Tetrahedron Letters Vol. 21, pp 3139 - 3142
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0040-4039/80/0808-3139$02.00/0

SYNTHESIS OF (±)-LITSENOLIDE C1

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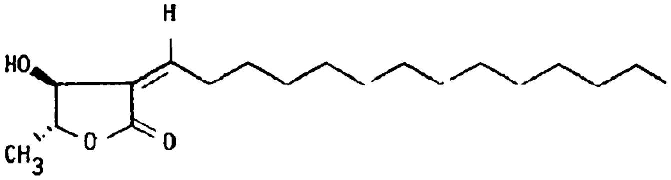
Summary: The β-hydroxy-γ-methyl-α,β'-unsaturated-γ-lactone, litsenolide C1, was synthesized in a highly stereoselective approach.

From the roots of Litsea japonica, growing off the shores of southern Japan, Ishii isolated the α,β'-unsaturated-γ-lactone, litsenolide C1 (1).[1] The structure of this interesting lactone is based upon spectral and chemical evidence and structural correlations with the similar cytotoxic obtusilactone class of natural products.[2,3]

Here we report a short and highly stereoselective approach to the synthesis of 1 which is also readily adaptable to large scale preparations of this substance. Although several methods have been developed for condensing carbonyl compounds with lactones, most of these represent syntheses of α-methylene lactones rather than α-alkylidene lactones. Further, these procedures give predominantly and frequently exclusively the E-alkylidene isomers and are thus unsuitable for generating the Z geometry of litsenolide C1.[4]

Refluxing a mixture of α-bromo-γ-valerolactone (2) in dimethyl sulfide - DMF (ratio 1:2) containing 1 mole-% NaI gave an isomeric mixture of isomers 3 in 92% distilled yield (bp 0.5 MM, 100°C).[5] The enolate from 3 formed rapidly in THF at -78°C using lithium diisopropylamide as base; condensation with dodecanal (-78°C, 1 h) formed the isomeric mixture of hydroxy sulfides 4 in 91% isolated yield.[6] Oxidation of the isomers with m-chloroperbenzoic acid proceeded rapidly at -20°C (0.5 h, 1.1 equiv) forming the sulfoxides. Upon heating, the sulfoxides underwent rapid elimination to the butenolides 5 (110°C, 10 min, 100%).

The methane sulfonate derivatives from 5 (CH_3SO_2Cl, Et_3N, Et_2O, 0°C, 15 min) undergo nucleophilic displacement with 1.0 equiv of sodium phenylselenide producing the unsaturated



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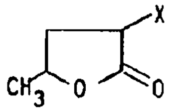
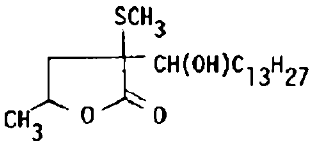


2 X = Br

3 X = SCH$_3$



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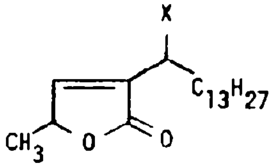
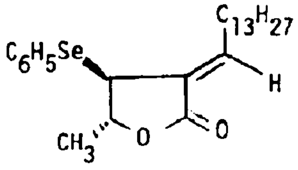


5 X = OH

6 X = OSO$_2$CH$_3$



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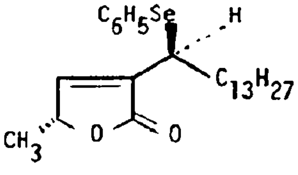

8

lactones 7 and 8 in a ratio of 2:1, respectively (93% combined yield). The formation of 7 is readily rationalized in terms of an Sn2'-type reaction that is likely to involve carbonyl participation. In this case, loss of the methane sulfonate group proceeds from the conformation leading to the less sterically hindered E-isomer (7). However, the formation of the pure isomer 8 suggests that this product is not formed by such a direct process. Further investigations of lactone 7 revealed that this substance undergoes rapid and complete conversion to lactone 8 on treatment with one equivalent of sodium phenylselenide (98% isolated yield). In addition, reaction of the methane sulfonates 6 with an excess (1.5 equiv) of sodium phenylselenide (-20°C, 1 h) produced lactone 8 as the sole product (97%). The evidence suggests that the α,β'-unsaturated lactone 7 is the primary reaction product and that in the presence of excess selenium nucleophile this substance undergoes further reaction by addition from the less hindered α-side of 7, forming the more thermodynamically stable α,β-unsaturated lactone 8.

The final conversion of 8 to litsenolide C1 (1) proceeds within minutes on treating selenide 8 with an excess of 30% aqueous hydrogen peroxide (87%). The product formed at 25°C in THF as solvent is contaminated with ca. 20% of the geometric isomer, litsenolide C2.[1] The latter is readily removed by one recrystallization from petroleum ether. Better results are achieved in the oxidation to litsenolide C1 by reaction of 8 in acetonitrile at -20°C with 3 equiv of hydrogen peroxide. In this way, litsenolide C1 is formed in 96% yield, contaminated with less than 3% litsenolide C2.[7] The synthetic material 1 was compared with a sample of the natural substance and was found to be identical in all respects.[8]

Acknowledgment is made to the donors of the Petroleum Research Fund administered by the American Chemical Society and to a National Starch and Chemical Corporation grant of Research Corporation.

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4. See R. A. Amos and J. A. Katzenellenbogen, *J. Org. Chem.*, **43**, 560 (1978) and references cited therein.

5. *Cf.* B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973).

6. All new compounds reported herein showed satisfactory microanalytical, infrared and proton magnetic resonance data.

7. The preference of [2,3]-sigmatropic rearrangements to form mainly E olefins has been previously noted. *Cf.* K. B. Sharpless, R. F. Lauer, A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973); H. J. Reich, *J. Org. Chem.*, **40**, 2570 (1975); R. W. Hoffmann, R. Gerlach and S. Goldmann, *Tetrahedron Lett.*, 2599 (1978); W. C. Still and A. Mitra, *J. Am. Chem. Soc.*, **100**, 1927 (1978) and references therein.

8. The author is grateful to Dr. H. Ishii of Shionogi Research Laboratories for his generous gift of authentic litsenolide C1.

(Received in USA 1 April 1980)