CHEMISTRY LETTERS, pp. 297-300, 1974. Published by the Chemical Society of Japan

SYNTHESIS OF TAXODIONE AND METHYL 11-HYDROXY-12-METHOXY-7-OXOABIETA-8,11,13-TRIEN-18-OATE

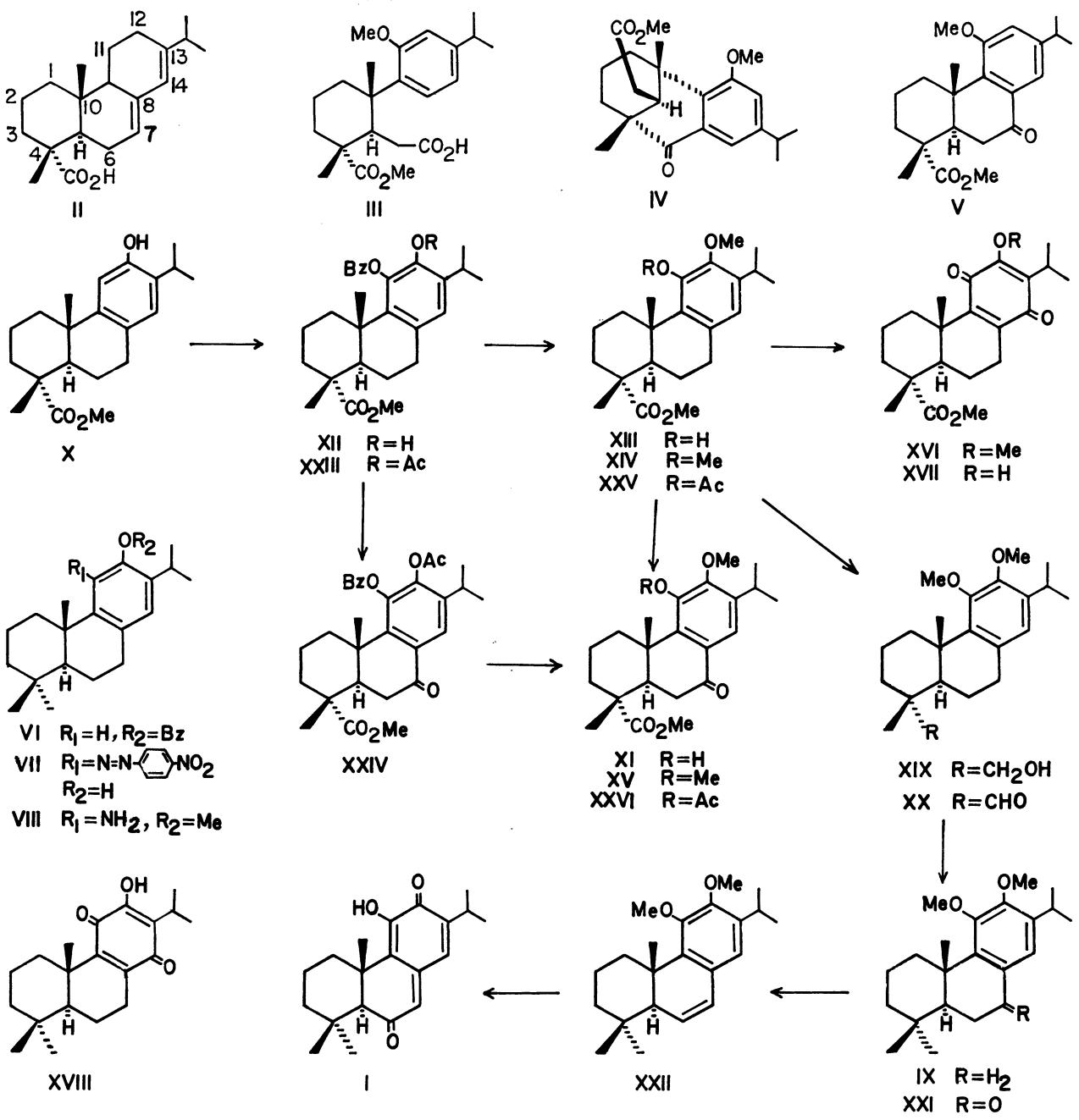
Takashi MATSUMOTO, Yasuo OHSUGA, and Kenji FUKUI
Department of Chemistry, Faculty of Science, Hiroshima University
Hiroshima 730

Oxidation of methyl 12-hydroxyabieta-8,11,13-trien-18-oate (X), prepared from (-)-abietic acid (II), with benzoyl peroxide gave methyl 11-benzoyloxy-12-hydroxyabieta-8,11,13-trien-18-oate (XII), which was converted to natural taxodione (I) and methyl 11-hydroxy-12-methoxy-7-oxoabieta-8,11,13-trien-18-oate (XI).

Taxodione (I), a tumor-inhibitory diterpene, has been isolated from Taxodium distichum Rich (Taxodiaceae) by Kupchan et al.[1] and subsequently, the synthesis of I was independently achieved by Mori and Matsui[2] and by us.[3] However, because of its significant tumor-inhibitory activity, we further planned the synthesis of I and other naturally occurring C_{11}-oxygenated diterpenes starting from easily available (-)-abietic acid (II). For the present purpose it is necessary to introduce a hydroxyl group or its derivative at the C-11 position of abietane skeleton. In a previous communication[4] the present authors reported that the intramolecular cyclization of 2,6-dimethyl-t-6-(4-isopropyl-2-methoxyphenyl)-t-2-methoxycarbonyl-r-1-cyclohexaneacetic acid (III)[5] prepared from II, gave the undesired ketone (IV) as a major product, along with the expected methyl 11-methoxy-7-oxoabieta-8,11,13-trien-18-oate (V) as a minor product. Since the yield of V was very low (4%), this intramolecular-cyclization procedure gave no synthetic utility. On the other hand, Wenkert et al.[6] have been reported the successful conversion of ferruginol benzoate (VI) to 11,12-dimethoxyabieta-8,11,13-triene (IX) via 11-(4-nitrophenylazo)-12-hydroxyabieta-8,11,13-triene (VII) and 11-amino-12-methoxyabieta-8,11,13-triene (VIII). However, since this method involves many steps and low overall yield (8%) we now attempted a direct introduction of a benzoyloxy group at the C-11 position of methyl 12-hydroxyabieta-8,11,13-trien-18-oate (X).[7] This communication will describe the synthesis

of I and methyl 11-hydroxy-12-methoxy-7-oxoabieta-8,11,13-trien-18-oate (XI) which was very recently isolated by Biellmann et al.[8] Oxidation of X with benzoyl peroxide[9] in refluxing chloroform gave methyl 11-benzoyloxy-12-hydroxyabieta-8,11,13-trien-18-oate (XII), mp 155-157°C, $[\alpha]_D$ + 83.1°, IR: 3575, 3375, 1735, 1718 cm^{-1}, NMR: 1.16 and 1.19 (each d and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.29 (s, $C_4-C\underline{H}_3$), 1.38 (s, $C_{10}-C\underline{H}_3$), 3.64 (s, $-CO_2C\underline{H}_3$), 5.26 (s, $-O\underline{H}$), 6.57 (s, $C_{14}-\underline{H}$), 7.45-7.70 (3H, m) and 8.21 (2H, dd, J=2 and 8 Hz) ($-C_6\underline{H}_5$), in 61% yield. In the NMR spectrum of XII, the downfield shift of a signal due to the methyl group at the C-10 position relative to the corresponding signal (δ 1.17 ppm) of X suggested the presence of a benzoyloxy group at the C-11 position. Methylation of XII with dimethyl sulfate and aqueous potassium hydroxide in refluxing methanol gave methyl 11-hydroxy-12-methoxyabieta-8,11,13-trien-18-oate (XIII), mp 146-147°C, $[\alpha]_D$ + 68.8°. This gave a positive Gibb's test[10] which suggested the presence of an aromatic proton para to a phenolic hydroxyl group, and the presence of the hydroxyl group at the C-11 position was supported from the pyridine-induced solvent shift ($\delta_{CCl_4} - \delta_{C_5H_5N}$ = - 0.26 ppm) of a signal due to the methyl group at the C-10 position. Further methylation of XIII in refluxing methyl ethyl ketone with dimethyl sulfate and anhydrous potassium carbonate gave the corresponding dimethyl ether (XIV, 54% from X), mp 92-92.5°C, $[\alpha]_D$ + 82.8°, which was oxidized with chromic anhydride in acetic acid to give methyl 11,12-dimethoxy-7-oxoabieta-8,11,13-trien-18-oate (XV), mp 101.5-102°C, $[\alpha]_D$ + 48.1°, IR: 1720, 1675 cm^{-1}, together with a small amount of methyl 12-methoxy-11,14-dioxoabieta-8,12-dien-18-oate (XVI), mp 139-140°C, $[\alpha]_D$ - 70.7°, IR: 1718, 1653, 1638, 1600 cm^{-1}. The NMR spectrum of XV showed a signal at δ 7.60 ppm due to an aromatic proton, suggesting the presence of the proton at the C-14 position. The quinone (XVI) was also obtained by oxidation of XIII with m-chloroperbenzoic acid in dichloromethane. Subsequently, XVI was demethylated with hydrochloric acid in boiling methanol to methyl 12-hydroxy-11,14-dioxoabieta-8,12-dien-18-oate (XVII), mp 149-150°C, $[\alpha]_D$ + 93.1°, IR: 3375, 1720, 1640, 1633, 1603 cm^{-1}, which corresponds to the C_4-methoxycarbonyl analog of royleanone (XVIII).[11,12] Conversion of XIV to IX was completed as follows. Reduction of XIV with lithium aluminum hydride afforded the corresponding alcohol (XIX), $[\alpha]_D$ + 79.7°, which by oxidation with chromic anhydride-pyridine complex gave an aldehyde (XX), $[\alpha]_D$ + 73.5°, NMR: 9.17 (s, $-C\underline{H}O$). Huang-Minlon reduction of XX gave IX[1,2,6] (29% from X), mp 89.5-90.5°C, $[\alpha]_D$ + 92.0° (EtOH). Since conversion of IX to I via 11,12-dimethoxyabieta-6,8,11,13-tetraene (XXII) has been achieved by Mori and Matsui,[2] the present work can be regarded as a new synthesis of taxodione. In the present study

XXII was prepared by an alternative method. That is, 11,12-dimethoxy-7-oxoabieta-8,11,13-triene (XXI)[13] $[\alpha]_D$ + 35.5°, prepared from IX, was reduced with lithium aluminum hydride to give the corresponding alcohol which was immediately dehydrated with p-toluenesulfonic acid in refluxing toluene to afford XXII,[2] $[\alpha]_D$ - 99.6°, NMR in $CDCl_3$: 0.96 and 1.03 (each s, C_4-($C\underline{H}_3$)$_2$), 1.13 (s, C_{10}-$C\underline{H}_3$), 1.18 and 1.22 (each d and J=7 Hz, -CH($C\underline{H}_3$)$_2$), 2.19 (t, J=3 Hz, C_5-$\underline{H}$), 3.77 (s, 2-O$C\underline{H}_3$), 5.86 (dd, J=3 and 9 Hz, C_6-$\underline{H}$), 6.41 (dd, J=3 and 9 Hz, C_7-$\underline{H}$), 6.63 (s, C_{14}-$\underline{H}$). Finally, the synthesis of XI was also carried out as follows. Acetylation of XII with isopropenyl acetate in the presence of p-toluenesulfonic acid gave an acetate (XXIII), mp 191-192°C, $[\alpha]_D$



+ 88.7°, which was then submitted to oxidation with chromic anhydride in acetic acid to give methyl 12-acetoxy-11-benzoyloxy-7-oxoabieta-8,11,13-trien-18-oate (XXIV), mp 178-180°C, $[\alpha]_D$ + 72.0°, IR: 1765, 1738, 1720, 1682 cm^{-1}. Alkaline hydrolysis of XXIV, followed by methylation with diazomethane gave XI,[14] mp 202.5-203.5°C, $[\alpha]_D$ + 33.8°, + 36.6° (EtOH), IR in CCl_4: 3500, 1730, 1685, 1607 cm^{-1}, NMR in $CDCl_3$: 1.25 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.32 (s, $C_4-C\underline{H}_3$), 1.41 (s, $C_{10}-C\underline{H}_3$), 3.62 (s, $-CO_2C\underline{H}_3$), 3.78 (s, $-OC\underline{H}_3$), 6.13 (s, $-O\underline{H}$), 7.59 (s, $C_{14}-\underline{H}$). The phenol XI was also obtained by alkaline hydrolysis of a ketone (XXVI), prepared from XIII via an acetate (XXV). The spectral data of the synthetic XI were identical with those of the natural substance.[8]

Acknowledgment. The authors are grateful to Arakawa Rinsan Kogyo Co., Ltd. for the supply of rosin. Thanks are also due to Dr. J. F. Biellmann, University of Louis Pasteur, Strasbourg, for his gift of spectral copies of natural sample. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education.

REFERENCES

IR spectra were taken in $CHCl_3$ and NMR spectra in CCl_4 at 60 MHz unless otherwise specified. Their chemical shifts are presented in terms of δ values; s: singlet, d: doublet, dd: double doublet, t: triplet, m: multiplet. Optical rotations were measured in $CHCl_3$ on a Yanagimoto OR-50D.

1) S. M. Kupchan, A. Karim, and C. Marcks, J. Amer. Chem. Soc., 90, 5923 (1968): J. Org. Chem., 34, 3912 (1969).
2) K. Mori and M. Matsui, Tetrahedron, 26, 3467 (1970).
3) T. Matsumoto, Y. Tachibana, J. Uchida, and K. Fukui, Bull. Chem. Soc. Japan, 44, 2766 (1971).
4) T. Matsumoto, S. Imai, M. Aizawa, H. Kitagawa, and K. Fukui, This Letters, 1972, 581.
5) IUPAC Bulletin No. 35, IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, Section E: Fundamental Stereochemistry.
6) C. H. Brieskorn, A. Fuchs, J. B. Bredenberg, J. D. McChesney, and E. Wenkert, J. Org. Chem., 29, 2293 (1964).
7) R. C. Cambie and R. A. Franich, Aust. J. Chem., 24, 117 (1971).
8) J. F. Biellmann, G. Branlant, M. Gero-Robert, and M. Poiret, Tetrahedron, 29, 1237 (1973).
9) D. H. R. Barton, P. D. Magnus, and M. J. Pearson, J. Chem. Soc. (C), 1971, 2231.
10) F. E. King, T. J. King, and L. C. Manning, J. Chem. Soc., 1957, 563.
11) O. E. Edwards, G. Feniak, and M. Los, Can. J. Chem., 40, 1540 (1962).
12) T. Matsumoto, Y. Tachibana, and K. Fukui, This Letters, 1972, 321.
13) E. Wenkert, J. D. McChesney, and D. J. Watts, J. Org. Chem., 35, 2422 (1970).
14) The melting point and specific rotation differ somewhat from those of natural substance (mp 194-196°C, $[\alpha]_D$ + 6° (EtOH)).

(Received January 16, 1974)