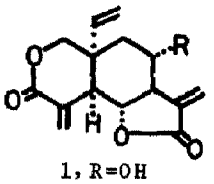
Tetrahedron Letters Vol. 21, pp 3409 - 3412 0040-4039/80/0822-3409$02.00/0

MODIFICATION OF α-SANTONIN VI. SYNTHESIS OF (+)-DEOXYVERNOLEPIN.

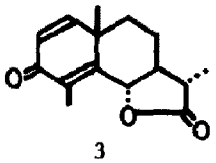
Yasuo Fujimoto*, Hidetoshi Miura, Takeshi Shimizu, and Takashi Tatsuno
The Institute of Physical and Chemical Research, Wako-Shi, Saitama 351, Japan.

Summary: (+)-Deoxyvernolepin is synthesized from α-santonin via angular methyl activation and subsequent furan ring opening.

Vernolepin(1)[1], an elemanolide-type bis-α-methylenelactone isolated from vernonia hymenolepis, is noteworthy for its pronounced antitumor activity against the Waker intramuscular carcinosarcoma 256. The biological activity and the unique framework of this novel sesquiterpene lactone have aroused much attention of organic chemists, and the synthetic approaches[2] and the total syntheses[3] of (±)-vernolepin have been reported by several groups.



1, R=OH
2, R=H



3

Recently, (±)-deoxyvernolepin(2) was synthesized and found to be at least an order of magnitude more potent than natural vernolepin against human lynphoblastic leukemia cells in culture by Grieco[4].

In continuation of our research on the modification of α-santonin[5], we now wish to describe the synthesis of (+)-deoxyvernolepin starting from α-santonin (3).

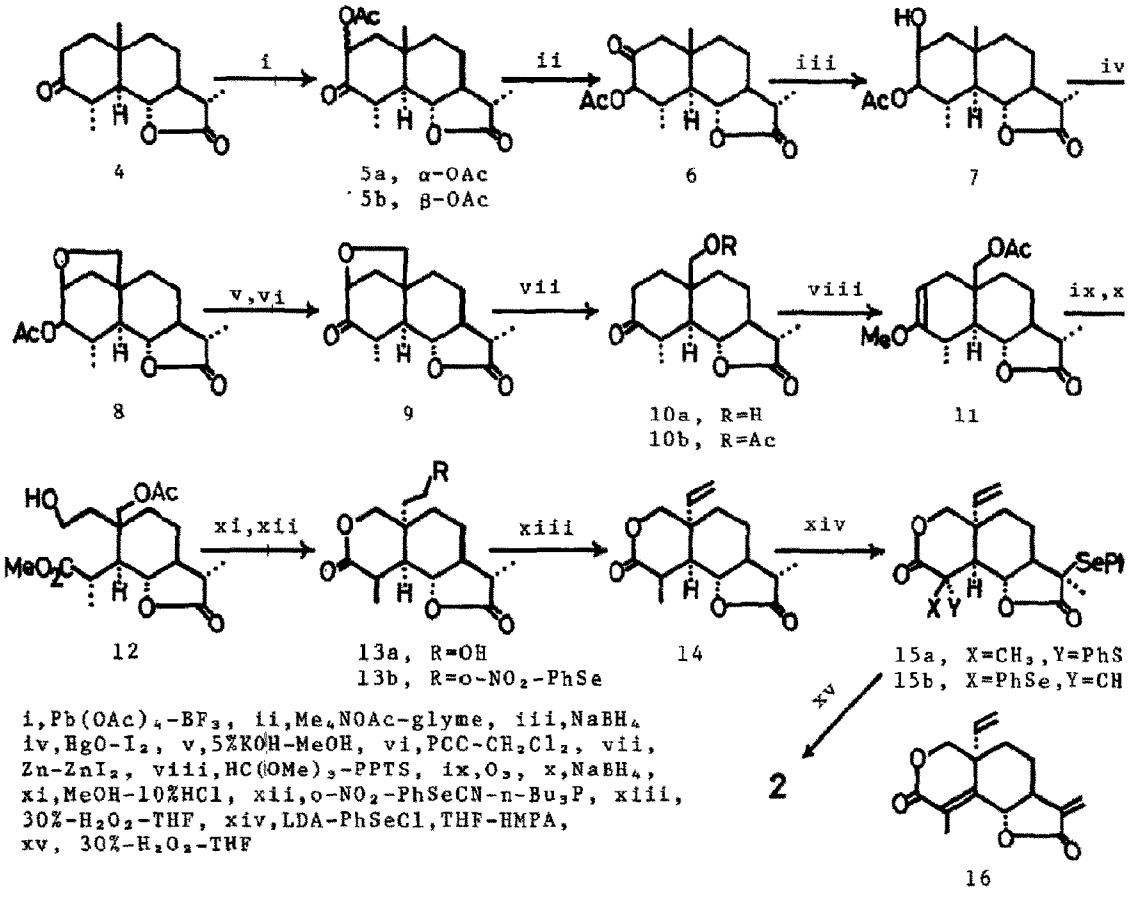
Tetrahydrosantonin(4)[6] obtained by known procedure was treated with lead tetraacetate in the presence of boron trifluolide etherate to give a mixture of 2α-acetoxy(5a) and 2β-acetoxytetrahydrosantonin(5b)[7] in a ratio of 1:1 (72% yield). When this mixture was treated with tetramethylammonium acetate(0.1 eq.) in glyme at reflux for 8 hr, the reaction reached to equilibrium between 5a and 2-oxo-3β-acetoxy-5α-santanolide(6)[8] [5a : 6 = 15 : 85].

After usual work up, the mixture was recrystallized from ethanol to give 6 (mp 214-216°). Reduction of 6 with sodium borohydride(-15~-10°, 30 min, MeOH~CH_2Cl_2 = 1 : 1) afforded an alcohol(7) [mp 158-169°][9] in quantitative yield.

Oxidation of 7 with mercuric oxide-iodine in refluxing benzene for 3 hr yielded an ether(8) [78.5% yield, mp 189-191°, ir(KBr) : 1775, 1728 cm^{-1}, nmr (δ, 60 MHz, $CDCl_3$) : 3.45, 4.07(2H, ABq, J=9.0 Hz), 4.25(1H, d, J=6.0 Hz), 4.38 (1H, d, J=10.0 Hz)].

Hydrolysis(5% MeOH-KOH) of acetyl group of 8 followed by oxidation of the resulting alcohol with pyridinium chlorochromate(PCC)[10](3.0 eq., CH_2Cl_2, room temp., 3 hr) gave a ketone(9)[90.3% yield, mp 196-198°, ir(KBr) : 1775, 1715 c nmr(δ, 60 MHz, $CDCl_3$) : 3.67, 4.32(2H, ABq, J=9.0 Hz, 4.32(1H, d, J=9.0 Hz)].

On treatment of 9 with zinc powder in refluxing acetic acid, the reductiv cleavage of tetrahydrofuran ring hardly occurred. However, the addition of zinc iodide or zinc chloride(0.1 eq.) in this reacrion system extremely accele rated the reaction to give a keto-alcohol(10a)[59% yield, mp 183-184°, ir(KBr) 3450, 1745 cm^{-1}, nmr(δ, 60 MHz, $CDCl_3$) : 3.66(1H, d, J=9.0 Hz), 4.25(1H, dd, J 2.0, 9.0 Hz)] and a keto-acetate(10b)[11][26% yield, mp 131-133°, ir(KBr) : 177(1740, 1690 cm^{-1}, nmr(δ, 60 MHz, $CDCl_3$) : 2.11(3H, s,), 4.42(2H, br.s,).



The cleavage of cyclohexanone ring and subsequent lactone ring formation were performed as follows.

The compound(10b) was reacted with methyl orthoformate in the presence o pyridinium p-toluenesulfonate(PPTS)[12] in methanol at reflux for 3 hr to affor a mixture of enol-ether(11) and dimethyl ketal which was then converted into

by heating with PPTS in refluxing benzene[11; 76.5% yield, mp 148-150°, ir(KBr) : 1775, 1740, 1665 cm^{-1}, nmr(δ, 60 MHz, $CDCl_3$) : 3.50(3H, s,), 3.88(1H, t, J=10.0 Hz), 4.00, 4.31(2H, ABq, J=12.0 Hz), 4.50(1H, br.d, J=7.0 Hz)].

Ozonization(MeOH-CH_2Cl_2, -78°) of 11 followed by reduction with sodium borohydride(-78~-20°) provided a ester(12)[79% yield, ir(KBr) : 3500, 1765, 1750(sh), 1740, 1720 cm^{-1}, nmr(δ, 60 MHz, $CDCl_3$) : 3.70(3H, s,), 3.82(2H, t, J=6.0 Hz), 3.93, 4.20(2H, ABq, J=12.0 Hz)] which was transformed to a dilactone(13a)[82% yield, ir(KBr) : 3450, 1765, 1725 cm^{-1}, nmr(δ, 60 MHz, $CDCl_3$) : 3.78(2H, t, J=6.0 Hz), 4.10, 4.33(2H, ABq, J=12.0 Hz) by heating in refluxing MeOH-10% HCl(1 : 2) for 15 min.

The reaction of 13a with o-nitrophenyl selenocyanate-tri-n-butylphosphine[13] gave a selenide(13b) which without purification was oxidised with 30% hydrogen peroxide to afford deoxytetrahydrovernolepin(14)[90.0% yield, mp 130-132°, ir (KBr) : 1765, 1740, 1730(sh), 1630 cm^{-1}, nmr(δ, 60 MHz, $CDCl_3$) : 4.10, 4.44(2H, ABq, J=12.0 Hz), 5.07~6.07(3H, typical vinyl pattern)].

Dienolate formation(lithium diisopropylamide, THF, -78°) of compound(14) followed by trapping with phenylselenyl chloride(THF-HMPA, -40°) provided a mixture of the selenides(15a)[nmr(δ, 60 MHz, $CDCl_3$) : 1.52(3H, s,), 1.58(3H, s,), 2.62(1H, d, J=10.0 Hz), 4.10(1H, br.t, J=10.0 Hz)] and (15b)[mp 180-182°, nmr(δ, 60 MHz, $CDCl_3$) : 1.55(3H, s,), 1.62(3H, s,), 4.03, 4.97(2H, ABq, J=12.0 Hz), 4.90 (1H, brt,J=10.0 Hz) in a ratio of 1 : 2.7(>90% yield) which was separated by high pressure liquid chromatography(HPLC)(silica gel, n-hexane-ethyl acetate = 3 : 1).

Oxidation of compound(15b) with 30% hydrogen peroxide gave (+)-deoxyvernolepin(2)[82% yield, $[\alpha]_D^{18°}$+37.5°($CHCl_3$, c, 0.33)], while the compound(15a) by the same treatment yielded 2(25% yield) and the isomer(16)[62% yield, nmr(δ, 100 MHz, $CDCl_3$) : 2.19(3H, d, J=2.0 Hz), 3.93, 4.07(2H, ABq, J=10.0 Hz), 4.81(1H, dq, J= 2.0, 12.0 Hz)].

The ir and nmr spectra of (+)-deoxyvernolepin were identical with those of (±)-deoxyvernolepin kindly provided by professor P. A. Grieco. Studies on the biological activities of (+)-deoxyvernolepin and some other α-methylene-γ-lactones derived from α-santonin, and introduction of the hydroxyl group on the C-8 position required for the synthesis of vernolepin are now in progress.

Acknowledgment: We are indebted to professor P. A. Grieco(University of Pittsburg) for providing us with the copies of ir and nmr charts of (±)-deoxyvernolepin. This research was supported by a grant from the Ministry of Education, Science and Culture.

References

1. S. M. Kupchan, R. J. Hemingway, D. Werner, A. Karim, A. T. MacPhail, and G. A. Sim, J. Am. Chem. Soc., 90 3596(1968); S. M. Kupchan, R. J. Hemingw D. Werner, and A. Karim, J. Org. Chem., 34 3903(1969); S. M. Kupchan, M. A. Thomas, J. Med. Chem., 14 1147(1971).
2. a) J. A. Marshall and D. E. Seitz, J. Org. Chem., 40 534(1975).
   b) C. G. Chavdarian, S. L. Woo, R. D. Clark, and C. H. Heathcock, Tetrahedron Letters, 1769(1976).
   c) S. Torii, T. Okamoto, and S. Kadono, Chem. Lett., 495(1977).
   d) T. Wakamatsu, H. Hara, and Y. Ban, Tetrahedron Letters, 1227(1979).
3. a) P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovie, J. Am. Chem Soc., 98 1612(1976).
   b) S. Danishefsky, T. Kitahara, P. F. Schuda, S. J. Etheredge, J. Am. Che Soc., 98 3028(1976).
   c) G. R. Kieczykowski, and R. H. Schlessinger, J. Am. Chem. Soc., 100 1938(1978).
   d) M. Isobe, H. Iio, T. Kawai, and t. Goto, J. Am. Chem. Soc., 100 1940 1978).
   e) F. Zutterman, H. De Wilde, T. Mijngheer, P. De Clercq and M. Vandewall Tetrahedron, 35 2389(1979)
4. P. A. Grieco, J. A. Noguez, and U. Masaki, J. Org. Chem., 42 495(1977)
5. Modification of α-santonin V, H. Miura, Y. Fujimoto, and T. Tatsuno, Synthesis, 898(1979).
6. a) M. Yanagita and A. Tahara, J. Org. Chem., 20 959(1955).
   b) W. Cocker and T. B. H. Mcmurry, J. Chem. Soc., 4549(1956).
   c) M. Yanagita and H. Ogura, J. Org. Chem., 22 1092 (1957).
7. a) H. Miura, Y. Fujimoto, and T. Tatsuno, Synthesis, 898(1979).
   b) K. Yamakawa, J. Org. Chem., 24 897(1959).
   c) P. L. Kamat and A. M. Shaligram, A. S. Rao, Ind. J. Chem., 14B 157(197
8. K. Yamakawa, S. Kidokoro, N. Umino, R. Sakaguchi, T. Takakuwa, and M. Suzuki, Chem. Pharm. Bull., 21 296(1973).
9. K. Yamakawa, K. Nishitani, and K. Kasahara, Chem. Pharm. Bull., 27 953 (1979).
10. E. J. Corey, and J. W. Suggs, Tetrahedron Letters, 2647(1975).
11. The Synthesis of this compound by the different method was reported by Yoshikoshi; M. Watanabe and A. Yoshikoshi, the 23rd Symposium on the Chem stry of Terpenes, Essential Oils, and Aromatics, Tottori, 1979, Abstracts of Papers, P. 239.
12. M. Miyashita, A. Yoshikoshi, and P. A. Grieco, J. Org. Chem., 42 3772(197
13. P. A. Grieco, S. Gilman, M. Nishizawa, J. Org. Chem., 41 1485(1976).

(Received in Japan 30 May 1980)