CHEMISTRY LETTERS, pp.603-605, 1974. Published by the Chemical Society of Japan

SYNTHESIS AND ABSOLUTE CONFIGURATION OF TRANS-MERANZINIC ACID

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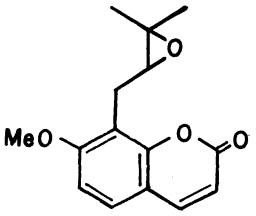
Trans-meranzinic acid, (+)-II, was synthesized from 2-hydroxy-4-methoxy-3-(3-methylbut-2-enyl)benzaldehyde (V) via (±)-2,3-dihydro-7-formyl-2-(1-hydroxy-1-methylethyl)-4-methoxybenzofuran (VII) and (±)-II which was successfully resolved by means of cinchonidine. Subsequently, (+)-II was subjected to exhaustive ozonolysis to afford known (+)-(R)-3-hydroxy-4,4-dimethylbutyrolactone (X). Thus, the stereochemistry of C-2 in (+)-II was assigned as R-configuration.

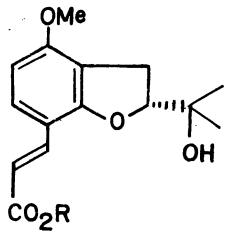
Meranzin (I)[1] has been isolated from the essential oil of Citrus Aurantium L. by Böhme and Pietsch.[2] Treatment of I with sodium methylate gave a dihydrobenzofuran derivative, named trans-meranzinic acid,[1] $C_{15}H_{18}O_5$, mp 204°C, $[\alpha]_D$ + 90.4° (EtOH). Three possible structures (II-IV)[2,3] were proposed for the acid. Recently, Venturella et al.[4] reported the structure of trans-meranzinic acid to be II on the basis of spectroscopic studies. However, since the absolute configuration of the acid is as yet unknown the present authors attempted a synthesis of II to confirm the proposed structure and to elucidate the stereochemistry. In this communication we wish to report the synthesis and absolute configuration of trans-meranzinic acid.

Oxidation of 2-hydroxy-4-methoxy-3-(3-methylbut-2-enyl)benzaldehyde (V)[5,6] with m-chloroperbenzoic acid in chloroform gave the corresponding epoxide (VI) which was immediately subjected to isomerization on silica gel to afford an alcohol (VII: 78%), mp 100-101°C, NMR (CCl_4): 1.17 and 1.28 (each s, 2-C$\underline{H}_3$), 2.96 (d, J=9.0 Hz, -C$\underline{H}_2$-), 3.33 (s, -O$\underline{H}$), 3.79 (s, -OC$\underline{H}_3$), 4.63 (t, J=9.0 Hz, -C$\underline{H}$O-), 6.30 (d, J=9.5 Hz, C_5-$\underline{H}$),

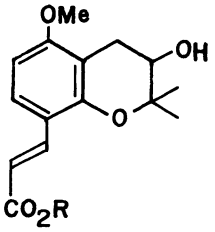
7.37 (d, J=9.5 Hz, C_6-H), 9.83 (s, -CHO), along with the recovered V (14%) and a small amount of another alcohol (VIII: 3%), mp 137-137.5°C, NMR: 1.39 (s, 2-CH_3), 2.66 (dd, J=18 and 6.0 Hz) and 2.95 (dd, J=18 and 5.0 Hz) (-CH_2-), 2.92 (s, -OH), 3.87 (s, -OCH_3), 3.87 (overlap, -CH(OH)), 6.50 (d, J=8.5 Hz, C_6-H), 7.74 (d, J=8.5 Hz, C_7-H), 10.31 (s, -CHO). In the NMR spectra it is known[4,7] that the signal of methine proton on the C-2 position of 2,3-dihydro-2-(1-hydroxy-1-methylethyl)benzofuran derivative appears at δ ca. 4.7 ppm, while that on the C-3 position of 2,2-dimethyl-3-hydroxychroman derivative at δ ca. 3.9 ppm. Therefore, the structures of VII and VIII were assigned as (±)-2,3-dihydro-7-formyl-2-(1-hydroxy-1-methylethyl)-4-methoxybenzofuran and (±)-2,2-dimethyl-8-formyl-3-hydroxy-5-methoxychroman, respectively. Condensation of (±)-VII with malonic acid in pyridine with a trace of piperidine gave (±)-trans-meranzinic acid (II: 86%), mp 199°C, Mass m/e: 278 (M^+), which was methylated with diazomethane to give methyl (±)-trans-meranzinate (IX), mp 105-108°C, NMR: 1.26 and 1.40 (each s, 2-CH_3), 2.06 (s, -OH), 3.13 (d, J=9.0 Hz, -CH_2-), 3.78 and 3.85 (each s, -CO_2CH_3 and -OCH_3), 4.75 (t, J=9.0 Hz, -CHO-), 6.44 (d, J=9.0 Hz, C_5-H), 6.54 (d, J=16 Hz, =$CHCO_2$-), 7.24 (d, J=9.0 Hz, C_6-H), 7.70 (d, J=16 Hz, -CH=$CHCO_2$-). The NMR spectrum of IX was identical with that published.[4] Subsequently, (±)-II was resolved by means of cinchonidine, and the diastereomeric salts, mp 134.5-135°C, $[\alpha]_D$ + 63.5°, and mp 133-134°C, $[\alpha]_D$ - 14.5°, were decomposed with dilute hydrochloric acid to give respectively (+)-II, mp 202.5-203°C, $[\alpha]_D$



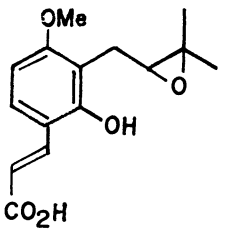
I



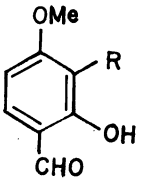
II R=H
IX R=Me



III R=H
XI R=Me

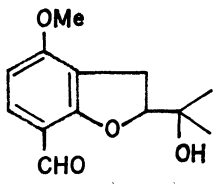


IV

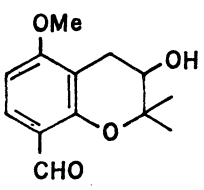


V R=$CH_2CH=CMe_2$

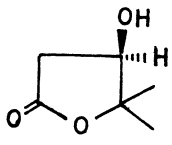
VI R=$CH_2CH(O)CMe_2$



VII



VIII



X

+ 79.9° (EtOH);[8] and (-)-II, mp 201-203°C, $[\alpha]_D$ - 43.0° (EtOH).[8]

For elucidation of the absolute configuration of (+)-trans-meranzinic acid, the synthetic (+)-II was subjected to exhaustive ozonolysis in a mixture of methanol and chloroform at 0°C, followed by oxidation with alkaline hydrogen peroxide to give known (+)-(R)-3-hydroxy-4,4-dimethylbutyrolactone (X),[9] $[\alpha]_D$ + 7.6°, NMR: 1.39 and 1.45 (each s, 2-CH_3), 2.49 (dd, J=18 and 3.0 Hz) and 2.98 (dd, J=18 and 6.0 Hz) (-CH_2-), 2.95 (s, -OH), 4.13 (dd. J=6.0 and 3.0 Hz, -CH(OH)). Thus, the stereochemistry of the C-2 position in (+)-II was assigned as R-configuration.

Similarly, (±)-VIII was also condensed with malonic acid to afford (±)-III acid, mp 187.5-188.5°C, which gave the corresponding methyl ester, (±)-XI, mp 121-122°C, NMR: 1.37 (s, 2-CH_3), 2.32 (s, -OH), 2.75 (dd, J=18 and 5.5 Hz) and 3.00 (dd, J=18 and 4.5 Hz) (-CH_2-), 3.76 and 3.82 (each s, -CO_2CH_3 and -OCH_3), ca. 3.8 (overlap, -CH(OH)), 6.44 (d, J=9.0 Hz, C_6-H), 6.44 (d, J=16 Hz, =$CHCO_2$-), 7.36 (d, J=9.0 Hz, C_7-H), 7.95 (d, J=16 Hz, -CH=$CHCO_2$-).

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Optical rotations were measured in $CHCl_3$ on a Yanagimoto OR-50D and NMR spectra were taken in $CDCl_3$ unless otherwise specified. Their chemical shifts are presented in terms of δ values: s: singlet, d: doublet, dd: double doublet, t: triplet.

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(Received March 18, 1974)