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SHORT COMMUNICATIONS

Racemic Sulprostone

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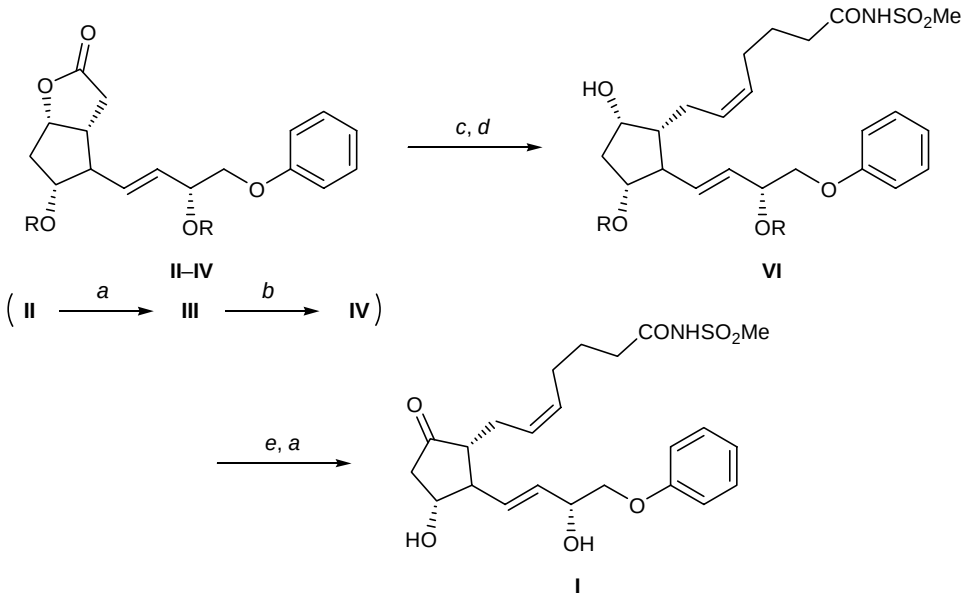
Sulprostone (**I**) is a metabolically more stable analog of prostaglandin E_2, which is widely used in biomedical research [1, 2] and is known in gynecologic practice as an efficient agent (in combination with RU-486 or without it) for abortion [3–5]. The chemical synthesis of sulprostone and structurally related compounds, *N*-methylsulfonyl-16-phenoxyprostaglandincarboxamides, was described in [6]. Corey *et al*. [7] obtained sulprostone from optically active aldehyde; it was isolated as a colorless powder with mp 78.5–79.5°C (from ethyl acetate–diethyl ether); however, no α_D value was given. According to patent [8], the melting point of sulprostone is 76°C, but its optical rotation is also missing. Commercial sulprostone produced by Cayman has mp 84–86°C (purity ≥98%); insofar as its α_D value is absent, it is not clear whether this product is racemic or optically active. To elucidate this problem and compare biological properties of the products we have synthesized racemic sulprostone according to a modified procedure [9].

Using standard methods, stereoisomerically pure bis-trimethylsilyl ether **II** [9] was converted (through dihydroxy lactone **III**) into bis-ethoxyethyl ether **IV** which was reduced with *i*-Bu_2AlH to the corresponding hydroxy lactone, and the latter was subjected to Wittig olefination with ylide generated from triphenylphosphonium salt **V**. The final steps in the synthesis of **I** were oxidation of the hydroxy group in **VI** with Collins' reagent and removal of protecting groups by acid hydrolysis.

Sulprostone (**I**) thus obtained was purified first by column chromatography on silica gel and was then



II, R = Me_3Si; **III**, R = H; **IV**, **VI**, R = $CH_3CH_2OCH(CH_3)$; *a*: 3% HCl–THF, yield 95%; *b*: ethyl vinyl ether, CH_2Cl_2, PPTS, yield 93%; *c*: *i*-Bu_2AlH, CH_2Cl_2, –78°C, yield 95%; *d*: $[Ph_3P^+(CH_2)_4CONHSO_2CH_3]Br^-$ (**V**), *t*-BuOK, THF, 0°C, 1 h, yield 80%; *e*: $CrO_3 \cdot 2Py$, yield 85%.

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subjected to HPLC; finally, the product was recrystallized from a mixture of ethyl acetate with diethyl ether. The crystalline product had mp 123–125°C, and its ^{1}H and ^{13}C NMR spectra, as well as analytical data, unambiguously indicated its chemical homogeneity and correspondence to structure **I**. Presumably, samples of sulprostone described in the literature and commercially available product differ in optical (and probably chemical) purity; therefore, they are characterized by lower melting points than racemic sulprostone. The fact that the racemic product has a higher melting point than the corresponding enantiomers indicates that the former crystallizes as a molecular (±)-complex. If enantiomers are incapable of forming a molecular adduct, the corresponding racemic compound crystallizes as a simple mechanical mixture (conglomerate) of equal amounts of crystals of each enantiomer. It melts at a lower temperature than individual enantiomers or their mixtures with any composition.

(+)-16-Phenoxy-17,18,19,20-tetranorprostaglandin E_2 methanesulfonamide (I). mp 123–125°C. ^{1}H NMR spectrum, δ, ppm: 1.45 m (2H), 1.75–2.35 m (9H), 2.60 d.d (1H, J = 7, 18 Hz), 3.13 s (3H, CH_3), 3.40 br.s (2H, 2OH), 3.82 d (2H, 16-H, J = 5.1 Hz), 4.00 m (1H, 15-H), 4.30 m (1H, H), 5.10 m (1H, NH), 5.25 m (2H, 4H, 5H), 5.60 d.d (1H, 13-H, J = 7.8, 15.4 Hz), 5.72 d.d (1H, 14-H, J = 7.8, 15.4 Hz), 6.90 m (3H), 7.25 m (2H). ^{13}C NMR spectrum, δ_C, ppm: 23.74 (C^3); 24.35 (C^6); 25.88 (C^4); 34.72 (C^2); 40.86 (CH_3); 46.69 (C^{10}); 52.37 (C^8); 53.39 (C^{12}); 69.29 (C^{16}); 70.80 (C^{15}); 71.77 (C^{11}); 114.38, 120.44, 129.41, 158.46 (C_{arom}); 126.92, 131.70 (C^5, C^6); 130.12, 132.26 (C^{13}, C^{14}); 172.39 (C^1); 215.01 (C^9). Found, %: C 59.17; H 6.59; N 3.12; S 6.70. $C_{23}H_{31}NO_7S$. Calculated, %: C 59.34; H 6.71; N 3.01; S 6.89.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal reference. Silica gel L (100–160 μm, Lachema) was used for column chromatography, and TLC was performed on Silufol plates.

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