Aromatics to Triquinanes: *p*-Cresol to (±)-$\Delta^{9(12)}$-Capnellene†

Vishwakarma Singh,* S. Prathap, and M. Porinchu

Department of Chemistry, Indian Institute of Technology, Powai, Bombay 400 076

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A novel, efficient and stereospecific synthesis of the marine natural product capnellene from *p*-cresol is described. Generation of 4-methyl-6,6-spiroepoxycyclohexa-2,4-dienone (**9**) from 5-methylsalicyl alcohol (**8**), its in situ cycloaddition with cyclopentadiene (in situ), and the photochemical oxa-di-π-methane reaction of an *endo* tricyclo[5.2.2.$0^{2,6}$]undecenone are the key features of our strategy. An efficient synthetic route to appropriately designed *endo* tricyclo[5.2.2.$0^{2,6}$]undecenones (compounds **6**, **11**−**13**) endowed with most of the structural and stereochemical features of capnellene, from the keto epoxide **7**, are described. The photochemical reaction of **6,** and **11b,d** upon sensitized irradiation readily gave the oxa-di-π-methane products **5**, **14**, and **15** respectively. The tetracyclic compound **5** was elaborated to capnellene after cleavage of the peripheral cyclopropane bond, Barton's deoxygenation, deprotection of the carbonyl group, and Wittig reaction.

Recently, there has been a worldwide interest in the chemistry of tricyclopentanoids.[1,2] This resurgence is partly due to the occurrence and isolation of many natural products having linearly fused *cis:anti:cis* cyclopentane rings in their molecular framework and also because many of these products exhibit a wide spectrum of biological activity. As a consequence, the past decade has witnessed a flurry of activity in the design and development of synthetic routes to triquinanes. The search of methods for efficient and rapid acquisition of cyclopentanoids is continuing.[1]

The marine soft coral *Capnella imbricata* is a rich source of an important class of triquinane sesquiterpene metabolites designated as capnellanes.[3] The metabolites **1**−**3** (Figure 1) represent a few members of this family. These compounds display biological activities similar to those of their terrestrial counterparts, the hirsutanes, which possess antibacterial and antitumor properties. Capnellanes appear to serve as chemical defense agents within the coral reef biomass toward algae and microbial growth and prevent larval settlement.[3] Capnellene (**1**), is one of the most popular targets for synthesis[4−7] presumably because of its interesting molecular architecture, disposition of methyl groups, exocyclic olefinic linkage, and role in the defense mechanism and biosynthesis[3] of oxygenated capnellenes. Moreover, capnellene has also served as a test case to demonstrate the potential of new methodologies for cyclopentane synthesis.

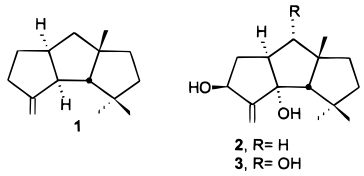

Figure 1.

In continuation of our interest[8] in the synthesis of polyquinanes, we report herein[9] a novel and efficient total synthesis of (±)-capnellene from *p*-cresol employing $\pi^{4s} + \pi^{2s}$ cycloaddition of spiroepoxycyclohexa-2,4-dienone and photochemical 1,2-acyl shift, as key features.

† Dedicated to Professor James B. Hendrickson on the occasion of his 70th birthday.

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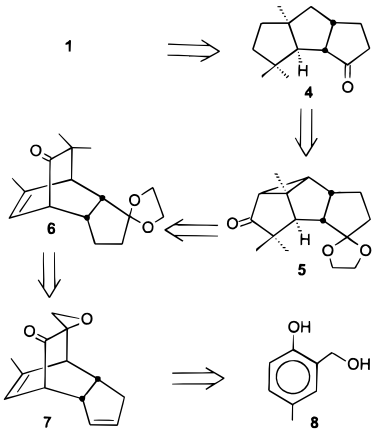
Scheme 1



Strategy

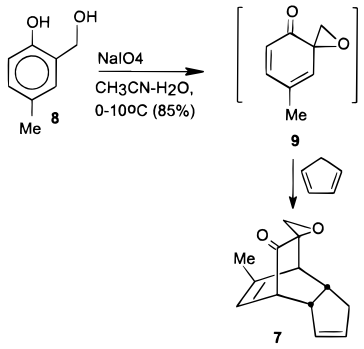
Our plan for the synthesis of capnellene is presented in the Scheme 1. The *cornerstone of our strategy is the recognition of the structural and functional relationship between capnellene (**1**) and the endo-annulated tricyclo-[5.2.2.0^{2,6}]undecenone **6** via the intermediate **5** which was thought to be readily amenable from **6** in a single stereoselective sequence by triplet-sensitized 1,2-acyl shift or oxa-di-π-methane rearrangement*.[10] It was envisaged that the tetracyclic system **5** would be readily elaborated to capnellene via reductive cleavage of the peripheral cyclopropane bond, deoxygenation of the carbonyl group, regeneration of the carbonyl group in the third cyclopentane ring, and Wittig reaction (Scheme 1). It was further recognized that the crucial tricyclic system **6** is related to *p*-cresol derivative **8** via the epoxy ketone **7** which appeared to be easily accessible in a single step from the oxidation of **8** and subsequent interception of the resulting spiroepoxycyclohexa-2,4-dienone **9** following a procedure recently developed in our laboratory.[8]

There are several noteworthy features of the present strategy. For example, 13 (out of 15) carbon atoms of capnellene are derived from 5-methylsalicyl alcohol (**8**) and cyclopentadiene and assembled in a single step to form the tricyclic system **7**. Remarkably, all three *cis:anti:cis*-fused five-membered rings, the angular methyl group, and one of the geminal methyl groups of capnellene are contained in the adduct **7** in latent form. Transformation of the oxirane moiety of **7** into a geminal dimethyl group and functionalization of the five-membered ring rapidly generate the chromophoric system **6** endowed with all the structural and functional features of capnellene. Moreover the photochemical reorganization of **6** into the tetracyclic intermediate **5** with desired stereochemical disposition of rings, substituents, and functional groups in a single stereoselective sequence is another novel feature of our plan.

Results and Discussion

Synthesis of the Desired Tricyclic Chromophoric Systems 6, and Congeners 11−13. Conceptually, the *endo* tricyclic system **6** could be obtained from inverse demand $\pi^{4s} + \pi^{2s}$ cycloaddition of the cyclohexa-2,4-dienone such as **10** and cyclopentadiene and subsequent manipulation of the resulting adduct. However, it is difficult in practice due to lack of suitable methods for the preparation of cyclohexa-2,4-dienones of type **10**. Though cyclohexa-2,4-dienones are well-known in the literature, there are only a few routes for their preparation.[11] Oxidation of phenols with lead tetraacetate, a method generally employed for the preparation of cyclohexa-2,4-dienones, however, produces 6-acetoxycyclohexa-2,4-dienones.[11a,b] Moreover, the preparation of 6,6-dialkyl-substituted cyclohexa-2,4-dienones by alkylation of *ortho*-substituted phenols proceeds in low yields.[11c] A recent method developed by Schultz and co-workers[11e] also appeared unsuitable for our purpose. We therefore developed an indirect route to the *endo* tricyclic systems of type **6** via in situ generation of spiroepoxycyclohexa-2,4-dienone **9**, its interception with cyclopentadiene, and subsequent manipulation of the resulting adduct **7** following a method developed in our laboratory.[8]

Scheme 2



Thus, 5-methylsalicyl alcohol (**8**) was prepared by hydroxymethylation of *p*-cresol. Though the hydroxymethylation of *p*-cresol with formaldehyde in the presence of sodium hydroxide gave both the products arising from mono- and dihydroxymethylation, the desired monohydroxymethylated product **8** was readily prepared in large quantities by hydroxymethylation[12] under controlled conditions followed by a routine chromatography. Oxidation of the phenol **8** with sodium metaperiodate and subsequent interception of the resulting spiroepoxycyclohexa-2,4-dienone **9** in situ with freshly cracked cyclopentadiene in acetonitrile−water furnished exclusively the adduct 7 in excellent yield (85%, Scheme 2).

Though the above cycloaddition gave a single product apparently arising from π^{4s} (cyclohexadienone) + π^{2s} (cyclopentadiene) mode of addition,[13] the cyclohexa-2,4-dienone **9** could react with cyclopentadiene to give many other adducts such as **I** and **II** (Figure 3). It may also be mentioned that there exists a mechanistic dichotomy regarding the mode of addition and the mechanism of

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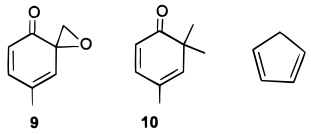


Figure 2.

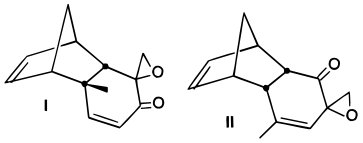


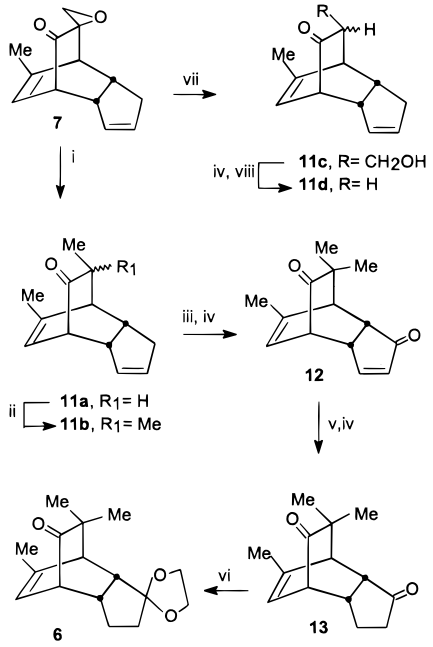
Figure 3.

formation of the adducts during the cycloaddition of cyclohexa-2,4-dienones with dienes.[14] The adduct of type **7** may also arise via 3,3-shift in the compounds of type **I** which may be formed during initial stages of cycloaddition.[14a−c] However, we could not isolate the adducts of type **I** or **II** in this case.

The structure of the adduct **7** was deduced from its ^{1}H NMR, and ^{13}C NMR spectra[15] and by comparison with similar adducts prepared in our laboratory. The stereochemical orientation of the oxirane group was suggested on the basis of the general tendency of cyclohexa-2,4-dienones to be approached by the dienophile *syn* to the smaller oxa bridge during their cycloaddition[16] and by comparison with spectral features of related compounds.[8] This spiroenter would be next converted to the *gem*-dimethyl center, and its stereochemistry would then become inconsequential.

To convert the spirooxirane moiety into geminal methyl groups, the keto epoxide **7** was reduced with zinc[17] in dry dioxane containing NH_4Cl to give the monomethyl compound **11a** as a major product (77%) along with minor amounts of the keto alcohol **11c** (Scheme 3). The compound **11a** was alkylated with methyl iodide in the presence of NaH−THF to give the desired dimethyl compound **11b** whose structure was clearly revealed from its spectral data. Furthermore, the epoxy ketone **7** was reduced with zinc in protic solvent (MeOH−H_2O) containing ammonium chloride to give the keto alcohol **11c** (*syn*:*anti* mixture) as a major product (78%) along with minor amounts of **11a**. The solvent dependent reduction of the adduct **7** provided a simple method to obtain both the compounds **11a** and **11c** selectively in good amounts for further manipulations. Thus, the keto alcohol **11c** was oxidized with Jones reagent, and the resulting keto acid was decarboxylated to give the parent dienone **11d**. The ketone **11b** was oxidized with selenium dioxide[18] in

Scheme 3[a]



[a] Reagents/conditions: (i) Zn, NH_4Cl, dioxane, Δ (77%), (ii) NaH, CH_3I, THF, Δ (89%), (iii) SeO_2, KH_2PO_4, dioxane−water, Δ (63%), (iv) Jones reagent (78%), (v) $NaBH_4$, MeOH, 0 °C, (vi) ethylene glycol, *p*TsOH, benzene (64%), (vii) Zn, NH_4Cl, MeOH−H_2O, rt (78%), (viii) $Ba(OH)_2$, THF−H_2O, Δ (44%).

buffered dioxane−water at ∼100 °C, which gave a stereoisomeric mixture of allylic alcohols which was further oxidized with Jones reagent[19] to give the enone **12**.

Toward the synthesis of the desired tricyclic chromophoric system **6**, the enone group of **12** was selectively reduced with sodium borohydride[20] at ∼10 °C to give a keto alcohol which was directly oxidized with Jones reagent to give the dione **13**. The dione thus obtained was selectively protected with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid to give the desired ketal **6**.

Synthesis of Capnellene: Photochemical Reactions of 11b,d and 6. There has been a great deal of interest in the photochemical reactions of β,γ-unsaturated ketones in the past,[10,21,22] which was recently further enhanced because of their synthetic potential and versatility.[8,23] While β,γ-unsaturated ketones may undergo photoreactions characteristic of olefin and carbonyl chromophores. They generally undergo two unique photoreactions, i.e. oxa-di-π-methane rearrangement and 1,3-acyl shift as a result of extensive interaction between the alkene and carbonyl chromophore. The nature of the photoreactions observed upon excitation of β,γ-enones depend on the excited state, and structure of the chro-

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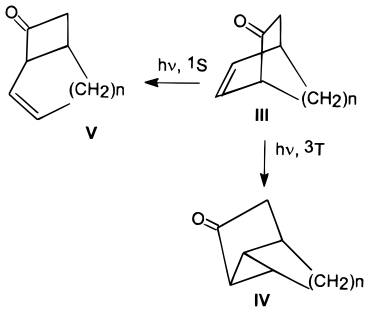
Scheme 4

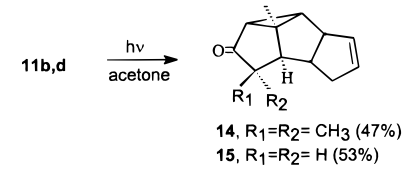


mophoric systems.[10,25] It has been observed that sensitized irradiation of β,γ-unsaturated enones constrained in bicyclic rigid framework causes a 1,2-shift of acyl group leading to a cyclopropyl ketone of type **IV** (Scheme 4). This photochemical rearrangement is known as oxa-di-π-methane rearrangement[10,21−23] because of its similarity to the well-known "di-π-methane" or "Zimmerman rearrangement".[24] The direct irradiation of β,γ-enones, however, causes a 1,3-acyl shift[22,25] leading to cyclobutanone of type **V**. The mechanisms of oxa-di-π-methane rearrangement and 1,3-acyl shift have been studied in great detail, and a correlation between excited state−spin multiplicity and electronic configuration with reaction type has been established.[10,22−26] The 1,3-acyl migration is initiated by photolytic α-cleavage of the ketone to an acyl/allyl radical which may undergo a recombination at alternative allylic position and form the 1,3-shift product. This reaction occurs from the n-π* excited singlet S_1 and/or T_2 (n-π*), respectively. In a similar specific manner, the lowest lying triplet state, T_1 (π-π*), is responsible for oxa-di-π-methane rearranged product; excitation to S_1 on direct light absorption by the starting ketone should be avoided. Also, the triplet energies of the enone and sensitizer ought to be carefully adjusted. E_T of the sensitizer should be between T_1 and T_2 of the enone, so that the energy transfer can be directed to lowest lying triplet otherwise a mixture of products may result.

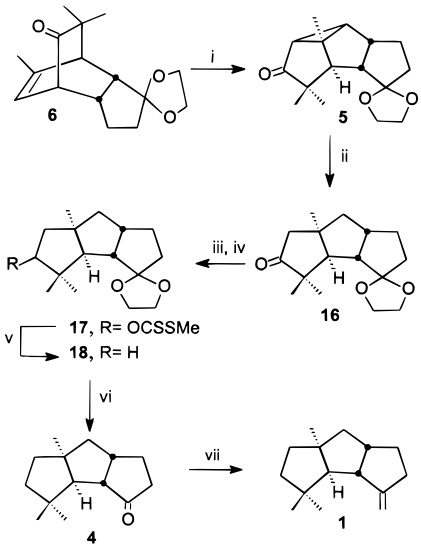
Some time ago we recognized[8,27] that the oxa-di-π-methane rearrangement in *endo* tricyclic systems of type **6** would directly provide a novel and efficient entry into a variety of tetracyclic systems of type **5** which could be readily elaborated to linearly fused *cis:anti:cis* triquinanes. It may be mentioned that earlier studies on photoreactions of β,γ enones were mainly focused on simple bicyclic systems, and their synthetic potential was not realized until recently.[8,23,27] It may be mentioned that, though the scope of oxa-di-π- methane rearrangement is fairly wide, it is quite sensitive to the structure of the chromophoric systems, nature of the substituent, and functional groups.[28]

In view of the above, we first examined the photoreaction of tricyclic compounds **11b,d** upon sensitized irradiation in acetone (both as a solvent and sensitizer) which smoothly gave the rearranged products **14** and **15** (Scheme 5), respectively, in good yields (47 and 53%). Irradiation of the dienone **12**, however, gave a mixture of products presumably due to competing photoreactions.

Scheme 5



Scheme 6[a]



[a] Reagents/conditions: (i) *hν*, acetone, pyrex, 400 W Hg vapor lamp, ∼1.5 h (64%), (ii) H_2/Pd, CH_3OH (85%), (iii) $NaBH_4$, MeOH, rt (90%), (iv) NaH, CS_2, MeI, THF, imidazole (90%), (v) $(Bu)_3SnH$, toluene, AlBN, Δ (76%), (vi) HCl, acetone−H_2O, rt (87%), (vii) PPh_3=CH_2, toluene, Δ (72%).

Toward the synthesis of capnellene, we irradiated a solution of the compound **6** in acetone using a 400 W Hg vapor lamp for ∼1.5 h. Removal of solvent under vacuum followed by a careful chromatography on silica gel furnished the tetracyclic product **5** (Scheme 6) whose structure was thoroughly established by spectral and analytical data. A solution of the tetracyclic keto ketal **5** was stirred in MeOH at room temperature with palladium on carbon in an atmosphere of hydrogen for 12 h in a Parr reactor (12 kg pressure). Removal of the catalyst followed by chromatography gave the compound **16** as a result of the desired peripheral cleavage[29] of the cyclopropane ring.

Having rapidly and efficiently constructed the requisite carbon framework, we removed the carbonyl group present in tricyclic product **16** by using Barton's deoxygenation procedure.[30] Thus, the carbonyl group of triquinane **16** was reduced with $NaBH_4$, and the resulting hydroxyl group was converted into the thiocarbamate **17** by treatment with NaH, CS_2, and MeI in THF containing a catalytic amount of imidazole. After purification on silica gel, the thiocarbamate was reduced with tributyltin

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hydride in toluene containing a catalytic amount of AIBN to give **18** (Scheme 6). Hydrolysis of the ketal **18** with HCl in acetone−water gave the known[7a] intermediate **4**, whose spectral data compared well with those reported. Finally, Wittig reaction of **4** with triphenylphosphonium methylide generated the natural product capnellene (**1**) whose spectral data are in good agreement with those reported in the literature.[4b,7a]

Conclusion

In summary we have presented in this paper a novel total synthesis of capnellene, a marine natural product, from the simple precursors, *p*-cresol derivative **8** and cyclopentadiene, employing inverse demand $\pi^{4s} + \pi^{2s}$ cycloaddition of 6,6-spiroepoxy-4-methyl-cyclohexa-2,4-dienone (**9**) with cyclopentadiene and photochemical oxa-di-π-methane rearrangement (or 1,2-acyl shift) as key features, in a fully stereoselective fashion. The present route *constitutes a rare example of synthesis which is equivalent to opening of an aromatic ring and restiching with cyclopentadiene in a fashion so as to obtain the 13 carbons of capnellene with appropriate connectivity and desired framework with correct stereochemical orientation in a highly efficient manner (cf. **6** to **5**).* It may be further mentioned that the 13 carbons (out of 15) of capnellene are assembled in just a single step from **8** and cyclopentadiene to form the precursor **7** which contains all the structural and stereochemical features of capnellene in latent form. Introduction of one more carbon to the precursor **7**, functionalization followed by photorearrangement to the framework of capnellene, and Wittig reaction completed the total synthesis. *Thus, the present route also satisfies one of the most important criteria of synthesis design, i.e., generation of maximum molecular complexity in the very begining of the synthesis itself.*[31]

Experimental Section

General Remarks. Melting points are uncorrected. All the organic extracts were dried over anhydrous sodium sulfate. Reactions were monitored with thin-layer chromatography and spots visualized by exposure to iodine vapor. Column chromatography was performed on silica gel (60−120/100−200 mesh), and the elution was done with petroleum ether (bp 60−80 °C) and ethyl acetate mixtures. The fractions eluted from column were concentrated at reduced pressure on a rotary evaporator. The reported yields are for the isolated compounds.

10-Methyl-9-spiroepoxy-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (7). To a solution of the compound **8** (1.0 g, 7.24 mmol) in acetonitrile (20 mL) was added freshly cracked cyclopentadiene (4 mL, excess), and the reaction mixture was cooled in ice bath (0−5 °C). A solution of $NaIO_4$ (3.0 g, 14.02 mmol) in water (25 mL) was then added dropwise to the reaction mixture with stirring. After stirring for 6 h, the reaction mixture was filtered and extracted with ether. The organic layer was washed with brine and dried. Removal of solvent followed by chromatography [petroleum ether−ethyl acetate (95:5)] of the crude product on silica gel yielded the adduct **7** (1.20 g, 85%) as a liquid: IR (neat) ν_{max}: 1735 cm^{-1}; UV (MeOH) λ_{max}: 213, 310 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (m, 1H), 5.67 (m, 1H), 5.42 (m, 1H), 3.33 (m, 1H), 3.27 (dd, J = 6, 3 Hz, 1H), 3.10 (part of an AB system, J = 6 Hz, 1H), 3.00 (complex m, 1H), 2.88 (part of an AB system, J = 6 Hz, 1H), 2.60 (m, 1H), 2.38 (dd, J = 2.5, 2.5 Hz, 1H), 1.98 (m, 1H) and 1.92 (d, J = 2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.80 (CO), 141.54 (s), 133.16 (d), 129.33 (d), 119.86 (d), 57.76 (s), 51.90 (d), 51.80 (t), 49.23 (d), 48.80 (d), 37.64 (t), 35.72 (d), 22.87 (q). MS *m/z*: 202 (M$^+$).

9,10-Dimethyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (11a). To a suspension of activated zinc (5 g, excess) and ammonium chloride (0.250 g, excess) in dry dioxane (20 mL) was added a solution of the compound **7** (1.0 g, 4.95 mmol) in dioxane. The reaction mixture was refluxed for 6 h. It was then cooled and filtered to remove zinc. The dioxane was removed in vacuo, and the residue was diluted with water (10 mL) and extracted with ether. The combined ether layer was washed with water and brine and dried. The solvent was removed under vacuum, and the residue was chromatographed over silica gel. Elution with petroleum ether−ethyl acetate (94:6) gave the compound **11a** (0.71 g, 77%) as a *syn:anti* mixture (1:4): IR (neat) ν_{max}: 1720 cm^{-1}; UV (MeOH) λ_{max}: 206, 297 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.67 (m, 1H), 5.56 (m, 1H), 5.39 (m, 1H), 3.18−3.0 (cluster of m, 2H), 2.84 and 2.7 (pair of m, total 1H), 2.6−2.5 (cluster of m, 2H), 2.08−1.9 (complex multiplets, 2H), 1.86 (merged doublets, 3H), 1.12 (d, J = 6 Hz, total 3H). MS *m/z*: 188 (M$^+$).

9,9,10-Trimethyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (11b). To a suspension of sodium hydride (0.6 g, 25 mmol) (which was previously washed with dry light petroleum) in dry tetrahydrofuran (10 mL) was added a solution of the ketone **11a** (1.1 g, 5.85 mmol) in tetrahydrofuran (5 mL), and the reaction mixture was refluxed for 1 h. Methyl iodide (5 mL, excess) in THF (3−4 mL) was then added dropwise to the reaction mixture, and the reaction mixture was further refluxed for 6 h. The reaction mixture was cooled and quenched by careful addition of water, and it was filtered on a Celite pad. The filtrate was concentrated under vacuum. The residue was diluted with water and extracted with ether. The combined extract was washed with water and brine and dried. Removal of solvent followed by chromatography [petroleum ether−ethyl acetate (96:4)] of the residue on silica gel furnished the alkylated product **11b** (1.0 g, 89%): IR (neat) ν_{max}: 1720 cm^{-1}; UV (MeOH) λ_{max}: 207, 300 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.66 (m, 1H), 5.55 (d, J = 7 Hz, 1H), 5.38 (m, 1H), 3.1 (br d, J = 9 Hz, 1H), 3.0 (dd, J = 7, 2.5 Hz, 1H), 2.94 (complex m, 1H), 2.50 (dd, J = 17, 10 Hz, 1H), 2.42 (dd, J = ~3, 3 Hz, 1H, methine H), 1.90 (m, 1H), 1.88 (d, J = ~2.5 Hz, 3H), 1.11 (s, 3H) and 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.34 (CO), 144.36 (s), 132.74 (d), 130.10 (d), 117.74 (d), 54.16 (d), 52.83 (d), 48.14 (d), 43.92 (s), 37.75 (t), 35.26 (d), 26.04 (q), 24.54 (q) and 23.69 (q). MS *m/z*: 202 (M$^+$)

10-Methyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (11d). To a suspension of zinc (8.0 g, excess) in methanol−water (50:7, 30 mL) was added a solution of the epoxy ketone **7** (1.0 g, 4.95 mmol) in methanol (5 mL) and ammoium chloride (0.3 g). The reaction mixture was stirred at ambient temperature (~30 °C) for about 7 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum. It was diluted with water and extracted with ethyl acetate. The combined extract was washed with water and brine and dried. Removal of solvent followed by chromatography [petroleum ether−ethyl acetate (85:15)] of the product gave the keto alcohol **11c** as a mixture of *syn:anti* isomers (0.8 g, 78%): IR (neat) ν_{max}: 3410, 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68 (m, 1H), 5.60 (d, J = 5.5 Hz, 1H), 5.39 (dd, J = 5.6, 2.2 Hz, 1H,), 3.87 (dd, J = 11, 7.5 Hz, 1H), 3.67 (m, 1H), 3.08 (m, 3H), 2.82−2.68 (m, 2H), 2.52 (dd, J = 17, 8.6 Hz, 1H), 2.24 (m, 1H), 1.95 (m, 1H), 1.89 and 1.88 (two sets of d, J = 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 216.07, 214.5 (CO), 144.5, 143.29, 133.01, 132.94, 129.78, 129.73, 119.73, 118.08, 63.81, 62.12, 53.07, 52.55, 51.41, 49.74, 49.42, 47.74, 45.07, 44.99, 39.92, 37.84, 34.60, 23.63, 22.72 for methine, methylene, and methyl carbons of both the isomers. MS *m/z*: 204 (M$^+$). The keto alcohol thus obtained was subjected to Jones oxidation and decarboxylation as follows. To a solution of the keto alcohol **11c** (3.0 g, 14.7 mmol) in acetone (40 mL) was added freshly prepared Jones reagent dropwise at ~5 °C. After the reaction was complete (TLC), acetone was removed under vacuum and the residue diluted with water and extracted with ethyl acetate. The combined extract was washed with water

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and brine and dried. Removal of solvent followed by chromatography [petroleum ether−ethyl acetate (75:25)] of the crude product gave keto acid (IR) (1.87 g, 70%) which was taken up in tetrahydrofuran (25 mL), and aqueous barium hydroxide was added to it. The reaction mixture was refluxed for about 12 h, after which tetrahydrofuran was removed *in vacuo*, and the aqueous medium was extracted with ether. The combined extract was washed with a solution of sodium bicarbonate and dried. The solvent was removed, and the residue was chromatographed. Elution with petroleum ether−ethyl acetate (95:5) gave the titled compound **11d** (0.44 g, 44%) as a colorless liquid: IR (neat) ν_{max}: 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.65 (m, 1H,), 5.58 (d, J = 7 Hz, 1H), 5.38 (m, 1H), 3.16 (complex m, 1H), 3.05 (dd, J = 7, 3 Hz, 1H), 2.74 (m, 1H), 2.66 (m, 1H), 2.54 (dd, J = 17, 10 Hz, 1H), 2.05 (m, 2H), 1.92 (complex m 1H), 1.87 (d, J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.80 (CO), 143.46, 132.40, 129.97, 119.00, 52.62, 48.38, 42.70, 39.67, 39.57, 38.02, 22.56. MS m/z: 174(M$^+$).

9,9,10-Trimethyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-4,10-diene-3,8-dione (12). To a stirred solution of selenium dioxide (1.01 g, 9 mmol) in dioxane (10 mL) and water (1.5 mL) was added potassium dihydrogen orthophosphate (0.2 g). To this was added a solution of the compound **11b** (0.08 g, 3.96 mmol) in dioxane (10 mL) dropwise at 90 °C. The reaction mixture was heated at 90 °C for 12 h. It was brought to room temperature, filtered over a Celite pad, and washed with ether. The filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with ether. The combined extract was washed with water and brine and dried. The solvent was removed under reduced pressure, and the residue was chromatographed. Elution with petroleum ether−ethyl acetate (75:25) afforded allylic alcohol as a stereoisomeric mixture (0.548 g, 63%): IR (neat) ν_{max}: 3410, 1730 cm^{-1}; UV (MeOH) λ_{max}: 218, 299 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.77 (m, 1H, olefinic H), 5.64 (d with fine structure, J = 5.7 Hz, 1H), 5.47 (d, J = 6 Hz, 1H), 4.36 (m, 1H), 3.4−3.18 (m, 2H), 3.01 (dd, J = 6.4, 2.3 Hz, 1H), 2.65 (dd, J = 5.3, 3 Hz, 1H), 2.59 (t of d, J = 8 Hz, 1H), 1.88 (d, J = 1.7 Hz, 3H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.07 (CO), 144.35, 135.54, 134.39, 117.78, 81.23, 52.41, 47 92, 47.40, 47.17, 43.33, 25.82, 23.97 and 23.55 (signals for the major stereoisomer). MS m/z: 192 (M$^+$)]. The alcohol thus obtained was subjected to oxidation as follows.

To a solution of the above alcohol (1.0 g, 4.58 mmol) in acetone (20 mL) 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 ether. The ether extract was washed with sodium bicarbonate, water, and brine and dried. The solvent was removed, and the residue was chromatographed on a short column of silica gel. Elution with petroleum ether−ethyl acetate (80:20) furnished the dienedione **12** (0.77 g, 78%): mp 146−148 °C; IR (KBr) ν_{max}: 1725, 1690 cm^{-1}; UV (MeOH) λ_{max}: 221, 300 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (dd, J = 6, 2.5 Hz, 1H), 6.25 (dd, J = 6, 1.5 Hz, 1H), 5.36 (d with structure, J = 7 Hz, 1H), 3.32 (complex m, 1H), 3.20 (dd, J = 7, ∼2 Hz, 1H), 2.82 (br, 1H), 2.80 (dd, overlapped with another signal, J = 8, 4 Hz, 1H), 1.77 (d, J = 1.5 Hz, 3H), 1.11 (s, 3H) and 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.93, 209.36 (CO groups), 162.44, 145.04, 137.44, 115.80, 51.87, 50.52, 45.26, 43.14, 42.32, 25.67, 23.35, 22.51. MS m/z: 216 (M$^+$). Anal. Found: C, 77.64; H, 7.40%. Calcd for $C_{14}H_{16}O_2$: C, 77.77; H, 7.40%.

9,9,10-Trimethyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-10-ene-3,8-dione (13). Sodium borohydride (0.145 g, 3.84 mmol) was added in small portions to a solution of the enone **12** (0.77 g, 3.56 mmol) in methanol (10 mL) at 0 °C during 20 min, after which the reaction was found to be complete (TLC). The solvent was removed in vacuo, and the residue was diluted with water and extracted with dichloromethane. The combined organic extract was then washed with brine and dried. Removal of solvent followed by column chromatography [petroleum ether−ethyl acetate (85:15)] gave a keto alcohol (0.70 g, 89%) as a liquid (which showed an IR absorption band at 3535 cm^{-1} for OH and 1720 cm^{-1} for the carbonyl group. It also showed a signal at δ 5.62 corresponding to only one olefinic proton in its ^{1}H NMR spectrum (60 MHz, $CDCl_3$)). The keto alcohol thus obtained was directly subjected to oxidation with Jones reagent to give the diketone **13** (0.47 g, 68%): IR (neat) ν_{max}: 1719, 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (d with structure, J = 6 Hz, 1H), 3.11 (dd, J = 6, 2 Hz, 1H), 2.89 (m, 2H), 2.81 (dd, J = 3, 2 Hz, 1H), 2.26−2.10 (complex m, 3H), 1.81 (d, J = ∼1.5 Hz, 3H), 1.69 (complex m, 1H), 1.08 (s, 3H) 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.5, 215.6 (CO groups), 147.7 (s), 117.9 (d), 54.6 (d), 51.6 (d), 48.8 (d), 42.8 (s), 38.6 (t), 36.2 (d), 25.3 (q), 24.8 (t), 24.1 (q), 23.0 (q). Anal. Found: C, 76.75; H, 8.51. Calcd for $C_{14}H_{18}O_2$: C, 77.06; H, 8.25%. MS m/z: 218 (M$^+$).

9,9,10-Trimethyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-3-(1,3-dioxolane)-10-en-8-one (6). To a solution of the diketone **13** (0.22 g, 1.02 mmol) in dry benzene (20 mL) were added ethylene glycol (2 equiv) and *p*-toluenesulfonic acid (catalytic amount), and the reaction mixture was refluxed using a Dean−Stark apparatus for 2 h. The reaction mixture was brought to room temperature, and the benzene layer was separated. It was washed with sodium bicarbonate, water, and brine and dried. Removal of solvent and column chromatography [petroleum ether−ethyl acetate, (93:7)] on silica gel furnished the ketal **6** (0.170 g, 64%): IR (neat) ν_{max}: 1715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.65 (d with structure, J = ∼3 Hz, 1H), 3.90 (complex m, 4H), 2.90 (dd, J = 6, 2 Hz, 1H), 2.70 (d, J = ∼9 Hz, 1H), 2.53 (m, 1H), 2.43 (d, J = 2 Hz, 1H), 1.92 (d, J = 1.5 Hz, 3H), 1.90−1.42 (complex m, 4H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.5 (CO), 148.1, 119.5, 117.4, 65.4, 63.9, 54.6, 51.2, 47.7, 43.5, 39.1, 36.8, 27.9, 26.2, 24.2, 23.1. MS m/z: 262 (M$^+$).

3,6,6-Trimethyltetracyclo[6.3.0.0^{2,6}.0^{3,7}]undeca-10-en-5-one (14). A solution of the compound **11b** (0.6 g, 2.97 mmol) in acetone (300 mL) was irradiated with mercury vapor lamp (250 W, Hanovia) in a Pyrex immersion well under nitrogen for 3.5 h. The solvent was removed in *vacuo*, and the residue was chromatographed [(petroleum ether−ethyl acetate) (95:5)] on silica gel to give the rearranged product **14** (0.28 g, 47%): IR (neat) ν_{max}: 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73 (br s, 2H), 2.80 (d, J = 6 Hz, 1H), 2.70 (dd, J = 16, 9 Hz, 1H), 2.56 (dd, J = 16, 9 Hz, 1H), 2.32 (dd with structure, J = 16, 9 Hz, 1H), 2.14 (s, 1H), 1.8 (part of an AB system, J = 10 Hz, 1H), 1.56 (s, 3H), 1.52 (part of an AB system, J = 10 Hz, 1H), 1.16 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.40 (CO), 133.07, 131.51, 59.67 (d), 53.36 (s), 50.70 (d), 50.60 (d), 42.48 (s), 41.37 (d), 39.95 (d), 38.45 (t), 28.63 (q), 19.46 (q), 18.27 (q). MS m/z: 202 (M$^+$).

3-Methyltetracyclo[6.3.0.0^{2,4}.0^{3,7}]undeca-10-en-5-one (15). A solution of the compound **11d** (0.24 g, 1.38 mmol) in acetone (300 mL) was irradiated under nitrogen for 3 h. Solvent was removed, and the residue was chromatographed on silica gel. Elution with petroleum ether−ethyl acetate (95:5) yielded the tetracyclic product **15** (0.128 g, 53%): IR (neat): ν_{max} 1725 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$):δ 5.72 (s, 2H), 3.08(br m, 1H), 2.75−2.4 (complex m, 5H), 2.0−1.5 (complex m, 3H), 1.48 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 215.30 (CO), 133.10, 131.68, 57.10, 51.36, 49.13, 47.57, 45.02, 42.96, 42.55, 38.53, 18.41. MS (m/z): 174 (M$^+$).

3,6,6-Trimethyltetracyclo[6.3.0.0^{2,4}.0^{3,7}]undeca-9-(1,3-dioxolane)-5-one (5). A solution of the compound **6** (0.18 g, 0.687 mmol) in dry acetone (300 mL) (both as solvent and sensitizer) was irradiated by a mercury vapor lamp (400 W, APP) in a Pyrex immersion well under nitrogen. After 1.5 h, acetone was removed in vacuo, and the residue was chromatographed on silica gel. Elution with ethyl acetate−light petroleum (60−80 °C) [7:93] first gave some unchanged starting material (0.035 g). Further elution with the same solvent furnished the desired rearranged product **5** (0.115 g, 64%): mp 62 °C; IR (neat) ν_{max}: 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.98−3.83 (complex m, 4H), 2.50 (m, 1H), 2.27 (s, 1H), 2.23 (d, J = 5 Hz, 1 H), 1.92−1.76 (complex m, 4H), 1.60 (m hidden under peak due to water in $CDCl_3$ as revealed through D_2O exchange, 1H), 1.51 (s, 3H), 1.41 (d, J = 10 Hz, 1H), 1.16 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.9 (CO), 118.1, 65.1, 64.0, 58.1, 56.7, 53.4, 44.7, 43.9, 43.6,

40.9, 35.7, 29.4, 28.9, 18.9, 18.3. Anal. Found: C, 73.51; H, 8.7. Calcd for $C_{16}H_{22}O_3$: C, 73.28; H, 8.39%. MS (*m/z*): 262 (M^+).

3,3,6-Trimethyltricyclo[6.3.0.0^{2,6}]undeca-11-(1,3-dioxolane)-4-one (16). A solution of the tetracyclic ketone **5** (0.14 g, 0.534 mmol) in methanol (20 mL) was stirred at room temperature with palladium on carbon in an atmosphere of hydrogen (12 kg pressure) for 12 h in a Parr autoclave. The catalyst was removed by filtration and washed with methanol. The filtrate was concentrated, and the residue was chromatographed. Elution with petroleum ether−ethyl acetate, (96:4) yielded the triquinane **16** (0.12 g, 85%): mp 41 °C; IR (neat) ν_{max}: 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (complex m, 4H), 2.62 (complex m, 1H), 2.47 (m, 1H), 2.31−2.10 (merged m, 3H), 1.95 (dd, J = 12, 9 Hz, 1H), 1.88−1.66 (m, 3H), 1.41 (m, 2H), 1.24 (s, 3H), 1.18 (s, 3H) and 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 224.7 (CO), 118.5, 65.1, 64.5, 59.6, 54.1, 49.6, 49.3, 47.9, 47.3, 40.3, 35.0, 28.9, 28.3, 28.2, 24.1. Anal. Found: C, 72.31; H, 8.85. Calcd for $C_{16}H_{24}O_3$: C, 72.72; H, 9.09%. MS *m/z*: 264 (M^+).

3,3,6-Trimethyltricyclo[6.3.0.0^{2,6}]undeca-11-(1,3-dioxolane) (18). To a solution of the compound **16** (0.11 g, 0.417 mmol) in methanol (10 mL) at room temperature−30 °C was added sodium borohydride (0.040 g, 1.05 mmol) in small portions during 10 min. Methanol was removed under vacuum, and water was added to the residue and extracted with dichloromethane. The combined organic layer was washed with water and brine and dried. Removal of solvent followed by chromatography of the crude product on silica gel [ethyl acetate−petroleum ether, (15:85)] furnished a mixture of stereoisomeric alcohols (0.10 g, 90.23%) which was directly subjected to further reaction as follows. A mixture of the above hydroxy ketal (0.100 g, 0.376 mmol), NaH (0.1 g, 1.74 mmol), and imidazole (0.005 g) was taken up in dry THF (5 mL) and refluxed with stirring for 3 h under nitrogen. CS_2 (1 mL) in THF (2 mL) was then added to the reaction mixture. After refluxing for a further 45 min, MeI (1 mL) was added and the refluxing continued for another 30 min. The reaction mixture was brought to room temperature and quenched with acetic acid (0.3 mL), diluted with water and extracted with ether. The combined organic layer was washed with water and brine and dried. The solvent was removed in vacuo, and the residue was chromatographed [petroleum ether−ethyl acetate, (98:2)] on silica gel to give the thiocarbamate **17** (0.109 g, 90.2%) (IR and ^{1}H NMR). The thiocarbamate thus obtained was subjected to reduction as described below.

To a boiling solution of the above thiocarbamate (0.109 g, 0.306 mmol) in toluene (5 mL) containing AIBN (catalytic amount) was added tributyltin hydride (0.15 g, 0.514 mmol) in an argon atmosphere, and the reaction mixture was refluxed for 4 h. The reaction mixture was brought to room temperature, the solvent was removed, and the crude product was chromatographed on silica gel. Elution with petroleum ether removed the organotin impurities. Further elution with ethyl acetate−petroleum ether (2:98) furnished the compound **18** (0.058 g, 76%) as a liquid: IR (neat) ν_{max}: 2947, 2867 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.9 (complex m, 4H), 2.6 (complex m, 1H), 2.3 (m, 1H), 1.94−1.7 (complex m, 5H), 1.52−1.34 (complex m, 6H), 1.2 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H). MS *m/z*: 250 (M^+).

3,3,6-Trimethyltricyclo[6.3.0.0^{2,6}]undeca-11-one (4). To a solution of the compound **18** (0.025 g, 0.10 mmol) in acetone (5 mL) was added two drops of HCl (50%), and the reaction mixture was stirred for 5 h at room temperature (∼30 °C). Acetone was removed under vacuum, and water was added to the residue and extracted with ether. The organic layer was washed with brine and dried. The solvent was removed under vacuum, and the residue was chromatographed on a short column of silica gel. Elution with petroleum ether−ethyl acetate (98:2) gave the compound **4** (0.018 g, 87%), the known precursor of capnellene: IR (neat) ν_{max}: 1737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.8 (m, 1H), 2.36−2.26 (overlapped m, 3H), 2.0 (complex m, 1H), 1.95 (br d, J = ∼1.5 Hz, 1H), 1.86−1.74 (m, 2H), 1.60−1.4 (m, 4H), 1.14−1.09 (m, superimposed with a singlet, 1H), 1.11 (s, 3H), 1.07 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 223.5 (CO), 64.30, 57.49, 53.10, 47.73, 42.48, 42.30, 41.77, 40.20, 35.07, 30.98, 30.45, 26.20, 24.06. MS *m/z*: 206 (M^+). The above spectral features are in agreement with those reported earlier.[7a]

(±)-Δ$^{9(12)}$-Capnellene (1). To a suspension of methyltriphenyl phosphonium iodide (0.050 g, 0.124 mmol) in dry toluene (3 mL) was added potassium *tert*-butoxide (0.012 g, 0.107 mmol) followed by a solution of the compound **4** (0.014 g, 0.068 mmol) in toluene (2 mL). The reaction mixture was heated at 70 °C for 2 h. It was brought to ambient temperature and quenched with a saturated solution of NH_4Cl. It was then extracted with ether. The combined organic extract was washed with brine and dried. Removal of solvent under vacuum followed by chromatography (petroleum ether) of the residue on silica gel furnished the natural product **1** (0.010 g, 72%) as a liquid: IR (neat) ν_{max}: 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.85 (br m, 1H, olefinic H), 4.79 (br m, 1H, olefinic H), 2.70−2.3 (complex m, 4H), 1.8−1.64 (m, 3H), 1.56−1.42 (m, 5H), 1.20 (dd, J = ∼13, 9.5 Hz, 1H), 1.15 (s, 3H), 1.06 (s, 3H) 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.04, 69.13, 52.35, 47.96, 46.07, 41.74, 40.63, 31.89, 31.58, 30.88, 29.11, 26.12 [quaternary carbons not shown]. MS *m/z*: 204 (M^+). These spectral features are in agreement with those reported.[4b,7a]

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Supporting Information Available: Copies of ^{1}H NMR spectra including some expanded spectra and ^{13}C NMR spectra (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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