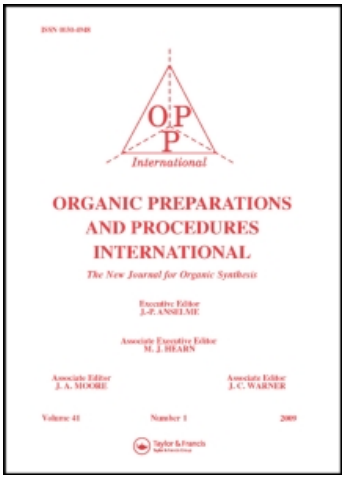

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OXIDATION OF 3β-ACETOXY-5α-LANOST-8-ENE WITH CHROMYL CHLORIDE. THE PREPARATION OF 5α,8β-LANOST-9(11)-EN-7-ONE DERIVATIVES

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OXIDATION OF 3β-ACETOXY-5α-LANOST-8-ENE WITH CHROMYL CHLORIDE. THE PREPARATION OF 5α,8β-LANOST-9(11)-EN-7-ONE DERIVATIVES

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(04/13/94)

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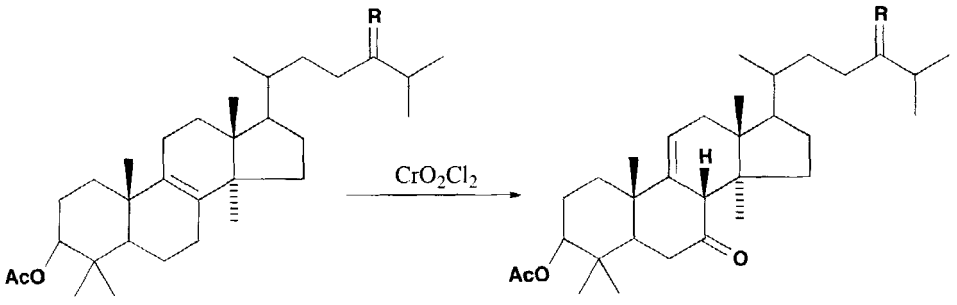
8β-Lanostane derivatives, which possess a $\Delta^{9(11)}$-double bond and a carbonyl group in position 7, are the only substrates for the preparation of 9β,11β-epoxylanostane derivatives.[1] The real importance of 9β,11β-epoxides is their effective rearrangement to 19(10→9β)*abeo* tetracyclic triterpenes (cucurbitacins).[2] Several methods of preparation of lanost-9(11)-en-7-one from either the respective Δ^8-olefin or $\Delta^{7,9(11)}$-diene have been described.[3-6] Over the years, we have carried out numerous oxidations of dihydrolanosteryl or dihydroagnosteryl acetates and their side chain modified derivatives. These oxidations were found to be irreproducible[7] and resulted, for example, in low yield of the expected unconjugated enone **2a** from **1a**. Usually, the crude reaction product of the oxidation of 3β-acetoxy-5α-lanost-8-ene or 3β-acetoxy-5α-lanosta-7,9(11)-diene with chromium trioxide was a mixture of 8-en-7,11-dione, 9(11)-en-7-one and a large proportion of overoxidized products. The isolation of **2a** required tedious chromatographic separation irrespective of the substrate used in the oxidation. In the best procedure,[7] two additional synthetic steps, the preparation of the respective $\Delta^{7,9(11)}$-diene *via* the 8,9-epoxide, were also necessary. We explored other reagents and reaction conditions in order to find a better oxidation system for direct transformation of Δ^8-olefin to $\Delta^{9(11)}$-7-oxo compounds.

Thus, chromyl chloride appears to be the reagent of choice for the oxidation of 3β-acetoxy-5α-lanost-8-ene (**1a**) to 3β-acetoxy-5α,8β-lanost-9(11)-en-7-one (**2a**). When the reaction was carried out in methylene chloride at low temperature (-23°) a pure product **2a** was isolated upon chromatography and crystallization in 62% yield. The best yield was obtained when the oxidant was added in one portion and the reaction was carried out for 1 hour. The yield of the enone **2a** was similar on 1 g and 5 g scale. The ^{1}H NMR spectrum of **2a** showed all the features characteristic of the unconjugated enone system and also indicated no admixture of the 8α- or Δ^8 isomers, while the position of the characteristic 8β-proton signal at δ 2.87 confirmed the configuration of C-8.[5]



1a R = H_2
1b R = O

2a R = H_2
2b R = O

Oxidation of the lanostane derivative modified in the side chain, 3β-acetoxy-5α-lanost-8-en-24-one[8] (**1b**), in the same reaction conditions, afforded the enedione **2b** in 41% yield.

EXPERIMENTAL SECTION

Oxidation products were analyzed by ^{1}H NMR [Varian Gemini 300 VT (300 MHz) and Tesla BS-587A (80 MHz)], IR (Perkin-Elmer 580) and TLC (Merck No 5554).

Preparation of 3β-Acetoxy-5α,8β-lanost-9(11)-en-7-one (2a).- To the stirred solution of compound (**1a**) (1.00 g, 2.14 mmol) in CH_2Cl_2 (20 mL) under argon at -23° chromyl chloride (0.3 mL) was added in 5 min. and stirring was continued for 1 hr. Then ether (100 mL) was added and the organic layer was washed successively with sodium sulfite (10%, 50 mL), sodium hydroxide (5%, 25 mL) water, brine and water. It was dried over magnesium sulfate and evaporated to dryness to give 1.03 g of the crude product which was chromatographed on silica gel (Merck No 9385) with methylene chloride as eluent to give pure compound **2a** (650 mg, 62%). Crystallization from methanol gave **2a** mp. 150-152°, lit. 5 mp. 149-150°. Its ^{1}H NMR spectrum was identical with that of an authentic sample.

3β-Acetoxy-5α,8β-lanost-9(11)-ene-7,24-dione.- Oxidation of **1b** (200 mg, 0.428 mmol) carried out as above gave **2b** (85 mg, 41%), mp. 166-167°; $[\alpha]_D$ = +46.2 (c= 0.01); IR: 1725, 1710, 1705 and 1670 cm^{-1}; ^{1}H NMR: δ 5.40 (1 H, m, 11-H), 4.51 (1 H, m, 3α-H), 2.89 (1 H, d, J 2.8 Hz, 8β-H), 2.61 (1 H, septet, J 7 Hz, 25-H), 2.07 (3 H, s, CH_3COO), 1.12 (3 H, s, 19-CH_3), 1.09 (6 H, d, J 6 Hz, 26 and 27-CH_3), 0.93, 0.91, 0.83, 0.76, 0.67 (methyl groups); ^{13}C NMR: δ 212.9 (C-8), 209.7 (C-24), 170 (CH_3COO), 144.7 (C-9), 118.1 (C-11), 80.5 (C-3), 57.2 (C-8); MS: m/z 498 (M^+), 483, 465, 455, 438, 371, 330, 278.

Anal. Calcd for $C_{32}H_{50}O_4$: C, 77.05; H, 12.84. Found: C, 76.95; H, 12.59

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A SIMPLE PROCEDURE FOR THE PREPARATION OF 2-PHOSPHORYLATED FURANOSES

Submitted by (*03/22/94*)

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Furanoic carbohydrates which bear a phosphate group in the 2-position play particularly important roles in certain metabolic key processes. For example, 2-phosphorylated ribonucleosides belong to the most potent inhibitors of ribonuclease T_1[1] and dihydrofolate reductase.[2] Usually the synthesis of sugar phosphates employs neutral phosphotriesters as intermediates, which allow purification and further transformations in organic solvents as well as specific deprotection to the free phosphate.[3] Diphenyl phosphorochloridate and other diorganophosphoryl chlorides have been the subject of manifold applications in the introduction of the phosphoryl group. Unfortunately, the reaction of sterically hindered hydroxy functions as in the 2-position of furanoses with phosphorochloridates, is known to be difficult and low-yielding.[4,5] Therefore a general and efficient approach to 2-phosphorylated and phosphinylated riboses and arabinoses was sought.

Herein we report that the transformation of a partially protected furanose with a phosphorochloridate and 1-methylimidazole (NMI) leads to the corresponding sugar-2-phosphate in high yields. Compared to 5-chloro-1-methylimidazole,[5] which is also known as an active phosphorylating