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Prostanoids: LXXVII.* Synthetic Approaches to Sterically Overcrowded Cyclopentenones**

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Abstract—Condensation of (±)-5-allyl-2,3,5-trichloro-4,4-dimethoxy-2-cyclopentenone with phenylethynylmagnesium bromide in THF gave (±)-5α-allyl-2,3,5β-trichloro-4,4-dimethoxy-1α-phenylethynyl-2-cyclopenten-1β-ol which chemoselectively reacted with ozone at the terminal double bond, affording (±)-2,3,5β-trichloro-5α-formylmethyl-4,4-dimethoxy-1α-phenylethynyl-2-cyclopenten-1β-ol. Oxidation of the latter with H_2CrO_4 yielded a mixture of the expected product, (±)-5α-carboxymethyl-2,3,5β-trichloro-4,4-dimethoxy-1α-phenylethynyl-2-cyclopenten-1β-ol, and anomalous profound oxidation product, (±)-2,3,5β-trichloro-5α-carboxymethyl-4,4-dimethoxy-1α-(2-oxo-2-phenylacetyl)-2-cyclopenten-1β-ol. Attempts to remove protective methoxy groups in these compounds under standard conditions were unsuccessful.

We previously showed [2, 3] that methylmagnesium iodide and sodium tetrahydridoborate chemoselectively react with trichlorocyclopentenone **I** to form 1,2-addition products at the carbonyl group, the corresponding *cis*-chlorohydrins. In the present work we examined a similar condensation of compound **I** with phenylethynylmagnesium bromide and some transformations of the resulting adduct in view of obtaining analogs of marine prostanoids **II** [4, 5]. Ketone **I** smoothly reacted with phenylethynylmagnesium bromide in THF, affording 70% of alcohol **III** with high stereoselectivity. The attack by the organomagnesium reagent is controlled by the presence of a bulky chlorine atom in position *5*, and it occurs from the opposite side. As a result, *cis*-chlorohydrin **III** is formed exclusively; the corresponding *trans* isomer was not detected. We failed to effect acid hydrolysis of the dimethyl acetal moiety in **III**, which remained unchanged even under severe conditions. The stereochemistry of phenylethynylmagnesium bromide addition to the carbonyl group of **I** is consistent with our previous data [2–4]. The structure of compound **III** is unambiguously confirmed by the lack of spontaneous intramolecular cyclization of the products obtained by oxidative cleavage of the terminal double bond in **III**.

We succeeded in effecting selective cleavage of the side-chain allyl double bond in **III** by oxidation with ozone. Aldehyde **IV** thus obtained was treated with the Jones reagent to isolate 73% of a mixture of products **V** and **VI** in comparable amounts (Scheme 1). Presumably, diketone **VI** was formed due to intramolecular assistance by the tertiary hydroxy group to oxidation of the acetylenic bond.

Despite the presence in structures **V** and **VI** of two functional groups, OH and COOH, which should activate acid hydrolysis, we failed to remove the dimethyl acetal protection. Although the possibility for selective generation of enone system in compounds **V** and **VI** remains questionable, diketo acid **VI** and cross-conjugated enyne **V** can be regarded as pharmacologically promising bioisosters of target compounds **II**.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples prepared as thin films or Nujol mulls. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument operating at 300 MHz for ^1H and 75.47 MHz for ^{13}C; $CDCl_3$ was used as solvent, and TMS, as internal reference.

* For preceding communication, see [1].

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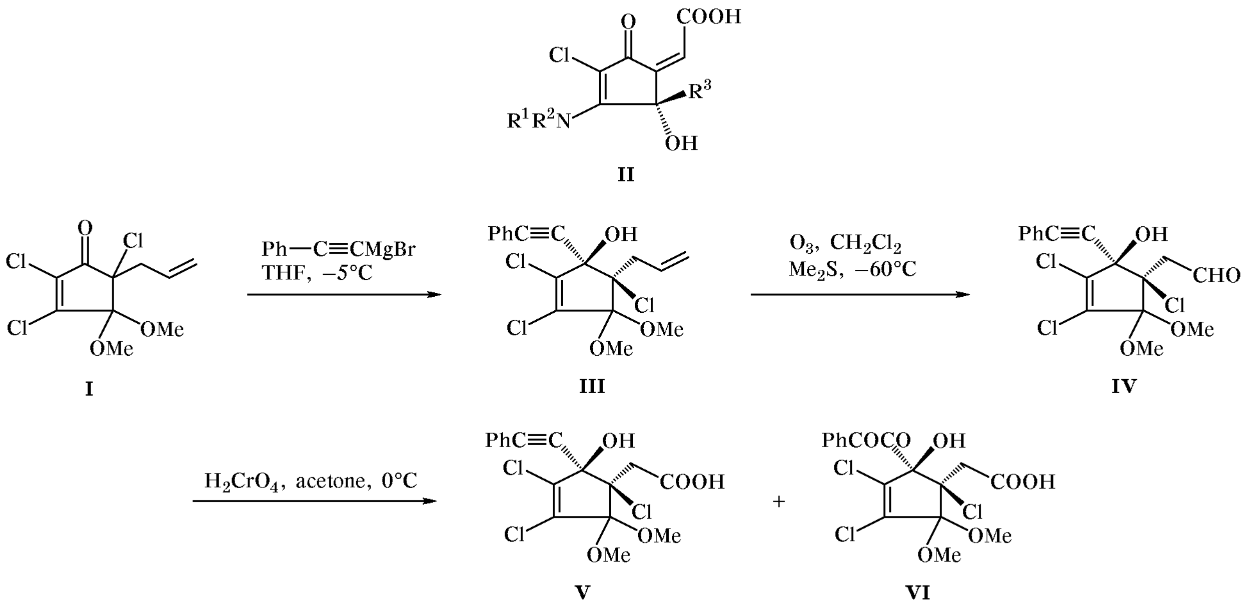
Scheme 1.



The mass spectra (electron impact, 70 eV) were recorded on an MKh-1320 mass spectrometer with direct admission of samples into the ion source heated to 100–120°C.

(±)-5α-Allyl-2,3,5β-trichloro-4,4-dimethoxy-1α-phenylethynyl-2-cyclopenten-1β-ol (III). A solution of 0.3 ml of ethyl bromide in 3 ml of anhydrous THF was added dropwise with stirring to a mixture of 0.09 g of magnesium and 3 ml of anhydrous THF, and the mixture was stirred on heating until the metal dissolved completely. It was then cooled to –5°C, and 0.4 ml of phenylacetylene was added dropwise. The mixture was stirred for 1 h at –5°C, a solution of 0.28 g of ketone **I** in 3 ml of THF was added, and the mixture was stirred for 1 h at –5–0°C, treated with a saturated solution of ammonium chloride, and extracted with methylene chloride (3×30 ml). The combined extracts were dried over $MgSO_4$, the solvent was removed, and the residue was purified by column chromatography on silica gel to isolate 0.22 g (70%) of product **III** as an oily substance. IR spectrum, ν, cm^{-1}: 3540, 2260, 1650, 1615, 945, 780, 715. ^1H NMR spectrum, δ, ppm: 2.90 d.d (1H, CH_2, J = 8.0, 14.8 Hz) and 3.30 m (2H, CH_2, OH), 3.50 s (3H, OCH_3) and 3.56 s (3H, OCH_3), 5.16 m (2H, $=CH_2$), 5.91 m (1H, =CH), 7.37–7.50 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 41.49 (CH_2), 50.76 (OCH_3), 51.79 (OCH_3), 78.86 (C^5), 82.96 (C^1), 84.35 and 88.36 (C≡C), 103.47 (C^4), 118.49 ($=CH_2$), 132.07 (=CH), 121.26, 128.04, 128.81, 131.52, 131.52, 131.75 (Ph), 131.93 (C^2), 137.61 (C^3). Mass spectrum, m/z: 390, 388, 386 [M^+], 359, 357, 355 $[M-OCH_3]^+$, 353, 351 $[M-Cl]^+$, 321, 319 $[M-Cl-CH_3OH]^+$, 288, 286, 284 [M–PhC≡CH], 257, 255, 253 $[M-PhC{\equiv}CH-OCH_3]^+$ (I_{rel} 100%), 102 [PhC≡CH].

(±)-2,3,5β-Trichloro-5α-formylmethyl-4,4-dimethoxy-1α-phenylethynyl-2-cyclopenten-1β-ol (IV). An ozone–oxygen mixture was passed through a solution of 0.68 g of compound **III** in 15 ml of methylene chloride, stirred at –60°C, until it turned blue. Excess ozone was removed from the mixture by purging with argon, 5 ml of dimethyl sulfide was added, and the mixture was stirred for 30 min at –60°C and for 4 h at room temperature. It was then treated with an equal volume of a saturated solution of sodium chloride, and the organic phase was separated, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel to isolate 0.42 g (61%) of aldehyde **IV** as an oily substance. ^1H NMR spectrum, δ, ppm: 3.40–3.48 m (2H, CH_2), 3.52 s (3H, OCH_3), 3.55 s (3H, OCH_3), 7.35–7.65 m and 8.11 m (5H, C_6H_5), 9.6 t (1H, CHO, J = 2.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 47.93 (CH_2), 53.27 and 51.97 (OCH_3), 70.93 (C^5), 77.30 (C^1), 93.77 and 98.04 (C≡C), 101.30 (C^4), 127.71, 128.37, 128.51, 129.24, 130.54, 131.78 (C_6H_5), 133.76 (C^2), 134.52 (C^3), 195.73 (CHO).

(±)-5α-Carboxymethyl-2,3,5β-trichloro-4,4-dimethoxy-1α-phenylethynyl-2-cyclopenten-1β-ol (V) and 5α-carboxymethyl-2,3,5β-trichloro-4,4-dimethoxy-1α-(2-oxo-2-phenylacetyl)-2-cyclopenten-

1β-ol (VI). Jones' reagent, 7 ml, was added dropwise to a solution of 0.37 g of aldehyde **IV** in 20 ml of acetone, vigorously stirred at 0°C. The mixture was stirred for 1 h at 0°C and for 2–3 h at room temperature, cooled again to 0°C, and treated with isopropyl alcohol to decompose excess Jones' reagent. The mixture was filtered through a thin layer of silica gel, the filtrate was evaporated, and the residue was extracted with ethyl acetate (3 × 20 ml). The combined extracts were washed with a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel to obtain 0.16 g (42%) of oily acid **V** and 0.13 g (31%) of crystalline diketo acid **VI**.

Compound V. IR spectrum, ν, cm^{-1}: 3600, 3424, 2344, 2232, 1736, 1600, 1448, 952, 760, 712. ^1H NMR spectrum, δ, ppm: 3.40–3.63 m (2H, CH_2), 3.51 s (3H, OCH_3), 3.53 s (3H, OCH_3), 7.37–7.54 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 41.92 (CH_2), 51.71 and 52.23 (OCH_3), 76.52 (C^1), 79.50 (C^5), 88.60 and 93.07 (C≡C), 103.15 (C^4), 120.80, 127.79, 128.37, 128.46, 129.81, 132.24 (C_6H_5), 130.74 (C^2), 135.11 (C^3), 170.37 (CO_2H).

Compound VI. mp 81–83°C. IR spectrum, ν, cm^{-1}: 3600–2952, 1752, 1732, 1712, 1608, 1460, 936, 808, 708. ^1H NMR spectrum, δ, ppm: 3.09 d (1H, J = 16.25 Hz) and 3.38 d (1H, CH_2, J = 16.23 Hz), 3.47 s (3H, OCH_3), 3.49 s (3H, OCH_3); 7.45 t (2H, J = 7.7 Hz), 7.55 t (1H, J = 7.52 Hz) and 8.03 d (2H, C_6H_5, J = 7.18 Hz), 11.05 br.s (1H, CO_2H). ^{13}C NMR spectrum, δ_C, ppm: 41.66 (CH_2), 51.57 and 53.33 (OCH_3), 70.45 (C^5), 77.31 (C^1), 102.34 (C^4); 128.58, 129.24, 130.28, 133.97 (C_6H_5); 133.97 (C^2), 156.51 (C^3), 172.36 (CO_2H), 174.47 and 187.47 (CO). Found, %: C 46.40; H 3.40; Cl 24.50. $C_{11}H_{14}ClNO_5$. Calculated, %: C 46.62; H 3.42; Cl 24.34.

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