CHEMISTRY LETTERS, pp. 69-72, 1986.

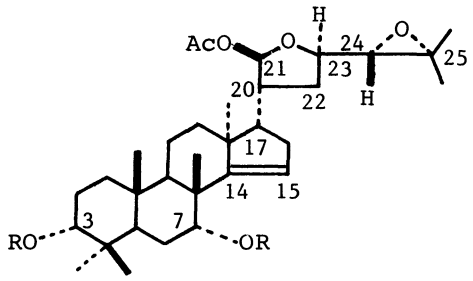
THE STRUCTURE OF A NEW NATURAL APOTIRUCALLANE-TYPE TRITERPENE AND THE STEREOCHEMISTRY OF THE RELATED TERPENES. X-RAY AND ^{13}C NMR SPECTRAL ANALYSES

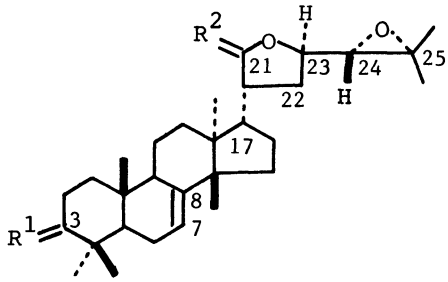
Tsutomu NAKANISHI,* Akira INADA, Masatoshi NISHI,
Takuichi MIKI, Ryozi HINO,† and Takaji FUJIWARA†
Faculty of Pharmaceutical Sciences, Setsunan University, Hirakata, Osaka 573-01
†Faculty of Science, Shimane University, Matsue 690

The structure of a new apotirucallane-type triterpene, 21-O-acetyl toosendantriol, isolated from the fruit of Melia toosendan was determined by X-ray analysis. Based on comparison of the ^{13}C chemical shifts, the steric structures of the side chains of two epimeric 21-acetates derived from a tirucallane-type terpene, melianone were also clarified.

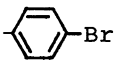
A Chinese crude drug named Chuan-Lian-Zi (Sen-Ren-Shi in Japanese), i.e. the air-dried fruit of Melia toosendan Sieb. et Zucc.[1] [M. azedarach L. var. toosendan (Sieb. et Zucc.) Makino[2]](Meliaceae) has so far been used in China as an anodyne for stomach ache due to roundworms, gripe, etc.,[1,2a] and also as a vermicide.[1,2b] Chemical investigation of the fruit of the plant has led us to the isolation of a new apotirucallane-type triterpene named as 21-O-acetyl toosendantriol (**1**) and the structure of **1** has been established based on X-ray analytical and spectral evidence. The stereo-structures of the side chains of two epimeric 21-acetates (**3a** and **3b**) derived from natural melianone (**2**)[3] have also been elucidated by comparison of their ^{13}C chemical shifts with those of **1**. These details are communicated in this paper.

Methanol extract of air-dried fruits of M. toosendan was suspended in water and extracted with petroleum ether and chloroform, subsequently. The chloroform layer was repeatedly chromatographed over silica gel to give 21-O-acetyl toosendantriol (**1**; 0.12% yield from the extract), $C_{32}H_{50}O_6$,[6] a white powder, $[\alpha]_D^{25}$ -3.6°(c 0.26, $CHCl_3$), the spectral data of which are: IR ($CHCl_3$) 3550 (OH), 1740, 1210 (ester) cm^{-1}; ^1H NMR[7] ($CDCl_3$, 400 MHz) δ 6.24 (1H, d, J = 4.0 Hz, H-21α), 5.47 (1H, m, H-15), 3.92 (2H, m, H-7β and H-23α), 3.40 (1H, brs, H-3β), 2.67 (1H, d, J = 7.5 Hz, H-24β), 2.06 (3H, s, OCOMe), 1.33, 1.29 (3H each, both s, Me-26 and Me-27), 1.05, 1.03, 0.94, 0.89, 0.84 (3H each, all s, 5 x tert.Me); ^{13}C NMR ($CDCl_3$; 100 MHz) Table 1 and Ref. 8. The MS, ^1H and ^{13}C NMR data showed that this terpene belongs to the apotirucallane-type triterpene, and a gross structure (**1**) without the stereo-chemistry of the side chain part was inferred for 21-O-acetyl toosendantriol.





1: R = H

1a: R = -CO-  -Br

2: R^1 = O, R^2 = H, OH
(C-21 epimeric mix.; ca. 1:1)

3a: R^1 = O, R^2 = α-OAc, β-H

3b: R^1 = O, R^2 = β-OAc, α-H

4: R^1 = β-OH, α-H, R^2 = H, OH
(C-21 epimeric mix.; ca. 1:1)

The structure for **1** was established by the single crystal X-ray analysis of the corresponding di-p-bromobenzoate (**1a**), $C_{46}H_{56}O_8Br_2$, mp 263-265 °C.[9] Crystals of **1a**, obtained by slow crystallization from methanol-chloroform, are orthorhombic with space group $P2_12_12_1$, a = 12.972(4), b = 18.333(3), c = 18.563(4) Å, Z = 4, U = 4414.6(5) $Å^3$, D_c = 1.349 g cm^{-3}. Intensities of 1131 (Fo > 3 Fo) independent reflections with 2θ values up to 54.9° were collected on a Rigaku AFC-5 diffractometer with graphite monochromated Mo-Kα radiation, using the ω-2θ scanning technique. The structure was solved by direct method using MULTAN 78 program[10] and refined by block diagonal least squares method[11] to an R value of 0.058 for all non-hydrogens anisotropic.[12] Figure 1 shows a computer-generated perspective drawing (PLUTO) of the molecule **1a**, indicating an apotirucallane-type nucleus with $C_{(21\beta)}$-OAc (R), $C_{(23\alpha)}$-H (R), and $C_{(24\beta)}$-H (S) configurations. Thus, the structure of 21-O-acetyl toosendantriol is now defined as formula **1**.[13]

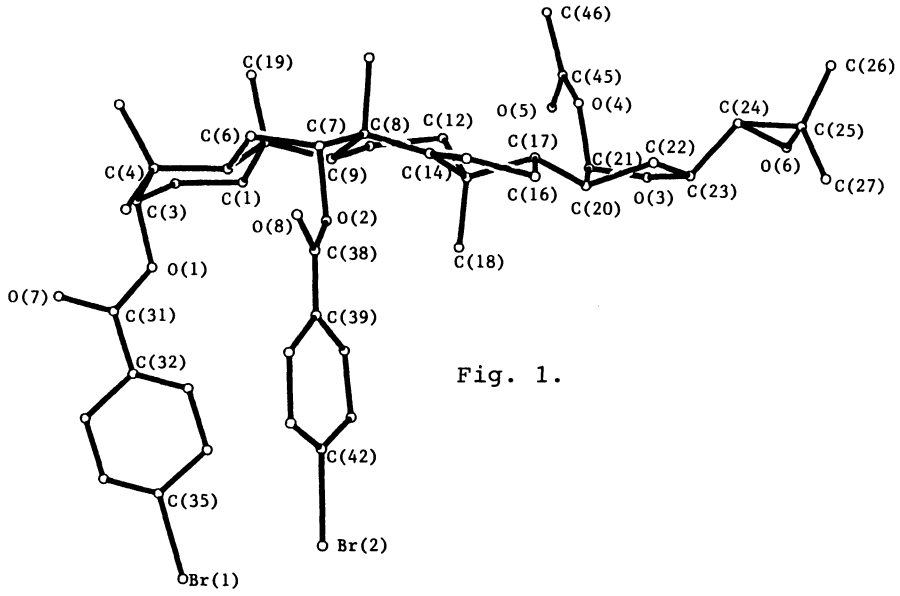


Fig. 1.

A series of tirucallane- and apotirucallane-types triterpenes, represented by melianone,[3] melianol,[3] etc.,[14,15] carry analogous side chains to that of **1**. However, the steric structures of these side chains have remained unclear up to date. The following ^{13}C NMR study has now revealed the steric structures of the side chains of melianone (**2**), its two acetates (**3a** and **3b**), and melianol (**4**). Melianone (**2**)[3] was acetylated in a usual manner to give the corresponding two acetates, the epimer at C-21 (**3a** and **3b**), the ^{13}C NMR data of which were compared with those of **1**. The chemical shifts for the carbons on the side chains of these terpenes are listed up in Table 1.

Table 1. ^{13}C Chemical Shifts of the Side Chains' Carbons of **1**, **3a**, and **3b** [δ(ppm) relative to TMS; multiplicities in parentheses]

	C-20(d)	C-21(d)	C-22(t)	C-23(d)	C-24(d)	C-25(s)
1	44.32	96.77	31.48	79.75	66.79	57.11
3a	47.40	100.73	33.83	78.95	64.98	57.04
3b	45.98	96.89	30.82	79.81	66.84	57.13

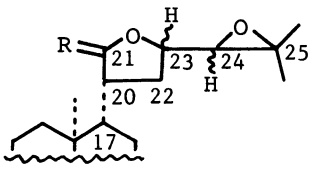
The assignments for these related carbons were made based on proton noise-decoupled, off-resonance decoupled, and selective proton-decoupled[16] experiments. Chemical shift of each carbon (from C-20 to C-25) on the side chain of **3b** coincided very closely with that of **1**, indicating that both side chains of **1** and **3b** have the same steric structure. On the other hand, C-20 and C-21 of **3a** exhibited large downfield shifts compared with those of **1** and **3b**, and oppositely, C-24 and C-23 of **3a** showed upfield shifts, suggesting that **3a** is assigned to the $C_{(21\alpha)}$-OAc epimer. Thus, the complete structure of melianone is now defined as formula **2**. Natural melianol[3] was chemically correlated with natural melianone (**2**),[17] indicating that melianol has also the same side chain structure as melianone and thus, is shown in formula **4**.

References

1) "Dictionary of Chinese Crude Drugs (Zhong-Yao-Da-Ci-Dian in Chinese)," ed by Chiang Su New Medical College, Shanghai Scientific Technologic Publisher, Shanghai (1977), p.232 (in Chinese).

2) a) S. Kitamura and G. Murata, "Coloured Illustrations of Woody Plants of Japan," Hoikusha Publishing Co., Ltd, Osaka (1976), Vol.1, p.308 (in Japanese); b) "Hirokawa's Dictionary of Medicinal Plants," ed by M. Konoshima, S. Shibata, T. Shimomura, and T. Higashi, Hirokawa Publishing Co., Tokyo (1980), p.193 (in Japanese).

3) Previously, the following gross structure has been authorized for the side chain part of both melianone[4,5] and melianol.[4]



R = H, OH (epimeric mix.; ca. 1:1)

4) T. Nakanishi, A. Inada, and D. Lavie, Chem. Pharm. Bull., in press.
5) J. Polonsky, Z. Varon, R. M. Rabanal, and H. Jacouemin, Isr. J. Chem., 16, 16 (1977).
6) The molecular formula was determined based on the following MS data: EIMS m/z(%) 530(M^+, 3), 470.340[$(M-AcOH)^+$, $C_{30}H_{46}O_4$ = 470.339, 93], 330.256 [(M - side chain - H)$^+$, $C_{22}H_{34}O_2$ = 330.257, 83]; FDMS m/z(%) 530(M^+, 15).
7) The full ^1H assignments have been achieved after the structures of **1a** and also **1** had been established by X-ray analysis.
8) 16.30(t), 23.85(t), 25.11(t), 32.60(t), 32.62(t), 35.09(t), 37.08(s), 37.79(s), 40.55(d), 41.60(d), 44.49(s), 46.73(s), 52.64(d), 72.35(d, C-7), 76.17(d, C-3), 119.25(d, C-15), 162.37(s, C-14), 15.23, 19.38, 19.59, 22.14, 24.94, 27.91, 28.07(all q, 7 x tert.Me), 21.48(q, MeCO), 169.88(s, MeCO).
9) Usual treatment of **1** with p-bromobenzoyl chloride and pyridine gave the corresponding di-p-bromobenzoate (**1a**), $[\alpha]_D^{20}$ -40.3° (c 0.11, $CHCl_3$). IR (KBr) 1745, 1705, 1590, 1170, 1115, 1105, 1010 cm^{-1}; ^1H NMR[7] ($CDCl_3$, 400 MHz)δ 6.24(1H, d, J = 3.8 Hz, H-21α), 5.45(1H, m, H-15), 5.32(1H, brs, H-7β), 4.83(1H, brs, H-3β), 3.86(1H, ddd, J = 10.3, 7.6, 7.2 Hz, H-23α), 2.64(1H, d, J = 7.6 Hz, H-24β), 2.06(3H, s, OCOMe), 1.31, 1.25(3H each, both s, Me-26 and Me-27), 1.19, 1.04, 1.02, 0.97, 0.75(3H each, all s, 5 x tert.Me), 7.71, 7.42(2H each, A_2B_2q, J = 8.7 Hz, 4 x aromatic H), 7.89, 7.59(2H each, A_2B_2q, J = 8.7 Hz, 4 x aromatic H); FDMS m/z(%) 898(M^+, 3), 896(M^+, 5), 894(M^+, 3); EIMS m/z[%] 838[$(M-AcOH)^+$, 10], 836[$(M-AcOH)^+$, 19], 834[$(M-AcOH)^+$, 9].
10) P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, "MULTAN 78; A System of Computer Programs for the Atomic Solution of Crystal Structure from X-Ray Diffraction Data," Univ. of York, England (1978).
11) "The Universal Crystallographic Computation System Program-Osaka," The Computation Center, Osaka University, Osaka (1979).
12) Atomic coordinates, structure and temperature factors, bond distances and angles will be deposited with the Cambridge Crystallographic Data Centre.
13) A triterpene named compound D was isolated from Chisocheton paniculatus (Meliaceae) and for it, an inferred structure [with $C_{(21\alpha)}$-OAc and with undefined steric configurations at C-23 and C-24] different from structure **1** has been provided.[14] However, the ^1H and ^{13}C NMR data published for compound D[14] appear to be similar to those for **1**.
14) J. D. Connolly, C. Labbé, D. S. Rycroft, and D. A. H. Taylor, J. Chem. Soc., Perkin Trans. 1, 1979, 2959.
15) For example; C. W. L. Bevan, D. E. U. Ekong, T. G. Halsall, and D. Toft, J. Chem. Soc., C, 1967, 820; A. Mondon, B. Epe, U. Oelbermann, and V. Sinnwell, Tetrahedron Lett., 1982, 3551.
16) The ^1H NMR assignments for the side chain parts of **1**, **3a**, and **3b** were performed by a two-dimensional NMR experiment (COSY), and based on these established ^1H assignments, selective proton-decoupled ^{13}C NMR experiments were carried out.
17) Natural melianol was identical in IR(KBr), ^1H NMR($CDCl_3$, 400 MHz), and co-TLC with the authentic material derived from natural melianone by $NaBH_4$ reduction.

(Received October 28, 1985)