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Intramolecular Diels–Alder reaction in 1-oxaspiro[2.5]octa-5,7-dien-4-one and sigmatropic shifts in excited states: novel route to sterpuranes and linear triquinanes: formal total synthesis of (±)-coriolin

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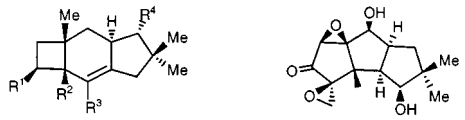
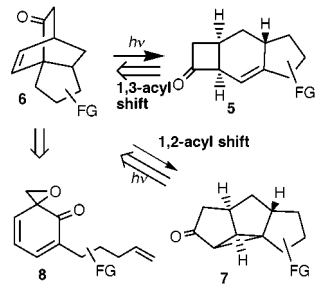
A novel, stereoselective synthesis of sterpuranes and coriolin *via* modulation of the photochemical reactivity of a tricyclic system having a β,γ-enone chromophore, which was assembled *via* intramolecular $\pi^{4s} + \pi^{2s}$ cycloaddition of 1-oxaspiro[2.5]octa-5,7-dien-4-ones, is presented.

The fungal metabolites **1**–**3** and coriolin **4** are natural products of the sterpurane[1] and triquinane[2] families of sesquiterpenes, respectively, which are biogenetically derived from humulene



cyclization cascades.[1f] Coriolin[3] and other triquinanes have witnessed a high level of sustained interest which has led to the development of several new and elegant methods for the construction of tricyclopentanoids.[3–5] However, sterpuranes have elicited only modest interest[6] despite their unique structure, which contains a cyclobutane ring fused to a hydrindane system, and their role in silver leaf disease[1] and phytotoxicity.[6e] There are only a few methods for the synthesis of sterpuranes and most of these generate the carbocyclic framework in an iterative fashion wherein the cyclobutane ring is formed *via* intermolecular $\pi^{2s} + \pi^{2s}$ photocycloaddition.[6b–f] The elegant routes devised by Okamura[6g] and Krause,[6h] although efficiently generating the framework, begin with a precursor containing a cyclobutane ring. In continuation[7] of our efforts to develop new methods for the synthesis of natural products derived from humulene cyclization cascades, we contemplated a novel and general strategy to create the tricyclic sterpurane framework in a single stereoselective sequence which does not rely upon $\pi^{2s} + \pi^{2s}$ photocycloaddition for the formation of the cyclobutane ring. Remarkably, this strategy also provides a new route to linearly fused triquinanes from the same precursor *via* modulation of the chemical reactivity in the excited state.

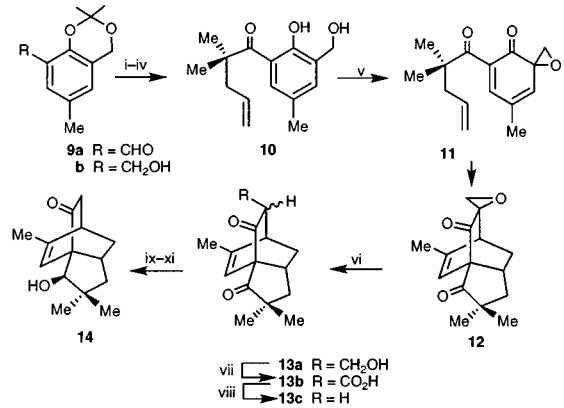
The cornerstone of our strategy is the recognition of the structural and functional relationship between the sterpurane framework and the tricyclic system **6** containing a β,γ-enone chromophore. It was envisaged that a 1,3-acyl shift[8] in **6** upon singlet excitation would readily furnish the sterpurane framework **5** in such a fashion as to create all three rings in the correct relative stereochemical orientation and the double bond at the desired position, in a single step (Scheme 1). It was further thought that the key tricyclic precursor **6** might be synthesized *via* intramolecular $\pi^{4s} + \pi^{2s}$ cycloaddition of 1-oxaspiro-[2.5]octa-5,7-dien-4-ones of type **8** and further manipulation of the resulting adduct. In addition, we also visualized that triplet sensitized 1,2-migration[8,9] of the acyl group in **6** would lead to the tetracyclic system **7** (Scheme 1), which upon cleavage of the



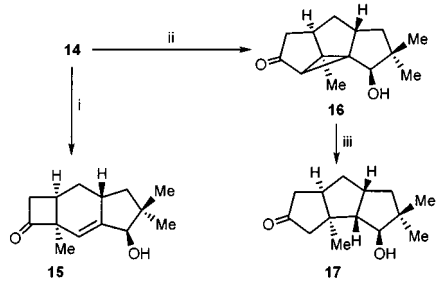
Scheme 1

cyclopropane ring might lead to linearly fused *cis*:*anti*:*cis*-:triquinanes. We report herein our exploratory results leading to a novel and general entry to sterpuranes and a formal total synthesis of coriolin from a common precursor.

Towards our objective, the key precursor **10** was prepared from aldehyde **9a**, which was obtained from alcohol **9b**.[10] Thus, the addition of Grignard reagent prepared from 4-bromobutene to aldehyde **9a** and subsequent oxidation of the resulting alcohol, followed by alkylation and removal of the acetonide protection, readily furnished the desired precursor **10**. Oxidation of **10** with $NaIO_4$ in MeCN–H_2O at 0 °C smoothly furnished the adduct **12** (Scheme 2) in excellent yield (71%). The adduct **12** is formed as a result of *in situ* generation of **11** during the oxidation and subsequent intramolecular Diels–Alder reaction. The structure and stereochemistry of the adduct were deduced from its high field ^{1}H NMR, COSY and NOE spectra. † The orientation of the oxirane ring is suggested on the basis of the general tendency of cyclohexa-2,4-dienones during addition.[7,11] It should be mentioned that there are only a few



Scheme 2 *Reagents and conditions*: i, Mg, 4-bromobutene, THF, 85%; ii, PDC, CH_2Cl_2, 87%; iii, NaH, THF, MeI, 93%; iv, $HClO_4$, MeOH–H_2O, 81%; v, $NaIO_4$ MeCN–H_2O, 71%; vi, Zn, NH_4Cl, MeOH–H_2O, 78%; vii, Jones oxidation, 90%; viii, THF–H_2O, Δ, 71%; ix, ethylene glycol, benzene, TsOH, quant.; x, $NaBH_4$, THF–MeOH–H_2O, 85%; xi, HCl, acetone–water, 86%.



Scheme 3 *Reagents and conditions*: i, *hν*, benzene, 0.5 h, 55%; ii, *hν*, acetone, 1 h, 78%; iii, Bu_3SnH, AIBN, benzene, Δ, 5 h, 70%.

methods[12] for the preparation of bicyclo[2.2.2]octenones of type **12** annulated through bridgeheads.

The reduction of **12** with zinc and NH_4Cl in aqueous MeOH gave the β-keto alcohol **13a** [as a *syn*:*anti* mixture, ^{1}H NMR (300 MHz)] which was oxidized with Jones' reagent, and the resulting β-keto acid **13b** was subjected to decarboxylation to furnish the tricyclic system **13c** in good yield. Protection of the carbonyl group at the ethano bridge as a ketal and subsequent reduction of the resulting keto ketal with $NaBH_4$ in THF–MeOH–H_2O followed by deprotection of the ketal group efficiently gave the desired chromophoric system **14**. The stereochemical orientation of the hydroxy group is suggested from the down field signal of the C*H*OH proton (δ 4.06, br s) which was further confirmed *via* its transformation to the known triquinane **17** (*vide infra*).

Towards the synthesis of sterpuranes, a solution of **14** in dry benzene was irradiated with a mercury vapour lamp (125 W, Applied Photophysics) for about 30 min, upon which a clean reaction occurred (TLC, IR). Removal of the solvent followed by chromatography gave the tricyclic compound **15** in good yield (55%)‡ as a result of 1,3-acyl shift (Scheme 3). The structure of the photo-product **15** was clearly revealed from its spectral data.§

On the other hand, the triplet sensitized irradiation of **14** in acetone (sensitizer as well as solvent) in a Pyrex immersion well under nitrogen furnished the tetracyclic compound **16** in good isolated yield (78%) [83% conversion, unchanged starting material was recovered] whose structure was deduced from spectral data¶ and comparison with the spectral features of its precursor.[13] Cleavage of the peripheral cyclopropane bond with Bu_3SnH–AIBN[14] in refluxing benzene gave triquinane **17** (mp 117–118 °C) (Scheme 3), which has already been elaborated to coriolin.[15] The physical and spectral characteristics of **17** compared well with the reported data.[15] Thus, the formal synthesis of coriolin was complete.

In summary, we have described a novel and stereoselective method for the synthesis of sterpuranes which has wide synthetic potential, and a formal total synthesis of (±)-coriolin employing the intramolecular $\pi^{4s} + \pi^{2s}$ cycloaddition of 1-oxaspiro[2.5]octa-5,7-dien-4-one and sigmatropic shifts in excited states. This method, in turn, also provides a new and efficient avenue to annulated bicyclo[2.2.2]octenones of type **12**–**14** which are not readily accessible otherwise.

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Notes and references

†All the compounds were thoroughly characterised with the help of spectral and analytical data. *Selected data* for adduct **12**: mp 66 °C; ν_{max}(KBr)/cm^{-1} 1755, 1716; δ_H(300 MHz, $CDCl_3$) 5.41 (br s, 1H), 3.16 (part of an AB system, J_{AB} ~7, 1H), 2.84 (part of AB system, J_{AB} ~7, 1H), 2.75 (m, 1H), 2.47–2.38 (complex m, 1H), 2.34 (m, 1H), 2.02 (dd, J_1 ~ 12, J_2 ~ 6.5, 1H), 1.94 (d with str, J ~ 2 , allylic coupling, 3H), 1.50 (superimposed dd, J_1 = J_2 = ~12 , 1H), 1.32 (ddd, J_1 ~ 12, J_2 ~ 7.5 , J_3 ~ 1.7, 1H), 1.14 (s, 3H), 1.09 (s, 3H,); δ_C(75 MHz, $CDCl_3$) 214.72 (CO), 197.55 (CO), 148.03, 118.25, 65.61, 56.87, 51.38, 48.24, 44.84, 42.39, 37.07, 27.81, 25.25, 23.92, 20.16; *m/z* 246 (M^+).

‡ All yields refer to isolated yields. Some unchanged starting material was recovered (~ 65% conversion).

§ *Selected data* for **15**: ν_{max}(film)/cm^{-1}: 3427,1773; δ_H(300 MHz, $CDCl_3$) 5.54 (br s, 1H), 3.99 (br m, 1H), 3.0 (d, of part of an AB system, J_1 18, J_2 9, 1H), 2.77 (d of part of an AB System, J_1 18, J_2 7, 1H), 2.55 (m, 1H), 2.37 (m, 1H), 2.0–1.92 (complex m, 2H), 1.60 (br d, J ~ 6, 1H, O-H), 1.29 (s, 3H, CH_3), 1.20 (dd, J_1 12, J_2 9, 1H, CH_2), 1.07 (dd, J_1 12, J_2 ~ 5, 1H, CH_2), 1.0 (s, 6H); δ_C(50 MHz, $CDCl_3$–CCl_4) 209.9, 150.5, 124.1, 82.5, 64.0, 46.14, 43.4, 41.3, 31.9, 31.5, 28.0, 27.8, 21.5, 21.1; *m/z* 220 (M^+).

¶ *Selected data* for **16**: mp 136–138 °C; ν_{max}(KBr)/cm^{-1} 3395, 1691; δ_H(300 MHz, $CDCl_3$) 3.42 (br d, 1H), 2.70-2.45 (m, 3H), 2.7 (s,1H), 1.95 (dd, J_1 12, J_2 9, 1H), 1.86-1.68 (m, 3H),1.40 (s, 4H, CH_3 and OH), 1.29 (dd, J_1 12, J_2 ~7, 1H), 1.08 (s, 3H), 1.02 (s, 3H); δ_C(75 MHz, $CDCl_3$) 215.25, 79.08, 56.53, 46.81, 46.56, 46.28, 46.23, 46.14, 45.43, 44.06, 42.10, 26.69, 21.98, 14.51; *(m/z* 220(M^+).

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