CHEMISTRY LETTERS, pp. 1021 - 1024, 1984.

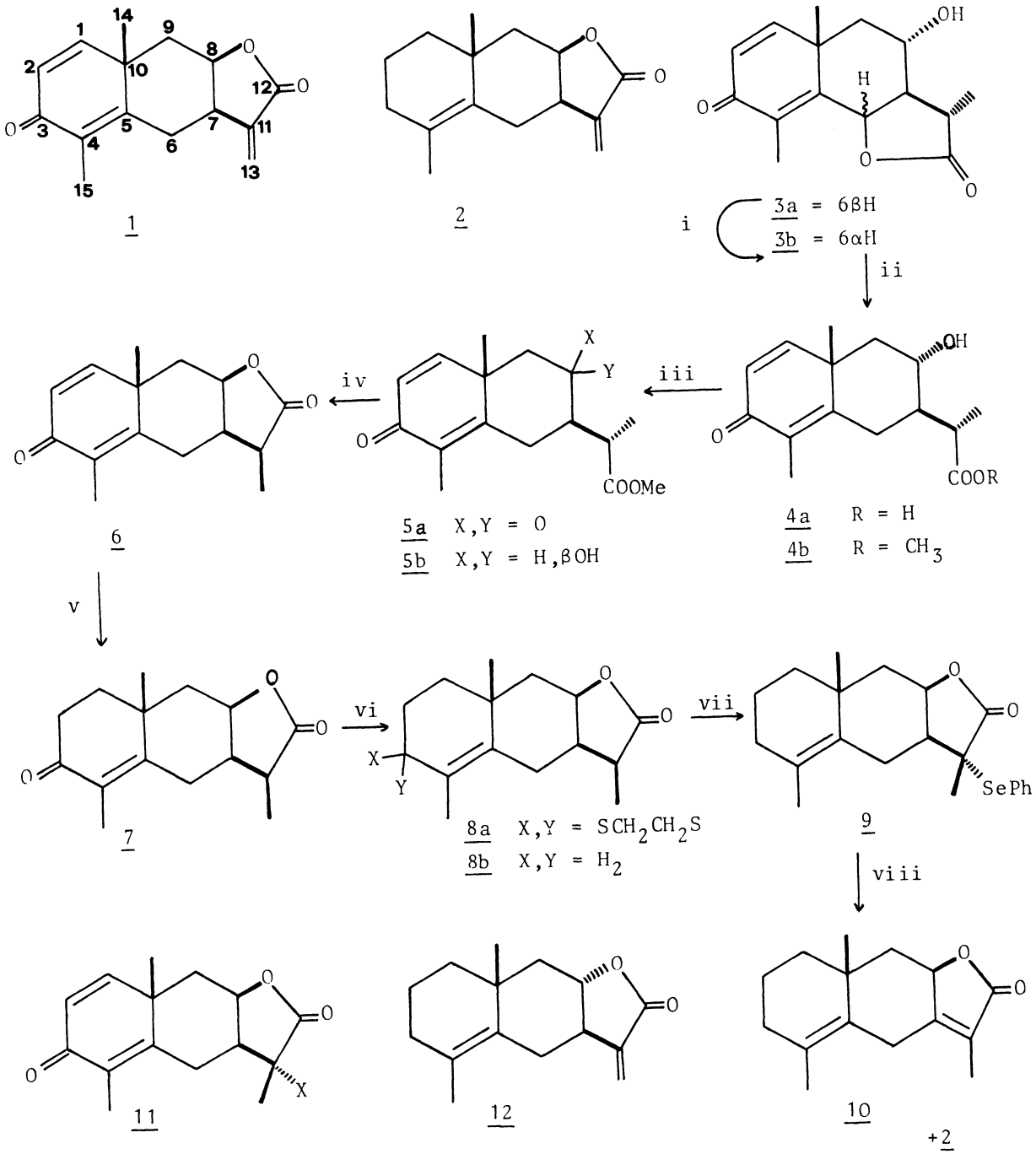
TRANSFORMATION OF ARTEMISIN INTO YOMOGIN AND 1-DEOXYIVANGUSTIN

Manuel ARNÓ, Miguel CARDA, J. ALBERTO MARCO, and Eliseo SEOANE*
Departamento de Química Orgánica, Facultad de Químicas,
Burjasot, Valencia, Spain

Partial syntheses of the sesquiterpene lactones yomogin and 1-deoxyivangustin from artemisin are disclosed.

Yomogin 1 and 1-deoxyivangustin 2 are two sesquiterpene lactones with eudesmane framework, isolated[1] for the first time from Artemisia princeps Pamp. and Inula helenium L., respectively. We have recently[2,3] started a synthetic program, aimed at the preparation of sesquiterpene lactones from available chiral precursors, such as artemisin 3a. This natural eudesmanolide has been obtained by total synthesis,[4] so that its transformation into the above mentioned sesquiterpene lactones also constitutes a real total synthesis of them. Racemic yomogin has been obtained recently by total synthesis,[5] whereas the natural (−)-form was prepared from α-santonin.[6] 1-Deoxyivangustin has not been synthesized as yet, neither totally nor partially. The known cytotoxic[7] properties of α-methylene-γ-lactones confer a high interest to synthetic efforts toward these compounds. A recent disclosure[8] covers in depth the main advances in this field during the last decade.

A key step for the desired transformation of the 12,6-lactone into a 12,8-lactone moiety is the reductive cleavage of the C_6-O bond. This was achieved, as already reported[9] for α-santonin, by C-6 epimerization[10] of artemisin (3a → 3b) followed by treatment with activated Zn powder at reflux in methanol containing acetic acid. The acid 4a was not isolated but methylated in situ with excess ethereal diazomethane. Column chromatography of the crude methylation product enabled the isolation of 4b in 35% overall yield from 3a: oil, $[\alpha]_D^{25}$ −14°; IR(film): 3450, 1727, 1654 cm^{-1}; NMR: δ 3.73 (3H, s, COOMe), 4.3-3.8, m (H-8β); UV, λ_{max}: 240 nm (ε_{max} 11700). In order to invert the configuration at C-8, the methyl ester 4b was oxidized with Ratcliffe's reagent,[11] furnishing the diketone 5a as an oil: $[\alpha]_D^{25}$ −100°; IR (film): 1727, 1712, 1660 cm^{-1}; NMR: δ 3.68 (3H, s, COOMe); UV, λ_{max}: 241 nm (ε_{max} 8600). 5a was reduced with $LiAlH(OBu^t)_3$, affording 5b, mp 160-161 °C ; $[\alpha]_D^{25}$ −138°; IR (KBr): 3480, 1732, 1655 cm^{-1}; NMR: δ 3.72 (3H, s, COOMe), 4.20, m ($W_{1/2}$=7 Hz, H-8α); UV, λ_{max}: 241 nm (ε_{max} 9300), in 80% overall yield[12] from 4b. 5b could be cyclized to 6, in essentially quantitative yield, by heating at reflux in benzene containing a catalytic amount of p-toluensulfonic acid. The lactone 6, mp 178-179 °C, $[\alpha]_D^{25}$ −136°; IR (KBr): 1778, 1660, 1630 cm^{-1}; NMR: δ4.5, m ($W_{1/2}$= 10 Hz, H-8α); UV, λ_{max}: 238 (ε_{max} 9900), 262 (sh, ε ∿ 5200) nm, is a dihydro derivative of yomogin and was already converted into the latter product by Yamakawa and coworkers,[6] using Grieco's procedure[13] via 11 (X=SePh).



i) 5% HCl/DMF, 90 °C, 4 h. ii) Zn, AcOH/MeOH/Δ, 15 min, then excess CH_2N_2. iii) 1: $CrO_3.(py)_2/CH_2Cl_2$/0 °C, 6 h; 2: $LiAlH(OBu^t)_3$(2.5 equiv.)/THF/0 °C, 3 h. iv) cat. TsOH/C_6H_6/Δ, 90 min. v) H_2, Wilkinson cat., C_6H_6/EtOH,RT, 12 h. vi) 1: $(CH_2SH)_2$ (7 equiv.)/AcOH, cat. $BF_3.Et_2O$/RT, 4 h; 2: excess Raney Ni/EtOH/RT, 10 min. vii) LDA/TMEDA/THF/-25 °C, 1 h, then PhSeCl/HMPT/-25 °C, 1 h. viii) 30% H_2O_2/AcOH/THF/0 °C, 1 h.

Compound 6 was hydrogenated (Wilkinson cat.) to the enone 7[6] in 95% yield: mp 103-104 °C; $[\alpha]_D^{25}$ + 92°; IR (KBr): 1765, 1660 cm^{-1}; NMR: δ 4.50, br q ($W_{1/2}$ =10 Hz, H-8α); UV, λ_{max}: 244 nm (ε_{max} 15000). Reductive elimination of the keto group was achieved via tioketalization to 8a and subsequent treatment with freshly prepared Raney Ni in EtOH at room temperature. 8b was obtained in 50% overall yield as an oil, $[\alpha]_D^{25}$ + 47°; IR (film): 1760 cm^{-1}; NMR: δ 4.50, m ($W_{1/2}$ =12 Hz, H-8α).[14] Dehydrogenation of 8b to 2 turned out to be rather troublesome. The best yield in the phenylselenenylation step (60%) was obtained by treating the lactone 8b, dissolved in THF, with 4 equiv. of LDA and 12 equiv. of TMEDA at -25 °C, stirring at the same temperature for 1 h and then adding 4 equiv. of each PhSeCl and HMPT in THF. After 1 h of further stirring at -25 °C, the reaction was quenched with 1M HCl and worked up as usual, yielding 9, mp 134-135 °C; IR (KBr): 1765 cm^{-1}; NMR: δ 7.6-7.1, m (5 arom. H); 5.0, m (H-8α). The oxidative elimination step 9 → 2 was carried out with 30% aqueous H_2O_2 (6 equiv.) in THF containing AcOH (2 equiv.). After stirring for 1 h at 0 °C, working up and column chromatography on silica gel (elution with 5% EtOAc in hexane), 2 was isolated as an oil in 10% yield,[15] $[\alpha]_D^{25}$ + 46°, along with ca. 60% of another product, presumably the endocyclic[6] double-bond isomer 10. This latter product was very unstable and could not be satisfactorily[17] identified.

2 showed all expected[1b] spectroscopic characteristics: IR (film): 1760 cm^{-1}; MS: M^+, m/e 232.1456 (Calcd. for $C_{15}H_{20}O_2$: 232.1463). The ^1H NMR spectrum at 200 MHz was identical with that of an authentic sample[1b] of 1-deoxyivangustin: δ6.23 d (J=2.5 Hz, H-13'), 5.60 d (J=2.5 Hz, H-13); 4.49 distorted q (H-8α); 1.66 s (Me-15); 1.08 s (Me-14). Specially noteworthy is the distorted quadruplet at δ 4.49 (H-8α), with an apparent coupling constant of J∿7 Hz, which points to a cis ring-junction between the lactone and the cyclohexane ring.[1b,18]

The authors wish to express their deep appreciation to Prof. Dr. D.H.R. Barton for a generous gift of artemisin, to Prof. Dr. F. Bohlmann for the sending of spectra of natural 1-deoxyivangustin and to Dr. Miguel Feliz, University of Barcelona, for the performing of NMR spectra at 200 MHz. One of us (M.C.) thanks the I.N.A.P.E. for a fellowship.

References

1) a) T.A. Geissman, J.Org.Chem., 31, 2523 (1966); b) F. Bohlmann, P.K. Mahanta, J. Jakupovic, R.C. Rastogi, and A.A. Natu, Phytochemistry, 17, 1165 (1978).
2) These data have been taken from the Ph.D. thesis of M.C., which also contains various transformations of artemisin into other natural sesquiterpene lactones. These results will be reported in due course. All products gave satisfactory spectral (IR, UV, NMR, high-resolution MS) analyses. NMR spectra, unless otherwise stated, were recorded at 60 MHz in $CDCl_3$ solution. Specific rotations were measured in $CHCl_3$ solution at a concentration of about 0.2 g/100 mL. UV spectra were measured in EtOH solution.
3) M. Arnó, B. García, J.R. Pedro,and E. Seoane, Tetrahedron Lett., 1983, 1741.
4) M. Nakazaki and K. Naemura, Bull.Chem.Soc.Japan, 42, 3366 (1969).

5) D. Caine and G. Hasenhuettl, J.Org.Chem., 45, 3278 (1980).
6) K. Yamakawa, K. Nishitani, and A. Yamamoto, Chem.Lett., 1976, 177; K. Yamakawa, K. Nishitani, A. Murakami, and A. Yamamoto, Chem.Pharm.Bull., 31, 3397 (1983). See also the following paper: ibid, 31, 3411 (1983), in which the authors describe the obtainment of 8b under slightly different conditions as a non separable mixture with another compound. Moreover, the physical properties of 5b (mp 160-161 °C) and Yamakawa's product with the same structure, reported to be an oil, are surprisingly different.
7) K.-H. Lee, I.H. Hall, E.-C. Mar, C.O. Starnes, S.A. ElGebaly, T.G. Waddell, R.I. Hadgraft, C.G. Ruffner, and I. Weidner, Science, 196, 533 (1977).
8) N.H. Fischer, E.J. Olivier, and H.D. Fischer, Fortschr.Chem.Org.Naturst., 38, 47 (1979).
9) H. Ishikawa, Yakugaku Zasshi, 76, 504 (1956); T. Miki, ibid, 75, 410 (1955); T. Nozoe, T. Asao, M. Ando, and K. Takase, Tetrahedron Lett., 1967, 2821.
10) M. Sumi, J.Am.Chem.Soc., 80, 4869 (1958). The author reports a yield of 6% in 6-epiartemisin: with a slight modification of the reaction conditions (reaction time: 4 h) and isolation procedure (chromat. on silica gel, elution with EtOAc-hexane 1:1), higher yields (55-60%) are always obtained.
11) R.W. Ratcliffe, Org.Synth., 55, 84 (1976).
12) In the reduction of 5a, a 18:1 mixture of 5b and 4b was obtained.
13) H.J. Reich, "Organoselenium Oxidations," in "Oxidation in Organic Chemistry," ed. by W.S. Trahanovsky, Academic Press, Inc., N. York, S. Francisco, London (1978), Vol. 5-C, p.61.
14) 8b has been reported to be a solid but inconsistent physical constants (no spectral data) have been given in the literature: K. Naemura and M. Nakazaki, Tetrahedron Lett., 1969, 33 ; S. Nakazawa, J.Am.Chem.Soc., 82, 2229 (1960).
15) Either phenylselenenylation under standard Grieco's conditions, omission of TMEDA, using only 2 equiv. of LDA or working at lower temperatures led to recovery of the starting compound. Attempts to bypass the preferent formation of 10 by α-halogenation[16] of the lactone 8b (trans-elimination of HX would give only 2) met with failure. The same result was also observed in the case of 6, which could not be transformed into 11 (X=Hal).
16) M.W. Rathke and A. Lindert, Tetrahedron Lett., 1971, 3995; A.E. Greene, J.-C. Muller,and G. Ourisson, J.Org.Chem., 39, 186 (1974); R.T. Arnold and S.T. Kulenovic, ibid., 43, 3687 (1978).
17) Some provisory spectroscopic features of 10 are: IR (film): 1750, 1685 cm^{-1}; UV, λ_{max} (ε_{max}): 216 (9900), 272 (5800) nm ; NMR: δ 4.7, br t (1H); 3.3, m (1H); 1.9, br s (3H).
18) The 8-epimer of 2, 1-deoxy-8-epiivangustin 12, has also been synthesized by us for comparison purposes. The hydrogen H-8β appears as a double doublet of doublets centered at δ 4.12, with Js= 12, 11, and 4 Hz (results to be published).

(Received March 30, 1984)