o-Vanillyl Alcohol as a Synthetic Equivalent of 2-Methoxycyclohexa-2,4-dienones: a Novel Synthesis of Linearly Fused *cis*: *anti*: *cis* Tricyclopentanoids

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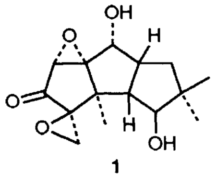
A novel and efficient synthesis of tricyclopentanoids *via* inverse demand $\pi^{4s} + \pi^{2s}$ cycloaddition and photochemical reaction of annulated[2.2.2]octenones having an α-alkoxy-β,γ-unsaturated carbonyl chromophore, is described.

There has been a world wide interest in the chemistry of polyquinane natural products derived from humulene cyclisation cascade,[1] because of their intricate molecular framework composed of fused cyclopentane rings and also owing to diverse biological properties exhibited by some of the natural products. For example, coriolin **1** shows antitumour and antibacterial activities,[2] while hirsutic acid **2** has antibiotic properties.[3] Though a variety of methods have been developed[4,5] for the synthesis of tricyclopentanoids, most of them are target oriented, lack adaptability and generate triquinane framework after multistep sequence. In this context we recently reported[6] a unified approach towards linearly fused triquinanes *via* tetracyclic intermediate **3**, which however, required selective cleavage of the cyclopropane sigma bond.

In order to circumvent the aforementioned problem in our earlier approach, we envisaged that photochemical 1,2-acyl-shift or oxa-di-π-methane rearrangement[6,7] of tricycloundecadienones having α-alkoxy-β,γ-unsaturated carbonyl chromophore, such as **6** would produce the tetracyclic structure **5** which could be easily transformed into the desired *cis* : *anti* : *cis* tricyclopentanoids of type **4**. We further thought that the desired chromophoric systems should be amenable through inverse demand $\pi^{4s} + \pi^{2s}$ cycloaddition of the appropriate cyclohexa-2,4-dienone and dienophile.



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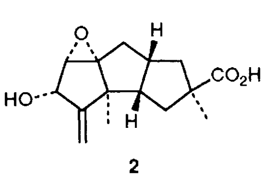

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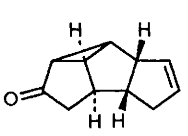

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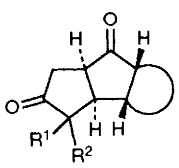

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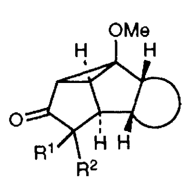

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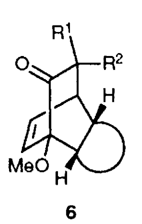

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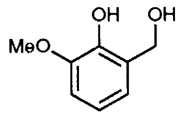

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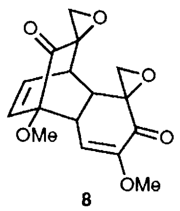

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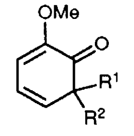
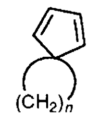
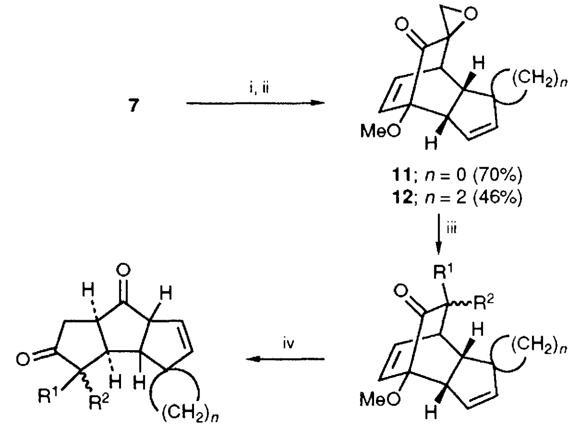


9a; $R^1 = R^2 = \text{-CH}_2\text{O-}$
b; $R^1 = \text{Me}, R^2 = \text{H}$
c; $R^1 = R^2 = \text{Me}$



10a; $n = 0$
b; $n = 2$



17; $R^1 = \text{Me}, R^2 = \text{H}, n = 0$ (73%)
18; $R^1 = R^2 = \text{Me}, n = 0$ (55%)
19; $R^1 = \text{Me}, R^2 = \text{H}, n = 2$ (48%)
20; $R^1 = R^2 = \text{Me}, n = 2$ (48%)

13; $R^1 = \text{Me}, R^2 = \text{H}, n = 0$ (67%)
14; $R^1 = R^2 = \text{Me}, n = 0$ (88%)
15; $R^1 = \text{Me}, R^2 = \text{H}, n = 2$ (54%)
16; $R^1 = R^2 = \text{Me}, n = 2$ (47%)

Scheme 1 *Reagents and conditions*: i, $NaIO_4$, $CHCl_3$–H_2O (1 : 1), CTAB, room temp., 3 h; ii, **10a, b**; iii, (*a*) Zn, NH_4Cl, dioxane, heat; (*b*) NaH, tetrahydrofuran, MeI; iv, *hv*, acetone, 3 h

In this communication, we report a novel, efficient and versatile route to functionalised triquinanes (**17–20**) *via* a one-step photoreaction of the chromophoric systems (**13–16**). We also report a general approach towards synthesis of annulated bicyclo[2.2.2]octenones having α-alkoxy-β,γ-unsaturated carbonyl chromophore employing *o*-vanillyl alcohol as a simple, inexpensive synthetic equivalent of 2-alkoxy-6-alkylcyclohexa-2,4-dienones (**9b, c**).

The synthesis of the desired chromophoric systems, though conceptually simple, appeared to be a difficult task in practice, because of the lack of methods for preparation of 2-alkoxycyclohexa-2,4-dienones. Oxidation of phenols with lead tetraacetate[8] is occasionally employed for this purpose, however it often produces a very complex mixture of products. Other oxidising agents such as thallium trinitrate[9] gives mainly *o*-quinones upon treatment with alkoxy phenols. We, therefore, explored the possibility of employing the readily available[10] dimer **8** or its derivative as a source of cyclohexa-2,4-dienone **9** *via* its retro Diels–Alder reaction. However, all the attempts to generate and subsequently trap the dienone **9a** following an analogous procedure[6,11] were futile. Furthermore, attempts to manipulate the oxirane ring into suitable derivatives were also unsuccessful, presumably because of sensitive enol ether moiety present in the cyclohexane ring.

After these unsuccessful attempts, we devised a new one-pot preparation of annulated bicyclo[2.2.2]octenones† **11, 12** *via* biphasic oxidation of *o*-vanillyl alcohol **7** with sodium metaperiodate in the presence of cetyltrimethylammonium bromide(CTAB) and subsequent interception of the resulting 2-methoxy-6,6-methylenoxy cyclohexa-2,4-dienone **9a** through $\pi^{4s} + \pi^{2s}$ cycloaddition with dienes **10a** and **10b** respectively‡ (Scheme 1). It is notable that the cycloaddition occurred in a highly regio- and stereo-specific manner to give a single *endo* adduct, during which the dienone **9a** behaved as a diene (π^4 component) and the cyclopentadiene **10a**, and spiroheptadiene[11] **10b** as a dienophile (π^2 component). The presence of oxirane ring adjacent to the carbonyl group in the adducts **11** and **12** provided further opportunities for their elaboration to chromophoric systems (**13–16**). The reduction of **11** and **12** with zinc in dry dioxane containing ammonium chloride, directly gave **13, 15** (as *syn* : *anti* mixture),[12] which were alkylated[6] to give **14** and **16** respectively (Scheme 1).

A solution of the ketone **14** in acetone was irradiated (Hg vapour lamp 125 W, Applied Photophysics) under nitrogen for 3 h. Removal of solvent followed by chromatography over silica gel gave the triquinane **18** in good yield. The structure of **18** was clearly revealed through its spectral and analytical data. While ^{1}H NMR of **18** lacked a resonance signal for the OMe group, its ^{13}C NMR displayed two signals for carbonyl groups δ 219.44, 217.02 and signals at 41.31(t), 35.83(t) for two CH_2 groups respectively.§

Other chromophoric systems (**13, 15, 16**) were also found to give the corresponding *cis* : *anti* : *cis* tricyclopentanoids (**17, 19, 20**) smoothly upon sensitized irradiation in acetone¶ (Scheme 1). This photochemical transformation apparently proceeded through an initial 1,2-acylshift to give the tetracyclic intermediate of type **5** which upon photochemical cleavage of the peripheral cyclopropane sigma bond and loss of methyl radical followed by hydrogen abstraction[13] finally gives the product.‖ However, we have not yet been able to isolate the intermediate, 1,2-acylshift product. It appears that photoreactions of α-alkoxy-β,γ-unsaturated ketones have not been recorded in the literature except for an isolated instance,[13] where similar cleavage was observed, in a simple system.

In summary, we have developed a novel and efficient route to linearly fused *cis* : *anti* : *cis* functionalised tricyclopentanoids, which has wide synthetic potential and adaptability. We have also demonstrated the utility of *o*-vanillyl alcohol as an equivalent of various 2-methoxy cyclohexa-2,4-dienones, and their inverse demand $\pi^{4s} + \pi^{2s}$ cycloaddition towards the synthesis of annulated bicyclo[2.2.2]octenones having α-methoxy-β,γ-unsaturated carbonyl chromophoric systems.

We are investigating the scope and limitation of this approach towards synthesis of natural products and other higher polyquinanes.

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† All the compounds were fully characterised through spectral and analytical data.

‡ This method appears to be general.

§ *Selected data* for **18**: m.p. 56 °C, ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.44 (CO), 217.02 (CO), 132.90 (-C=), 127.45 (-C=), 60.9(CH), 55.59 (CH) 49.12 (quartenary C), 44.91 (CH), 41.31 (CH_2), 38.24 (CH), 35.83 (CH_2), 24.81 (CH_3), 19.32 (CH_3), Mass spectrum, *m/z*: 204 (M^+), 176, 161, 107, 66.

¶ Irradiation of epoxyketones **11, 12** gave a complex mixture of products.

‖ This type of cleavage is normally not observed during oxa-di-π-methane rearrangement.

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