Pergamon

Tetrahedron 58 (2002) 9729–9736

TETRAHEDRON

Synthesis and photoreactions of 3-oxa-tricyclo[5.2.2.0^{1,5}]undecenones: a novel, stereoselective route to oxa-triquinanes and oxa-sterpuranes

Vishwakarma Singh,* S. Q. Alam and G. D. Praveena

Department of Chemistry, Indian Institute of Technology, Mumbai 400 076, India

Received 28 January 2002; revised 11 September 2002; accepted 3 October 2002

Abstract—The synthesis of 11-methyl-3-oxa-tricyclo[5.2.2.0^{1,5}]undecenones and their photochemical reactions upon triplet (^{3}T) and singlet (^{1}S) excitation is described. Oxidation of hydroxymethylphenol gave a ketoepoxide by intramolecular cycloaddition. Manipulation of the oxirane ring furnished the chromophoric systems. Triplet excitation of these gave tetracyclic compounds containing an oxatriquinane framework. Singlet excitation furnished the tricyclic compound having an oxasterpurane ring system in a stereoselective fashion.

1. Introduction

Triquinanes have aroused intense interest in the recent past due to their novel molecular architecture and wide spectrum of biological activities.[1,2] Recently, the tricyclic compounds **1**–**3** having an oxa-triquinane framework (Fig. 1) were found to have potent in vitro cytotoxic activity against murine lymphoma L1210 cells and human epidermoid carcinoma KB cells.[3a] Some of these compounds and their derivatives have also proved to be useful for the treatment of leukaemia, osteosarcoma, breast cancer and ovarian cancer.[3b] While a plethora of methods have been developed for the syntheses of carbocyclic triquinanes,[1,2] only a few methods are known[3a,c,d] for the synthesis of oxa-triquinanes and other hetero analogues of triquinanes.

In view of the important biological properties of oxa-triquinanes, we thought to develop a novel stereoselective method for their synthesis. We visualised that a 1,2-acyl shift or oxa-di-π-methane rearrangement[4] in the tricyclic systems of type **4** would readily give the compounds of type **5** in a stereoselective fashion, which may be elaborated to oxa-triquinanes. It was also considered that the tricyclic systems of type **4** may be prepared from the aromatic precursor of type **7** via its oxidation and intramolecular Diels–Alder reaction in the resulting cyclohexa-2,4-dienone. Interestingly, it was also thought that a 1,3-acyl shift in **4** would give the tricyclic compound **6**, oxa-analogue of sterpuranes, another class of biologically important sesquiterpenes[5] (Scheme 1). We wish to report herein an efficient synthesis of the desired tricyclic systems of type **4** from a simple aromatic precursor of type **7** and syntheses of oxa-triquinane frame **5** and oxa-sterpuranes **6** by modulation of chemical reactivity of **4** in excited triplet and singlet states.[6]

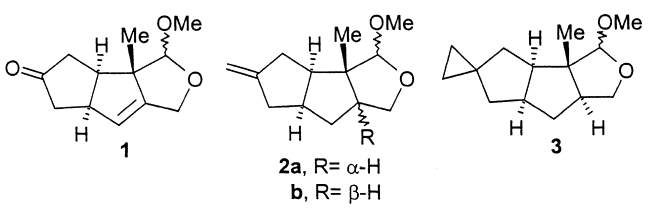
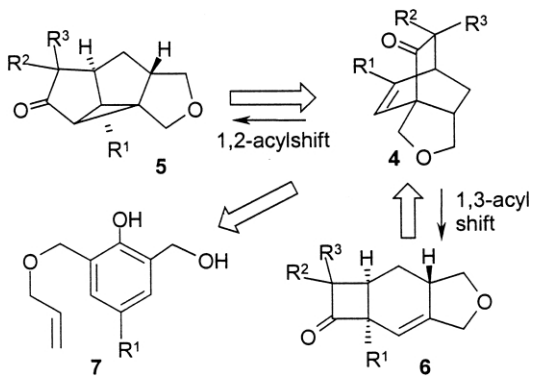


Figure 1.



Scheme 1.

Keywords: Diels–Alder reaction; cycloaddition; photo-chemistry; oxa-polyquinanes.

* Corresponding author. Tel.: +91-22-576-7168; fax: +91-22-572-3480; e-mail: vks@chem.iitb.ac.in

0040–4020/02/$ - see front matter
PII: S0040-4020(02)01280-2

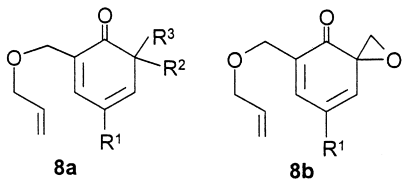


Figure 2.

2. Results and discussion

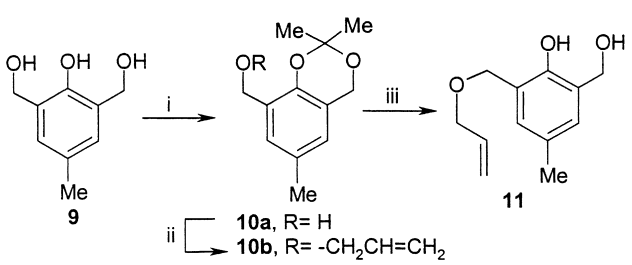
2.1. Synthesis of the tricyclic chromophoric system of type 3 and congeners

In principle, the desired tricyclic compound **4** may be obtained by the intramolecular Diels–Alder reaction of cyclohexa-2,4-dienone of type **8a** containing a tether at C2 (Fig. 2). However, there are no methods for preparation of cyclohexa-2,4-dienones of type **8a**. Therefore, an indirect route to **4** was devised via intramolecular Diels–Alder reaction of 6-spiroepoxycyclohexa-2,4-dienone of type **8b** and manipulation of the resulting adduct, since the spiroepoxy dienone **8b** was thought to be readily generated by oxidation of the *o*-hydroxymethyl phenol of type **7**.[7]

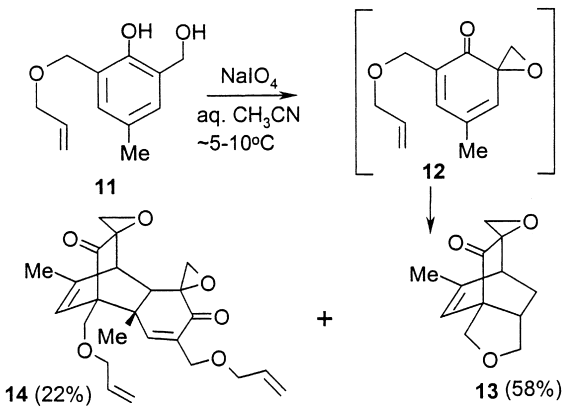
Towards this objective, the hydroxymethyl phenol **11** containing the desired appendage was readily prepared from *p*-cresol. Hydroxymethylation of *p*-cresol gave the bishydroxymethyl derivative **9** in good yield.[8] Protection of the phenolic hydroxyl and one of the hydroxymethyl groups by treatment of **9** with 2,2-dimethoxypropane in the presence of *p*-TsOH gave the compound **10a** in good yield.[9] Subsequent alkylation of **10a** with allyl bromide in NaH–THF readily gave O-alkylated derivative **10b** which was hydrolysed with HCl in THF–H_2O to give the precursor **11** (Scheme 2).

Oxidation of the aromatic precursor **11** in acetonitrile with aqueous sodium *meta*periodate at ~5–10°C gave the adduct **13** in reasonably good yield (58%) via generation and intramolecular cycloaddition in **12** along with the dimer **14** formed due to competing intermolecular Diels–Alder reaction (Scheme 3). The structure of the adduct **13** was deduced from its spectral, analytical data and COSY spectra as briefly presented below.

Thus, the ^{1}H NMR (300 MHz) spectrum of the adduct **13** exhibited a characteristic signal at δ 5.60 (br m) for only one olefinic proton. It also showed signals at δ 4.25 (part of an AB system, J_{AB}=8.8 Hz, 1H), 3.94 (part of an AB system,



Scheme 2. *Reagents and conditions*: (i) 2,2-dimethoxypropane, dry acetone, *p*-TSA (cat.), 4 Å molecular sieves, rt, 12 h (92%); (ii) NaH, allyl bromide, THF, (94%); (iii) 1N HCl/THF (1:1), rt 12 h (88%).



Scheme 3.

J_{AB}=8.8 Hz, 1H), δ 4.07 (superimposed dd, J_1=J_2=7.5 Hz, 1H) and 3.30 (dd, J_1=11.0 Hz, J_2=7.5 Hz, 1H) for oxy-methylene protons at C2 and C4. The methylene protons of the oxirane ring appeared at δ 3.19 (part of an AB system, J_{AB}=6.0 Hz, 1H), and δ 2.91 (part of an AB system, J_{AB}=6.0 Hz, 1H). Further, signals were observed at δ 2.74–2.62 (complex m, 1H) and 2.41 (br m, 1H) due to protons at C5 and C7 (bridgehead) respectively. Interestingly, one of the methylene protons at C6 showed a downfield signal at δ 2.32–2.22 as a complex multiplet while the other at high field δ 1.30 (ddd, J_1=12.5 Hz, J_2=6.6 Hz, J_3=1.5 Hz, 1H). This is presumably due to large difference in the chemical shifts of *exo* and *endo* protons, since the *endo* protons are generally shielded and appear at high field.[10] The methyl group showed a characteristic signal at δ 1.96 (d, J=1.6 Hz, 3H, CH_3) due to other protons. The above assignments were also confirmed with the help of a COSY spectrum, which showed a COSY relationship between the olefinic proton and the signal at δ 2.41 assigned to the bridgehead proton (C7). The signal at δ 2.41 also exhibited a COSY cross-peak with the multiplet at δ 2.32–2.22, assigned to one of the methylene (*exo*) at C6. Furthermore, the multiplet at δ 2.74–2.62 showed a COSY cross-peak with four signals at δ 2.32, 1.30 (assigned to methylene at C6) and 4.07, 3.30 (assigned to oxy-methylene at C4) (Fig. 3). These relationships between protons clearly established the structure of the adduct.

The ^{13}C NMR (75 MHz, $CDCl_3$) spectrum also supported its formulation as it displayed resonances at δ 201.3, 146.0 and 122.7 due to carbonyl and olefinic carbons, respectively, in addition to signals for other carbons. The stereochemical orientation of the oxirane ring is suggested on the basis of the general tendency of cyclohexa-2,4-dienones to be approached by the dienophile *syn* to the oxygen of the oxirane ring during their cycloaddition.[7,11]

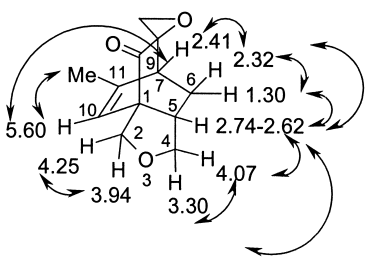
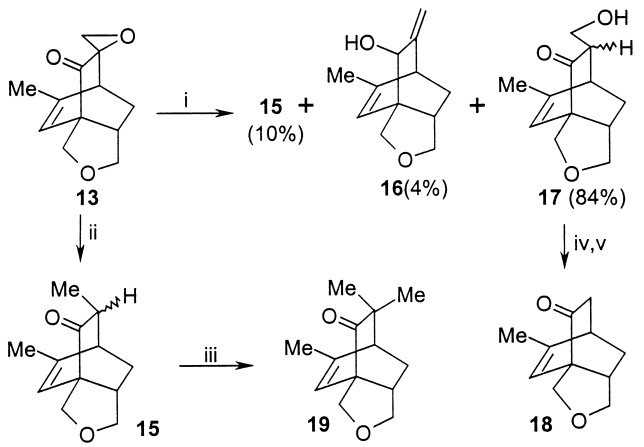


Figure 3.



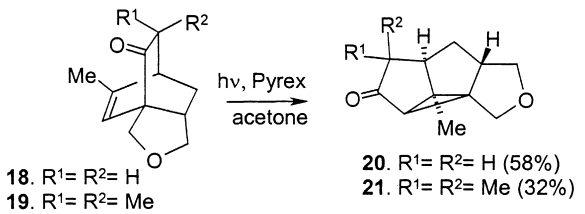
Scheme 4. *Reagents and conditions*: (i) Zn, NH_4Cl, MeOH–H_2O; (ii) Zn, NH_4Cl, dioxane, Δ, 60%; (iii) NaH, THF, MeI, Δ, 65%; (iv) Jones oxidation; (v) aq. THF, Δ, 67%.

Towards synthesis of the desired chromophoric systems, the adduct **13** was treated with Zn in aqueous methanol containing ammonium chloride at ambient temperature.[12] A careful chromatography of the product mixture furnished the desired keto–alcohol **17** (84%, as a mixture of *syn/anti* isomers, ^{1}H NMR) as a major product in addition to the ketone **15** and the allylic alcohol **16** in minor amounts. The keto-alcohol **17** was oxidised with Jones' reagent[13] and the resulting β-keto-acid was decarboxylated[14] to give the tricyclic compound **18** in good yield (67%) (Scheme 4). Interestingly, the reduction of the adduct **13** with zinc in refluxing dry dioxane selectively gave the ketone **15** (as a mixture of *syn/anti* isomers, ^{1}H NMR) in major amounts. Alkylation of **15** with MeI in the presence of NaH–THF gave the chromophoric system **19** (Scheme 4). The structures of all the products were ascertained from their spectral data. It may be mentioned that tricyclic compounds of type **13**, **15**–**19** having a β,γ-unsaturated carbonyl chromophore are not readily available and this method provides a new, efficient and versatile avenue to such systems.

2.2. Sigmatropic 1,2- and 1,3-acyl shifts in tricyclic systems 18 and 19 having β,γ-unsaturated carbonyl chromophore

The photochemical reactions of β,γ-enones have generated a great deal of interest in the past,[15,16] which has further enhanced recently because of their synthetic potential and versatility.[4,17] Rigid β,γ-enones undergo two unique reactions i.e oxa-di-π-methane rearrangement or 1,2-acyl shift and 1,3-acyl shift as a result of interaction between alkene and carbonyl chromophore.[16,17] Though these reactions are quite characteristic of their excited states (e.g. 1,2-shift from lowest triplet (T_1) and 1,3-shift from singlet (S_1) or higher triplet (T_2) state), small changes in the structure of the chromophore and substituents are known to control the outcome in a subtle fashion.[17] Moreover, selective population of excited states are also required for specific photochemical reaction.

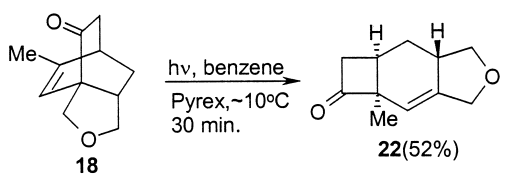
We realized that, while 1,3-acyl shift in tricyclic systems of type **18** would give the carbocyclic framework of oxa-sterpurane, a 1,2-acyl shift (oxa-di-π-methane rearrangement) would furnish the oxa-triquinane framework, respectively, in a stereoselective fashion. Towards synthesis of the oxa-triquinane framework, we first explored the photochemical reaction of **18** upon irradiation. Thus, a solution of the compound **18** in degassed dry acetone (both as a solvent as well as sensitizer) was irradiated in a Pyrex immersion well under nitrogen for 1.5 h. Removal of solvent in vacuo and chromatography furnished the tetracyclic compound **20** in good yield (58%) as a colourless crystalline solid (Scheme 5).



Scheme 5.

The structure of the photo-product was revealed from its spectral data. Thus, the IR spectrum of the photoproduct showed an absorption band at 1726 cm^{-1} suggesting the presence of a carbonyl group in a cyclopentane ring. The ^{1}H NMR (300 MHz) spectrum of **20** did not show a signal for any olefinic proton. It exhibited resonances at δ 3.90 as a doublet of part of an AB system (J_{AB}=9.5 Hz, J_2=7.0 Hz, 1H) and δ 3.78 also as a doublet of part of an AB system (J_{AB}=9.5 Hz, J_2=2.5 Hz, 1H) due to the oxa-methylene protons adjacent to the ring junction. Other oxy-methylene protons appeared as parts of AB systems at δ 3.70 and 3.62 (J_{AB}=9.5 Hz). Other protons were observed as multiplets clustered together at δ 2.76–2.54 (3H) and δ 1.92–1.84 (4H). The methyl group appeared as a singlet at δ 1.40 (3H). These spectral features suggested structural reorganisation during the irradiation via 1,2-acyl shift (or oxa-di-π-methane rearrangement). The ^{13}C NMR (75 MHz) spectrum also supported the structure **20** for the photo-product since it did not show any signal for olefinic carbons. Signals were observed at δ 214.6 (s), 73.5 (t), 67.2 (t), 51.0 (s) due to carbonyl, oxy-methylene and one of the quaternary carbons. In addition, signals were observed at δ 46.0, 45.7, 45.1, 44.2, 43.2,13.2 (q) (one of the quaternary carbons was not observed). Similarly, irradiation of **19** in acetone gave a mixture of products from which the oxa-polyquinane **21** was isolated in moderate yield.

In order to explore 1,3-acyl shift, a solution of compound **18** in dry benzene was irradiated with a mercury vapour lamp (125 W, Applied Photo physics), in a Pyrex immersion well (>290 nm) for about half an hour upon which a clean reaction occurred. Removal of solvent in vacuo and a careful chromatography of the photolysate gave a colourless solid **22** as a result of 1,3-acyl shift in good isolated yield



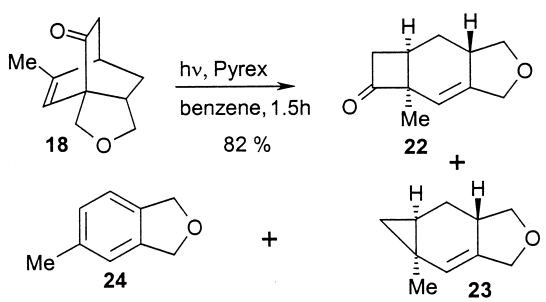
Scheme 6.

(52%) along with some unchanged starting material (15%) (Scheme 6). The structure of the photo-product was deduced from the following spectral data and comparison with the spectral features of **18**. The IR spectrum of **22** showed an absorption band at 1778 cm^{-1} that clearly suggested the presence of carbonyl group in a four membered ring. This indicated that 1,3-acyl shift had occurred during the irradiation. The ^1H NMR (300 MHz) spectrum exhibited a characteristic signal for the olefinic proton at δ 5.34 as a broad multiplet. The methyl group showed an upfield (compared to the precursor **18**) resonance at δ 1.32 as a broad singlet, which also suggested a 1,3-acyl shift during the photoreaction. The four oxy-methylene protons appeared at δ 4.49 (m of d, J=13.0 Hz, 1H), 4.35–4.27 (as a cluster of multiplets, 2H) and 3.34 (dd, J_1=10.5 Hz, J_2=7.5 Hz, 1H). The methylene protons α to CO showed signals at δ 3.0 (d of part of an AB system, J_{AB}=17.0 Hz, J_2=8.5 Hz, 1H) and 2.80 (d of part of an AB system, J_{AB}=17.0 Hz, J_2=8.5 Hz, 1H). In addition, signals were observed at δ 2.60 (m, 1H), 2.44 (m, 1H), 2.04 (ddd, J_1=12.5 Hz, J_2=6.0 Hz, J_3=2.5 Hz, 1H) and 1.12 (ddd, J_1~12.0 Hz, J_2=8.5 Hz, J_3=4.0 Hz, 1H) for other methine and methylene protons. ^{13}C NMR (75 MHz) spectrum showed signals at δ 209.7 (CO), 143.5, 115.9, 73.7, 70.2, 63.0, 46.0, 34.8, 31.2, 22.8 and 20.5. It is interesting to note the selectivity during the above reaction since no product arising out of oxa-di-π-methane rearrangement was observed.

In order to increase the photochemical conversion during the above reaction, a solution of **18** in benzene was irradiated for a longer duration (~1.5 h). However, while the photochemical conversion was good, it gave a mixture of products. Chromatography of this mixture gave a less polar product (tlc) in excellent yield (82%), which was identified as a mixture of tricyclic compound **23** having a cyclopropane ring and an aromatic compound **24** (^1H NMR, 300 MHz), in addition to minor amount of 1,3-acyl shift product **22** (Scheme 7).

Though it was difficult to separate the compounds **23** and **24**, ^1H NMR (300 MHz) spectrum of the mixture clearly suggested their presence. It appears that these products are formed as a result of further photoreaction during the prolonged irradiation. Such photoreactions involving ketene elimination and aromatisation though not common, have been observed in a few instances.[18a]

The detailed mechanism of formation of **23** and **24** is difficult to suggest at the moment. It appears that the product



Scheme 7.

23 containing cyclopropane ring is formed from the initial 1,3-acylshift product **18** as a result of decarbonylation,[18] while the aromatic compound **24** is generated from **18** via ketene elimination followed by aromatisation.[18a] However, formation of **23** and **24** from the diradical intermediate formed after initial α-cleavage may not be ruled out.

3. Conclusions

In conclusion, an efficient method for the synthesis of bicyclo[2.2.2]octenones **13**–**19**, by intramolecular $\pi^{4s}+\pi^{2s}$ cycloaddition in spiroepoxycyclohexa-2,4-dienone and a stereoselective route to oxa-triquinane and oxa-sterpurane frameworks via modulation of chemical reactivity in the excited state is presented. Manipulation of the adduct readily gave the desired tricyclic systems having a β,γ-enone chromophore. It is interesting to note the generation of molecular complexity (**11**→**13**, **18** and **19**) from a simple aromatic precursor, one of the most desirable features of synthetic method and strategy.[19,20] Photochemical reactions of the tricyclic systems **18** and **19** upon triplet and singlet excitation gave oxa-sterpurane and oxa-triquinane frameworks in a single stereoselective step.

4. Experimental

4.1. General

IR spectra were recorded on a Perkin–Elmer 681 and Nicolet FT-IR instrument Impact 400. UV spectra were recorded on Schimadzu 260 instrument. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian VXR 300S instrument. All the samples were dilute solutions in $CDCl_3$ with $SiMe_4$ as internal standard. HRMS were recorded on Bruker Daltronics Apex 3 Telsa FTMS. Melting points were taken on a Veego apparatus and are uncorrected. All the organic extracts were dried over anhydrous sodium sulfate. Reactions were monitored with tlc and spots visualised by exposure to iodine vapour. Chromatographic separations were done on silica gel.

4.1.1. 8-(2-Oxa-pent-4-ene)-2,2,6-trimethyl-1,3-benzodioxin (10b). To a suspension of sodium hydride (0.5 g (50%), 20.8 mmol, previously washed with dry light petroleum) in dry tetrahydrofuran (30 mL) was added compound **10a** (1.0 g, 4.7 mmol) and the reaction mixture was refluxed for 3 h after which allyl bromide (2 mL, excess) in THF (5 mL) was added drop wise to the reaction mixture and the reaction mixture was further refluxed for 4 h. After completion of reaction (tlc), the reaction mixture was brought to room temperature and quenched with cold water. It was then saturated with sodium chloride after which two layers were formed. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic extract was washed with brine (2×10 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was chromatographed on a silica gel column. Elution with petroleum ether–ethyl acetate (97:3) furnished the title compound as a colourless liquid (1.12 g, 94%). IR (neat) ν_{max}: 1483 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.09 (br s,

1H, aromatic H), 6.70 (br s, 1H, aromatic H), 6.4–5.91 (complex m, 1H, C*H*=CH_2), 5.33 (m of d, J=14.0 Hz, 1H, C=CH_2), 5.20 (m of d, J=9.0 Hz, 1H, C=CH_2), 4.80 (s, 2H, OCH_2), 4.55 (s, 2H, OCH_2), 4.06 (ddd, J_1=2.5 Hz, J_2=2.0 Hz, J_3=1.3 Hz, 2H, OCH_2), 2.26 (s, 3H, CH_3), 1.52 (s, 6H, $C(CH_3)_2$). Mass (*m/z*): 248 (M^+). ESI HRMS Calcd for $C_{15}H_{20}O_3$ [M^++Na]: 271.1035. Found 271.1035.

4.1.2. 2-Hydroxymethyl-4-methyl-6-(2-oxa-pent-4-ene)-phenol (11). To a solution of **10b** (1 g, 4.03 mmol) in tetrahydrofuran (40 mL) was added hydrochloric acid (1N, 40 mL) and the reaction mixture was stirred for 12 h at ambient temperature (~30°C). The organic solvent was removed under reduced pressure at ~40°C. The aqueous solution was extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with sodium bicarbonate solution (2×10 mL), brine (2×15 mL) and dried over anhydrous sodium sulphate. Solvent was removed at ~35–40°C under reduced pressure and the crude product was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate (9:1) gave the title compound **11** as a colourless liquid (0.73 g, 88%). IR (neat) ν_{max}: 3356, 1483 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (s, 1H, O*H*), 6.95 (s, 1H, aromatic H), 6.8 (s, 1H, aromatic H), 6.2–5.88 (complex m, 1H, C*H*=CH_2), 5.32 (m of d, J=14.0 Hz, 1H, C=CH_2), 5.25 (m of d, J=9.0 Hz, 1H, C=CH_2), 4.7 (br s, 2H, OCH_2), 4.67 (s, 2H, OCH_2), 4.08 (m of d, J=6.0 Hz, 2H, OCH_2), 2.54 (br s, 1H, O*H*), 2.24 (s, 3H, CH_3). Mass (*m/z*): 208 (M^+). ESI HRMS: Calcd for $C_{12}H_{16}O_3$ [M^++Na]: 231.0992. Found 231.0999.

4.1.3. 3-Oxa-11-methyl-8-spiroepoxy-*endo*-tricyclo-[5.2.2.0^{1,5}]undec-10-en-9-one (13). To a solution of **11** (1 g, 4.8 mmol) in acetonitrile (50 mL) was added a solution of sodium *meta*periodate (5 g, 23.3 mmol, in water (50 mL)) in about 1 h, at ~10°C. The reaction mixture was stirred for 12 h. It was then saturated with sodium chloride and acetonitrile layer was separated. It was washed with brine (2×10 mL) and dried over anhydrous sodium sulfate. The remaining aqueous layer was extracted with ethyl acetate (3×30 mL) and washed with brine (3×10 mL). It was dried over anhydrous sodium sulfate. Both the acetonitrile and ethyl acetate extracts were combined and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate (95:5) gave the adduct **13** (0.57 g, 58%) as a solid which was recrystallized from petroleum ether–ethyl acetate (97:3). mp 102°C. IR (KBr) ν_{max}: 1727 cm^{-1}. UV (MeOH), λ_{max}: 220 and 305 nm. ^1H NMR (300 MHz, $CDCl_3$): δ 5.60 (br m, 1H, olefin H), 4.25 (part of an AB system, J_{AB}=8.8 Hz, 1H, OCH_2), 4.07 (superimposed dd, J_1=J_2=7.5 Hz, 1H), 3.94 (part of an AB system, J_{AB}=8.8 Hz, 1H), 3.30 (dd, J_1=11.0 Hz, J_2=7.5 Hz, 1H, OCH_2) for oxy-methylene protons and 3.19 (part of an AB system, J_{AB}=6.0 Hz, 1H, oxirane CH_2), and 2.91 (part of an AB system, J_{AB}=6.0 Hz, 1H, oxirane CH_2), 2.74–2.62 (complex m, 1H), 2.41 (m, 1H), 2.32–2.22 (complex m, 1H), 1.96 (d, J=1.6 Hz, 3H, CH_3), 1.30 (ddd, J_1=12.5 Hz, J_2=6.6 Hz, J_3=1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3 (CO), 146.0, 122.7, 71.2, 68.5, 60.5, 56.9, 51.6, 45.2, 43.7, 23.7, 20.0. Mass (*m/z*): 206 (M^+). Analysis: Found C, 70.16; H, 6.86% requires C, 69.9, H, 6.7% for $C_{12}H_{14}O_3$.

Continued elution with petroleum ether–ethyl acetate (88:12) gave the dimer **14** as a crystalline colourless solid (0.21 g, 22%), mp 88–89°C. IR (KBr) ν_{max}: 1728, 1689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.76 (s, 1H, β proton of α, β-enone), 5.84–5.98 (complex m, 2H, olefin proton), 5.77 (m, 1H, olefin proton of β,γ-enone), 5.32 (m, 1H), 5.27 (m, 1H), 5.22 (m, 1H), 5.19 (m, 1H), 4.14 (d, J=1.6 Hz, 2H), 4.07–3.99 (m, 4H), 3.89 (AB system, J_{AB}=8.4 Hz, 2H), 3.16 (part of an AB system, J_{AB}=6.0 Hz, 1H, OCH_2), 2.96 (part of an AB system, J_{AB}=6.0 Hz, 1H, OCH_2), 2.85 (AB system, J_{AB}=6.0 Hz, 2H), 2.6 (br m, 1H), 2.2 (d, J=1.8 Hz, 1H), 1.88 (d, J=1.6 Hz, 3H, CH_3), 1.4 (s, 3H, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 203.8, 191.7, 147.5, 143.1, 136.5, 134.3, 134.2, 124.8, 117.3, 117.1, 72.7, 71.8, 66.1, 65.6, 62.3, 58.4, 58.1, 58.0, 53.0, 48.2, 46.2, 45.6, 23.9, 20.8 (24 carbons). Mass (*m/z*): 206 (M^+/2) (it undergoes retro Diels–Alder reaction during mass spectrometry). ESI HRMS: Calcd for $C_{24}H_{28}O_6$ [M^++Na]: 435.1778. Found 435.1785.

4.1.4. 3-Oxa-8,11-dimethyl-*endo*-tricyclo [5.2.2.0^{1,5}]-undec-10-ene-9-one (15). To a solution of the adduct **13** (1 g, 4.86 mmol) in 30 mL dry dioxane, was added activated zinc (5 g, excess) and ammonium chloride (1 g, 18.7 mmol, excess) and the reaction mixture was refluxed for 8 h. After completion of reaction, the reaction mixture was filtered through a celite pad, which was then washed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was diluted with water (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extract was washed with brine (2×20 mL) and dried over anhydrous sodium sulphate. Removal of solvent under reduced pressure gave the crude product, which was chromatographed (petroleum ether–ethyl acetate, 95:5) to give the compound **15** (mixture of *syn*/*anti* isomers) as a solid (0.56 g, 60%) mp 56–58°C. IR (KBr) ν_{max}: 1712 (CO) cm^{-1}. UV (MeOH) ν_{max}: 219 and 291 nm. ^1H NMR (300 MHz, $CDCl_3$): δ 5.48 (m, 1H, β H of β,γ-enone group), 4.19 (two sets of part of an AB system, J_{AB}=9.0 Hz, total 1H, OCH_2), 3.99 (two sets of superimposed dd, J=7.5 Hz, total 1H), 3.88 (part of an AB system, J_{AB}=9.0 Hz, 1H, OCH_2), 3.20 (dd, J_1=11.0 Hz, J_2=7.5 Hz, 1H), 2.64–2.57 (m, 1H), 2.45–2.30 (m, 1H), 2.12–1.96 (m, 2H), 1.91 and 1.90 (two sets of d, J=1.5 Hz, total 3H, CH_3), 1.24–1.15 (m partly hidden under methyl signal, 1H), 1.14 and 0.99 (two sets of d, J=6.0 Hz, total 3H, CH_3). Analysis: Found: C, 74.79%, H, 8.6%; Calcd: C, 75%, H, 8.3% for $C_{12}H_{16}O_2$.

4.1.5. 3-Oxa-11-methyl-8-hydroxymethyl-*endo*-tricyclo-[5.2.2.0^{1,5}]undec-10-ene-9-one (17). To a suspension of activated zinc (7 g, excess) in MeOH–H_2O (7:1, 25 mL) was added a solution of adduct **13** (1 g, 3.85 mmol), followed by addition of ammonium chloride (1 g, 18.7 mmol, excess) and the reaction mixture was stirred at room temperature (~30°C) for about 12 h. The reaction mixture was filtered through a celite pad, which was further washed with ethyl acetate (6×10 mL). The filtrate was concentrated in vacuo. The residue was diluted with water (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extract was washed with water (2×10 mL), brine (2×10 mL) and dried over anhydrous sodium sulphate. Removal of solvent under reduced

pressure gave the crude product, which was chromatographed over silica gel. Elution with petroleum ether–ethyl acetate (97:3) furnished a small quantity of deoxygenated compound **15** as a colourless solid (0.093 g, 10%). Continued elution with petroleum ether–ethyl acetate (95:5) furnished a very small amount of the dienol **16** as a colourless liquid (0.04 g, 4%), which was briefly characterized. IR (neat) ν_{max}: 3414 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.56 (br m, 1H, olefin H), 5.08 (d, J=2.1 Hz, exocyclic olefin, 2H), 4.0–3.9 (m, 4H, 3 protons of OCH_2 and one proton of *H*–C–OH), 3.10 (dd, J_1=10.7 Hz, J_2=7.0 Hz, 1H), 2.88 (m, 1H), 2.62 (complex m, 1H), 2.0 (br s, 1H, O*H* exchangeable with D_2O), 1.94–1.84 (m, 1H), 1.82 (d, J=1.5 Hz, 3H, CH_3), 1.18 (ddd, J_1=12.0 Hz, J_2=7.0 Hz, J_3=2.0 Hz, 1H).

Further elution with petroleum ether–ethyl acetate (88:12) furnished β-keto alcohol **17** (as a mixture of *syn*/*anti* isomers) as a thick colourless liquid (0.85 g, 84%). IR (neat) ν_{max}: 1712 (CO), 3396 (broad, OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.52 and 5.51 (br m, total 1H, olefinic H), 4.20 (merged d, J=8.5 Hz, 1H), 4.02 (overlapped m, 1H), 3.9 (set of two d, J=8.5 Hz, for each set, total 1H), 3.8 and 3.7 (set of two dd, J_1=11.5 Hz, J_2=7.0 Hz, for each set, total 1H), 3.65 (m, partly merged with the dd at 3.7, 1H), 3.2 (two sets of dd, J_1=9.5 Hz, J_2=6.0 Hz, total 1H), 2.8 (m, 1H), 2.64–2.20 (sets of m, total 3H), 2.08–1.99 (m, 1H), 1.93 (two sets of d, J=1.5 Hz, total 3H, CH_3), 1.25, 1.16 (m of dd, J_1=13.0 Hz, J_2=7.0 Hz, total 1H). Mass (*m*/*z*): 208 (M^+), 190 (M^+-H_2O). ESI HRMS: Calcd for $C_{12}H_{16}O_3$ [M^++Na]: 231.0992. Found: 231.0995.

This keto-alcohol was immediately subjected to oxidation and decarboxylation as described below.

4.1.6. 3-Oxa-11-methyl-*endo*-tricyclo[5.2.2.0^{1,5}]undec-10-ene-9-one (18). To a solution of the β-keto alcohol **17** (3 g, 14.42 mmol) in acetone (80 mL) was added dropwise a freshly prepared Jones' reagent with stirring at ~5–10°C. After the reaction was complete (tlc, 2 h), the solvent was removed under reduced pressure at ~30°C. It was diluted with water (75 mL) and extracted with ethyl acetate (5×30 mL). The combined extract was washed with water (2×10 mL), brine (1×10 mL) and dried over anhydrous sodium sulphate. Removal of solvent gave the β-keto acid (3.08 g (96%). IR (KBr) ν_{max}: 3500, 1740 cm^{-1}) which was directly subjected to decarboxylation as follows. The β-keto acid thus obtained was dissolved in tetrahydrofuran–water (3:2; 50 mL) and the reaction mixture was refluxed for 12 h. Tetrahydrofuran was removed in vacuo and the remaining aqueous medium was diluted with water (50 mL). It was then extracted with ethyl acetate (3×50 mL). The combined extract was washed with saturated sodium bicarbonate (2×10 mL), water (2×10 mL), brine (2×10 mL) and dried over anhydrous sodium sulphate. Removal of solvent followed by column chromatography petroleum ether–ethyl acetate (95:5) furnished title compound **18** as a colourless solid (1.74 g, 67%), mp 76–77°C. IR (KBr): 1707 cm^{-1}. UV λ_{max} (MeOH): 218 and 289 nm. ^1H NMR (300 MHz, $CDCl_3$): δ 5.49 (m, 1H), 4.21 (part of an AB system, J_{AB}=9.0 Hz, 1H), 4.01 (superimposed dd, J_1=J_2=7.5 Hz, 1H), 3.90 (part of an AB system, J_{AB}=9.0 Hz, 1H), 3.20 (dd, J_1=12.0 Hz, J_2=7.5 Hz, 1H), 2.8 (m, 1H), 2.5 (complex m, 1H), 2.12 (m of part of an AB system, J_{AB}=12.0 Hz, 1H); 2.08 (m of part of an AB system, J_{AB}=12.0 Hz, 1H) ($\Delta\nu/J_{AB}$=~1, total 2H); 1.98–1.92 (m, 1H), 1.90 (d, J=1.5 Hz, 3H), 1.24 (dd, J_1=12.5 Hz, J_2=6.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2 (s), 148.4 (s), 121.2 (d), 71.5 (t), 69.0 (t), 60.9 (s), 42.56 (d), 39.4 (d), 38.1 (t), 26.6 (t), 19.6 (q). Mass (*m*/*z*): 178 (M^+), 136 [M^+–(CH$_2$=C=O)]. Analysis Found: C, 73.99; H, 7.81%. Calcd: C, 74.15; H, 7.86% for $C_{11}H_{14}O_2$.

4.1.7. 3-Oxa-8, 8,11-trimethyl-*endo*-tricyclo [5.2.2.0^{1,5}]-undec-10-ene-9-one (19). Sodium hydride (60% suspension in oil, 0.550 g, 12.5 mmol) was placed in a flask fitted with a nitrogen inlet and condenser. It was washed with dry petroleum ether to remove the oil and dry THF (10 mL) was added. To this was added a solution of the compound **15** (0.25 g, 1.38 mmol) in dry THF (10 mL) and the reaction mixture was refluxed for 1 h after which it was brought to room temperature, and MeI (4 mL, excess) in dry THF (10 mL) was added in a drop wise manner. The reaction mixture was further refluxed for 8 h. After completion of reaction, the reaction mixture was brought to room temperature and carefully quenched with cold water. It was saturated with NaCl, after which two layers were formed. The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (3×20 mL). Combined organic extracts were washed with brine and dried over anhydrous sodium sulphate. Removal of solvent followed by column chromatography (petroleum ether–ethyl acetate, 96:4) gave the compound **19** as a colourless low melting solid (0.173 g, 65%). IR (film) ν_{max}: 1721 cm^{-1}, UV λ_{max} (MeOH): 223 and 290 nm, ^1H NMR (250 MHz, $CDCl_3$): δ 5.44–5.42 (m, 1H); 4.17 (part of an AB system, J_{AB}=8.8 Hz, 1H), 3.98 (superimposed dd, J=7.5 Hz, 1H), 3.88 (part of an AB system, J_{AB}=8.8 Hz, 1H), 3.18 (dd, J_1=10.7 Hz, J_2=7.5 Hz, 1H), 2.52–2.45 (m, 1H), 2.42–2.38 (m, 1H), 2.18–2.08 (J_1=12.5 Hz, J_2=8.7 Hz, J_3=3.5 Hz, 1H), 1.91 (d, J=1.5 Hz, 3H, CH_3), 1.16–1.08 (m overlapped with a s, 1H), 1.11 (s, 3H, CH_3), 1.06 (s, 3H, CH_3). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 212.6, 149.1, 119.9, 71.7, 69.2, 60.7, 51.31, 43.8, 42.2, 25.2, 24.4, 23.7, 21.1. Mass (*m*/*z*): 206 (M^+). HRMS: Calcd for $C_{13}H_{18}O_2$: 206.1301. Found 206.1307.

4.1.8. 2-Methyl-10-oxa-tetracyclo[6.3.0.0^{1,3}.0^{2,6}]undecan-4-one (20). A solution of the compound **18** (0.075 g, 0.42 mmol) in dry acetone (110 mL) was irradiated under nitrogen with a mercury vapour lamp (125 W, Applied Photophysics) in a Pyrex immersion well for about 1.5 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate (92:8) furnished the compound **20** as a colourless solid (0.043 g, 58%), mp: 57–59°C. IR (KBr) ν_{max}: 1726 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.90 (d of part of an AB system, J_{AB}=9.5 Hz, J_2=7.0 Hz, 1H), 3.78 (d of part of an AB system, J_{AB}=9.5 Hz, J_2=2.5 Hz, 1H), 3.70 (part of an AB system, J_{AB}=9.5 Hz, 1H), 3.62 (part of an AB system, J_{AB}=9.5 Hz, 1H), 2.76–2.54 (m, 3H), 1.92–1.84 (m, 4H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.6 (s), 73.5 (t), 67.2 (t), 51.0 (s) (due to carbonyl, oxymethylene and one of the quaternary carbons), 46.0, 45.7, 45.1, 44.2, 43.2 (it was difficult to ascertain their multiplicities since these are clustered together), 13.2 (q) (one

quaternary carbon was not observed). Mass (*m*/*z*): 178 (M^+). Analysis: found C, 74.17; H, 7.93%. Calcd. C, 74.15; H, 7.86% for $C_{11}H_{14}O_2$.

4.1.9. 2,5,5-Trimethyl-10-oxa-tetracyclo[6.3.0.0^{1,3}.0^{2,6}]undecan-4-one (21). A solution of the compound **19** (0.075 g, 0.36 mmol) in dry acetone (110 mL) was irradiated under nitrogen with a mercury vapour lamp (125 W, Applied Photophysics) in a Pyrex immersion well for 1 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate (92:8) gave the compound **21** (0.024 g, 32%) as a colourless liquid. IR (KBr) ν_{max}: 1728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 3.88–3.58 (m, 4H), 2.26–2.21 (m, 2H), 2.01–1.97 (m, 2H), 1.76–1.68 (m, 1H), 1.42 (s, 3H), 1.01 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 216.2, 73.7, 67.4, 58.4, 51.2, 50.7, 43.8, 43.0, 40.9, 40.6, 28.7, 18.0, 14.3. Mass (*m*/*z*): 206 (M^+). HRMS: Calcd for $C_{13}H_{18}O_2$: 206.1301. Found 206.1303.

4.1.10. 3-Methyl-10-oxa-tricyclo [6.3.0.0^{3,6}] undec-1-en-4-one (22). A solution of the compound **18** (0.11 g, 0.061 mmol) in dry benzene (100 mL) was irradiated under nitrogen with a mercury vapour lamp (125 W, Applied Photophysics) in a Pyrex immersion well with cold-water circulation (~10°C) for about 0.5 h. Benzene was removed in vacuo at ~40°C and the residue was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate (96:4) furnished the compound **22** as a colourless solid (0.057 g, 52%), mp 39–40°C. IR (KBr): 1778 cm^{-1}. UV λ_{max} (MeOH): 217 and 289 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34 (br m, 1H), 4.49 (m of d, J=13.0 Hz, 1H), 4.35–4.27 (overlapped m, 2H), 3.34 (dd, J_1=10.5 Hz, J_2=7.5 Hz, 1H), 3.0 (d of part of an AB system, J_{AB}=17.0 Hz, J_2=8.5 Hz, 1H), 2.80 (d of part of an AB system, J_{AB}=17.0 Hz, J_2=8.5 Hz, 1H), 2.60 (m, 1H), 2.44 (m, 1H), 2.04 (ddd, J_1=12.5 Hz, J_2=6.0 Hz, J_3=2.5 Hz, 1H), 1.32 (s, 3H, CH_3), 1.12 (ddd, J_1~12.0 Hz, J_2=8.5 Hz, J_3=4.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.7 (CO), 143.5, 115.9, 73.7, 70.2, 63.0, 46.0, 34.8, 31.2, 22.8, 20.5. Mass (*m*/*z*): 178 (M^+).

Acknowledgements

We are thankful to RSIC, IIT Bombay for spectral facilities. Financial support from BRNS is gratefully acknowledged. G. D. P. is thankful to CSIR New Delhi for a fellowship.

References

1. (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671, and references cited therein. (b) Little, R. D. *Chem. Rev.* **1996**, *96*, 93. (c) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647. (d) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*, Springer: New York, 1987; Vol. 26. pp 1–225.
2. (a) Takasu, K.; Maiti, S.; Katsumata, A.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 2157. (b) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett.* **2000**, *41*, 8985. (c) Ergueden, J.-K.; Moore, H. W. *Org. Lett.* **1999**, *1*, 375. (d) Biju, P. J.; Subba Rao, G. S. R. *Tetrahedron Lett.* **1999**, *40*, 9379. (e) MacDougall, J. M.; Santora, V. J.; Verma, S. K.; Turnbull, P.; Hernandez, C. R.; Moore, H. W. *J. Org. Chem.* **1998**, *63*, 6905.
3. (a) Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K. *Tetrahedron* **1993**, *49*, 11189. (b) Fukumoto, K.; Toyoda, S.; Japan Patent 95, 179, 449, 1995; *Chem. Abst.* **1995**, *123*, 257083d. (c) Amey, D. M.; Blakemore, D. C.; Drew, M. G. B.; Gilbert, A.; Heath, P. *J. Photochem. Photobiol. A: Chem.* **1997**, *102*, 173. (d) Ader, T. A.; Champey, C. A.; Kuznetsova, L. V.; Li, T.; Lim, Y.-H.; Rucando, D.; Sieburth, S. M. *Org. Lett.* **2001**, *3*, 2165.
4. (a) Zimmerman, H. E.; Armesto, D. *Chem. Rev.* **1996**, *96*, 3065, and references cited therein. (b) Katayama, S.; Hiramatsu, H.; Aoe, K.; Yamaguchi, K. *J. Chem. Soc., Perkin Trans 1* **1997**, 561. (c) Singh, V.; Porinchu, M. *Tetrahedron* **1996**, *52*, 7087. (d) Uyehara, T.; Murayama, T.; Sakai, K.; Ueno, M.; Sato, T. *Tetrahedron Lett.* **1996**, *37*, 7295.
5. (a) Mehta, G.; Sreenivas, K. *Tetrahedron Lett.* **2002**, *43*, 703. (b) Ishii, S.; Zhao, S.; Mehta, G.; Knors, C. J.; Helquist, P. *J. Org. Chem.* **2001**, *66*, 3449. (c) Strunz, G. M.; Bethell, R.; Dumas, M. T.; Boyonoski, N. *Can. J. Chem.* **1997**, *75*, 742. (d) Sterner, O.; Anke, T.; Sheldrick, W. S.; Steglich, W. *Tetrahedron* **1990**, *46*, 2389. (e) Murata, Y.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1981**, *22*, 4313. (f) Ayer, W. A.; Saeedi-Ghomi, M. H.; Van Engen, D.; Tagle, B.; Clardy, J. *Tetrahedron* **1981**, *37*, 279.
6. Preliminary communication: Singh, V.; Alam, S. Q. *Bioorg. Med. Chem. Lett.* **2000**, 2517.
7. (a) Adler, E.; Holmberg, K. *Acta. Chem. Scand.* **1974**, 465. (b) Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324. (c) Singh, V.; Prathap, S.; Porinchu, M. *J. Org. Chem.* **1998**, *63*, 4011.
8. Hampton, P. D.; Bencze, Z.; Tong, W.; Daitch, C. E. *J. Org. Chem.* **1994**, *59*, 4838.
9. (a) Clark, D. A.; Riccardis, F. D.; Nicolaou, K. C. *Tetrahedron* **1994**, *50*, 11391. (b) Tsubaki, K.; Otsubo, T.; Tanaka, K.; Fuji, K. *J. Org. Chem.* **1998**, *63*, 3260.
10. Jackman, L. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. Pergamon: Oxford, 1969.
11. Singh, V.; Bedekar, A. V.; Caira, M. R. *J. Chem. Res. (S)* **1995**, 452.
12. Singh, V.; Deota, P. T.; Bedekar, A. V. *J. Chem. Soc., Perkin Trans 1* **1992**, 903.
13. Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*. Wiley: New York, 1967; pp 142–144.
14. House, H. O. *Modern Synthetic Reactions*. W. A. Benzamin: Menlo Park, CA, 1972.
15. (a) Hixon, S. S.; Mariano, P. S.; Zimmerman, H. E. *Chem. Rev.* **1973**, *73*, 531. (b) Dauben, W. G.; Lodder, G.; Ipaktschi, J. *Top. Curr. Chem.* **1975**, *76*, 1. (c) Houk, K. N. *Chem. Rev.* **1976**, *76*, 1.
16. (a) Zimmerman, H. E.; Grunewald, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 183. (b) Zimmerman, H. E.; Binkley, R. W.; Givens, R. S.; Sherwin, M. A. *J. Am. Chem. Soc.* **1967**, *89*, 3932. (c) Givens, R. S.; Oettle, W. F.; Coffin, R. L.; Carlson, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 3957.
17. (a) Schuster, D. I. *Rearrangement in Ground and Excited States*, de Mayo, P., Ed.; Academic: New York, 1980; Vol. 3, pp 232–279 and references cited therein. (b) Demuth, M. *Organic Photochemistry*, Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. 11, pp 37–97.
18. (a) EcKersley, T. J.; Parker, S. D.; Rogers, N. A. J.

Tetrahedron **1984**, *40*, 3749. (b) Singh, V.; Thomas, B.; Sharma, U. *Tetrahedron Lett.* **1995**, *36*, 3421.
19. Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*. Wiley: New York, 1989.
20. Chanon, M.; Barone, R.; Baralotto, C.; Julliard, M.; Hendrickson, J. B. *Synthesis* **1998**, 1559.