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STEREOSTRUCTURES OF SEVERAL SOLIDAGOLACTONES (ELONGATOLIDES)

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Summary: The structures of several clerodane-type diterpenes [solidagolactones II (elongatolide C), III, IV (elongatolide A), V, VI (elongatolide D), elongatolide B, and elongatolide E] have been revised , all of which are cis-clerodanes.

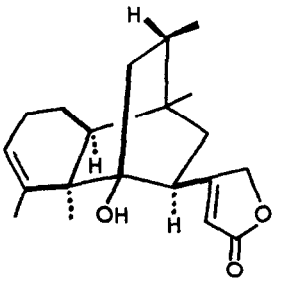
In connection with the new type of diterpene, tricyclosolidagolactone (1) which must be derived from the precursor of a cis-clerodane,[1] we further examined bitter principles of the plant Solidago altissima L., and could newly isolate solidagolactone VII (elongatolide E)[2] and the several known substances which had already been isolated by Okazaki et al.[3] As pointed out by them,[3] solidagolactones II, IV, and VI are identical to elongatolides C, A, and D, respectively, all of which have been isolated from the plant Solidago elongata N. by Anthosen and McCrindle.[2] Recently, Bohlmann et al. have also accepted the trans-clerodane-type structures for elongatolide A (solidagolactone IV) and elongatolide E (solidagolactone VII).[4] In the present paper, however, we wish to describe the revised structures of these bitter principles, all of which belong to the cis-clerodane group of diterpenes.

According to essentially the same procedure as reported by Okazaki et al.,[3] followed by repeated preparative TLC [Kieselgel PF_{254}] using a combination of two different solvent systems [EtOAc - $CHCl_3$ (1 : 10) and EtOAc - $CHCl_3$ (1 : 5)], the known solidagolactones I - V[5] were isolated from the same plant, in addition to solidagolactone VII which is regarded as elongatolide E[2] on the basis of their spectral data. In the light of the stereostructure of tricyclosolidagolactone (1),[1] the structures of solidagolactones II - VII and elongatolide B were reexamined and unambiguously established as 2, 3, 4, 5, 6, 7, and 8, respectively, as discussed below.

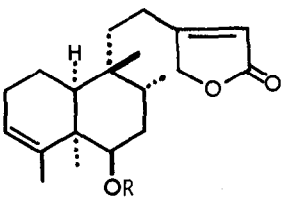
As suggested by Okazaki et al.,[3] solidagolactones II, III, and IV (2, 3, and 4) are quite

similar to one another. Furthermore, solidagolactone V (5) has been obtained from 4 on Jones' oxidation. This ketone (5) was reconverted into 4 on $NaBH_4$ reduction in EtOH (room temp., 8 h), which was further treated with Ac_2O - pyridine (1 : 2) to afford the corresponding acetate (8),[6] whose NMR spectrum is completely identical with that of elongatolide B.[2] Furthermore, the coupling constant of the signal at δ 4.90(1H, t, J= 5Hz) assignable to C_6-H indicates that the AcO group must be in an axial configuration. Finally, these diterpenes were converted into the known furano compound (9),[7] as described below.

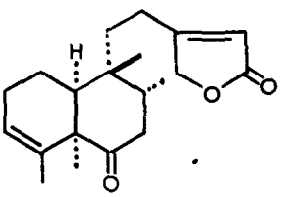
On reduction with DIBAL in THF (-20 ~ -25 °C, 2.5 h) followed by addition of 10% H_2SO_4, the acetate (8) was readily converted into the corresponding furan (10)[8] in 37% yield, which was further treated with $LiAlH_4$ in Et_2O (reflux, 5 h) to give a hydroxyfuran (11),[9] in 59% yield.



1



2 R = Ang. 4 R = H
3 R = Tig. 8 R = Ac



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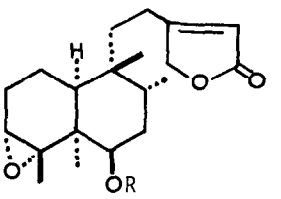
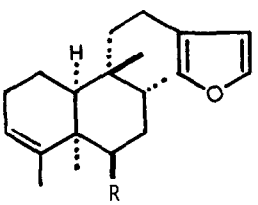
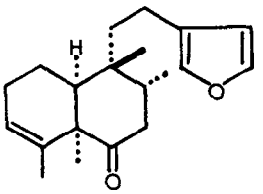


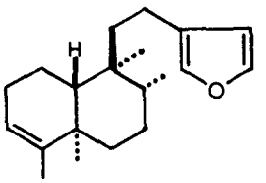
6 R = Ac
7 R = Ang.



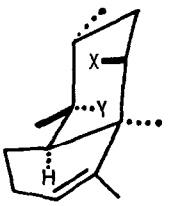
9 R = H 12 R = OAng.
10 R = OAc 13 R = OTig.
11 R = OH



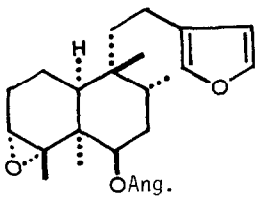
14



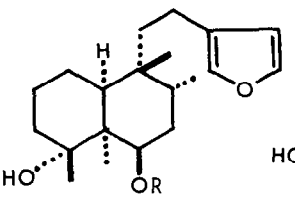
15



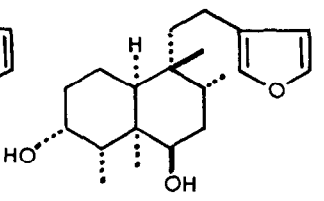
16



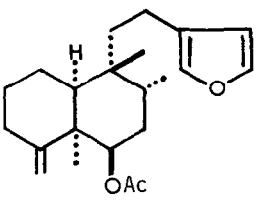
17



18 R = H
20 R = Ac



19



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This compound (11) was also derived from solidagolactones II and III via the corresponding furano intermediates (12 and 13),[10] respectively, under the similar conditions as that of 8. Finally, 11 was oxidized with pyridinium chlorochromate in CH_2Cl_2 (room temp., 9 h) to afford a ketone (14),[11] in almost quantitative yield, which was subjected to Wolff-Kishner reduction to afford the known furan (9)[7,12] in 18% yield. The NMR spectrum of 9 is quite different from that of the trans isomer (15), which has been derived from hardwickiic acid[13] as well as from solidagolactone I[3]. Particularly, the C_8-Me doublet (δ0.90) in 9 is observed in higher magnetic field as compared with the C_9-Me singlet (δ1.08), while the latter (15) has the C_9-Me singlet (δ0.74) in higher magnetic field rather than the C_8-Me doublet (δ0.86). Clearly, these differences indicate that 15 has the axial C_9-Me group whereas the corresponding Me group in 9 must be in an equatorial configuration. The same phenomena as that of 9 are also observed in the case of the cis-clerodane group of diterpenes cited herein,[14] regardless of the substituents (OH, OAc, and so on) at C_6-position. Accordingly, the stereostructures of solidagolactones II - IV and elongatolide B can be represented by 16 (X = oxygen function; Y = side chain). We further examined the structures of solidagolactones VI (6) and VII (7) (elongatolide E[2]) [7: $C_{25}H_{36}O_5$ (m/e 416(M^+)); ν_{max}(film) 1780, 1750, 1710, and 1640 cm^{-1}; δ($CDCl_3$) 0.86(3H, d, J= 6Hz), 1.03(3H, s), 1.22(3H, s), 1.30(3H, s), 1.98(3H, complex), 1.99(3H, complex), 2.72(1H, s), 4.71(2H, d, J= 2Hz), 5.35(1H, t, J= 3Hz), 5.76 (1H, t, J= 2Hz), and 5.98(1H, qq, J= 7, 1.5Hz)]. The physical data of these lactones are quite similar to each other, except for the oxygen functions at C_6-position, as judged from their NMR spectra. As described later, the stereostructures of these compounds were established by chemical conversion of 7 to the known furano compound (10).

When treated with DIBAL in THF (-20 ~ -25 °C, 2.5 h) followed by addition of 10% H_2SO_4, the angelate (7) was converted into the corresponding furan (17),[15] in 79% yield, which was reduced with $LiAlH_4$ in Et_2O (reflux, 5 h) to give two diols (18 and 19),[16] in 36 and 31% yields, respectively. The former was further treated with Ac_2O - pyridine (1 : 2) (100 °C, 9 h) to a monoacetate (20),[17] which was subjected to dehydration using $POCl_3$- pyridine (65 °C, 10 h) to afford two olefins (10 and 21),[18] in 22 and 57% yields, respectively, one of which was identical to the furano compound (10) obtained from solidagolactone IV (4). In this case, the formation of the two olefins suggests that the tertiary OH group at C_4-position must be in an axial configuration compatible with the presence of the α-epoxide ring in the original lactone.

From a biogenetic point of view, it is quite interesting that the above mentioned bitter

principles belong to the cis-clerodane group of diterpenes, all of which have the oxygen functions at C_6-position, whereas solidagolactone I is a trans-clerodane,[3] which has no oxygen function at the same position. Furthermore, it is noted that solidagolactone V (5) is regarded as the direct precursor of tricyclosolidagolactone (1).[1]

The authors wish to thank Prof. A. Ohsuka (Osaka City University) for the IR and NMR spectra of the authentic samples.

References and Notes

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2. T. Anthonsen and R. McCrindle, Acta Chem. Scand., 23, 1068 (1969).
3. T. Okazaki, A. Ohsuka, and M. Kotake, Nippon Kagaku Kaishi, 1973, 584 and references cited therein.
4. F. Bohlmann, U. Fritz, R.M. King, and H. Robinson, Phytochemistry, 19, 2655 (1980).
5. These diterpenes so far obtained in our laboratory were identified by comparing their IR and NMR spectra with those of solidagolactones II - V.
6. Spectral data of the acetate: ν_{max} (film) 1790, 1740br., 1640, 1250, 1030 cm^{-1}; δ($CDCl_3$) δ0.89(3H, d, J= 6Hz), 1.08(3H, s), 1.20(3H, s), 1.56(3H, s), 1.98(3H, s), 4.74(2H, d, J= 2Hz), 4.90(1H, t, J= 5Hz), 5.48(1H, t, J= 7Hz), and 5.80(1H, t, J= 2Hz).
7. T. Anthonsen, M.S. Henderson, A. Martin, R.D.H. Murray, R. McCrindle, and D. McMaster, Can. J. Chem., 51, 1332 (1973).
8. 10: $C_{22}H_{32}O_3$ (m/e 344(M^+)); ν_{max} (film) 1740, 1250, 1030, and 870 cm^{-1}; δ($CDCl_3$) 0.88(3H, d, J= 6Hz), 1.08(3H, s), 1.27(3H, s), 1.58(3H, s), 2.00(3H, s), 4.94(1H, t, J= 5Hz), 5.51(1H, br.s), 6.26(1H, m), 7.20(1H, m), and 7.33(1H, m); ^{13}C NMR ($CDCl_3$): 15.4(q), 18.4(q), 19.0 (t), 21.3(q), 21.7(t), 24.4(q), 26.5(t), 28.4(q), 31.6(t), 31.9(d), 36.7(t), 38.4(s), 42.7 (s), 44.3(d), 74.2(d), 110.7(d), 124.3(d), 125.4(s), 137.6(s), 138.1(d), 142.4(d), and 169.6(s).
9. 11: $C_{20}H_{30}O_2$ (m/e 302(M^+)); ν_{max} (film) 3580br. and 870 cm^{-1}; δ($CDCl_3$) 0.86(3H, d, J= 7Hz), 1.05(3H, s), 1.21(3H, s), 1.68(3H, br.s), 3.64(1H, t, J= 5Hz), 5.76(1H, t, J= 7Hz), 6.19(1H, s), 7.12(1H, s), and 7.26(1H, s).
10. 12: $C_{25}H_{36}O_3$ (m/e 384(M^+)); ν_{max} (film) 1710, 1650, and 870 cm^{-1}; δ($CDCl_3$) 0.86(3H, d, J= 6Hz), 1.08(3H, s), 1.28(3H, s), 1.56(3H, s), 1.82(3H, complex), 1.96(3H, complex), 4.94(1H, t, J= 5Hz), 5.40(1H, br.s), 5.90(1H, qq, J= 7, 1.5Hz), 6.17(1H, m), 7.10(1H, m), and 7.22(1H, m). 13: $C_{25}H_{36}O_3$ (m/e 384(M^+)); ν_{max}(film) 1705, 1655, and 870 cm^{-1}; δ($CDCl_3$) 0.85 (3H, d, J= 6Hz), 1.08(3H, s), 1.28(3H, s), 1.56(3H, s), 1.80(6H, s), 4.91(1H, t, J= 5Hz), 5.43 (1H, t, J= 8Hz), 6.19(1H, m), 6.70(1H, qq, J= 7, 2Hz), 7.12(1H, m), and 7.24(1H, m).
11. 14: $C_{20}H_{28}O_2$ (m/e 300(M^+)); ν_{max} (film) 1715 and 875 cm^{-1}; δ($CDCl_3$) 0.87(3H, d, J= 6Hz), 1.24 (6H, s), 1.54(3H, br.s), 5.60(1H, br.s), 6.22(1H, s), 7.16(1H, s), and 7.30(1H, s).
12. 9: $C_{20}H_{30}O$ (m/e 286(M^+)); ν_{max} (film) 875 cm^{-1}; δ(CCl_4) 0.90(3H, d, J= 6Hz), 1.08(3H, s), 1.17 (3H, s), 1.62(3H, s), 5.24(1H, br.s), 6.10(1H, m), 7.06(1H, m), and 7.18(1H, m).
13. M.S. Henderson, R.D. Murray, R. McCrindle, and D. McMaster, Can. J. Chem., 51, 1322 (1973); R. McCrindle and E. Nakamura, ibid., 52, 2029 (1974) and references cited therein.
14. On the basis of these two C8- and C9-Me signals, methyl 6-acetoxykolavenate and related substances seem to be cis-clerodanes (see ref. 2).
15. 17: $C_{25}H_{36}O_4$ (m/e 400(M^+)); ν_{max} (film) 1700, 1645, and 870 cm^{-1}; δ($CDCl_3$) 0.87(3H, d, J= 6Hz), 1.04(3H, s), 1.26(3H, s), 1.30(3H, s), 1.97(3H, complex), 2.00(3H, complex), 2.70(1H, s), 5.36 (1H, dd, J= 2.5, 2Hz), 5.96(1H, qq, J= 7, 1.5Hz), 6.16(1H, m), 7.09(1H, m), and 7.21(1H, m).
16. 18: $C_{20}H_{32}O_3$ (m/e 320(M^+)); mp 157 - 161 °C (from benzene-hexane); ν_{max} (film) 3430br. and 875 cm^{-1}; δ($CDCl_3$) 0.86(3H, d, J= 6Hz), 1.00(3H, s), 1.08(3H, s), 1.23(3H, s), 2.14(2H, br.s, OH), 3.82(1H, t, J= 2.5Hz), 6.16(1H, m), 7.10(1H, m), and 7.22(1H, m). 19: $C_{20}H_{32}O_3$ (m/e 320 (M^+)); ν_{max}(film) 3200 and 875 cm^{-1}; δ($CDCl_3$) 0.87(3H, d, J= 6Hz), 1.08(3H, d, J= 5Hz), 1.16(6H, s), 3.58(1H, br.s), 3.68(1H, br.s), 5.60(2H, br.s), 6.34(1H, m), 7.81(1H, m), and 7.22(1H, m).
17. 20: $C_{22}H_{34}O_4$ (m/e 302(M^+ - AcOH)); ν_{max} (film) 3500br., 1720, and 870 cm^{-1}; δ($CDCl_3$) 0.85(3H, d, J= 6Hz), 1.03(3H, s), 1.20(3H, s), 1.26(3H, s), 2.10(3H, s), 5.04(1H, t, J= 2.5Hz), 6.28 (1H, m), 7.22(1H, m), and 7.35(1H, m).
18. 21: $C_{22}H_{32}O_3$ (m/e 344(M^+)); ν_{max} (film) 1725, 1630, and 870 cm^{-1}; δ($CDCl_3$) 1.03(3H, d, J= 6Hz), 1.18(3H, s), 1.28(3H, s), 2.04(3H, s), 4.83(1H, d, J= 2Hz), 4.93 - 5.01(2H, complex), 6.24 (1H, m), 7.20(1H, m), and 7.32(1H, m).

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