Tetrahedron. Vol. 26. pp. 4287 to 4292. Pergamon Press 1970 Printed in Great Britain

CYCLIZATION OF POLYENES[1]—V

SYNTHESIS OF α-CHAMIGRENE BY THE CYCLIZATION OF *CIS*- AND *TRANS*-MONOCYCLOFARNESOLS[2]

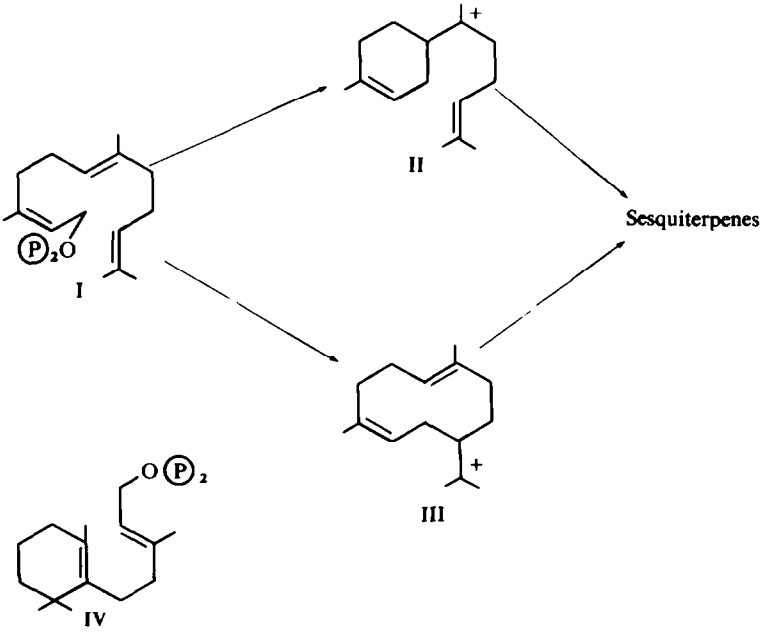
T. KATO, S. KANNO and Y. KITAHARA*

Department of Chemistry, Faculty of Science, Tohoku University, 2-1-1 Katahiracho, Sendai, Japan

(*Received in Japan* 22 *April* 1970; *Received in the UK* 15 *May* 1970)

Abstract—*Trans*-Monocyclofarnesic acid (IXa) was obtained from dihydro-β-ionone (X) and triethyl phosphono-acetate in moderate yield. *Cis*-Monocyclofarnesic acid (IXb) was separated from the mixture of the Wittig reaction. Cyclization of both *cis*- and *trans*-monocyclofarnesols with iodine afforded α-chamigrene (V).

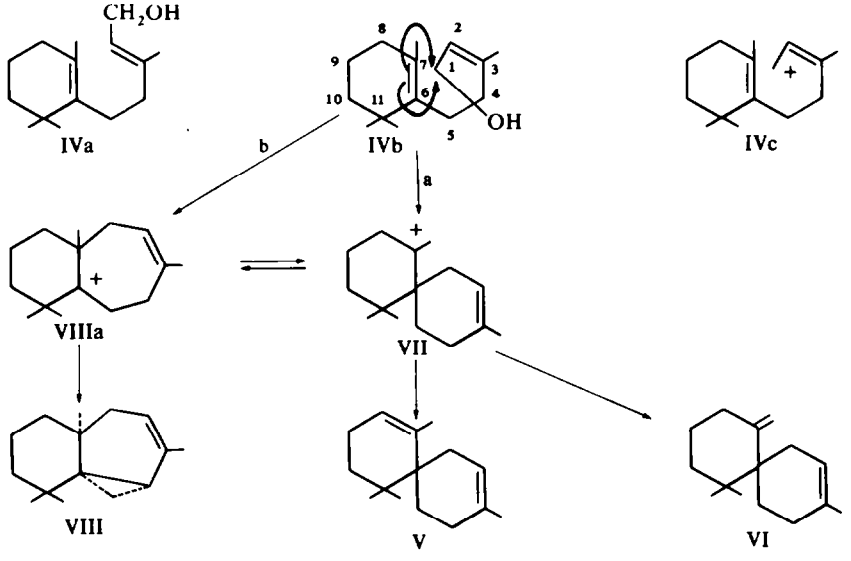
SESQUITERPENES are assumed to originate by appropriate cyclization of acyclic farnesol pyrophosphate (I) and several intermediates such as bisabolenium (II) and macrocyclic ions (III) have been proposed for their biogenesis.[3] However, little attention has been given to monocyclofarnesol (IV) as a possible intermediate. This may be due to the fact that, despite the abundance of sesquiterpenes in nature and the variety of structural types, few compounds possessing the monocyclofarnesyl skeleton have been found in nature until recently.



* To whom all inquiries should be addressed.

As the structure of many sesquiterpenes has been established, and several have the monocyclofarnesyl skeleton, the possibility exists that monocyclofarnesol could be an intermediate in the biogenesis of some kinds of sesquiterpenes.

α- and β-chamigrenes (V, VI)[4, 5] are bicyclic sesquiterpenes with the unique spirocarbon skeleton and monocyclofarnesol (IV) could be an intermediate. Joining C_1 of IVb with C_6 leads to the formation of V and VI through the intermediate cation VII (path a). A possible biogenesis of thujopsene (VIII), which coexists[6] with chamigrene (VI), would be bond formation between C_1 and C_7 of monocyclofarnesol (IV) (path b) as illustrated in the Fig.[7]



Although chamigrene has already been synthesized,[8, 9] our interest in a biogenetic-type synthesis of the chamigrene skeleton prompted us to examine the cyclization of *cis*- and *trans*-monocyclofarnesols (IVa and IVb).

It has been reported that monocyclofarnesol is easily obtained from the corresponding acid (IX), which is synthesized by application of Reformatsky or Grignard (EtOC≡C—MgBr) reactions[10, 11] to dihydro-β-ionone (X) and also by the acid-catalyzed partial cyclization[12] of acyclic farnesic acid (XI). The yield from dihydro-β-ionone (X) is, however, limited and the following Wittig reaction was applied to improve the yield.

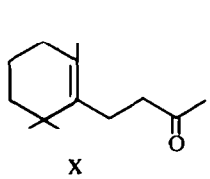
The Wittig reaction of dihydro-β-ionone with triethyl phosphonoacetate and sodium hydride in dioxan yielded a mixture of ethyl esters which were hydrolyzed to the crystalline *trans*-monocyclofarnesic acid (IXa) in 30% yield.

After removal of the *trans*-carboxylic acid and esterification of the remaining acids with diazomethane, the mixture of esters was separated by chromatography on $AgNO_3$–SiO_2 to give the methyl esters of IXa, IXb, XII, XIII and XIV. The structure of these compounds was deduced from the physical evidence summarized in Table 1.

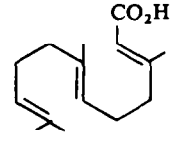
Considerable amounts of methoxy acid (XIV) was formed during the hydrolysis when methanol was used, so that hydrolysis should be done in an inert solvent such as dioxan.

TABLE 1

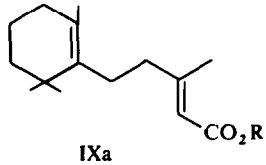
Compounds	Chemical shifts (ppm) in CCl_4				
	C_2–H	C_3–CH_3	C_4–, C_5–H	C_7–, and C_{11}–Methyls	Others
IXa				1·00 (6 H)	
R = Me	5·60 (m)	2·14	2·15 (s)	1·60 (3 H)	3·60 (OMe)
IXb				1·00 (6 H)	
R = Me	5·55 (m)	1·93	1·94 (s)	1·67 (3 H)	3·61 (OMe)
XII				0·96 (6 H)	3·58 (OMe)
R = Me	2·95 (s)	—	2·70 (s)	1·52 (3 H)	4·82 (C_2–H, bs)
XIII			5·12 (C_4–H, d, 6·5 Hz)	0·96 (6 H) 1·52 (3 H)	3·62 (OMe)
R = Me	3·00 (s)	1·74 (d, 2 Hz)	2·70 (C_5–H, d, 6·5 Hz)		
XIV	2·43	1·24		0·99 (6 H)	3·16 (OMe)
R = Me				1·58 (3 H)	3·60 (OMe)



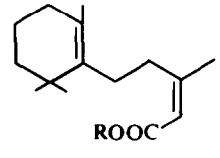
X



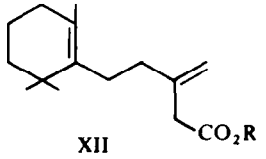
XI



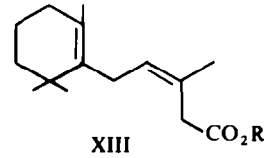
IXa



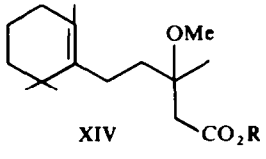
IXb



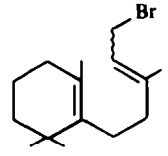
XII



XIII



XIV



XVa *trans*
XVb *cis*

Since isolation of the *cis*-ester (IXb, R = Me) by chromatography is time consuming and tedious, purification of the mixture with benzylthiuronium chloride was attempted and only the benzylthiuronium salt of compound XII was obtained after repeated recrystallization. Photo-isomerization of *trans*-carboxylic acid (IXa) was also tried and yielded a 1:1 ratio of *trans* to *cis* after irradiation for 4 hr with 400 W mercury lamp. Further irradiation afforded XIII and all the starting material was completely changed to this isomer (XIII) after 20 hr.

When the Wittig reaction was carried out in benzene solution at 0–5°, *trans* IXa was formed predominantly in 60% yield.

Reduction of *trans* and *cis*-carboxylic esters with LAH gave the corresponding alcohols (IVa and IVb), which were converted to bromides (XVa and XVb) by treatment with phosphorous tribromide.

The chemical shifts of C_3-methyls in *trans* and *cis* isomers are regularly shifted by changing the esters into the corresponding alcohols and bromides. Down field shift of C_3-methyl in *trans*-ester was observed as compared with that of *cis*-isomer (Δ *cis*-*trans* = 0·21 ppm), whereas the C_3-methyls of *trans* isomers are upfield shifted as compared with *cis*-forms by 0·09 ppm in alcohols and 0·08 ppm in bromo derivatives, respectively. These relations are in good accord with the assigned structures.[13]

Having the desired *cis* and *trans* monocyclofarnesols, their cyclization was tried. Although solvolysis of tosylate of *cis*-alcohol seemed to be promising for the cyclization to chamigrene, its tosylate could not be formed by the usual ways. *cis*-Alcohol is unstable under acidic conditions and is changed on contact with silica gel.

After several trials, the dehydration and simultaneous cyclization of *cis* alcohol (IVb) was carried out with iodine in benzene solution at room temperature to give three compounds which were separated by chromatography on $AgNO_3$–SiO_2 in the yields of 23, 25 and 26% respectively. One of the components (25%) was identical with natural α-chamigrene by comparison of the IR and NMR spectra.

Although the structure of the other two products was not clarified, mass spectra of one of one component (26%) shows the presence of an iodine atom in the molecule (mol wt, 330), and the other (23%) could be polycyclic since no vinyl proton was detected in the NMR spectrum.

TABLE 2

Compounds	Chemical Shifts (ppm) in CCl_4			
	C_1–H	C_2–H	C_3–CH_3	C_7–, and C_{11}–Methyls
IVa	4·05 (d, 6·5 Hz)	5·34 (t, 6·5 Hz)	1·69 (d, 1 Hz)	1·00 (6 H) 1·60 (3 H)
IVb	4·03 (d, 7 Hz)	5·34 (t, 7 Hz)	1·78 (d, 1·5 Hz)	1·01 (6 H) 1·63 (3 H)
XVa	3·90 (d, 8 Hz)	5·47 (t, 8 Hz)	1·75 (m)	0·99 (6 H) 1·58 (3 H)
XVb	3·92 (d, 8 Hz)	5·46 (t, 8 Hz)	1·83 (m)	1·03 (6 H) 1·66 (3 H)

Interestingly, *trans*-alcohol (IVa) gave the same three compounds, although the relative rate of dehydration was different from that of the *cis*-alcohol, indicating that *trans-cis* isomerization occurred during the reaction.

Formation of α-chamigrene could proceed via the intermediate IVc, where, although the distances between C_1–C_6 and C_1–C_7 are almost equal, the bond formation between C_1 and C_6 may be preferable, since a cation at C_7 would be more stabilized by hyperconjugation.

EXPERIMENTAL

Wittig reaction of dihydro-β-ionone (X). To a stirred mixture of 50% NaH (28 g) and anhyd dioxan (800 ml) was added dropwise a soln of triethylphosphono acetate (90 g) in anhyd dioxan (100 ml) and the stirring was continued for 1½ hr when a clear soln was obtained. A soln of dihydro-β-ionone (42 g) in anhyd dioxan (50 ml) was added dropwise to the Wittig reagent and after refluxing for 6 hr, the dioxan was removed by distillation under reduced press.

The residual mixture was extracted with ether and the ether soln was washed with water and dried ($MgSO_4$). Evaporation of ether afforded a mixture of esters which was treated with KOH (84 g) in a 2:1 mixture of dioxan–H_2O (1·5 l) and heated under reflux for 3 days. After removal of the solvent by distillation, water and ether was added to the residue. The aqueous layer was separated from the ether, acidified with dil H_2SO_4 and extracted with ether.

To the mixture of carboxylic acids obtained by evaporation of the ether, n-hexane (50 ml) was added and the mixture kept in refrigerator overnight. The crude crystalline (30%) product was filtered off and recrystallized from n-hexane–cyclohexane (3:1) to yield pure *trans*- IXa, m.p. 118–119° (15%). The residue of crude carboxylic acids was dissolved in MeOH and diazomethane in ether was added to the MeOH soln.

The mixture of methyl esters (5 g), thus obtained, was chromatographed on silica gel (250 g) impregnated with 10% $AgNO_3$. From the fraction eluted with cyclohexane–benzene (4:1) the methyl ester of *cis*- IXb (500 mg) was obtained. Further elution with cyclohexane–benzene (1:1 and 1:3) afforded the pure methyl esters of IXa, XII and XIII. If the mixture of the Wittig reaction products was hydrolyzed with KOH in MeOH instead of dioxan–water, XIV was isolated in addition to the above compounds. After removal of IXa by crystallization, the ratio of the methyl esters was estimated by gas chromatography to be 18% (IXa), 16% (IXb), 15% (XII), 23% (XIII) and 28% (XIV), respectively.

Separation of XII *with benzylthiuronium salt.* After removal of *trans* carboxylic acid, the crude residual carboxylic acids (16 g) were dissolved in EtOH–water (5:1, 130 ml) and neutralized with 2 N NaOH using phenolphthalein as indicator. To this soln benzylthiuronium chloride (20 g) was added in hot EtOH (200 ml) and kept overnight in a refrigerator.

The ppt was filtered off and purified by repeated recrystallization from EtOH to afford benzylthiuronium salt, m.p. 157–159°. Ether and 1 N HCl were added to the salt and XII was obtained from the ether layer.

Wittig reaction of dihydro-β-ionone (X). To an ice-cooled mixture (3–6°) of 50% NaH (48 g) and anhyd benzene (300 ml) triethylphosphono acetate (250 g) was added with stirring under N_2 atmosphere and stirring was continued for an hr to obtain a clear soln. X (160 g) was added dropwise with stirring below 5° and the mixture was kept in a refrigerator for 2 days, poured into ice-water and extracted with ether. From the ether soln, after being washed with water and dried over $MgSO_4$, a crude mixture of esters was obtained and hydrolyzed as described. Crude *trans*-carboxylic acid (60%, m.p. 103–113°) was obtained and purified by recrystallization. Pure *trans* IXa was obtained in a 32% yield.

Reduction of methyl monocyclofarnesate (IXa. or IXb. R = Me). Methyl monocyclofarnesate (2 g) in anhyd ether (20 ml) was added dropwise to a stirred suspension of LAH (200 mg) in anhyd ether (20 ml) and the stirring was continued for 2 hr at room temp. The mixture was poured into ice water, acidified with HCl and extracted with ether. From the ether soln, after being washed with water and dried over $MgSO_4$, monocyclofarnesol (IVa, or IVb) was obtained in a 95% yield.

Monocyclofarnesyl bromide (XVa, or XVb). To a stirred mixture of monocyclofarnesol (2·58 g), anhyd pyridine (0·13 ml) and light petroleum (16 ml) a soln of PBr_3 (1·27 g) in light petroleum (5 ml) was added dropwise and the mixture was stirred for 2 hr at room temp. The mixture was poured into ice-water and extracted with ether. The ether soln was washed with $NaHCO_3$ aq, water and then dried over $MgSO_4$ in a refrigerator. Evaporation of solvent below 40° afforded XVa, or XVb in 95% yield.

Cyclization of monocyclofarnesol. After a mixture of *cis*-monocyclofarnesol (1·3 g), I_2 (3·7 g) and anhyd benzene (100 ml) was stirred at room temp for 2 hr, the mixture was successively washed with $NaHSO_3$ aq, $NaHCO_3$ aq and water, and then dried over $MgSO_4$. After concentration of the solvent, the residual material was passed through a short silica gel and alumina column, and hydrocarbon fractions were collected in 50% yield. These fractions were passed through a 10% $AgNO_3$–silica gel (35 g) column using light petroleum. Successive elution with light petroleum–benzene (10:1) afforded A and B, in 23 and 25% yields. Elution with light petroleum–benzene (1:1) gave C, in 26% yield. IR and NMR spectra in CCl_4 of B (25%) were identical with those of natural α-chamigrene.

Acknowledgment—The authors thank Professor A. Yoshikoshi for his generous gift of α-chamigrene, they also thank Takasago Perfumery Co. for gift of β-ionone.

REFERENCES

[1] Part IV of this series, Y. Kitahara, T. Kato and S. Kanno, *J. Chem. Soc.* C, 2397 (1968)
[2] A part of this paper was reported in a preliminary communication; S. Kanno, T. Kato and Y. Kitahara, *Chem. Commun.* 1257 (1967)
[3] For example, J. H. Richards and J. B. Hendrickson, *The Biosynthesis of Steroids, Terpenes, and Acetogenins.* Benjamin, New York (1964)
[4] S. Ito, K. Endo, T. Yoshida, M. Yatagai and M. Kodama, *Chem. Commun.* 186 (1967)
[5] Y. Ohta and Y. Hirose, *Tetrahedron Letters* 2483 (1968)
[6] T. Yoshida, K. Endo, S. Ito and T. Nozoe, *J. Pharm. Soc. Japan* **87**, 434 (1967)
[7] Other biogeneses have been proposed:
[a] C. Enzell and H. Erdtman, *Tetrahedron* **4**, 361 (1958);
[b] K. Sisido, H. Nozaki and T. Imagawa, *J. Org. Chem.* **26**, 1964 (1961);
[c] W. G. Dauben and P. Oberhansli, *Ibid.* **31**, 315 (1966);
[d] Ref 6
[8] A. Tanaka, H. Uda and A. Yoshikoshi, *Chem. Commun.* 188 (1967)
[9] A. Tanaka, H. Uda and A. Yoshikoshi, *Ibid.* 56 (1968)
[10] A. Caliezi and H. Schinz, *Helv. Chim. Acta* **33**, 1129 (1950)
[11] M. E. Lederer, C. Collin-Asselineau and J. Polonsky, *Bull. Soc. Chim. Fr.* 715 (1950)
[12] G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.* **77**, 5068 (1955)
[13] J. W. K. Burrell, R. F. Garwood, L. M. Jackman, E. Oskay and B. C. L. Weedon, *J. Chem. Soc* C, 2144 (1966) and refs therein