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TOTAL SYNTHESIS OF 5-EPIKESSANE AND DEHYDROKESSANE

Hsing-Jang Liu* and Sing Ping Lee
Department of Chemistry, University of Alberta
Edmonton, Alberta, Canada T6G 2G2

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Sesqui- and diterpenoids based on hydroazulene skeleton are widely distributed in nature and many possess fragrant or medicinal properties[1]. The mounting interest in synthesizing these rather complex molecules has led to considerable effort in recent years in the search for new efficient methods for the construction of functionalized hydroazulenes[2]. We wish to report a highly stereoselective total synthesis of the titled compounds, 1 and 2[3], which demonstrates a new approach to hydroazulenes. This route should also be applicable to other sesquiterpenoids of the guaiazulene family[1].

Irradiation (450 W Hanovia high-pressure mercury-vapor lamp and Pyrex filter) of a benzene solution of 4-acetoxy-2-cyclopentenone[4] and 1-acetoxy-2-carbomethoxycyclopentene[5] at room temperature followed by brief treatment of the crude photoadducts with p-toluenesulfonic acid in benzene gave, in a total yield of 80%, enone 3 (~60%) and a mixture of two diastereomers (syn and anti) 4. The incorporation of a methyl group into 3 was effected by methylmagnesium bromide-copper(I) iodide complex[6] at 0° in ether and keto ester 5 was obtained as the only stereoisomer in 56% yield. The same transformation could also be achieved using lithium dimethylcuprate[6] but the yields were less reproducible. The stereochemistry of 5 at the newly introduced chiral center could be readily assigned on the basis of the known preferential attack of the reagents from the sterically less hindered face of the molecule[6,7]. Furthermore, sodium borohydride reduction of 5 induced concomitant cyclization to give lactone 6. This finding requires the stereochemistry of 5 at the ring junctures as shown[8] and that of its precursor 3 follows.

Thioketalization of 5 with 1,2-ethanedithiol and boron trifluoride etherate followed by desulfurization using W-2 Raney nickel resulted in the removal of the ketone carbonyl to give ester 7 in 62% yield. The ester groups of 7 were subsequently reduced with Lithium Aluminum hydride and the resulting alcohol 8

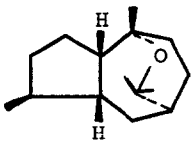
(95% yield) was treated with p-toluenesulfonyl chloride in pyridine at room temperature for 18 hr. Under these reaction conditions, 8 underwent fragmentation smoothly to give an 83% yield of ketone 9: ir (CCl_4) 3090, 1710, 1645 and 900 cm^{-1}; nmr (CCl_4) δ 0.96 (d, J = 6.5 Hz, 3H), 4.76 (d, J = 1 Hz, 1H) and 4.80 (d, J = 1 Hz, 1H); ms M^+ 178.1360 (calcd. for $C_{12}H_{18}O$: 178.1360). That the chiral center adjacent to the ketone remained intact during the transformation was evident from the fact that, when 8a was subjected to the fragmentation, complete loss of deuterium was observed.

The introduction of an isopropyl unit required to complete the kessane carbon skeleton (and that of guaiazulenic sesquitepenoids in general) was achieved by the following two steps. Carbomethoxylation of 9 with sodium hydride and dimethyl carbonate in 1,2-dimethoxyethane afforded keto ester 10 existing partially in the chelated enol form. When the enolate ion of 10 generated by sodium hydride was reacted with methyllithium[9], a 57% yield of ketol 11[10] was obtained.

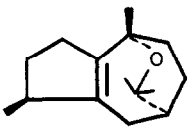
Treatment of 11 with mercuric acetate in tetrahydrofuran effected the ether ring formation and the resulting organomercury compound without isolation was reduced with sodium borohydride[11] to ether 12[10,12] (61% yield). Direct removal of the ketone carbonyl by either Wolff-Kishner reduction or Clemmensen reduction using various conditions proved unsuccessful nor could its conversion to thioketal be effectively achieved. The difficulties encountered were apparently due to steric congestion of the carbonyl as well as the observed instability of the ether linkage towards strongly acidic conditions. Alternatively, 12 was reduced wtih lithium aluminum hydride to alcohol 13 in quantitative yield. Its stereochemistry could be readily assigned on the basis of the following spectral data. The nmr spectrum taken in deuteriochloroform showed signals at δ 0.99 (d, C-15 methyl), 1.51 (s, C-12 methyl), 1.92 (m, C-5 H) and 2.31 (m, C-4 H). When the nmr spectrum was taken in pyridine-d_5, the C-12 methyl singlet and the C-4 methine multiplet shifted downfield to δ 1.92 and 2.80 respectively whereas the other two signals remained virtually unchanged (<0.08 ppm shift). These findings require that the ether bridge and the C-4 hydrogen atom be in close proximity to the hydroxyl group and that the C-15 methyl and the C-5 proton be distant from it[13] and thus the stereochemistry of 13 as depicted.

Subsequent treatment of 13 with phosphorus oxychloride-pyridine at 0° induced its dehydration with simultaneous migration of the double bond to give a 73% yield of dehydrokessane (2)[14]: ir (CCl_4) 1100 cm^{-1}; nmr (CCl_4) δ 0.91 (s, 3H), 1.03 (d, J = 6.5 Hz, 3H) and 1.25 (s, 6H); ms m/e (M-15) 205.1592 (calcd. for $C_{14}H_{21}O$: 205.1590). Conversion of 13 to the corresponding phosphorodiamidate derivative 14 using N,N-dimethylphosphoramidic dichloride and dimethylamine[15] followed by lithium-ethylamine reduction[16] of 14 afforded, in 71% yield, 5-epikessane (1): ir (CCl_4) 1100 cm^{-1}; nmr ($CDCl_3$) δ 0.95 (d, 3H, J = 6.5 Hz),

1.10 (s, 3H), 1.22 (s, 3H) and 1.26 (s, 3H); ms M^+ 222.1983 (calcd. for $C_{15}H_{26}O$: 222.1983).



1



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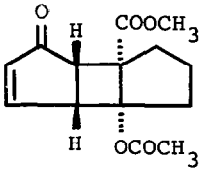

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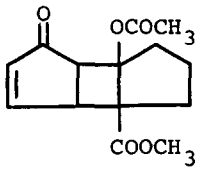

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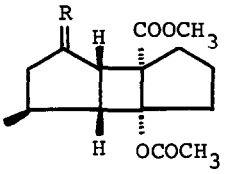
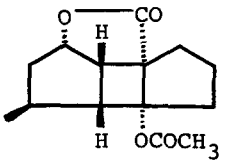
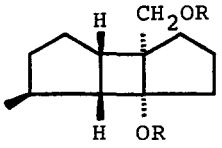


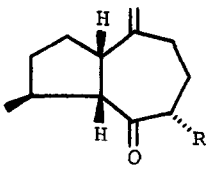
5 R = O
7 R = H_2



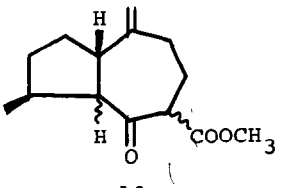
6



8 R = H
8a R = D



9 R = H
11 R = $(CH_3)_2COH$



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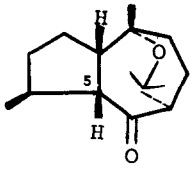
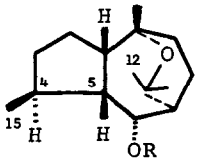


12



13 R = H
14 R = $PO[N(CH_3)_2]_2$

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References and Notes

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2. For a recent review see J. A. Marshall, Synthesis, 517 (1972).

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4. C. H. Depuy, M. Isaks, K. L. Eilers, and G. F. Morris, J. Org. Chem., 29, 3503 (1964).

5. Prepared in 85% yield by acetylation of 2-carbomethoxycyclopentanone with acetyl chloride and pyridine.

6. H. O. House, W. L. Respess and G. M. Whitesides, J. Org. Chem., 37, 3128 (1966).

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8. Other arrangements are sterically forbidden.

9. R. M. Coates and J. S. Shaw, Chem. Commun., 515 (1968); S. N. Huckin and L. Weiler, Can. J. Chem., 52, 1379 (1974).

10. Its stereochemistry follows from that of 13. Additional spectral evidences will be detailed elsewhere.

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12. It should be noted that epimerization of 12 at C-5 followed by removal of the ketone carbonyl should lead to kessane. So far we have been unable to accomplish the epimerization in spite of numerous attempts using both kinetically and thermodynamically controlled conditions.

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14. The same transformation was also effected by thionyl chloride. The Δ^5-isomer of 2 could be isolated along with 2 when the reaction was carried out at 0° using methanesulfonyl chloride-pyridine. The purification of the formal compound by column chromatography was attempted without success due to its rapid isomerization to 2.

15. H. J. Liu, S. P. Lee and W. H. Chan, submitted for publication.

16. R. E. Ireland, D. C. Muchmore, and U. Hengartner, J. Amer. Chem. Soc., 94, 5098 (1972).