Sigmatropic 1,3-Acyl Shift in Excited State: a Novel, Stereoselective Route to Protoilludanoids

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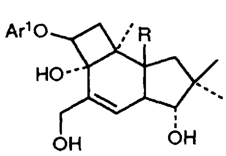
A novel, efficient and general route to protoilludane frameworks *via* photochemical 1,3-acyl shift of *endo*-annulated bicyclo[2.2.2]octenones is described.

There has been an upsurge of interest in the sesquiterpenoids of the protoilludane family.[1–3] This is due to the occurrence and isolation of a variety of fungal metabolites having the protoilludane framework **1**, which exhibit antitumour, antibiotic and antibacterial activity.[1b–g] Moreover, some members of this family such as illudol, protoilludene and their congeners play an important role in biosynthesis of a host of biologically active sesquiterpenoids.[3] The unique carbocyclic structure composed of fused four-, six- and five-membered rings, the unusual functionality and promising biological activity have further enhanced the interest in the synthesis and chemistry of protoilludanes.

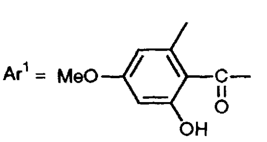
While, there have been no attempts towards synthesis of recently isolated protoilludanoids,[1b–f] surprisingly, only a few routes are available for protoilludene and illudol[1a,2] despite their early discovery.[1g] These routes, like other approaches for polycycle synthesis,[4] create the tricyclic framework after a long multistep, nonstereoselective sequence.[2a–f]

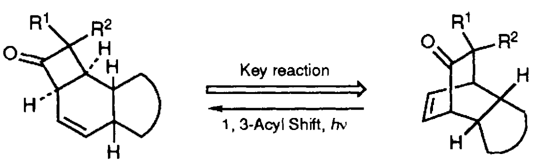
In order to develop a short, efficient and general strategy to protoilludanes, we contemplated that a photochemical 1,3-sigmatropic shift[5,6] of acyl group in an *endo* tricyclic system containing a β,γ-unsaturated carbonyl chromophore, such as **2**, would directly provide the *cis* : *anti* : *cis* protoilludanes **3** in a single stereospecific step. It was further thought that the requisite chromophore should be amenable through $\pi^{4s} + \pi^{2s}$ cycloaddition of appropriate cyclohexa-2,4-dienone and dienophile.

We report here, our exploratory results on sigmatropic

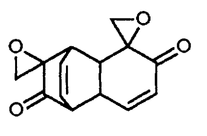


1a; R = H
b; R = OH





3 **2**



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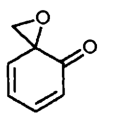

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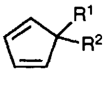
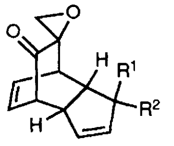
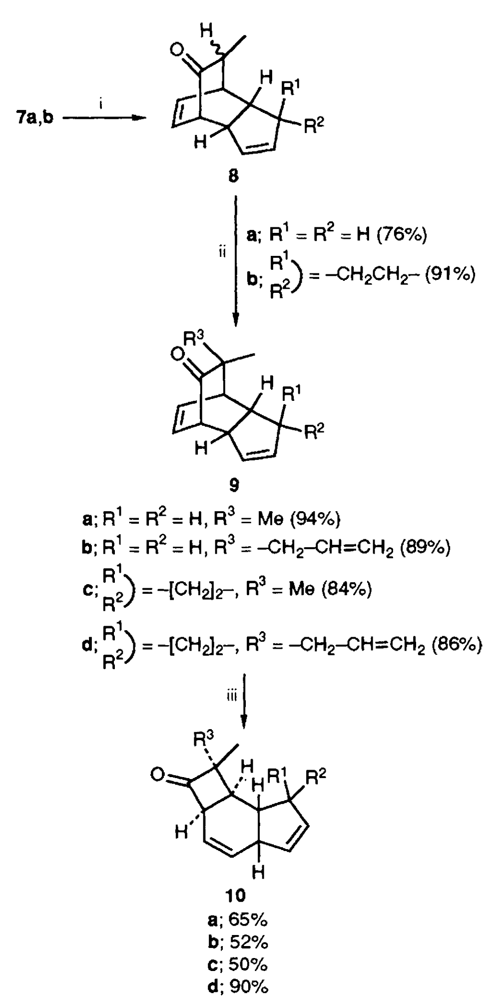


6a–c



7a–c

a; R^1 = R^2 = H
b; R^1,R^2 = –(CH_2)_2–
c; R^1, R^2 = =C(Me)Me



Scheme 1 *Reagents and conditions*: i, Zn, NH_4Cl, dioxane, heat; ii, NaH, tetrahydrofuran, MeI/CH_2=CH–CH_2Br, heat; iii, *hν* benzene (Pyrex), 3 h

1,3-acyl shift of *endo* tricyclo[5.2.2.$0^{2,6}$]undecadienones **9a–d** leading to a novel, efficient and stereoselective route to protoilludanoids **10a–d**, which has a wider synthetic potential. Synthesis of the desired chromophoric systems **9a–d** from epoxy ketones **7a,b**, which are readily assembled *via* inverse demand $\pi^{4s} + \pi^{2s}$ cycloaddition is also described (Scheme 1).

The epoxy ketones **7a–c** were prepared *via in situ* generation of 6-methylenoxycyclohexa-2,4-dienone **5** by oxidation of salicyl alcohol with sodium metaperiodate and subsequent $\pi^{4s} + \pi^{2s}$ cycloaddition with dienes **6a–c**; a method developed in our laboratory. All the cycloadditions gave single *endo* adducts.† It is remarkable that dimethylfulvene **6c** reacted with **5** exclusively as the π^2 component although several symmetry allowed modes such as $\pi^{4s}_{\text{dienone}} + \pi^{6s}_{\text{fulvene}}$, $\pi^{2s}_{\text{dienone}} + \pi^{4s}_{\text{fulvene}}$ are also possible.[7] In this context, it may be noted that although cyclohexa-2,4-dienones have long been known,[8] there are no methods for the preparation of 6-methylenoxycyclohexa-2,4-dienone **5**. Moreover, the attempts to generate **5** from its dimer **4**, following an analogous procedure[9] were also futile.

The adducts **7a,b** were transformed into the chromophoric systems **9a–d**, *via* reductive deoxygenation with zinc followed by alkylation with appropriate electrophiles (Scheme 1). It is interesting to note that alkylation of **8a,b** with allyl bromide occurred stereoselectively to give **9b** and **9d**, respectively. Such stereoselectivity during the alkylation of simple bicyclic ketones has also been observed by Stork *et al.* and Paquette *et al.*[10]

Towards the photochemical 1,3-acyl shift, a benzene solution of the ketone **9a** was irradiated (200 W mercury-vapour lamp, Hanovia) in a quartz immersion well. However, it gave a very complex mixture of products, containing only small amounts of the desired cyclobutanone (IR spectroscopy). We, therefore, irradiated a solution of **9a** in benzene in a Pyrex immersion well upon which a clean reaction occurred (thin layer chromatography, IR). Careful chromatography of the photolysate over silica gel furnished the desired 1,3-acyl shift product **10a** in good yield (65%) followed by unconverted starting material. The structure of **10a** was clearly revealed from its spectral and analytical data. It showed a strong absorption band at 1785 cm^{-1} in its IR spectrum, characteristic of a cyclobutanone carbonyl. The ^1H NMR spectrum of **10a** displayed resonances for four olefinic protons at δ 5.6 (complex m) and at δ 3.7 (m of dd, J_1 8.5, J_2 4.8 and J_3 2 Hz, 1H, H_1), 3.15 (m of d, *J* 8.5 Hz, 1H, H_4) for protons at the cyclobutanone ring junction. The ^{13}C NMR spectrum also showed signals at δ 214.77 and 133.26, 129.42, 128.38, 119.14 for cyclobutanone carbonyl and olefinic carbons, respectively.‡ Similarly, the irradiation of other chromophoric systems **9b–d** in benzene also gave the corresponding protoilludanoids **10b–d**, respectively (Scheme 1).

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† All compounds gave satisfactory spectral and analytical data.

‡ *Selected data* for **10a**: IR ν_{max} 1785 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 5.6 (complex m, 4H, olefinic H), 3.7 (m of dd, J_1 8.5, J_2 4.8, J_3 2 Hz, 1H), 3.15 (m of d, *J* 8.5 Hz, 1H), 2.65 (d of superimposed dd, $J_1 = J_2 = J_3 = 8$ Hz, 1H), 2.50 (m of dd, J_1 16, J_2 8.5 Hz, 1H, CH_2), 2.44 (d with structure, *J* 8.5 Hz, 1H), 2.15 (m of dd, J_1 16, J_2 8.5 Hz, 1H, CH_2), ^{13}C NMR (75 MHz, $CDCl_3$): δ, 214.77 (CO), 133.26, 129.42, 128.38, 119.14, (olefinic carbons), 60.61, 53.74, 42.23, 38.98, 37.39, 33.04, 24.47, 18.78. Mass (*m/z*): 188 (M^+).

The 1,3-acyl shift of tricycloundecadienones has not been explored nor its synthetic potential fully appreciated. Most of the earlier studies on 1,3-acyl shift in simple bicyclic enones were conducted in conjunction with oxa-di-π-methane rearrangement, in order to elucidate the mechanism and resolve singlet triplet dichotomy.[5,6]

In summary, the synthetic potential of photochemical 1,3-acyl shift in annulated bicyclo[2.2.2]octenones has been demonstrated. A new, general and stereoselective route to protoilludanoids has been developed. The strategy is flexible and easily adaptable for the synthesis of natural protoilludanes and their analogues.

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