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THE STRUCTURE OF NEW LATHYRANE DITERPENES, JOLKINOLS A, B, C, AND D, FROM EUPHORBIA JOLKINI BOISS.

Daisuke Uemura, Kazunori Nobuhara, Yutaka Nakayama, Yoshikazu Shizuri, and Yoshimasa Hirata

Chemical Institute, Faculty of Science, Nagoya University, Chikusa, Nagoya, Japan

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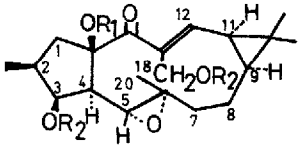
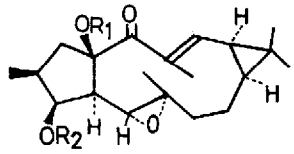
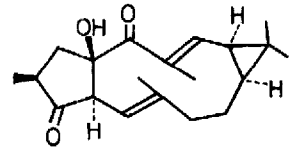
Our previous reports[1] described the isolation and structures of toxic principle and abietane diterpenes from Euphorbia jolkini Boiss. (Euphorbiaceae). Further investigation from biogenetic interests of ingenol and high-oxygenated diterpenes[2] gave four new diterpenes, which were named jolkinols A (1), B (2), C (3), and D (4). Now, we report herein the structural elucidation of these new diterpenes on the basis of the chemical transformation of jolkinol B (2) to lathyrol (5) whose structure has been determined by E. Hecker[3], the interrelation of jolkinols, NOE experiments with jolkinol C (3), and epoxidation of the isolated carbon-carbon double bond between C-5 and C-6 in jolkinol D (4).



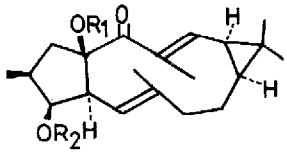
(1) R_1= cinnamoyl, R_2= H
(9) R_1= cinnamoyl, R_2= Ac



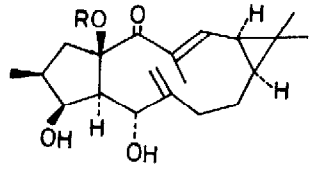
(2) R_1= cinnamoyl, R_2= H
(8) R_1= cinnamoyl, R_2= Ac
(10) R_1= $COCH_2CH_2Ph$, R_2= Ac
(11) R_1= R_2= H
(18) R_1= Ac, R_2= H



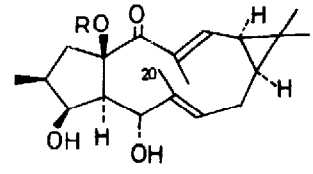
(3)



(4) R_1= Ac, R_2= H
(14) R_1= $COCH_2CH_2Ph$, R_2= Ac
(17) R_1= R_2= H



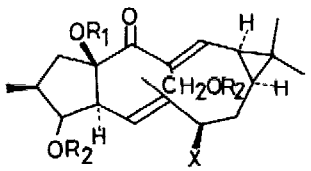
(5) R= H
(7) R= cinnamoyl



(6) R= cinnamoyl

The molecular formulas, physical constants, and spectral data of jolkinols are as follows: jolkinol A (1), $C_{29}H_{36}O_6$: $[\alpha]_D^{20}$= -91° (c, 0.73 in $CHCl_3$); M^+ 480.2511 (calcd. 480.2512), 350, 332; IR ($CHCl_3$) 3520, 1720, 1640, 1590 cm^{-1}; NMR (δ, $CDCl_3$, 100 MHz) 0.88 (3H, s), 1.12 (3H, d, J= 7 Hz), 1.16 (3H, s), 1.31 (3H, s), 1.74 (1H, dd, $J_{9,11}$= 8 Hz, $J_{11,12}$= 11 Hz, H-11), 2.88 (2H, br.s, OH), 3.50 (1H, dd, J= 6, 10 Hz, H-1α), 3.68 (1H, d, $J_{4,5}$= 9 Hz, H-5), 4.16 (1H, t, J= 3 Hz, H-3), 4.34, 4.54 (2H, AB q, J= 12 Hz, H-18), 6.44 (1H, d, J= 16 Hz), 7.12 (1H, d, $J_{11,12}$= 11 Hz, H-12), 7.2-7.5 (5H, m), 7.68 (1H, d, J= 16 Hz); jolkinol B (2), $C_{29}H_{36}O_5$: $[\alpha]_D^{20}$= -120° (c, 0.48 in $CHCl_3$); M^+ 464.2571 (calcd. 464.2563), 334, 316; IR ($CHCl_3$) 3520, 1720, 1630, 1580 cm^{-1}; NMR (δ, $CDCl_3$, 100 MHz) 0.85 (3H, s), 1.13 (3H, d, J= 7 Hz), 1.16 (3H, s), 1.21 (3H, s), 1.88 (3H, d, J= 2 Hz, H-18), 3.54 (1H, dd, J= 7, 12 Hz, H-1α), 3.65 (1H, d, $J_{4,5}$= 10 Hz, H-5), 4.14 (1H, t, J= 4 Hz, H-3), 6.44 (1H, d, J= 16 Hz), 7.00 (1H, d, $J_{11,12}$= 11 Hz, H-12), 7.2-7.5 (5H, m), 7.72 (1H, d, J= 16 Hz); jolkinol C (3), $C_{20}H_{28}O_3$: $[\alpha]_D^{20}$= +5° (c, 1.3 in $CHCl_3$); M^+ 316.2080 (calcd. 316.2038), 298; IR ($CHCl_3$) 3460, 1740, 1630, 1610 cm^{-1}; NMR (δ, $CDCl_3$, 100 MHz) 1.02 (3H, s), 1.05 (3H, s), 1.29 (3H, d, J= 2 Hz, H-20), 1.32 (3H, d, J= 7 Hz), 1.95 (3H, d, J= 2 Hz, H-18), 2.87 (1H, d, J= 10 Hz, H-4), 3.00 (1H, s, OH), 3.40 (1H, dd, J= 12, 16 Hz, H-1α), 5.50 (1H, br.d, J= 10 Hz, H-5), 7.40 (1H, br.d, J= 10 Hz, H-12); jolkinol D (4), $C_{22}H_{32}O_4$: $[\alpha]_D^{20}$= +27° (c, 0.52 in $CHCl_3$); m.p. 186-188°; M^+ 360.2318 (calcd. 360.2301), 318, 300; IR ($CHCl_3$) 3580, 1740, 1640, 1610 cm^{-1}; NMR (δ, $CDCl_3$, 100 MHz) 1.04 (3H, s), 1.09 (3H, d, J= 7 Hz), 1.18 (3H, s), 1.46 (3H, d, J= 2 Hz, H-20), 1.83 (3H, d, J= 2 Hz, H-18), 2.00 (3H, s), 3.51 (1H, dd, J= 8, 14 Hz, H-1α), 3.90 (1H, t, J= 3 Hz, H-3), 5.68 (1H, br.d, J= 11 Hz, H-5), 6.66 (1H, br.d, J= 11 Hz, H-12).

The treatment of jolkinol B (2) on alumina (Woelm, neutral, activity I) at 60° without any solvent yielded compounds (6) and (7) [(6): M^+ 464, NMR (δ, $CDCl_3$, 100 MHz) 1.67 (3H, br.s, H-20), 5.27 (1H, dd, J= 6, 11 Hz, H-7), 5.47 (1H, d, J= 7 Hz, H-5); (7): M^+ 464, NMR (δ, $CDCl_3$, 100 MHz) 4.88 (1H, s, H-20), 4.91 (1H, d, J= 6 Hz, H-5), 4.98 (1H, s, H-20)]. Compound (7), a minor product, was saponified with an aqueous KOH solution in methanol to give a triol (5). The triol (5) was identified as lathyrol by the mixed m.p. and by the comparison of the IR (KBr) and NMR spectra with those of an authentic specimen. The presence of the tertiary alcohol esterified with cinnamic acid in jolkinol B was suggested by its molecular formula and a down-field shift of 1.31 ppm of the signal of H-3 in the NMR spectrum of the acetate (8) of jolkinol B. Consequently, the structure of jolkinol B (2) was determined except the configuration of C-6. On the other hand, from the NMR spectra of jolkinols A and B it is suggested that a hydroxy methylene group (δ 4.34 and 4.54) in jolkinol A corresponds to an allylic methyl group (δ 1.88)



(12) R_1= cinnamoyl, R_2= Ac, X= Cl
(13) R_1= cinnamoyl, R_2= Ac, X= OAc
(15) R_1= $COCH_2CH_2Ph$, R_2= Ac, X= Cl
(16) R_1= $COCH_2CH_2Ph$, R_2= Ac, X= H

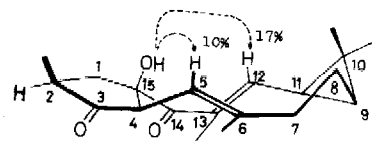


Fig.1. The conformation of jolkinol C.

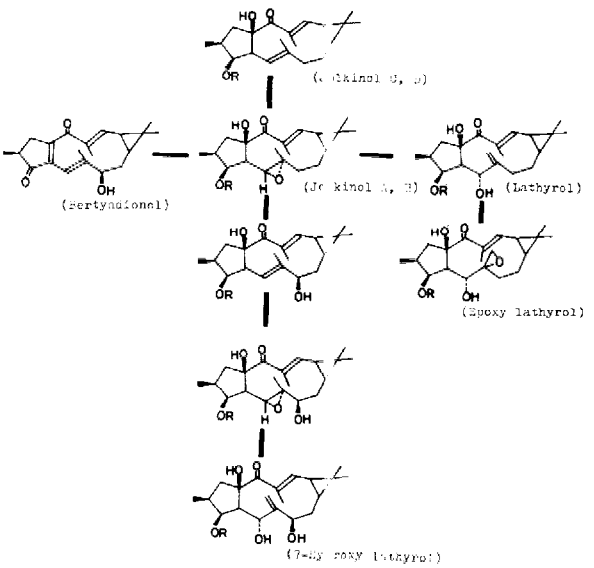


Fig.2. The biogenetic interrelationships of lathyrane-type diterpenes

in jolkinol B. In practice, a diacetate (9) of jolkinol A, whose NMR spectrum showed the presence of the tertiary alcohol esterified with cinnamic acid in jolkinol A, was converted to compound (10) with the aid of Pd-C as a catalyst under a hydrogen atmosphere in ethyl acetate. Hydrolysis of compound (10) gave a diol (11) which was obtained with cinnamic acid by hydrolysis of jolkinol B. Further interrelation of jolkinols were performed as follows. The treatment of the acetate (9) of jolkinol A (1) with HCl gas in acetic acid for 30 minutes at room temperature afforded an allyl chloride (12) and a diacetate (13). The structure of compound (12) was suggested by its NMR spectrum. The signal of the proton attached at the carbon bearing chlorine atom appeared at δ 4.18 as a doublet of doublets (J= 3, 12 Hz), and the signal attributed to three protons of methyl group and the signal assigned to the proton attached at a new double bond appeared at δ 1.64 as a broad singlet and at δ 6.19 as a broad doublet (J= 12 Hz), respectively. It is supposed that the epoxide ring in compound (9) was cleaved by the action of acid, followed by the competitive attack of the Cl^- or acetic acid for the resulting allyl cation or allyl alcohol[4]. Hydrogenation and hydrogenolysis of the chloride (12) with the aid of Pd-C as a catalyst in ethyl acetate under a hydrogen atmosphere yielded a compound (14). Compounds (15) and (16), which were obtained as by-products, were also converted to compound (14) by the same procedure. The following groups are arranged in order of the ease with which

they have been reduced in compound (12): the double bond in a cinnamoyl group > allyl chloride > allyl acetoxyl. Hydrolysis of compound (14) with methanol-aqueous 5% KOH yielded a diol (17), which was identical with a compound derived from jolkinol D (4) by hydrolysis with the above procedure. Compound (14) was also obtained from the monoacetate (8) of jolkinol B by treatment with HCl gas in acetic acid followed by reduction and hydrolysis. Oxidation of the diol (17) with CrO_3-H_2SO_4 in acetone afforded jolkinol C (3).

The trans configuration of the $\Delta^{5,6}$-double bond in jolkinols C and D was unequivocally established by the observation of NOE between H-5 and OH and between H-12 and OH as shown in Figure 1[5]. Furhtermore, the configuration at C-6 in jolkinols A and B was confirmed by the results of the following reactions. The epoxidation of jolkinol D (4) with m-chloroperbenzoic acid yielded an epoxide (18), which was saponified with an aqueous KOH solution in methanol to give a diol (11). The diol (11) was identical with the compound derived from jolkinol B by hydrolysis. Since the α-configuration of the oxygen substituent at C-5 in jolkinol B is secured by the transformation of jolkinol B to lathyrol, the stereochemistry corresponds to epoxidation from the less hindered (α-side) of the trans double bond in jolkinol D.

The pattern of the cleavage of the epoxide in jolkinols A and B, and the stereospecific epoxidation of jolkinol D indicate that some lathyrane-type diterpenes may be oxidatively derived from jolkinols in their biosynthetic process, as shown in Figure 2.

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REFERENCES

1) D. Uemura and Y. Hirata, Tetrahedron Letters, 881 (1973); D. Uemura and Y. Hirata, ibid., 1387 (1972);D. Uemura and Y. Hirata, Chemistry Letters, 819 (1974).

2) D. Uemura, Y. Hirata, Y.P. Chen, and H.Y. Hsu, Tetrahedron Letters, 169[illegible] (1975); D. Uemura and Y. Hirata, ibid., 1701 (1975); D. Uemura, C. Katayama, E. Uno, K. Sasaki, Y. Hirata, Y.P. Chen, and H.Y. Hsu, ibid., 1703 (1975).

3) D. Taub, R.D. Hoffsommer, H.L. Slates, C.H. Kuo, and N.L. Wendler, J. Amer. Chem. Soc., 82, 4012 (1960).

4) W. Adolf and E. Hecker, Experientia, 27, 1393 (1971).

5) E.L. Ghisalberti, P.R. Jefferies, T.G. Payne, and G.K. Worth, Tetrahedron, 29, 403 (1973).