Oxidative Cleavage of 5(Z)-Carbacyclins

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Selective Lemieux-Johnson oxidation of the 5,6-double bond in preference to the 13,14-double bond of 5(Z)-carbacyclin analogs afford the 5-ketone in 60% yield.

Among the many synthetic prostacyclin-analogs, the carbacyclins, in which the cyclic enol ether oxygen has been replaced by a methylene group, are of particular interest. Although carbacyclin 3a (R² = H) has only moderate biological activity, variation of the lower side chain led to iloprost (2Z, 3b, R² = H) with practically the same biological profile and activity as natural PGI₂.

A key step in the synthesis of iloprost (3b; R² = H) and most of the other carbacyclins is the Wittig reaction of the substituted bicyclo[3.3.0]octane derivatives 1 with 4-carboxybutyridinethiophosphorane (2), which invariably leads to mixtures of the desired biologically highly active (E)-isomers 3 and the much less active (Z)-isomers 4. Therefore a multistep reaction has been developed to convert 4 via the 5,6-epoxides into the desired (E)-isomers 3. Furthermore a different synthetic scheme has recently been described, in which a 4,6-diene is selectively reduced to the desired (E)-isomer 3.

![Chemical structure](image)

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In this communication, we describe the Lemieux-Johnson-oxidation of the undesired (Z)-isomer 4b derived from our synthesis of iloprost 3b to the 5-ring ketone 1b in 60% yield, which can thus be reused. As a side product, we isolate in ~7% yield a mixture of the 13,14-dihydroxy ketones 5. Variations of reaction temperature and time did not lead to any improvement of the yield of 1.

![Chemical structures](image)

Obviously, the electrophilic osmium tetroxide attacks primarily the more nucleophile trisubstituted 5,6-double bond in 4b and only partially the less nucleophile and more hindered 13,14-trans-olefin. Since acetylenic bonds are not oxidized, it can be anticipated that this application of the Lemieux-Johnson-oxidation will be even more effective with carbacyclin analogs having only triple bonds in the lower side chain.

Oxidation of 5[(Z)-(15,5,5,6,S,7-R)-7-tetrahydropropynolaxy-6{(E)-15,5,5,6,S,7}(3,4,4)-3-(2-tetrahydropropylxy)-4-methyl-1-octene-6-ynyl]-bicyclo[3,3.0]octane-3,3-ylidene]-pentanone acid 4b:

To a stirred solution of 4b (0.52 g, 1 mmol) in dioxane (25 ml) and water (16 ml), is added in succession sodium dihydrogen phosphate dihydrate (0.27 g, 2 mmol), disodium monohydrogen phosphate monohydrate (0.35 g, 2 mmol) and analytically pure sodium peroxide (0.42 g, 2 mmol). Osmium tetroxide (8.7 mg, 0.034 mmol) is then added whereupon the mixture turns brown after several minutes. After stirring for 10-15 h at 24°C, the T.L.C. control (eluent, toluene/ethyl acetate, 2:1) shows the presence of only 1b (Rₚ = 0.36) and none of 4b (Rₚ = 0.29). After filtration of the inorganic salts, the filtrate is diluted with dichloromethane (50 ml). The organic phase is washed with saturated sodium thiosulfate solution (25 ml) and the aqueous phase is reextracted with dichloromethane (25 ml). The combined organic phase is washed with brine (25 ml), dried with sodium sulfate, and evaporated. The residue (0.6 g) is passed through a column of neutral alumina (activity III) using dichloromethane as eluent. The first 300 ml of the eluate affords on evaporation 1b as an oil whose I.R. spectrum is identical with that of an authentic sample; yield: 0.28 g (56-64%).

Further elution with methanol affords the crude 13,14-dihydroxy compound 5, which is purified by chromatography on silica gel (10 g) using toluene/ethyl acetate (1:1) as eluent; yield: 33 mg (7%).

C₁₂H₁₄O₇ (478.6)
I. R. (Film): \( v = 3460 \text{ (OH)}, 1740 \text{ cm}^{-1} \text{ (C==O)} \).

1H-N.M.R. (CDCl\(_3\)/TMS): \( \delta = 0.8 - 1.1 \text{ (m, 3 H, CH\(_3\))}; 1.8 \text{ (s, 3 H, C==C—CH\(_3\))}; 3.3 - 4.3 \text{ (m, 2 H, CH—OThp)} \text{ ppm}; \) no olefinic hydrogens.

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