

A TOTAL SYNTHESIS OF (±)-OCCIDENTALOL

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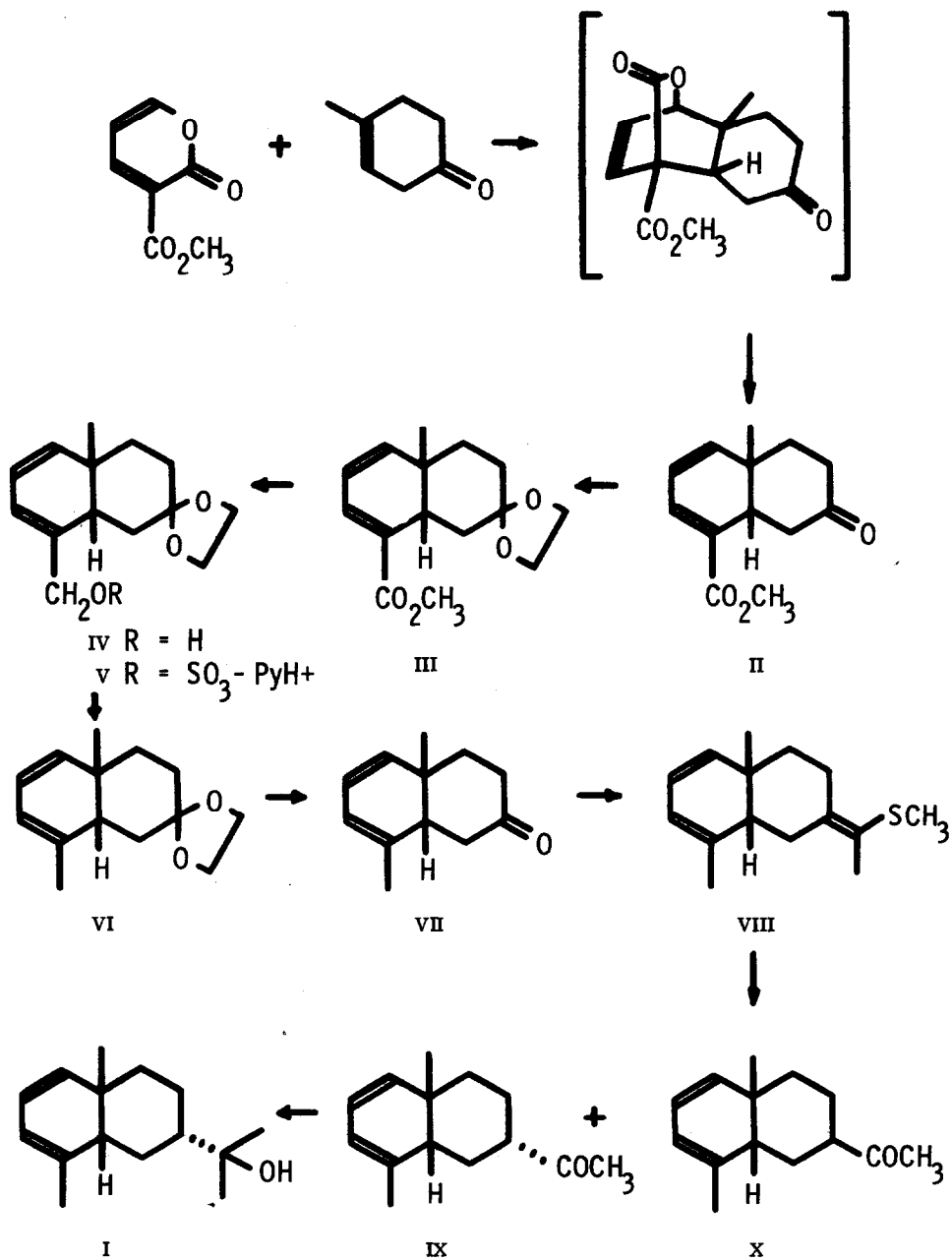
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Interest in the sesquiterpene occidentalol (I) has centered around the intriguing combination of a cis-fused decalin system and a homoannular 1,3-diene unit. The structure of occidentalol was investigated by von Rudloff and Erdtman (1) and subsequently modified by Hortmann and De Roos (2a). We wish to report a simple total synthesis (2b) of occidentalol (I) which illustrates a direct approach for the construction of the cis-fused bicyclo[4.4.0]decane skeleton and which further demonstrates the utility of other methodology (3, 4) developed in these laboratories.

The Diels-Alder reaction of 3-carbomethoxy-2-pyrone (5) and 4-methyl-3-cyclohexenone (6) at 150° for 24 hr. under nitrogen provided the ketoester II stereoselectively in 25-40% yield (7). The initial adduct underwent decarboxylation under the conditions of the Diels-Alder reaction and could not be detected in the product. The structure (8) of the ketoester II was assigned principally on the basis of its nmr spectrum (9). The yield suffered from the propensity of the ketoester II to sustain unwanted secondary reactions (7), but the fixation of both the correct ring fusion and cis-diene functionality in one operation made this substance an attractive intermediate (10). The orientation of the Diels-Alder addition which yields II and the unreactivity of various 4-substituted 1-methylcyclohexenes as dienophiles relative to 4-methyl-3-cyclohexenone are considered as indicating that the enol form of the latter is the species which adds to the pyrone.

Since the synthetic plan involved the reaction of methylolithium with a carbonyl group to form the 2-hydroxy-2-propyl side chain of occidentalol, the prior conversion of the carbomethoxy group of II to a methyl group was in order. Ketalization (ethylene glycol, *p*-TsOH, benzene, 80°, 12 hr.) of the ketoester II and reduction (LiAlH₄, ether) of the ketal ester III provided the ketal dienol IV in 94% yield. The intermediate IV was converted to the pyridinium sulfate derivative V (2.5 eq. pyridine--SO₃, THF, 0°, 42 hr.) which readily underwent reduction (3) (25 eq. LiAlH₄, THF, 0° for 1 hr., 25° for 22 hr.) to furnish the ketal diene VI in 70% yield. Hydrolysis (1:2 1 M HCl--HOAc, 25°, 7 hr.) then provided the ketodiene VII in quantitative yield.

To complete the sequence, the ketodiene VII was elaborated to the vinyl thioether VIII in 72% yield by



a Wadsworth-Emmons reaction employing diethyl 1-(methylthio)ethylphosphonate (4) (3 eq. in hexamethylphosphoric amide--dimethoxyethane (1:4), 62°, 12 hr.). Exposure of the vinyl thioether VIII to aqueous mercuric chloride (2 eq., 25% aqueous CH_3CN , 25°, 53 hr.) provided a 2.9:1 mixture of the 7 α - and 7 β -acetyldienes IX and X, respectively, in 70% yield. These epimeric ketones were separated by preparative thick layer chromatography on pH = 7 buffered Merck silica gel (1:9 ether--hexane). The addition of methyl lithium (ether, -78°, 1 hr) to the 7 α -acetyldiene IX afforded in 72% yield synthetic (\pm)-occidentalol (11) (I) which was identified by comparison with an authentic sample of natural (+)-occidentalol (12, 13).

References

1. E. von Rudloff and H. Erdtman, Tetrahedron, **18**, 1315 (1962).
2. (a) A. G. Hortmann and J. B. De Roos, J. Org. Chem., **34**, 736 (1969); (b) A synthesis of occidentalol by a different route has recently been achieved in the laboratory of Prof. A. G. Hortmann. We thank Drs. Hortmann, Daniel, and Martinelli for making available to us a preprint of their synthesis of occidentalol; private communication, July 1972.
3. (a) E. J. Corey and K. Achiwa, Tetrahedron Lett., 1837 (1969); (b) E. J. Corey and K. Achiwa, J. Org. Chem., **34**, 3667 (1969).
4. E. J. Corey and J. I. Shulman, J. Org. Chem., **35**, 777 (1970).
5. The procedure of Windholz was modified (7) to allow preparation of the crystalline methyl ester in 53% yield from 1,1,3,3-tetramethoxypropane and dimethyl malonate: T. B. Windholz, L. H. Peterson, and G. J. Kent, J. Org. Chem., **28**, 1443 (1963).
6. The Birch reduction of p-methylanisole (A. J. Birch, J. Chem. Soc., 596 (1946)) and subsequent hydrolysis of the enol ether (10% sulfuric acid in aqueous methanol) furnished the β,γ -unsaturated isomer free of the α,β -unsaturated isomer.
7. For details, see D. S. Watt, Ph.D. Thesis, Harvard University, 1972.
8. Infrared, nmr, and exact mass spectra were consistent with the assigned structures in this paper.
9. Nmr (CDCl_3): 1.03 (s., 3, angular methyl), 1.6-2.6 (m., 6, C-5, 6 and 8 methylene), 2.93 (d. of d. of d., 1, $J[8a, 8\alpha] = 12.3$ Hz, $J[8a, 8\beta] = 5.3$ Hz, $J[4, 8a] = 1.2$ Hz, C-8a methine), 3.86 (s., 3, methoxyl), 6.05 (d. of t., 1, $J[3, 4] = 9.6$ Hz, $J[2, 4] = J[4, 8a] = 1.3$ Hz, C-4 vinyl), 6.21 (d. of d., 1, $J[3, 4] = 9.5$ Hz, $J[2, 3] = 5.2$ Hz, C-3 vinyl) and 7.03 (d. of d., 1, $J[2, 4] = 1.3$ Hz, $J[2, 3] = 5.3$ Hz, C-2 vinyl).
10. The keto ester II has also served as a key intermediate in a total synthesis of copaene and ylangene which will be reported shortly.

11. The crude product did contain an 8% yield of 7-epi-occidentalol which was readily removed by chromatography on silica gel.
12. We wish to thank Dr. Y. Hirose and Dr. E. von Rudloff for a generous gift of (+)-occidentalol.
13. This work was assisted financially by grants from the National Institutes of Health and the National Science Foundation.