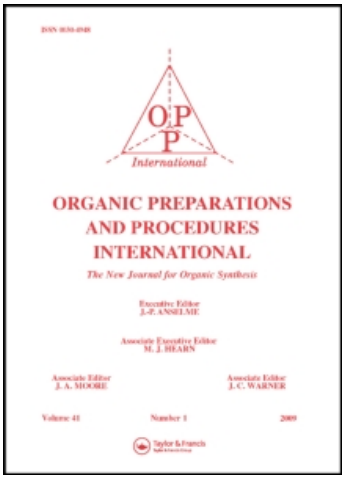

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SYNTHESIS OF CARBENOXOLONE ANALOGS FROM ARGENTATIN B

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SYNTHESIS OF CARBENOXOLONE ANALOGS FROM ARGENTATIN B†

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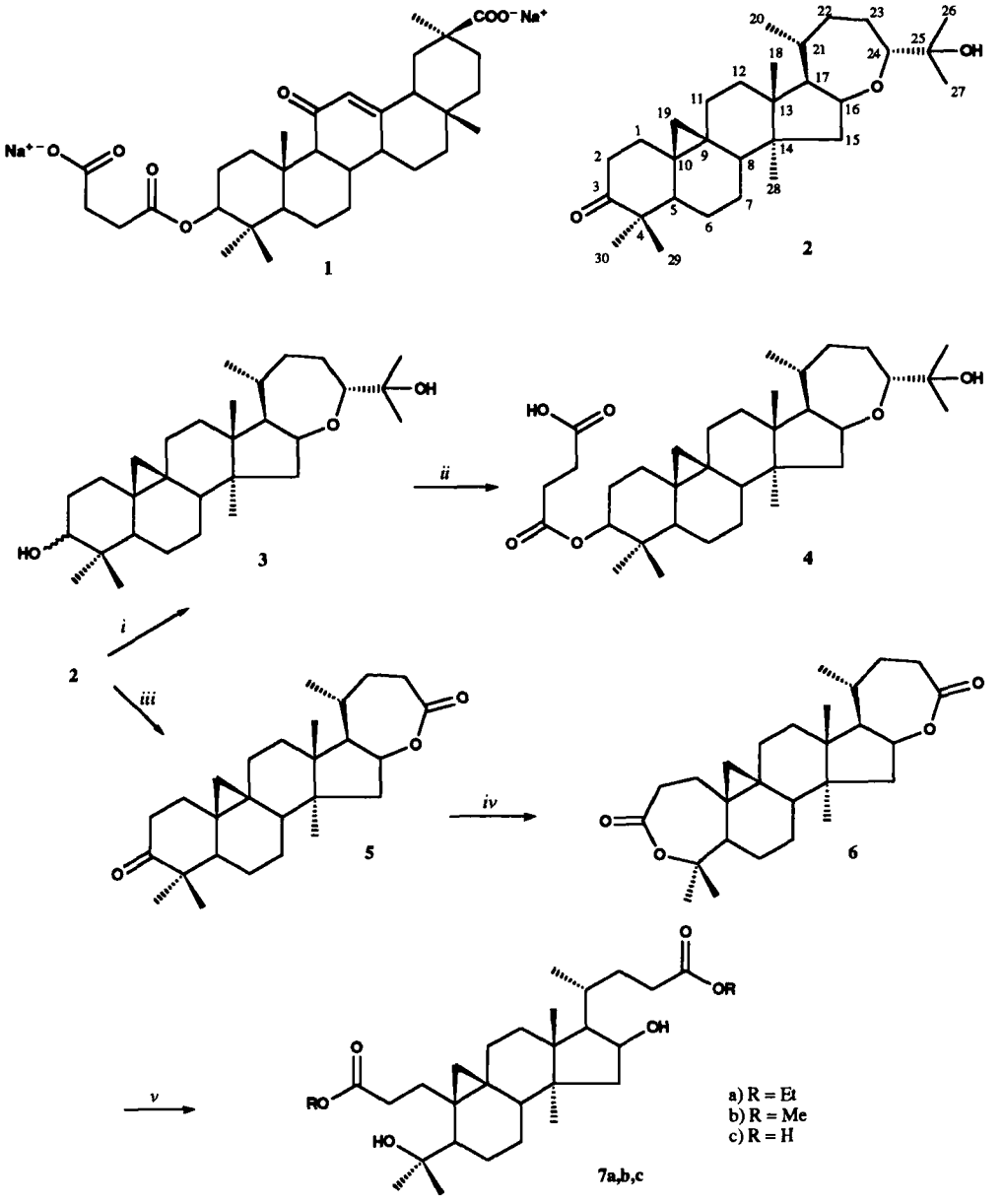
The triterpenes of the cyclolanostane type named argentatins are one of the principal components of the resin of the Mexican rubber plant, guayule (*Parthenium argentatum*), a common desert shrub in North Mexico and Southwestern USA.[1] Guayule has been intensively studied as a renewable native source of natural rubber,[2] and it is known that for each pound of natural rubber obtained, there also is produced one pound of a by-product named resin.[3] Taking into account that the annual production of guayule rubber is expected to be 500-1500 million pounds by the year 2000 [4] and that the argentatins comprise 27% of the resin,[5] then at the predicted levels of guayule rubber production,

argentatins will be available in large amounts. Therefore this process has potential as a source of chiral chemical substances that are suitable for transformation to triterpene- and steroid-like compound with biological properties.[6-8] On the other hand, the introduction of carbenoxolone [3-(3-carboxy-1-oxopropoxy)-11-oxo-olean-12-en-29-oic acid] as its disodium salt **1** as an antiulcer [9] began in 1968. Since then, research on the carbenoxolone series has been very active and has led to various



i) $NaBH_4$, THF *ii*) Succinic anhydride, DMAP *iii*) CrO_3, AcOH
iv) *m*-C/PBA, CH_2Cl_2 *v*) (a) EtOH, KOH (b) MeOH, KOH (c) H_2O, KOH

modifications of the basic structure.[10] In order to investigate structure-activity properties of carbenoxolone analogs and as a part of a program directed towards the synthesis of argentatins derivatives[11] with possible pharmacological activities, we describe here the synthesis of compounds **3-7** from Argentatin B **2** [(16β,24R)-16,24-epoxy-25-hydroxy-9,19-cyclolanostan-3-one].

Treatment of **2** with sodium tetrahydroborate in tetrahydrofurane gave the epimeric mixture[12] of **3** that was treated with succinic anhydride and dimethylaminopyridine[13] as catalyst to yield **4**. Conversion of **2** to the lactone **5** was carried out with chromic anhydride in acetic acid.[1] Lactone **5** was oxidized with *m*-chloroperoxybenzoic acid and potassium carbonate in dichloromethane to give the dilactone **6**.[14] When this compound was treated with potassium hydroxide in ethanol, it was converted to diethyl ester **7a**. Hydrolysis of **6** with potassium hydroxide in methanol or water afforded **7b** and **7c**, respectively. All structural assignments are consistent with their ^{1}H and ^{13}C-NMR and mass spectra.

EXPERIMENTAL SECTION

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Varian VXR-300S instrument operating at 300 MHz for hydrogen and 75 MHz for carbon (TMS internal standard). Mass spectra were determined on a Hewlett-Packard 5985-A quadropole instrument at 70 eV. The IR spectra were recorded on a Nicolet FT-55X spectrophotometer. Reactions were monitored by TLC on silica gel (Merck type 60H) plates and developed in ethyl acetate-hexane mixtures and visualized with a UV lamp. where appropriate and by dipping in aqueous sulfuric acid-ceric nitrate followed by heating. Flash chromatography was carried out on silica gel G (Merck).

Epimeric mixture of 16,24-epoxy-3,25-dihydroxy-9, 19-cyclolanostane (3).- To a stirred solution of **2** (3.93 g, 80 mmol) in THF (50 mL) was added a solution of $NaBH_4$ (1.75 g, 46 mmol) in THF (20 mL) and the mixture stirred at room temperature for 1 hr. Then was extracted with ethyl acetate (4 x 50 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. Removal of solvent gave the epimeric mixture **3** as a colorless oil (2.60 g, 65%).^{1}H and ^{13}CNMR agree with the date in ref. 1.

3-(3-Carboxy-1-oxopropoxy)-16, 24-epoxy-9,19-cyclolanostan-25-ol (4) .- To a stirred solution of **3** (1 g, 2.2 mmol) in dichloromethane (50 mL) was added 4-dimethylaminopyridine (0.32 g, 2.6 mmol), succinic anhydride (0.49 g, 4.9 mmol). The solution was heated to reflux for 21 hrs, then cooled and diluted with water (50 mL). The dichloromethane extract was washed with 1N aqueous HCl (3 x 50 mL), 2N aqueous NaOH (3 x 50 mL), water and dried over anhydrous $Na_2 SO_4$. Removal of solvent gave **4** as a colorless oil (0.63 g, 51%). $[\alpha]_D$ = -16.0 ($CHCl_3$); IR ($CHCl_3$): 3521 (hydroxyl), 1720 (carbonyl) cm^{-1}. ^{1}H NMR: 0.35 (d, 1H, 19-H), 0.60 (d, 1H, 19H), 0.87 (s, 3H, 28-H, 0.88 (d, 3H, 21-H), 0.95 (s, 3H, 18-H), 1.07 (s, 6H, 29-H and 30-H), 1.12 (s, 3H, 26-H), 1.26 (s, 3H, 27-H), 3.6 (d, 1H, 3-H), 4.6 (bq, 1H, 16-H), 5.3 (s,1H, CO_2H). MS (EI): m/z (%) 558 [M^+](20).

Anal. Calcd. for $C_{34}H_{54}O_6$: C, 73.08 ; H, 9.74. Found: C, 72.98 ; H, 9.71.

(16S,17R,20S)-3-Oxo-16-hydroxy-25-nor-lanostan-24-oic Acid Lactone (5).- To a stirred solution of **2** (3.4g, isolated from guayule)[1] in glacial HOAc (10 mL) was added dropwise an aqueous solution of CrO_3 (1.0 g /5mL H_2O) at 0-5°. The solution was stirred at 0-5° for an additional 15 minutes and at room temperature for 3 hrs. The mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4, filtered and evaporated to give the crude reaction product as a solid that was crystallized from dichloromethane-hexane to yield **5** (0.27 g, 30%), mp. 258-260°, lit.[1] 256-258°. $[\alpha]_D$ = -7.1; IR ($CHCl_3$): 1730 (lactone), 1701 (ketone) cm^{-1}. ^1H NMR: 0.61 (d, 1H, 19-H), 0.85 (d, 1H, 19-H), 0.95 (s, 3H, 25-H), 1.00 (d, 3H, 21-H), 1.05 (s, 3H, 26-H), 1.11 (s, 3H, 27-H), 1.18 (s, 3H, 18-H), 4.92 (q, 1H, 16-H). MS (EI): m/z (%) 412 $[M]^+$ (29), 397 (51), 55 (100).

(16S,17R,20S)-4,16-Dihydroxy-25-nor-3,4-seco-lanostan-3,24-dioic Acid Dilactone (6).- To a stirred solution of **5** (2.7 g, 67.3 mmol) in dichloromethane (50 mL) was added *m*-*Cl*PBA (1.58 g, 12 mmol) and an aqueous 10% $NaHCO_3$ solution (50 mL). After 1 hr at room temperature the organic layer was separated and was washed with an aqueous 10% $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered and evaporated to afford a slight yellow oil. Flash chromatography on Merck silica-gel and elution with hexane-ethyl acetate (1:1) gave **6** (1.43 g, 50%), mp. 210-212°. $[\alpha]_D$ = -29.0 (EtOH); IR ($CHCl_3$): 1726, 1718 (lactone) cm^{-1}; ^1H NMR: 0.65 (d, 1H, 19-H), 0.71 (d, 1H, 19-H), 0.95 (s, 3H, 25-H), 1.0 (d, 3H, 21-H), 1.15 (s, 3H, 18-H), 1.40 (s, 3H, 27-H), 1.49 (s, 3H, 26-H); 4.92 (dd, 1H, 16-H). MS (EI): m/z (%) 428 $[M]^+$ (8.2), 413 (17.2), 91(100).

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66 ; H, 9.41. Found : C, 75.60 ; H, 9.39

1a-(2-Ethoxycarbonylethyl)-2-(1-methyl-1-hydroxyethyl)-4b,7a-dimethyl-7-(1-methyl-3-ethoxycarbonylpropyl)-1,1a,2,3,4.4a,4b,5,6,7,7a,8-dodecahydro-9H-cyclopenta[a]cyclopropa[e]naphthalen-6-ol (7a).- To a stirring **6** (1.48 g, 3.46 mmol) in ethanol (30 mL) was added KOH (3.88 g, 6.80 mmol) and the solution stirred and heated to reflux for 40 min. The reaction mixture was cooled, acidified with 10% aqueous HCl to neutrality and was extracted with ethyl acetate (4 x 50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4. The reaction product was flash chromatographed on silica gel and eluted with hexane-ethyl acetate (1:1) to afford ethyl ester **7a** as an oil (0.4 g, 22%) .$[\alpha]_D$ = + 4.95 (EtOH); IR ($CHCl_3$): 3600 (-OH), 1724 (ester) cm^{-1}; ^1H NMR (DMSO-d_6): 0.56 (d, 1H, 19-H), 0.69 (d, 1H, 19-H), 0.92 (s, 3H, 27-H), 0.95 (d, 3H, 21-H), 1.14 (s, 3H, 18-H), 1.20 (s, 3H, 25H), 1.22 (s, 3H, 26-H), 4.10 (q, 4H, 2 x -OCH_2CH_3), 4.25 (bs, 2H, 16-H + OH).MS (EI) m/z (%) 456 [M-H_2O-CO] (10.5), 59 (100).

Anal. Calc. for $C_{31}H_{52}O_6$: C, 71.50; H, 10.06. Found : C, 71.47 ; H, 9.98

1a-(2-Methoxycarbonylethyl)-2-(1-methyl-1-hydroxyethyl)-4b,7a-dimethyl-7-(1-methyl-3-methoxycarbonylpropyl)-1,1a,2,3,4,4a,4b,,5,6,7,7a-dodecahydro-9H-cyclopenta[a]cyclopropa[e]-naphthalen-6-ol (7b).- Compound **6** (0.571 g, 1.33 mmoles) was treated in methanol (15 mL) with KOH (0.150 g, 2.66 mmoles) as described above for **7a** to afford a slight yellow oil. Flash chromatography on Merck silica-gel and elution with hexane-ethyl acetate (1:1) gave **7b** (0.197 g, 30%), mp. 118-120°. IR ($CHCl_3$): 3600 (alcohol), 1725 (ester) cm^{-1}; ^1H NMR: 0.56 (d, 1H, 19-H), 0.70 (d,

1H, 19-H), 0.93 (s, 3H, 27-H), 0.97 (s, 3H, 21-H), 1.14 (s, 3H,18-H),1.20 (s, 3H, 25-H), 1.22 (s, 3H, 26-H), 3.65 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 4.5 (bs, 1H, 16-H). MS (El): m/z (%) 474 $[M-18]^+$ (10.0), 59 (100).

Anal. Calcd. for $C_{29}H_{48}O_6$: C, 70.70; H, 9.82. Found : C, 70.66; H, 9.79

1a-(2-Carboxyethyl)-2-(1-methyl-1-hydroxyethyl)-4b,7a-dimethy-l7-(1-methyl-3-carboxyl)1,1a,2,3,4,4a,4b,5,6,7a,8-dodecahydro-9H-cyclopenta[a]cyclopropa[e]naphthalen-6-ol (7c).- Dilactone **6** (1.34 g, 3.14 mmol) was treated in water (50 mL) with KOH (0.36 g, 0.80 mmol) as described above for **7a** to afford **7c** (1.10 g, 76%), mp. 159-160°. IR (nujol): 3571-2677 (hydroxyl), 1767 (carbonyl) cm^{-1}; ^1H NMR (CD_3OD): 0.54 (d, 1H, 19-H), 0.73 (d, 1H, 19-H), 0.95 (s, 3H, 21-H), 0.96 (s, 3H, 27-H), 1.16 (s, 3H, 18-H), 1.20 (s, 6H, 26-H, 25-H), 4.45 (bs, 1H, 16-H). MS (EI): m/z (%) 431 $[M-33]^+$ (8.3).

Anal. Calcd. for $C_{27}H_{44}O_6$: C, 69.79 ; H, 9.54. Found : C, 69.76 ; H, 9.52

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SIMPLE AND CONVENIENT PROCEDURE FOR THE PREPARATION OF 1-METHYL-4-NITROBENZIMIDAZOLE

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(05/24/93)

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The application of the Gould-Jacobs reaction[1] for the preparation of 4-, 5-, 6-, and 7-substituted-1-methylbenzimidazoles[2,3] has been hampered by the unavailability of the starting 1-methyl-4-nitrobenzimidazole. The title compound 1-methyl-4-nitrobenzimidazole (**1**) has been obtained by alkaline methylation of 4(7)-nitrobenzimidazole,[4,5] a method which produces also the corresponding 7-nitro-substituted isomer. Another approach to **1** starts from 1-methyl-5-nitrobenzimidazole, which is first reduced to the amino derivative, then protected by tosylation to allow subsequent nitration at the desired 4-position. The final product is obtained after deprotection and deamination.[6] Another low-yield method employs 2,3-dinitroaniline as a starting material.[5] We now describe a simple and convenient synthesis of the latter.

In analogy to the reaction of 4-nitro-1,2-phenylenediamine with formaldehyde in methanolic hydrogen chloride to give 1-methyl-6-nitrobenzimidazole,[7] a reaction starting from 3-nitro-1,2-phenylenediamine would be expected to give the desired 1-methyl-4-nitrobenzimidazole. Thus, a