaction to the dimers **7a** and **7b**. The diene **8** can be trapped with cyclopentadiene affording the *exo*-adduct **9a** and the *endo*-adduct **9b**. The norbornene double bond in the adduct **9a** can be selectively oxidized to the *cis-exo*-diol **10**.

As we were interested in the synthesis of suitable substituted perhydrofluorenone systems, we tried to synthesize the 2,3 - dimethylene - 6 - methoxyindanone in order to use the diene system in a Diels-Alder reaction.

The starting material, the 2,3 - dimethyl - 6 - methoxyindenone **1**, is synthesized through an $AlCl_3$ catalyzed addition of 3 - methoxybenzoyl chloride to 2 - butyne, and cyclization of the intermediate β - chlorovinyl ketone[1] (Scheme I). In this cyclization a small amount of a white crystalline product is formed, which is identified as the *endo* - head - to - tail dimer of the indenone **1**. This dimer is thought to be formed by an $AlCl_3$ catalyzed dimerization, which is also observed with other 6 - methoxyindenones.[2] The β,β - dichloro ketone **3** is an important side product, probably formed by addition of 3-methoxybenzoyl chloride to 2 - chloro - 2 - butene, which in turn is formed by addition of HCl, liberated in the cyclization of **2**, to 2-butyne. The β,β-dichloro ketone **3** cannot be cyclized with $AlCl_3$ to the indenone **1**. This cyclization can be performed by refluxing the β,β-dichloro ketone **3** in dimethylaniline, probably also via the β-chlorovinyl ketone **2** as intermediate.

Treatment of the indenone **1** with one equivalent



SCHEME I

of bromine in chloroform at −20°C, affords the bromoindenone **4**, probably via a 1,3-bromine migration (Scheme II). This bromoindenone **4** is also formed by treatment of the indenone **1** with one equivalent N-bromosuccinimide. When two equivalents N-bromosuccinimide are used, the dibromoindenone **5** can be obtained in good yield.

Debromination of the dibromoindenone **5** in ethanol with zinc dust, affords not the expected 2,3 - dimethylene - 6 - methoxyindanone, but the 2 - methylene - 3 - bromomethyl - 3 - ethoxy - 6 - methoxy - indenone **6** (Scheme III). This can be explained by the high reactivity of the C_3 in the indenone system to nucleophilic attack. The zinc dust is probably necessary to form stronger nucleophilic ethoxide ions, as without zinc, no reaction takes place. Zinc chloride or aluminum chloride in ethanol is even more effective than zinc dust.

Attempts to use the 2-methyleneindanone **6** as a dienophile with cyclopentadiene were not successful: unchanged **6** was recovered.

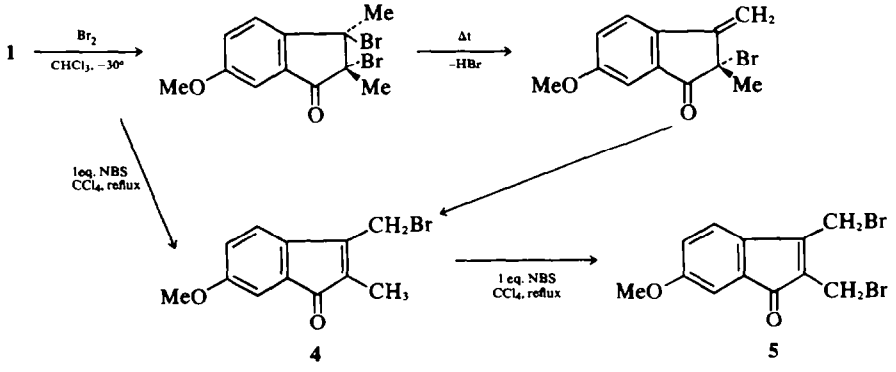
Debromination of the dibromoindenone **5** with zinc dust in ether with acetic acid as catalyst leads to two bromine-free products, which are identified as dimers **7** of the 2,3 - dimethylene - 6 - methoxyindanone **8** (Scheme IV)

Debromination of **5** with NaI in acetone gives the same results. The NMR spectra of these two dimers do not allow to differentiate between the structure **7a** and **7b**.

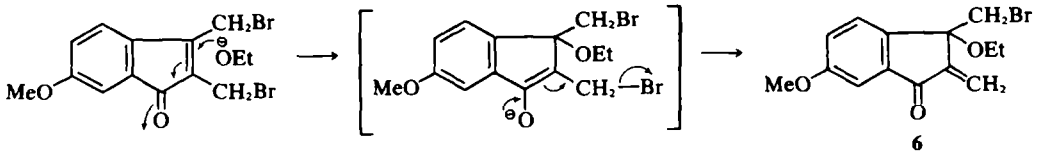
Attempts to trap the diene system of **8** with methyl acrylate or with maleic anhydride were not successful: only the dimers **7a** and **7b** were isolated. When the debromination is performed in the presence of a hundred fold excess of cyclopentadiene, the *exo* adduct **9a** (carbonyl in *exo*) is formed in high yield (81%) together with small amounts of the *endo*-adduct **9b** (6%). The *exo*- and *endo*-adducts **9a** and **9b** could be differentiated by their 100 MHz NMR spectra. An NMR analysis of the norbornene absorptions, including decoupling experiments and comparison with the NMR data of other norbornene derivatives,[4] made it possible to determine the chemical shift value of every proton and to observe its ASIS-value.[5] These results are given in Table 1.

Looking at the ASIS-values of the norbornene protons of **9a**, the protons 7a and 6x show negative values which means that they are located at the side of the carbonyl oxygen,[5] as is the case in the *exo*-adduct **9a**. For the same reason in the isomer **9b** the protons 3 ($\Delta = -0{\cdot}09$) and 6n ($\Delta = -0{\cdot}14$) should be located at the side of the carbonyl oxygen, while the proton **7a** ($\Delta = +0{\cdot}12$) must be located at the other side. Consequently **9b** must be the *endo*-adduct. Another difference between the isomers **9a** and **9b** is the low field absorption of H_{6x} (2·34 ppm) and H_{7a} (2·38 ppm) in **9a** compared to the absorptions of H_{6x} (1·98 ppm) and H_{7a} (1·90 ppm) in **9b**. This can be explained by a deshielding influence of the carbonyl in **9a**.

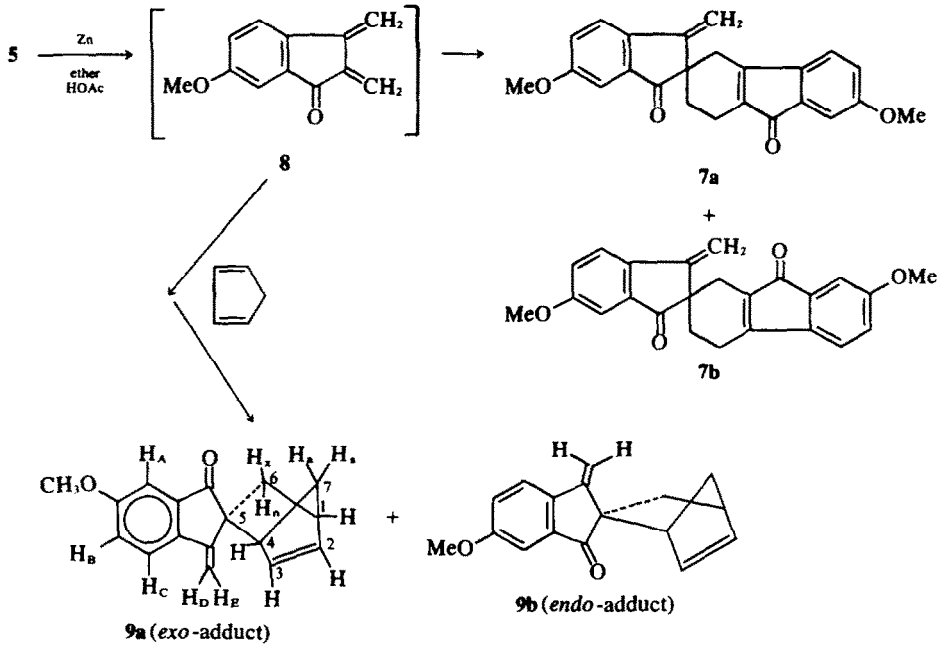
With osmium tetroxide-sodium periodate[6] we tried to cleave selectively the norbornene double bond in **9a** in order to perform in subsequent steps a ring closure on the 3-methylene double bond,



SCHEME II



SCHEME III



SCHEME IV

Table 1

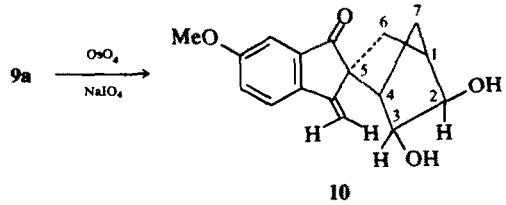
	Proton	H_1	H_2	H_3	H_4	H_{6x}	H_{6n}	H_{7s}	H_{7n}
9a	δ-value (CDCl₃)	3·08	6·45	6·06	2·72	2·34	1·35	2·38	1·32
	coupling constants	broad s	$J_1 = 2·5$ $J_3 = 5·5$	$J_2 = 5·5$ $J_4 = 2·5$	broad s	$J_1 = 4$ $J_{6n} = -11·5$	$J_{6x} = -11·5$ $J_{7S} = 3$	$J_{7n} = -9$ broadened	multiplet
	Δ(ASIS)[a]	+0·20	+0·22	+0·09	+0·07	−0·08	+0·10	−0·27	0
9b	δ-value (CDCl₃)	3·08	6·43	5·91	2·60	1·98	1·68	1·90	1·47
	coupling constants	broad s	$J_1 = 2·5$ $J_3 = 5·5$	$J_2 = 5·5$ $J_4 = 2·5$	broad s	$J_1 = 3·5$ $J_{6n} = -12$	$J_{6x} = -12$ $J_{7s} = 2·5$	$J_{7n} = -9$ broadened	$J_{7n} = -9$ broadened
	Δ(ASIS)[a]	+0·18	+0·03	−0·09	+0·06	+0·16	−0·14	+0·12	+0·05

[a] $\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$

leading to the gibbane skeleton. This oxidation afforded as identifiable product only 30% of the *cis-exo* diol **10**.

Oxidations with osmium tetroxide alone or with osmium tetroxide –$KClO_3$ yielded also the diol **10** but in much lower yields. The structure assignment of the diol was made on basis of the NMR data. The coupling constant of 6 c/s between H_2 and H_3 excludes the trans diol structure[7]; the small coupling constants between H_2 and H_1 and between H_3 and H_4 are not in agreement with a *cis-endo* diol but can be compared with those observed in other *cis*-exonorbornanediols.[7] The ASIS Δ-values of H_{6x} (−0·16), H_{7s} (−0·27), H_{7n} (−0·06) and H_{6n} (+0·27), confirm the *exo*-position of the indanone carbonyl.

Further studies on this selective oxidation are in progress.



10

EXPERIMENTAL

The IR spectra have been recorded with a Perkin Elmer 257 grating spectrophotometer. The NMR spectra have been taken on a Varian A-60 and on a Varian XL-100 spectrometer. For the mass spectra a AEI-MS-12 was used; the ionisation energy was 70 eV and samples were injected directly at a temperature between 100 and 200°.

2,3 - *Dimethyl* - 6 - *methoxyindenone* 1.

3-Methoxybenzoyl chloride (68 g; 0·4 mole) and $AlCl_3$ (53·32 g; 0·4 mole) were stirred in 600 ml dry dichloromethane at room temp until all the $AlCl_3$ had dissolved. The soln was cooled to −20°C and 32 ml (0·4 mole) 2-butyne dissolved in 200 ml dry dichloromethane were added slowly to this vigorously stirred soln. After all the 2-butyne was added, the mixture was allowed to warm up and stirred for 5 hr at room temp. The mixture was worked up with ice − 10% HCl, washed successively with water, $NaHCO_3$ aq and water. After drying on $MgSO_4$, the solvent was evaporated and the resulting red viscous oil was treated with cold hexane. About 4 g of white powder which did not dissolve in cold hexane were removed. Crystallisation from hexane afforded white crystals, m.p. 177°C, which were identified as the *endo* - head - to - tail dimer of 1: IR (CCl_4): 1710 cm^{-1} ($\nu_{c=o}$); NMR ($CDCl_3$): 7·20 (2p, dxd, Ar - 4 - H), 7·00 (2p, dxd, Ar - 5 - H), 6·60 (2p, d, Ar - 7 - H), 3·62 (6p, s, 6 MeO), 1·38 and 1·42 (12p, 2xs, 2- and 3- Me); ms: 376 (0·1), 188 (100): (Found: C, 76·56; H, 6·71; calc. for $C_{24}H_{24}O_4$: C, 76·57; H, 6·43%). The *endo* structure has been proposed on basis of the low δ-values for the aromatic protons, which can be explained by a mutual shielding of the aromatic rings, which is only possible in the *endo* isomer.

The head - to - tail structure has been proposed in analogy with the dimer of the 2 - methyl - 6 - methoxyindenone.[2] After removal of the dimer the mixture was chromatographied on 200 g silica gel (0·06–0·2 mm) with hexane-benzene. The red-orange coloured band was collected separately. Crystallisation of this fraction from hexane afforded 5 g red crystals, m.p. 111°, which were identified as 1: IR ($CHCl_3$): 1715 cm^{-1} ($\nu_{c=o}$), 1630 cm^{-1} ($\nu_{c=c}$); NMR ($CDCl_3$): 6·60 − 7·05 (3p, m, Ar − H), 3·80 (3p, s, 6 − MeO), 2·05 (3p, q, 3 − Me), 1·75 (3p, q, 2 − Me) (Found: C, 76·64; H, 6·43; calc. for $C_{12}H_{12}O_2$: C, 76·57; H, 6·43%). From the mother liquor of this crystallisation and the other chromatographic fractions, compounds 2, 3 and the 2,3 - dimethyl - 4 - methoxyindenone could be isolated by subjecting 1 g to a preparative GLC separation on a 6 ft 20% OV-17 column.

β-Chlorovinyl ketone 2: IR (CCl_4): 1675 cm^{-1} ($\nu_{c=o}$); NMR ($CDCl_3$): 2·05 (6p, s, 2- and 3-Me), 3·85 (3p, s, MeO), 7·0–7·60 (4p, m, Ar-H) (Found: C, 64·24; H, 5·90; calc. for $C_{12}H_{13}ClO_2$: C, 64·25; H, 5·79%).

β,β-Dichlorovinyl ketone 3: IR (CCl_4): 1695 cm^{-1} ($\nu_{c=o}$); NMR ($CDCl_3$): 1·46 (3p, d, CH-C<u>H</u>$_3$), 2·32 (3p, s, $-CCl_2-C\underline{H}_3$), 3·86 (3p, s, CH_3-O-), 4·48 (1p, q, CH-C<u>H</u>$_3$), 7·0–7·80 (4p, m, Ar-H); ms: 260 (8·0), 224 (1·0), 189 (1·4), 135 (100). (Found: C, 56·83; H, 5·75; calc. for $C_{12}H_{14}Cl_2O_2$: C, 55·22; H, 5·40%).

2, 3 - Dimethyl - 4 - methoxyindenone: IR (CCl_4): 1715 cm^{-1} ($\nu_{c=o}$), 1630 cm^{-1} ($\nu_{c=c}$); NMR ($CDCl_3$): 1·75 (3p, q, 2-Me), 2·25 (3p, q, 3-Me), 3·83 (3p, s, 4-MeO), 6·60–7·30 (3p, m, Ar-H). (Found: C, 76·62; H, 6·33; calc. for $C_{12}H_{12}O_2$: C, 76·57; H, 6·43).

The remainder of the mother liquor (66 g) was refluxed in 500 ml dimethylaniline for 4 hr. The mixture was poured into 2N HCl and extracted with ether. The ether extracts were successively washed with 2N HCl, $NaHCO_3$ aq and water. After drying and evaporating the solvent, the residue was chromatographed on 200 g silica gel (0·06–0·20 mm) with hexane-benzene. The red-orange coloured band was collected separately and this fraction was crystallized from hexane: 35 g of 1 (total yield 40 g, i.e. 53%).

2-*Methyl* - 3 - *bromomethyl* - 6 - *methoxyindenone* 4

Bromine (0·80 g; 5 mmoles) in 10 ml $CHCl_3$ were added slowly to 1 (0·94 g; 5 mmoles) dissolved in 10 ml $CHCl_3$ and cooled in an ice-bath. The resulting yellow soln was concentrated in vacuum. The oily residue looses HBr on standing at room temp. This dehydrobromination could be completed by refluxing the product for 2 hr in CCl_4. Crystallisation from CCl_4 afforded red needles, m.p. 120°: IR (CCl_4): 1715 cm^{-1} ($\nu_{c=o}$); NMR ($CDCl_3$): 6·75–7·45 (3p, m, Ar-H), 4·36 (2p, s, 3-CH_2Br), 3·85 (3p, s, 6-MeO), 1·85 (3p, s, 2-Me); ms: 266 (73), 187 (100), 186 (46), 159 (35), 144 (35). (Found: C, 54·57; H, 3·97; calc. for $C_{12}H_{11}BrO_2$: C, 53·95, H, 4·15%).

2,3-*Di*(*bromomethyl*)-6-*methoxyindenone* 5: Compound 1 (4·23 g; 22 mmoles) and N-bromosuccinimide (8·9 g; 50 mmoles) were refluxed in 100 ml CCl_4 with 200 mg AIBN. After 3 hr the mixture was filtered while warm. The remaining succinimide was repeatedly treated with warm CCl_4 until colourless. The filtrate was washed with water to remove the dissolved succinimide and after drying the CCl_4 the soln was concentrated until crystallisation. Repeated crystallisation from CCl_4 afforded red needles of 5, mp 143° (yield 72%). IR ($CHCl_3$): 1720 cm^{-1} ($\nu_{c=o}$); NMR: 6·75–7·45 (3p, m, Ar-H), 4·42 (2p, s, 3-CH_2Br), 4·22 (2p, s, 2-CH_2Br), 3·85 (3p, s, 6-MeO); ms: 344 (1·2), 265 (30), 264 (7), 186 (100), 171 (7·5), 158 (3·8), 143 (5·5), 115 (29). (Found: C, 41·76; H, 3·03; Br, 46·36; calc. for $C_{12}H_{10}Br_2O_2$: C, 41·65; H, 2·95; Br, 46·19%).

2 - *Methylene* - 3 - *bromomethyl* - 3 - *ethoxy* - 6 - *methoxyindanone* 6 Compound 5 (344 mg; 0·001 mmole) was treated with a soln of $AlCl_3$ (133 mg) in 50 ml dry EtOH. This mixture was stirred for about 1 hr at room temp with 100 mg ZnO until the red-orange indenone colour had disappeared. The mixture was filtered, treated with water and extracted with dichloromethane. After drying the dichloromethane soln was evaporated and the residue chromatographed on a silica gel thin layer with benzene. This afforded 280 mg of a colourless oil: IR (CCl_4): 1715 cm^{-1} ($\nu_{c=o}$) 1648 cm^{-1}, ($\nu_{c=c}$); NMR ($CDCl_3$): 1·08 (3 p, t, $-O-CH_2-CH_3$), 3·0 (2p,m $-O-\underline{CH}_2-CH_3$), 3·7 (2p, s, $-CH_2$Br), 3·88 (3p, s, 6-MeO), 5·87 (1p, s, $=CH_2$), 6·49 (1p, s, $=CH_2$), 7·17–7·75 (3p, m, Ar-H); ms: 310 (3·9), 265 (4·4), 217 (100), 202 (1·5), 189 (65), 186 (18).

Dimers 7a *and* 7b

Dibromoindenone (348 mg; 1 mmole) dissolved in 20 ml ether was stirred with 130 mg Zn dust (2 mmoles). To this mixture AcOH (0·12 ml) was added. After 5 min the red-orange soln had turned slightly yellow. The Zn dust and the zinc bromide were removed by filtration and the filtrate washed with $NaHCO_3$ aq and with water. After drying and evaporating the solvent, the residue was chromatographed on silica gel with benzene–CCl_4–CH_2Cl_2 (20/10/4). Two bands were isolated, (A) and (B) in order of decreasing R_f values, affording 27 mg (A) and 83 mg (B) (60% debrominated product). The products A and B were identified as the dimers 7a and 7b, but it was not possible to assign a definite structure to either dimer A or dimer B.

Dimer A: IR ($CHCl_3$): 1710 cm^{-1} ($\nu_{c=o}$); NMR ($CDCl_3$): 1·50–2·0 (m, 2p), 2·20–2·95 (m, 4p), 3·80 (s, 3p), 3·86 (s, 3p), 5·09 (s, 1p), 5·58 (s, 1p), 6·70–7·75 (m, 6p); ms: 372 (100), 357 (22), 344 (4·9), 329 (5·2), 301 (2), 186 (19·5), 171 (2·7), 143 (2·7), 115 (10·5).

Dimer B: IR ($CHCl_3$): 1710 cm^{-1} ($\nu_{c=o}$); NMR ($CDCl_3$): 1·67–2·07 (m, 2p), 2·36–2·84 (m, 4p), 3·79 (s, 3p), 3·85 (s, 3p), 5·08 (s, 1p), 5·56 (s, 1p) 6·60–7·70 (m, 6p); ms: 372

(100), 357 (11), 344 (3·4), 329 (3·2), 301 (1·2), 186 (89), 171 (4), 143 (3·4), 115 (14).

Cyclopentadiene adducts **9a** *and* **9c**

Compound **5** (2·96 g; 8·5 mmoles) activated zinc dust (1·1 g; 1·7 mmoles) and 100 ml cyclopentadiene were stirred vigorously in 700 ml ether at −20°C. To this mixture AcOH (2·4 ml) were added and the mixture allowed to warm up at room temp. Suddenly the orange soln turned slightly yellow, almost colourless. If this decolouration does not take place within 10 min at room temp, a second portion of Zn dust and AcOH should be added. This was repeated if necessary. When the orange colour had disappeared, the soln was filtered, the filtrate washed with $NaHCO_3$ aq. This slightly yellow soln was quickly evaporated to remove the cyclopentadiene before it dimerized again. The resulting oil was chromatographed on silica gel (0·06–0·2) with benzene-hexane (1/4). Two fractions were collected: 1·6 g pure **9a** and 0·43 g of a mixture of **9a** and **9b** which was subjected to a TLC separation on silica gel, affording 0·15 g **9a** and 0·12 g **9b** (total yield of **9a**: 81%; total yield of **9b**: 6%). These two products are oils which loose cyclopentadiene on standing; they could not be crystallized. Spectral data: **9a**: IR (CCl_4: 1715 cm^{-1} ($\nu_{c=o}$), 1640 cm^{-1} ($\nu_{c=c}$); NMR ($CDCl_3$): 7·59 (1p, d, H_c), 7·10–7·30 (2p, m, H_A and H_B), 5·44 (1p, s, H_D), 4·86 (1p, s, H_E), 3·87 (3p, s, Ar-MeO), see also Table 1; ms: 252 (6·6), 186 (100), 171 (6·0), 158 (4·2), 143 (6·6), 115 (47·0), 66 (31·0). **9b**: IR (CCl_4): 1720 cm^{-1} ($\nu_{c=o}$), 1640 cm^{-1} ($\nu_{c=c}$); NMR ($CDCl_3$): 7·68 (1p, d, H_c), 7·13–7·30 (2p, m, H_A and H_B), 5·62 (1p, s, H_D), 5·22 (1p, s, H_E), 3·88 (3p, s, Ar-MeO), see also Table 1; ms: 252 (10·3), 186 (100), 171 (6·1), 158 (5·6), 143 (7·0), 115 (52), 66 (76).

Oxidation of the adduct **9a**

Adduct **9a** (480 mg; 1·9 mmoles) was dissolved in 12 ml dioxane and OsO_4 (100 mg) added. After stirring this mixture for 15 min, 4 ml water was added and 814 mg (3·8 mmoles) $NaIO_4$ dissolved in 7 ml water added slowly. When all the $NaIO_4$ had been added the mixture was stirred for 6 hr and then extracted with dichloromethane. These extracts were saturated with H_2S and the black ppt filtered off on celite. The colourless filtrate was evaporated and the residue subjected to a TLC separation on silica gel with EtOAc-heptane (1/1). This afforded 168 mg of the diol **10**. Recrystallisation from $CHCl_3$-hexane gave white crystals, m.p. 154°: IR ($CHCl_3$): 3600–3100 cm^{-1} (ν_{OH}), 1715 cm^{-1} ($\nu_{c=o}$), 1640 cm^{-1} ($\nu_{c=c}$); NMR ($CDCl_3$): 7·61 (1p, d, H_c), 7·14–7·28 (2p, m, H_A and H_B) 5·68 (1p, s, H_D), 4·91 (1p, s, H_E), 4·33 (1p, broad d, $J_{2,3} = 6$ c/s, H_2), 3·99 (1p, broad d, $J_{2,3} = 6$ c/s, H_3), 3·86 (3p, s, Ar-MeO), 2·45–2·90 (2p, broad, 2- and 3-OH), 2·39 (1p, broad d, $J_{1,6x} = 5$ c/s, H_1), 2·22 (1p, d x d, $J_{1,6x} = 5$ c/s, $J_{6x,6n} = -13$ c/s, H_{6x}), 2·20 (1p, broad d, $J_{7a,7s} = -11$ c/s, H_{7a}), 1·96 (1p, broad s, H_4), 1·81 (1p, broad d, $J_{7a,7s} = -11$ c/s, H_{7s}), 1·37 (1p, d x d, $J_{6x,6n} = -13$ c/s, $J_{6n,7s} = 2.5$ c/s, H_{6n}); ms: 286 (16), 268 (11), 188 (100) (Found: C, 70·01; H, 6·43; calc. for $C_{17}H_{18}O_4$: C, 71·31; H, 6·34%).

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