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Synthesis of the Eudesmanolide with Proposed Structure for Septuplinolide

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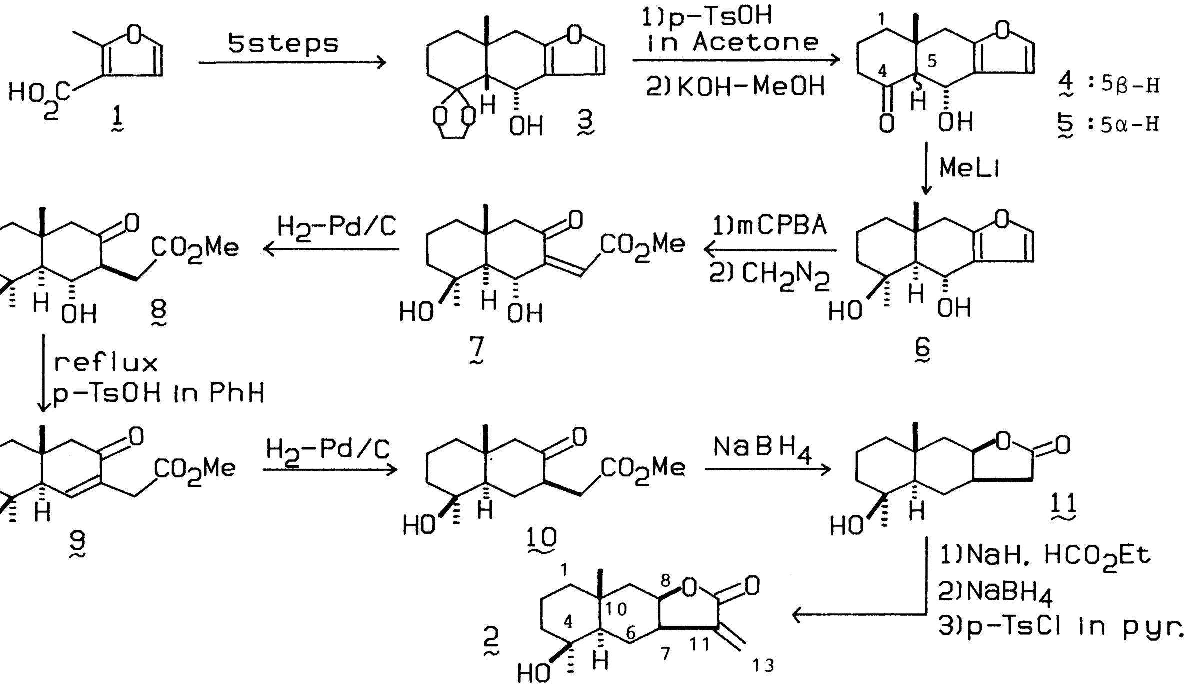
An eudesmanolide which has a proposed structure for septuplinolide was synthesized stereo-selectively. The spectral data of synthesized eudesmanolide are not identical with the reported data of septuplinolide to show that the proposed structure of septulpinolide is incorrect.

There are many sesquiterpene lactones which were reported to show various biological activities, such as allergenic agent, growth inhibitor, antibacterial agents and antitumor agents.$^{1-3)}$ Previously we reported an efficient synthesis of eudesmanolides, isoalantolactone and dihydrocallitrisin by a route involving alkylation-annulation reaction of 2-methyl-3-furoic acid 1 followed by oxidation of furan ring to create γ-lactone ring.$^{4)}$ In 1987, Ober and Fischer reported the isolation of a sesquiterpene lactone, septuplinolide 2 whose structure was proposed to be an eudesmanolide with 4β-hydroxyl group.$^{5)}$ Brief synthesis of septuplinolide was seemed to be possible *via* our alkylation-annulation route of 2-methyl-3-furoic acid. We report herein a stereo-selective synthesis of "septuplinolide" whose spectral data are not identical with the reported values of natural septuplinolide.

An important intermediate alcohol 3 was synthesized previously by 5 steps from 2-methy-3-furoic acid in high yield.$^{4)}$ Methylation at C-4 of 3, reductive elimination of the hydroxyl group at C-6, and the conversion of the furan ring to α-methylene-γ-lactone should give "septuplinolide".

An acetal group at C-4 of the alcohol 3 (J_{5-6}=5.8 Hz) was deprotected by acetal exchange reaction in acetone and p-TsOH to form an A/B cis keto-alcohol (4) which was epimerized solely to the A/B trans isomer 5 with KOH-MeOH (yield 70.5 % from 3). The stereochemistry at C-5, C-6 and C-10 of 5 was deduced from NOE peaks between 10-Me and 6-H in NOESY spectrum and from coupling constant (J_{5-6}=8.5 Hz). Stereoselective methylation of 5 with 5.4 equiv. of methyl lithium in ether gave a diol 6 whose stereochemistry was proved by the observation of NOE between 10-Me and 6-H and between 4-Me and 5-H in NOESY spectrum and by coupling constant (J_{5-6}=8.5 Hz) (81%). Oxidation of the furan ring of diol 6 with 2 equiv. of mCPBA in CH_2Cl_2 afforded a carboxylic acid (quantitative yield) which was converted to methyl ester 7 with CH_2N_2. Hydrogenation of the unsaturated ester 7 with H_2, 5%-Pd/C produced an ester 8 (6-H: δ 3.98, t, J=10 Hz)(96%) selectively. Selective dehydration of 6-OH group by reflux in benzene-TsOH for 3 h to give an enone 9 [IR 1670 cm^{-1}, ^{13}C-NMR δ 146.7, 134.4, ^{1}H-NMR δ 7.00 (1H, d, J=1.5 Hz)]. The observation of NOE between 4-Me and 5-H and between 4-Me and 6-H of 9 showed the stereochemistry of 9 clearly. The double bond of 9 was reduced selectively with H_2, 5%-Pd/C to the keto-ester 10 in quantitative yield. Reduction of 10 with $NaBH_4$ in MeOH formed lactone 11 directly (92%). The stetreochemistry of 11 was deduced from the observation of NOE between 5-H and 7-H and between 7-H and 8-H. Finally α-methylene group was introduced on the γ-lactone ring of 11 by consecutive reactions (i NaH-HCOOEt, ii $NaBH_4$ in MeOH, iii TsCl-pyridine) to give the desired compound 2 (24%).⁶⁾ The spectral data of the compound 2⁷⁾ is entirely different from the reported data of septuplinolide. The structure of synthesized compound 2 is quite definite from the NMR experiment on the intermediates as described above. The difference of chemical shifts of 10-Me (δ 1.13; in the lit. δ 0.94) and 5-H (δ 1.08; in the lit. δ 1.45-1.56) in the ^1H-NMR may suggest that the proposed stereochemistry at C4 of septuplinolide is opposite.



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7) Compound 2: MS, m/z 250 (M^+), IR 3480, 2904, 1746, 1665, 1450, 1372, 1329, 1295, 1267, 1189, 1132 cm^{-1}, ^1H-NMR($CDCl_3$) δ 6.13(1H, d, J=1.2 Hz), 5.59(1H, br.d, J=1.2 Hz), 4.47(1H, ddd, J=5.0, 5.0, 1.7 Hz), 2.98(1H, m), 2.06(1H, dd, J=15.5, 1.5 Hz), 1.21(3H, s), 1.13(3H, s), 1.08(1H, dd, J=13.0, 2.5 Hz), ^{13}C-NMR($CDCl_3$) δ 170.6(s), 142.2(s), 120.1(t), 77.0(d), 71.2(s), 48.8(d), 44.4(t), 42.0(t), 41.5(t), 41.1(d), 32.5(s), 30.4(q), 24.9(t), 20.0(q), 17.3(t).

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