RESOLUTION OF A RACEMIC COREY LACTONE via ENANTIOSELECTIVE ESTERIFICATION

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Received May 21, 1991
Accepted June 11, 1991

Dedicated to Professor Miroslav Ferles on the occasion of his 70th birthday.

The (−)-enantiomer of Corey lactone *Ia* has been separated from its (+)-enantiomer *Ib* via enantioselective esterification of the latter using glycerol tributyrate and a catalytic amount of lipase from *Candida cylindracea* (EC 3.1.1.3) in an aprotic solvent at 20 to 40°C during 5 to 48 h. The *Ic* obtained has been separated from *Ia* by column chromatography and converted back to *Ib* by acid catalyzed transesterification with methanol.

The hydrolytic enzymes such as lipases, esterases, and proteases are extensively utilized nowadays as catalysts in enantioselective and regioselective syntheses[1,2]. A number of chiral synthons with hydroxyl group were prepared in high optical purity with the help of enzymatic hydrolysis[3-5], esterification[6], or transesterification[7-9] in organic solvents. The present communication describes our experience with application of lipase from *Candida cylindracea* (EC 3.1.1.3) to the preparation of optically pure (−)-enantiomer *Ia* and the corresponding (+)-enantiomer *Ib* from the racemic Corey alcohol (*Ia* + *Ib*).

The racemic alcohol (*Ia* + *Ib*) and its (−)-enantiomer *Ia* are important intermediates in syntheses of natural prostaglandins and their analogues[10]. The preparation of the optically active form *Ia* was paid considerable attention in the past, and the methods described so far concern resolution of a suitable precursor of the alcohol *Ia* via separations of diastereoisomeric salts[11,12] or applications of microbial reduction[13]. An alternative procedure of resolution of the alcohol (*Ia* + *Ib*) by application of diastereoisomeric salts of optically active amines with hemiesters of the Corey lactone is described in our previous communication[14]. Our present strategy of preparation of the individual enantiomers *Ia* and/or *Ib* is based on the ability of lipase to catalyze transesterificiation reactions with tributyrin[8] in media of organic solvents. With regard to the relatively limited solubility of the alcohol (*Ia* + *Ib*) in hydrocarbons, the transesterification reaction was carried out in the medium of dichloromethane or 1,2-dichloroethane. In chloroform, the transesterification

reaction at identical conditions (ratio of reaction components, temperature, stirring) does not practically proceed. In all the experiments we adopted a lipase with specific activity of 500 unit/mg solid (anchored on lactose with the enzyme/substrate ratio of 1 : 5 by wt.). The separation and recycling of the enzyme is made easier by adding a suitable carrier (e.g. Sorsilen, Spheron, Chromosorb) to the reaction mixture. A preliminary anchoring of the enzyme to carrier[13] did not bring any advantages or yield improvements. It was found that one of important factors for a successful course of the transesterification reaction investigated consists in the presence of an optimum amount of water in the reacting system. The reaction almost does not proceed in anhydrous media, whereas in the presence of excess water the catalyst is coagulated whereby the reaction is substantially slowed down (see Table I, Experiment No. 2). It was found that the optimum water content in the reaction mixture can be ensured by application of tributyrin half saturated with 0·1M phosphate buffer solution with pH 8 (anhydrous tributyrin is mixed with equal volume of saturated tributyrine – see Experimental). During the reaction, it is necessary to prevent decreases in water content in the reaction mixture (Table I, Experiment No. 1), hence the transesterification must be performed in a closed system. The reaction course was followed by means of HPLC analysis, and the reaction was interrupted after reaching 50 to 55% conversion. The possibility of recycling of the catalyst was verified in four subsequent cycles. From Table I (Experiments Nos. 5 to 9) it is obvious that the catalyst activity decreases only slowly, hence the required conversion can be reached by an adequate prolongation of the reaction time. The products were isolated from the reaction mixture by column chromatography: the first frac-

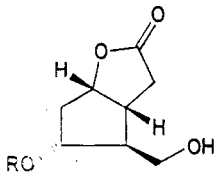
TABLE I

Transesterification of racemic Corey alcohol (*Ia* + *Ib*) with tributyrin

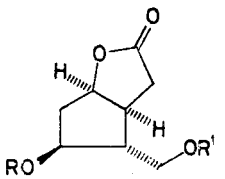
Experiment No.	Solvent	Carrier	Conversion[a]			
1	dichloromethane	—	7·1/16	15/45[b]	51/66	57/90
2	dichloromethane[c]		0·5/1	4·4/3	21/20	24/42
3	1,2-dichloroethane		14/4	48/22	65/75	—
4	1,2-dichloroethane	Spheron 40	14/7	31/24	45/48	55/72
5	1,2-dichloroethane	Sorsilen	27/7	45/24	50/30	—
6	1,2-dichloroethane	Sorsilen[d]	37/17	54/41	—	—
7	1,2-dichloroethane	Sorsilen[d]	50/28	57/52	—	—
8	1,2-dichloroethane	Sorsilen[d]	48/43	53/56	—	—
9	1,2-dichloroethane	Sorsilen[d]	46/45	53/72	—	—

[a] % *Ic*/h; [b] 0·2 ml buffer was added after 45 h; [c] 0·1 ml buffer was added at the beginning; [d] the catalyst recovered from the previous experiment was used.

tion was formed by ester *Ic* (75–80%) which was transformed to the (+)-enantiomer *Ib* (91%) by acid catalyzed transesterification with methanol in the presence of ion exchanger in H^+ cycle. Further chromatographic fractions were submitted to repeated chromatography and subsequent crystallization to give ca 14% racemic lactone (*Ia* + *Ib*) and 55–65% required natural (−)-isomer *Ia*. The results of individual experiments are given in Table I.



Ia



Ib, R' = H
Ic, R' = OCC_3H_7

R = 4-$C_6H_5C_6H_4CO$

EXPERIMENTAL

The temperature data are not corrected. The TLC analyses were carried out on the plates Merck GF_{254}, 5 × 10 cm, 0·2 mm layer, in the system of chloroform with 5% methanol, detection with a 1% solution of cerium(IV) sulfate in 10% sulfuric acid. The HPLC analysis was carried out on a Spectra Physics 8000B apparatus, a column Separon Six Tessek, 150 × 3·2 mm, 5 μm silicium(IV) oxide, the mobile phase of hexane with 10% isopropyl alcohol, flow rate 1 ml/min, detector UV (254 nm). The optical rotation was measured with a JASCO DIP-181 polarimeter in a 10 cm cell in chloroform (*c* 1 mol/l). The NMR spectra were measured with a Bruker AM 400 apparatus in deuteriochloroform with tetramethylsilane as the internal standard. The chemical shifts are given in ppm (δ scale). The IR spectra were measured with a Philips PU 9800 FTIR apparatus in Nujol suspension (the wavenumbers are given in cm^{-1}), and the mass spectra were measured with a JEOL JMS-D-300 apparatus (electron impact, 70 eV). The column chromatography was carried out with the silica gel Silpearl for TLC (Kavalier). Tributyrin and lipase (triacetylglycerol-acylhydrolase EC 3.1.1.3, type VII from *Candida cylindracea*) from Sigma (U.S.A.), No. L-1754.

General Procedure of Transesterification

A mixture of 2 g racemic alcohol (*Ia* + *Ib*), 50 ml solvent (see Table I), 400 mg lipase (with 2 g carrier or without carrier), 4 ml anhydrous tributyrin, 4 ml half-saturated tributyrin (i.e. tributyrin which was equilibrated with 0·1M phosphate buffer (pH 8) before use 24 h) in a closed Erlenmeyer flask was shaken at room temperature. The reaction course was followed by means of HPLC chromatography. After reaching the required conversion, the solid phase was separated by centrifugation, the clear supernatant was removed, the precipitate was mixed with 20 ml solvent of identical composition, and the centrifugation was repeated. The two liquid portions were combined, and the separated lipase was reused (see Table I) in several cases:

[3a*R*(3aα, 4α, 5β, 6aα)]-(−)-5-(1,1'-*Biphenyl*-4-*carbonyloxy*)*hexahydro*-4-*hydroxymethyl*-2*H*-*cyclopenta*[*b*]*furan*-2-*one* (Ia). The chromatography of the supernatant obtained from Experiment

No. 5 (Table I) on a column of 25 g silica gel (the column diameter 24 mm) with elution with 150 ml 1,2-dichloroethane, and evaporation of the resultant fraction gave 8·6 g oily mixture containing ester *Ic* according to TLC. Subsequent fraction (the eluent 200 ml mixture 1,2-dichloroethane–methanol 95 : 5) was evaporated to give 1·70 g residue which was repeatedly submitted to column chromatography (column of 20 mm diameter, eluent 1,2-dichloroethane–methanol 95 : 5) to give 1·2 g raw product, $[\alpha]_D^{22}$ −49·6°. A fractional crystallization gave 0·28 g (14%) racemate (*Ia* + *Ib*), $[\alpha]_D^{22}$ −4·9°, and 0·6 g (60%) of the required (−)-enantiomer *Ia*, m.p. 130–131°C, $[\alpha]_D^{22}$ − 82°, whose physico-chemical and spectral characteristics are identical with those of the authetic standard[14].

[3a*S*(2aα, 4α, 5β, 6aα)-(+)-5-(1,1′-*Biphenyl*-4-*carbonyloxy*)-4-(*butyryloxymethyl*)*hexahydro*-2*H*-*cyclopenta*[*b*]*furan*-2-one (Ic). Repeated chromatography of 8·6 g raw mixture (see above) on a silica gel column (25 g silica gel, diameter 24 mm, eluens 1,2-dichloroethane–hexane 1 : 1) gave 1·0 g raw product which was recrystallized from hexane–ether (5 : 1) mixture to give 0·90 g, (76%) ester *Ic*, m.p. 69–72°C, $[\alpha]_D^{22}$ +57·8°. For $C_{25}H_{26}O_6$ (422·5) calculated: 71·07% C, 6·20% H; found: 71·43% C, 6·32% H. ^{1}H NMR spectrum: 0·95 (t, 3 H, CH_3); 1·65 (m, 2 H, CH_2); 2·32 (t, 2 H, $COCH_2$); 2·35–2·98 (cm, 6 H, $COCH_2$, CHCH; CH_2CHO); 4·15 (d, 2 H, CH_2OCO); 5·11 (dt, 1 H, CHO); 5·38 (m, 1 H, $CHOCOCH_2$); 7·40–8·11 (cm, 9 H, arom.). IR spectrum: 2 693 m, 1 752 s, 1 723 s, 1 277 s, 1 271 s, 1 103 s, 1 007 m, 783 m, 747 s, 696 m. Mass spectrum, *m/z* (% rel. int.): 422 (40, M^+), 181 (100, $C_6H_5C_6H_4CO$), 198 (60, $C_6H_5C_6H_4$.COOH).

[3a*S*(3aα, 4α, 5β, 6aα)]-(+)-(1,1′-*Biphenyl*-4-*carbonyloxy*)*hexahydro*-4-*hydroxymethyl*-2*H*-*cyclopenta*[*b*]*furan*-2-*one* (Ib). A mixture of 500 mg ester *Ic*, 20 ml methanol, and 1 g of ion exchanger Amberlite IR-120 in H^+ cycle was boiled with stirring 20 h. Then the ion exchanger was collected by suction, washed with 2 ml methanol, and the combined solvent was evaporated in vacuum. The distillation residue (430 mg) was submitted to column chromatography (15 g silica gel, the column diameter 18 mm, the eluent 1,2-dichloroethane with 5% methanol) and gave 415 mg evaporation residue which was recrystallized from a mixture of hexane and ethanol (5 : 1, 5 ml). Yield 380 mg (91%) alcohol *Ib*, m.p. 128–131°C, $[\alpha]_D^{22}$ +82·3°, whose spectral characteristics are identical with those of the authetic standard.

The authors are indebted to the team of Central Laboratory, Prague Institute of Chemical Technology: Analytical Department (Head Dr L. Helešic) for elemental analyses; NMR Department (Head Dr P. Trška) for the measurements of ^{1}H NMR spectra; IR Department (Head Dr Kohoutová) for the measurements of IR spectra, and to Dr A. Čapek, Research and Development Division, Chemical Works Spolana for the measurements of mass spectra.

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Translated by J. Panchartek.