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DETERMINATION OF ABSOLUTE CONFIGURATION OF CHLOROVULONES BY CD MEASUREMENT AND BY ENANTIOSELECTIVE SYNTHESIS OF (-)-CHLOROVULONE II[1]

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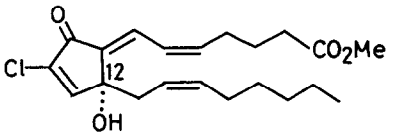
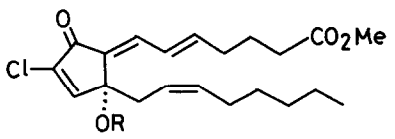
Abstract: Absolute configuration of chlorovulones, new halogenated marine prostanoids with an antitumor activity isolated from the stolonifer Clavularia viridis Quoy and Gaimard, has been established on the basis of the CD measurement of the chlorovulone derivatives and of the enantioselective synthesis of (-)-chlorovulone II.

Previously the isolation and structures of chlorovulones, new halogenated marine prostanoids with an antitumor activity, from the Japanese stolonifer Clavularia viridis Quoy and Gaimard have been reported.[2] In this paper we wish to describe evidences for the absolute configuration at the C-12 position of chlorovulone I, II, III and IV as depicted in 1, 2, 3 and 4, respectively. The stereochemistry of the chiral center was established by means of the CD measurement of the chlorovulone derivatives and of the enantioselective synthesis of (-)-chlorovulone II.

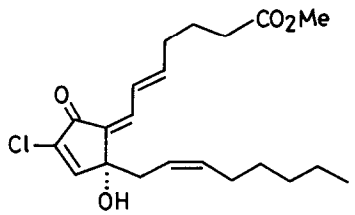
Spectroscopic elucidation of the stereochemistry of the chiral center at the C-12 position for chlorovulones was carried out as follows. Reduction of



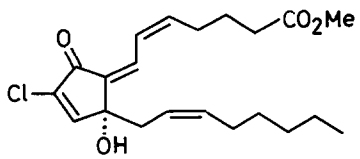
1 chlorovulone I



2 R = H chlorovulone II
5 R = Ac



3 chlorovulone III



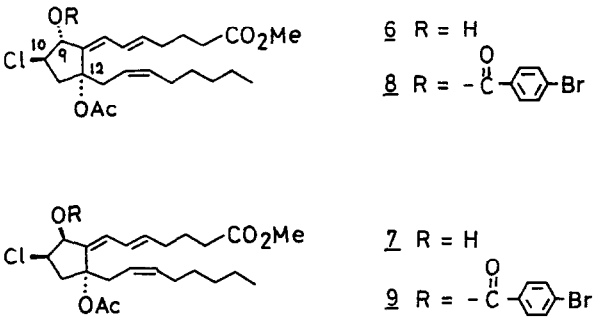
4 chlorovulone IV

chlorovulone II acetate (5)[2] with sodium borohydride (MeOH, 25°C) gave two epimeric alcohols 6[3,4] and 7[4] in 35% and 30% yield, respectively. High dilution IR measurement of the alcohol 6 in carbon tetrachloride (4×10^{-3} M) showed an absorption at 3500 cm^{-1} due to the intramolecular hydrogen bond between the hydroxyl group at C-9 and the acetoxyl group at C-12, indicating the cis configuration between these oxygen functional groups. On the other hand, the IR spectrum of 7 (3.5×10^{-3} M) showed an absorption at 3605 cm^{-1} due to a free hydroxyl group, indicating the trans configuration for 7.

Application of the exciton chirality method[5] for the p-bromobenzoates of 6 and 7 provided the evidence for the absolute configurations at the C-9 position, thus indicating the absolute configuration at the C-12 position. The CD spectra of the p-bromobenzoates 8[6] and 9[6] prepared from 6 and 7 (p-bromobenzoyl chloride, pyridine, DMAP, 60°C), respectively, are shown in Fig.1. In 8 the positive Cotton effect at 254nm ($\Delta\varepsilon$+21.8) caused by the interaction between the two chromophores (the diene and p-bromobenzoyl groups) is observed, while the negative Cotton effect at 253nm ($\Delta\varepsilon$-21.3) is observed in 9. The positive Cotton effect in 8 indicates the positive chirality of the two chromophores, showing the R configuration at the C-9 position in 8 and 6, and thus the R configuration at C-12 in 6.

These results lead to the assignment of the absolute configuration for chlorovulone II as shown in the structure 2. The same absolute configuration was assigned for chlorovulone I (1) and III (3) [and IV (4)[7]], since these compounds were chemically correlated each other by photoisomerization.[2,7]

The same conclusion for the absolute configuration of chlorovulones was obtained by the enantioselective total synthesis of (-)-chlorovulone II (18). Applying the synthetic method for the enantioselective syntheses of clavulones[8] and the clavulone analog,[9] (S)-4-hydroxy-2-cyclopentenone was transformed to (-)-chlorovulone II (18).



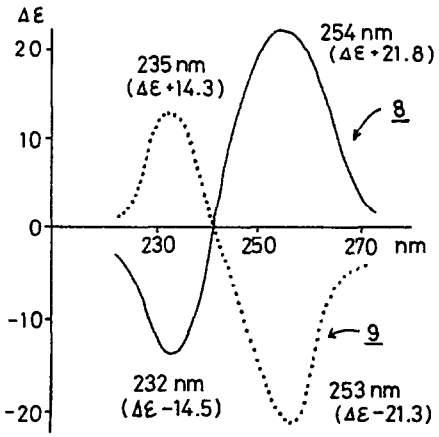
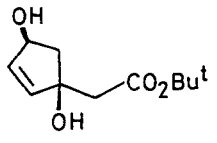


Fig.1 CD spectra of 8 and 9

The optically active diol 10,[8] $[\alpha]_D$ -45.9°(c 1.12, $CHCl_3$), which is readily available from (S)-4-hydroxy-2-cyclopentenone,[10] was converted to the α-chlorocyclopentenone 11,[3] $[\alpha]_D$ -12.5°(c 0.53, $CHCl_3$), by three step sequence in 75% overall yield: 1) Jones oxidation (acetone, 0°C); 2) protection of the tertiary hydroxyl group as methoxymethyl ether ($ClCH_2OMe$, $i\text{-}Pr_2NEt$, $ClCH_2CH_2Cl$, 60°C); 3) treatment with chlorine gas (Et_2O, 25°C) and then with excess amount of triethylamine. Reduction of 11 ($NaBH_4$, $CeCl_3$, MeOH, 25°C) followed by silylation gave 12 ($t\text{-Bu(Me)}_2SiCl$, imidazole, DMF, 25°C) as a diastereomeric mixture which was reduced with lithium alminium hydride (Et_2O, 0°C) to give the alcohol 13 in 93% yield from 11. Swern oxidation of 13 followed by Wittig reaction using n-hexylenetriphenylphosphorane (THF-HMPA, -42°C) gave the Z-olefin 14. After de-



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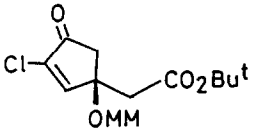

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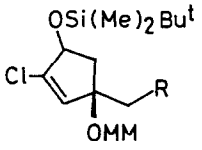
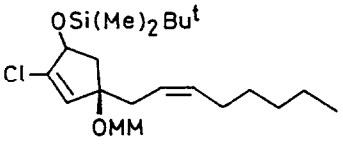


12 R = CO_2Bu^t

13 R = CH_2OH



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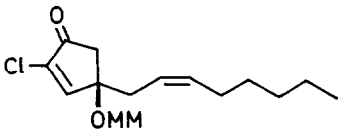
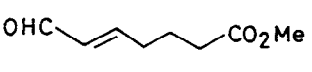


15



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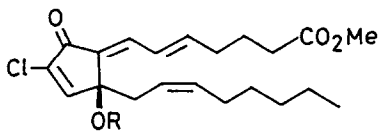
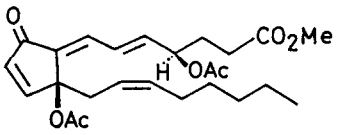


17 R = CH_2OMe

18 R = H



clavulone II

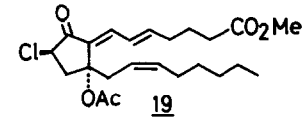
protection of the t-butyldimethylsilyl group in 14, the resulting alcohol was oxidized with Jones reagent (acetone, 0°C) to give the enone 15[11] in 68% yield from 14. Reaction of the lithium enolate, prepared from 15 and 1 equiv of lithium diisopropyl amide, with 1 equiv of the α,β-unsaturated aldehyde 16[12] in THF at -78°C for 10 min and then warmed to -42°C over 30 min to afford 17[13] as a single isomer in 68% yield. Finally, removal of the methoxymethyl group in 17 with a 1:50 mixture of 36% hydrochloric acid and acetic acid at 25°C provided 70% yield of 18.

The ^{1}H-NMR, IR, UV and mass spectra of synthetic chlorovulone II were identical with those of natural chlorovulone II (2) in every respect. The only difference was the sign of optical rotation: synthetic chlorovulone II (18) proved to be levorotatory, $[\alpha]_D$ -29.6°(c 0.27, $CHCl_3$), while the natural chlorovulone II (2) is dextrorotatory, $[\alpha]_D$ +22.7°(c 0.075, $CHCl_3$).[2] This synthesis established the absolute configuration of chlorovulones unambiguously and also provided a method for enantioselective total synthesis of chlorovulones.

It is noted that the absolute configuration of chlorovulones is opposite to that of clavulones,[14] while both compounds coexist in the same marine animal and are structurally related to each other.

References and Notes

1. This paper constitutes Part XIII of "Studies on Marine Natural Products."
2. K.Iguchi, S.Kaneta, K.Mori, Y.Yamada, A.Honda, and Y.Mori, Tetrahedron Lett., in press.
3. All new compounds have been fully characterized by IR, ^{1}H-NMR(400 MHz), and high resolution mass spectroscopy and/or combustion analysis.
4. 6: $[\alpha]_D$ +4.7°(c 0.17,$CHCl_3$); UV(EtOH) 247nm(ε 4,500); ^{1}H-NMR(400 MHz,$CDCl_3$) δ 2.02(3H,s), 2.35(1H,dd,J=6.5,13.7 Hz,H-11β), 2.83(1H,dd,J=10.7,13.7 Hz,H-11α), 3.66(3H,s), 3.85(1H, brd,D_2O exchangeable), 4.08(1H,ddd,J=4.6,6.5,10.7 Hz,H-10), 4.25(1H,br,H-9), 5.79(1H,td, J=7.1,14.3 Hz), 6.40(2H,m).
   7: $[\alpha]_D$ -42.7°(c 0.15,$CHCl_3$); UV(EtOH) 248nm(ε 7,200); ^{1}H-NMR(400 MHz,$CDCl_3$) δ 2.02(3H,s), 2.43(1H,dd,J=7.3,12.9 Hz,H-11β), 2.60(1H,dd,J=11.5,12.9 Hz,H-11α), 3.66(3H,s), 3.79(1H, ddd,J=7.3,8.7,11.5 Hz,H-10), 4.80(1H,brd,J=8.7 Hz,H-9), 5.75(1H,td,J=7.3,14.5 Hz), 6.21 (1H,dd,J=2.3,11.5 Hz), 6.43(1H,dd,J=11.5,14.5 Hz).
   Oxidation of each alcohol with PCC gave the same dienone 19, showing that 6 and 7 are epimeric at the C-9 position. The relative stereochemistries between C-9 and C-10 for 6 and 7 were suggested by the coupling constants between H-9 and H-10, respectively.



19

5. N.Harada, J.Iwabuchi, Y.Yokota, H.Uda, and K.Nakanishi, J.Am.Chem.Soc., 103, 5590(1981).
6. 8: $[\alpha]_D$ +40°(c 0.035,$CHCl_3$); UV(EtOH) 247nm(ε 20,700); ^{1}H-NMR(400 MHz,$CDCl_3$) δ 5.68(1H,d, J=4.4 Hz,H-9), 7.60(2H,d,J=8.6 Hz), 7.99(2H,d,J=8.6 Hz).
   9: $[\alpha]_D$ -41°(c 0.022,$CHCl_3$); UV(EtOH) 248nm(ε 20,700); ^{1}H-NMR(400 MHz,$CDCl_3$) δ 6.16(1H,d, J=7.1 Hz,H-9), 7.60(2H,d,J=8.4 Hz), 7.93(2H,d,J=8.4 Hz).
7. Chlorovulone IV (4) was not isolated as a pure state and its structure was suggested on the basis of the spectra of its corresponding acetate.[2] The same absolute configuration of 4 as those of chlorovulone I, II and III was indicated by the formation of chlorovulone IV acetate in the photoisomerization reaction of 5 (fluorescent lamp, C_6H_6).
8. H.Nagaoka, T.Miyakoshi, and Y.Yamada, Tetrahedron Lett., 25, 3621(1984).
9. H.Nagaoka, T.Miyakoshi, J.Kasuga, and Y.Yamada, Tetrahedron Lett., in press.
10. K.Ogura, M.Yamashita, and G.Tsuchihashi, Tetrahedron Lett., 759(1976).
11. 15: $[\alpha]_D$ -40.2°(c 0.90,$CHCl_3$); ^{1}H-NMR(400 MHz,$CDCl_3$) δ 0.88(3H,t,J=6.8 Hz), 2.00(2H,dd,J=7.3, 14.1 Hz), 2.58(1H,d,J=18.8 Hz), 2.79(1H,d,J=18.8 Hz), 3.37(3H,s), 4.62(1H,d,J=7.6 Hz), 4.69(1H,d,J=7.6 Hz), 5.34(1H,m), 5.59(1H,m), 7.39(1H,s).
12. The ester aldehyde 16 was prepared by the sequence (1) methanolysis of δ-valerolactone (MeONa, MeOH, rt), (2) oxidation of primary hydroxyl group (DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, and then Et_3N, -78°C to 0°C), (3) Wittig reaction (Ph_3P=CHCHO, $ClCH_2CH_2Cl$, 80°C).
13. 17: $[\alpha]_D$ +14.5°(c 0.6, $CHCl_3$); ^{1}H-NMR(400 MHz,$CDCl_3$) δ 0.87(3H,t,J=6.8 Hz), 2.65(1H,dd,J= 8.3,14.1 Hz), 2.78(1H,dd,J=6.8,14.1 Hz), 3.36(3H,s), 3.67(3H,s), 4.45(2H,s), 5.26(1H,m), 5.51(1H,m), 6.27(1H,td,J=7.0,15.1 Hz), 6.66(1H,tdd,J=1.3,11.8,15.1 Hz), 7.08(1H,d,J=11.8 Hz), 7.23(1H,s).
14. a) H.Kikuchi, Y.Tsukitani, K.Iguchi, and Y.Yamada, Tetrahedron Lett., 23, 5171(1982); b) H.Kikuchi, Y.Tsukitani, K.Iguchi, and Y.Yamada, ibid, 24, 1549(1983). Erratum; Expression of the absolute configuration at C-12 of clavulones as R in the reference 14b should be read as S. See also the references for claviridenones; M.Kobayashi, T.Yasuzawa, M.Yoshihara, H.Akutsu, Y.Kyogoku, and I.Kitagawa, Tetrahedron Lett., 23, 5331(1982); M.Kobayashi, T.Yasuzawa, M.Yoshihara, B.W.Son, Y.Kyogoku, and I.Kitagawa, Chem.Pharm.Bull., 31,1440(1983).

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