[Chem. Pharm. Bull. 21(6)1378—1380(1973)]

UDC 547.597.057

Synthesis of β-Amyrin-23,23-d_2 from Methyl Hederagenate

Tohru Kikuchi, Mineo Niwa, and Toshio Yokoi

Faculty of Pharmaceutical Sciences, Kyoto University[1]

(Received November 21, 1972)

Recently nuclear magnetic resonance (NMR) pseudo-contact shift using shift reagents such as tris(dipivalomethanato)europium and tris(dipivalomethanato)praseodymium has been found to be useful for the structure analyses of organic compounds.[2] We have concerned with the application of this technique for the methyl resonances of triterpene acetates. During this work it became necessary to estimate the location of the coordinating metal ion and for this purpose we synthesized β-amyrin acetate-23,23-d_2 starting from methyl hederagenate.[3]

First we examined the reduction of methyl 23-O-tosylhederagenate with lithium aluminum deuteride, but the product was intractable mixture.

Next we attempted the oxidation of methyl hederagenate (I) with silver carbonate reagent according to the method of Fetizon and Golfier.[4] In this reaction, only the primary alcohol group was selectively oxidized to give methyl gypsogenate (IIa)[3] in good yield.

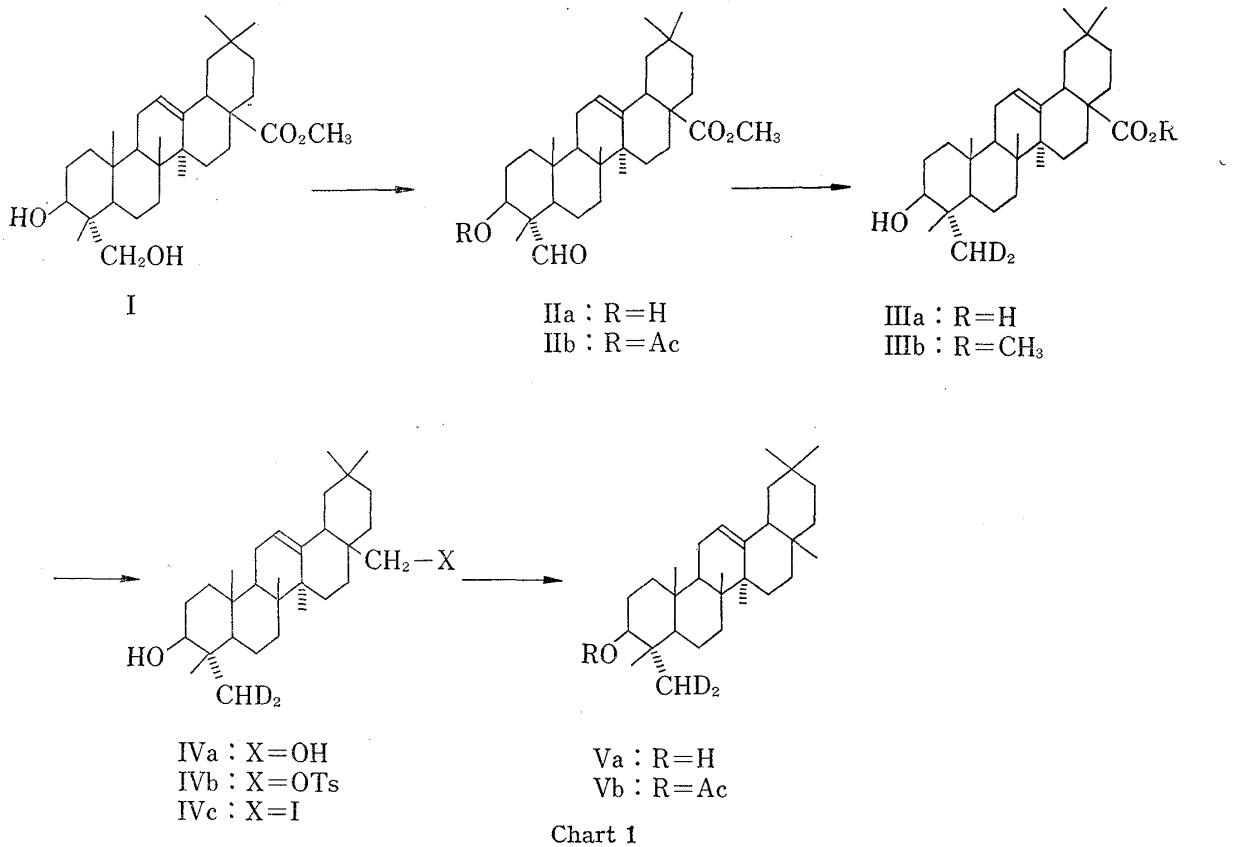

Chart 1

1) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*
2) C.C. Hinckley, M.H. Williames, and F. Patil, *J. Am. Chem. Soc.*, **93**, 2417 (1971); R. von Ammon and R.D. Fischer, *Angew. Chem.*, **84**, 737 (1972).
3) As to the stereochemistry of hederagenin and gypsogenin see A. Vogel, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **34**, 2321 (1951); C. Djerassi, J. Osiecki, and W. Closson, *J. Am. Chem. Soc.*, **81**, 4587 (1959).
4) M. Fetizon and M. Golfier, *Compt. Rend.*, **267**, 900 (1968).

Gypsogenin was already transformed into oleanolic acid by Ruzicka, *et al.*[5] and the latter compound into β-amyrin by Prelog, *et al.*[6] We prepared β-amyrin-23,23-d_2 in the analogous manner.

Methyl acetylgypsogenate (IIb) was submitted to the Wolff–Kishner reduction using hydrazine-d_4 in DMSO-d_6 and the product (IIIa) was treated with diazomethane to give 23,23-dideuterated methyl oleanolate (IIIb) in fairly good yield. Lithium aluminum hydride reduction of IIIb, followed by partial tosylation gave a monotosylate (IVb), which was subsequently treated with sodium iodide in acetone to yield an iodide (IVc). Hydrogenation of the iodide (IVc) over Raney nickel gave β-amyrin-23,23-d_2 (Va), mp 197—200°, which was acetylated in the usual manner to give β-amyrin acetate -23,23-d_2 (Vb), mp 243—244°.

Application of NMR shift reagents to Vb will be presented in the forthcoming paper.

Experimental[7]

Methyl Acetylgypsogenate (IIb)——Silver carbonate reagent precipitated on celite (2.5 g), freshly prepared according to the method of Fetizon and Golfier,[4] was suspended in a benzene solution (60 ml) of methyl hederagenate (I) (500 mg). After some of benzene was distilled azeotropically, the mixture was gently refluxed for 3 hr. The mixture was then filtered with suction and the filtrate was evaporated *in vacuo* to give an oily substance (IIa) (*ca.* 550 mg), which was dissolved in acetic anhydride (2 ml) and pyridine (2 ml) and allowed to stand at room temperature for 24 hr. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed successively with 3% HCl and dil. Na_2CO_3, dried ($MgSO_4$), and evaporated. The residue (499 mg) was subjected to preparative thin-layer chromatography (TLC) and then recrystallized from CH_2Cl_2–MeOH to give colorless prisms (IIb) (450 mg), mp 197—198°. $[\alpha]_D^{20}$ +75° (c=0.98, $CHCl_3$). Mass Spectrum m/e: 526 (M^+). *Anal.* Calcd. for $C_{33}H_{50}O_5$: C, 73.03; H, 9.29. Found: C, 74.84; H, 9.70. IR ν_{max} cm^{-1}: 2700, 1710, 1250. NMR τ: 0.68 (1H, s, -CHO), 4.70 (1H, t, J=3 Hz, olefinic H), 5.01 (1H, q, J=6, 9 Hz, C<u>H</u>-OAc), 6.39 (3H, s, $COOCH_3$), 8.05 (3H, s, Ac), 8.85—9.26 (6×CH_3).

Methyl Oleanolate-23,23-d_2 (IIIb)——The above aldehyde (IIb) (340 mg) was dissolved in a solution of ND_2ND_2 in DMSO-d_6 (10 ml) which had been prepared by distilling a mixture of anhydrous ND_2ND_2–D_2SO_4 (5 g), anhydrous Na_2CO_3 (6 g), and DMSO-d_6 (10 ml) and the solution was heated at 130—140° for 2 hr. Then NaOD (*ca.* 1 g) was added and the mixture was heated at 180—190° for 1.5 hr. Thereafter the reaction mixture was diluted with water, washed with CH_2Cl_2, and the water layer was acidified with HCl, extracted with CH_2Cl_2. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to give an oily substance (IIIa) (330 mg). This was dissolved in ether and treated with diazomethane at room temperature. Removal of the solvent and purification by preparative TLC gave a methyl ester (IIIb), which was recrystallized from ether–MeOH to afford a pure sample (230 mg), mp 201—202°. Mass Spectrum m/e: 472 (M^+) ($C_{31}H_{48}D_2O_3$). IR ν_{max} cm^{-1}: 3570, 3400, 1715, 2200. NMR τ: 4.73 (1H, br., olefinic H), 6.38 (3H, s, $COOCH_3$), 6.80 (1H, q, J=6.5, 9 Hz, C<u>H</u>-OH), 8.87—9.26 (6×CH_3).

Erythrodiol-23,23-d_2 (IVa)——The methyl ester (IIIb) (225 mg) was treated with excess $LiAlH_4$ (150 mg) in boiling ether (10 ml) for 2 hr. After the excess reagent was decomposed with water, the mixture was acidified with dil. HCl and extracted with CH_2Cl_2. The organic layer was washed with dil. Na_2CO_3, dried ($MgSO_4$), and evaporated. Recrystallizations of the residue (188 mg) from CH_2Cl_2–MeOH gave colorless needles (IVa) (170 mg), mp 235—237°. Mass Spectrum m/e: 444 (M^+) ($C_{30}H_{48}D_2O_2$). IR ν_{max} cm^{-1}: 3600, 3450, 2200. NMR τ: 4.79 (1H, br, olefinic H), 6.43, 6.82 (2H, ABq, J=11 Hz, C<u>H</u>$_2$-OH), 8.83—9.21 (6×CH_3).

Partial Tosylation of the Diol (IVa)——To a mixture of IVa (164 mg), pyridine (4 ml), and benzene (5 ml) was added a solution of *p*-toluenesulfonyl chloride (150 mg) in benzene (7 ml) and the mixture was gently refluxed for 20 hr. After cooled, the reaction mixture was diluted with water and extracted with ether. The organic layer was washed successively with 3% HCl and with dil. Na_2CO_3, dried ($MgSO_4$), and evaporated. The residue (500 mg) was separated by preparative TLC into two fractions. The polar fraction

5) L. Ruzicka and G. Giacomello, *Helv. Chim. Acta*, **19**, 1136 (1936).
6) V. Prelog, J. Norymberski, and O. Jeger, *Helv. Chim. Acta*, **29**, 360 (1946).
7) All the melting points were measured with a Kofler-type apparatus and are uncorrected. NMR spectra were taken on a Varian Associates A-60 NMR Spectrometer in deuterated chloroform solutions using tetramethylsilane as the internal reference and chemical shifts are recorded in τ values. Infrared (IR) spectra were measured for solutions in chloroform. Preparative thin-layer chromatography was performed on Merck Kieselgel GF_{254} with chloroform and plates were examined under UV light (for UV- absorption materials on GF_{254} plates) unless otherwise noted. For extraction of substances from the Kieselgel methylene chloride was used as solvent.

gave the starting material (98 mg) and the less polar fraction gave a monotosylate (IVb) (66 mg), mp 203—205°. Mass Spectrum *m/e*: 598 (M^+) ($C_{37}H_{54}D_2O_4S$). IR ν_{max} cm^{-1}: 3600, 3400, 2200, 1360, 1170. NMR τ: 2.22, 2.70 (4H, A_2B_2q, J=8 Hz, aromatic protons), 4.91 (1H, t, J=3 Hz, olefinic H), 6.10, 6.48 (2H, ABq, J=9 Hz, C<u>H</u>$_2$-OTs), 6.80 (1H, q, J=6, 9 Hz, C<u>H</u>-OH), 7.56 (3H, s, aryl-CH_3), 8.90—9.44 (6×CH_3).

***β*-Amyrin-23,23-d_2 (Va)**——A mixture of the monotosylate (IVb) (66 mg), NaI (90 mg), and abs. acetone (3 ml) was heated in a sealed tube at 160° for 37 hr. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with dil. Na_2CO_3, dried ($MgSO_4$), and evaporated. Purification of the residue by preparative TLC afforded an iodide (IVc) (47 mg). IR ν_{max} cm^{-1}: 3600, 3400, 2260. NMR τ: 4.75 (1H, t, J=3 Hz, olefinic H), 6.64, 6.99 (2H, ABq., J=10 Hz, C<u>H</u>$_2$I), 6.80 (1H, q, J=6, 9 Hz, C<u>H</u>-OH), 8.84—9.21 (6×CH_3).

The above iodide (IVc) (47 mg) was then hydrogenated over W-2 Raney nickel (1.2 g) in EtOH (5 ml) at room temperature and atmospheric pressure, until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue (35 mg) was separated by preparative TLC (Merck Kieselgel GF_{254} impregnated with silver nitrate) and then recrystallized from CH_2Cl_2–MeOH to afford colorless needles (Va) (28 mg), mp 198—200°. $[\alpha]_D^{22}$ +88° (c=0.96, $CHCl_3$). Mass Spectrum *m/e*: 428 (M^+) ($C_{30}H_{46}D_2O$). IR ν_{max} cm^{-1}: 3600, 3450, 2200. NMR τ: 4.81 (1H, t, J=3.5 Hz, olefinic H), 6.79 (1H, q, J=6, 9 Hz, C<u>H</u>-OH), 8.86—9.21 (7×CH_3).

***β*-Amyrin Acetate-23,23-d_2 (Vb)**——A solution of Va (28 mg) in pyridine (0.5 ml) and acetic anhydride (0.5 ml) was left stand overnight at room temperature. Working up of the mixture in the usual manner afforded a crystalline product (30 mg), which was recrystallized from CH_2Cl_2–MeOH to give β-amyrin acetate-23,23-d_2 (Vb) (18 mg) as colorless needles, mp 243—244°. $[\alpha]_D^{20}$ +70° (c=1.02, $CHCl_3$). Mass Spectrum *m/e*: 470 (M^+) ($C_{32}H_{48}D_2O_2$). IR ν_{max} cm^{-1}: 1720, 2200, 1250. NMR τ: 4.81 (1H, t, J=3 Hz, olefinic H), 5.49 (1H, q, J=6, 9 Hz, C<u>H</u>-OAc), 7.95 (3H, s, Ac), 8.86—9.16 (7×CH_3).

Acknowledgement The authors express their deep gratitude to Professor Y. Inubushi of this Faculty for his hearty encouragement. They are also indebted to Dr. T. Shingu and Dr. K. Kitamura for NMR measurments, Mr. A. Kato for taking mass spectra, Miss Y. Mano and collaborators for microanalyses.

[Chem. Pharm. Bull. 21(6)1380—1382(1973)]

UDC 547.466.1.057

Studies on Peptides. XXXV.[1,2] Some *p*-Methoxybenzyloxycarbonyl-Amino Acid Derivatives

HARUAKI YAJIMA, FUSAKO TAMURA, YOSHIAKI KISO and MASAYUKI KUROBE

Faculty of Pharmaceutical Sciences, Kyoto University[3]

(Received December 19, 1972)

Recently we published a new procedure for the preparation of Z(OMe)-amino acids utilizing *p*-methoxybenzyl mixed carbonates.[4] From the practical standpoint, *p*-methoxybenzyl-8-quinolyl carbonate has a superior property to the others. We now have modified the procedure for the preparation of this carbonate, with which we have been able to produce a number of Z(OMe)-amino acids, including some new derivatives in fairly good yield, except for histidine derivatives. For the preparation of the latter derivatives, the classical azide procedure[5] is preferable because of the easiness with which it renders to purification. In this report, we wish to record physical data of these new derivatives.

For the detection of Z(OMe)-derivatives, spraying with 10% $SbCl_5$ in chloroform,[6] besides $Ce(SO_4)_2$,[4] is convenient, since it gives specific red-purple color for these derivatives on thin-layer plate.

1) Part XXXIV: H. Yajima and K. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 682 (1973).
2) Amino acids and their derivatives mentioned here are of the L-configuration. Abbreviation: Z(OMe)=*p*-methoxybenzyloxycarbonyl.
3) Location: *Sakyo-ku, Kyoto.*
4) H. Yajima, F. Tamura and Y. Kiso, *Chem. Pharm. Bull.* (Tokyo), **18**, 2574 (1970).
5) F. Weygand and K. Hunger, *Chem. Ber.*, **95**, 1 (1962).
6) K.G. Krebs, D. Heusser and H. Wimmer "Thin-Layer Chromatography," ed. by E. Stahl, Springer-Verlag, Berlin, 1969, p. 858.