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Molecular complexity from aromatics: Synthesis and photoreaction of *endo*-tricyclo[5.2.2.0^{2,6}]undecane—A stereoselective route to tricyclic framework of protoilludanes

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Abstract—A stereoselective route towards protoilludanoids from simple aromatic precursor is described. The methodology involves in situ generation of spiroepoxycyclohexadienone and cycloaddition with cyclopentadiene and photochemical 1,3-acyl shift.

Protoilludanes are a unique class of naturally occurring sesquiterpenoids that possess a tricyclic structure composed of a four-membered ring angularly fused to a *cis*-hydrindane ring system in a cis:anti:cis fashion. The fungus Basidiomycetes is a rich source of such secondary metabolites, and a variety of protoilludanes having a variety of substitution and functionalisation pattern have been isolated.[1–3] While protoilluden-6-ol **1** is one of the older members of this family, the melleolides of type **2** (Fig. 1) were isolated recently from the cultured mycelia *Armillariella mellea*[4a] and *Armillaria novae-zelandiae*.[4b] Many of these fungal metabolites and their congeners exhibit promising biological activities.[5] The unusual carbocyclic structure coupled with their role in biosynthesis and the interesting biological properties have generated renewed interest in the chemistry of protoilludanes.[6] Surprisingly, however, only a few methods have been developed.[6,7] Many of these employ a photochemical $\pi^{2s} + \pi^{2s}$ cycloaddition for the creation of cyclobutane ring.

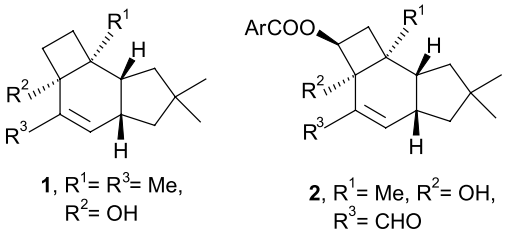
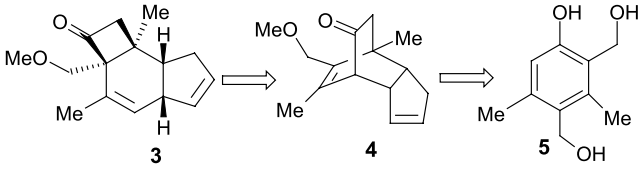


Figure 1.

In view of the above and our interest in development of new methodology employing photochemical reactions of complex β,γ-enones,[8] we thought to develop a stereoselective route to functionalised protoilludane framework. It was considered that the tricyclic compound of type **3** having a cis:anti:cis protoilludane network may be generated in a single stereoselective step from the endo-annulated tricyclic system **4** containing a β,γ-enone chromophore via a 1,3-acyl shift.[9,10] The desired chromophoric system **4** was thought to be prepared from the aromatic precursor **5** via its oxidation to the corresponding spiroepoxycyclohexadienone, cycloaddition with cyclopentadiene and manipulation of the resulting adduct (Scheme 1). In this communication, we report on the synthesis of the tricyclic compound **4** and its photochemical reaction leading to a stereoselective route to tricyclic framework of protoilludanes.

Towards the above objective, the aldehyde **6** was prepared from 3,5-dimethyl phenol and subjected to



Scheme 1.

Keywords: Cycloaddition; Photochemical 1,3-acyl shift.
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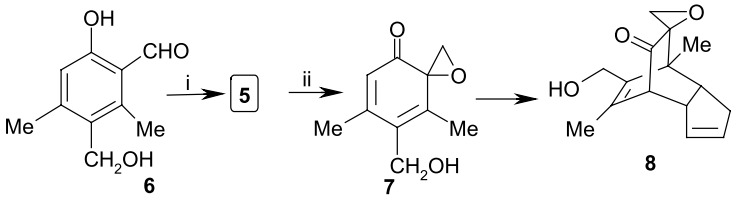
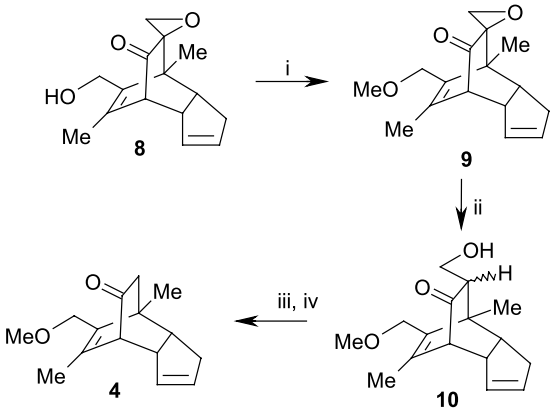


Scheme 2. Reagents: (i) $NaBH_4$, MeOH–H_2O; (ii) $NaIO_4$, CH_3CN–H_2O, cyclopentadiene (75%).

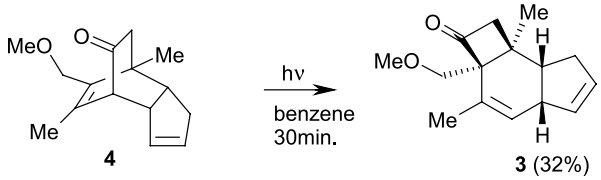
reduction with sodium borohydride. Though the reduction proceeded well (TLC), the isolation of the product **5** proved to be difficult. Therefore, the aldehyde **6** was reduced and the resulting bis-hydroxymethyl compound **5** was directly subjected to oxidation with sodium metaperiodate in the presence of cyclopentadiene, following a procedure developed in our laboratory.[11] Usual work-up and chromatography furnished the endo adduct **8** as a result of in situ generation of spiroepoxycyclohexa-2,4-dienone **7** and interception with cyclopentadiene (Scheme 2). The structure of the adduct was deduced from its spectral data[12] and comparison with other analogous compounds.

Towards the synthesis of the chromophoric system **4**, the hydroxymethyl group in the adduct **8** was protected as methyl ether to give **9**. Reduction of **9** with zinc in aqueous methanol containing ammonium chloride furnished the keto-alcohol **10** as a mixture of syn–anti isomer (^{1}H NMR, 300 MHz). The keto-alcohol **10** was then oxidised with Jones reagent and the resulting β-keto-acid was decarboxylated to furnish the desired tricyclic compound **4** (Scheme 3), whose structure was clearly revealed from its spectral data.

After assembly of the tricyclic compound **4** containing a β,γ-enone chromophore, its photochemical reaction in the excited singlet state was explored. Photochemical reaction of β,γ-enones has stimulated a sustained interest for a long time, which is further enhanced due to the synthetic potential.[9,10] In general, β,γ-enones undergo two unique reactions; that is, triplet excitation leads



Scheme 3. Reagents and conditions: (i) NaH, THF, MeI, Δ, 60%; (ii) Zn, NH_4CI, MeHO–H_2O, rt, 54%; (iii) Jones' oxidation; (iv) THF–H_2O, Δ, 40% (for iii and iv).



Scheme 4.

to oxa-di-π-methane rearrangement whereas singlet excitation induces a 1,3-acyl migration.[9,10,13] However, the exact nature of photoreaction depends upon the structure of the chromophore and the functional groups in a subtle fashion. Considering the above possibilities, a solution of the compound **4** was irradiated with a high pressure mercury vapour lamp (400 W, APP) in a Pyrex immersion well for half an hour. Chromatography of the photolysate furnished the tricyclic compound **3** having protoilludane framework as a result of a stereoselective 1,3-acyl shift (Scheme 4).

The IR spectrum of the photoproduct showed a characteristic absorption band at 1769 cm^{-1} for the cyclobutanone carbonyl. ^{1}H NMR (300 MHz) spectrum of **3** exhibited three olefinic signals at δ 5.71 (br m, 1H), 5.66 (br m, 1H) and 5.39 (br s, 1H) in addition to other resonances. The presence of cyclobutanone carbonyl group in the IR spectrum and three olefinic protons in the ^{1}H NMR spectrum clearly indicated that a 1,3-acyl shift had occurred during the irradiation. The above formulation was also supported from the ^{13}C NMR spectrum, which exhibited signals at δ 205.06, and 131.52, 130.80, 126.16, 125.83 for the carbonyl carbon and olefinic carbons, respectively. In addition, signals were observed at δ 70.91, 67.61, 59.18, 55.70, 43.51, 43.24, 34.81, 33.63, 23.54, 20.23 for the other carbons.

In summary, we have described an efficient synthesis of tricyclic compounds of type **4** containing a β,γ-enone chromophore from a simple aromatic precursor and photoreaction in singlet excited state that provides a stereoselective entry into functionalised protoilludane framework in a single step.

Acknowledgments

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12. Data for compound **8**, IR: 3443, 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CCl_4) δ: 5.68 (m, 1H, olefinic proton), 5.42 (m, 1H, olefinic proton), 4.29 (part of an AB system, J_{AB} = 11.7 Hz, 1H, CH_2OH), 4.04 (part of an AB system, J_{AB} = 11.7 Hz, 1H, CH_2OH), 3.29 (m of d, J = 9 Hz, 1H, methine H), 3.09 (d, J = 2.1 Hz, 1H, methine proton), 2.95 (part of an AB system, J_{AB} = 6 Hz, 1H, CH_2O–), and 2.85 (part of an AB system, J_{AB} = 6 Hz, 1H, CH_2O–), 2.67 (m, 1H), 2.54–2.4 (m, 1H), 2.09 (m of d, J = 17.1 Hz, 1H, methylene H), 1.8 (s, 3H, CH_3), 1.34 (s, 1H), 1.13 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4) δ: 205.32 (CO), 137.20, 134.20, 133.36, 129.16 (olefinic carbons), 57.61, 49.74, 37.01 (methylene carbons), 58.55, 49.92, 42.67 (methine carbons), 18.44, 12.18 (methyl carbons), 44.04 and 37.01 (quaternary carbons). The above assignment was made on the basis of DEPT spectrum. Mass (*m*/*z*): 246 (M^+).
    Data for compound **4**: IR: 1734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.65 (m, 1H, olefinic proton), 5.41 (m, 1H, olefinic proton), 3.99 (part of an AB system, J_{AB} = 11.1 Hz, 1H, CH_2OMe), 3.89 (part of an AB system, J_{AB} = 11.1 Hz, 1H, CH_2OMe), 3.25 (s, 3H, OMe), 3.22 (m merged with singlet due to OMe, 1H, methine H), 2.97 (d, J = 2.3 Hz, 1H, methine H), 2.4 (merged m, 2H), 2.15–2.10 (m, 1H, methine H), 1.98 (s, 2H, methylene H), 1.78 (s, 3H, vinylic CH_3) and 1.32 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213 (CO), 135.03, 134.72, 133.03, 129.43 (olefinic carbon), 67.21, 60.26, 57.44, 49.75, 47.76, 46.65, 42.70, 36.54, 19.86 and 18.37 for methine, methylene, quaternary and methyl carbons. Mass (*m*/*z*): 217 [M^+–(OMe)].
    Data for compound **3**: mp 70–71 °C; IR ν_{max}: 1769 cm^{-1}. ^1H NMR ($CDCl_3$–CCl_4) δ: 5.71 (br m, 1H, olefinic proton), 5.66 (br m, 1H, olefinic proton), 5.39 (br s, 1H, olefinic proton), 3.68 (part of an AB pattern, J_{AB} = 10.2 Hz, 1H, CH_2OMe) and 3.45 (part of an AB pattern, J_{AB} = 10.2 Hz, 1H, CH_2OMe), 3.29 (s, 3H, OMe), 3.21 (s, 1H), 3.16 (s, 1H), 2.47–2.32 (m, 3H), 2.19 (m, 1H), 1.70 (s, 3H, vinylic CH_3), 1.27 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4) δ: 205.06 and 131.52, 130.80, 126.16, 125.83 (carbonyl carbon and olefinic carbons), 70.91, 67.61, 59.18, 55.70, 43.51, 43.24, 34.81, 33.63, 23.54, 20.23..
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