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TOTAL SYNTHESIS OF RACEMIC FRULLANOLIDE

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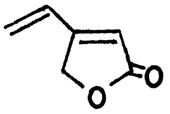
2,4,5,5a,6,7,8,9a,9bα-Decahydro-9aβ-hydroxy-5aβ-methoxycarbonyl-9β-methyl-2-oxo-naphtho[1,2-b]furan, the major annulation product from 4-vinylfuran-2(5*H*)-one and 2-methoxycarbonyl-6-methylcyclohexanone, was transformed into racemic frullanolide.

Previously a new lactone annulation reaction of 1,3-dicarbonyl compounds with β-vinylbutenolide (1) was reported by us.[1] To illustrate efficiency of this reaction in the synthesis of sesquiterpene lactones, we describe the total synthesis of frullanolide (2), an allergenic eudesmanolide isolated from *Frullania*,[2] in the racemic form.[3]



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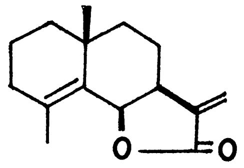
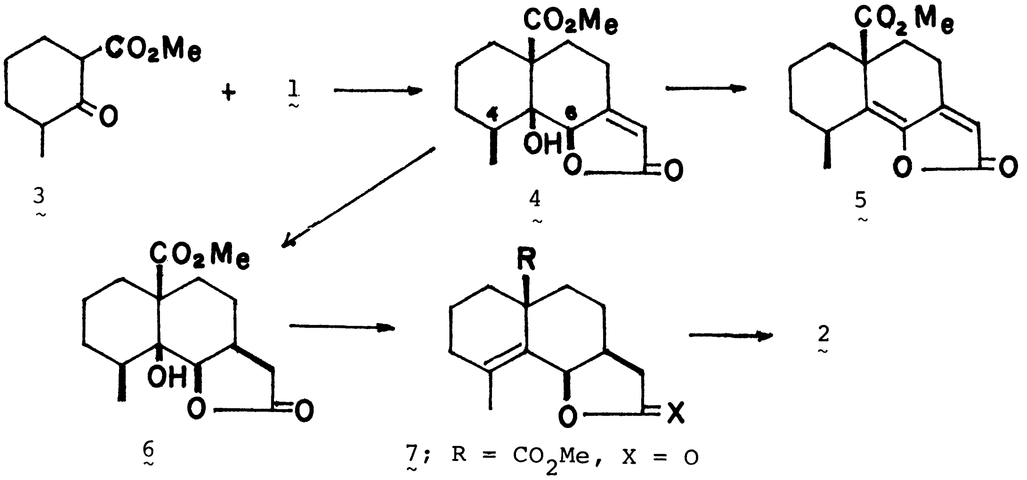


2

The reaction of the sodium enolate of 2-methoxycarbonyl-6-methylcyclohexanone[4] (3) with 1 (THF, room temperature) gave the butenolide (4) as the major product, m.p. 168-169°C (33% yield) (Scheme). The stereochemistry at the C-4 and C-6 positions were assigned as follows;[5] the chemical shift value (δ, 5.27) of the butenolide γ-proton in 4 was observed at a higher magnetic field than that of its C-6 epimer[6] (δ, 5.72) which was obtained on base treatment of 4, demonstrating a trans disposition of the C-5 hydroxyl and the γ-proton in the former butenolide. Dehydration of 4 ($SOCl_2$-pyridine, 0°C) yielded the dehydration product (5) (87% yield). The PMR spectrum of the product 5 showed the allylic C(4)-proton as a broad signal (δ, 3.28; *W/2* = 7 Hz) on irradiation of the C(4)-methyl doublet at δ 1.02. This indicates a quasi-axial configuration of the C(4)-methyl in 5.

The butenolide (4) was reduced to the γ-lactone (6), m.p. 99-100°C ($NaBH_4$-$NiCl_2$;[7] quantitative yield), which was further dehydrated to the unsaturated lactone (7), m.p. 92-93°C ($SOCl_2$-pyridine; 74% yield). In contrast to the case of 4, the regioselectivity of dehydration was completely reversed as shown above.

Treatment of 7 with diisobutylaluminium hydride, followed by trimethyl orthoformate and pyridinium p-toluenesulfonate catalyst,[8] gave a mixture of the acetal (8), m.p. 71-72°C (54% yield) and its epimer with respect to acetal methoxyl group, m.p. 108-110°C (21% yield). To avoid the presumable spectral and chromatographic complexity, we proceeded with the major acetal (8). The acetal was reduced to the alcohol (9) ($LiAlH_4$) which was then oxidized to the aldehyde (10) (Collins reagent). The product was successively submitted to Huang-Minlon reduction and then to oxidation to the lactone (11), m.p. 121-122 °C (Jones reagent; 32% overall yield from 8). Introduction of methylene group into 11 was performed according to the procedure described by Grieco and Hiroi[9] (lithium diisopropylamide-formaldehyde; methanesulfonyl chloride; DBU) affording racemic frullanolide (2), m.p. 90.5-92°C, as identified by spectral comparison (IR and PMR).



7; R = CO_2Me, X = O
8; R = CO_2Me, X = H, OMe
9; R = CH_2OH, X = H, OMe
10; R = CHO, X = H, OMe
11; R = Me, X = O

Scheme

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References and Notes

1) F. Kido, T. Fujishita, K. Tsutsumi, and A. Yoshikoshi, J. Chem. Soc. Chem. Commun., 1975, 337. 2) G. W. Perold, J.-C. Muller, and G. Ourisson, Tetrahedron, 28, 5797 (1972). 3) An alternative approach to racemic 2 has been described: W. C. Still and M. J. Schneider, J. Am. Chem. Soc., 99, 948 (1977). For the transformation of α-santonin into (-)-2, see A. E. Greene, J.-C. Muller, and G. Ourisson, J. Org. Chem., 39, 186 (1974). 4) E. J. Corey, R. B. Mitra, and H. Uda, J. Am. Chem. Soc., 86, 485 (1964). 5) For the assignment of the cis decalol stereochemistry, see Ref. 1. 6) This epimer was also the minor product in the annulation reaction. 7) T. Satoh, K. Nanba, and S. Suzuki, Chem. Pharm. Bull., 19, 817 (1971). 8) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, J. Org. Chem., 42, 3772 (1977). 9) P. A. Grieco and K. Hiroi, J. Chem. Soc. Chem. Commun., 1972, 1317.

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