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SYNTHESIS OF MARINE TERPENOIDS III
SYNTHESIS OF (±)-ISOCAESPITOL [1]

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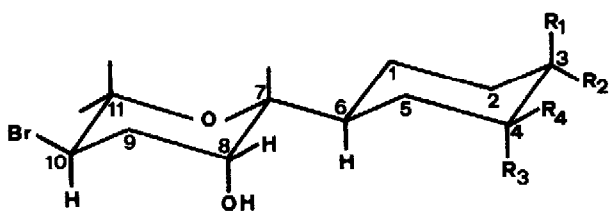
Isocaespitol (1) and caespitol (3) are two polyhalogenated sesquiterpenes isolated from the marine seaweed Laurencia caespitosa (Lamx). Chemical degradation[2] and X-ray crystallographic [3] studies have led to the assignment of structure 1 to isocaespitol. We here describe the first total synthesis of (±)-isocaespitol.

The object of this synthesis was (±)-didehalocaespitol 19, as being easily convertible into (±)-isocaespitol. In the event, treatment of 19, readily available by degradation of isocaespitol [2], with bromine chloride [4] at -78° gave 1:3 mixture of isocaespitol (1) and its isomer 2, which were separated by fractional crystallization from hexane [5].



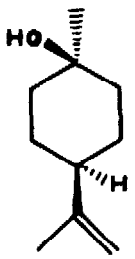
1 R_1=Br R_2=CH_3 R_3=Cl R_4=H
2 R_1=Cl R_2=CH_3 R_3=Br R_4=H
3 R_1=CH_3 R_2=Cl R_3=H R_4=Br

trans-β-Terpineol (4), prepared from (+)-limonene by lithium aluminium hydride reduction of the limonene 1,2-oxides [6], was subjected to ozonolysis in ethyl acetate at -70° giving the ketone 5 in 65% yield. The ketoalcohol 5 was converted into the methyl ester 6 in 78% yield by reaction with trimethyl phosphonoacetate in dimethylformamide-sodium hydride [7](-20° for 30 min and 60° for 12 hr). NMR analysis [8] showed the methyl ester 6 to be a 1:1 mixture of cis and trans isomers (vinyl methyl signals at 1.83 and 2.11 respectively). After lithium aluminium hydride reduction, the cis-alcohol 7 was purified by chromatographic means [9], mp 60-62°, NMR, 1.22 and 1.39 (s, 3H each), 3.55 (1H, m), 4.15 (2H, d, J = 8Hz) and 5.40 (1H, t, J = 8Hz). Acetylation of 7 with acetic anhydride pyridine gave the monoacetate 9, which was further acetylated to 10 by treatment with acetic anhydride-trimethylamine and a catalytic amount of N,N-dimethyl-4-pyridinamine [10] for 12 hr at 25° (94% yield). Hydrolysis of the

diacetate 10 with potassium carbonate in methanol gave the acetoxyalcohol 11. The conversion to the bromide 12 was accomplished using a slight equivalent excess of phosphorous tribromide in hexane at 0°; the bromide 12 was then used to alkylate ethyl acetoacetate, after generation of its anion with sodium methoxide in methanol. The resulting ketoester 13 (81% yield from 10) was brominated by a modification of the Kosower [11] method (cupric and lithium bromide-sodium hydride in dimethylformamide) to give the bromo ketoester 14 in 92% yield. This last substance, on treatment at 0° for 30 min with barium hydroxide in ethanol, underwent deacylation to give the bromoester 15 (87% yield).

Conversion of bromoester 15 to the bromohydrin 16 was accomplished in 54% yield (63% based on recovered starting material) by treatment with 1.2 equiv of methylmagnesium bromide in ether at -20°. Chromatographic separation gave pure 16, mp 51-53°, NMR, 1.36, 1.38, 1.48, 1.67 and 2.03 (s, 3H each), 3.99 (1H, dd, J = 11 and 4Hz) and 5.20 (1H, t, J = 8Hz). Epoxidation of 16 with 1 equiv of m-chloro-perbenzoic acid in methylene chloride at 0° containing sodium bicarbonate as an acid acceptor gave, in 94% yield, a mixture of 17 and 18 with the desired isomer 17 predominating by 8:1 as determined by NMR signals due to oxirane methyl at 1.27 and 1.30 respectively. Attempted epoxidation under usual conditions (benzoyl peroxide-methylene chloride) led to rapid attack on the epoxide ring by the tert hydroxyl group, giving a product containing a tetrahydrofuran ring [12]. Separation of this mixture of epoxides was achieved by column chromatography followed by crystallization to give pure 17, mp 78-81°, NMR, 1.27 (s, 3H), 1.38 (s, 6H), 1.48 and 2.03 (s, 3H each), 3.02 (1H, dd, J = 8 and 6Hz) and 4.18 (1H, dd, J = 10 and 6Hz). The NMR spectra of the compounds 16 and 17 clearly indicate that the bulk of the substituents hold the molecules in a rigid conformation, thus the stereoselectivity of the epoxidation process is predicted by assuming attack of the reagent on the less hindered face of the double bond [13].

The stereoselective generation of the caespitol and/or isocaespitol skeleton is produced by acid opening of the epoxide ring in 17 [12]. Thus, treatment of 17 with acid-washed alumina in refluxing hexane for 3 hr gave a mixture with the racemates of (±)-didehalocaespitol 19 and its diastereomer 20 in 63% yield. (±)-Didehalocaespitol 19 was successfully isolated as the less soluble component by fractional crystallization from hexane, mp 115-116°, identical with natural 19 by TLC, IR, NMR and mass spectral comparison [14]. This was converted to (±)-isocaespitol (identical with natural material by TLC, NMR and infrared comparison) as described above.



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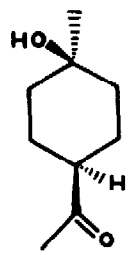

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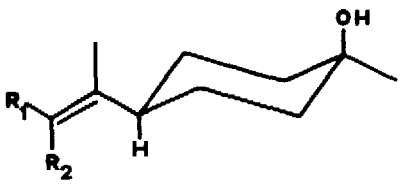
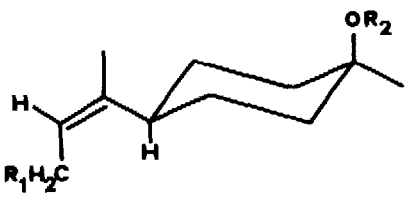
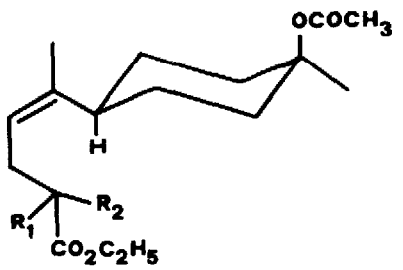


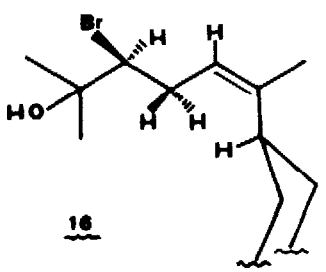
6a $R_1 = H$ $R_2 = CO_2CH_3$
6b $R_1 = CO_2CH_3$ $R_2 = H$
7 $R_1 = H$ $R_2 = CH_2OH$
8 $R_1 = CH_2OH$ $R_2 = H$



9 $R_1 = OCOCH_3$ $R_2 = H$
10 $R_1 = OCOCH_3$ $R_2 = COCH_3$
11 $R_1 = OH$ $R_2 = COCH_3$
12 $R_1 = Br$ $R_2 = COCH_3$



13 $R_1 = H$ $R_2 = COCH_3$
14 $R_1 = Br$ $R_2 = COCH_3$
15 $R_1 = Br$ $R_2 = H$



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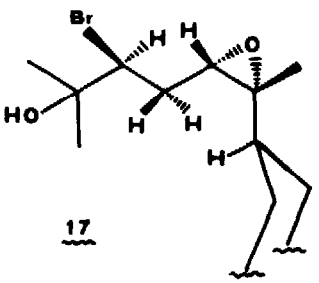

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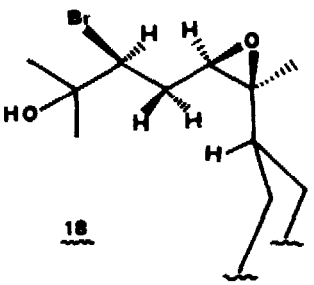

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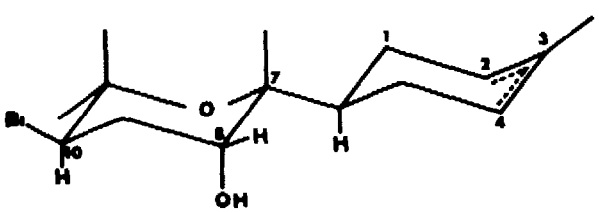

19 Δ^3
20 Δ^2

REFERENCES AND NOTES

1 For paper II in this series see: A G González, J D Martín, C Pérez and M A Ramírez Tetrahedron Letters 137 (1976)

2 A G González, J Darias, J D Martín and C Pérez Tetrahedron Letters 1249 (1974)

3 A G González, J Darias, J D Martín, C Pérez, J J Sims, G H Y Lin and R M Wing Tetrahedron 31 2449 (1975)

4 H J Hageman and E Havinga Rec Trav Chim 85 1141 (1966)

5 Compound 2 (acetate), mp 123-124°, NMR 1.21, 1.34, 1.41, 1.74 and 2.16 (s, 3H each), 4.17 (1H, dd, J = 12 and 4Hz), 4.45 (1H, W1/2 = 5Hz) and 4.70 (1H, t, J = 3Hz)

6 E E Royals and J C Leffingwell J Org Chem 31 1937 (1966); H Kuczynski and K Piatkowski Roczniki Chem 33 299 311 (1959) GV Pigulevski J Gen Chem USSR 28 1471 (1958)

7 W S Wadsworth and W S Emmons J Amer Chem Soc 83 1733 (1961)

8 NMR were measured at 90 MHz in $CDCl_3$. Shifts are expressed as δ-value.

9 trans-Alcohol 8, oil, NMR 1.21 and 1.71 (s, 3H each), 3.55 (1H, m), 4.16 (2H, d, J = 8Hz) and 5.45 (1H, t, J = 8 Hz)

10 W Steglich and G Höfle Angew Chem internat Ed 8 981 (1969)

11 E M Kosower, W J Cole, G-S Wu, D E Cardy and G Meisters J Org Chem 28 630 (1963)

12 Related cyclizations have been observed with cyclic and acyclic epoxy alcohols: J A Marshall and M T Pike J Org Chem 33 435 (1968); M Mousseron-Canet, C Levallois and H Huerre Bull Soc Chim France 658 (1966); H B Henbest and B Nicholls J Chem Soc 221 (1959)

13 The epoxidation of the bromohydrin, obtained by a similar method from the trans-alcohol 8, is not stereoselective and an equimolecular mixture of two isomers containing tetrahydrofuran rings is produced.

14 The other pure racemate 20 was undoubtedly produced although we did not isolate it.