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FUNCTIONALIZATION AT C-12 IN LABDANIC DITERPENES: SYNTHESIS OF THE NATURAL DITERPENIC LACTONES ISOLATED FROM CISTUS LADANIFERUS L.

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Abstract.- Oxidative cyclization of Labdanediol (XII) and methyl Labdanolate (Ib) with $Pb(OAc)_4$, and subsequent oxidation with reagents as RuO_4, O_3, CrO_3 or $(Bu^t)_2CrO_4$ affords, in excellent yield, the natural diterpenic lactones II, III, VII, VIII, XI and XIII, isolated from Cistus ladaniferus L.

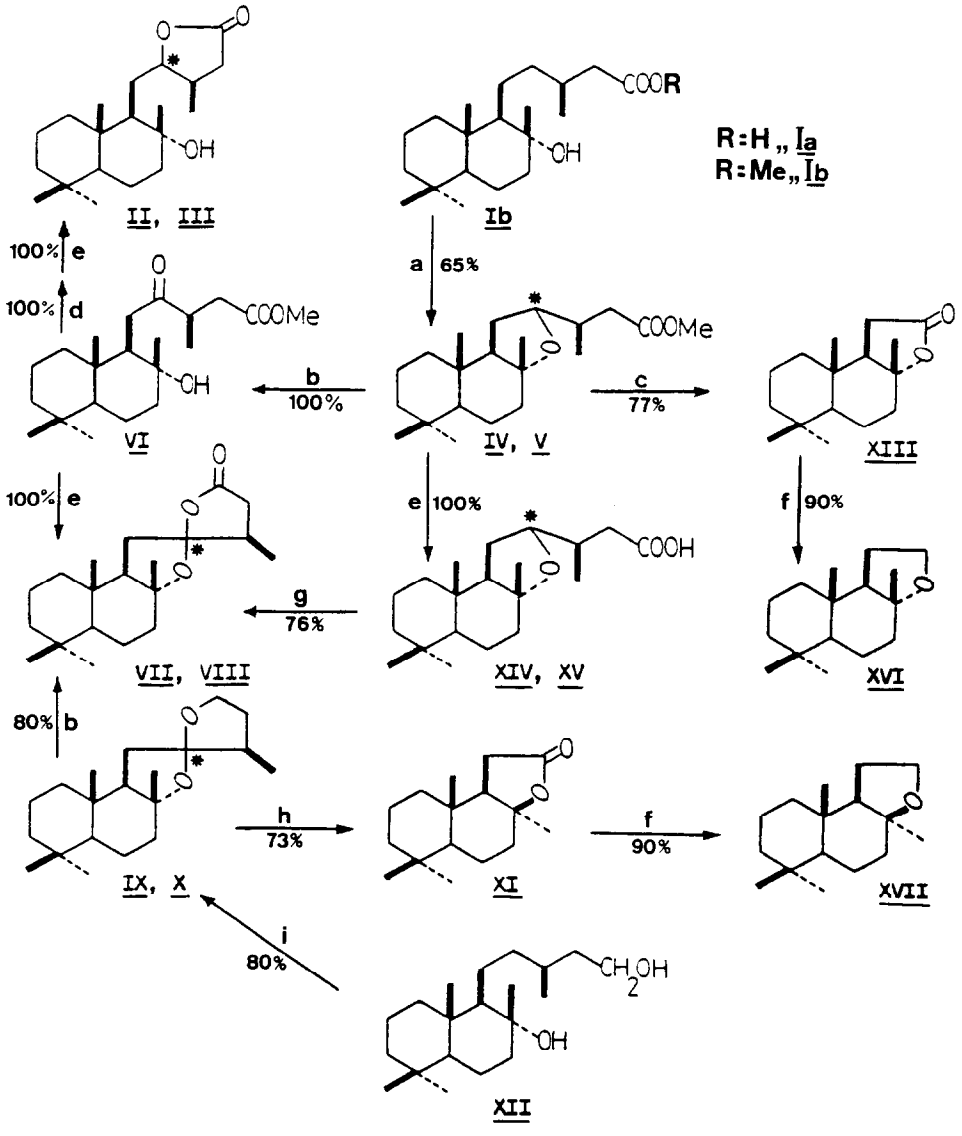
Labdanolic acid (Ia) and Labdanediol (XII) are the main components of the acid (40%) and neutral (30%) fractions, respectively, from the n-hexane extract of Cistus ladaniferus L. ("Rock-rose")[1]. We report here their use as raw material for the synthesis of diterpenic lactones such as Labdanolide and 12-Epi-labdanolide (II and III), α- and β-Levantanolides (VII and VIII), and of nor-diterpenic lactones as 12-Nor-ambreinolide (XIII) and 8-Epi-12-nor-ambreinolide (XI), which have all been isolated as natural products from Cistus ladaniferus L.[2]

These lactones have also economic interest, since they can be easily transformed in perfume fixers with "ambergris" smell as Ambrox (XVI) and Isoambrox (XVII)[3,4]. We open here, thus, a possibility for the industrial use of C. Ladaniferus L.

The syntheses of these compounds have been carried out through the novel epimeric cyclic ethers IV and V, and through the spiroketals IX and X, obtained by oxidative cyclization of I and XII, respectively.

It is worth noting that the succesful preparation of the versatile intermediates IV, V and VI represents a satisfactory solution to the classical problem of the functionalization at C-12 in the labdane skeleton, thus opening a possible way for the synthesis of a great number of natural products containing this skeleton.

Lactones II and III can be directly obtained as a (6:1) mixture in 20% yield by reaction of Ia with $Pb(OAc)_4$ in benzene[5]. Alternatively, they can be prepared



[a] $Pb(OAc)_4$ / I_2 , C_6H_6, C_5H_5N, 10°C; [b] RuO_2 / $NaIO_4$, Me_2CO / H_2O; [c] CrO_3 / AcOH; [d] $NaBH_4$ / MeOH; [e] KOH / MeOH and after HCl / H_2O; [f] B_2H_6 / $F_3B.Et_2O$ or successive treatment with $LiAlH_4$ / Et_2O, ClTs / C_5H_5N and heating; [g] O_3 / SiO_2, -80°C; [h] $(Bu^t)_2CrO_4$ / Ac_2O / AcOH; [i] $Pb(OAc)_4$ / I_2 , cyclohexane, $CaCO_3$, 80°C.

in 65% overall yield (6:1), following the sequence Ib → (IV,V) → VI → (II,III), by reduction of VI with $NaBH_4$ / MeOH and subsequent treatment with KOH / MeOH and aqueous HCl.

The cyclic ethers IV and V are obtained by treatment of methyl labdanolate, Ib, with $Pb(OAc)_4$ / I_2 at 10ºC, under " hypoiodite reaction " conditions[6], with a yield of 66% (1:1).

Oxidation of IV and/or V with CrO_3 / AcOH[7] affords 77% of lactone XIII. If the oxidation is carried out with RuO_2 / $NaIO_4$[8], the ketoester VI is obtained in quantitative yield. Saponification and subsequent acidification of VI leads quantitatively to a (3:1) mixture of spirolactones VII and VIII (65% overall yield). These spiro-γ-lactones can also be directly synthesized by reaction of Ia with LTA / I_2, but the yield is only 26% (3:1).

Oxidative cyclization of 8,15-labdanediol, XII, with $Pb(OAc)_4$ / I_2 yields 80% of the spiroketals[9] IX and X (3:1) which, when oxidized with RuO_2 / $NaIO_4$, give 80% yield of the spirolactones VII and VIII (3:1). If the oxidation of IX and/or X is carried out with $(Bu^t)_2CrO_4$ / Ac_2O / AcOH[10] a 73% yield of lactone XI is obtained[11].

On the other hand, VII and VIII can be prepared from the acids XIV and XV by the " dry ozonation " method[12] with yield of 76% (3:1).

The mixtures of epimers II/III, IV/V, VII/VIII and IX/X have been perfectly resolved: II/III, VII/VIII and IX/X have been separed by column chromatography on silica, eluting with n-hexane / diethyl ether, followed by recrystallization in n-hexane. On the other side, IV and V were separated by preparative H.P.L.C. on silica, eluting with n-hexane / diethyl ether (9:1). The absolute configuration at C-12 in all of the epimers was determined by comparative studies of their ^1H N.M.R. (200 MHz) and ^{13}C N.M.R. (50 MHz) spectra. Moreover, the absolute configuration at C-12 of II and III, has been corroborated by applying the " Horeau method "[13] to the triols obtained by reduction of II and III with $LiAlH_4$.

All compounds reported in this study gave satisfactory microanalyses, and were perfectly characterized by their physical and spectroscopic properties.

Moreover, the properties of the lactones synthesized by us, were identical to those of the correspondent natural products, isolated from n-hexane extract of Cistus ladaniferus L.[1].

REFERENCES AND NOTES

1.-(a):J.D. Cocker, T.G. Halsall and A. Bowers, J. Chem. Soc., 4259(1956); (b):J. de Pascual Teresa, J.G. Urones, A, San Feliciano, An. Quim., 727, 68 B, (1972); (c): C. Tabacik Wlotzka, M. Mousseron and A. Chafai, Bull. Soc. Chim. Fr., 2299, (1963).

2.- J. de Pascual Teresa, J. G. Urones, P. Basabe Barcala and F.H. Aubanell, An.Quim., 335, 70, (1979).

3.- XVI and XVII can be directly prepared[14, 15, 16] from XIII and XI, respectively, by reduction either with B_2H_6 / $BF_3.Et_2O$ or with $LiAlH_4$ up to the diol stage, followed by heating with Al_2O_3 at 230ºC. Alternatively, the primary hydroxyl group of this diol can be converted into a p-toluenesulphonate, which is then cyclized by heating. The overall yield for conversion of the lactones XIII and XI into Ambrox and Isoambrox is 90%.

4.-(a): E. J. Brunke, Dragoco Report, 9, (1980); (b): E. Lederer, Fortschr. Chem.-Org. Naturst., 120, 6, (1950).

5.-R. N. Butler in Synthetic Reagents, John Wiley, New-York, 1977, vol 3, p. 277.

6.- J. Kalvoda and K. Heusler, Synthesis, 525, (1971).

7.- K. Nakanishi and L.F. Fieser, J. Am. Chem. Soc., 3910, 74, (1952).

8.- D.M. Piatak, H.B. Bhat and E. Caspi, J. Org. Chem., 34, 112, (1969).

9.- A. G. González, C. G. Francisco, R. Freire, R. Hernandez, J.A. Salazar and E. Suarez, Tetrahedron Lett., 2725, 31, (1976).

10.-E. Menini and J.K. Norymberski, J. Biochem., 195, 84, (1962).

11.-Also, XI is obtained by epimerization of XIII with AcOH / H_2SO_4.

12.-Z. Cohen, H. Varkony and E. Keiman in Organic Syntheses, John Wiley Ed., New-York, 1979, vol 59, p. 176.

13.-A. Horeau and A. Novaille, Tetrahedron Lett., 1939, 22, (1971).

14.-M. Hinder and M. Stoll, Helv. Chim. Acta., 1308, 33(5), (1950).

15.-G. Ohloff, Fortschr. Chem. Org. Naturst., 185, 12/2, (1969).

16.-R.C. Cambie, K.N. Joblin and A.F. Preston, Aust. J. Chem., 583, 24, (1971).

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