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Synthesis of Tricyclo[7.2.2.0^{2,8}]tridecanes and Photoreaction in the Excited Singlet State: A Novel Entry to the DCB Carbon Framework of Phorbol

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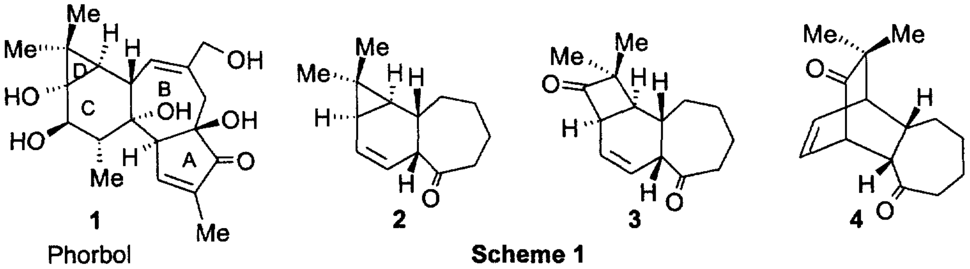
Abstract: Synthesis of 10,10-dimethyltricyclo[7.2.2.0^{2,8}]tridec-12-ene-3,11-dione **4** and its photoreaction to tricyclic compound **2** is presented.

Keywords: cycloaddition, decarbonylation, photochemistry, Diels-Alder reaction

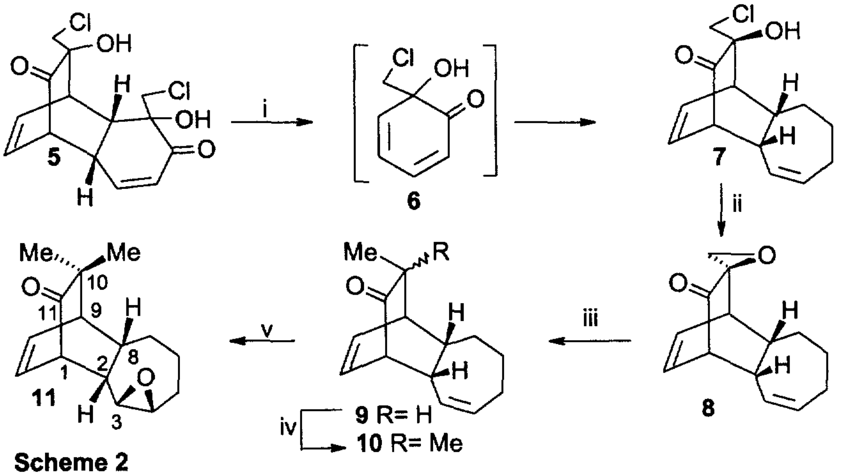
Recently, there has been an upsurge of interest[1-5] in the synthesis of phorbol esters and analogues because they control intracellular signal transduction through protein kinase C (PKC). Several approaches involving intramolecular oxido-pyrylium-alkene cycloaddition,[1] transannular cyclization,[2] intramolecular nitrile oxide cycloaddition,[3] Diels-Alder reaction,[4] and carbonyl ylide cyclization[5] have been employed to generate various rings of phorbol. The intramolecular oxido-pyrylium-alkene cycloaddition methodology by Wender and co-workers has led to a synthesis of phorbol.[1] In continuation of our studies towards development of new synthetic methods employing photoreaction of β,γ-enones[6] and the interest in phorbol, we considered it possible to generate a tricyclic system of type **2** having the DCB carbon framework of phorbol, *via* decarbonylation of an annulated bicyclo[2.2.2]octenone **4** on singlet excitation, either directly, or through the intermediacy of the 1,3-acylshift product **3** (scheme 1). We now wish to report an efficient synthesis of the dione **4** and its photoreaction to **2** having the D, C and B rings of phorbol.



Scheme 1

PII: S0040-4039(99)00015-5

The dione **4** was synthesised from the readily available[7] dimer **5** and cyclohepta-1,3-diene *via* generation of cyclohexa-2,4-dienone **6** and cycloaddition with 1,3-cycloheptadiene followed by manipulation of the resulting adduct (schemes 2 & 3). Thus, pyrolysis of **5** in o-dichlorobenzene containing 1,3-cycloheptadiene at ~140°C, for about 6h furnished the *endo* adduct **7** in good yield, whose structure was deduced from the spectral data. The stereochemical orientation of the hydroxyl group is suggested on the basis of general tendency of the cyclohexa-2,4-dienones during their cycloaddition [7a] and by comparison with analogous compounds prepared in our laboratory.[7c] The stereochemistry at this centre would become inconsequential since the hydroxyl and chloromethyl groups would be next converted to *gem* dimethyl groups. Treatment of **7** with aqueous KOH in chloroform readily gave the ketoepoxide **8** in quantitative manner.[8] The reduction of **8** with zinc-NH_4Cl in dry dioxane[7c] gave the monomethyl ketone **9** (as a mixture of *syn*: *anti* isomers) which on alkylation with methyl iodide in the presence of NaH-THF afforded the methylated ketone **10** in excellent yield. Regioselective epoxidation of **10** with *m*-chloroperbenzoic acid in CH_2Cl_2 at ambient temperature (~30°C) gave the epoxyketone **11** whose structure was discerned from the following data. The ^1H NMR (300MHz, $CDCl_3$) spectrum of **11** exhibited two signals at δ 6.59 (dd, J_1, J_2 ~ 7.5Hz, 1H) and 6.21 (dd, J 7.5Hz, 1H) corresponding to the olefinic protons of the β,γ–enone moiety. It also showed resonances at δ 3.39 (d, J ~7.5Hz, 1H) and 2.48 (d, J 7.5Hz, 1H) due to the bridgehead protons at C1 and C9 respectively. Furthermore, signals were observed at δ 2.94 (m, 1H) and 2.74 (dd, J_1, J_2 4Hz, 1H) corresponding to the protons at C4 and C3 respectively, in addition to resonances for other methine, methylene and methyl protons. These assignments were confirmed by a COSY spectrum. Comparison of these spectral features with those of the precursor **10** suggested that the olefinic linkage present in the seven-membered ring of **10** had undergone epoxidation, a manifestation of the homoconjugation of the olefinic moiety present in the bicyclo[2.2.2]octane framework.

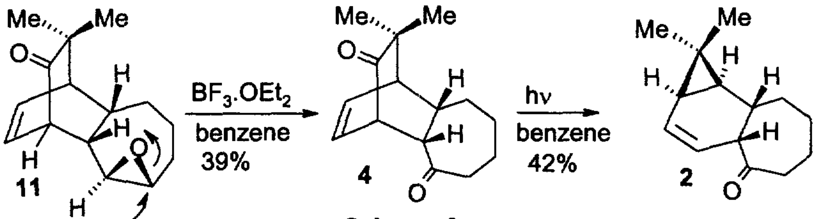


Scheme 2

Reagents and Conditions: i, 1,3-cycloheptadiene, o-dichlorobenzene, 140°C, 51%; ii, KOH(aq), CTAB, $CHCl_3$ 93%; iii, Zn, NH_4Cl, Dioxane, Δ, 72%; iv, NaH, MeI, Δ, 78%; v, *m*-chloroperbenzoic acid, CH_2Cl_2, r.t., 94%

Rearrangement of the epoxide **11** in presence of $BF_3.OEt_2$ in benzene gave a diketone to which the structure **4** (scheme 3) was assigned on the basis of the following. The presence of two carbonyl groups was clearly revealed from its ^{13}C spectrum which showed signals at δ 215.93 and 214.04 along with other resonances. The ^1H NMR spectrum (300MHz) displayed a characteristic signal at δ 6.39 (dd, J, J_2 7Hz, 1H), 6.18 (ddd, J_1, J_2 7Hz, J_3 1.5Hz, 1H), and 3.60 (d, J 7Hz, 1H) for olefinic and the bridgehead proton at C1 respectively. It further showed signals at δ 2.9 (m, 1H) partly overlapped with another signal at δ 2.82 (m, 1H) and 2.58 (br d, J ~7Hz, 1H) for the ring junction protons at C8, C2 and the bridgehead proton at C9 respectively, in addition to signals for other methylene and methyl protons. These assignments were confirmed with the help of a COSY spectrum which revealed correlation between the signals at δ 6.39, 6.18 and 2.58. Similarly the olefinic signal at δ 6.18, assigned to the β proton of the β,γ-enone moiety, showed a correlation with resonances at δ 6.39, 3.60. Further, it also showed a small correlation with the signal at δ 2.82 (partly merged with the signal at δ 2.9) assigned to the ring junction proton at C2. The multiplet at δ 2.9 assigned to the ring junction proton at C8, showed correlation with the signals at δ 2.82 and methylene protons at δ 2.00, and 1.10 (hidden under methyl signals). These relationships between the protons clearly suggested the structure **4** for the above compound. The regioselective rearrangement of the epoxide **11** to **4** could be due to steric interaction between the protons at C1 and C3.

Towards the synthesis of **2**, a solution of the dione **4** in dry benzene was irradiated with a mercury vapour lamp (400 W, Applied photophysics) for 2h, in a Pyrex immersion well. Removal of the solvent followed by chromatography gave the tricyclic compound **2**[9] in good yield (42%) as a result of decarbonylation.[10] Preliminary observations indicate that this photoreaction apparently proceeds through the 1,3-acyl shift intermediate which undergoes decarbonylation to give the final product. It may be mentioned that creation of the ring D *ie* the cyclopropane ring having geminal dimethyl groups appears to be one of the most important and difficult tasks in the synthesis of phorbol.



Scheme 3

In summary, we have described a novel route to bicyclo[2.2.2]octenone annulated with a seven membered ring and its photochemical reaction directly leading to the tricyclic DCB framework of phorbol in a single stereoselective sequence.

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8. Data for compound **8** : mp. 124-125°C. IR ν_{max}: 1730 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 6.54 (dd, J_1, J_2 7.5Hz, 1H), 6.30 (dd, J_1, J_2 7.5Hz, 1H), 5.63 (complex m, 1H), 5.29 (br d, J= 10Hz, 1H), 3.38 (d, J 7.5Hz, 1H), 3.28(br d, J ~7.5Hz, 1H), 3.14(part of an AB system, J ~7Hz, 1H), 2.84 (part of an AB system, J ~7Hz, 1H), 2.39 (m, 2H), 2.21-1.97 (m, 2H), 1.6-1.39 (m, 4H).^{13}C NMR (75MHz, $CDCl_3$): δ 205.69 (CO), 135.19, 130.36, 128.50, 128.16, 57.86, 54.12, 53.23, 46.90, 39.65, 38.55, 28.99, 24.90, 21.60. Mass: 216 (M^+). Analysis: Found, C, 77.41; H, 7.46%, calcd C, 77.77; H, 7.40% for $C_{14}H_{16}O_2$.
9. Data for compound **2**: IR ν_{max}: 1711 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 6.06 (ddd, $J_1$10Hz, J_2 6Hz, J_3~3Hz,1H), 5.22 (dd, J_1 10Hz, J_2 ~2.5Hz, 1H), 2.8 (br d, J 9Hz, 1H), 2.48-2.30 (m, 2H), 2.04-1.94 (m, 1H), 1.66-1.58 (m, 1H), 1.24-1.18 (m, 1H), 1.12 (s, 3H, CH_3), 1.06-1.00 (m, 4H), 0.95 (s, 3H, CH_3), 0.90 (m, 1H, cyclopropyl proton), 0.82 (dd, J_1 6Hz, J_2 ~1Hz, 1H, cyclopropyl proton). ^{13}C NMR (75MHz, $CDCl_3$): δ 128.54, 121.05, 50.59, 42.70, 34.11, 32.62, 30.87, 30.17, 29.87, 25.19, 22.43, 15.98, 14.73, (carbonyl carbon not observed). Mass: 204(M^+)
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