LARGE-SCALE SYNTHESIS OF RACEMIC "COREY LACTONE"

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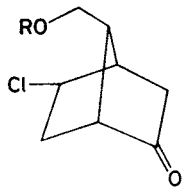
Very convenient synthesis of Corey lactone — (3aα,4α,5β,6aα)-5-(1,1'-biphenyl-4-carbonyloxy)-hexahydro-4-hydroxymethyl-2*H*-cyclopenta[*b*]furan-2-one (*VI*) was developed. The title compound was obtained in five steps starting from 7-anti-hydroxymethyl-5-*exo*-chloro-bicyclo[2.2.1]-heptan-2-one (*I*) in a very good overall yield.

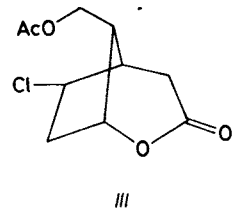
A great deal of effort has been directed towards the development of numerous synthetic routes for syntheses of prostaglandins and their analogues[1]. The new procedures appear continuously in literature[2,3]. Derivatives of 2-norbornanone are frequently used as the starting material[4-6].

We report here a very easy and simple synthetic procedure for the preparation of the "Corey lactone", a well-known prostanoid synthetic intermediate[1,7], starting from an easily accessible[7-12] hydroxyketone *I*.

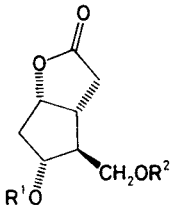
Thus, acetylation of *I* using the standard pyridine-acetanhydride procedure possessed the acetate *II* in a nearly quantitative yield. Lactone *III* was obtained using commercial 40% peroxyacetic acid in acetic acid or 1,2-dichloroethane as solvents. The product in question was obtained in a very good yield and excellent isomeric purity (isomeric product could not be even detected by means of GLC, HPLC, as well as by ^{1}H NMR spectroscopy). The lactone *III* was subsequently treated with one equivalent of lithium hydroxide in tetrahydrofurane–hydrogen peroxide mixture and the reaction yielded in the pure γ-lactone *IV*, which was in turn acylated with 4-phenylbenzoyl chloride in the presence of one equivalent of triethylamine and the resulting crude product 4-phenylbenzoate *V* was obtained in a nearly quantitative yield. The difference in the reactivity of both the ester groups in *V* allowed us to elaborate conditions for the selective methanolysis of the acetate, so that Corey lactone *VI* was obtained in excellent purity using the treatment with sulfuric acid in methanol. The overall yield of this simple procedure exceeds 50% even in multimolar scale.

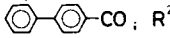
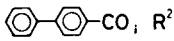


I, R = H
II, R = Ac



III



IV, R^1 = H; R^2 = Ac
V, R^1 =  ; R^2 = Ac
VI, R^1 =  ; R^2 = H

EXPERIMENTAL

Boiling and melting points are uncorrected. ^{1}H NMR spectra were measured in CW mode on Varian XL-100 spectrometer at 100 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale), the assignment of multiplets was carried out according to published data on related compounds[12]. Mass spectra were taken on a Gas Chromatograph-Mass Spectrometer LKB 9 000. IR spectra were measured on a Perkin–Elmer 325 Spectrophotometer in chloroform solution; wavenumbers are given in cm^{-1}. High performance liquid chromatography (HPLC) was performed on a Spectra Physics SP-8 000B chromatograph using a sillica column SI VSK 10 (Laboratorní přístroje, Praha), 250 × 4·5 mm and a hexane–isopropanol mixture (95 : 5) as the eluent. The H–P 5 840 Gas chromatograph, equipped with glass column 250 × 0·3 cm packed with 5% OV-17 on Gaschrom Q 60/80, was used for gas chromatography (GLC). The authentic sample of "Corey lactone" was obtained from Aldrich (24926—2).

7-*anti*-Acetoxymethyl-5-*exo*-chloro-bicyclo[2.2.1]heptan-2-one (*II*)

Hydroxyketone *I* (2·62 g, 15 mmol), dry pyridine (1·43 g, 18 mmol) and acetanhydride (1·84 g, 18 mmol) were stirred at room temperature for 6 h. Dichloromethane (10 ml) was added and the resulting mixture was washed with diluted hydrochloric acid (1 : 4, 8 ml) and saturated solution of sodium hydrogencarbonate (10 ml), dried with anhydrous magnesium sulfate and evaporated in vacuo (2·6 kPa, bath temperature 50°C). The yield was 3·23 g (99%) of the crude *II*, m.p. 71—72°C. An analytical sample was crystallized from aqueous methanol. For $C_{10}H_{13}ClO_3$ (216·6) calculated: 55·44% C, 6·05% H, 16·36% Cl; found: 55·89% C, 6·16% H, 16·35% Cl.

^{1}H NMR spectrum: 1·80—2·55 m, 5 H (2 × H-3, 2 × H-6, H-7); 1·95 s, 3 H (Ac); 2·73 m, 1 H (H-4); 2·88 m, 1 H (H-1); 4·08 m, 1 H (H-5); 4·23—4·70 m, 2 H (OCH_2-7). Mass spectrum, *m/z* (relative intensity, %): 216 (M^+, 0·2), 174 (9), 112 (8), 93 (13), 92 (7), 91 (9), 79 (18), 77 (10), 60 (20), 43 (100), 39 (11).

8-*anti*-Acetoxymethyl-6-*exo*-chloro-2-oxabicyclo-[3.2.1]-octan-3-one (*III*)

To the stirred solution of *II* (3·04 g, 14 mmol), sodium acetate (3 g) in acetic acid (30 ml) and commercial 40% peroxyacetic acid (15 ml, 70 mmol) were added in the course of 10 min. The reaction mixture was cooled occasionally in order to keep temperature below 26°C for 2 h and then set aside overnight. An ice-water mixture (300 g) was added and the excess of peracid was destroyed by addition of sodium sulfite. The product was extracted with dichloromethane (100 ml) and ether (4 × 100 ml), combined organic layers were washed with saturated solution of sodium hydrogen carbonate (2 × 20 ml) and water (2 × 20 ml), dried over anhydrous magnesium sulfate and evaporaed in vacuo. The residue was crystallized from dichloromethane–cyclohexane mixture. Yield 2·41 g (74%), m.p. 102—104°C. For $C_{10}H_{13}ClO_4$ (232·7) calculated: 51·62% C, 5·63% H, 15·24% Cl; found: 51·73% C, 5·52% H, 15·29% Cl. ^{1}H NMR spectrum: 2·12 s, 3 H (Ac); 2·25—3·19 m, 6 H (2 × H-4, H-5, 2 × H-7, H-8); 4·26 m, 1 H (H-6); 4·31 m, 2 H ($AcOCH_2$-8); 4·87 m, 1 H (H-1). Mass spectrum, *m/z* (relative intensity, %): 97(24), 93 (87), 83 (87), 79 (28), 77 (17), 67 (14), 55 (21), 43 (100), 41 (24).

(3aα4α,5β,6aα)-4-Acetoxymethyl-hexahydro-5-hydroxy-2*H*-cyclopenta[*b*]furan-2-one (*IV*)

To the solution of *III* (0·475 g, 2 mmol) in tetrahydrofurane (5 ml), hydrogen peroxide (30%, 10 ml, 98 mmol) was added, followed by 2M aqueous solution of lithium hydroxide (1 ml) under stirring. The temperature increased slightly and the mixture was stirred for 4 h. Then sodium sulfite was added in excess, in order to destroy the peroxide. The reaction mixture was evaporated in vacuo (2·6 kPa, bath temperature 30°C), extracted with dichloromethane (6 × 10 ml), the extracts combined, dried with anhydrous magnesium sulate and evaporated. The crude product of at least 95% purity according to the GLC was obtained, (0·385 g, 90%). This product was used for the next step without further purification. ^{1}H NMR spectrum: 2·12 s, 3 H (Ac); 1·80 to 3·00 m, 7 H (2 × H-3, H-3a, H-4, 2 × H-6, OH), 4·06 d, 2 H (CH_2–O); 3·65—4·40 m, 1 H (H-5); 4·90—5·15 m, 1 H (H-6a). IR spectrum: 3 620 s (free OH); 3 500 m (bonded OH); 1 770 s (γ-lactone); 1 740 s (COOR).

(3aα,4α,5β,6aα)-4-Acetoxymethyl-5-(1,1′-biphenyl-4-carbonyloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (*V*)

To the solution of *IV* (0·385 g, 1·8 mmol) in dichloromethane (5 ml), 4-phenylbenzoyl chloride (0·55 g, 1·8 mmol) and triethylamine (0·4 ml, 2·9 mmol) were added and the reaction mixture was stirred at the ambient temperature for 24 h. Two drops of water were added and the reaction mixture was stirred for further 30 min, diluted with dichloromethane (5 ml) and washed with saturated sodium hydrogen carbonate (2 × 4 ml). The combined organic phases were dried with anhydrous magnesium sulfate, filtered through 5 g of aluminium oxide (activity II). Solids were thoroughly washed with dichloromethane (15 ml) and the solution was evaporated in vacuo yielding 0·7 g (100%) of the product *V*. For $C_{23}H_{22}O_6$ (394·4), calculated: 70·04% C, 5·62% H found: 69·51% C, 5·58% H. ^{1}H NMR spectrum: 2·02 s, 3 H (Ac), 2·35—2·95 m, 6 H (2 × H-3 H-3a, H-4, 2 × H-6); 4·10 m, 2 H (CH_2O); 5·00 m, 1 H (H-6a); 5·30 m, 1 H (H-5); 7·10—7·90 m 9 H (H-arom.). IR spectrum: 1 775 s (γ-lactone); 1 745 s (Ac); 1 715 s (ArCOO). Mass spectrum

m/z (relative intensity, %): 394 ($M^{\ddagger}$, 25), 199 (18), 198 (71), 182 (21), 181 (100), 153 (29), 152 (29), 151 (13), 43 (39).

(3aα,4α,5β,6aα)-5-(1,1'-Biphenyl-4-carbonyloxy)-hexahydro-4-hydroxymethyl-2*H*-cyclopenta[*b*]furan-2-one (*VI*)

The acetate *V* (1·24 g, 3·14 mmol) in methanol (20 ml) was treated with concentrated sulfuric acid (30 mg), refluxed for 5 h and stirred for additional 72 h at ambient temperature. The acid was neutralized with triethylamine (50 µl) and the solid material was collected. The total yield 814 mg (73%) was obtained after trituration of the evaporated mother liquor from the first crystallization with methanol (5 ml). The product exhibited identical chromatographic and spectral data with the authetic sample, ref.[13].

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