PREPARATION OF OPTICALLY PURE ENANTIOMERS OF COREY LACTONE BY RESOLUTION OF THE RACEMATE

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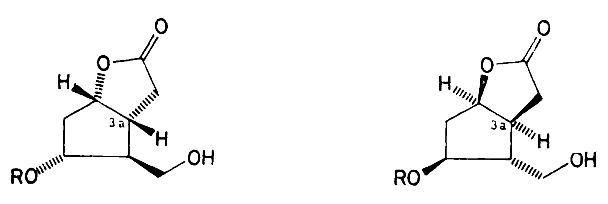
Racemic hydrogen butanedioates (*IIa, IIb*) and hydrogen pentanedioates (*IIIa, IIIb*), prepared by reaction of racemic Corey alcohol *Ia*, *Ib* with the corresponding acid anhydride, were resolved by optically active bases [(1*R*,2*S*)-(−)-ephedrine, (*S*)-(−)-1-phenylethylamine, quinine] to give the optically pure diastereoisomeric salts from which the individual enantiomers of hydrogen butanedioate *IIa* and *IIb* and hydrogen pentanedioate *IIIa* and *IIIb* were liberated. Acid-catalyzed transesterification with methanol converted these optically pure enantiomers into the pure(−)-enantiomer *Ia* and (+)-enantiomer *Ib* of the Corey lactone.

The steady increase of clinical use of natural prostaglandins, particularly their synthetic analogues and derivatives, in human medicine[1,2] stimulates the search for their effective and large-scale synthesis. Still important among the many suggested procedures[3–6] is the already classical synthesis by Corey and coworkers[7], using the so-called Corey lactone, [3a*R*(3aα,4α,5β,6aα)]-(−)-5-(1,1'-biphenyl-4-carbonyloxy)hexahydro-4-hydroxymethyl-2*H*-cyclopenta[*b*]-furan-2-one (*Ia*) as the key intermediate. Besides synthetic procedures, preparing the "natural" (−)-enantiomer *Ia* via various optically active intermediates obtained by resolution of their



Ia, R = $C_6H_5C_6H_4CO$
IXa, R = H

Ib, R = $C_6H_5C_6H_4CO$
IXb, R = H

a = (−) - enantiomer (configuration 3a*R*)
b = (+) - enantiomer (configuration 3a*S*)

SCHEME 1

racemates[8-11], and excepting cases of optical induction[12,13], several natural compounds, e.g. (*S*)-(−)-malic acid[14] or 3-deoxy-D-glucose[15], have been suggested as starting chiral material (Scheme 1). Most of the suggested procedures, however, are more or less of theoretical interest only and have found no application to large-scale preparation of the (−)-enantiomer of the Corey lactone *Ia*.

As a continuation of our previous studies[16,17] leading to advantageous synthesis of racemic Corey lactone (*Ia*, *Ib*), we tried to resolve this compound into the (−)-enantiomer *Ia* and its (+)-antipode *Ib*. We have chosen the method based on the preparation of monoesters of dicarboxylic acids and their subsequent resolution with suitable bases[18-20].

The racemate (*Ia*, *Ib*) was esterified with butanedioic or pentanedioic anhydride[21-23] either in pyridine with 4-dimethylaminopyridine as catalyst or in ethyl acetate in the presence of 1·05−1·3 molar excess of triethylamine. Acidification of the reaction mixture with hydrochloric acid liberated the lactone acids (*IIa*, *IIb*) and (*IIIa*, *IIIb*), respectively which were isolated in high yield. We have proven that the presence of water (more than 0·01 wt. %) strongly reduces the yield of the desired hemiesters. In the next reaction step, the racemic hydrogen butanedioate (*IIa*, *IIb*) was treated with 0·5−1 molar amount of (1*R*,2*S*)-(−)-ephedrine in ethyl acetate to give the (−)-diastereoisomer *IVa* in excellent yield. This salt was further subjected to fractional crystallization from a mixture of ethyl acetate–ethanol. The material from the mother liquors on repeated crystallization from dioxane afforded the (+)-diastereoisomer *IVb*. The assumption that the (−)-diastereoisomer *IVa* corresponds to the (−)-enantiomer of Corey lactone *Ia* has been confirmed in the following way: treatment of the ephedrine salt *IVa* with dilute hydrochloric acid afforded the (−)-enantiomer of the hydrogen butanedioate *IIa* which upon acid-catalyzed transesterification with methanol at elevated temperature furnished the (−)-enantiomer of Corey lactone *Ia* which had identical physicochemical constants with those reported by Corey and coworkers[7]. After removal of the *p*-phenylbenzoyl group by action of potassium carbonate in methanol we isolated optically pure [3a*R*(3aα,4α,5β,6aα)]-(−)-5-hydroxy-4-hydroxymethylhexahydro-2*H*-cyclopenta[*b*]-furan-2-one (*IXa*). Specific rotations and elemental analyses of the prepared compounds are given in Table I.

Using the same procedure, the (+)-enantiomer *IIb*, obtained from (+)-diastereoisomeric salt *IVb*, was converted into the known[24] lactone *Ib* which on subsequent transesterification with methanol in the presence of potassium carbonate afforded the (+)-enantiomer of diol *IXb*, described only recently[25] (Scheme 2).

In order to find optimum conditions for resolution of hydrogen butanedioates (*IIa*, *IIb*) we also tried (*S*)-(−)-1-phenylethylamine and (−)-quinine as optically active bases. In the first case the usual work-up of the reaction mixture gave the (−)-diastereoisomer *VIa* (which crystallised preferentially) in a relatively low yield (17%) and fractional crystallization of the mother liquors from ethyl acetate afforded

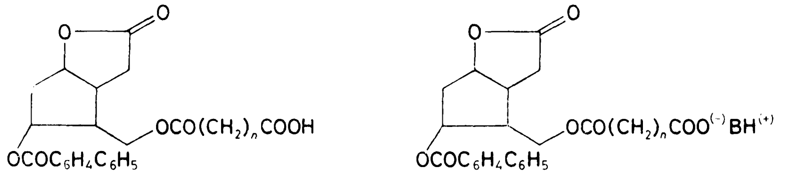
TABLE I

Elemental analyses and optical rotations of compounds *I*—*VIII*

Compound	Formula (M.w.)	Calculated/Found			$[\alpha]_D^{22}$, ° (c 1·0, $CHCl_3$)
		% C	% H	% N	
Ia	$C_{21}H_{20}O_5$	71·58	5·72		−88·9
	(352·4)	71·04	5·77		
Ib	$C_{21}H_{20}O_5$	71·58	5·72		+88·6
	(352·4)	71·41	5·78		
IXa	$C_8H_{12}O_4$	[a]	[a]		−43·2[b]
	(172·1)				
IXb	$C_8H_{12}O_4$	[a]	[a]		+43·39[b]
	(172·1)				
(*IIa*, *IIb*)	$C_{25}H_{24}O_8$	66·36	5·35		
	(452·5)	66·21	5·38		
IIa	$C_{25}H_{24}O_8$	66·36	5·35		−87·1
	(452·5)	66·21	5·24		
IIb	$C_{25}H_{24}O_8$	66·36	5·35		−87·6
	(452·5)	66·17	5·35		
(*IIIa*, *IIIb*)	$C_{26}H_{26}O_8$	66·94	5·68		
	(466·5)	66·82	5·60		
IIIa	$C_{26}H_{26}O_8$	66·94	5·62		−86·2
	(466·5)	67·32	5·59		
IIIb	$C_{26}H_{26}O_8$	66·94	5·62		+89·1
	(466·5)	67·01	5·55		
IVa	$C_{35}H_{39}NO_9$	68·06	6·36	2·27	−76·8[c]
	(617·7)	67·78	6·39	1·99	
IVb	$C_{35}H_{39}NO_9$	68·06	6·36	2·27	+55·7
	(617·7)	68·00	6·63	2·29	
Va	$C_{45}H_{48}N_2O_{10}$	69·57	6·63	3·61	−120·0
	(776·9)	68·68	6·14	2·95	
Vb	$C_{45}H_{48}N_2O_{10}$	69·57	6·23	3·61	+1·3
	(776·9)	69·63	6·25	3·30	
VIa	$C_{33}H_{35}NO_8$	69·10	6·15	2·44	−73·3
	(573·6)	69·17	6·26	2·51	
VIb	$C_{33}H_{35}NO_8$	69·10	6·15	2·44	+66·4
	(573·6)	69·05	6·22	2·45	
VIIa	$C_{36}H_{41}NO_9$	68·45	6·54	2·22	−73·1
	(631·7)	68·49	6·48	2·12	
VIIb	$C_{36}H_{41}NO_9$	68·45	6·54	2·22	+55·1
	(631·7)	68·43	6·41	2·34	
VIIIa	$C_{34}H_{37}NO_8$	69·49	6·35	2·38	−75·4
	(587·7)	70·01	6·26	2·50	

[a] Not determined; [b] *c* 1·5, methanol; [c] *c* 1·1.

the (+)-diastereoisomer *VIb* in 13% yield. On the other hand, using (−)-quinine we obtained the (+)-diastereoisomer *Vb* in 93% yield and the mother liquors afforded only minimum amount (7%) of the (−)-diastereoisomer *Va*. An analogous approach was applied also to resolution of hydrogen pentanedioate (*IIIa*, *IIIb*) with (1*R*,2*S*)-(−)-ephedrine and (*S*)-(−)-1-phenylethylamine. In both cases we first isolated the respective (−)-diastereoisomers *VIIa* (29%) and *VIIIa* (44%). The mother liquors afforded pure crystalline (+)-diastereoisomer *VIIb* (12%); however, from all the solvents employed (ethanol, dioxane, ethyl acetate, acetone and their mixtures) the phenylethylammonium salt *VIIIb* was isolated only as an oil for which no satisfactory analytical data could be obtained. From the salts *Va* – *VIIIa* and *Vb* – *VIIb* we liberated the corresponding (−)-enantiomers *IIa* and *IIIa*, and the (+)-enantiomers *IIb* and *IIIb* which afforded the desired (−)-isomer of the "natural" Corey lactone *Ia* and its (+)-antipode *Ib*.



IIa, $n = 2$ *IIIa*, $n = 3$
IIb, $n = 2$ *IIIb*, $n = 3$

	n	B		n	B
IVa	2	E	*VIIa*	3	E
IVb	2	E	*VIIb*	3	E
Va	2	CH	*VIIIa*	3	PH
Vb	2	CH	*VIIIb*	3	PH
VIa	2	PH			
VIb	2	PH			

In formulae *II* – *VIII*: *a* = (−)-diastereoisomer; *b* = (+)-diastereoisomer;
E = (1*R*,2*S*)-(−)-ephedrine; CH = quinine; PH = (*S*)-(−)-1-phenylethylamine

SCHEME 2

Our results show that for the studied combination of lactone-acids *IIa*, *IIb* and *IIIa*, *IIIb* and optically active bases the best way to the desired (−)-isomer of the Corey lactone *Ia* consists in the resolution of hydrogen butanedioate (*IIa*, *IIb*) with (1*R*, 2*S*)-(−)-ephedrine whereas for the synthesis of the (+)-enantiomer the resolution with (−)-quinine represents the method of choice.

EXPERIMENTAL

The temperature data are uncorrected. The melting points were determined on a Boetius block (Zeiss, Jena). Specific rotations were measured on a Jasco DP-181 instrument in chloroform (*c* 1) unless stated otherwise. IR spectra were taken on a Perkin-Elmer 325 spectrometer in chloroform (unless stated otherwise) and the wavenumbers are given in cm^{-1}. ^1H NMR spectra were obtained with a Varian XL 100-15 instrument in deuteriochloroform with tetramethylsilane as an internal standard and the chemical shifts are given in ppm (δ-scale), the coupling constants in Hz. Mass spectra were measured on a Jeol DX 303 spectrometer (electron impact; 70 eV).

Chemicals. Racemic Corey lactone (*Ia*, *Ib*), m.p. 149–151°C, was obtained from Spolana, Neratovice, (1*R*, 2*S*)-(−)-ephedrine and (*S*)-(−)-1-phenylethylamine were Merck products, quinine was purchased from Fluka. Butanedioic anhydride had m.p. 119–120°C, pentanedioic anhydride m.p. 52–54°C.

[3a*R*,*S*(3aα,4α,5β,6aα)]-(±)-[5-(1,1′-Biphenyl-4-carbonyloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-on-4-yl]methyl Hydrogen Butanedioate (*IIa*, *IIb*)

A mixture of racemic Corey lactone *Ia*, *Ib* (35·2 g, 0·10 mol), butanedioic anhydride (12 g, 0·12mol), triethylamine (20 g, 0·2 mol) and ethyl acetate (350 ml) was refluxed for 8 h. After this time the reaction mixture contained no starting lactone (TLC on silica gel Merck, eluent chloroform–methanol 95 : 5). After cooling, the crude product was extracted with water (3 × 100 ml) as its triethylammonium salt. The combined aqueous extracts were acidified with dilute hydrochloric acid (60 ml, 1 : 1) under stirring, the separated crystalline product was collected on filter, washed with water (2 × 50 ml) and dried at 60°C under diminished pressure. The crude product was dissolved in glacial acetic acid (130 ml) at about 60°C, the solution was filtered with charcoal and diluted with water (60 ml) to slight turbidity. After standing at room temperature for 24 h, the separated crystals were filtered, washed with water (2 × 50 ml) and dried to give 40·2 g (88%) of material m.p. 134–141°C. Recrystallization from aqueous acetic acid (1 : 1) afforded 30·1 g (66·4%) of (*IIa*,*IIb*), m.p. 139–141°C. IR spectrum: 3 020 (CH arom.); 1 770, 1 738, 1 715 (C=O lactone, ester, carboxyl); 1 610, 1 580 (C=C arom.); 1 272, 1 175 (C—O ester). ^1H NMR spectrum: 2·35–3·00 m, 10 H (2 × CH, CH_2, 3 × CH_2CO); 4·18 d, 2 H (CH_2O, *J* = 6); 5·10 t, 1 H (CH—O, *J* = 5); 5·38 m, 1 H (CH—O); 7·40–8·10 m, 9 H (H arom.). Mass spectrum, *m*/*z* (%): 452 (M^+, 33), 198 (88, $C_6H_5C_6H_4COOH$), 181 (100, $C_6H_5C_6H_4CO$), 152 (17, $C_6H_5C_6H_4$ − 1), 101 (9, $COCH_2CH_2COOH$), 59 (45, CH_2COOH).

[3a*R*,*S*(3aα,4α,5β,6aα)]-(±)-[5-(1,1′-Biphenyl-4-carbonyloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-on-4-yl]methyl Hydrogen Pentanedioate (*IIIa*, *IIIb*)

Pentanedioic anhydride (2·4 g, 20 mmol), followed by triethylamine (4·1 g, 40 mmol), was gradually added to a solution of racemic Corey lactone (*Ia*, *Ib*; 5 g, 14 mmol) in ethyl acetate (100 ml) and the reaction mixture was refluxed for 12 h. Analogous work-up procedure as described for (*IIa*, *IIb*) afforded 5·6 g (86%) of (*IIIa*, *IIIb*), m.p. 104–109°C, which after recrystallization from dilute (1 : 1) acetic acid melted at 107–109°C. IR spectrum: 3 020 (CH arom.); 1 768, 1 738, 1 712 (C=O lactone, ester, carbonyl); 1 603 (C=C arom.); 1 273, 1 160 (C—O ester). ^1H NMR spectrum: 1·95 m, 2 H (CH_2); 2·35–3·00 m, 10 H (2 × CH, CH_2, 3 × CH_2CO); 4·15 m, 2 H (CH_2O); 5·12 t, 1 H (CH—O, *J* = 6); 5·38 m, 1 H (CH—O); 7·35 to 8·10 m, 9 H (H arom.). Mass spectrum, *m*/*z* (%): 467 (M^+, 6), 198 (92, $C_6H_5C_6H_4COOH$), 181 (100, $C_6H_5C_6H_4CO$), 153 (22, $C_6H_5C_6H_4$), 152 (23, $C_6H_5C_6H_4$ − 1), 83 (11); 73 (13); 71 (11); 69 (13), 60 (12), 57 (20).

Resolution of Racemate (*IIa*, *IIb*) with (1*R*, 2*S*)-(−)-Ephedrine

A solution of ephedrine (5·8 g, 35 mmol) in ethyl acetate (20 ml) was added to a solution of racemate (*IIa*, *IIb*) (15 g, 33 mmol) in boiling ethyl acetate (75 ml). The mixture was cooled to 10—15°C and set aside for 8 days at room temperature. The separated crystals were collected, washed with ethyl acetate (3 × 10 ml) and dried. This crude product (8·2 g) was fractionally crystallized from ethyl acetate–ethanol (9 : 1) to give 5·2 g (50%) of analytically pure salt *IVa*, m.p. 140—141°C. IR spectrum: 3 040, 3 020 (CH arom.); 1 770, 1 735, 1 715 (C=O lactone, ester); 1 610 (C=C arom.); 1 565, 1 410 (COO^-); 1 275 (C—O ester). ^1H NMR spectrum: 1·07 d, 3 H (CH_3, $J = 7$); 2·26—3·18 m, 13 H (CH_3N, 2 × CH, CH_2, 3 × CH_2CO); 4·12 m, 2 H (CH_2O); 5·04 t, 1 H (CH—O, $J = 5$); 5·28 m, 2 H (CH—O); 5·96 m, 3 H (NH_2, OH); 7·22—8·60 m, 14 H (H arom.).

The mother liquors were concentrated in vacuo and the residue (about 20 ml) was set aside at 0 to −5°C for 72 h. The separated crystals were collected on filter, washed with ethyl acetate (3 × 5 ml) and repeatedly crystallized from dioxane to give 2·5 g (24%) of analytically pure salt *IVb*, m.p. 92—95°C. IR spectrum: 3 035, 3 010 (CH arom.); 1 772, 1 737, 1 713 (C=O lactone, ester); 1 605 (C=C arom.); 1 560, 1 405 (COO^-); 1 270 (C—O ester). ^1H NMR spectrum: 1·08 d, 3 H (CH_3, $J = 7$); 2·25—3·20 m, 13 H (CH_3N, 2 × CH, CH_2, 3 × CH_2CO); 4·13 m, 2 H (CH_2O); 5·06 t, 1 H (CH—O, $J = 5$); 5·28 m, 2 H (CH—O); 5·92 bs, 3 H (NH_2, OH); 7·20—8·50 m, 14 H (H arom.).

Resolution of Racemate (*IIa*, *IIb*) with (−)-Quinine

A solution of the lactone-acid (*IIa*, *IIb*) (15 g, 33 mmol) in ethyl acetate (50 ml) was slowly added to a boiling suspension of quinine (11·5 g, 35 mmol) in ethyl acetate (60 ml). After short boiling, the clear solution was allowed to crystallize at room temperature for 48 h. The crystals were collected, washed with cold ethyl acetate (3 × 15 ml) and dried at 60°C in a vacuum oven; the obtained crude salt *Vb* (15·1 g) was fractionally crystallized from ethyl acetate–ethanol (5 : 1) to give 12·0 g (93%) of pure product *Vb*, m.p. 175—176°C. IR spectrum: 3 040, 3 020 (CH arom.); 2 470 (N—H ammonium salt); 1 770, 1 735, 1 715 (C=O lactone, ester); 1 620, 1 610 (C=C arom.); 1 590, 1 350 (COO^-); 1 275 (C—O ester). ^1H NMR spectrum: 4·20 m, 2 H (CH_2O); 5·35 m, 1 H (CH—O); 7·30—8·10 m, 9 H (H arom.).

The mother liquors (about 140 ml) from the crystallization of *Vb* were concentrated under diminished pressure to about 20 ml and allowed to crystallize first at room temperature and then at −10°C to −5°C. The solid material was filtered, washed with cold ethyl acetate (3 × 15 ml) and dried. The obtained crude salt (4·1 g) was fractionally crystallized from ethyl acetate to give 1·1 g (7%) of the product *Va*, m.p. 102—108°C. IR spectrum: 3 042, 3 030 (CH arom.); 2 472 (N—H ammonium salt); 1 770, 1 737, 1 718 (C=O lactone, ester); 1 620, 1 610 (C=C arom.); 1 593, 1 350 (COO^-); 1 275 (C—O ester). ^1H NMR spectrum: 4·20 m, 2 H (CH_2O); 5·35 m, 1 H (CH—O); 7·30—8·10 m, 9 H (H arom.).

Resolution of Racemate (*IIa*, *IIb*) with (*S*)-(−)-1-Phenylethylamine

A solution of (*S*)-(−)-1-phenylethylamine (2·8 g, 23 mmol) in ethyl acetate (5 ml) was gradually added at 60—65°C to a stirred solution of the lactone acid (*IIa*, *IIb*) (10 g, 22 mmol) in ethyl acetate (25 ml). The obtained clear solution was set aside at room temperature for 24 h and then at −5°C to −10°C for 48 h. The separated crystals were collected, washed with ethyl acetate (2 × 10 ml) and dried in a vacuum oven to yield 3·4 g of crude product, $[\alpha]_D^{22}$ −50°. Several crystallizations from ethyl acetate afforded 1·1 g (17%) of the pure product *VIa*, m.p. 122—124°C. IR spectrum (KBr): 3 030 (CH arom.); 1 780, 1 720 (C=O lactone, ester); 1 635, 1 610 (C=C arom.); 1 560, 1 535 (COO^-); 1 280, 1 185 (C—O ester); 760, 700 (C—H arom.).

The concentrated mother liquors (about 10 ml) were allowed to stand at −5°C to −10°C for

16 days and after the usualwork-up procedure afforded 3·2 g of the crude product, $[\alpha]_D^{22}$ +45°, which on fractional crystallization from ethyl acetate gave 0·8 g (13%) of the pure salt *VIb*, m.p. 113—116°C. IR spectrum (KBr): 3 025 (CH arom.); 1 782, 1 720 (C=O lactone, ester); 1 636, 1 610 (C=C arom.); 1 565, 1 534 (COO^-); 1 283, 1 180 (C—O ester); 760, 700 (C—H arom.).

Resolution of Racemate (*IIIa*, *IIIb*) with (1*R*, 2*S*)-(−)-Ephedrine

Ephedrine (3·7 g, 22·4 mmol), dissolved in boiling ethyl acetate (10 ml) was added to a stirred boiling solution of racemate (*IIIa*, *IIIb*) (10 g, 21·4 mmol) in ethyl acetate–ethanol (2 : 1; 45 ml). The mixture was slowly cooled to −5°C to −10°C and after 3 days the crystals were collected on filter, washed with ethyl acetate (2 × 20 ml) and dried. The obtained crude salt (8 g), $[\alpha]_D^{22}$ −55°, was subjected to fractional crystallization from ethyl acetate–dioxane (3 : 1) and afforded 1·97 g (29%) of pure salt *VIIa*, m.p. 87—89°C. IR spectrum (KBr): 3 370—3 500 (O—H); 3 030 (CH arom.); 1 768, 1 730, 1 715 (C=O lactone, ester); 1 607 (C=C arom.); 1 555, 1.382 (COO^-); 1 172, 1 147 (C—O ester); 750, 705 (C—H arom.).

The combined mother liquors were concentrated under diminished pressure, the oily residue (5·8 g) was dissolved in ethyl acetate (20 ml) and left to crystallize at −5°C to −10°C for 20 days. The crude product (2·05 g), $[\alpha]_D^{22}$ +50°, was fractionally crystallized from ethyl acetate, affording 0·8 g (12%) of the salt *VIIb*, m.p. 79—82°C. IR spectrum (KBr): 3 350—3 450 (O—H); 3 030 (CH arom.); 1 769, 1 726, 1 708 (C=O lactone, ester); 1 603 (C=C arom.); 1 560, 1 386 (COO^-); 1 172, 1 145 (C—O ester); 760, 703 (C—H arom.).

Resolution of Racemate (*IIIa*, *IIIb*) with (*S*)-(−)-1-Phenylethylamine

A solution of phenylethylamine (2·7 g, 22 mmol) in ethyl acetate (10 ml) was added to a solution of the racemate (*IIIa*, *IIIb*) (10 g, 21·4 mmol) in ethyl acetate (50 ml). The usual work-up of the reaction mixture afforded 5·2 g of the crude salt, $[\alpha]_D^{22}$ −45·1°, which on repeated crystallization gave 2·8 g (44%) of product *VIIIa*, m.p. 99—101°C. IR spectrum (KBr): 3 030 (CH arom.); 1 780, 1 720 (C=O lactone, ester); 1 636, 1 610 (C=C arom.); 1 565, 1 534 (COO^-); 1 283, 1 180 (C—O ester); 760, 700 (C—H arom.).

[3a*R*(3aα,4α,5β,6aα)]-(−)-[5-(1,1′-Biphenyl-4-carbonyloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-on-4-yl]methyl Hydrogen Butanedioate (*IIa*)

Dilute hydrochloric acid (1 : 1; 5 ml) was gradually added to a solution of the ephedrine salt *IVa* (6·2 g, 10 mmol) in water (50 ml) at 60°C so as the mixture had pH 2. After cooling, the oily product was separated and the aqueous layer extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with sodium chloride solution (5 ml), dried over magnesium sulfate and the solvent was evaporated in vacuo. The solid residue (4·4 g, 96%), $[\alpha]_D^{22}$ −84·0° (*c* 1, chloroform) was dissolved in acetic acid (15 ml) at 60—65°C and then water was added to slight turbidity (total 5 ml). After standing at room temperature for 2 days, the crystals were collected and washed successively with dilute (1 : 1) acetic acid (15 ml) and water (15 ml) and dried in a vacuum oven. Yield 3·82 g (84%) of lactone-acid *IIa*, m.p. 121—123°C. IR spectrum: 3 025 (CH arom.); 1 775, 1 738, 1 710 (C=O lactone, ester, carboxyl); 1 612, 1 555 (C=C arom.); 1 275, 1 170 (C—O ester). ^{1}H NMR spectrum: 2·32—3·00 m, 10 H (2 × CH, CH_2, 3 × CH_2CO); 4·17 d, 2 H (CH_2O, $J = 6$); 5·12 t, 1 H (CH—O); 5·36 m, 1 H (CH—O); 7·42 to 8·05 m, 9 H (H arom.). Mass spectrum, *m/z* (%): 452 (M^+, 26), 352 (3, M − 100), 198 (76, $C_6H_5C_6H_4COOH$), 181 (100, $C_6H_5C_6H_4CO$), 153 (21, $C_6H_5C_6H_4$), 152 (20), 101 (9, $COCH_2.CH_2COOH$), 73 (3, CH_2CH_2COOH), 59 (40, CH_2COOH).

Using an analogous procedure, the lactone-acid *IIa* was liberated from the phenylethylammonium salt *VIa* in a yield of 71% (m.p. 122—123°C from water–acetic acid), $[\alpha]_D^{22}$ −87·0°, and from the quinine salt *Va* in 50% yield, m.p. 121—123°C, $[\alpha]_D^{22}$ −87·0°, whose spectral characteristics were identical with those of the above-described product.

[3a*S*(3aα,4α,5β,6aα)]-(+)-[5-(1,1′-Biphenyl-4-carbonyloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-on-4-yl]methyl Hydrogen Butanedioate (*IIb*)

A solution of the salt *Vb* (12 g, 15 mmol) in water (100 ml) was acidified at 60°C with dilute (1 : 1) hydrochloric acid (5 ml). After cooling, the oily product was separated and the aqueous layer was extracted with chloroform (3 × 20 ml). The combined organic portions were washed with brine (5 ml), dried over magnesium sulfate and the solvents were evaporated in vacuo. The residue (6·8 g; 97% $[\alpha]_D^{22}$ +83°) was dissolved in acetic acid (15 ml) and the warm (50°C) solution was slowly diluted with water (7 ml) to slight turbidity. After standing for 24 h at room temperature, the crystals were collected, washed successively with dilute acetic acid (1 : 1; 15 ml) and water (15 ml) and dried in a vacuum oven; yield 5·1 g (74%) of the lactone-acid *IIb*, m.p. 126—127°C. IR spectrum: 3 020 (CH arom).; 1 775, 1 738, 1 715 (C=O lactone, ester, carboxyl); 1 612, 1 585 (C=C arom.); 1 276, 1 175 (C—O ester). ^{1}H NMR spectrum: 2·34—3·10 m, 10 H (2 × CH, CH_2, 3 × CH_2CO); 4·17 d, 2 H (CH_2O, $J = 6$); 5·10 t, 1 H (CH—O); 5·35 m, 1 H (CH—O); 7·40—8·10 m, 9 H (H arom.). Mass spectrum, *m/z* (%): 452 (M^+, 21), 352 (5, M − 100), 198 (81, $C_6H_5C_6H_4COOH$), 181 (100, $C_6H_5C_6H_4CO$), 153 (19, $C_6H_5C_6H_4$), 101 (9, $COCH_2.CH_2COOH$), 73 (2, CH_2CH_2COOH), 59 (45, CH_2COOH).

[3a*R*(3aα,4α,5β,6aα)]-(−)-[5-(1,1′-Biphenyl-4-carbonyloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-on-4-yl]methyl Hydrogen Pentanedioate (*IIIa*)

Dilute hydrochloric acid (1 : 1; 5 ml) was slowly added at 60—65°C to a solution of ephedrine salt *VIIa* (6·32 g, 10 mmol) in water (50 ml). The mixture had pH 1·5—2. After cooling, the organic phase was separated and the aqueous one was extracted with chloroform (3 × 20 ml). The combined organic portions were washed with brine (5 ml), dried over magnesium sulfate and the solvents were evaporated under diminished pressure. Recrystallization of the residue from dilute acetic acid (1 : 1) afforded 4·2 g (90%) of the product *IIIa*, m.p. 111—113°C. IR spectrum: 3 025 (CH arom.); 1 768, 1 735, 1 710 (C=O lactone, ester, carboxyl); 1 603, (C=C arom.); 1 273, 1 160 (C—O ester). ^{1}H NMR spectrum: 1·96 m, 2 H (CH_2); 2·30—3·00 m, 10 H (2 × CH, 3 × CH_2CO); 4·17 m, 2 H (CH_2O); 5·15 t, 1 H (CH—O, $J = 6$); 5·40 m, 1 H (CH—O); 7·35—8·15 m, 9 H (H arom.). Mass spectrum, *m/z* (%): 466 (M^+, 20), 198 (90, $C_6H_5C_6.H_4COOH$), 181 (100, $C_6H_5C_6H_4CO$), 153 (18, $C_6H_5C_6H_4$), 152 (19, $C_6H_5C_6H_4 - 1$), 83 (9), 73 (8), 71 (10), 69 (12).

[3a*S*(3aα,4α,5β,6aα)]-(+)-[5-(1,1′-Biphenyl-4-carbonyloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-on-4-yl]methyl Hydrogen Pentanedioate (*IIIb*)

The usual processing of the ephedrine salt *VIIb* (6·3 g, 10 mmol) afforded 4·5 g (96%) of the crude product, $[\alpha]_D^{22}$ +83·0°; which upon recrystallization from dilute acetic acid (1 : 1) gave 3·2 g (68%) of lactone-acid *IIIb*, m.p. 111—114°C. IR spectrum: 3 025 (CH arom.); 1 770, 1 740, 1 715 (C=O lactone, ester, carboxyl); 1 603, (C=C arom.); 1 275, 1 160 (C—O ester). ^{1}H NMR spectrum: 1·96 m, 2 H (CH_2); 2·34—3·05 m, 10 H (2 × CH, CH_2, 3 × CH_2CO); 4·18 m, 2 H (CH_2O); 5·15 t, 1 H (CH—O, $J = 6$); 5·38 m, 1 H (CH—O); 7·34—8·06 m, 9 H (H arom.). Mass spectrum, *m/z* (%): 466 (M^+, 19), 198 (93, $C_6H_5C_6H_4COOH$), 181 (100, $C_6H_5C_6H_4CO$), 153 (22, $C_6H_5C_6H_4$), 152 (23, $C_6H_5C_6H_4 - 1$), 83 (11), 73 (13), 71 (11), 69 (13), 60 (12), 57 (20).

[3a*R*(3aα,4α,5β,6aα)]-(−)-5-(1,1′-Biphenyl-4-carbonyloxy)hexahydro-4-hydroxymethyl-2*H*-cyclopenta[*b*]furan-2-one (*Ia*)

Concentrated sulfuric acid (0·6 ml) was added at 60—65°C to a stirred solution of lactone-acid *IIa* (34·0 g; 74 mmol) in methanol (180 ml). The mixture was refluxed for 14 h, cooled and neutralized with triethylamine (4 ml). The solvents were distilled off in vacuo, the oily residue was dissolved in chloroform (150 ml), the solution was washed with water (2 × 30 ml) and dried over magnesium sulfate. After evaporation of solvents, the solid crystalline residue (40 g) was crystallized from ether to give 25 g (96%) of product, m.p. 131—132°C; $[\alpha]_D^{22}$ −86·0°, which on further crystallization from dichloromethane–heptane (1 : 1) afforded 22·1 g (84%) of Corey lactone *Ia*, m.p. 131—133°C, $[\alpha]_D^{22}$ −88·9° (*c* 1, $CHCl_3$) (identical with the published[7] data). IR spectrum: 3 020, 2 950, 2 880 (CH arom.); 1 770, 1 710 (C=O lactone, ester); 1 610, 1 490, 1 460, 1 420, 1 408, 1 328 (C=C arom.); 1 280 (C—O ester). ^1H NMR spectrum: 2·20—2·93 m, 6 H (2 × CH, 2 × CH_2); 3·70 m, 2 H (CH_2O); 5·10 m, 1 H (H-6); 5·42 m, 1 H (H-5); 7·40—8·10 m, 9 H (H arom.). Mass spectrum, *m*/*z* (%): 352 (M^+, 34), 198 (82, $C_6H_5C_6H_4COOH$); 181 (100, $C_6H_5C_6H_4CO$); 153 (27, $C_6H_5C_6H_4$); 152 (31, $C_6H_5C_6H_4$ − 1); 125 (10).

Analogously, the lactone-acid *IIIb* (4·7 g; 9·9 mmol) gave 2·05 g (59%) of lactone *Ia* which had identical physico-chemical characteristics as a standard.

[3a*S*(3aα,4α,5β,6aα)]-(+)-5-(1,1′-Biphenyl-4-carbonyloxy)-4-hydroxymethyl-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (*Ib*)

A mixture of compound *IIb* (17·0 g; 37 mmol), methanol (100 ml) and conc. sulfuric acid (0·5 ml) was refluxed for 15 h, cooled, neutralized with triethylamine (3 ml) and the solvents were evaporated under diminished pressure. The dry residue (22·3 g) was dissolved in chloroform (100 ml), the solution was washed with water (30 ml), dried over magnesium sulfate and the solvent was distilled off. The solid residue (19 g) was chromatographed on a column of silica gel (250 g, eluent methanol (0—3%) in chloroform) to give 12 g of product which was dissolved in dichloromethane (20 ml) and hexane was added dropwise to turbidity (6·5 ml). After standing at room temperature for 24 h, the needle-like crystals were collected and washed with dichloromethane–hexane (1 : 1); yield 8·05 g of compound, m.p. 134—135°C. Further portion (2·3 g) was obtained by crystallization from the mother liquors. Total yield 10·35 g (78%) of lactone *Ib*, m.p. 134 to 135°C, $[\alpha]_D^{22}$ +88·6° (*c* 1, $CHCl_3$). IR spectrum: 3 025, 2 950, 2 880 (CH arom.); 1 770, 1 710 (C=O lactone, ester); 1 610, 1 490, 1 460, 1 420, 1 408, 1 328, 1 312 (C=C arom.); 1 280 (C—O ester). ^1H NMR spectrum: 2·20—2·93 m, 6 H (2 × CH, 2 × CH_2); 3·70 m, 2 H (CH_2O); 5·10 m, 1 H (H-6); 5·42 m, 1 H (H-5); 7·40—8·10 m, 9 H (H arom.). Mass spectrum, *m*/*z* (%): 352 (M^+, 35), 198 (81, $C_6H_5C_6H_4COOH$); 181 (100, $C_6H_5C_6H_4CO$); 153 (25, $C_6H_5C_6H_4$); 152 (30, $C_6H_5C_6H_4$ − 1); 125 (8).

Analogously, the lactone-acid *IIIb* (10 g, 21 mmol) afforded 4·5 g (60%) of product *Ib*, m.p. 134—135°C, $[\alpha]_D^{22}$ +88·2°, of spectral characteristics identical with those of a standard.

[3a*R*(3aα,4α,5β,6aα)]-(−)-5-Hydroxy-4-hydroxymethyl-hexahydro-2*H*-cyclopenta[*b*]-furan-2-one (*IXa*)

Anhydrous potassium carbonate (1·4 g) was added to a solution of lactone *Ia* (2·1 g, 6 mmol) in dichloromethane–anhydrous methanol (1 : 1, 30 ml). After stirring for 3 h at room temperature, the solid was filtered off, the filtrate neutralized with dilute hydrochloric acid to pH 5·5—6 and the solvents were evaporated. Crystalization of the residue from ethyl acetate–acetone gave 872 mg (85%) of diol *IXa*, m.p. 116—118°C, $[\alpha]_D^{22}$ −43·4° (*c* 1, CH_3OH) (reported[10] m.p. 116—117°C, $[\alpha]_D^{22}$ −43·2°).

[3a*S*(3aα,4α,5β,6aα)]-(+)-5-Hydroxy-4-hydroxymethyl-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (*IXb*)

A mixture of lactone *Ib* (2·5 g, 7·1 mmol), a dichloromethane–anhydrous methanol mixture (1 : 1, 36 ml) and anhydrous potassium carbonate (1·7 g) was stirred at room temperature for 3 h. The usual work up procedure gave 925 mg (77%) of diol *IXb*, m.p. 115—117°C (ethyl acetate–acetone), $[\alpha]_D^{22}$ +43·6° (*c* 1, CH_3OH) (reported[25] m.p. 116—117·5°C, $[\alpha]_D^{22}$ +43·5° (*c* 1, CH_3OH)).

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