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TOTAL SYNTHESIS OF (±)-ANNONENE, A *TRANS*-CLERODANE DITERPENE

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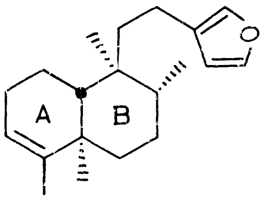
Total synthesis of (±)-annonene, 1-[2-(3-furanyl)ethyl]-1,2,3,4,4a,7,8,*cis*-8a-octahydro-1,*trans*-2,*trans*-4a,5-tetramethylnaphthalene, which is a *trans*-clerodane diterpene, is described.

The clerodane diterpenoids have the basic skeletons derived from labdane through a backbone rearrangement with successive hydride and methyl shifts, and have been interested from the aspect of biological activity.[1] Clerodanes can be classified, depending on the junction mode of their skeletons, into *trans* and *cis* groups, as exemplified by annonene (1)[2] and the compound (2),[3] respectively. The typical clerodanes have four asymmetric centers assembling in their B rings, as in 1, and the introduction of these asymmetric centers has been the problem in the syntheses of clerodanes. Recently the synthetic study of kolavelool (3) has been reported by ApSimon et al.[4] However, there has so far been no report on the total synthesis of clerodanes. Here we wish to describe the first total synthesis of a *trans*-clerodane, annonene (1), which was isolated from *Annona coriacea*.[2]



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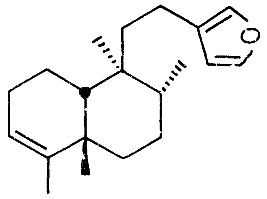

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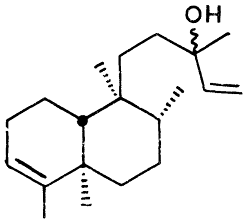

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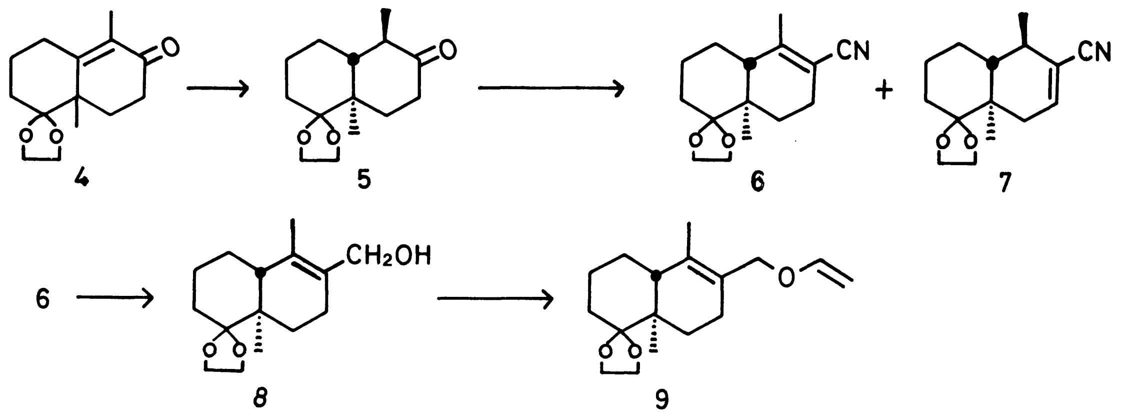
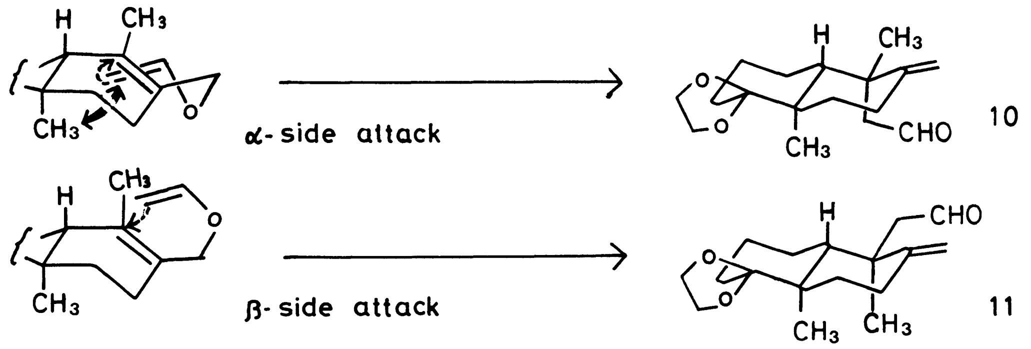
As the starting material, we chose the *trans*-decalone (5), which was easily obtainable by the Birch reduction of the Wieland-Miescher ketone (4).[5] The *trans* ring junction of 5 has been strictly established.[6] The ketone (5) was treated with potassium cyanide and acetic acid, and the resulting cyanohydrin was dehydrated with thionyl chloride in pyridine, giving the nitriles, (6) and (7) (1:1 ratio), in 84% yield from 5. These isomers were separated by chromatography (silica gel; benzene as an eluting solvent): 6; bp 115-119° (0.35 mm); ν(CHCl$_3$) 2220 (CN) cm^{-1}; δ(CDCl$_3$) 0.95 (3H,s), 1.97 (3H,s). 7; bp 125-133°(0.8 mm); mp 53-54°; δ(CDCl$_3$) 1.00 (3H,s), 1.22 (3H,d,J=6.0 Hz), 6.58 (1H,m). The nitrile (6) was converted into the allyl alcohol (8); mp 68°, in 60% yield by reduction of 6 with diisobutylaluminumhydride

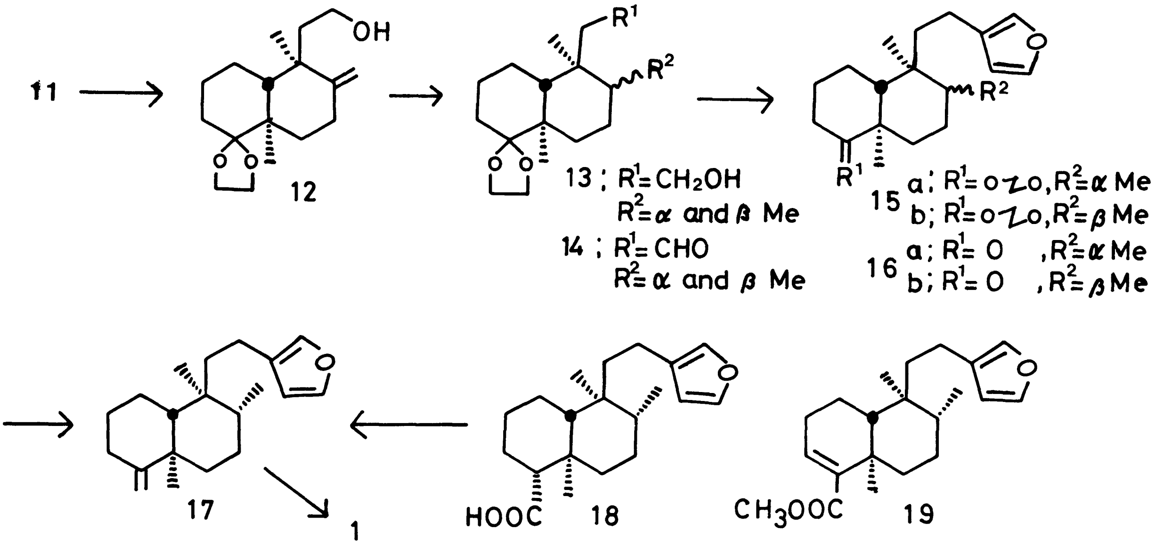


and subsequent treatment of the resulting aldehyde with sodium borohydride. The alcohol (8) was vinylated with ethyl vinyl ether and mercuric acetate to afford the vinyl ether (9) in 73% yield, and the vinyl ether was subjected to the Claisen rearrangement. In the rearrangement,[7] the tetrasubstituted olefin can be attacked by the vinyl group from two possible sides as shown in the scheme. The β-side attack seemed to be preferable because of the absence of a steric repulsion which was present between the angular methyl and the vinyl terminal in the case of the α-side attack. This preference of the β-side attack may result in the predominant formation of 11, which can serve as a key intermediate for the synthesis of annonene (1).



The vinyl ether was heated at 200° in decalin for 6 h, and a mixture of two aldehydes was obtained in 95% yield. The nmr spectrum of the product showed two aldehyde signals at δ 9.75 and 9.60, intensities of which were in the 85:15 ratio. These isomers were separated by chromatography on silica gel, and the major aldehyde was isolated in 70% yield from 9. This aldehyde was assigned to the structure 11; oil; δ($CDCl_3$) 1.10 (3H,s,Me), 1.20 (3H,s,Me), 2.52 (2H,d,J=3 Hz, CH_2-CHO), 4.74 (1H,bs,=CH), 4.90 (1H,bs,=CH), 9.75 (1H,t,J=3 Hz), from a consideration of the following facts. Owing to the sterically crowded α-axial orientation, the formyl methyl group (-CH_2-CHO) of the minor aldehyde (10) exhibited an ABX pattern in its nmr spectrum, while that of the major aldehyde (11) showed A_2X pattern because of relatively free rotation. Furthermore, in the nmr spectrum of 11, irradiation at δ2.52 (CH_2-CHO) resulted in a 6-8% increase of the intensity of the signal at δ 4.75 (=CH). This NOE effect was quite consistent with the equatorial orientation of the side chain of 11.

The aldehyde (11) was reduced with sodium borohydride, and the alcohol (12) was hydrogenated on palladium-charcoal in ethanol to produce 13 in 84% yield. The nmr study using tris(heptafluorobutanoylpivaloylmethanato)europium as a shift reagent revealed that 13 was composed of 1:1 epimers at C-8. This mixture was oxidized with pyridinium chlorochromate to the dihydroaldehyde 14, which on treatment with (1) 3-furyl lithium, followed by (2) acetylation and (3) reductive removal of the acetoxyl group with calcium-liquid ammonia gave rise to 15a and 15b (72% from 13), which were separated by chromatography on silica gel: 15a; δ $(CDCl_3)$ 0.72 (3H,s,Me), 0.80 (3H,d,J=6.0 Hz,CH-Me), 1.06 (3H,s,Me), 3.88 (4H,bs,OCH_2CH_2O), 6.20 (1H,bs,βH of furan), 7.15 (1H,bs, αH of furan), 7.27 (1H,t,J=1.5 Hz, αH of furan), 15b; δ $(CDCl_3)$ 0.95 (3H,s), 1.00 (3H,d,J=5.5 Hz), 1.10 (3H,s), 3.90 (4H,bs), 6.20 (1H,bs), 7.15 (1H,bs), 7.27 (1H,t,J=1.5 Hz). Each isomer was deacetalized by



acid in quantitative yield. Of the resulting two isomers, 16a; mp 58°; δ$(CDCl_3)$ 0.82 (3H,s), 0.83 (3H,d,J=6.0 Hz), 1.15 (3H,s), and 16b; mp 124°; δ$(CDCl_3)$ 0.95 (3H,d,J=6.5 Hz), 1.07 (3H,s), 1.20 (3H,s), the former was supposed to have the "natural" configuration at C-8, since the chemical shifts of the three methyl signals in the nmr spectrum of 16a (*vide supra*) corresponded well to those of methyl hardwickiate[8] (19); δ$(CDCl_3)$ 0.80 (3H,s) 0.85 (3H,d,J=6.0 Hz), 1.27 (3H,s). The ketone (16a) was then treated with methylenetriphenylphosphorane, giving 78% yield of 17; ν(neat) 890 cm^{-1}; δ$(CDCl_3)$ 0.75 (3H,s), 0.85 (3H,d,J=6.0 Hz), 1.06 (3H,s), 4.45 (2H,bs,=CH_2), 6.20 (1H,bs), 7.18 (1H,bs), 7.25 (1H,bs), the ir and nmr spectra of which were superimposable on those of optically active 17, derived from natural acid , (-)-18,[9] by the reported method.[2] The optically active 17 has already been converted to (-)-annonene (1),[2] and by use of the same procedure, racemic 17 was isomerized to racemic annonene (1); oil; ν$(CHCl_3)$ 1620, 1500, 1385, 1160, 1125 870 cm^{-1}; δ$(CDCl_3)$ 0.75 (3H,s), 0.85 (3H,d,J=6.0 Hz), 1.00 (3H,s), 1.57 (3H,bs, CH=CMe), 5.18 (1H,m,=CH), 6.24 7.18, 7.32 (each 1H,bs's,furan H's). These spectral properties were also identical with those reported for natural annonene (1).[2]

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REFERENCES AND NOTES

1) a) I. Kubo, Y. -W. Lee, V. Balogh-Nair, K. Nakanishi, and A. Chapya, J. Chem. Soc., Chem. Commun., 949 (1976).
   b) S. Hosozawa, N. Kato, and K. Munakata, Phytochemistry, 13, 308 (1974).
2) M. Ferrari, F. Pelizzoni, and G. Ferrari, Phytochemistry, 10, 3267 (1971).
3) A. B. Anderson, R. McCrindle, and E. Nakamura, J. Chem. Soc., Chem., Commun., 453 (1974).
4) J. W. ApSimon and K. Yamasaki, Chem. Lett., 1453 (1977).
5) Y. Kitahara, A. Yoshikoshi, and S. Oda, Tetrahedron Lett., 1763 (1964).
6) D. J. France, J. J. Hand, and M. Los, Tetrahedron, 25, 4011 (1969).
7) R. F. Church, R. E. Ireland, and J. A. Marshall, J. Org. Chem., 27, 1118 (1962).
8) R. Misra, R. C. Pandey, and S. Dev, Tetrahedron Lett., 3751 (1964).
9) Dr. F. Pelizzoni, Università di Milano, kindly sent us the natural acid [(-)-18] as a reply to our request on a sample of natural annonene, because the latter is unstable and cannot be stored for a long time. We, therefore, made direct comparison of synthetic 17 with optically active 17, which was derived from (-)-18.

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