Intramolecular Cycloaddition in Cyclohexa-2,4-dienone and Photochemical Reactions: An Efficient Route to Azatriquinane and Azasterpurane Frameworks

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Abstract: A novel, efficient and stereoselective entry to azatriquinane and azasterpurane frameworks from simple aromatic precursor, is described. The methodology involves in situ generation of cyclohexa-2,4-dienones containing a tether and intramolecular π4s+π2s cycloaddition that leads to a bicyclo[2.2.2]octenone-annulated five-membered ring that contains nitrogen. Further manipulation of the resulting adduct followed by photochemical sigmatropic shifts readily furnished the azatriquinane and azasterpurane frameworks.

Key words: cyclohexa-2,4-dienone, cycloaddition, oxa-di-π-methane rearrangement, 1,3-acyl shift photochemistry

The efficient creation of molecular complexity from simple precursors, atom economy and stereoselectivity are some of the important criteria in the design and development of new synthetic methods.[1–3] Cascades of reactions[2d,f] or reactions in tandem[2c,e,3] and multicomponent reactions[4] are often employed to achieve this objective. Triquinanes have stimulated intense interest on account of their molecular structure and biological activity.[5–7] Recently, heteroanalogues of polyquinanes, especially the tricyclic compounds of type **1** and **2** (Figure 1) and their congeners having oxatriquinane framework were found to exhibit potent in vitro cytotoxic activity against murine lymphoma L1210 cells and human epidermoid carcinoma KB cells.[8a,b] While there are a number of methods for the synthesis of carbocyclic triquinanes only a few methods exists for oxatriquinanes[8] and azapolyquinanes.[9]

In view of the biological significance of heteropolyquinanes and our continuing interest in this area, we considered developing a route to azapolyquinanes of the type **3** and compounds of type **4** which are aza-analogues of sterpuranes, a unique class of sesquiterpenes.[10] We envisaged that a 1,2-acyl shift in the tricyclic system of the type **5** would furnish the azatriquinane **3** whereas a photochemical 1,3-acyl shift in **5** would provide an entry into azasterpuranes **4** (Scheme 1). Further, it was thought that the chromophoric systems of type **5** could be derived from the ketoepoxide **6** which in turn may be obtained by the intramolecular Diels–Alder reaction in cyclohexa-2,4-dienones of type **7**, derived from the aromatic precursor **8** (Scheme 1).

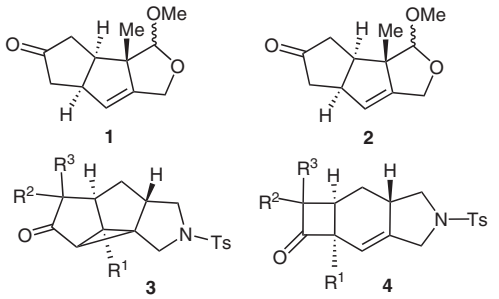
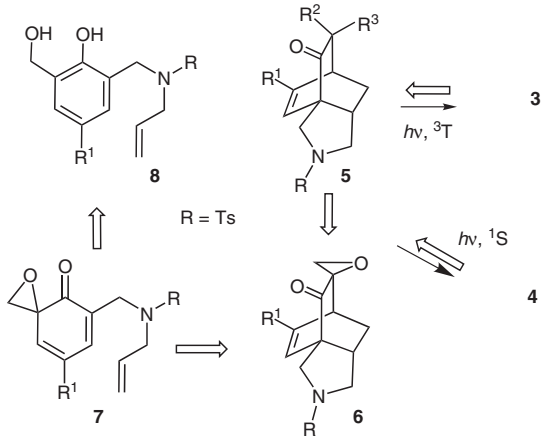


Figure 1



Scheme 1

Towards our objective, the benzylic alcohol **9a**, readily available from *p*-cresol, was treated with triphenylphosphine and bromine[11] to give the bromide **9b** in a good yield. Reaction of **9b** with *N*-allyl tosylamine in the presence of K_2CO_3 gave the N-alkylated product **10** in quantitative yield which on acid-catalyzed hydrolysis furnished the desired aromatic precursor **11** with excellent yield. A solution of **11** in acetonitrile was oxidized with aqueous sodium metaperiodate[12a,b] at 0–5 °C, according to a procedure developed in our laboratory.[12c] Chromatography of the product gave the adduct **13** in a good yield (72%; Scheme 2). The structure of the adduct **13** was deduced from ^{1}H NMR and COSY spectroscopic analysis and confirmed by further transformations (vide infra).[13]

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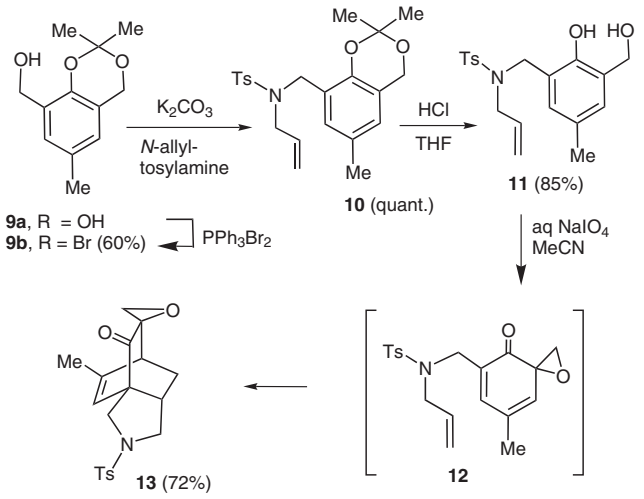
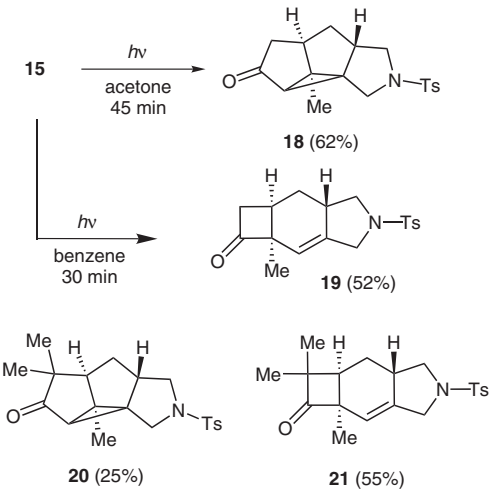
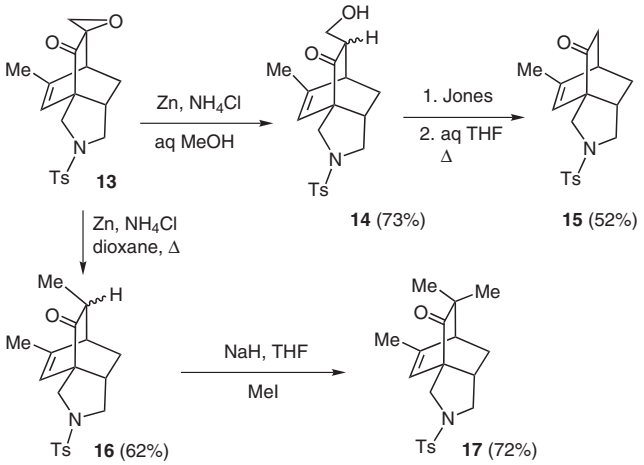


Scheme 2



Scheme 4



Scheme 3

The presence of ketoepoxide functionality in the adduct **13** provided opportunity for further manipulation. Thus, the adduct **13** was treated with Zn in aqueous methanol containing ammonium chloride at ambient temperature to give the β-keto alcohol **14** (*syn*/*anti* mixture, 73% yield) as the major product. Oxidation of **14** with Jones reagent and subsequent decarboxylation furnished the azatricyclic compound **15** (Scheme 3).[14] Alternatively, the reduction of adduct **13** with Zn–NH_4Cl in refluxing anhydrous dioxane gave **16** as a result of deoxygenation of the oxirane ring. Alkylation of **16** with methyl iodide in the presence of NaH–THF gave the compound **17** in good yield (Scheme 3). The structures of all the compounds were supported by spectral data. The stereostructure of compound **15** was further confirmed by a single-crystal X-ray structure determination[14] and hence it also established the structure of the adduct **13** and other related compounds.

Photoreaction of rigid β,γ-enones has generated interest for long time which has enhanced recently because of synthetic potential.[15,16] In general β,γ-enones undergo a 1,2-acyl shift or oxa-di-π-methane rearrangement upon triplet excitation, whereas a 1,3-acyl shift is observed upon singlet excitation. Though, these reactions are general and quite characteristic of their excited states, small structural changes and functional groups often control the reaction in a subtle fashion. Keeping this in mind, a solution of **15** in acetone (both sensitizer and solvent) was irradiated with a 125-W mercury vapor lamp in a Pyrex immersion well for one hour and the tetracyclic ketone **18** was obtained in a good yield as a result of 1,2-acyl shift (Scheme 4).[17] Similarly, irradiation of **15** in anhydrous benzene in a Pyrex immersion well for about half an hour led to a clean reaction and gave the tricyclic compound **19** as a result of 1,3-acyl shift in a good yield (52%).[18] Similar irradiation of **17** also gave the compounds **20** and **21** after sensitized and direct irradiation, respectively.

In summary, a novel stereoselective route to azatriquinane and azasterpurane frameworks is described. Intramolecular cycloaddition of the in situ generated cyclohexa-2,4-dienone and photochemical reactions in the triplet and singlet excited states are the key features of methodology.

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(13) All the compounds gave satisfactory spectral and analytical data. Data for adduct **13**: mp 159–161 °C. IR: 1733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.74 (m, 2 H), 7.31–7.37 (m, 2 H), 5.20–5.24 (br m, 1 H, β-H of β,γ-enone moiety), 3.60–3.68 (m merged with part of an AB system, J_{AB} = 10.6 Hz, 2 H), 3.52 (part of an AB system, J_{AB} = 10.6 Hz, 1 H), 3.14 (part of an AB system, J_{AB} = 6.0 Hz, 1 H), 2.85–2.92 (m merged with another signal, 1 H), 2.84 (part of an AB system, J_{AB} = 6.0 Hz, 1 H), 2.45 (s, 3 H, Me), 2.12–2.34 (m, 3 H), 1.87 (d, *J* = 1.5 Hz, 3 H, Me), 1.26 (ddd, J_1 = 12.1 Hz, J_2 = 5.1 Hz, J_3 = 1.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.9 (CO), 146.4, 143.8, 133.9, 129.8, 127.3, 121.6, 58.8, 56.6, 52.0, 51.8, 49.2, 44.6, 41.5, 24.8, 21.5, 20.2. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{22}SNO_4$: 360.1270; found: 360.1274.

(14) Data of the compound **15**: mp 164–166 °C. IR: 1723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 5.00 (br m, 1 H, β-H of β,γ-enone moiety), 3.60–3.64 (m, 2 H), 3.44 (d, *J* = 10.3 Hz, 1 H), 2.71–2.79 (m, 2 H), 2.44 (s, 3 H), 1.83–2.18 (m, 4 H), 1.79 (d, *J* = 1.8 Hz, 3 H), 1.16–1.21 (m of dd, J_1 = 12.5 Hz, J_2 = 5.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.6 (CO), 148.7, 143.6, 134.3, 129.9, 127.5, 120.2, 59.3, 52.4, 49.6, 40.6, 38.9, 37.9, 28.0, 21.7, 19.8. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}SNO_3$: 332.1320; found: 332.1306. Crystal data: $C_{18}H_{21}NO_3S$, M = 331.42, crystal size = 0.23 × 0.18 × 0.15 mm, monoclinic, $P2_{1/n}$, *Z* = 4, *a* = 11.4521(8), *b* = 10.5769(7), *c* = 13.7991(9) Å, λ = 0.71073 Å, α = 90.000 β = 103.366(6)°, *V* = 1626.18(19) $Å^3$, D_{calcd} = 1.354 mg/m^3, *T* = 150 (2) K, *F*(000) = 704. Reflections collected/unique = 9895/1761, [*R*(int) = 0.0581], final *R* indices [I > 2σ(I)], *R*1 = 0.0581, *wR*2 = 0.1019, *R* indices (all data), R_1 = 0.1126, wR_2 = 0.1161. The complete crystal data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif quoting the CCDC number 677807.

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(17) Data for compound **18**: IR: 1726 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.0 Hz, 2 H, ArH), 7.29 (d, *J* = 8.0 Hz, 2 H), 3.22–3.27 (m, 2 H), 2.94 (superimposed dd, J_1 = 9.0 Hz, 1 H), 2.78 (d, *J* = 9.7 Hz, 1 H), 2.64 (dd, J_1 = 9.7 Hz, J_2 = 5.2 Hz, 1 H), 2.50 (dd, J_1 = 18.3 Hz, J_2 = 10.0 Hz, 1 H), 2.27–2.46 (s merged with a m, 4 H), 1.86–1.89 (m, 1 H), 1.69–1.80 (m, 2 H), 1.34 (s, 3 H), 1.18–1.21 (br m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.9, 144.2, 131.5, 129.9, 128.2, 53.1, 48.7, 48.6, 46.7, 46.0, 45.5, 45.4, 45.2, 41.8, 21.7, 13.5. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}SNO_3$: 332.1320; found: 332.1309.

(18) Data for compound **19**: mp 132–134 °C. IR: 1772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 5.29 (br s, 1 H), 4.06 (m of d, *J* = 14.3 Hz, 1 H), 3.89 (superimposed dd, $J_1 = J_2$ = 8.0 Hz, 1 H), 3.74 (m of d, *J* = 14.3 Hz, 1 H), 2.95 (dd, J_1 = 17.7 Hz, J_2 = 9.1 Hz, 1 H), 2.67–2.74 (m, 2 H), 2.50–2.58 (m, 1 H), 2.44 (s, 3 H, Me), 2.34–2.42 (m, 1 H), 2.00 (ddd, J_1 = 12.3 Hz, J_2 = 6.1 Hz, J_3 = 2.4 Hz, 1 H), 1.22 (s, 3 H), 1.00–1.07 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.8, 143.8, 139.8, 133.4, 129.9, 127.8, 118.7, 63.1, 53.7, 51.4, 46.1, 33.9, 30.8, 23.8, 21.7, 20.3. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{21}SNO_3Na$: 354.1140; found: 354.1143.