A Stereospecific Approach to Advanced Precursors of the Dictyol Diterpenes using the Alicyclic Claisen Rearrangement

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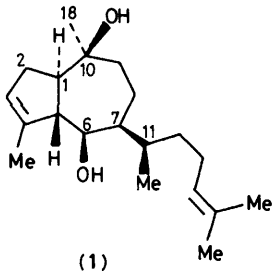
The perhydroazulenes (**9a**) and (**9b**), potential precursors of the Dictyol diterpenes, have been obtained by stereospecific alicyclic Claisen rearrangements of silyl enolates derived from the lactones (**8a**) and (**8b**).

The Dictyols are a small group of diterpenes which have been isolated from various marine algae; some members of the group display significant antimicrobial activities.[1] Their overall structure, exemplified by Dictyol C (**1**), is based on a hydroazulene ring system and variations include a C-10–C-18 *exo*-methylene group in place of the C-10 tertiary alcohol function, an ether bridge between C-6 and C-10, further hydroxy groups at C-2, C-9, and C-11 together with modifications of the isoprenyl side chain. The central hydroazulene unit in the Dictyols is closely related to that found in the more numerous sesquiterpene lactones, such as Cumambrin B (**2**) and Ambrosin (**3**), belonging to the Guaianolide and Pseudo-



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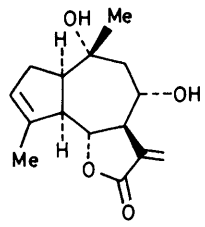

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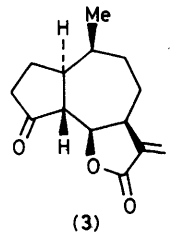

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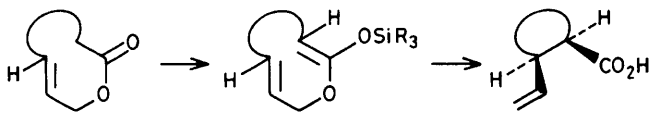
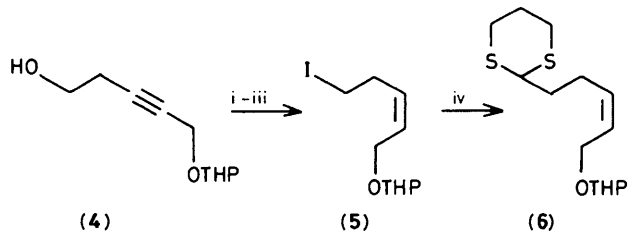


Scheme 1

guaianolide families respectively.[2] Two major problems are apparent in synthetic approaches to these three classes of compounds. Firstly, appropriate functionality must be present at C-4 and C-10 in any general precursor to allow independent manipulation of these two centres. Secondly, the relative stereochemistries of the various chiral centres must be controlled. A particular difficulty in this respect is control of the relative stereochemistries at C-1 and C-7. A number of groups[3] have recently reported that the enolate–Claisen rearrangement, originally developed by Ireland *et al.*,[4] can be applied to unsaturated lactones and results in stereospecific routes to substituted carbocycles (Scheme 1). Molecular models indicated to us that such a reaction, which has been referred to as an alicyclic Claisen rearrangement,[3] when applied to an appropriate lactone, could provide hydroazulenes suitable for use in syntheses of the Dictyol diterpenes. Herein, we report the successful outcome of our preliminary studies in this area.

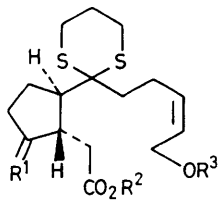
Our starting material was the readily available mono-protected pent-2-yn-1,5-diol (**4**)[5] which was converted into the 1,3-dithiane (**6**), *via* the iodide (**5**), in 51% overall yield, as outlined in Scheme 2. Conjugate addition of the carbanion derived from (**6**) [Bu^{n}Li, tetrahydrofuran (THF), −30 °C, 1 h] to cyclopent-2-enone at −78 °C in the presence of hexamethylphosphoramide (HMPA)[6] or 1,3-dimethylpyrimidin-2-one (DMPU),[7] followed by *in situ* trapping of the resulting cyclopentanone enolate with ethyl bromoacetate, afforded the *trans*-cyclopentanone (**7a**)† in 65% yield. The ketone group in (**7a**) was protected as the dioxolane derivative using standard conditions [$(CH_2OH)_2$, toluene-*p*-sulphonic acid (*p*-TSA), C_6H_6, reflux], which resulted in simultaneous removal of the tetrahydropyranyl (THP) group, to provide the alcohol (**7b**)† in 87% yield. Using ^{13}C n.m.r. spectroscopy, we were unable to detect more than traces of the *cis*-2,3-disubstituted cyclopentanone isomer of (**7b**), but the spectrum did reveal the presence of *ca.* 10% of the corresponding *trans*-allylic alcohol.

† Satisfactory spectroscopic and analytical data have been obtained for all new compounds reported herein.

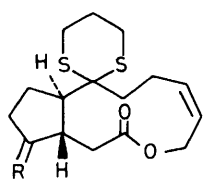


(4) (5) (6)

Scheme 2. *Reagents:* i, Lindlar catalyst, H_2, MeOH; ii, *p*-$MeC_6H_4SO_2Cl$, pyridine; iii, NaI, Me_2CO; iv, 2-lithio-1,3-dithiane, THF.



(7) **a**; R^1 = O, R^2 = Et, R^3 = THP
b; R^1 = $-O[CH_2]_2O-$, R^2 = Et, R^3 = H
c; R^1 = $-O[CH_2]_2O-$, R^2 = R^3 = H
d; R^1 = O, R^2 = R^3 = H
e; R^1 = O, R^2 = Et, R^3 = H
f; R^1 = $NNMe_2$, R^2 = Et, R^3 = H
g; R^1 = $NNMe_2$, R^2 = R^3 = H



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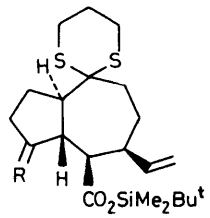


(9)

a; R = $NNMe_2$
b; R = $-O[CH_2]_2O-$

Although the ester group in (**7b**) could be readily saponified (KOH, EtOH, H_2O), all attempts to liberate the free hydroxy-acid (**7c**), an obvious precursor of the key lactone (**8b**), even under the most carefully controlled conditions, resulted in complete loss of the dioxolane protecting group to give only the unprotected hydroxy-acid (**7d**). Presumably, this is because of the close proximity of the carboxylic acid and dioxolane functions in (**7c**). Efforts to re-protect the ketone group in (**7d**) were not successful. In an attempt to circumvent this problem, the initial conjugate addition product (**7a**) was deprotected (*p*-TSA, MeOH) and the resulting hydroxy-ester (**7e**), which was isolated in 88% yield, treated with 1,1-dimethylhydrazine (neat, reflux, 24 h) to provide the hydrazone (**7f**) in 68% yield. Unfortunately, the ester group in (**7f**) proved resistant to hydrolysis and a satisfactory yield of the required hydroxy-acid (**7g**) was not realised. However, we were pleased to discover that the hydroxy-ester (**7f**) could be directly lactonised by formation of the corresponding lithium alkoxide (Bu^{n}Li, −40 °C), followed by reflux in 0.4% HMPA–THF [*ca.* 1 ml per mg of (**7f**)] for 20 h. In this way, the required lactone (**8a**) was isolated in 45% yield, as an oil, after column chromatography. Under identical conditions, lactonisation of the dioxolane derivative (**7b**) gave (**8b**), m.p. 146—147 °C, in 52% isolated yield.

The crucial Claisen rearrangements were effected by sequential treatment of (**8a**) or (**8b**) with lithium di-

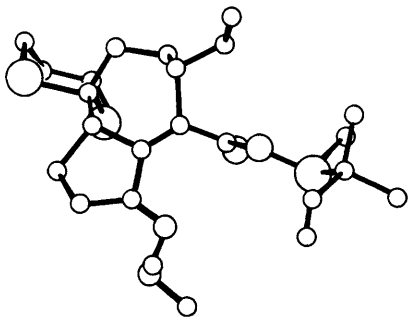
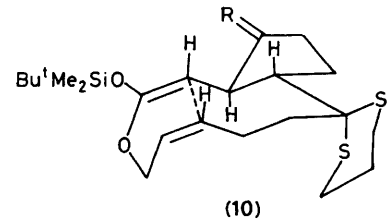


Figure 1. Molecular structure of compound (**9a**).

isopropylamide and t-butyldimethylchlorosilane[3] to give the corresponding silyl enolates, which were refluxed in toluene for 0.75 h. Subsequent purification by column chromatography afforded the hydroazulenes (**9a**), m.p. 148—149 °C, and (**9b**), m.p. 146 °C, in yields of 35 and 64% respectively. Spectral data, especially ^1H and ^{13}C n.m.r., clearly showed that each compound was stereochemically homogeneous and, furthermore, no other isomers were found in the reaction mixture. Although predictions based on molecular models (see below) strongly suggested that the major or exclusive products from these rearrangements would be (**9a**) and (**9b**), the spectral data did not allow completely unambiguous structural assignments to be made, and we have therefore confirmed the proposed structures by *X*-ray crystallography.

Crystals of the hydrazone (**9a**) separated from ether–n-hexane. *Crystal data:* $C_{24}H_{42}N_2O_2S_2Si$, M = 482.81, monoclinic, space group $P2_1/c$, a = 17.336(2), b = 10.987(1), c = 16.497(2) Å, β = 115.65(1)°, U = 2832.69 Å^3, Z = 4, D_c = 1.13 g cm^{-3}. Intensity data were collected with Cu-K_α radiation on an Enraf–Nonius CAD4 diffractometer and 2684 independent reflections [with $I > 3\sigma(I)$] were considered observed. The structure was solved by direct methods using the Multan program and refined to a final R value of 5.58%.‡ The molecular structure is shown in Figure 1. Comparisons of the spectral data exhibited by (**9a**) and (**9b**) clearly showed



(10)

that the latter also possessed the same relative stereochemistry, as shown.

Previous studies[3] have shown that alicyclic Claisen rearrangements proceed *via* a boat-like transition state, rather than the more usual chair form, owing to the constraints imposed by the remainder of the lactone ring. Therefore, it seems most likely that the rearrangements of the silyl enolates derived from (**8a**) and (**8b**) involved transition states (**10**), in which the cyclopentanone residue assumes a favourable pseudo-equatorial position, leading only to the hydroazulenes (**9a**) and (**9b**), which possess the correct relative stereochemistry for further elaboration to the Dictyols. Work in this direction is in progress.

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‡ The atomic co-ordinates for the structure of (**9a**) are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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