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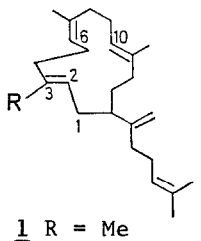
CONFIRMATION OF THE STRUCTURE OF CERIFEROL AND ITS RELATED SESTERTERPENES BY THE TOTAL SYNTHESIS[1)]

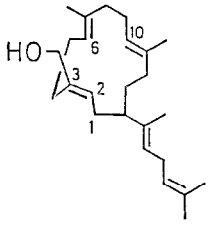
Shigeki Fujiwara, Mario Aoki, Tadao Uyehara, and Tadahiro Kato*
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

Abstract: The dl-synthesis of the revised formula of ceriferol and ceriferol-I was achieved, leaving no doubt that the revised structure has been correctly formulated.

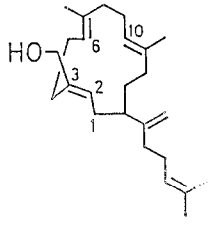
Many sesterterpenoids have been isolated from the insect wax secreted by Ceroplastes (genus) as exemplified by ceriferol. Although it is apparently estimated from physical evidence that these sesterterpenes have one cis and two trans double bonds within the 14-membered cembrene skeleton, there was controversy on the arrangement of the annular double bonds, particularly of the cis double bond.[2)] The current widespread interest in naturally occurring 14-membered macrocycles prompted us to explore the synthetic route of these sesterterpenes. When we initiated the synthetic work, the structure (1) was proposed for cericerene, a hydrocarbon derived from cericerol-I(2).[3)] Our preliminary synthetic study has, however, served to demonstrate unequivocally that the cericerene cannot be constituted as originally proposed.[4)] Almost simultaneously with our synthesis, Naya and her coworkers have revised the structure on the basis of detailed spectroscopic analysis, showing 3a and 3b for ceriferol and ceriferol-I, respectively.[5)] The cis double bond of all the sesterterpenes from the C.ceriferus is revised to C_2- instead of C_6-position in the new structure. In this paper, we wish to delineate the synthesis of the revised formula, revealing that the new structure has been correctly formulated.



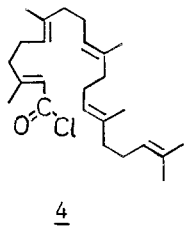
1 R = Me
2 R = CH_2OH



3a



3b



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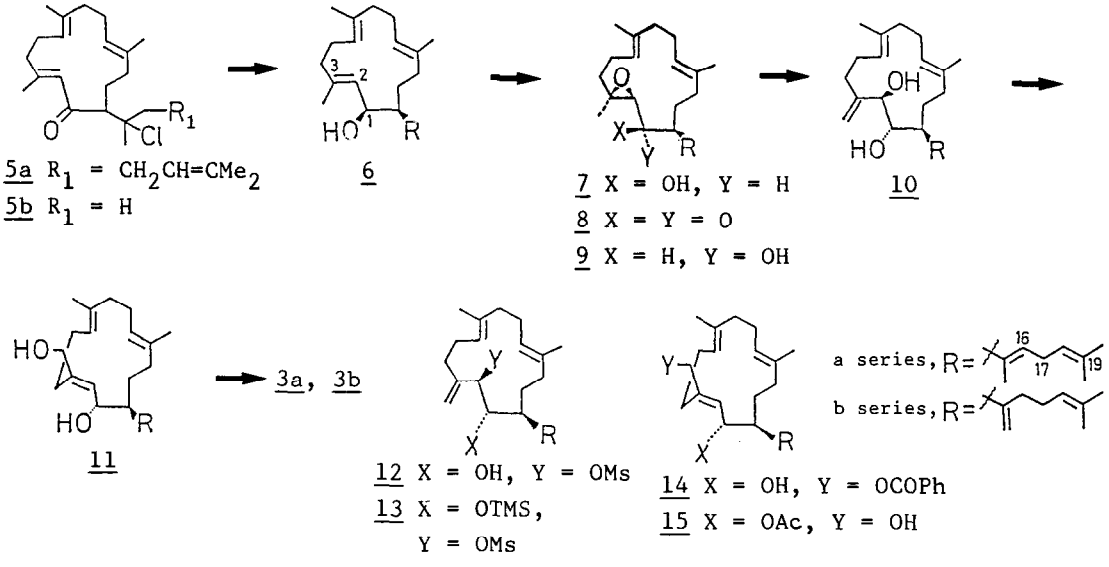
Careful retrosynthetic analysis suggested that elaboration of ceriferols (3a and 3b) might well be pursued by the route shown in the scheme 1. Adop-

tion of this protocol would require that hydroxylation of C_3-Me of the chloroketone (5a)[6] be implemented in a manner that would set the change of geometry of the C_2-C_3 double bond. In this connection, we have already had the precedent in our asperdiol synthesis,[7] in which dihydroxy-2Z-cembrene A (11, R = isopropenyl) was efficiently constructed from the analogous chloroketone (5b).[8]

SCHEME 1; SYNTHETIC ROUTE OF CERIFEROLS



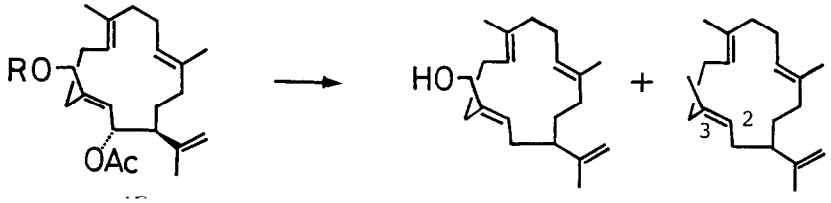
The ceriferol skeleton (5a) was constructed from 4 by the action of $SnCl_4$. Dehydrochlorination followed by reduction (AlH_3 in ether, -78°C) gave a 1:1 mixture of 6a and 6b in 40% yield which was surrendered to chromatographic coaxing to get physical data.[9] The structure including the stereochemistry indicated in 6a and 6b rests upon ^{1}H- and ^{13}C-NMR spectra;[10] each chemical shift of ring carbons in the ^{13}C-NMR spectra is completely correlated with that of the analogous compound (6, R = isopropenyl). In the ^{1}H-NMR spectrum of 6a, irradiation of C_{17}-protons (δ 2.70) resulted in simultaneous 5% enhancement of the signals for C_{15}-Me (δ 1.64) and C_{19}-Z Me (δ 1.58), thus revealing the E geometry of the newly formed C_{15}-C_{16} double bond. Since it is quite troublesome to separate each alcohol, the following reactions were carried out using the mixture. The Sharpless oxidation (1.0 eq of t-BuOOH, $VO(acac)_2$ in C_6H_6 at 7°C overnight) gave the syn epoxides (7a, 7b) exclusively by virtue of the hydroxyl group,[11] which underwent Collins oxidation (8 eq of $CrO_3 \cdot Py_2$ / CH_2Cl_2, rt) to provide epoxy ketones (8a, 8b). Reduction of the ketones with $LiAlH(OBu^t)_3$ proceeded stereoselectively from less hindered β-side,[12] giving the isomeric alcohols (9a, 9b). The relative stereochemistry of C_3-Me with respect to C_1-OH group of 7 and 9 was corroborated by checking the chemical shifts of C_3-Me. The former appeared at δ1.25 while the latter exhibited at δ1.33 ppm, respectively. Treatment of the epoxy alcohols (9a, 9b) with $Ti(OPr^i)_4$ in C_6H_6

at 70°C overnight furnished a 1:1 mixture of rearranged diols (10a, 10b),[13] which was easily separated by usual SiO_2 column chromatography. 10a and 10b were obtained in 11% each yield from the mixture of 6a and 6b.

Mesylation of 10a under discriminating conditions (1.2 eq of MsCl in CH_2Cl_2 containing 2 eq of Et_3N at -78°C and then at 20°C) provided sufficient selectivity of the reaction, furnishing monomesylate (12a), which was further treated with TMSCl (5 eq) and Et_3N (6 eq) plus DMAP (catalyst) in the same pot. The resulting trimethylsiloxy mesylate (13a) was exposed to benzoic acid (2 eq) in the presence of DBU (2 eq) and catalytic amounts of NaI in DMF at 70°C for 12 h.[14] The rearrangement of the mesylate with simultaneous desilylation resulted in conversion to hydroxy benzoate (14a), which was further treated with methanolic KOH to afford dihydroxy derivative (11a) in 56% overall yield from 10a. In a separate event, 10b was transformed into 11b in 61% overall yield. The geometry of the newly formed C_2-C_3 double bond in 11a and 11b was confirmed by ^{1}H-NMR spectra.

Now all that is required to make ceriferols is the selective removal of C_1-hydroxyl group from the diol (11a and 11b). Our model experiments using isopropenyl derivative (16) have revealed that selective removal of secondary acetoxyl group can be executed efficiently under controlled conditions to give 17 as shown in Table 1. When primary hydroxyl group was protected with ^{t}Bu-Me_2Si or THP group, the ether group was also reduced, giving rise to the formation of a hydrocarbon identical with 2Z-cembrene A (18).[15] Formation of the hydrocarbon is indicative of the complete retention of the geometry of C_2-C_3 double bond during the reductive removal of the acetoxyl group.

Table 1
Reductive removal of acetoxyl group



(16) (17) (18)

R	Conditions	Yield (%)	
^{t}BuMe$_2$Si	Li (10 eq)/EtNH$_2$/-78°C	0	89
THP	"	0	82
H	"	42	27
H	Li (10 eq)/^{t}BuOH (10 eq) EtNH$_2$/-78°C	80	12

After selective protection of the primary hydroxyl group of 11a with $^{t}BuMe_2SiCl/Et_3N$ and DMAP, acetylation of the remaining secondary hydroxyl group with Ac_2O and Et_3N in the presence of catalytic amounts of DMAP followed by acid hydrolysis (AcOH in aq THF, rt, overnight) led to the formation of hydroxy acetate (15a) in 45% overall yield. 11b was similarly converted into 15b in 55% overall yield. Each of the hydroxy acetate (15a and 15b) was processed in the same way as the model experiment, furnishing 3a and 3b in 65 and 50% yields, respectively, upon treatment with $Li/^{t}BuOH/EtNH_2$. ^{1}H- and ^{13}C-NMR spectra of the alcohols (3a, 3b) were identical with those of natural specimen. The present synthetic study leaves no doubt that the revised structure of the sesterterpenes has been correctly formulated.

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7) M. Aoki, Y. Tooyama, T. Uyehara, and T, Kato, Tetrahedron Lett.,24, 2267 (1983).
8) Since it was not possible to envision the exact conformation of the cembrene skeleton due to the macrocyclic nature, we have examined the rearrangement of 10 and its stereoisomers (R = isopropenyl) in details in our asperdiol synthesis.
9) Reduction of the dehydrochlorinated product gave a ca 2:1 mixture of cis (6) and trans alcohols, which was roughly separated by repeated SiO_2 column chromatographies. The resultant mixture of 6a and 6b was submitted to the $AgNO_3$-SiO_2 column chromatography.
10) The structure of all the compounds described herein was supported by satisfactory physical data and elemental analyses or molecular ion in the mass spectra.
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12) The stereochemistry of C_1-positon is highly effected by the neighboring substituents although exact conformation of the skeleton is obscure and no explanation is possible for the selectivity.
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