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CHEMICAL TRANSFORMATION OF (-)-ARTEMISIN INTO (+)-MELITENSIN

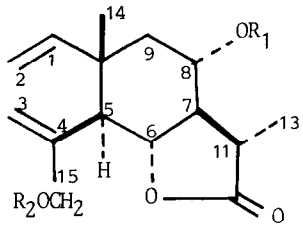
Manuel Arnó, Begoña García, José R.Pedro and Eliseo Seoane*
Organic Chemistry Department of Valencia University (Spain)

Abstract. Partial Synthesis of Melitensin from Artemisin is described.

In the study of Centaurea aspera stenophylla we have isolated melitensin and other sesquiterpene lactones[1]. Melitensin[2] (Ib) is a sesquiterpene lactone, whose structure has been correlated to cnicin[3,4]. But as the artemisin was prepared by total synthesis[5], and for some time was commercialy available, its transformation into melitensin would be a real total synthesis and a design to obtain it. This is the aim of present report. Antitumor activity[6] of related compounds makes this research very interesting[7].

Chemical transformation of (-)-artemisin into (+)-melitensin. A solution of artemisin (II) (1.800 g; 6.87 mmol) in acetone (48 mL) was hydrogenated (35 min) using Pd/C 5% (0.419 g) as the catalyst. The hydrogenation mixture, dissolved in dimethylformamide (50 mL), was treated with tert-butyldimethylsilyl chloride[8] (3.654 g, 24.24 mmol) and imidazole (4.671 g) to protect the hydroxyl group and to facilitate the separation of stereisomers. The temperature of the mixture was raised to 30-40°C, with stirring over a period of 3.5 h. A careful chromatography column (silica-gel, hexane-ether 7:3) of reaction product allowed to isolate two products: IIIa (0.625 g; 18.6%; an oil) and IVa (1.444 g; 55.3%, m.p. 176-178°C). Compounds IIIa and IVa gave by cleavage of silyl group with Bu_4NF in THF IIIb (m.p. 213-215°$\{\alpha\}_D$+46.7) and IVb (m.p. 227-229°, $\{\alpha\}_D$+50) respectively, in good agreement with δ- and γ-tetrahydroartemisin of the literature[9].

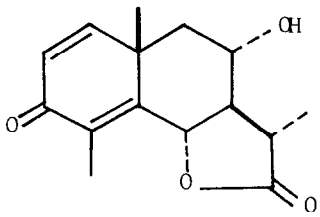
The next step was the formation of a double bond $\Delta^{2,3}$ through a Shapiro reaction. Thus, the keto-lactone (IVa) (0.294 g; 0.77 mmol) was transformed into the corresponding tosylhydrazone, by treatment with tosylhydrazine (0.176 g; 0.95 mmol) in benzene (2 mL) and $BF_3.Et_2O$ (a drop) over 3 h. The tosylhydrazone obtained, dissolved in THF (4 mL), was treated at -78°C (15 min) with lithium



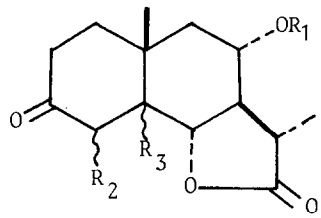
Ia: R_1=$SiMe_2Bu^t$;R_2=H

Ib: R_1=R_2=H

Ic: R_1=R_2=$COCH_3$



II

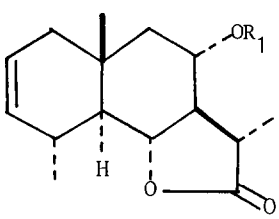


IIIa: R_1=$SiMe_2Bu^t$;R_2=β-Me;R_3=β-H

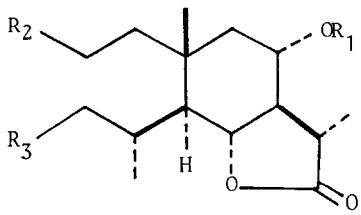
IIIb: R_1=H;R_2=β-Me;R_3=β-H

IVa: R_1=$SiMe_2Bu^t$;R_2=α-Me;R_3=α-H

IVb: R_1=H;R_2=α-Me;R_3=α-H



V: R_1=$SiMe_2Bu^t$

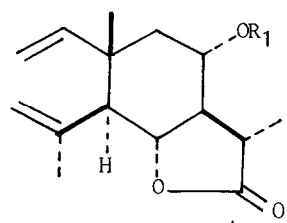


VI: R_1=$SiMe_2Bu^t$;R_2=R_3=OH

VII: R_1=$SiMe_2Bu^t$;R_2=R_3=o-NO_2-C_6H_4-Se-

VIII: R_1=$SiMe_2Bu^t$;R_2=o-NO_2-C_6H_4-Se-

R_3=OH



IXa: R_1=$SiMe_2Bu^t$

IXb: R_1=H

diisopropylamide (prepared from 0.996 g of diisopropylamine in 7.5 mL of THF and 6.1 mL of a 1.6 M solution of n-butyl-lithium in hexane). The temperature of the mixture was raised to 0°, and the reaction continued with stirring over 2 h. Usual work up of the mixture followed by column chromatography allowed to isolate a crystalline product (0.142 g; 50%), m.p. 127-128°C (hexane-ether)identified as the olefin (V): IR (KBr), 3020 and 1770 cm^{-1}; NMR (CCl_4) δ 5.4 (2H, br s., CH=CH).

The olefin V (0.407 g; 1.11 mmol) in ethanol (49 mL) at -78°C was treated with a saturated solution of ozone in methylene chloride (49 mL, ca. 1.20 mmol of ozone) at -78°C. At 15 min. intervals sodium borohydride (0.196 g; 4.80 mmol) was added at -78°C over 1 h. The reaction mixture warmed to 0°C (30 min.) and worked up in the usual way afforded a crystalline product (0.386 g; 87%), m.p. 151-152°C (ethyl acetate) identified as the diol (VI): IR (KBr), 3500-3200 and 1775 cm^{-1}. NMR ($CDCl_3$) δ 3.4-4.4 (6H, overlapped signals, 2 CH_2OH, 6-H, 8-H).

The synthesis was continued by treatment of diol (VI) (0.375 g; 0.937 mmol) with excess of o-nitrophenyl selenocyanate[10] (1.020 g; 4.490 mmol) in THF (7.8 mL), and tri-n-butylphosphine[11] (0.906 g; 4.490 mmol) over 6 h at room temperature under an atmosphere of argon. After removal of the solvent, the residue was carefully chromatographed (silica-gel, hexane-ether 1:1) to obtain two yellow products. The first eluted product (0.569 g; 79%) was identified as the bis-o-nitrophenylselenide (VII): IR (KBr), 3080, 1775, 1590, 1565 and 1510 cm^{-1}; NMR (CCl_4), δ 2.7-3.2 (4H, m, $2CH_2Se$), 7.0-7.6 (6H, m, aromatics) and 8.0-8.35 (2H, m, aromatics). The second eluted product (0.072 g; 13%) m.p. 112-115°C (hexane-ether) was identified as the monoselenide (VIII): IR (KBr) 3600-3200, 3060, 1770, 1590, 1565 and 1510 cm^{-1}; NMR ($CDCl_3$), δ 3.0 (2H, m, $-CH_2Se$), 3.55 (2H, d, J=7.3, CH_2OH), 7.1-7.65 (3H, m, aromatics) and 8.25 (1H, d,J=8, aromatics). The bis-selenide/monoselenide relation obtained is rather variable and in the worst experiment was as low as 1.8.

By oxidation of bis-o-nitrophenyl selenide (VII) (0.569 g; 0.740 mmol) in THF (7 mL) with 50% aqueous hydrogen peroxide (0.4 mL) at 0°C, followed by spontaneous elimination of o-nitrophenylselenenic acid at room temperature over 3.5 h the product (IXa) (0.229 g; 85%) was obtained. This product presents the following constants: m.p. 174-175°C (hexane-ether); IR (KBr), 3080, 1780 and 1640 cm^{-1}; NMR (CCl_4), δ 4.7 and 5.05 (2H, two broad singlets, $CH_2=C$) and 4.7-6.05 (3H, m, typical vinyl pattern, $-CH=CH_2$). IXa gave by cleavage of silyl group (+)-temisin (IXb), a natural sesquiterpene lactone[12], m.p. 227-228°C (ethyl acetate); $\{\alpha\}_D^+$ 63°(EtOH); m.s. peaks at m/e (rel. int). 250 (2.12%,M^+), and 41 (100%); IR (KBr), 3500-3400, 3070, 1755 (1770 in $CHCl_3$), 1640, 1140, 985, 965 and 890 cm^{-1}; NMR ($CDCl_3$, 100 MHz), δ 1.09 (3H, s, 10-Me), 1.39 (3H, d, J= 7,11-Me), 1.77 (3H, s, 4-Me) 2.26 (1H, d. J=11.9, 5-H), 2.65 (1H, dq, J=7 and 12, 11-H), 3.95 (1H, dt, J=4.7 and 10, 8-H), 4.12 (1H, t, J=11, 6-H), 4.7 and 5.05 (2H, two broad singlets, $CH_2=C$) 4.8-6.0 (3H, typical vinyl pattern, $-CH=CH_2$)

The allylic oxidation of (IXa) (0.058 g, 0.159 mmol) with SeO_2 (8.7 mg) and 80% t-BuOOH (0.04 mL) in CH_2Cl_2(0.12 mL), over 30 min. at room temperature affords Ia (0.030 g, 50%) as a white solid m.p. 180-181°(hexane-ether); IR (KBr)

3520, 3080, 1755 and 1640 cm^{-1}; NMR ($CDCl_3$) δ 3.7-4.4. (4H, overlapped signals, 6-H, 8-H, CH_2OH) and 4.7-6.05 (5H, typycal vinyl pattern $-CH=CH_2$ and $CH_2=C$).

Cleavage of the silyl ether Ia allows one to obtain Ib, melitensin, m.p. 180-183°C (AcOEt-hexane); $\{\alpha\}_D 60°$ (EtOH); m.s. peaks at m/e (rel. int.)266(0.65%, M^+) and 149 (100%); IR (KBr), 3600-3400, 3090, 1755, (1775 in $CHCl_3$), 1635, 1140, 1050, 980, 965, and 910 cm^{-1}; NMR ($CDCl_3$, 100 MHz), δ 1.10 (3H, s, 10-Me), 1.39 (2H, d, J=7, 11-Me), 2.40 (1H, d, J=11.3, 5-H), 2.54 (1H, dq, J=7 and 11, 11-H), 3.98 (1H, dt, J=4.6 and 10.4, 8-H), 4.03 (2H, s, $-CH_2-OH$) 4.15 (1H, t, J=11.5, 6-H), 4.8-6.0 (3H, typical vinyl pattern $CH=CH_2$), 4.95 and 5.39 (2H, two broad singlets $CH_2=C$). Its diacetate (Ic) melts 139-140°C (hexane-ether) and shows the expected spectroscopic properties.

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REFERENCES

1.- M.Picher, E.Seoane and A.Tortajada, unpublished work.

2.- A.G.González, J.M.Arteaga, J.Bermejo and J.L.Bretón, Anal.Quím. 67, 1243 (1971).

3.- A.G.González, J.M.Arteaga and J.L.Bretón, Anal.Quím. 70, 158 (1974).

4.- A.G.González, J.M.Arteaga and J.L.Bretón, Phytochem. 14,2039 (1975).

5.- M.Nakasaki and K.Naemura. Bull.Chem.Soc.Jap. 42, 3366 (1969).

6.- S.M.Kupchan, M.A.Eakin and A.M.Thomas J.Med.Chem. 14, 1147 (1971).

7.- N.H.Fischer, E.J.Olivier and H.D.Fischer, Fortschr.Chem.Org.Naturst. 38, 47 (1979).

8.- E.J.Corey and A.Venkateswartu, J.Amer.Chem.Soc. 94, 6190 (1972).

9.- M.Sumi, J.Amer.Chem.Soc. 80, 4869 (1958).

10.- H.Bauer, Ber. 46, 92 (1913).

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

12.- M.Nishizawa, P.A.Grieco, S.D.Burke and W.Metz, J.C.S.Chem.Comm. 76 (1978).

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