Tetrahedron Letters,Vol.25,No.26,pp 2809-2812,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

PISCICIDAL *cis*-CLERODANE DITERPENES FROM *SOLIDAGO ALTISSIMA* L: ABSOLUTE CONFIGURATIONS OF 5α,10α-*cis*-CLERODANES

Chikao Nishino[a*], Shunichi Manabe[a], Masami Kazui[b] and Takao Matsuzaki[b]
[a]Mitsubishi-Kasei Institute of Life Sciences, 11 Minamiooya, Machida, Tokyo 194, Japan
[b]Research Center of Mitsubishi Chemical Industries, 1000 Kamoshida-cho, Midori-ku, Yokohama
Kanagawa 227, Japan

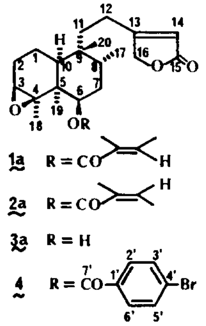
Summary: From *Solidago altissima L.* (Compositae), a new 5α,10α-*cis*-clerodane diterpene (Solidagolactone VIII) and known solidagolactones were isolated as piscicidal constituents. The structures of the constituents including absolute configurations were determined, and a revised structure was given to solidagolactone VII.

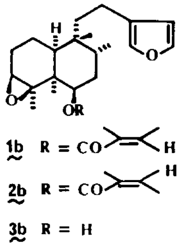
Continuing our investigations[1] of the biologically active constituents of a heinous rank weed, *Solidago altissima* L. (a goldenrod, Compositae), we isolated four piscicidal constituents with the 5α,10α-*cis*-clerodane skeleton [activity, around 10 ppm in TLm (median tolerance limit) to killifish (*Oryzias latipes*)] from the aerial parts of the plant. One (**1a**) of the four was elucidated to be a new compound named as solidagolactone VIII. The others were assigned to known solidagolactones, VII (**2a**), IV (**5**) and V (**6**), isolated by Yamamura *et al.*[2] from the plant. They revised the structures of the solidagolactones to *cis*-clerodanes from *trans*-clerodanes proposed by McCrindle[3] and Okazaki[4]. In this paper, on the basis of chemical transformations, spectral and X-ray analytical data, the structures of the piscicidal solidagolactones are reported, giving new (**1a**) and a revised (**7** → **2a**) structure to solidagolactones VIII and VII, respectively. Also the first description is made of on the absolute structure of the 5α,10α-*cis*-clerodane diterpenes.

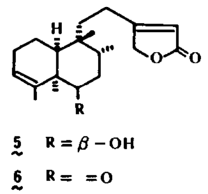
By monitoring by piscicidal activity, from the methanol extract of the aerial parts (except for flowers) (3.4 Kg) of the plant, **2a** (2.7 g) and **5** (1.4 g) were first isolated after successive chromatographies of the extract on Florisil[5a], silicagel[5b] and alumina[5c]. To isolate **1a** (124mg) and **6** (250mg), further $AgNO_3$(10%)-silicagel[5d] and silicagel[5e] chromatographies were required. The physical data of the compounds were as follows: **1a** (solidagolactone VIII): $C_{25}H_{36}O_5$; $[\alpha]_D$ -27.4° (*c* 0.3)[6a]; UV: λ_{max} 209.1 nm (ε 25700)[6b]; IR (film): ν_{max} 1780, 1750, 1705, 1650, 1640, 1268 cm^{-1}; ^1H NMR[6c]: δ 0.88 (3H, d, *J* = 6.4, H_3-17), 1.03 (3H, s, H_3-20), 1.21 (3H, s, H_3-19), 1.29 (3H, s, H_3-18), 1.81 [3H, d, *J* = 6.8, $CH_3(CO)C\overset{Z}{=}CH(C\mathit{H}_3)$], 1.89 [3H, m, $C\mathit{H}_3(CO)C\overset{Z}{=}CH(CH_3)$], 2.75 (1H, bs, H-3), 4.75 (2H, d, *J* = 1.8, H-16), 5.40 (1H, dd, *J* = 2.4, 3.5, H-6), 5.84 (1H, tt, *J* = 1.5, 1.8, H-14), 6.90 [1H, qq, *J* = 1.2, 6.8, $CH_3(CO)C\overset{Z}{=}C\mathit{H}(CH_3)$]; MS: *m/z* 416 ($M^+$), 401 ($M^+-CH_3$), 398 ($M^+-H_2O$), 333 [$M^+-CH_3(CO)C{=}CH(CH_3)$] (exact MS: 333.2076, $C_{20}H_{29}O_4$), 317 [$M^+-CH_3(CO_2){=}CH(CH_3)$] (317.2118, $C_{20}H_{29}O_3$). **2a** (solidagolactone VII): $C_{25}H_{36}O_5$ (Anal,Calcd.: C, 72.08; H, 8.71. Found: C, 72.48; H, 8.76); mp 119°-120° (hexane-EtOAc); $[\alpha]_D$ -28.4° (*c* 1.2); λ_{max} 211.8 nm (ε 26500); ν_{max} (KBr) 1780, 1745, 1695, 1640, 1272, 1248 cm^{-1}; δ 0.88 (3H, d, *J* = 6.6, H_3-17), 1.03 (3H, s, H_3-20), 1.22 (3H, s, H_3-19), 1.31 (3H, s, H_3-18), 1.97 [3H, m, $C\mathit{H}_3(CO)C\overset{E}{=}CH(CH_3)$], 2.03 (3H, d, *J* = 7.0, $CH_3(CO)C\overset{E}{=}CH(C\mathit{H}_3)$], 2.75 (1H, bs, H-3), 4.76 (2H, d, *J* = 1.8, H-16), 5.44 (1H, dd, *J* = 2.5, 3.6, H-6), 5.84 (1H, tt, *J* = 1.5, 1.8, H-14), 6.07 [1H, qq, *J* = 1.2, 7.0, $CH_3(CO)C\overset{E}{=}C\mathit{H}(CH_3)$]; *m/z* 416 ($M^+$), 401 ($M^+-CH_3$), 398 ($M^+-H_2O$), 333 [$M^+-CH_3(CO)C{=}CH(CH_3)$], 317 [$M^+-CH_3(CO_2)C{=}CH(CH_3)$]. **5** (solidagolactone IV): $C_{20}H_{30}O_3$ (Anal. Calcd.: C, 75.43; H, 9.50. Found: C, 75.84; H, 9.68); mp 137°-138° (hexane-EtOAc); $[\alpha]_D$ +3.6° (*c* 0.9); λ_{max} 204.9 nm (ε 18100); ν_{max} (KBr) 3530, 3480 (sh), 1800, 1750, 1640 cm^{-1}; δ 0.88 (3H, d, *J* = 6.8, H_3-17), 1.03 (3H, s, H_3-20), 1.15 (3H, s, H_3-19), 1.70 (3H, bs, H_3-18), 3.71 (1H, t, *J* = 2.8, H-6), 4.75 (2H, d, *J* = 1.8, H-16), 5.83 (2H, m, H-3 and H-14); *m/z* 318 (M^+), 300 (M^+-H_2O), 285. **6** (solidagolactone V): $C_{20}H_{28}O_3$; mp 106.5°-107° (hexane); $[\alpha]_D$ +125.2° (*c* 1.2); λ_{max} 205.3 nm (ε 20800); ν_{max} (film) 1780, 1750, 1705, 1668, 1640 cm^{-1}; δ 0.83 (3H, d, *J* = 6.8, H_3-17), 1.22 (6H, s, H_3-19 and 20), 1.52 (3H, d, *J* = 1.2, H_3-18), 4.75 (2H, d, *J* = 1.8, H-16), 5.63 (1H, m, H-3), 5.82 (1H, tt, *J* = 1.5, 1.8, H-14); *m/z* 316 (M^+) (316.2032), 301 (M^+-CH_3), 287.

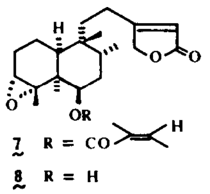
The presence of a β-substituted $\Delta^{\alpha,\beta}$-butenolide ring was suggested in IR (ν_{max} 1800 or 1780, 1750 or 1745, 1640 cm^{-1}) and ^1H NMR (δ 4.76 or 4.75, 5.82 - 5.84) of all the compounds. The other IR and ^1H NMR spectral characteristics in **2a**, **5** and **6** resembled those in solidagolactones VII, IV and V, respectively, and the spectra were identical with those presented by Yamamura[2].

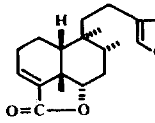
Similarity between **1a** and **2a** was observed in their mass spectra [*m/z* 416 (M^+), 401, 398, 333, 317]. In the ^1H NMR spectra, similar resonances also appeared for the signals of protons on the clerodane skeleton and its pendant methyls (H-3, H-6, H_3-17, H_3-18, H_3-19 and H_3-20). Chemical shifts, splitting patterns and coupling constants of the signals at δ 1.97, 2.03 and 6.07 in **2a** were due to protons on angelate moiety, whereas those at δ 1.81, 1.89 and 6.90 in **1a** to protons on tiglate moiety. Thus the structure **1a** could be given to the new compound.



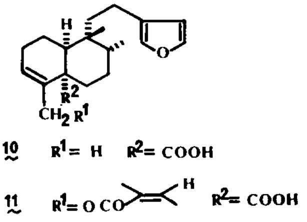








9



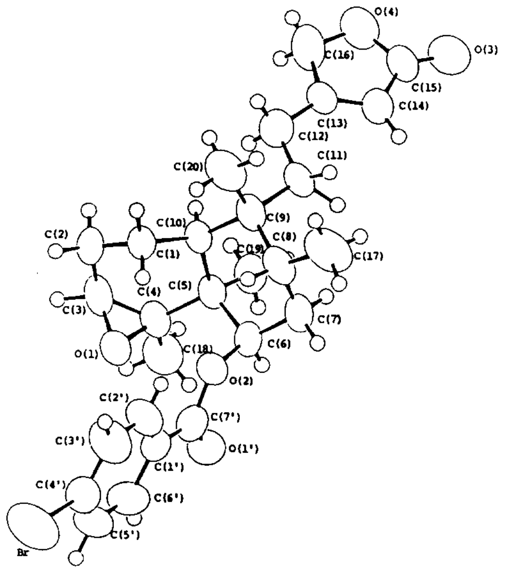


Figure 1. ORTEP drawing of the molecular structure of *p*-bromobenzoate (**4**).

The four piscicidal compounds were structurally correlated. Solidagolactone V (**6**) was derived from **5** (Jones' oxidation). Epoxybutenolides, **1a** and **2a**, were respectively converted into epoxyfurano-compounds, **1b**[7] and **2b**[8], with DIBAL (THF, -35° → -20°, 3.5 hr). The presence of a β-substituted furan ring was indicated in the IR band (ν_{max} 880 cm^{-1}) and ^{1}H NMR signals [δ 6.25 (1H, m), 7.21 (1H, m), 7.35 (1H, t, J = 1.5)] of **1b** and **2b** which yielded the same compound with a hydroxyl group (**3b**)[9] [ν_{max} (film) 3480 cm^{-1}; δ 1.37 (3H, s, H$_3$-18), 3.01 (1H, d, J = 2.4, H-3), 4.13 (1H, t, J = 2.6, H-6), 5.44 (1H, bs, OH)] on LiAlH$_4$ reduction (THF, 15°, 3hr). Solidagolactone IV (**5**) was also correlated with **3b**. On treatment with *p*-bromoperbenzoic acid (CH$_2$Cl$_2$, room temp, 1 hr), **5** yielded two epoxides, **3a**[10] and **8**[11] (yield ratio, 1.7:1). According to the usual epoxidation mechanism of homoallylic alcohols[12], the main product, **3a**, was expected to have an epoxide ring with the same configuration (β-epoxide) as the β-OH group. In the IR (CHCl$_3$) of **3a**, an absorption of intramolecular hydrogen bond of the OH[13] was shown at 3470 cm^{-1}, which was unaffected by dilution, but the spectrum showed no absorption at 3600 cm^{-1} (free OH) which appeared in the IR (CHCl$_3$) of **8**. In **8**, a weak IR band was observed at 3475 cm^{-1} which was affected by dilution. The hydrogen bonding nature of the OH[14] in **3a** was suggested by a sharpened broad singlet signal in very lower field (δ 5.41), whereas the OH proton of **8** resonated at δ around 1.8 (m). These evidences suggest the presence of an intramolecular hydrogen bonding between the β-OH group and the oxygen atom of a β-oriented epoxide ring (δ 1.37 (3H, s, H$_3$-18), 3.02 [1H, d, J = 2.4, H-3]) in **3a**. In **8**, no such interaction of the α-oriented epoxide [δ 1.40 (3H, s), 3.11 (1H, d, J = 5.1)] causes a free form of the β-OH group. Because of similar chemical shift (δ 5.44) of the OH proton of **3b** to that of **3a**, **3a** was reacted with DIBAL (THF, -35° → -25°, 3.5 hr) to yield a furano-derivative which was identified as **3b**. Accordingly, the structure of solidagolactone VII was revealed to revise to **2a** from **7** proposed by Yamamura *et al.*[2]

In *cis*-clerodane type diterpenes, the absolute configuration for a 5β,10β-*cis*-clerodane was determined for **9** by a structural correlation[15] of this compound with (-)-hardwickiic acid with a confirmed absolute structure[16]. For 5α,10α-*cis*-clerodanes, McCrindle[17] attempted to establish the absolute configurations of solidagoic acid A (**10**) and B (**11**) based on Cotton effects in the CD curves of a C-2 ketone and a similar enone derivative. He left however some ambiguities in the entire absolute structure, since interpretation for the signs of Cotton effects were affected by possible conformations for the derivatives.

Crystalline *p*-bromobenzoate (**4**)[18] was obtained from **3a**, and its absolute structure was established by X-ray analysis (Fig. 1). Hence, the absolute configuration could be determined for the piscicidal compounds as the first example for 5α,10α-*cis*-clerodane diterpenes.

Crystal data[19]: Monoclinic, a = 11.782 (2), b = 10.526 (3), c = 10.273 (2) Å, β = 96.13 (1)°, U = 1267 Å, Z = 2, D_c = 1.356, μ = 27.191 cm^{-1}, space group $P\ 2_1$. Intensity data for 5539 reflections ($2\theta<150°$) were measured with an Enraf-Nonius (AD4 diffractometer using graphite monochromated Cu-Kα Radiation and an $\omega/2\theta$ scanning technique. After averaging the intensities of Friedel pairs, 2373, independent reflections with $|F| > 3\sigma(|F|)$ were used. The structure was solved by the direct method and refined by the full-matrix least squares methods, including all non-hydrogen atoms with anisotropic temperature factors and 5 hydrogen atoms with isotropic temperature factors. The final R-index for 2373 reflections were 0.097 at the calculated positions. The absolute configuration was determined by comparing the observed and calculated structure factors of 23 Friedel pairs which supported the absolute configurations shown in Fig. 1.

Acknowledgment: We wish to thank Prof. S. Yamamura, Keio University, for the IR and ^1H NMR spectra of solidagolactones VII, IV and V.

References and Notes

1. C. Nishino and T. Tsuzuki, *Bōtyu-Kagaku*, 40, 62 (1975).
2. M. Niwa and S. Yamamura, *Tetrahedron Letters*, 22, 2789 (1981).
3. T. Anthonsen and R. McCrindle, *Acta Chem. Scand.*, 23, 1068 (1969).
4. T. Okazaki, A. Ohsuka and M. Kotake, *Nippon Kagaku Kaishi*, 1973, 584.
5. a: EtOAc (active fraction) after hexane; b: hexane-EtOAc 10% stepwise; Activity, 70% and 80% EtOAc in hexane. c: Benzene-EtOAc 5% stepwise; Activity, 30-40% (2a), 40-50% (to subsequent chromatographies to isolate 1a and 6) and 55-60% (5) EtOAc in benzene. d: Hexane-EtOAc 5% stepwise; Activity, 90-95% (1a) and 100% (to final chromatography to obtain 6) EtOAc in hexane. e: Benzene-EtOAc (4:1); Activity, fractions 10-13 (6).
6. a: In EtOH at 25°. B: In EtOH. c: In $CDCl_3$ at 90 MHz. Coupling constant (*J*) in Hz.
7. 1b: $C_{25}H_{36}O_4$ (Anal. Calcd.: C, 74.96; H, 9.06. Found: C, 75.17; H, 9.21); mp 84.5°-86° (hexane); $[\alpha]_D$ -31.9° (*c* 0.4); ν_{max} (film) 1710, 1655, 1270, 880 cm^{-1}; δ 0.85 (3H, d, *J* = 6.6, H_3-17), 1.04 (3H, s, H_3-20), 1.27 (3H, s, H_3-19), 1.29 (3H, s, H_3-18), 1.80 [3H, d, *J* = 6.8, $C\mathit{H}_3(CO)C{=}CH(CH_3)$], 1.90 [3H, m, $CH_3(CO)C{=}CH(C\mathit{H}_3)$], 2.75 (1H, bs, H-3), 5.41 (1H, dd, *J* = 2.4, 3.5, H-6), 6.26 (1H, m, furanoid), 6.91 [1H, qq, *J* = 1.2, 6.8 $CH_3(CO)C{=}C\mathit{H}(CH_3)$], 7.21 (1H, m, furanoid), 7.35 (1H, t, *J* = 1.5, furanoid); *m/z* 400 (M^+), 385 (M^+-CH_3), 382 (M^+-H_2O), 317 [$M^+-CH_3(CO)C{=}CH(CH_3)$], 301 [$M^+-CH_3(CO_2)C{=}CH(CH_3)$].
8. 2b: $C_{25}H_{36}O_4$; $[\alpha]_D$ -23.6° (*c* 1.1); ν_{max} 1712, 1650, 1238, 878 cm^{-1}; δ 0.86 (3H, d, *J* = 6.4, H_3-17), 1.03 (3H, s, H_3-20), 1.27 (3H, s, H_3-19), 1.31 (3H, s, H_3-18), 1.99 [3H, m, $C\mathit{H}_3(CO)C{=}CH(CH_3)$], 2.04 [3H, d, *J* = 6.8, $CH_3(CO)C{=}CH(C\mathit{H}_3)$], 2.75 (H, bs, H-3), 5.44 (1H, dd, *J* = 2.2, 3.5, H-6), 6.06 [1H, qq, *J* = 1.1, 6.8, $CH_3(CO)C{=}C\mathit{H}(CH_3)$], 6.25 (1H, m, furanoid), 7.21 (1H, m, furanoid), 7.35 (1H, t, *J* = 1.6, furanoid); *m/z* 400 (M^+), 385 (M^+-CH_3), 382 (M^+-H_2O), 317 [$M^+-CH_3(CO)C{=}CH(CH_3)$] (317.2124, $C_{25}H_{29}O_3$), 301 [$M^+-CH_3(CO_2)C{=}CH(CH_3)$] (301.2155, $C_{25}H_{29}O_2$).
9. 3b: $C_{20}H_{30}O_3$; $[\alpha]_D$ -28.0° (*c* 0.9); ν_{max} (film) 3480, 875 cm^{-1}; δ 0.85 (3H d, *J* = 7.0, H_3-17), 1.02 (3H, s, H_3-20), 1.19 (3H, s, H_3-19), 1.37 (3H, s, H_3-18), 3.01 (1H, d, *J* = 2.4, H-3), 4.13 (1H, t, *J* = 2.6, H-6), 5.44 (1H, bs, OH), 6.25 (1H, m, furanoid), 7.20 (1H, m, furanoid), 7.35 (1H, t, *J* = 1.5, furanoid); *m/z* 318 (M^+) (318.2192), 300 (M^+-H_2O).
10. 3a: $C_{20}H_{30}O_4$; $[\alpha]_D$ -27.2° (*c* 1.1); ν_{max} ($CHCl_3$) 3470, 1785, 1750, 1640 cm^{-1}; δ 0.87 (3H, d, *J* = 6.8, H_3-17), 1.00 (3H, s, H_3-20), 1.14 (3H, s, H_3-19), 1.37 (3H, s, H_3-18), 3.02 (1H, d, *J* = 2.4, H-3), 4.13 (1H, bt, *J* = 2.7, H-6), 4.75 (2H, d, *J* = 1.8 H-16, 5.41 (1H, bs, OH), 5.83 (1H, tt, *J* = 1.5, 1.8, H-14); *m/z* 334 (M^+) (334.2145), 316 (M^+-H_2O).
11. 8: $C_{20}H_{30}O_4$; $[\alpha]_D$ -17.1° (*c* 1.3); ν_{max} ($CHCl_3$) 3600, 3475, 1785, 1750, 1640 cm^{-1}; δ 0.87 (3H, d, *J* = 6.4, H_3-17), 0.97 (3H, s, H_3-20), 1.16 (3H, s, H_3-19), 1.40 (3H, s, H_3-18), around 1.8 (1H, OH), 3.11 (1H, d, *J* = 5.1, H-3), 3.82 (1H, bt, *J* = 2.6, H-6), 4.73 (2H, d, *J* = 1.8, H-16), 5.82 (1H, tt, *J* = 1.5, 1.8, H-14) *m/z* 334 (M^+) (334.2183), 319 (M^+-CH_3), 316 (M^+-H_2O).
12. E.W. Colvin, S.M. Mälchenko, R.A. Raphael and J.S. Roberts, *J. Chem. Soc. Perkin I*, 1973, 1989.
13. P.C. Chamberlain, M.L. Roberts and G.H. Whitham, *J. Chem. Soc. (B)*, 1970, 1374.
14. S. Mynderse and R.E. Moore, *J. Org. Chem.*, 43, 4359 (1978).
15. M.S. Henderson, R.D.H. Murray, R. McCrindle and D. McMaster, *Can. J. Chem.*, 51, 1322 (1973). A.B. Anderson, R. McCrindle and E. Nakamura, *J. Chem. Soc. Chem. Comm.*, 1974, 453. R. McCrindle, E. Nakamura and A.B. Anderson, *J. Chem. Soc. Perkin I*, 1976, 1590.
16. R. Misra, R.C. Pandey and S. Dev, *Tetrahedron Letters*, 1968, 2681.
17. T. Anthonsen, M.S. Henderson, A. Martin, R.D.H. Murray, R. McCrindle and D. McMaster, *Can. J. Chem.*, 51, 1332 (1973).
18. 4: $C_{27}H_{33}O_5Br$ (Anal. Calcd.: C, 62.67; H, 6.43; Br, 15.44. Found: C, 62.75; H, 6.31; Br, 15.50); mp 192.5° - 194°; $[\alpha]_D$ -10.7° (*c* 0.5); λ_{max} 242.9 (ε 17200), 200.6 nm (ε 34000); ν_{max} (KBr) 1790, 1750, 1715, 1645, 1598, 1490 cm^{-1}; δ 0.89 (3H, d, *J* = 6.6, H_3-17), 1.07 (3H, s, H_3-20), 1.26 (3H, s, H_3-19), 1.30 (3H, s, H_3-18), 2.75 (1H, d, *J* = 1.5, H-3), 4.76 (2H, d, *J* = 1.8, H-16), 5.57 (1H, dd, *J* = 2.4, 3.5, H-6), 5.86 (1H, tt, *J* = 1.5, 1.8, H-14), 7.58 (2H, d, *J* = 8.7, aromatic), 7.97 (2H, dm, *J* = 8.7, aromatic); *m/z* 518 (M^++2)/516 (M^+) (1:1), 503 (M^++2-CH_3)/501 (M^+-CH_3) (1:1), 333 ($M^+-BrC_6H_4CO$), 316 ($M^+-BrC_6H_4CO_2H$).
19. The atomic co-ordinates for this work are available on request from the director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

(Received in Japan 13 March 1984)