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Aromatics to Triquinanes. Synthesis of 1, 4, 4,11-Tetramethyltricyclo[6.3.0.0^{2,6}]undeca-3, 7,10-trione: A Potential Precursor for Coriolin and congeners

Vishwakarma Singh*, Beena Thomas and Punitha Vedantham

Department of Chemistry, Indian Institute of Technology, Bombay 400 076 (INDIA).

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Abstract: Synthesis of a highly functionalised triquinane **4** from 2-hydroxy-3-methoxy-6-methylbenzyl alcohol is reported.

There has been a world wide interest in the chemistry of triquinane natural products during the past decades, which has led to explosive growth in the methodology for the synthesis of triquinanes.[1-4] The sesquiterpene coriolin **1** is a metabolite of micro-organism *Coriolius* consors. Coriolin and its derivative diketocoriolin **2** exhibit antitumor activity.[3] The richly adorned functionalities on a *cis:anti:cis* triquinane framework of coriolin has drawn attention of many synthetic chemists.[4] We recently reported a novel, general and efficient method for the synthesis of linearly fused *cis:anti:cis* tricyclopentanoids employing cycloaddition of spiroepoxycyclohexa-2,4-dienone and photoreaction of α-methoxy-β,γ-enone chromophore as key features of our strategy.[5] We now wish to report on the synthesis of 1,4,4,11-tetramethyltricyclo[6.3.0.0^{2,6}]undeca-3,7,10-trione **4**, a potential precursor of coriolin and its analogues, from 2-hydroxy-3-methoxy-6-methyl-benzyl alcohol.

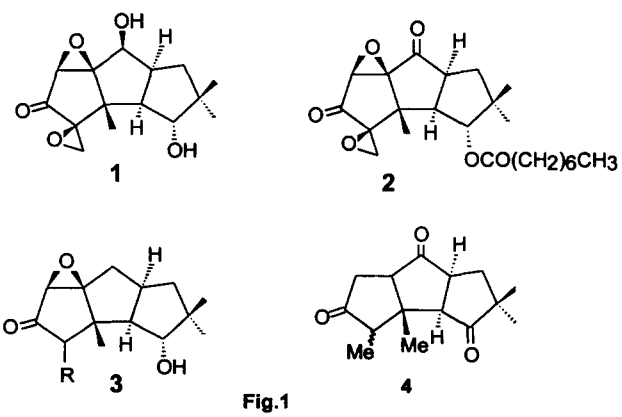

Fig.1

Keeping in view, the stereogenic centres, substituents and functional groups present in coriolin **1** and diketocoriolin, we devised a retrosynthetic strategy as shown in scheme-1. We considered the trione **4**

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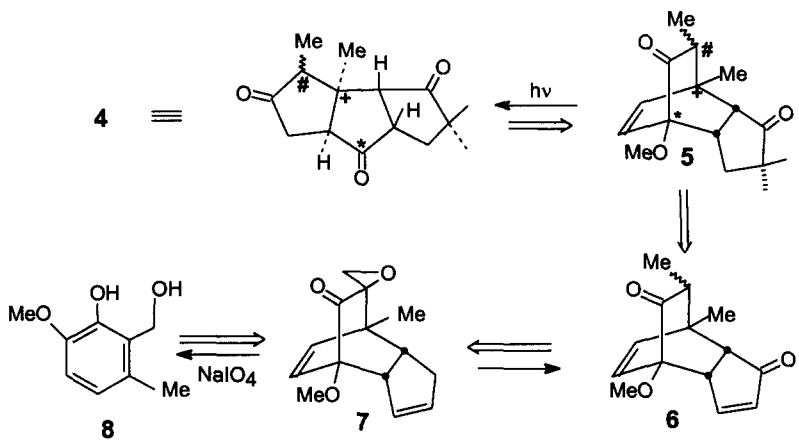
as an advanced, potential precursor to coriolin and its analogues since the triquinane **4** is endowed with most of the structural, functional and stereochemical features of coriolin. It contains all the fifteen carbon atoms of coriolin, geminal and angular methyl groups and carbonyl groups in all the three cyclopentane rings at appropriate centres.

We envisaged that the intermediate **4** could be obtained from triplet (^{3}T) sensitized photoreaction[5] of appropriately constituted *endo*-tricyclo[5.2.2.0^{2,6}]undecenedione such as **5** which in turn was thought to be amenable from the epoxy ketone **7** *via* an appropriate sequence of chemical reactions. Furthermore, it was thought that the epoxy ketone **7** could be readily obtained from the phenol **8** *via in situ* generation of spiroepoxycyclohexa-2,4-dienone **9** and its subsequent interception with cyclopentadiene, following a methodology developed in our laboratory.[5]



Scheme 1

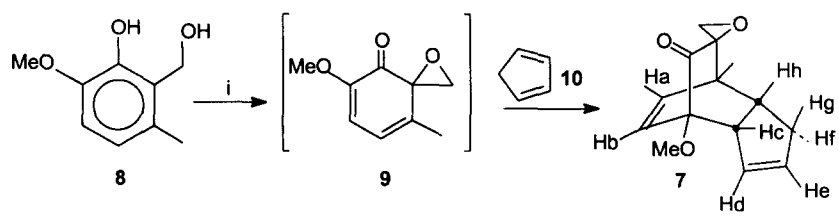
The advantages of the proposed strategy are that all the groups required in the intermediate **4** are embodied in the *endo*-tricyclo[5.2.2.0^{2,6}]undecenedione **5**. It is also interesting to note that the carbonyl group in the central ring of the intermediate **4** is present in latent form (as OMe group at the bridgehead carbon) in the chromophoric system **5**. Moreover, the thirteen carbons (out of fifteen required in **5** and/or the triquinane intermediate **4**) are derived from the *endo* tricyclic compound **7** which is assembled in a single step from the aromatic precursor **8** and cyclopentadiene. It may be mentioned that all the other approaches[4] towards coriolin focus on the synthesis of triquinanes of type **3** and then generate oxygen functionality in the central five membered ring.

RESULTS AND DISCUSSION

Synthesis of the desired tricyclo[5.2.2.0^{2,6}]undecenedione (5)

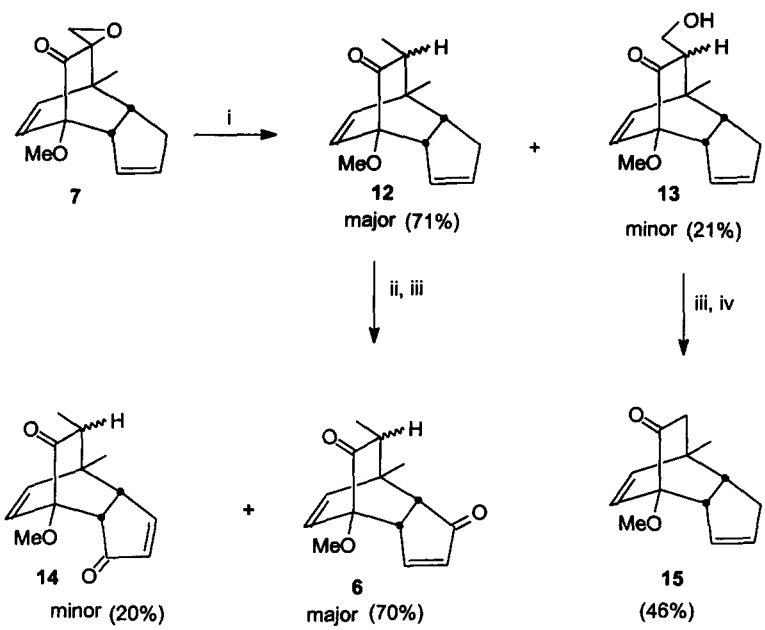
Tricyclo[5.2.2.0^{2,6}]undecenedione **5** was synthesized from the aromatic precursor **8** as described below. Thus, 2-hydroxy-3-methoxy-6-methylbenzyl alcohol **8** was oxidized with $NaIO_4$ and the resulting 2-

methoxy-5-methyl-6-spiroepoxycyclohexa-2,4-dienone **9** was trapped with cyclopentadiene, to give the spirooxiranetricyclo[5.2.2.0^{2,6}]undecadienone **7** in good yield (60%, Scheme-2). The epoxy ketone **7** was thoroughly characterized from its spectral and analytical data. The high field ^{1}H-NMR (300 MHz) spectrum of **7** displayed a signal at δ 6.16 (d of part of an AB system, J_{AB}=8.5 Hz, J_2=~1Hz, 1H) which was assigned to the γ proton, H_a of the β,γ-enone moiety[6] while the signal shown at δ 6.03 (d of part of an AB system, J_{AB}=8.5 Hz, J_2=~1Hz, 1H) was assigned to the β-proton, H_b of the β,γ-enone group. The other olefinic signals were observed at δ 5.80 (m of d, J= 6Hz, 1H) and 5.65 (m of d, J=6 Hz, 1H). The signal for OMe appeared at δ 3.59 (s, OCH_3) and methyl group at the bridgehead showed its resonance at δ 1.10 (s, CH_3). The protons of OCH_2 group showed their signals separately at δ 3.08 (part of an AB system, J_{AB}=6 Hz, 1H) and at δ 2.95 (part of an AB system, J_{AB}=6 Hz, 1H). The proton at the allylic ring junction H_c exhibited its resonance at δ 3.41 (complex m of d, J=9 Hz,1H).The proton H_h at the other ring junction displayed its signal at δ 2.83 (ddd, J_1=J_2=9 Hz, J_3=3 Hz, 1H). The methylene protons H_g and H_f of the cyclopentene ring with large geminal coupling were shown at δ 2.54 (m of dd, J_1=18 Hz, J_2=9 Hz, 1H) and 2.12 (complex m of d, J=18 Hz 1H) respectively. The structure of the adduct was also supported by its ^{13}C-NMR data which exhibited the following resonances at δ 204.46 (CO), 135.80 (d), 134.14 (d), 129.50 (d) and 127.65 (d) for olefinic carbons. The methine, methylene and methyl carbons were shown at δ 86.71, 59.41, 53.55, 49.57, 43.38, 41.27, 37.18 and 14.74. The above assignments were made on the basis of chemical shifts, coupling constants and comparison of the above spectral features with similar compounds prepared in our laboratory. The stereochemical orientation of the oxirane ring was suggested on the basis of the general tendency of the cyclohexa-2,4-dienones during their cycloaddition[7] and comparison with other related adducts.[8] It is remarkable to note the selectivity during the above cycloaddition especially since the cyclohexa-2,4-dienone could react with cyclopentadiene in various pericyclic modes.[9] It may be mentioned that the tricyclic systems of type **7** were not known prior to the preliminary report from our laboratory.[5]



Scheme 2

Reagents/conditions: i, $NaIO_4$, CH_3CN-H_2O, r.t.



Scheme 3

Reagents and conditions: i, Zn, NH_4Cl, dioxane, Δ, ii, SeO_2, KH_2PO_4, dioxane-H_2O, Δ, iii, Jones reagent, iv, THF,Δ

The epoxy adduct **7** was then reduced with zinc in dry dioxane containing ammonium chloride[10] which gave the deoxygenated compound **12** as the major product [71%, *syn:anti* (1:8) mixture, ^{1}H-NMR 300 MHz] and the keto alcohol **13** as a minor product (20%) (Scheme-3). The compound **12** was oxidized with SeO_2[11] in refluxing dioxane-water to give a regioisomeric mixture of allylic alcohols which was further oxidized with Jones' reagent to give the α,β-conjugated enones **6** and **14**, which were separated by chromatography. Furthermore, the ketoalcohol **13** was easily converted into the parent tricyclic system **15** *via* oxidation and decarboxylation (Scheme 3).The structures of the enones were determined by detailed analysis of their spectral data and comparison with analogous compounds.[12] The high field ^{1}H-NMR (500 MHz) spectrum of the less polar enone **6** (*syn:anti*, 1:6) displayed characteristic signals (major stereoisomer) at δ 7.5 (multiplet, 1H) and at δ 6.26 (d with long range coupling, J=5.5 Hz, 1H) for the β- and α-protons of α,β-enone system. It further showed signals at δ 6.03 (d, J=8.5 Hz, 1H), 5.97 (d, J=8.5 Hz, 1H) for the γ and β protons of the β,γ-enone group respectively. The methoxy group showed a signal at δ 3.60 (s, 3H). The signal at δ 3.26 (multiplet of d, J=5 Hz, 1H) was assigned to the proton at the allylic ring junction while the proton at the other ring junction (α to the conjugated carbonyl group) displayed its signal

at δ 2.52 (d, J=5 Hz, 1H). The resonance signal at δ 1.95 (q, J=~6 Hz, 1H) was assigned to the proton α to the carbonyl group present in the bicyclo[2.2.2]octenone framework. The methyl group at the bridgehead exhibited its signal at δ 1.52 (s, 3H) while the other methyl group appeared at δ 1.13 (d, J=~6 Hz, 3H).

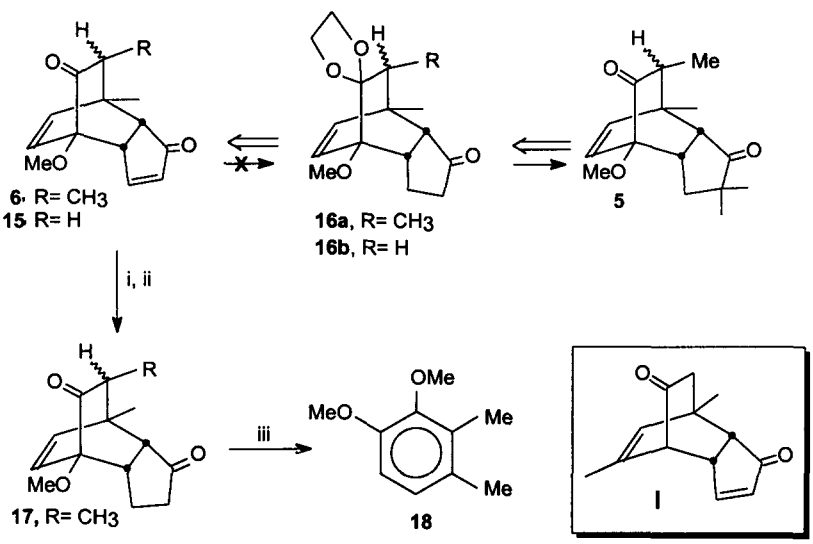
The structure of the isomeric enone **14** was also discerned from its spectral data. ^{1}H-NMR (300 MHz) spectrum of **14** showed signals (major stereoisomer) at δ 7.53 (m of d, J=5.5 Hz, 1H) and 6.25 (d, J=5.5 Hz, 1H) corresponding to the β– and α- protons of the α,β-enone moiety. The γ and β protons of the β,γ-enone group were displayed at δ 5.91 (d, J=8.5 Hz, 1H) and 5.80 (d, J=8.5 Hz, 1H), respectively. The ring junction protons were shown at δ 3.21 (m of d, J=5 Hz, 1H) and 2.75 (d, J=5 Hz, 1H). The signal at δ 1.99 (q with str., J=~7 Hz, 1H) was assigned to the proton α to the carbonyl group present in the bicyclo[2.2.2]octene framework and the methyl group at the ethanobridge appeared at δ 1.05 (d, J=~7 Hz, 3H). The signals for methoxy and methyl group at the bridgehead were observed as singlets at δ 3.62 and 1.33, respectively.

At this juncture, it was thought to transform the keto-enone **6** into the tricyclo[5.2.2.0^{2,6}]undecendione **5** along the lines delineated in scheme-4. In this context, preferential protection of the CO group present in the bicyclo[2.2.2]octenone framework of **6** was desired, prior to reduction of the olefinic linkage of the cyclopentenone ring and introduction of the geminal dimethyl groups. Unfortunately, all the attempts to protect the carbonyl group present in the bicyclo[2.2.2]octene framework were unsuccessful. It appears that electronic factors (electron withdrawing effect) due to the presence of OMe group at the bridgehead carbon of the keto-enone **6** to be one of the reasons which prevented the protection of the carbonyl group. In order to test the above contention, we attempted the protection of the CO group in **15**. However, here too all the attempts to protect the carbonyl on the bicyclo[2.2.2]octenone framework were futile. These results suggest that the failure of the carbonyl group to undergo ketalization is due to electronic rather than steric factors. It may be mentioned that protection of the carbonyl group in a similar system such as **I** which does not contain a methoxy group at the bridgehead proceeds smoothly.[13]

We therefore, devised alternate strategy for the synthesis of the tricyclic system **5** from the dione **17** which was obtained from the ene-dione **6** (Scheme-4). Thus, the diene-dione **6** was treated with excess of $NaBH_4$ in MeOH at ~-10^{0}C (ice/calcium chloride bath) and the resulting product was directly oxidized with Jones' reagent to give the required diketone **17** as an epimeric mixture at C_8 from which the pure *anti* stereoisomer was obtained after crystallization for the purpose of characterization (Scheme-4). The structure of the diketone **17** was established on the basis of spectral and analytical data. The presence of an absorption band at 1724 cm^{-1} in its IR spectrum indicated that the 1,4-reduction of the α,β-enone moiety of **6** had occurred. The ^{1}H-NMR (500 MHz) spectrum of **17** displayed characteristic signal for γ and β protons of the β,γ-enone moiety at δ 6.24 (d, J=~8.5 Hz, 1H) and 6.09 (d, J=~8.5 Hz, 1H), respectively. The methoxy group showed a signal at δ 3.58 (s, 3H) and the bridgehead CH_3 group appeared as a singlet at δ 1.44, while the methyl group α to carbonyl showed a signal at δ 1.09 (d, J=~7 Hz, 3H). The signal at δ 2.56 (d, J=~9.5 Hz, 1H) was assigned to the ring junction proton α to carbonyl group while the signal at δ 2.82

(superimposed dd, J=~9.5 Hz, 1H) was assigned to the proton at the other ring junction. The other methylene protons were displayed at δ 2.18-2.10 (complex m, 3H) and 2.0-1.91 (complex m, 1H). It also showed a characteristic signal at δ 1.86 (q, J=7 Hz, 1H) for the methine proton α to CO group at the bridge. The ^{13}C-NMR provided further support for the structure of dione **17**. The ^{13}C-NMR spectrum showed resonances at δ 219.54 (CO), 211.08 (CO), 140.85, 128.49 for the olefinic carbons, 86.09 (q), 43.45, 52.02, 48.51, 42.79 (q), 40.45, 39.15, 20.81, 19.25 and 11.96, respectively accounting for all the 14 carbon atoms in its molecular structure.

In view of the difference in the reactivities of the carbonyl groups in **17,** we thought it possible to do regioselective alkylation of the ketone **17** to the desired chromophoric system **5** under suitable experimental conditions. Thus, the epimeric mixture of the dione **17** was treated with potassium tert-butoxide and CH_3I in THF. However, a highly unexpected aromatic product **18** was obtained from the above reaction as a result of fragmentation. Presumably, the product **18** is formed *via* abstraction of the proton from C_8 followed by fragmentation of C_6-C_7 and C_2-C_1 bond, and subsequent O-methylation of the resulting carbanion. Alkylation of the dione **17** in the presence of LDA at -78°C was also unsuccessful and gave the compound **18** (Scheme 4).

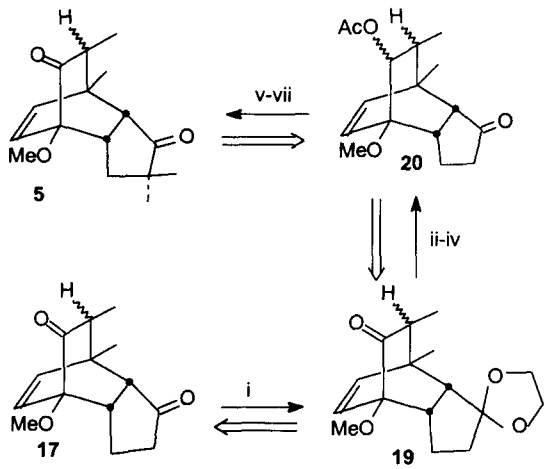


Scheme-4

Reagents/ conditions: i, $NaBH_4$, MeOH, -10°C, ii, Jones reagent, iii, KO ^{t}Bu, BuOH, MeI

In view of the above unforeseen events, we had to adopt a rather longer route for the preparation of tricyclic system **5**. Thus, the carbonyl group at C_5 of the dione **17** was first protected as ketal with ethylene glycol. This regioselective monoprotection proceeded quantitatively and with great ease in

refluxing benzene containing ethyleneglycol and *p*-toluenesulphonic acid. The keto-ketal **19** was reduced with $NaBH_4$ and acetylated to give a ketal acetate, the ketal group of which was hydrolyzed to give the ketoacetate **20**. Alkylation of the ketoacetate **20** followed by hydrolysis of the acetate and oxidation gave the much desired diketone **5** (as an epimeric mixture at C_8) as shown in scheme-5. The structure of the chromophoric system **5** was clearly revealed from its spectral and analytical data.



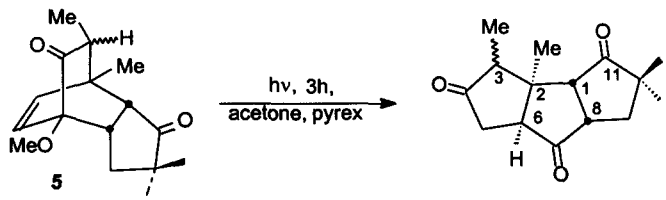
Scheme 5

Reagents/conditions: i,p-TSA, ethylene glycol,Δ, ii, $NaBH_4$, MeOH iii, AcCl,Py, iv, p-TSA, acetone, water, v, NaH,THF, MeI, vi, KOH, MeOH-H_2O, vii, Jones oxidation

Photochemical reaction of 5 in triplet (^{3}T) excited state: Synthesis of the intermediate(4)

Towards the synthesis of the triquinane **4**, a solution of the dione **5** in acetone (solvent as well as sensitizer) was irradiated with a mercury vapour lamp (125W, Applied Photophysics) for 3h. Removal of solvent in *vacuo* followed by a careful chromatography gave the desired intermediate **4** as a stereoisomeric mixture at C_3 (Scheme-6) from which the stereoisomer **4a** was obtained as a colourless solid after a careful crystallization. The structure of the photoproduct **4a** was readily discerned from its spectral data. The IR spectrum of **4a** showed an absorption band at 1735 cm^{-1} for the carbonyl group. The ^{1}H-NMR (300 MHz) of **4a** did not show signals due to olefinic protons and methoxy group which strongly suggested the formation of the rearranged product. It showed signals for three methyl groups as singlets at δ 1.16, 1.09 and 1.05 while the signal for methyl group at C_3 was observed at δ 1.25 (d, J=~7 Hz). The other methine and methylene protons showed resonances at δ 3.31 (q, J=~10Hz, 1H), 2.81 (m, 3H), 2.29 (dd, J_1=~13 Hz, J_2=~10 Hz, 1H), 2.19 (m, 2H) and 1.72 (dd, J_1=~13 Hz, J_2=11 Hz, 1H). The mass spectrum of **4a** showed a peak at (m/z) 248 for its molecular ion. The orientation of the methyl group at C_3 was determined on the

basis of chemical shift and comparison with a similar compound.[14] It appears that the above photoreaction proceeds through triplet (^{3}T) sensitized 1,2-acyl shift leading to a tetracyclic intermediate which upon cleavage of the cyclopropane ring and loss of methyl radical followed by hydrogen abstraction gives the final product .[15,5]



Scheme 6

4a, α methyl
4b, β methyl

To summarize, we have synthesized a highly functionalized triquinane precursor containing most of the structural and stereochemical features of coriolin from a simple aromatic precursor employing the cycloaddition of spiroepoxycyclohexa-2,4-dienone and photochemical reaction of α-methoxy-β,γ-enone chromophore as key steps.

EXPERIMENTAL

1-Methoxy-7-methyl-8-spiroepoxy-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,10-dien-9-one (7):

To a mixture of 2-hydroxy-3-methoxy-6-methylbenzyl alcohol **8** (1.17g, 6.9mmol), cyclopentadiene (6ml, excess) in acetonitrile (20ml), was added an aqueous solution of sodium metaperiodate (6.0g, 28.0mmol) dropwise with stirring at ~5°C. After stirring for 6h, the organic layer was separated and the aqueous layer was extracted with ethylacetate (4 x 50ml). The combined organic extract was washed with water (2 x 20ml), brine (2 x 20ml) and dried. Removal of solvent in *vacuo* followed by chromatography [(petroleum ether-ethyl acetate) (95:5)] of the crude product on silica gel gave the adduct **7** (0.96g, 60%). mp. 102°C. UV (MeOH) λ_{max} : 311 (w), 228 (s)nm. IR (KBr) ν_{max} : 1737 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.16 (d of part of an AB system, J_{AB}=8.5 Hz, J_2=~1 Hz, 1H, γ proton of the β,γ-enone moiety), 6.03 (d of part of an AB system, J_{AB}=8.5 Hz, J_2=~1 Hz, 1H, β proton of the β,γ-enone group), 5.80 (m of d, J=6 Hz, 1H, olefinic H), 5.65 (m of d, J=6 Hz, 1H, olefinic H), 3.59 (s, 3H, OCH_3), 3.41 (complex m of d, J=9 Hz, 1H, allylic ring junction H), 3.08 (part of an AB system, J_{AB}=6 Hz, 1H, OCH_2 group), 2.95 (part of an AB system, J_{AB}=6 Hz, 1H, OCH_2 group), 2.83 (ddd, J_1=J_2=9 Hz, J_3=3 Hz, 1H, allylic ring junction H), 2.54 (m of dd, J_1=18 Hz, J_2=9 Hz, 1H, methylene H of the cyclopentene ring), 2.12 (complex m of d, J_1=18 Hz 1H, methylene H of the cyclopentene ring), 1.10 (s, 3H, bridgehead methyl). ^{13}C-NMR (75MHz, $CDCl_3$) δ: 204.46 (CO), 135.80 (d), 134.14 (d), 129.50 (d), 127.65 (d) (for olefinic carbons), 86.71, 59.41, 53.55,

49.57, 43.38, 41.27, 37.18, 14.74 (for the other methine, methylene and methyl carbons) (one carbon not shown). Analysis: Found C, 72.10, H, 6.99%. Calcd. for $C_{14}H_{16}O_3$, C, 72.42, H, 6.89 %. Mass (m/z) : 232 (M^+).

1-Methoxy-7,8-dimethyl-*endo*-tricyclo[5.2.2.$0^{2,6}$]undeca-3,10-dien-9-one (12) :

To a suspension of zinc (3.0g, excess) and ammonium chloride (2.0g, excess) in dry dioxane (50ml) was added a solution of the epoxy ketone **7** (2.0g, 8.6mmol) in dioxane. The reaction mixture was heated at reflux for about 3h. Usual work up and chromatography [(petroleum ether-ethyl acetate) (97:3)] on silica gel furnished the compound **12** (1.33g, 71%) as a *syn*:*anti* (1:8) mixture. Further elution [(petroleum ether-ethyl acetate) (80:20)] gave the keto alcohol **13** (0.4g, 20%).

Data of **12** : UV (MeOH) λ_{max} : 301 (w), 209 (s)nm. IR (neat) ν_{max} : 1728 cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$) δ: 6.10 (part of an AB system with str, J_{AB}=8.5 Hz, 1H, γ-proton of the β,γ-enone group), 6.03 (part of an AB system with str, J=~8.5 Hz, 1H, β-proton of the β,γ-enone moiety), 5.75 (d with str, J=~6 Hz, 1H, olefinic H), 5.61 (d with str, J=~6 Hz, 1H, olefinic H), 3.56 (s, 3H, OCH_3), 3.01 (m of d, J=9 Hz, 1H, ring junction proton), 2.72 (ddd with str, J_1=10 Hz, J_2=9 Hz, J_3=2.5 Hz, 1H, ring junction methine H), 2.46 (m of dd, J_1=15 Hz, J_2=10 Hz, 1H, methylene H of the cyclopentene ring), 2.05 (m of d, J=15 Hz, 1H, methylene H of the cyclopentene ring), 1.94 (q, J=7.5 Hz, 1H, $\underline{H}CCH_3$), 1.26 (s, 3H, bridgehead CH_3), 1.12 (d, J=7.5 Hz, 3H, $\underline{C}H_3CH$) (major isomer). Mass (m/z) : 218 (M^+).

Data for 1-Methoxy-7-methyl-8-hydroxymethyl-*endo*-tricyclo[5.2.2.$0^{2,6}$]undeca-3,10-dien-9-one **(13):** IR (neat) ν_{max} : 3435, 1729 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.13 (part of an AB system with str, J=~9 Hz, 1H, γ-proton of the β,γ-enone group), 6.05 (part of an AB system with str, J=~9 Hz, 1H, β-proton of the β,γ-enone moiety), 5.73 (m of d, J=~6 Hz, 1H, olefinic H), 5.62 (m of d, J=~6 Hz, 1H, olefinic H), 3.92 (dd, J_1=~11 Hz, J_2=4 Hz, 1H, $\underline{H}CHOH$), 3.76 (dd, J_1=~11 Hz, J_2=8 Hz, 1H, $HC\underline{H}OH$), 3.57 (s, 3H, OCH_3), 3.16 (m of d, J=9 Hz, 1H, ring junction methine H), 2.67 (ddd with str, J_1=12 Hz, J_2=9 Hz, J_3=6 Hz, 1H, ring junction methine H), 2.42 (dd with str, J_1=~17 Hz, J_2=10 Hz, 1H, methylene H of the cyclopentene ring), 2.07 (dd, J_1=8 Hz, J_2=~4 Hz, 1H, $\underline{H}C\text{-}CH_2OH$), 2.01 (complex m of d, merged with δ 2.07, 1H, methylene H of the cyclopentene ring), 1.35 (s, 3H, bridgehead CH_3) (OH not shown). ^{13}C-NMR (50MHz, $CDCl_3$) : 214.35 (CO), 139.26, 133.76, 127.90, 127.63 (olefinic carbons), 87.07 (C-OMe), 60.07 (methylene C), 54.38 (CH), 54.16 (CH), 53.58 (OCH_3), 42.90 (CH), 41.35 (CH), 36.99 (CH_2), 19.80 (CH_3). Mass (m/z) : 168 (M^+-66).

1-Methoxy-7,8-dimethyltricyclo[5.2.2 $0^{2,6}$]undeca-3,10-diene-5,9-dione (6):

To a stirred solution of selenium dioxide (3g, 27mmol) in dioxane (15ml) and water (5ml) was added potassium dihydrogen orthophosphate (0.18g, 1.3mmol) and compound **12** (1.5g, 6.8mmol). The reaction mixture was heated at ~100°C for 12h. It was filtered over a celite pad and washed with ethyl acetate (2 x

20ml). The solvent was removed under reduced pressure and the residue was diluted with water, and extracted with ethyl acetate (3 x 20ml). The combined extract was washed with water (2 x 20ml), brine (2 x 20ml) and dried. The solvent was removed in *vacuo* and the residue was chromatographed [(petroleum ether-ethylacetate) (75:25)] on silica gel to give the mixture of alcohols (1.0g, 63%). To the mixture of keto alcohols (1.0g, 4.2mmol) in acetone (25ml) was added freshly prepared Jones' reagent dropwise at ~5°C. After the oxidation was complete (tlc), acetone was removed under vacuum and the residue was diluted with water and extracted with ethyl acetate (4 x 25ml). The combined extract was washed with a saturated solution of sodium bicarbonate (2 x 20ml), water (2 x 20ml), brine (2 x 20ml) and dried. The solvent was removed and the residue was filtered through a short column of silica gel. Elution with petroleum ether-ethylacetate (90:10) furnished first the major diene-dione **6** (0.69g, 70%) as a *syn:anti* (1:6) mixture. Further elution [(petroleum ether-ethyl acetate) (80:20)] gave the other minor regioisomeric diene-dione **14** (0.2g, 20%).

Data of the diene-dione **6** : mp. 92°C. IR (KBr) ν_{max} : 1726, 1695 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.5 (m, 1H, β-proton of α,β-enone group), 6.26 (d with long range coupling, J=5.5 Hz, 1H, α-proton of the α,β-enone group), 6.03 (d, J=8.5 Hz, 1H, γ proton of the β,γ-enone group), 5.97 (d, J=8.5 Hz, 1H, β–proton of the β,γ-enone moiety), 3.60 (s, 3H, OCH_3), 3.26 (m of d, J=5 Hz, 1H, allylic ring junction proton), 2.52 (d, J=5 Hz, 1H, ring junction proton α to the carbonyl group), 1.95 (q, J=~6 Hz, 1H, proton α to the carbonyl on the bicyclic framework), 1.52 (s, 3H, bridgehead methyl), 1.13 (d, J=~6 Hz, 3H, C<u>H</u>$_3$-CH). Analysis: Found C, 72.63, H, 6.84%. Calcd. for $C_{14}H_{16}O_3$, C, 72.42, H, 6.89%. Mass (m/z) : 232 (M^+).

Data of compound **14** : mp. 89°C. UV (MeOH) λ_{max} : 210nm. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 7.53 (m of d, J=5.5 Hz, 1H, β proton of the α,β-enone moiety), 6.25 (d, J=5.5 Hz, 1H, α-proton of the α,β-enone group), 5.91 (d, J=8.5 Hz, 1H, γ-proton of the β,γ-enone moiety), 5.80 (d, J=8.5 Hz, 1H, β-proton of the β,γ-enone group), 3.62 (s, 3H, OCH_3), 3.21 (m of d, J=5 Hz, 1H, ring junction methine H), 2.75 (d, J=5 Hz, 1H, ring junction methine), 1.99 (q with str, J=~7 Hz, 1H, proton α to the carbonyl group on the ethano bridge), 1.33 (s, 3H, CH_3), 1.05 (d, J=~7 Hz, 3H, C<u>H</u>$_3$-CH). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 210.30 (CO), 204.89 (CO), 163.2, 138.75, 138.55, 127.72 (olefinic carbons), 86.28 (<u>C</u>-OMe), 54.02 (OCH_3), 47.98, 46.73, 46.47, 41.79, 19.7, 11.02 for other methine and methyl carbons. Analysis: Found C, 72.58, H, 6.82%. Calcd. for $C_{14}H_{16}O_3$, C, 72.42, H, 6.89%. Mass (m/z) : 232 (M^+).

1-Methoxy-7-methyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,10-dien-9-one (15):

A solution of the β-keto alcohol **13** (1.0g, 4.2mmol) in acetone (25ml) was oxidized with freshly prepared Jones' reagent. Solvent was removed and water was added to the residue and extracted with ethylacetate (4 x 20ml). The combined extract was washed with water (2 x 15ml) and saturated solution of sodium bicarbonate (3 x 25ml). The aqueous layer was acidified with cold 1:1 HCl. The acidified solution was extracted with ethyl acetate (3 x 25ml). The combined extract was washed with water (2 x 20ml), brine

(2 x 20ml) and dried. Removal of solvent gave the β-keto acid which was subjected to decarboxylation as follows. The β-keto acid thus obtained was taken in THF-water (4:1, 20ml) and was refluxed for about 2h. THF was removed under vacuum and the aqueous medium was extracted with ethyl acetate (4 x 20ml). The combined extract was washed with sodium bicarbonate (2 x 20ml), water (2 x 20ml), brine (2 x 20ml) and dried. Removal of solvent followed by chromatography [(petroleum ether-ethylacetate) (95:5)] gave the compound **15** (0.40g, 46%) as a colourless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 6.07 (part of an AB system with str, J_{AB}=8.5 Hz, 1H, γ-H of β,γ-enone moiety), 5.99 (part of an AB system with str, J_{AB}=8.5 Hz, 1H, β-H of β,γ-enone group), 5.73 (d with str, J=~5.5 Hz, 1H, olefinic H), 5.61 (d with str, J=~5.5 Hz, 1H, olefinic H), 3.57 (s, 3H, OCH_3), 3.26 (d with str, J=~9 Hz, 1H), 2.59-2.40 (multiplets, 2H), 2.08-1.98 (d overlapped with another signal, J=3 Hz, 3H), 1.29 (s, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ : 210.56 (s, CO), 137.71 (d), 133.76 (d), 128.66 (d), 128.41 (d) (olefinic carbons), 87.46 (s, C-OMe), 53.73 (d), 53.57 (OCH_3), 47.47 (d), 47.21 (t), 39.64 (s, C-Me), 37.32 (t), 22.12 (q, CH_3). Mass (m/z) : 204 (M^+).

1-Methoxy-7,8-dimethyltricyclo[5.2.2.0^{2,6}]undec-10-ene-5,9-dione (17):

Sodium borohydride (2.39g, 62.8mmol) was added to a solution of the diene-dione **6** (2.5g, 10.7mmol) in methanol (25ml) at ~0°C. The reaction mixture was stirred at room temperature for further 2h. After completion of the reaction (tlc) the reaction mixture was concentrated in *vacuo*, diluted with water (20ml) and extracted with ethyl acetate (3 x 30ml). The combined organic extract was washed with water (2 x 20ml), brine (2 x 20ml) and dried. The solvent was removed in *vacuo* and the crude product product was directly subjected to oxidation as follows. To a solution of the above product in acetone (30ml) was added Jones' reagent dropwise at ~5°C. After the completion of the reaction (tlc) the solvent was removed and and the residue was diluted with water (20ml), extracted with ethyl acetate (3 x 20ml). The organic extract was washed with water (2 x 20ml), brine and dried. Removal of the solvent followed by column chromatography on silica gel [(petroleum ether-ethyl acetate) (93:7)] gave the dione **17** (1.5g, 60%). mp. 105°C. UV (MeOH) λ_{max} : 306 (w), 209 (s)nm. IR (KBr) ν_{max} : 1724 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.24 (d, J=~8.5 Hz, 1H, γ-proton of β,γ-enone group), 6.09 (d, J=~8.5 Hz, 1H, β-proton of β,γ-enone moiety), 3.58 (s, 3H, OCH_3), 2.82 (superimposed dd, J=9.5 Hz, 1H, ring junction proton), 2.56 (d, J=~9.5 Hz, 1H, ring junction proton α to carbonyl), 2.18-2.10 (complex m, 3H), 2.0-1.91 (complex m, 1H), 1.86 (q, 1H, J=~7 Hz, HC-CH_3), 1.44 (s, 3H, bridgehead CH_3), 1.09 (d, J=7 Hz, 3H, CH_3 α to carbonyl group). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ : 219.54 (CO), 211.08 (CO), 140.85, 128.49 (olefinic carbons), 86.09 (q), 43.45, 52.02, 48.51, 42.79 (q), 40.45, 39.15, 20.81, 19.25 and 11.96. Analysis: Found C, 72.19, H, 7.62%. Calcd. for $C_{14}H_{18}O_3$, C, 71.79, H, 7.69%. Mass (m/z) : 234 (M^+).

1-Methoxy-4,4,7,8-tetramethyltricyclo[5.2.2.0^{2,6}]undec-10-ene-5,9-dione (5):

Ethylene glycol (1ml, excess) and p-toluenesulphonic acid (10mg) were taken in dry benzene (20ml) and the reaction mixture was refluxed using Dean-Stark apparatus, in order to remove traces of water. To

this was added the dione **17** (0.5g, 2.1mmol) and reflux continued till completion of reaction (tlc, ~2h). The reaction mixture was cooled and washed with saturated solution of sodium bicarbonate (2 x 10ml), brine (2 x 10ml). The benzene layer was dried and the solvent was removed under vacuum to give the keto ketal **19** (0.58g, 98%) [(^{1}H-NMR (500MHz, $CDCl_3$) δ : 6.26 (d, J=~8.5Hz, 1H, γ-H of the β,γ-enone group), 5.97 (d, J=~8.5Hz, 1H, β-H of the β,γ-enone moiety), 4.06-4.02 (m, 1H, O-HCH-CH_2-O), 3.91-3.82 (m, 3H, O-HCH-CH_2-O), 3.51 (s, 3H, OCH_3), 2.60-2.50 (multiplets, 2H), 1.81 (q, J=~7Hz, 1H, HC-CH_3), 1.75-1.71 (m, 2H), 1.55-1.48 (m, 2H), 1.24 (s, 3H, bridgehead CH_3), 1.02 (d, J=~7Hz, 3H, CH_3-CH)] The keto ketal thus obtained was then subjected to reduction as follows.

To a solution of the above product in methanol (10 ml) was added sodium borohydride (0.3g, excess) at ~5°C and stirring was continued. After the completion of the reaction (tlc, 1.5h), methanol was removed in *vacuo* and the residue was diluted with water (10ml) and extracted with ethyl acetate (3 x 10ml). The combined organic layer was washed with brine, and dried and solvent was removed in *vacuo*. The product thus obtained was taken in acetone-water (3:2, 10ml) to which a pinch of p-toluenesulphonic acid was added and the reaction mixture was stirred for 8h at room temperature. After removal of acetone under vacuum, the aqueous layer was extracted with ethyl acetate (3 x 10ml). The combined organic extract was washed with saturated solution of sodium bicarbonate (2 x 10ml), brine (2 x 10ml) and dried. Removal of the solvent in *vacuo* gave an alcohol which was acetylated with acetyl chloride (0.5ml,excess) and pyridine (2-3drops) in dry dichloromethane. The reaction mixture was stirred at room temperature for 1h, after which it was washed thoroughly with 1:1 HCl (3 x 20ml), water (3 x 20ml), brine (2 x 20ml) and dried. The solvent was removed under vacuum to give the ketoacetate **20** (0.28g, 50%) which was directly subjected to alkylation as follows.

To suspension of sodium hydride (0.12g, excess) in dry THF (10ml) was added a solution of the above product (0.2g) in THF(5ml). The reaction mixture was stirred at room temperature (30°C) for 0.5h. Methyl iodide (5ml, excess) was then added and stirring continued for 6h at room temperature. After the usual workup, the crude product was taken in methanol:water (4:1, 10ml) and KOH (~0.4g) was added to it and the reaction mixture was stirred for 3h at room temperature. Methanol was removed under vacuum and the residue was diluted with water and extracted with ethyl acetate (3 x 10ml). The organic extract was washed with water (2 x 10ml), brine (1 x 10ml) and dried. The solvent was removed under vacuum the resulting product was taken in acetone and Jones' reagent was added till the colour of the Jones reagent persisted (monitored also by tlc). Usual workup followed by column chromatography [(petroleum ether-ethyl acetate) (90:10)] of the crude product furnished the tetramethyl dione **5** (0.075g, 30%). UV (MeOH) λ_{max} : 304 (w), 209 (s)nm. IR (film) ν_{max} : 1731 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.18 (d, J=~8.5 Hz, 1H, γ-proton of β,γ-enone moiety), 6.07 (d, J=~8.5 Hz, 1H, β-proton of β,γ-enone moiety), 3.55 (s, 3H, OCH_3), 2.83 (m, 2H), 1.92-1.88 (m, 1H), 1.82 (q, J=~7 Hz, 1H, HC-CH_3), 1.63-1.60 (m, 1H), 1.52 (s, 3H, bridgehead CH_3), 1.07 (d, J=~7 Hz, 3H, CH_3-CH), 1.01 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 222 (s, CO), 212 (s, CO), 142 (d), 128 (d) (olefinic carbons), 87 (s, C-OCH_3), 54 (q, OCH_3), 49.5

(d), 48.5 (d), 47 (s), 42 (s), 37.5 (d), 37.4 (t), 27 (q), 22 (q), 19 (q), 12 (q) for the major isomer. Analysis: Found C, 72.93, H, 8.56%. Calcd. for $C_{16}H_{22}O_3$, C, 73.20, H, 8.39%. Mass (m/z) : 262 (M^+)

1,4,4,11-Tetramethyltricyclo[6.3.0.0^{2,6}]undeca-3,7,10-trione (4a):

Irradiation of a solution of the dione **5** (0.06g, 0.2mmol) in acetone (150ml) under nitrogen for 2.5h followed by removal of solvent under vacuum and column chromatography [(petroleum ether-ethyl acetate) (80:20)] of the residue yielded the tricyclic trione **4** (0.015g, 27%) as a diastereomeric mixture.

^{1}H-NMR (300 MHz, $CDCl_3$) (of the diastereomeric mixture **4**) δ for the major diastereomer : 3.31 (m, 1H), 2.90-2.64 (multiplets, 3H), 2.48-2.01 (multiplets, 3H), 1.72 (dd, J_1=13 Hz, J_2=11 Hz, 1H), 1.25 (d, J=~7 Hz, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.05 (s, 3H, CH_3). The signals for the minor diastereomer appeared at δ: 3.11 (m, 1H), 2.90-2.64 (multiplets, 3H, overlapped with the protons of the major stereoisomer), 2.48-2.01 (multiplets, 3H, overlapped with the protons of the major stereoisomer), 1.90-1.81(m, 1H), 1.12 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.05 (d, J=~7 Hz, 3H, CH_3), 0.99 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) (for diastereomeric mixture) δ : 219.77 (CO), 217.53 (CO), 215.46 (CO) and 58.12, 55.78, 54.32, 53.96, 53.79, 50.58, 50.27, 49.40, 46.61, 45.39, 40.61, 40.25, 38.49, 36.63, 25.69,25.29, 24.33, 23.78, 22.78, 18.22, 9.66, 7.71.

Careful recrystallization of the above mixture from petroleum ether-ethyl acetate mixture (90:10) gave a single diastereomer (0.005g, 9%).

Data of **4a** : mp. 117-118°C. IR (film) ν_{max} : 1735 cm^{-1}. UV (MeOH) λ_{max} : 209 (s)nm. ^{1}H-NMR (500MHz, $CDCl_3$) δ: 3.31 (q, J=~10 Hz, 1H), 2.81 (m, 3H), 2.29 (dd, J_1=~13 Hz, J_2=~10 Hz, 1H), 2.19 (m, 2H), 1.72 (dd, J_1=~13 Hz, J_2=11 Hz, 1H), 1.25 (d, J=~7 Hz, CH_3), 1.16 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.05 (s, 3H, CH_3). Mass (m/z) : 248 (M^+).

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