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CYCLIZATION OF POLYENES XXIV[1]

EFFECTIVE CONSTRUCTION OF ALBOCEROL SKELETON BY INTRAMOLECULAR ACYLATION OF GERANYLFARNESIC ACID CHLORIDE

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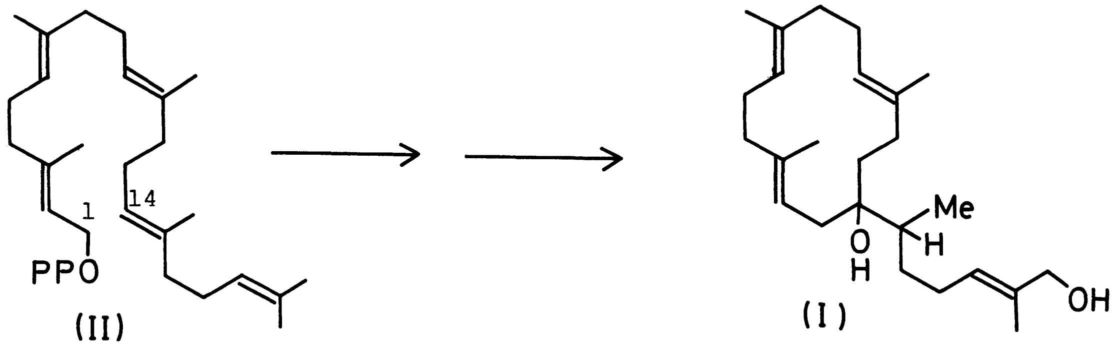
Albocerol skeleton (VI) was constructed effectively by intramolecular acylation of geranylfarnesic acid chloride (V). VI was converted to XIII, an analogue of the termite trail pheromone, neocembrene (XII). XIII showed the termite trail pheromone activity.

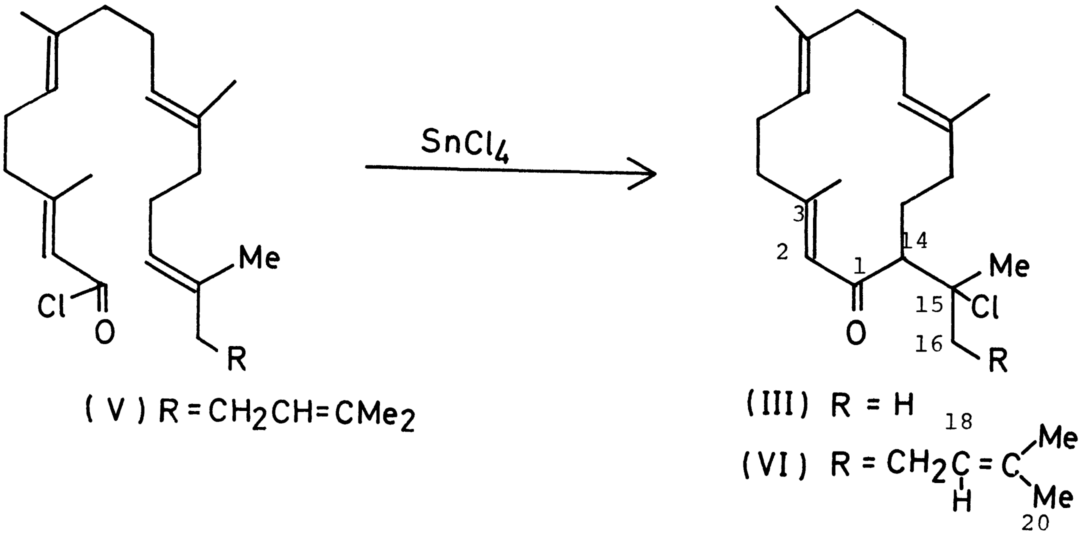
In addition to several kinds of cembrenoids[3], albocerol (I)[4] was elaborated from Ceroplastes albolineatus. I is one of sesterterpenes having a fourteen membered macrocyclic ring as in the skeleton of cembrenoids, and is presumably biosynthesized from geranylfarnesic pyrophosphate (II) by the bond formation between C_1 and C_{14} positions of the acyclic precursor. It is of particular interest to construct the albocerol skeleton based on the biogenetical consideration. Previously, we reported the synthesis of fourteen membered C_{20}-chloro ketone (III) by intramolecular acylation of geranylgeranic acid chloride (V, R=H)[5]. Application of the acylation reaction to geranylfarnesic acid chloride (V) is expected to be an effective method for the formation of albocerol skeleton. Here we report the biogenetic type synthesis of C_{25}-chloro ketone (VI) and its conversion into C_{25}-analogue (XIII) of neocembrene (XII).

Trans geranylfarnesic acid chloride (V) was prepared as follows. Geranylgeranyl acetone[6] was treated with a Wittig reagent [$(EtO)_2POCH_2CO_2Me/NaH/C_6H_6$, room temp. 48 hr] to give a 1 : 3 mixture of cis and trans methyl esters in 80% yield, which was separated by SiO_2 column chromatography eluting with n-hexane-EtOAc (30 : 1). Hydrolysis of the trans ester with aq KOH in dioxane (90° C, 12 hr) followed by SiO_2 chromatography [C_6H_6-isopropyl ether (4 : 1)] afforded the corresponding acid (IV) in 80% yield. PMR(CCl_4), δ 1.58 (C=C-Me x 5), 2.17 (C_3-Me), 5.06 (C=C-H x 4), 5.63 (C_2-H), and 11.6 ppm ($CO_2\underline{H}$).

The acid (IV, 450 mg) was converted to acid chloride (V) by treatment with $SOCl_2$ in C_6H_6 containing dry pyridine at 0° C for 1 hr. The crude acid chloride was, without purification, cooled to -78° C in dry CH_2Cl_2 (300 ml) and then $SnCl_4$ (160 mg, 0.5 mol eq.) in CH_2Cl_2 (12 ml) was dropped during 30 min. under N_2 atmos-



phere. Water was added to the reaction mixture and the organic layer was worked up as usual to give chloro ketone (VI, 460 mg).[7] Structure of VI was confirmed as follows. CMR spectrum (Table 1) and other physical data of VI are quite similar to those of C_{20}-chloro ketone (III). VI: IR(film), 1610 and 1670 cm^{-1}; PMR, δ 1.51 (C=C-Me x 1), 1.60 (C=C-Me x 3), 1.57 (sharp s, C_{15}-Me), 2.11 (C_3-Me), 2.8 (m, C_{14}-H), 4.9 (m, C=C-H x 3), and 5.93 ppm (s, C_2-H). When treated with $(n\text{-}Bu)_3SnH$ in refluxing cyclohexane containing catalytic amounts of AIBN for 3 hr, VI was dechlorinated affording VII in 50% yield from IV. VII: PMR, δ 0.83 (d, 6 Hz, C_{15}-Me), 1.50, 1.57, and 1.66 (C=C-Me x 1, 2, and 1, respectively), 2.07 (C_3-Me), 4.9 (C=C-H x 3), and 5.77 ppm (C_2-H). On the other hand, VI was catalytically hydrogenated with PtO_2 in EtOAc to give octahydro derivative (VIII). VIII: IR (film), 1700 cm^{-1}; PMR, δ 1.52 ppm (C_{15}-Me). VIII was quantitatively dehydrochlorinated with LiCl in DMF (100° C, 48 hr), giving a mixture of IX, X, and XI in a ratio of 2 : 2 : 1. PMR spectra revealed that the former two products were the mixture of cis and trans isomers concerning the double bond. All the evidence discussed above leads to the conclusion that the chloro ketone (VI) has the albocerol carbon skeleton.



(V) R = $CH_2CH{=}CMe_2$

(III) R = H

(VI) R = $CH_2CH{=}CMe_2$

TABLE 1

CMR spectra of C_{20}-, and C_{25}-chloro ketones (III and VI)

compounds	III	VI		III	VI
carbons			carbons		
1	201.42	202.01	14	61.05	59.92
2	126.72	126.80	15	72.04	76.65
3	157.73	158.39	16	31.48	42.89
4	37.03^a	36.97^a	17	-	26.03
5	23.99	23.94	18	-	123.66
6	125.60^b	125.92^b	19	-	132.27^c
7	133.15^c	133.42^c	20	-	23.62
8	38.78^a	38.82^a	3-Me	20.44	20.68
9	24.29	24.27	7-Me	14.51	14.47
10	126.66^b	126.36^b	11-Me	15.30	15.21
11	134.65^c	137.77^c	15-Me	29.60	26.62
12	39.44^a	39.41^a	19-Me	-	17.71
13	25.84	25.68			

a, b, and c in each vertical column may be reversed.[8]

Since neocembrene (XII) has been demonstrated to be a termite trail pheromone[9], it is of special interest to examine whether C_{25}-analogue (XIII) of XII has the similar pheromone activity. When stirred with LiBr/$LiCO_3$ in DMF (105° C, 8 hr),[10] VI was easily dehydrochlorinated and XIV was isolated in 70% yield after purification by SiO_2 chromatography. XIV: PMR, 1.55, 1.60, and 1.70 (C=C-Me x 1, 2, and 1, respectively), 2.06 (C_3-Me), 4.82 (C=$C\underline{H}_2$), 5.0 (C=C-H x 2), and 5.82 ppm (C_2-H). Reduction of XIV with AlH_3 in ether afforded 10 : 1 mixture of cis and trans alcohols (XV, a and b)[11] in 56% yield, which was separated by SiO_2 chromatography eluting with n-hexane-EtOAc (10 : 1). Acetylation of XVa with Ac_2O in pyridine followed by reduction with Li in $EtNH_2$ (-78° C, 1 hr) resulted in the formation of XIII, which was isolated in 17% yield from XVa. PMR, XVa; δ 1.58 and 1.67 (C=C-Me x 4 and 1, respectively), 4.25 (bd, 9 Hz, C_1-H), 5.33 (bd, 9 Hz, C_2-H), and 4.6 - 5.4 ppm (m, C=C-H x 5). Acetate (XVI); δ 1.56 and 1.68 (C=C-Me x 4 and 1, respectively), 5.30 (bd, 9 Hz, C_1-H), 5.52 (bd, 9 Hz, C_2-H), and 4.6 - 5.3 ppm (C=C-H x 5). XIII; δ 1.55 and 1.65 (C=C-Me x 4 and 1, respectively), 4.72 (C=$C\underline{H}_2$), and 5.0 ppm (m, C=C-H x 4).

Our preliminary bioassay exhibited that XIII had the pheromone activity toward a kind of Coptotermitinae of the same degree as dl-neocembrene (XII).[12]

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4. L. Quijano, R. Veloz, J. S. Calderon, and T. Rios, Rev. Latinoam. Quim., 6, 196 (1975).
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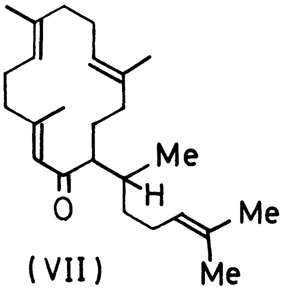
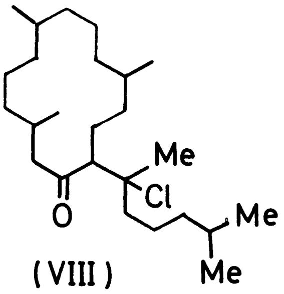
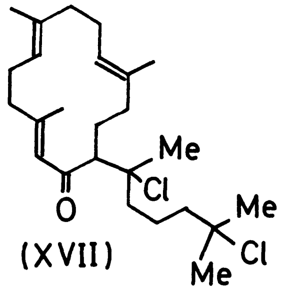
6. Authors are indebted to Takasago Perfumary Co. Ltd., for generous gift of geranylgeranyl acetone.
7. When the reaction time exceeded one hr, formation of dichloro ketone (XVII) was observed. XVII: PMR, δ 1.51 and 1.70 (each 3H, C=C-Me), 1.57 (CClMe x 3), 2.13 (C_3-Me), 2.8 (m, C_{14}-H), 4.9 (m, C=C-H x 3), and 5.93 ppm (C_2-H).
8. CMR spectra of some cembrenoids will be discussed elsewhere.
9. a, A. J. Birch, W. V. Brown, J. E. T. Corrie, and B. P. Moore, J. Chem. Soc., Perkin I, 2653 (1972); b, Y. Kitahara, T. Kato, T. Kobayashi, and B. P. Moore, Chem. Lett., 219 (1976).
10. By this reagent system, XIV and the isomeric 14,15-unsaturated ketone were formed in a ratio of 10 : 1.
11. Stereochemistry of the alcohols was determined by the method described in ref. 9b.
12. Details of the activity will be published elsewhere.


(VII)


(VIII)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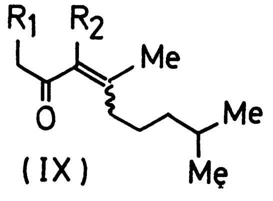
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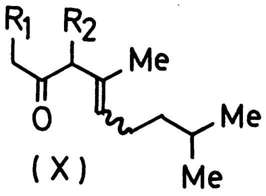
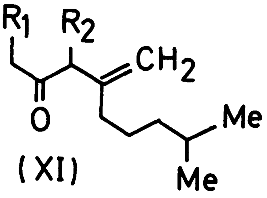
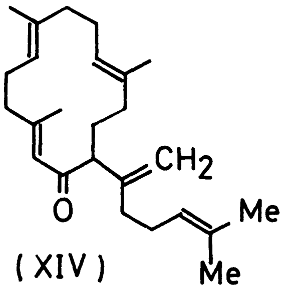
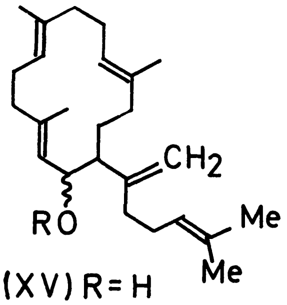
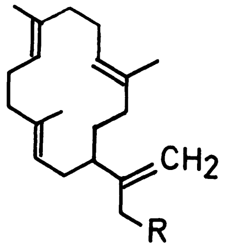

(X)


(XI)

$R_1 = -CHMe((CH_2)_3CHMe)_2(CH_2)_2- = R_2$


(XIV)


(XV) R = H
(XVI) R = Ac


(XII) R = H
(XIII) R = $CH_2CH{=}CMe_2$

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