$\pi^{4s}+\pi^{2s}$ Cycloaddition between electron deficient π-systems and photoreaction of β,γ-enones: a novel stereoselective entry into angular triquinanes

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Abstract—Cycloaddition of electron deficient partners such as cyclohexa-2,4-dienone and acrylates leading to an efficient synthesis of complex bicyclo[2.2.2]octenones having a β,γ-enone chromophore, and their transformation to angular triquinanes via photoreaction, is described. © 2003 Elsevier Science Ltd. All rights reserved.

The angularly fused triquinane ring system **1** having a tricyclo[6.3.0.0^{1,5}]undecane framework is present in a variety of naturally occurring terpenes such as pentalenene, isocomene and silphenene[1] (Fig. 1). Due to the unusual fusion of three cyclopentane rings around one carbon and their presence in structurally interesting natural products, some of which are biologically active, there has been significant interest in the development of methods to prepare angularly fused tricyclopentanoids.[1–3] Several ingenious synthetic approaches to angular triquinanes have been developed. However, except for a very few, most of the methods create the angular triquinane ring system in an iterative fashion. The search for new and efficient methods is continuing.[2,3] Recently, we developed the cycloaddition of electron deficient cyclohexa-2,4-dienones with electron rich 4π partners and the photoreactions of the resulting systems that led to syntheses of a variety of carbocyclic networks, and we also observed that cyclohexa-2,4-dienones react even with electron deficient 2π part-

ners.[4,5] In continuation of our studies in this area, we now wish to report the synthesis of annulated bicyclo[2.2.2]octenones of type **2** by the cycloaddition of cyclohexadienone **3** (and its congener) with electron deficient 2π systems and their photoreactions leading to a novel route to functionalised angular triquinanes.

It was envisaged that functionalised angular triquinanes of type **6** may be obtained in a stereoselective fashion from tricyclic compounds of type **2** via a photochemical oxa-di-π-methane rearrangement[4,6,7] to **5** followed by cleavage of the peripheral cyclopropane bond (Scheme 1). It was further considered that the tricyclic compounds of type **2** may be synthesized from the aromatic precursor **4** via oxidation to the spiroepoxycyclohexa-2,4-dienone **3** followed by interception with electron deficient dienophiles and manipulation of the resulting adduct.

Towards the aforementioned objective, the aromatic precursor **4** was readily prepared by controlled hydroxymethylation of indanol. A solution of **4** and ethyl acrylate in acetonitrile was subjected to oxidation with aqueous sodium metaperiodate[8] following a procedure developed in our laboratory.[4,9] Chromatography of the crude product gave the *endo* adduct **7a** in moderate yield (20%) along with a major amount of the dimer **8** (Scheme 2). The dimer **8** was formed as a single diastereomer (¹H and ¹³C NMR) and its stereochemical structure is tentatively suggested on the basis of the general tendency of spiroepoxycyclohexadienones during dimerisation and by comparison with other analogous dimers.[8a] It appeared that the formation of
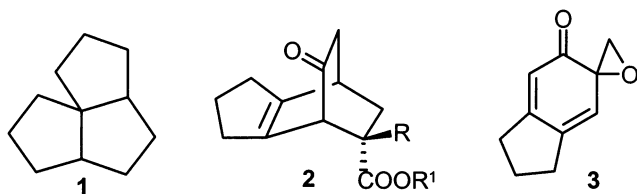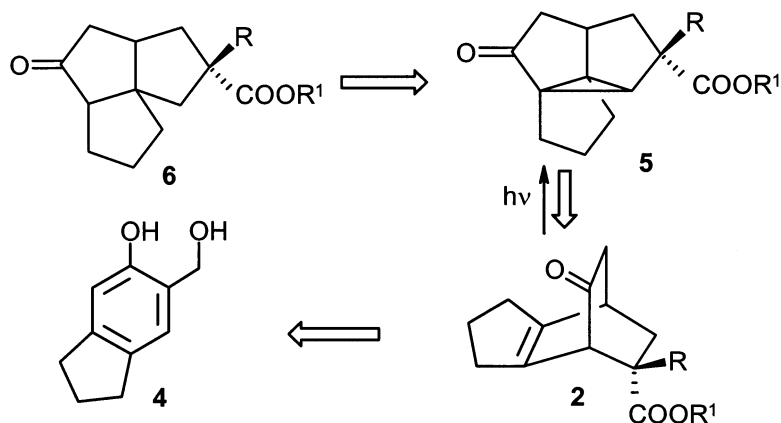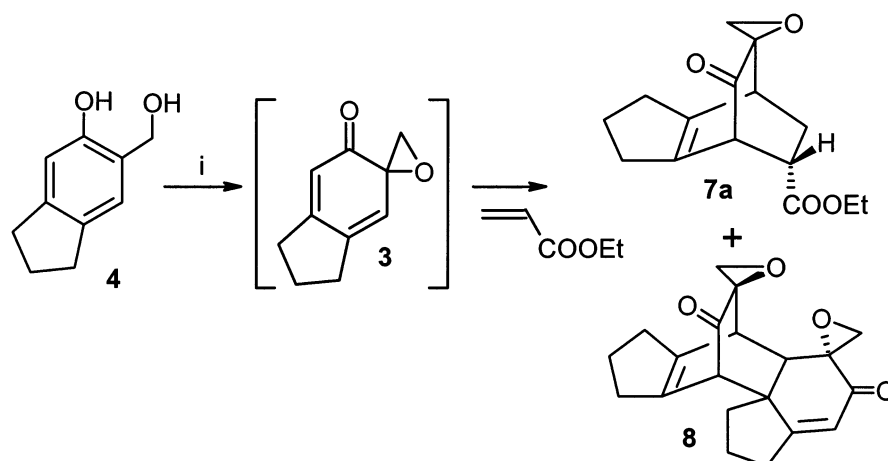
Figure 1.

Scheme 1.

Scheme 2. *Reagents and conditions*: (i) aq. NaIO$_4$, MeCN (**7a**, 20%; **8**, 45%).

the dimer **8** via cycloaddition between 2 mol of **3** competes more favorably than the interception of **3** with ethyl acrylate under the above conditions. Considering the structural complexity generated in a single

step, the transformation of **4** to the tricyclic ketoepoxide **7a** was reasonably good, nevertheless we developed an alternative route to **7a** from the dimer **8** as shown in Scheme 3.


a, R=H, R^1=Et
b, R= R^1= Me
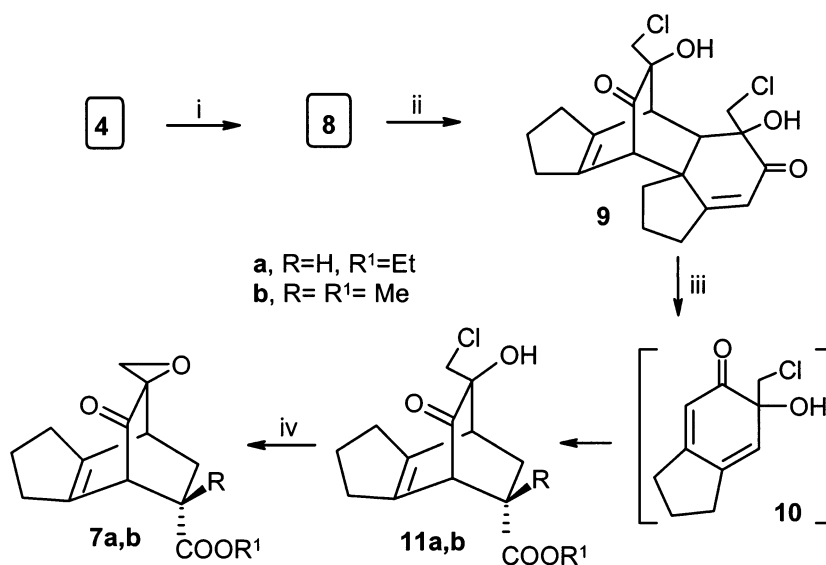
Scheme 3. *Reagents and conditions*: (i) aq. NaIO$_4$, THF, rt (46%); (ii) HCl, dioxane–H$_2$O (90%); (iii) *o*-dichlorobenzene, 130°C, ethyl acrylate (**11a**, 80%)/methyl methacrylate (**11b**, 75%), 8 h; (iv) aq. KOH, CTAB, CHCl$_3$, rt (**7a**, 97%; **7b**, 92%).

Thus, the dimer **8** was prepared by a slight modification of the aforementioned method and treated with HCl. The resulting bis-chlorohydroxy derivative **9** was heated with ethyl acrylate in *o*-dichlorobenzene in a sealed tube at 130°C. Interestingly, the adduct **11a** was obtained in a highly regio- and stereoselective fashion in excellent yield (80%) as a result of the generation of the cyclohexadienone **10** and its interception with ethyl acrylate. Similarly, the interception of **10** with methyl methacrylate gave the adduct **11b** in excellent yield. The adducts **11a,b** thus obtained were converted into **7a,b** by treatment with aq. KOH in chloroform containing cetyltrimethylammonium bromide (CTAB) in near quantitative yields. The structures of adducts **7a,b** and **11a,b** were deduced from their spectroscopic data,[†] COSY analysis and comparison with other related compounds.[5b] In order to obtain the desired chromophoric systems of type **2**, the ketoepoxides **7a,b** were reduced with activated zinc in aqueous methanol containing ammonium chloride, which gave the keto alcohols **12a,b** in good yield. Oxidation of **12a,b** with Jones' reagent followed by decarboxylation of the resulting β-keto-acid furnished the desired tricyclic compounds **2a,b** (Scheme 4) whose structures were clearly revealed from their spectroscopic data.

Towards the synthesis of angular triquinane, the photoreaction of tricyclic compounds **2a,b** containing a β,γ-enone chromophore was explored. Rigid β,γ-unsaturated carbonyl compounds undergo two unique photoreactions, viz. a 1,2-acyl shift or an oxa-di-π-methane rearrangement and a 1,3-acyl shift that are quite characteristic of the excited state. In general, the oxa-di-π-methane rearrangement is observed on triplet excitation (T2), while the 1,3-acyl shift is observed upon singlet (S1) excitation.[4,6,7] However, the structure of the β,γ-enone and its substituents are known to control the photoreaction in a subtle fashion.[7] In view of this, a solution of compound **2a** in acetone (solvent as well as sensitizer) was irradiated with a medium pressure mercury vapour lamp (125 W, APP, 300 nm) in a Pyrex vessel for 15 minutes. Chromatography of the photolysate gave the desired oxa-di-π-methane product **5a** in low yield (22%) along with a mixture of compounds containing the 1,3-acyl shift product **13** (32%, IR, NMR).

It is very difficult to understand the above photochemical reaction and the factors responsible for the formation of the undesired products during the sensitized irradiation. The unusual behavior of **2a** upon triplet excitation could presumably be due to the presence of a five membered ring annulated to the C=C double bond (electronic and/or steric factors) especially since simple bicyclo[2.2.2]octenones undergo efficient oxa-di-π-methane reactions.[7] In order to improve the efficiency of the oxa-di-π-methane reaction, we considered exploring the above photoreaction by irradiation with light of a
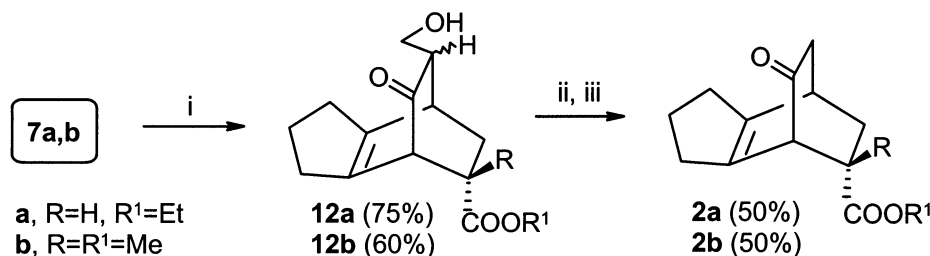
Scheme 4. *Reagents and conditions*: (i) Zn–NH$_4$Cl, MeOH–H$_2$O; (ii) Jones' oxidation; (iii) aq. THF, Δ.


[†] *Data for selected compounds*:

Compound **11a**: mp 55–57°C. IR ν_{max} (film): 3445, 1733 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 4.12 (m, 2H, CO$_2$C$\underline{H}_2$CH$_3$), 3.65 (d, partly merged with an AB system, $J=2.3$ Hz, 1H, bridgehead proton), 3.62 (part of an AB system, $J_{AB}=11.5$ Hz, C$\underline{H}_2$Cl, 1H), 3.35 (part of an AB system, $J_{AB}=11.5$ Hz, C$\underline{H}_2$Cl, 1H), 3.26 (t, $J=2.8$ Hz, 1H, bridgehead H), 3.10 (m, 1H, C$\underline{H}$-CO$_2$Et), 2.70 (br s, 1H), 2.60 (m, 1H, methylene H), 2.55–2.40 (m, 4H, methylene H), 2.05–1.95 (m, 2H, methylene H), 1.75 (ddd, $J_1=13.1$ Hz, $J_2=5.2$ Hz, $J_3=2.9$ Hz, 1H, methylene H), 1.25 (t, $J=7.1$ Hz, 3H, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 206.44 (bridge CO), 172.79 (ester CO), 145.73, 135.44 (olefinic carbons), 74.04, 61.09, 50.64, 50.25, 40.96, 40.11, 33.31, 33.22, 23.78, 23.51 and 14.17 for methine, methylene, quaternary and methyl carbons. HRMS (ESI): Found (M$^+$+Na) 321.0850; C$_{15}$H$_{19}$ClO$_4$ requires (M$^+$+Na), 321.0863.

Compound **2a**: IR ν_{max} (film): 1728 cm^{-1}. UV λ_{max} (methanol): 210, 297 nm. ^{1}H NMR (300 MHz, CDCl$_3$–CCl$_4$) δ: 4.10 (m, 2H, CO$_2$C$\underline{H}_2$CH$_3$), 3.54 (d, $J=1.8$ Hz, 1H, bridgehead H), 3.0 (m, 2H), 2.46–2.35 (m, 4H, methylene H), 2.02–1.8 (m, 6H, methylene H), 1.25 (t, $J=6.9$ Hz, 3H, CO$_2$CH$_2$C$\underline{H}_3$). ^{13}C NMR (75 MHz, CDCl$_3$–CCl$_4$) δ: 208.84 (bridge CO), 173.02 (ester CO), 147.04, 134.92 (olefinic carbons), 60.80, 52.34, 40.22, 40.14, 33.28, 32.64, 32.60, 29.64, 23.85 and 14.36 for methine, methylene, quaternary and methyl carbons. HRMS (ESI): Found (M$^+$+H) 235.1327; C$_{14}$H$_{18}$O$_3$ requires (M$^+$+H), 235.1329.

Compound **5a**: mp 48–49°C. IR ν_{max} (film): 1734, 1718 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$–CCl$_4$) δ: 4.16 (q, $J=7.2$ Hz, 2H, CO$_2$C$\underline{H}_2$CH$_3$), 2.91 (dd, $J_1=11$ Hz, $J_2=6$ Hz, 1H), 2.81–2.74 (m, 2H), 2.34–2.28 (m, 2H), 2.11–1.68 (m, 7H), 1.51–1.43 (m, 1H), 1.28 (t, $J=6.9$ Hz, 3H, CO$_2$CH$_2$C$\underline{H}_3$). ^{13}C NMR (75 MHz, CDCl$_3$–CCl$_4$) δ: 213.75 (cyclopentane CO), 173.94 (ester CO), 60.81, 59.32, 54.83, 49.79, 44.94, 43.44, 40.89, 37.65, 26.99, 26.78, 26.27 and 14.34 for methine, methylene, quaternary and methyl carbons. HRMS (ESI): Found (M$^+$+H) 235.1325; C$_{14}$H$_{18}$O$_3$ requires (M$^+$+H), 235.1329.

Compound **6a**: IR ν_{max} (film): 1734, 1722 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$–CCl$_4$) δ: 4.11 (q, $J=7.2$ Hz, 2H, CO$_2$C$\underline{H}_2$CH$_3$), 2.84 (m, 1H), 2.57–2.47 (m, 1H), 2.39 (m, 1H), 2.30–1.60 (cluster of m, 11H), 1.46–1.3 (m, 1H), 1.26 (t, $J=6.9$ Hz, 3H, CO$_2$CH$_2$C$\underline{H}_3$). ^{13}C NMR (75 MHz, CDCl$_3$–CCl$_4$) δ: 220.62 (cyclopentane CO), 174.56 (ester CO), 60.34, 59.45, 58.51, 46.12, 44.26, 44.07, 43.48, 41.83, 37.77, 31.06, 26.89 and 14.46 for methine, methylene, quaternary and methyl carbons. HRMS (ESI): Found (M$^+$+H) 237.1490; C$_{14}$H$_{20}$O$_3$ requires (M$^+$+H), 237.1485.
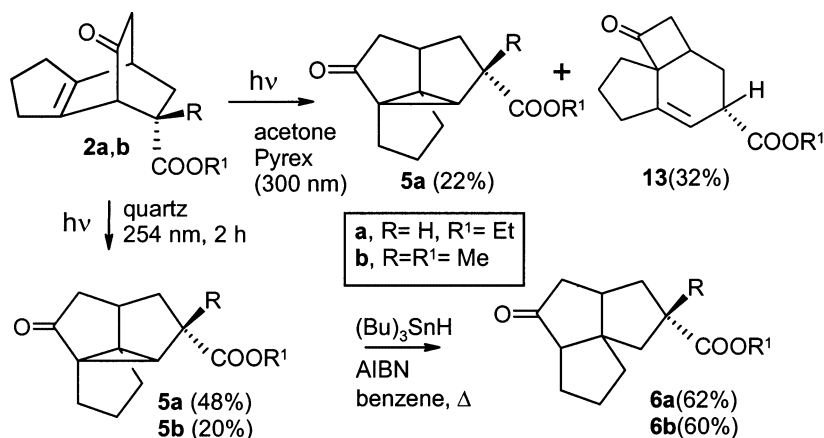
Scheme 5.

shorter wavelength. Thus, a solution of compound **2a** in acetone was irradiated with a mercury vapor lamp (16 W, 254 nm) in a quartz immersion well for 2 h. Indeed, removal of solvent followed by chromatography of the residue furnished the desired tetracyclic compound **5a** as the major compound in good yield (48%) and the formation of the other products was minimized (15%). However, similar irradiation of compound **2b** in acetone gave the desired tetracyclic compound **5b** in only a low yield (20%) along with a minor amount of the 1,3-acyl shift product (6%).

It is difficult to understand the aforementioned photochemical behavior of **2a,b**. Apparently, irradiation with a medium pressure lamp leads to excitation of both the acetone and β,γ-enone carbonyl of **2a,b** thus leading to competition between the 1,3-acyl shift product and the sensitized pathway, while irradiation with a low pressure lamp (254 nm) probably excites the acetone chromophore more efficiently than the β,γ-ketone of **2a,b**. Though the photoreactions of **2a,b** proceeded with only moderate efficiency, they provided clean and stereoselective routes to the tetracyclic compounds **5a,b** which are not otherwise readily accessible.

For the synthesis of angular triquinanes, a selective cleavage of the peripheral cyclopropane bond in the photoproducts **5a,b** was required. There are several methods for cleavage of carbonyl conjugated cyclopropane rings,[10,11] the radical induced cleavage was attempted.[11] Thus, the photoproducts **5a,b** were treated with tributyltin hydride in the presence of AIBN which gave the angular triquinanes **6a,b** in good yields (Scheme 5) whose structures were deduced from their spectroscopic data.

In summary, a new and stereoselective route to angular triquinanes from 5-indanol has been described. The methodology involves an efficient synthesis of complex bicyclo[2.2.2]octenones endowed with a β,γ-unsaturated carbonyl chromophore via a highly interesting cycloaddition of electron deficient cyclohexa-2,4-dienones with acrylates, and photochemical reactions of the resulting chromophoric systems.

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