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Structural Diversity Through Intramolecular Cycloaddition and Modulation of Chemical Reactivity in Excited State. Synthesis and Photoreactions of 3-Oxa-tricyclo[5.2.2.0^{1,5}]undecenones: Novel Stereoselective Route to Oxa-triquinanes and Oxa-sterpuranes

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Abstract—Synthesis of 11-methyl-3-oxa-tricyclo[5.2.2.0^{1,5}]undecenones by intramolecular Diels–Alder reaction of highly labile spiroepoxycyclohexa-2,4-dienones and its photochemical reactions upon triplet (^{3}T) and singlet (^{1}S) excitation leading to a stereoselective route to oxa-triquinane and oxa-sterpurane, respectively, is described.

Triquinanes have attracted intense interest in the recent past due to their novel molecular architecture and diverse biological properties.[1,2] Recently, the oxa-analogues of linear triquinanes such as **1**, **2** (Fig. 1) and congeners have shown promising biological activity and proved to be useful for the treatment of leukemia, osteosarcoma, breast cancer and ovarian cancer.[3a,b] While a number of methods have been developed for the synthesis of carbocyclic triquinanes,[1,2] only a couple of methods are known[3] for oxa-triquinanes and other hetero analogues of triquinanes.

In view of the important biological properties of oxa-triquinanes it was thought to develop a novel stereoselective method for their synthesis. We contemplated that a 1,2-acyl shift or oxa-di-π- methane rearrangement[4] in the tricyclic system **3** would readily give **4** in a stereoselective fashion, which may be elaborated to oxa-triquinanes. Interestingly, it was also thought that a 1,3-acyl shift in **3** would give the tricyclic compound **5**, 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 chromophore **3** from a simple aromatic precursor **6** and syntheses of oxa-triquinane frame **4** and oxa-sterpuranes **5** by modulation of chemical reactivity of **3** in excited triplet and singlet states.

Towards our objective, the key tricyclic chromophoric system **3** was prepared from a simple aromatic compound **6** which is readily available via *O*-alkylation of **7** with allyl bromide and removal of the protecting group. Oxidation of **6** with sodium *meta*periodate in aqueous acetonitrile following a procedure developed in our laboratory[6] furnished the adduct **9** in good yield (58%) via in situ generation of spiroepoxycyclohexa-2,4-dienone **8** and subsequent intramolecular cycloaddition. The structure of the adduct was deduced from its high field ^{1}H NMR, ^{13}C NMR, COSY and other spectroscopic and analytical data. The ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **9** 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, $J_{AB}=8.5$ Hz, 1H), 4.07 (superimposed dd, $J_1=J_2=7.5$ Hz, 1H), 3.94 (part of an AB system, $J_{AB}=8.5$ Hz, 1H), 3.30 (dd, $J_1=12$ Hz, $J_2=7.5$ Hz, 1H) for oxy-methylene protons and 3.19 (part of an AB system, $J_{AB}=\sim6$ Hz, 1H), and 2.91 (part of an AB system, $J_{AB}=\sim6$ Hz, 1H) due to methylene protons of the oxirane ring. Further, signals were observed at δ 2.74–2.62 (complex m, 1H), 2.41 (m, 1H), 2.32–2.22 (complex m, 1H), 1.96 (d, $J=1.5$ Hz, 3H; CH_3) and 1.30 (d of dd, $J_1=13$ Hz, $J_2=6$ Hz, $J_3=1.5$ Hz, 1H) due to other protons. The ^{13}C NMR (75 MHz, $CDCl_3$) spectrum also supported

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its formulation as it displayed resonances at δ 201.3 (CO), 146.0, 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]

Reduction of **9** with zinc–NH_4Cl in aqueous methanol gave the β-keto alcohol **10** as a major product (84%) which was subjected to Jones' oxidation to give β-keto acid **11** in excellent yield. Heating a solution of **11** in THF–water gave the desired tricyclic system **3**[8] having a β,γ-unsaturated carbonyl chromophore, in an efficient fashion (Scheme 2).

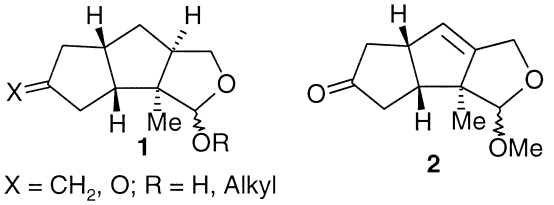
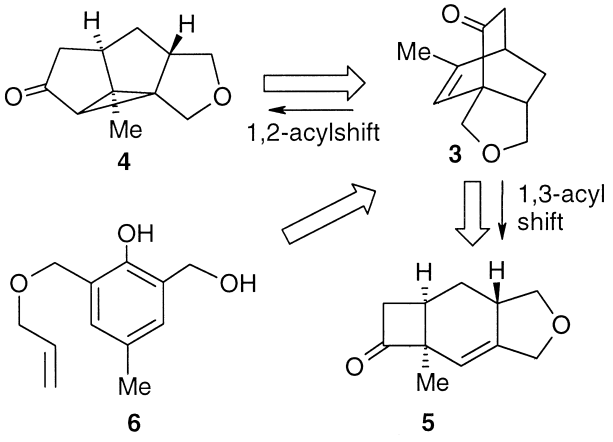


Figure 1.



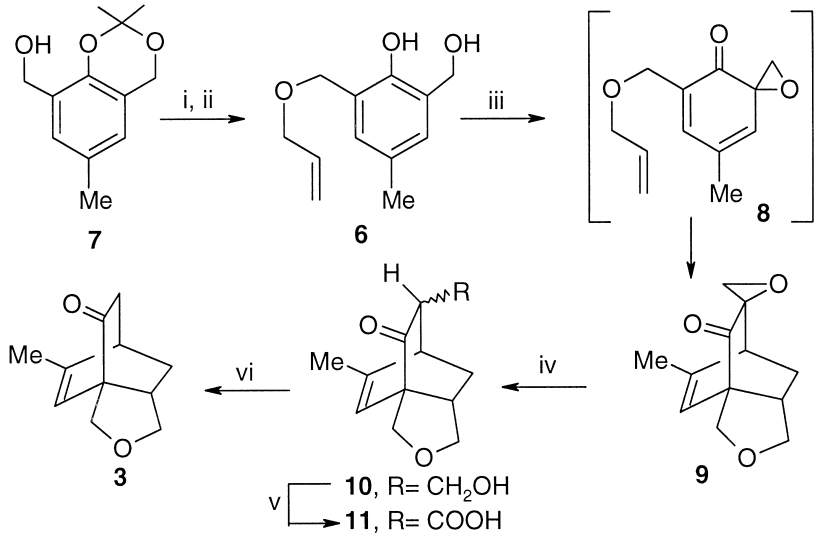
Scheme 1.

It may be mentioned that tricyclic compounds of type **3** endowed with a β,γ-enone chromophore are not readily available and this method provides a new, efficient and versatile avenue to such systems. It is also remarkable to note the generation of structural and functional complexity from a simple precursor (e.g. **6** to **9**–**11**, **3**), one of the most desirable features of synthesis design.[9]

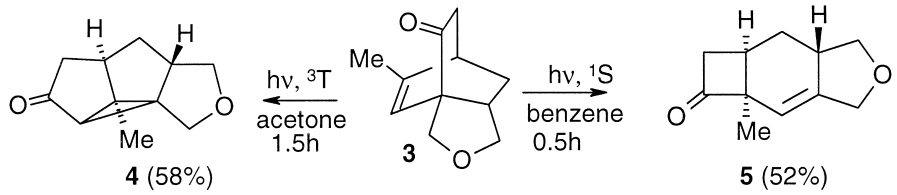
After having readily assembled the chromophoric system **3**, its photochemical reactions in the excited triplet state was explored. Thus, a solution of compound **3** in acetone (sensitizer as well as solvent) was irradiated with a mercury vapour lamp (125W, Applied Photophysics) under nitrogen for about 1.5 h. Removal of solvent followed by chromatography smoothly furnished the tetracyclic compound **4**[10] containing the oxa-triquinane framework in good yield (58%), as a result of a stereoselective 1,2-acyl shift or oxa-di-π- methane rearrangement (Scheme 3).

Towards the singlet excitation, a solution of **3** in dry benzene was irradiated at ~10 °C in a Pyrex immersion well for about 0.5 h. Removal of the solvent followed by chromatography of the residue gave a crystalline compound **5** (mp 39–40 °C) as a result of 1,3-acyl shift in good isolated yield (52%) along with some unchanged starting material (15%). The structures of both the photoproducts were readily deduced from their spectral data.[10]

In summary, we have presented an efficient synthesis of tricyclic systems of type **3** via intramolecular Diels–Alder reaction of spiroepoxycyclohexa-2,4-dienones and a novel stereoselective route to oxa-triquinane and oxa-sterpurane frameworks by modulation of photochemical reactivity of **3** in excited triplet and singlet states, respectively.



Scheme 2. Reagents and conditions: (i) NaH, THF, Δ, allyl bromide, 94%; (ii) 1 N HCl:THF (1:1), rt, 88%; (iii) $NaIO_4$, CH_3CN–H_2O, 5–10 °C, 58%; (iv) Zn, NH_4Cl, MeOH–H_2O, rt, 84%; (v) Jones' oxidation, 5–10 °C, 96%; (vi) THF–H_2O, Δ, 67%.



Scheme 3.

Acknowledgements

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8. Data for **3**: mp 76–77 °C; IR (film) ν_{max}: 1707 cm^{-1}; UV λ_{max} (MeOH): 218, 289 nm; ^1H NMR (300 MHz, $CDCl_3$): δ 5.49 (m, 1H), 4.21 (part of an AB system, $J_{AB}=9$ Hz, 1H), 4.01 (superimposed dd, $J_1=J_2=7.5$ Hz, 1H), 3.90 (part of an AB system, $J_{AB}=9$ Hz, 1H), 3.20 (dd, $J_1=12$ Hz, $J_2=7.5$ Hz, 1H), 2.8 (m, 1H), 2.50 (complex m, 1H), 2.12 (m of part of an AB system, $J_{AB}=12$ Hz, 1H), 2.08 (m of part of an AB system, $J_{AB}=12$ Hz, 1H), 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, 148.4, 121.2, 71.5, 69.0, 60.9, 42.5, 39.4, 38.1, 26.6, 19.6; Mass (*m*/*z*): 178 (M^+), 136 [$M^+-(CH_2=C=O)$]. Anal. Found: C, 73.99; H, 7.81%. Calcd: C, 74.15; H, 7.86% for $C_{11}H_{14}O_2$.
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10. (a) Data for **4**: mp 57–59 °C; IR: 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.90 (d of part of an AB system, $J_{AB}=9.5$ Hz, $J_2=7$ 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, 73.5, 67.2, 51.0, 46.0, 45.7, 45.1, 44.2, 43.2, 13.2 (one 'C' not observed). Anal. Found: C, 74.17; H, 7.93%. Calcd: C, 74.15; H, 7.86% for $C_{11}H_{14}O_2$. (b) Data for **5**: mp 39–40 °C; IR: 1778 cm^{-1}; UV λ_{max} (MeOH): 217, 289 nm; ^1H NMR (300 MHz, $CDCl_3$): δ 5.34 (br m, 1H), 4.49 (m of d, $J=13$ 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, $J_{AB}=17$ Hz, $J_2=8.5$ Hz, 1H), 2.80 (part of an AB system, $J_{AB}=17$ Hz, $J_2=8.5$ Hz, 1H), 2.60 (m, 1H), 2.44 (m, 1H), 2.04 (d of dd, $J_1=12.5$ Hz, $J_2=6$ Hz, $J_3=2.5$ Hz, 1H), 1.32 (s, 3H, CH_3), 1.12 (ddd, $J_1=\sim12$ Hz, $J_2=8.5$ Hz, $J_3=4$ 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^+).