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SYNTHESIS OF (+)-DEOXYVERNOLEPIN

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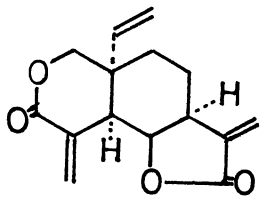
2,3,3aα,4,5,5a,6,9,9aα,9bβ-Decahydro-3α,9α-dimethyl-5aβ-methoxycarbonyl-2-oxonaphtho[2,3-b]furan (2) accessible from α-santonin was transformed into (+)-deoxyvernolepin (1). The preparation of some α-methylenelactones related to 1 has also been described.

A recent paper[1] that reported a potent growth-inhibitory activity of racemic deoxyvernolepin[2] (1) against human lymphoblastic leukemia cells attracted our attention since biological activities of chiral organic compounds, in general, largely depend on their enantiomeric forms.

Attempting to correlate the cytotoxic activity of this compound and its enantiomers, we synthesized optically active (dextrorotatory) deoxyvernolepin (1) from α-santonin as outlined below.



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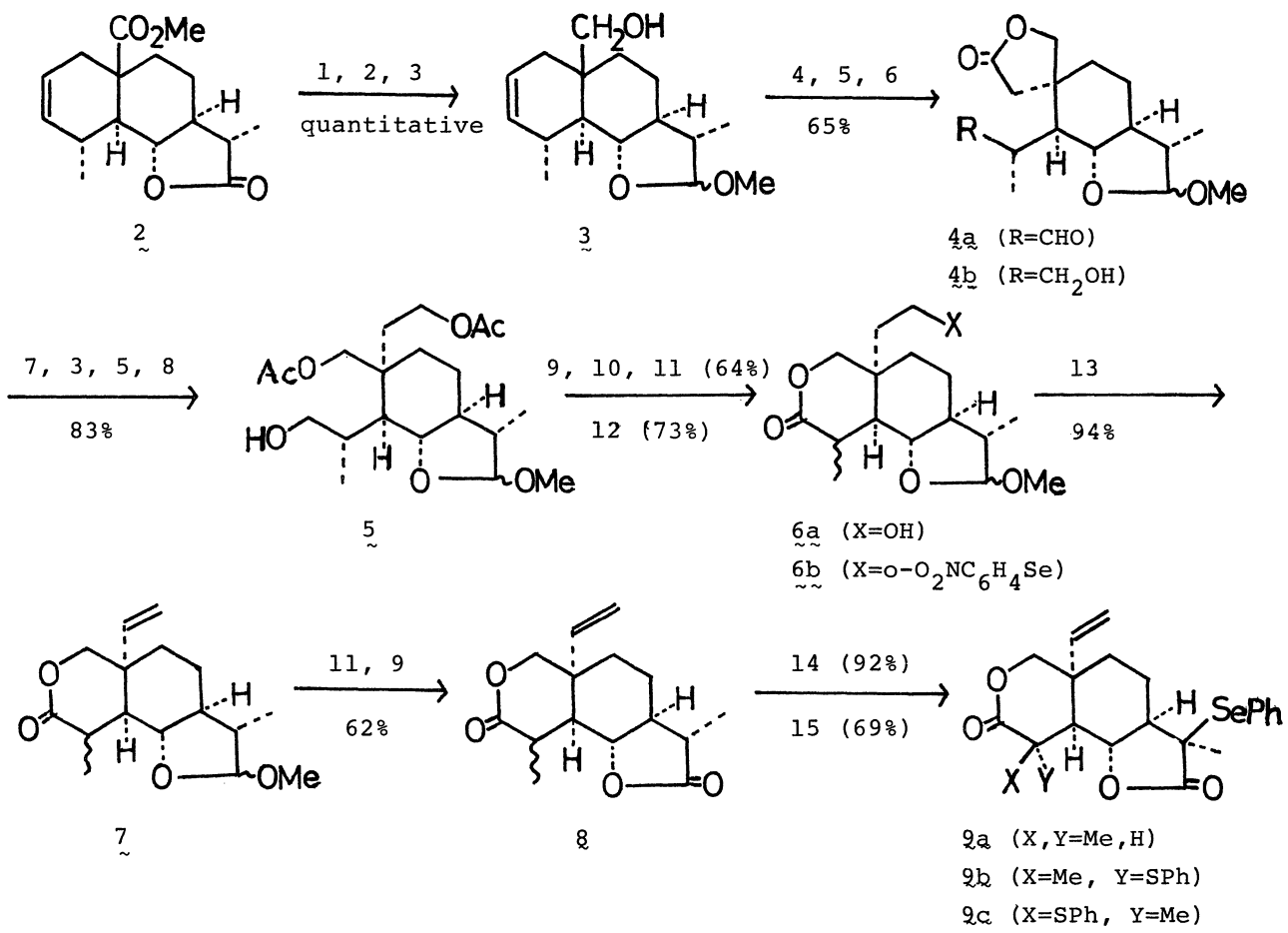
Unsaturated ester (2),[3] readily accessible from α-santonin, was reduced to the corresponding hemiacetal (Scheme). After protection of the hemiacetal group as methyl acetal,[4] the product was reduced to alcohol (3).[5] Ozonolysis of 3 followed by treatment with acetic anhydride at room temperature afforded unstable lactonic aldehyde (4a),[6] which was immediately treated with sodium borohydride to yield 4b. By employing pyridinium p-toluenesulfonate catalyst (PPTS),[7] tetrahydropyranylation of the hydroxy group of 4b proceeded without affecting the acetal function, and then the lactonic ring was reductively cleaved and acetylated. Deblocking of the tetrahydropyranyl group of the product with PPTS in methanol gave diacetate (5). Oxidation of the hydroxy group of 5 to the corresponding acid followed by alkaline hydrolysis of the acetyl groups, and acidic workup of the resulting product yielded hydroxylactone (6a).[8] The o-nitrophenylselenide (6b), mp 169°C (decomp), obtained from 6a according to Grieco et al.[9] was treated with hydrogen peroxide to lead to vinyl compound (7), whose acetal group was hydrolyzed

Scheme

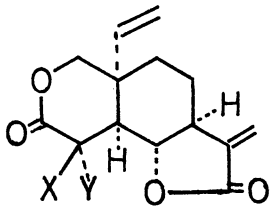


(1) i-Bu_2AlH, PhMe; (2) $CH(OMe)_3$, TsOH, CH_2Cl_2; (3) $LiAlH_4$, Et_2O; (4) O_3, CH_2Cl_2; (5) Ac_2O, C_5H_5N; (6) $NaBH_4$, MeOH; (7) dihydropyrane, PPTS, CH_2Cl_2; (8) MeOH, PPTS; (9) Jones reagent; (10) KOH, MeOH; (11) HCl, H_2O; (12) o-$O_2NC_6H_4SeCN$, n-Bu_3P, THF; (13) H_2O_2, THF; (14) Ph_2Se_2, i-Pr_2NLi, HMPA, THF; (15) Ph_2S_2, i-Pr_2NLi, HMPA, THF

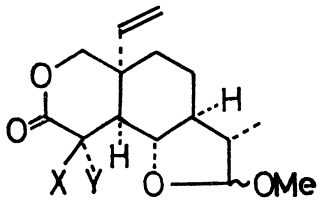
and then oxidized to γ-lactone (8), mp 132-133°C.

Attempted bis-phenylselenylation of the dilithium enolate of 8 with diphenyl diselenide was unsuccessful and the reaction ceased at the stage of the regioselective formation of monoselenide (9a), mp 114-115°C, in excellent yield as evidenced below. The configurational assignment of the phenylselenyl group of 9a was made on the basis of the well-documented β-face selenylation of santonin-related γ-lactones[10] as well as regioselective elimination to unsaturated lactone (10a), mp 173-174°C, on treatment of 9a with hydrogen peroxide (85% yield).

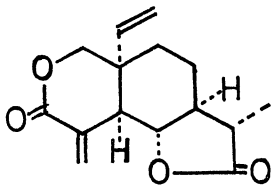
To discriminate the lactone ring in 8 that was susceptible to the selenylation from the other lactone ring, unsaturated δ-lactone (12) was prepared from 7. Phenylsulfenylation of 7 with diphenyl disulfide under standard conditions yielded a mixture of 11a and 11b in a ratio of 73:27 (62% yield). The minor product (11b) was desulfenylated on peracid oxidation leading to 11c,[11] which was then oxidized with Jones reagent to give 12 (60% overall yield). Spectral comparison



10a (X,Y=Me,H)
10b (X=PhS, Y=Me)
10c (X=Me, Y=PhS)



11a (X=Me, Y=PhS)
11b (X=PhS, Y=Me)
11c (X,Y=CH_2)



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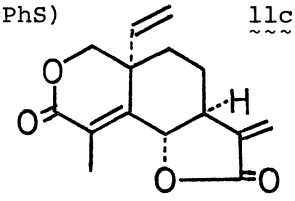

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demonstrated that both lactones 10a and 12 were double bond isomers to one another.

Phenylsulfenylation of 9a with diphenyl disulfide afforded an epimeric mixture of resinous 9b and 9c in a ratio of 75:25.[12] Attempted oxidative elimination of the selenyl group of the minor sulfenylation product (9c) with hydrogen peroxide unexpectedly produced a mixture of (+)-deoxyvernolepin (1), mp 113-116°C, $[\alpha]_D$ +19° (c, 0.32 in acetone)[13,14] and 10b in 64% combined yield (ratio, 84:16), while the same treatment of the major sulfenylated product (9b) afforded a mixture of 1, its endo isomer (13), mp 200-201°C, and 10c in 89% yield (ratio, 30:10:60). This result also allowed to assingn the stereochemistry at C-4 in 9b and 9c as depicted. Considerable formation of 10c in the latter oxidation would probably be ascribable to steric crowding surrounding the sulfur atom in 9b.

The cytotoxic activity of (+)-deoxyvernolepin and other unsaturated lactones obtained is currently under examination.

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References and Notes

1) P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, M. Nishizawa, A. Rosowsky, S. Oppenheim, and H. Lazarus, J. Med. Chem., 20, 71 (1977).

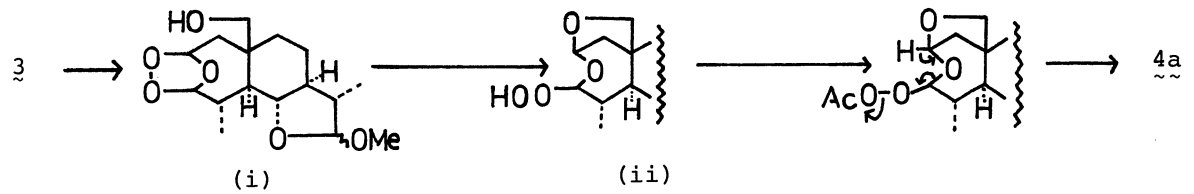
2) P. A. Grieco, J. A. Noguez, and Y. Masaki, J. Org. Chem., 42, 495 (1977)

3) M. Watanabe and A. Yoshikoshi, J. Chem. Soc. Chem. Communs., 1978, 748.

4) An epimeric mixture with respect to methoxy group.

5) All new compounds isolated gave satisfactory microanalytical and spectral data.

6) This unusual ozonization would be rationalized by ring cleavage of molozonide (i) by intramolecular attack of the hydroxy group leading to hydroperoxide (ii), which is then acetylated and undergoes fragmentation to yield 4a.



(i) (ii)

The structure of 4a was supported by the IR[(liquid) 1770 and 1715 cm^{-1}] and ^1H NMR spectra [$\delta(CDCl_3)$ 9.60 ppm (1H, s)].

7) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, J. Org. Chem., 42, 3772 (1977).

8) The configurational assignment at the C-4 position of this compound has not been confirmed.

9) P. A. Grieco, S. Gilman, and M. Nishizawa, J. Org. Chem., 41, 1485 (1976).

10) For example, see K. Yamakawa, K. Nishitani, and T. Tominaga, Tetrahedron Lett., 1975, 2829; idem, ibid., 1975, 4137.

11) The same reaction of 11b gave a 1:1 mixture of 11c and its endo double bond isomer quantitatively.

12) The yield described in the Scheme is based on the recovered 9a.

13) This compound was identified by spectral comparison with those of racemic dexoyvernolepin kindly provided by Professor P. A. Grieco, to whom we are grateful.

14) Very recently, an alternative synthesis of (+)-deoxyvernolepin was reported by Tatsuno et al. Y. Fujimoto, H. Miura, T. Shimizu, and T. Tatsuno, Tetrahedron Lett., 1980, 3409.

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