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Asymmetric Synthesis with Sugar Derivatives. I. The Conjugate Additions of Grignard Reagents to α, β-Unsaturated Esters of Sugar Derivatives

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Partial asymmetric syntheses were carried out in the reaction of Grignard reagents with crotonic and cinnamic esters of 1, 2 : 5, 6-di-*O*-cyclohexylidene-D-glucose, 1, 2 : 5, 6-di-*O*-isopropylidene-D-glucose, 1, 2-*O*-isopropylidene-5-deoxy-D-xylose and (−)-menthol. The reaction of 3-*O*-crotonyl-1, 2 : 5, 6-di-*O*-cyclohexylidene-D-glucose (Ic) with phenylmagnesium bromide, followed by the hydrolysis of the resulting ester, gave (−)-3-phenylbutyric acid (III) in 33% optical and 12% synthetic yields, while in the presence of cuprous chloride as a catalyst, III was obtained in 74% and 58% yields respectively. The reaction of 3-*O*-crotonyl-1, 2-*O*-isopropylidene-5-deoxy-D-xylose (Ie) with phenylmagnesium bromide gave (+)-acid (III) without cuprous chloride in 16% optical and 32% synthetic yields and (−)-acid (III) with cuprous chloride, in 58% and 61% yields respectively. The reaction of 3-*O*-cinnamoyl-1, 2 : 5, 6-di-*O*-cyclohexylidene-D-glucose (IVc) with benzylmagnesium chloride, followed by the saponification of the resulting ester, gave (−)-3, 4-diphenylbutyric acid (VI) in 18% optical and 62% synthetic yields without cuprous chloride, and in 17% and 58% yields with cuprous chloride. In the formation of acid (VI), cuprous chloride seemed to have no effect on optical and synthetic yields nor on the change in the sign of optical rotation. The steric courses of these reaction are discussed.

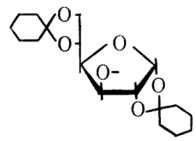
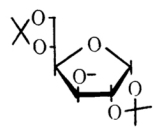
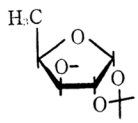
Numerous partial asymmetric syntheses have been made in an attempt to introduce a new asymmetric center into a carbon chain of organic acid under the influence of an optically active alkoxy group on the carbonyl carbon of the carboxylic ester. For example, 2-hydroxy-2-phenylpropionic acid (atrolactic acid) was asymmetrically synthesized by Grignard reaction from (−)-menthyl,[1] (+)-1-(2′, 4′, 6′-tricyclohexylphenyl) - ethyl[2] and (+)-α-phenyldihydrothebaine-isomethine[3] phenylglyoxylates, respectively, in 17, 66 and 91% optical yields. In these asymmetric syntheses, it is evident that the esters' asymmetric centers derived from the naturally-occurring terpenes or alkaloids play an important role in making one transient comformation of esters predominant over the others. However, sugar derivatives have been utilized as the alcohol to only a negligible extent in this field. Many oxygens on the asymmetric carbons of a sugar derivative are supposed to show a particular stereoselectivity in such reactions when organometallic compounds or metal catalysts are used. Thus, the authors were interested in the stereoselective addition of metallic compounds to the α, β-unsaturated esters of sugar derivatives.

Recently, Inouye and Walborsky[4] reported that a partial asymmetric synthesis of (+)-3-phenylbutyric acid (III) was achieved (5.4% optical yield) by the addition of phenylmagnesium bromide to (−)-menthyl crotonate (Ia), followed by the hydrolysis of the adduct (IIa) (Eq. 1); moreover, when the catalytic amount of cuprous chloride was added to the reaction mixture, the optical rotation of the acid III obtained had an opposite sign and its synthetic yield was somewhat increased, compared with the case of the absence of cuprous catalyst. However, the stereochemical course of the reactions has never been established. As to the conjugate addition of Grignard reagent to

$$\underset{\text{I}}{CH_3CH{=}CHC(=O)R} \xrightarrow[2)\ H_2O]{1)\ C_6H_5MgBr} \underset{\text{II}}{CH_3CHCH_2C(=O)R}\ (C_6H_5) \xrightarrow{KOH} \underset{\text{III}}{C_6H_5CHCH_2COOH}\ (CH_2C_6H_5) \quad (1)$$

$$\underset{\text{IV}}{C_6H_5CH{=}CHC(=O)R} \xrightarrow[2)\ H_2O]{1)\ C_6H_5CH_2MgCl} \underset{\text{V}}{C_6H_5CHCH_2C(=O)R}\ (CH_2C_6H_5) \xrightarrow{KOH} \underset{\text{VI}}{C_6H_5CHCH_2COOH}\ (CH_2C_6H_5) \quad (2)$$

1) A. McKenzie, *J. Chem. Soc.*, **1904**, 1249.
2) V. Prelog, Eva Phillin, E. Watanabe and M. Wilhelm, *Helv. Chim. Acta*, **39**, 1086 (1956).
3) J. A. Berson and M. A. Greenbaum, *J. Am. Chem. Soc.*, **80**, 445 (1958).
4) Y. Inouye and H. M. Walborsky, *J. Org. Chem.*, **27**, 2706 (1962).

R = a, (−)-Menthoxy
b, (±)-*sec*-Butoxy
c, 
d, 
e, 

crotonate, Munch-Petersen[5] described that (±)-*s*-butyl crotonate (Ib) with phenylmagnesium bromide gave (±)-*s*-butyl 3-phenylbutyrate (IIb) in a 67% yield in the presence of cuprous chloride, which had been known to catalyze predominantly a 1, 4-addition over a 1, 2-addition in the α, β-unsaturated carbonyl system (Eq. 1). He and his co-workers[6] also found that (—)-*s*-butyl cinnamate (IVb) with benzylmagnesium chloride gave (±)-*s*-butyl 3, 4-diphenylbutyrate (Vb) in a 63% yield; in this case, cuprous chloride has no catalytic effect (Eq. 2).

The present authors have studied[7] the partial asymmetric syntheses achieved by the 1, 4-addition of phenylmagnesium bromide to crotonic esters (Ic, Id and Ie) and of benzylmagnesium chloride to cinnamic esters (IVc, IVd and IVe), using three kinds of sugar derivatives, 1, 2 : 5, 6-di-*O*-cyclohexylidene-D-glucose (VII),[8] 1, 2 : 5, 6-di-*O*-isopropylidene-D-glucose (VIII)[9] and 1, 2-*O*-isopropylidene-5-deoxy-D-xylose (IX),[10] in the presence or absence of a cuprous catalyst.

Procedure and Results

The crotonic ester of each sugar derivative (Ic, Id and Ie) was prepared by the addition of crotonyl chloride to a solution of the sodium alcoholate of each sugar derivative in toluene, according to a modification of the method of Otey et al.[11] This method gave a better yield than the general reaction of the free hydroxy-group of a sugar with crotonyl chloride in pyridine-chloroform. The cinnamic ester of each sugar derivative (IVc, IVd and IVe) was obtained in a fairly good yield by the reaction of each sugar derivative with cinnamoyl chloride in pyridine-chloroform.

Their yields, physical properties and analyses are listed in Table III.

The Grignard reactions were carried out in ether at temperature from −17°C to −15°C by a method based on the procedure of Munch-Petersen.[12] A catalytic amount of cuprous chloride was added in four portions at regular intervals during the addition of the esters to the Grignard reagents. The adducts were not purified but were completely saponified by refluxing them with a large excess of potassium hydroxide in aqueous alcohol for 16 hr. The racemization of the asymmetric carbon atoms of 3-phenylbutyric acid (III) and 3, 4-diphenylbutyric acid (VI) did not occur during saponification (See Ref. 4 and the Experimental Section). 1, 2 : 5, 6-Di-*O*-cyclohexylidene-D-glucose (VII) and 1, 2 : 5, 6-di-*O*-isopropylidene-D-glucose (VIII) were recovered in 60—85% yields, but the recovery of 1, 2-*O*-isopropylidene-5-deoxy-D-xylose (IX) was poorer because the compound was readily soluble in water.

The 3-phenylbutyric acid (III) obtained was identified by a comparison of its infrared spectrum with that of an authentic sample.[4] Elemental analysis of the crystalline anilide of III was performed. The optical[13] and synthetic yields of III are shown in Table I.

In this reaction, Ic gave (−)-acid (III) in 33% optical and 12% synthetic yields without cuprous chloride (Exp. 3), while in the presence of cuprous chloride, it gave III with the same sign of optical rotation as that in the case of no catalyst in increased optical and synthetic yields, 74% and 58% respectively (Exp. 4). The effect of cuprous chloride on the reaction of Id (Exp. 6 and 7) showed a same tendency as that on the reaction of Ic. On the contrary, it is noteworthy that the reaction of Ie (Exp. 8) gave (+)-acid (III) in 16% optical and 32% synthetic yields without cuprous chloride, but (−)-acid (III) was afforded in much better optical (58%) and synthetic (61%) yields with cuprous chloride (Exp. 9). However, Ia gave (+)-acid (III) without cuprous catalyst in poor optical yields under the conditions of both Inouye[4] and us.

The 3, 4-diphenylbutyric acid (VI) obtained by the reaction of each sugar ester (IVc, IVd and IVe) or (−)-menthyl cinnamate (IVa) with benzylmagnesium chloride was identified by a comparison

5) J. Munch-Peterson, ibid., **22**, 170 (1957).
6) J. Munch-Peterson, P. Møller Jørgensen and S. Refn, *Acta Chem. Scand.*, **13**, 1955 (1959).
7) Most of the results and assumptions presented in this paper were reported at the 18th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1965.
8) R. C. Hockett, R. E. Miller and A. Sacttergood, *J. Am. Chem. Soc.*, **71**, 3072 (1949).
9) W. L. Glen, G. S. Myers and G. A. Grant, *J. Chem. Soc.*, **1951**, 2568.
10) P. A. Levene and J. Compton, *J. Biol. Chem.*, **111**, 325 (1935).
11) F. H. Otey and C. L. Mehltretter, *J. Am. Oil. Chemists' Soc.*, **35**, 455 (1958).
12) J. Munch-Petersen and V. K. Andersen, *Acta Chem. Scand.*, **15**, 271 (1961).
13) Calculated on $[\alpha]_D$ −57° : H. Rupe (*Ann.*, **369**, 311 (1909)) reported $[\alpha]_D^{20}$ −57.23° (α = −5.03, benzene).

TABLE I. ASYMMMETRIC SYNTHESES OF 3-PHENYLBUTYRIC ACID (III)

Ester	Exp. No.	Cat.	Optical yield %	Synthetic yield %	[α]D Crude	[α]D Pure (concn. in benzene)	Temp., °C	B. p. (0.5—1 mmHg) °C
Ia	1	no	9	51	+4°	+5° (7.61)	18	100—102
	2	Cu_2Cl_2	5	42	−0.0°	−3° (10.2)	18	98—103
	*1	no	5	46.1	—	+3.1 (10.3)	25	113—115*4
	*1	Cu_2Cl_2	10	63.5	—	−5.9°(—)	25	—
Ic	3	no	33	12	−14°	−19° (5.05)	20	98—100
	4	Cu_2Cl_2	74	58	−35°	−42° (4.01)	20	97— 99
Id	5	no	32	12	−14°	−18° (5.49)	20	97—100
	6	Cu_2Cl_2	68	50	−29°	−39° (5.11)	20	102—105
	7*2	Cu_2Cl_2	70	44	−36°	−40° (3.99)	16	104—106
Ie	8	no	16	32	+ 4°	+ 9° (5.54)	20	103—107
	9	Cu_2Cl_2	58	61	−22°	−33° (4.55)	18	97—100

Anilides of III

Ester	Exp. No.	n_D	Temp. °C	M. p. °C	[α]D (concn. in acetone) Temp. °C	Anal.*3 (Found) %, C	H	N
Ia	1	1.5153	17	135—137	+2° (5.48) 28	80.62	7.17	5.69
	2	1.5161	18	136—138	−1° (5.87) 25	80.15	7.25	5.82
	*1	1.5150	25	—	— — —	—	—	—
	*1	—	—	—	— — —	—	—	—
Ic	3	1.5179	19	134—135	−12° (5.47) 25	80.39	7.08	5.56
	4	1.5182	16	131—141	−25° (5.89) 18	80.13	6.80	5.82
Id	5	1.5179	19	134—136	−12° (5.56) 25	80.54	7.22	5.67
	6	1.5180	20	133—137	−24° (5.48) 28	80.58	7.05	5.65
	7*2	1.5189	16	133—140	−25° (3.52) 28	80.23	7.12	5.69
Ie	8	1.5168	20	132—136	+ 5° (5.83) 18	80.67	6.99	5.71
	9	1.5160	18	133—140	−22° (5.24) 18	80.10	6.86	5.83

*1 Data of Inouye et al. Ref. 4
*2 Alkaline saponification for 5 hr.
*3 Calcd. for $C_{16}H_{17}NO$: C, 80.36; H, 7.16; N, 5.85%
*4 3 mmHg

TABLE II. ASYMMETRIC SYNTHESES OF 3,4-DIPHENYLBUTYRIC ACID (VI)

Ester	Exp. No.	Cat.	Optical yield %	Synthetic yield %	[α]D Crude	[α]D Pure	Temp., °C (concn. in benzene)	B. p. (0.5—1 mmHg) °C	M. p. °C	Anal.*2 (Found) % C	H
IVa	10	no	32	59	−25°	−19° (6.04)	20	155—162	81—92	80.15	6.51
	11	Cu_2Cl_2	27	61	−24°	−16° (6.06)	20	155—160	81—91	80.01	6.64
IVc	12	no	18	62	− 9°	−11° (8.03)	20	150—158	84—93	80.27	6.47
	13*1	no	17	62	−10°	−10° (5.39)	20	155—165	89—93	80.23	6.78
	14	Cu_2Cl_2	17	58	− 8°	−10° (6.23)	18	155—158	86—93	79.89	6.50
IVd	15	no	18	49	−12°	−11° (9.63)	20	150—158	85—93	80.08	6.65
	16	Cu_2Cl_2	22	40	−12°	−13° (6.20)	15	148—153	84—92	79.99	6.41
IVe	17	no	18	53	− 7°	−11° (3.78)	20	147—149	84—94	79.70	6.34
	18	Cu_2Cl_2	17	56	− 8°	−10° (6.04)	20	158—167	80—89	80.05	6.95

*1 Alkaline saponification for 5 hr.
*2 Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%

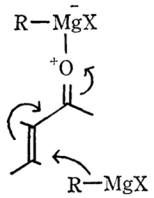
TABLE III. SUGAR ESTERS OF CROTONIC AND CINNAMIC ACIDS

Ester	Yield %	M. p. °C	[α]D (concn. in benzene) Temp. °C	IR $\nu_{max}^{cm^{-1}}$ (in $CHCl_3$) C=O	C=C	Molecular formula	C, % Found	C, % Calcd.	H, % Found	H, % Calcd.
Ic	76	glass	−18° (4.97) 18	1725	1660	$C_{22}H_{32}O_7$	64.61	64.68	8.06	7.90
Id	52	64—66	−36° (2.83) 18	1729	1661	$C_{16}H_{24}O_7$	58.70	58.52	7.14	7.37
Ie	28	47—49	+31° (2.80) 18	1723	1661	$C_{12}H_{18}O_5$	59.79	59.49	7.25	7.49
IVc	39	132—134	−54° (4.96) 22	1717	1641	$C_{27}H_{34}O_7$	68.84	68.92	6.87	7.28
IVd	76	glass	−70° (3.28) 18	1715	1639	$C_{21}H_{26}O_7$	64.84	64.60	6.52	6.71
IVe	84	73—75	+44° (4.72) 22	1715	1640	$C_{17}H_{20}O_5$	66.68	67.09	6.40	6.22

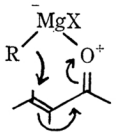
of its infrared spectrum with the sample prepared from an authentic ester (Vb).[6] Optically pure VI, $[\alpha]_D$ −60°, was obtained for the first time by the resolution of quinine salt in the present experiment. The optical[14] and synthetic yields of VI are shown in Table II. The reactions of IVc, IVd and IVe all gave (−)-acid (VI) in a 18% optical yield in the absence of cuprous chloride (Exp. 12, 15 and 17) and in 17, 22 and 17% yields respectively in the presence of cuprous chloride (Exp. 14, 16 and 18). The reaction of IVa gave (−)-acid (VI) in a 32% optical yield without cuprous chloride (Exp.10). It is interesting that cuprous chloride seems to have no effect on the optical and synthetic[6] yields in the reactions of cinnamates with benzylmagnesium chloride.

Discussion

Recently Munch-Petersen et al.[15] suggested that there were two types of mechanisms in the addition of Grignard reagents to conjugated esters, depending on the natures of the substrate and the Grignard reagent, i. e., the carbanion mechanism, A, and the cyclic mechanism, B. These mechanisms have



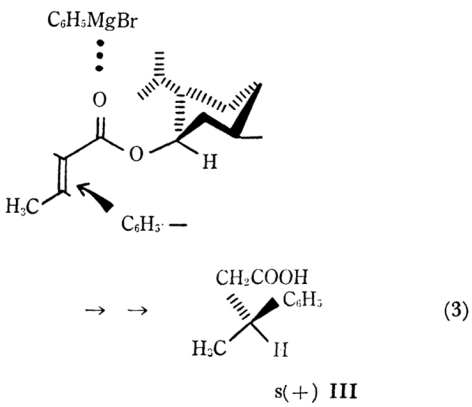
A



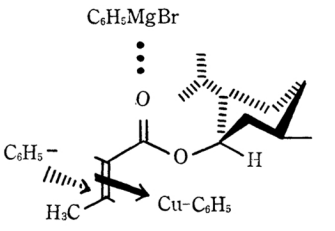
B

been considered to be irreversible. They also reported that the mode of the catalytic action of cuprous chloride was still obscure, but that it exerted its effect by way of complex formation between the cuprous ion and the carbon-carbon double bond.

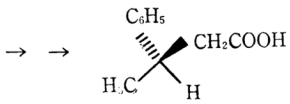
The results may be explained by the following



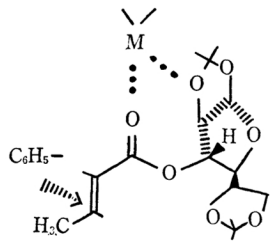
s(+) III (3)



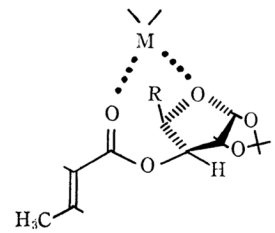
X



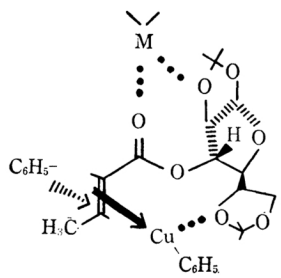
R(−) III (4)



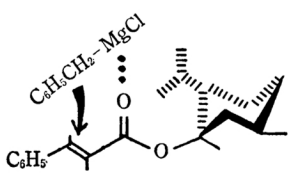
XI



XII



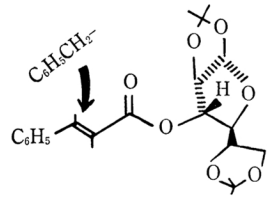
XIII



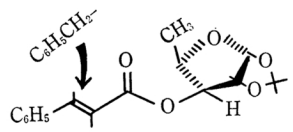
XIV

14) Calculated on $[\alpha]_D$ −60°.

15) S. Jacobsen, A. Jart, T. Kindt-Larsen, I. G. K. Andersen and J. Munch-Petersen, *Acta Chem. Scand.*, **17**, 2423 (1963).



XV



XVI

M=Mg or Cu

assumptions. If Prelog's rule[16] can be applied to these asymmetric syntheses, on the reaction of (−)-menthyl crotonate (Ia) the phenyl group in the Grignard reagent would preferrably enter from the least-hindered side of the double bond in the mechanism A to give s-(+)-acid (III) predominantly, as is shown in Eq. 3, because the absolute configurations of (−)-menthol[17] and III[18] have been established to be as depicted in Eqs. 3 and 4. In the presence of cuprous chloride, the initial attack of the phenyl copper[15,19] prepared from cuprous chloride and the Grignard reagent would be towards the least hindered side of the double bond to form a complex (X); then the phenyl group of the Grignard reagent or phenyl copper would enter from the other side to give R-(−)-acid (III) predominantly (Eq. 4).

On the reaction of both the sugar esters, Ic and Id, the model XI is expected to be most stable, since Prelog's model XII has the steric hindrance of the substituent at C-4 of the furan ring against the ester carbonyl. Furthermore, magnesium or copper could coordinate[20] with the unshared electron pairs of oxygen to make this model XI more rigid. This force is very useful in preventing free rotation between the sugar part and the acid part. Consequently, the attack of the phenyl group from the front side of the double bond according to the mechanism A would be sterically hindered by the 5, 6-*O*-cyclohexylidene group of Ic or the 5, 6-*O*-isopropylidene group of Id, and R-(−)-acid (III) would be more predominantly produced. When cuprous chloride is present, the oxygen at C-5 of glucose would contribute to form a copper complex which would fix the conformation as is shown in XIII.[21] This model (XIII) predicts not only that R-(−)-acid (III) will predominate, but that the optical yield will be high.

On the reaction of Ie, it is considered that the model XII (R=CH_3) would be rather stable because of the decrease of the bulkiness of the substituent at C-4 of the furan ring. Thus, the phenyl group would attack from the front side of the double bond, as a result of the steric effect of the methyl group, to give s-(+)-acid (III) predominantly by the mechanism A. Although the mode of action of cuprous chloride is not clear in this case, the increase in the optical yield with cuprous chloride suggests that the oxygen at C-2 of the furan ring participates in the formation of the similar chelation, as is shown in XIII. The acid III obtained, therefore, has a R-(−)-configuration in a good optical yield.

Meanwhile, the absence of any catalytic effect of cuprous chloride on the formation of 3, 4-diphenylbutyric acid (VI) suggests that the esters of cinnamic acid would react with the Grignard reagent according to the mechanism B. Though the absolute configuration of VI has not yet been established, the formation of VI, which has the same sign of optical rotation in every synthesis, may be attributed to the steric effect of the isopropyl group in (−)-menthol (XIV: Prelog's model), the 1, 2-*O*-cyclohexylidene or the 1, 2-*O*-isopropylidene group (XV: the most stable model) in IVc and IVd, and the methyl group (XVI: Prelog's model) in IVe, which block the backside-attack of the benzyl group on the double bond. In these models, the optical yields of VI prepared from the sugar esters would be lower than that of VI prepared from (−)-menthyl cinnamate (IVa), because there is no fixation between the ester carbonyl and the sugar part.

Experimental[22]

The Sugar Ester of Crotonic Acid.—The esters were prepared by a modification of the method of Otey et al.[11] Into a solution of 0.075 mol. of the sugar derivative, 1, 2 : 5, 6-di-*O*-cyclohexylidene-D-glucose (VII), 1, 2 : 5, 6-di-*O*-isopropylidene-D-glucose (VIII) or 1, 2-*O*-isopropylidene-5-deoxy-D-xylose (IX), in 100 ml. of dry toluene, there was stirred 6.0 g. of sodium powder in three portions over a 2 hr. period at room temperautre; the stirring was then continued overnight. To the solution, decanted from excess sodium, there was then stirred, drop by drop, a solution of 0.075 mol. of crotonyl chloride in 20 ml. of toluene

16) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).
17) A. J. Birch, *Ann. Reports*, **47**, 192 (1950); A. Fredga and J. K. Miettine, *Acta Chem. Scand.*, **1**, 371 (1947); J. Read and W. J. Grubb, *J. Chem. Soc.*, **1939**, 1779.
18) V. Prelog and H. Scherrer, *Helv. Chim. Acta*, **42**, 2227 (1959).
19) H. Gilman, R. G. Jones and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952).
20) M. L. Wolfrom and S. Hanessian, ibid., **27**, 1800 (1962).
21) H. B. Henbest and B. Nicholls (*J. Chem. Soc.*, **1959**, 227) reported a similar phenomenon in the methoxy-mercuration of 4-substituted cyclohexenes.
22) All melting points and boiling points are uncorrected. The infrared spectra were taken with a Perkin-Elmer 521 grating infrared spectrophotometer. The optical rotations were performed with a Hitachi No. 070-1 polarimeter, using a 1 dm. tube. Elemental analyses were performed by the Institute of Physical and Chemical Research.

at 0—5°C until the reaction mixture became acidic, a large excess of crotonyl chloride being avoided. Saturated aqueous sodium bicarbonate (ca. 40 ml.) was then added immediately with vigorous stirring to the reaction mixture, which was then extracted with ether and the ether layer was washed with water, dried over sodium sulfate and distilled. The residue was dissolved in chloroform-ligroin (1 : 1 v./v.) and chromatographed on a column of activated alumina. Elution with the same solvents first gave the pure sugar ester. The yield, physical properties and analytic results are recorded in Table III.

The Sugar Ester of Cinnamic Acid.—Into a solution of 0.20 mol. of the sugar ester, 1, 2 : 5, 6-di-*O*-cyclohexylidene-D-glucose (VII), 1,2 : 5,6-di-*O*-isopropylidene-D-glucose (VIII) or 1, 2-*O*-isopropylidene-5-deoxy-D-xylose (IX) in a mixture of 100 ml. of dry pyridine and 100 ml. of dry benzene, there was stirred a solution of 0.22 mol. of cinnamoyl chloride in 50 ml. of dry benzene for about 0.5 hr. at −5—0°C. After it had been stirred for 1 hr., the reaction mixture was allowed to stand overnight at room temperature and then poured into ice water. The mixture was then extracted with ether (or chloroform for VII). The extract was washed with ice water, mixed with ice, washed succesively with iced 3% aqueous sulfuric acid, cold water, saturated aqueous sodium bicarbonate and water, and dried over sodium sulfate. After the solvent had been removed, the residue was dissolved in chloroform-ligroin (1 : 1 v./v.) and chromatographed on a column of activated alumina. Elution with the same solvents first gave the pure sugar ester, except for IVc, which was recrystallized from ligroin. The yield, the physical properties and the analytical results are recorded in Table III.

The Asymmetric Synthesis of 3-Phenylbutyric Acid (III).—A solution of Grignard reagent was prepared from 1.82 g. (0.075 g.-atom) of magnesium and 11.8 g. (0.075 mol.) of bromobenzene in 60 ml. of dry ether. Into this solution of phenylmagnesium bromide, there was added, drop by drop, a solution of 0.03 mol. of the ester Ia,[13] Ic, Id or Ie, in 60 ml. of dry ether (dry tetrahydrofuran for Ic) at −17—−15°C for 1 hr. After the addition had been completed, the stirring was continued at the same temperature for 0.5 hr. and then at room temperature for 0.5 hr. The reaction mixture was poured into saturated aqueous ammonium chloride (250 ml.) with vigorous shaking. The ether layer was separated, and the water layer was extracted with ether. The combined ether layers were washed with water, dried over sodium sulfate, and removed. The residual oil, the infrared spectrum of which did not show the presence of the starting ester, was not purified but was hydrolyzed by reflux with 16.8 g. (0.3 mol.) of potassium hydroxide in a solution of 10 ml. of water and 70 ml. of ethanol for 16 hr. After the ethanol had been removed, the resulting solution, diluted with 50 ml. of water, was extracted with 100 ml. of ether and then with 100 ml. of chloform. The combined ether-chloroform extracts were treated as will be descrived below. The water layer was acidified with 6 N hydrochloric acid on cooling and extracted with ether. After the ether had been removed, 50 ml. of saturated aqueous sodium bicarbonate was added with vigorously shaking. The resulting solution was extracted with ether, and the water layer was acidified with 6 N hydrochloric acid and extracted with ether. The ether layer was washed with water, dried over sodium sulfate and then removed. The residue, the optical rotation of which had been measured, was distilled to give pure 3-phenylbutyric acid (III). Its infrared spectrum was identified with that of an authentic sample.[4] The yield and physical properties for III are recorded in Table I.

The ether-chloroform extracts were washed with water, dried over sodium sulfate, and removed. The residue, which had no absorption of ester carbonyl in the infrared spectrum, gave 1, 2 : 5, 6-di-*O*-cyclohexylidene-D-glucose (VII) or 1, 2 : 5, 6-di-*O*-isopropylidene-D-glucose (VIII) by recrystallization from ligroin in a 60—85% yield. 1, 2-*O*-Isopropylidene-5-deoxy-D-xylose (IX) was recovered in a 30—50% yield by extracting the residue with 23 ml. of water, and then extracting it with 150 ml. of ether.

In the case of the addition of cuprous chloride to the reaction mixture, the experiment was carried out similarly except that when the ester (0.03 mol.) was added, 107 mg. (1.4 mol. percent with respect to Grignard reagent) of cuprous chloride was added concurrently in four portions at the interval of 15 min., the first portion being added just before the addition of the ester and the last one, just after.

The Anilide of 3-Phenylbutyric Acid (III). — A mixture of 500 mg. (0.0030 mol.) of the acid III obtained by each of the above asymmetric syntheses and 1.0 g. (0.0084 mol.) of thionyl chloride was refluxed for 0.5 hr. To the solution there was added a solution of 2.0 g. (0.0215 mol.) of aniline in 15 ml. of dry benzene on cooling, and the mixture was refluxed for 2 min. After cooling, 20 ml. of ether was added and the mixture was washed successively with 5 ml. of water, 5 ml. of 6 N hydrochloric acid, 5 ml. of water, 5 ml. of 3 N sodium hydroxide, and 10 ml. of water. The organic solvents were removed, and the residue was recrystallized once from 50% aqueous ethanol, with treatment of charcol, to give anilide in a 80—95% yield. The physical properties and the results of the analysis for anilide are recorded in Table I.

(±)-3, 4-Diphenylbutyric Acid (VI).[23] — (±)-*s*-Butyl-3, 4-diphenylbutyrate (Vb), b. p. 150—155°C/1 mmHg, n_D^{20} 1.5356 (lit.[6] b. p. 157°C/1 mmHg, n_D^{20} 1.5333) was prepared by the method described by Munch-Petersen et al.[6] A mixture of 2.0 g. (0.0067 mol.) of Vb, 20 ml. of ethanol and 5.0 g. (0.089 mol.) of potassium hydroxide in 5.0 ml. of water was refluxed for 3 hr. After it had then been concentrated, 50 ml. of water was added and the solution was extracted with chloroform. The water layer was acidified with 6 N hydrochloric acid and extracted with ether. The ether which dried over sodium sulfate was removed, and the resulting product was recrystallized from ligroin - ethyl acetate (1 : 1 v./v.), with treatment of charcol, to give 1.2 g. of (±)-acid (VI), m. p. 94—96°C (lit.[23] m. p. 95—96°C).

Found: C, 79.70; H, 6.60. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

IR λ_{max}^{KBr}: 3030, 2920, 1709, 1435, 1414, 1245 cm^{-1}.
IR ν_{max}^{CHCl}: 3033, 2916, 1708, 1413 cm^{-1}.

The Asymmetric Synthesis of 3, 4-Diphenylbutyric Acid (VI).—A solution of Grignard reagent was prepared from 1.82 g. (0.075 g.-atom) of magnesium

23) S. Ruhemann, *J. Chem. Soc.*, **1910**, 460.

and 9.5 g. (0.075 mol.) of benzylchloride in 60 ml. of dry ether. Into this solution of benzylmagnesium chloride there was then stirred, drip by drop, a solution of 0.03 mol. of the ester IVa,[24] IVc, IVd or IVe in 60 ml. of dry ether (dry tetrahydrofuran for IVc) at −17——15°C for 1 hr; the stirring was then continued at the same temperature for 0.5 hr. and then at room temperature for an additional 0.5 hr. The reaction mixture was poured into saturated aqueous ammonium chloride (250 ml.) with vigorous shaking. The ether layer was separated, and the water layer was extracted with ether. The combined ether layer were washed with water, dried over sodium sulfate, and removed. The residual oil, the infrared spectrum of which did not show the presence of the starting ester, was not purified but was hydrolyzed by refluxing it with 6.2 g. (0.11 mol.) of potassium hydroxide in 5 ml. of water and 75 ml. of ethanol for 16 hr. After the ethanol had been removed and water had been added, the solution was extracted with 100 ml. of ether and 100 ml. of chloroform. The removal of organic solvents gave 1, 2 : 5, 6-di-*O*-cyclohexylidene-D-glucose (VII), 1, 2 : 5, 6-di-*O*-isopropylidene-D-glucose (VIII) or 1, 2-*O*-isopropylidene-5-deoxy-D-xylose (IX) in 80%, 70%, and 55% yields respectively, in the same manner described in the asymmetric synthesis of 3-phenylbutyric acid. The water layer acidified with 6 N hydrochloric acid on cooling and extracted with ether. The ether was washed with water, dried over sodium sulfate, and removed. The residue, the optical rotation of which had been measured, was distilled to give pure 3, 4-diphenylbutyric acid (VI). Its infrared spectrum (in chloroform) was identified with that of a racemic sample prepared from an authentic ester (Vb).[6] The yield, the physical properties and the results of the analysis for VI are recorded in Table II.

In the case of addition of cuprous chloride, the experiment was carried out in the same way described as asymmetric synthesis of 3-phenylbutyric acid (III).

The Resolution of 3, 4-Diphenylbutyric Acid (VI).—A mixture of 4.8 g. (0.02 mol.) of VI, m. p. 89—95°C, $[\alpha]_D^{28}$ −9° (*c* 2.25, benzene) which had been obtained by the above asymmetric synthesis, 6.5 g. (0.02 mol.) of quinine, and 70 ml. of ethanol was boiled until dissolution was complete. After the mixture had stood overnight at 0°C, the crystalline product was separated and washed with small quantities of ethanol. Weight of the dried product, 4.0 g.; $[\alpha]_D^{25}$ −95° (*c* 1.82, chloroform), m. p. 160—162°C. Three further recrystallizations from the same solvent gave 1.8 g. of quinine salt as needles, m. p. 165—166°C, $[\alpha]_D^{25}$ −101° (*c* 1.72, chloroform), as was indicated by its constant rotation when subjected to further recrystallization.

Found: C, 76.61; H, 7.07; N, 4.96. Calcd. for $C_{36}H_{40}N_2O_4$: C, 76.56; H, 7.14; N, 4.96%.

Decomposition in the usual manner gave a specimen of (−)-acid (VI) with a m. p. of 84—86°C, $[\alpha]_D^{28}$ −67° (*c* 0.81, chloroform), which after four recrystallizations from ligroin, had a m. p. of 87—88°C, $[\alpha]_D^{28}$ −60° (*c* 1.92, benzene). Yield, 280 mg. Further recrystallization led to no change in the optical rotation.

Found: C, 80.03; H, 6.50. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

The mother liquors containing the (+)-acid were concentrated and allowed to stand overnight at room temperature. After the precipitate had been filtered out, the filtrate was concentrated to dryness. The re-resulting solid (4.0 g.), which had a m. p. of 65—100°C, $[\alpha]_D^{25}$ −57° (*c* 1.63, chloroform), was recrystallized three times from 50% aqueous ethanol to give quinine salt of (+)-acid (VI) as needles, m. p. 110—111°C, $[\alpha]_D^{25}$ −66° (*c* 1.47 chloroform).

Found: C, 75.13; H, 7.14; N, 4.75. Calcd. for $C_{36}H_{40}N_2O_4 \cdot 1/2H_2O$: C, 75.36; H, 7.20; N, 4.88%.

Decomposition gave (+)-acid (VI) with a m. p. of 82—88°C, $[\alpha]_D^{27}$ +46° (*c* 1.24, benzene), which, after three recrystallizations from ligroin, had a m. p. of 86—88°C, $[\alpha]_D^{28}$ +59° (*c* 1.85, benzene). Yield, 200 mg. Further recrystallization led to no change in the optical rotation.

Found: C, 80.25; H, 6.64. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

IR_{max}^{KBr}: 3023, 2914, 1711, 1659, 1407, 1279 cm^{-1}.

Its infrared spectrum (in chloroform) was identified with that of racemic acid (VI).

Examination for the Optical Stability of (—)-3, 4-Diphenylbutyric Acid (VI) in an Alkaline Solution.—A mixture of 253 mg. of VI, m. p. 87—88°C, $[\alpha]_D^{28}$ −60° (*c* 1.92, benzene), 200 mg. of potassium hydroxide in 0.1 ml. of water and 2.5 ml. of ethanol was treated under the same conditions as that of saponification in the asymmetric synthesis of VI. (−)-Acid (VI) was recovered in a 93% yield; it had a m. p. of 86.5—89.0°C, $[\alpha]_D^{28}$ −61° (*c* 1.61, benzene).

Found: C, 80.24; H, 6.65. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

The infrared spectrum was identical in every respect with that of the starting material.

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24) J. B. Cohen and C. E. Weiteley, *J. Chem. Soc.*, **1901**, 1308; T. P. Hilditch, ibid., **1908**, 6.