709. *Partial Asymmetric Synthesis with Keto-esters. Part I.*

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The interaction of phenylmagnesium bromide with (−)-menthyl lævulate and (−)-menthyl γ-acetyl-*n*-butyrate is accompanied by partial asymmetric synthesis.

Numerous partial asymmetric syntheses were achieved by McKenzie and his co-workers (*J.*, 1904, **85**, 1249 and later papers; for bibliography see Ritchie, *Adv. Enzymology*, 1947, **7**, 65) by the interaction of Grignard reagents and the (−)-menthyl (or bornyl) esters of α-keto-acids, followed by removal by hydrolysis of the " fixed centre of asymmetry " initially present :

$$R{\cdot}CO{\cdot}CO_2R^* \xrightarrow{R'{\cdot}MgX} R{\cdot}CR'(O{\cdot}MgX){\cdot}CO_2R^* \longrightarrow R{\cdot}CR'(OH){\cdot}CO_2R^* \longrightarrow R{\cdot}CR'(OH){\cdot}CO_2H$$

For example, interaction of (−)-menthyl pyruvate and phenylmagnesium halide led to atrolactic acid containing a preponderance of the (+)- over the (−)-form. A much less conclusive result was observed in the reaction between phenylmagnesium bromide and (−)-menthyl lævulate.

For reasons given in Part III (*J.*, 1951, 3227), we have examined, in as quantitative a manner as appeared to us to be possible, the extent of partial asymmetric synthesis in the interaction of phenylmagnesium bromide with a series of (−)-menthyl esters, $CH_3{\cdot}CO{\cdot}[CH_2]_x{\cdot}CO_2{\cdot}C_{10}H_{19}$, where x is 2, 3, 4, and 8, McKenzie's experiments with (−)-menthyl pyruvate ($x = 0$) being repeated in order to obtain figures which would serve as a basis for comparison with those we recorded with other esters. We describe the preparation of (−)-menthyl γ-acetyl-*n*-butyrate, δ-acetyl-*n*-valerate, and ω-acetylpelargonate.

In order to secure reproducibility of result, we first worked out conditions for preparing ethereal phenylmagnesium bromide of known concentration. An excess of magnesium was initially used and the reagent filtered in a closed apparatus in an atmosphere of dry nitrogen.

The desired reaction of the Grignard reagent with the keto-group can be succeeded, if the reagent is present in excess, by reaction with the carbomenthoxy-group, glycols being formed. In order to reduce this secondary reaction to a minimum, the Grignard reagent was added to a stirred or shaken ethereal solution of the keto-ester. As complete and quantitative an analysis as possible was made of the reaction products in every experiment. The (−)-menthyl x-hydroxy-x-phenylalkanecarboxylates were hydrolysed and optical examination was made of either the free hydroxy-acids or their lactones, if such were obtainable.

Interaction of (−)-menthyl pyruvate with 1·25 molecular proportions of phenylmagnesium bromide led finally to a 50% yield of atrolactic acid having $[\alpha]_D^{29}$ +7·8° (in water), a figure in fair agreement with that of McKenzie (*J.*, 1906, **89**, 365), who found $[\alpha]_D^{16}$ +5·4°. From data given by McKenzie and Clough (*J.*, 1910, **117**, 1016) it can be calculated that our product contained 18% of (+)- and 82% of (±)-atrolactic acid.

McKenzie (*J.*, 1906, **89**, 365) treated (−)-menthyl lævulate with phenylmagnesium bromide but obtained strongly coloured products which could not be satisfactorily examined for optical rotation. The interaction of (−)-menthyl lævulate with 1·25 molecular proportions of phenylmagnesium bromide has now been studied in some detail. Preliminary experiments showed that partial asymmetric synthesis did occur, (+)-γ-hydroxy-γ-phenylvaleric acid being formed in slight excess over the (−)-form. The specific rotation of the partially active acid was low, but the corresponding lactone, the formation of which was accompanied by a reversal in sign of rotation and no detectable racemisation, had a relatively high specific rotation. In studying the effect of conditions of reaction on yield and degree of asymmetric synthesis, the lactone was therefore prepared in all cases. The yield of lactone was found to decrease and the degree of asymmetric synthesis to increase with the time taken to mix the ester and Grignard reagent. Stirring of the reaction mixture for a considerable period after mixing also increased the extent of asymmetric synthesis. Thus, while the yield of lactone varied with change of conditions from about 60% to 40%, the specific rotation (in alcohol) varied from $[\alpha]_{5780}^{25}$ −3·0° to −7·0°. Experiments carried out using 2·25 and 4·0 molecular proportions of phenylmagnesium bromide gave γ-phenyl-γ-valerolactone in 26% and 12% yield respectively, and specific rotation $[\alpha]_{5780}$ −2·2° (*c*, 4·55) and $[\alpha]_{5780}$ −3·1° (*c*, 1·625), respectively.

The crude hydroxyphenylvaleric acid often contained a small quantity of an unsaturated acid, doubtless 4-phenylpent-3-enoic acid.* This was readily separable from the lactone. Since

* Geneva nomenclature ($CO_2H = 1$).

the lactone obtained when addition was over a very short time contained a negligible amount of unsaturated acid, the conditions used for the decomposition and subsequent working-up of the Grignard reaction mixture must have been satisfactory. Kloetzel (*J. Amer. Chem. Soc.*, 1940, **62**, 1708) obtained 4-phenylpent-3-enoic acid as the main product of the interaction of methyl β-benzoylpropionate and methylmagnesium iodide, and a similar result had been recorded by Mayer and Stamm (*Ber.*, 1923, **56**, 1424), using the ethyl ester.

Racemic γ-hydroxy-γ-phenylvaleric acid, synthesised from ethyl lævulate and phenylmagnesium bromide, forms a well-defined brucine salt, crystallisation of which from water permits of its optical resolution. The (+)-acid had $[\alpha]_{5461}$ +5·7° ± 0·2° in ethyl alcohol and gave a lactone with $[\alpha]_{5461}$ −61·9° ± 0·4° in ethyl alcohol. The enantiomeric lactone was obtained with $[\alpha]_{5461}$ +61·8° ± 0·5° in ethyl alcohol. The most active lactone derived by partial asymmetric synthesis contains, according to calculation, 12·5% of the (−)- and 87·5% of the (±)-form.

A curious example of partial " spontaneous " resolution was observed when a solution of the lactone having $[\alpha]_{5461}$ −7·0° in aqueous potassium hydroxide was fractionally acidified. The three successive crops had $[\alpha]_{5461}$ +4·95°, −2·54° and +0·03°, the lactones formed from the first 2 crops having $[\alpha]_{5461}$ −52·1° and +26·2° (rotations all in ethyl alcohol). Moreover, fractional acidification of a solution in alkali of the lactone of rotation +26·2° gave as a first crop an acid with $[\alpha]_{5461}$ −4·65° (lactone, +50·8°).

Interaction of (−)-menthyl γ-acetylbutyrate with 1·25 molecular proportions of phenylmagnesium bromide was accompanied by small but definite partial asymmetric synthesis. For optical examination the 5-hydroxy-5-phenylhexanoic acid produced was converted into its lactone; in one experiment this had $[\alpha]^{25}_{5461}$ −2·52° ± 0·15° in ethyl alcoholic solution. In these experiments slower mixing of the reactants decreased the extent of asymmetric synthesis.

Interaction of (−)-menthyl δ-acetylvalerate with 1·25 molecular proportions of phenylmagnesium bromide led to the ultimate isolation in high yield of 6-hydroxy-6-phenylheptanoic acid with α^{25}_{5461} +0·09° ($l = 2$) in ethyl alcohol. Partial asymmetric synthesis is thus demonstrated, but it appears to be slight.

Interaction of (−)-menthyl ω-acetylpelargonate and phenylmagnesium bromide, leading finally to 10-hydroxy-10-phenylundecanoic acid, was not accompanied by detectable partial asymmetric synthesis.

Experimental.

(−)-Menthyl pyruvate, prepared (yield 24%) by McKenzie's method (*J.*, 1905, **87**, 1373), had b. p. 132·5—133·5°/10 mm., n^{16}_D 1·4565, $[\alpha]^{15}_D$ −46·64°, $[\alpha]^{15}_{5780}$ −48·75°, and $[\alpha]^{15}_{5461}$ −55·74° ($l = 0·5$).

(−)-Menthyl lævulate, prepared by McKenzie's method (*J.*, 1906, **89**, 365) (yield 71%), had b. p. 151°/2 mm., $n^{20·5}_D$ 1·4573, $d^{20·5}$ 0·9765, d^{25} 0·971, $[\alpha]^{20·5}_D$ −61·14°, $[\alpha]^{20·5}_{5780}$ −63·62°, $[\alpha]^{20·5}_{5461}$ −72·01°, $[\alpha]^{25}_{5780}$ −63·49°, $[\alpha]^{25}_{5461}$ −71·84°. The semicarbazone, prismatic needles from ethyl alcohol, had m. p. 156—156·5°.

(−)-*Menthyl* γ-*Acetyl*-n-*butyrate* (5-*Ketohexanoate*).—(a) γ-*Acetyl*-n-*butyric acid*. A solution of *cyclo*hexane-1 : 3-dione (56 g.) in 4N-potassium hydroxide (500 c.c.) was boiled under reflux for 12 hours. The cooled solution was acidified with concentrated hydrochloric acid and extracted with ether in a continuous liquid–liquid extractor. When the ethereal extract was evaporated and the residual oil was stirred with a little water, 64 g. (87%) of acetylbutyric acid monohydrate were obtained (after crystallisation from water it had m. p. 37—37·5°). (The semicarbazone, prisms from water, had m. p. 172·5—173·5°.) By heating the monohydrate at 80°/5 mm., the anhydrous acid was obtained.

(b) (−)-*Menthyl* γ-*acetyl*-n-*butyrate*. The general method of McKenzie was used and the *ester* obtained in 45% yield, with b. p. 154·5—155·5°/3 mm., $n^{20·5}_D$ 1·4588, d^{25} 0·973, $[\alpha]^{25}_{5780}$ −68·02°, $[\alpha]^{25}_{5461}$ −70·17° (Found: C, 72·2; H, 10·8. $C_{16}H_{28}O_3$ requires C, 71·6; H, 10·5%). The semicarbazone, plates from aqueous alcohol, had m. p. 125—125·5°.

(−)-*Menthyl* δ-*Acetyl*-n-*valerate* (6-*Ketoheptanoate*).—The method used for the preparation of δ-acetyl-*n*-valeric acid was essentially that used by McKennis and du Vigneaud (*J. Amer. Chem. Soc.*, 1946, **68**, 832). The (−)-*menthyl* ester, prepared from the acid by the general method of McKenzie, had b. p. 173—174°/3 mm., 186—187°/8 mm., $n^{20·5}_D$ 1·4600, d^{25} 0·9605, $[\alpha]^{25}_{5780}$ −58·74°, $[\alpha]^{25}_{5461}$ −66·50°. In chloroform solution the ester had $[\alpha]^{19}_{5780}$ −63·2°, $[\alpha]^{19}_{5461}$ −72·2° (*c*, 1·5; $l = 2$) (Found: C, 72·4; H, 10·7. $C_{17}H_{30}O_3$ requires C, 72·3; H, 10·7%). The semicarbazone, plates from aqueous alcohol, had m. p. 105—106°.

(−)-*Menthyl* ω-*Acetylpelargonate* (10-*Ketoundecanoate*).—This was prepared by applying McKenzie's general method to the parent acid, which was obtained essentially as described by Myddleton and Barrett (*J. Amer. Chem. Soc.*, 1927, **49**, 2258). The *ester* had b. p. 209—210°/3—4 mm., d^{18} 0·944, d^{25} 0·939, $[\alpha]^{18}_{5780}$ −48·67°, $[\alpha]^{18}_{5461}$ −55·09°, $[\alpha]^{25}_{5780}$ −48·59°, $[\alpha]^{25}_{5461}$ −55·01° (Found: C, 74·4; H, 11·2. $C_{21}H_{38}O_3$ requires C, 74·5; H, 11·3%). The semicarbazone, plates from aqueous alcohol, had m. p. 100·5—101°.

Preparation of Ethereal Phenylmagnesium Bromide Solution.—Magnesium turnings (0·5 g.) were covered with ether, a little bromobenzene added, and the flask heated, with simultaneous replacement

of air in the apparatus by nitrogen, until reaction set in. A further 9·1 g. of magnesium were then introduced and covered with ether (total Mg, 0·396 g.-atom). An ethereal solution of bromobenzene (in all, 20·65 g., 0·132 g.-mol.) was then added at such a rate that gentle boiling occurred without external thermal adjustment. When all the bromobenzene had been added, the mixture was gently boiled for 30 minutes. After cooling, the ethereal solution was siphoned through glass wool into a separatory funnel. Ether was then introduced in order to wash out the flask and the glass wool.

In order to determine the approximate amount of diphenyl present in a Grignard reagent so prepared, the solution was poured on ice, and the mixture acidified with 5N-sulphuric acid. The layers were separated and the aqueous layer was extracted twice with ether. The combined ethereal extracts were washed thrice with water, thrice with 10% sodium carbonate solution, and then twice with water, dried (Na_2SO_4), and evaporated at about 20 mm. The residual diphenyl was weighed. The mean of a number of such determinations showed that the yield of phenylmagnesium bromide was 95%.

Partial Asymmetric Synthesis of Atrolactic Acid.—To an ethereal solution of (−)-menthyl pyruvate (4·52 g., 0·02 g.-mol.) was added, under nitrogen, an ethereal solution of phenylmagnesium bromide (0·025 g.-mol.) with ice-cooling and shaking during 30 minutes. The pale yellow solution was gently boiled for 2½ hours, cooled, and poured on 20 g. of ice. After acidification with 5N-sulphuric acid (25 c.c.), the two layers were separated and the aqueous layer was extracted 4 times with 20 c.c. of ether. The last extract was devoid of optical activity. The combined ethereal solutions were washed twice with 20 c.c. of water, once with 20 c.c. of 10% sodium carbonate solution, and then once with 20 c.c. of water. All the aqueous washings were optically inactive. Concentration of the dried (Na_2SO_4) ethereal solution gave a pale yellow oil (5·49 g.) which was boiled with 5N-potassium hydroxide (5 c.c.) and ethyl alcohol (20 c.c.) for 4 hours. The mixture formed two layers and therefore 5 c.c. of the alkali, 5 c.c. of ethyl alcohol, and 10 c.c. of water were added, the resulting homogeneous solution being boiled for 0·5 hour. Ethyl alcohol was then removed by distillation and the residue extracted 5 times with 20 c.c. of ether (extracts *A*). The last extract was optically inactive, showing that all menthol had been removed. The aqueous layer was acidified with 5N-sulphuric acid and extracted five times with 20 c.c. of ether. The aqueous layer was then optically inactive. The combined ethereal extracts were dried (Na_2SO_4) and evaporated. The residue was dried in a vacuum over calcium chloride and paraffin wax and gave 1·23 g. (50%) of atrolactic acid as a pale yellow solid which had $[\alpha]_D^{20}$ +7·8°, $[\alpha]_{5780}$ +8·2°, $[\alpha]_{5461}$ +9·5° (*c*, 6·15 in water), and $[\alpha]_D^{16}$ +6·7°, $[\alpha]_{5780}$ +6·8°, $[\alpha]_{5461}$ +8·1° (*c* 3·075 in absolute ethyl alcohol).

The ethereal extracts *A* were freed from solvent, menthol, and diphenyl by steam-distillation. The residual organic material (1-methyl-1 : 2 : 2-triphenylethylene glycol) was optically inactive.

*Partial Asymmetric Synthesis of γ-Hydroxy-γ-phenyl-*n*-valeric Acid and γ-Phenyl-γ-valerolactone.*—A solution of (−)-menthyl lævulate (20·34 g., 0·08 g.-mol.) in ether (80 c.c.) was cooled in ice, and an ethereal solution of phenylmagnesium bromide (0·10 g.-mol.) added during 30 minutes, with stirring which was thereafter continued for 1 hour. The mixture was kept overnight at 0° and then treated with ice (50 g.) and 5N-sulphuric acid (100 c.c.). The two layers were separated and the aqueous layer was extracted with 50 c.c. of ether 4 times. The combined ethereal solutions were thrice washed with 50 c.c. of water, 3 times with 20 c.c. of 10% sodium carbonate solution, and then thrice with 25 c.c. of water. The ethereal solution was dried (Na_2SO_4) and the residue (27·8 g.) boiled for 4 hours under reflux with 2·5N-potassium hydroxide (40 c.c.) and ethyl alcohol (80 c.c.). The alcohol was then distilled off and the residue freed from menthol and other neutral products by ether-extraction (9 × 50 c.c.). The alkaline aqueous layer was acidified with 5N-sulphuric acid and extracted with ether. The ethereal extract was washed with water and dried (Na_2SO_4). The ether was evaporated and the residue dissolved in benzene (75 c.c.). The benzene was distilled off and the operation twice repeated. The residue from the third benzene distillation was heated under reduced pressure for ½ hour at 100° and then kept in a vacuum over paraffin wax. Crude γ-phenyl-γ-valerolactone (6·68 g., 47%) remained, with $[\alpha]_{5780}$ −6·6°, $[\alpha]_{5461}$ −7·5° (*c*, 10·06 in ethyl alcohol). An ethereal solution of the crude lactone was extracted repeatedly with aqueous sodium carbonate, which removed much colour, and dried (Na_2SO_4). Removal of the solvent gave γ-phenyl-γ-valerolactone with $[\alpha]_{5780}$ −6·82°, $[\alpha]_{5461}$ −7·71° ± 0·05° (*c*, 10·11 in absolute ethyl alcohol) (Found : C, 74·5; H, 7·2. Calc. for $C_{11}H_{12}O_2$: C, 75·0; H, 6·9%). A portion of the lactone was distilled : it had b. p. 134—139°/7 mm., n_D^{25} 1·5282 (Found : C, 75·6; H, 6·8%). The rest was heated with aqueous sodium hydroxide, and the cooled solution acidified, whereupon a microcrystalline specimen of γ-hydroxy-γ-phenyl-*n*-valeric acid was obtained with $[\alpha]_{5780}$ +0·60°, $[\alpha]_{5461}$ +0·73° ± 0·1° (*c*, 3·97 in absolute ethyl alcohol) (Found : C, 67·8; H, 7·1. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%).

A large number of experiments was performed in order to detect any variation of degree of asymmetric synthesis with reaction conditions. Four examples may be quoted in which the time of addition of Grignard reagent to menthyl lævulate was varied :

	Lactone		
Addition time (at 0°)	Yield, %	$[\alpha]_{5780}^{25}$	*c*
1 min.	61	−3·0°	15·00
1 hour	44	−5·5	15·12
3 hours	46	−5·3	10·23
4 hours	39	−5·1	8·57

When the addition time was 30 minutes (0°) and the mixture was then stirred for an hour at 0° and kept overnight, the yield of lactone was 47—51% and $[\alpha]_{5780}$ −6·1° to −6·6° (*c*, 13—10) in different experiments.

Subsequent examination of the products termed " lactone " showed that, in all experiments except where addition was very rapid, these contained sensible quantities of free acid, probably 4-phenylpent-3-enoic acid. Removal of the free acid by means of aqueous sodium carbonate gave a pure lactone, without any great change in optical rotation.

Crude lactone			Lactone present, %	Purified lactone		
$[\alpha]_{5780}$	$[\alpha]_{5461}$	c		$[\alpha]_{5780}$	$[\alpha]_{5461}$	c
−5·3°	−6·0°	10·2	78	−5·7°	−6·7°	4·2
−6·6	−7·5	10·1	85	−6·8°	−7·7°	10·1

" Resolution " of lactone. A sample of lactone (2·0 g.) having $[\alpha]_{5461}$ −7·0° was dissolved in aqueous potassium hydroxide and the solution acidified to *ca.* pH 5 in 3 stages. Filtration at these stages gave acids *a*, *b*, and *c* as follows:

	g.	M. p.	$[\alpha]_{5461}$
Acid *a*	0·57	117·0—118·5°	+4·95°
Acid *b*	0·73	109·5—111·5	−2·54
Acid *c*	0·32	103·5—104·5	+0·03

Acid *a* gave a lactone with $[\alpha]_{5461}$ −52·1°, and acid *b* gave a lactone with $[\alpha]_{5461}$ +26·2°. The latter was dissolved in aqueous potassium hydroxide and acidified in stages. The acid first precipitated (0·27 g.) had m. p. 119·5—121° and $[\alpha]_{5461}$ −4·65° and gave a lactone with $[\alpha]_{5461}$ +50·8°. The whole series of observations was reproducible on four times this scale.

Preparation of (±)-γ-Hydroxy-γ-phenylvaleric Acid.—An ethereal solution of phenylmagnesium bromide (1·25 g.-mol.) was added to ethyl lævulate (144 g., 1·0 g.-mol.) in ether (1 l.), with ice-cooling and stirring, during 20 minutes. Stirring was continued for a further 10 minutes and the mixture kept overnight at 0°. Ice (500 g.) and 5N-sulphuric acid (1 l.) were added. The aqueous layer was extracted with ether, and the extract washed with water, aqueous sodium carbonate, and water. The ethereal layer was dried (Na_2SO_4) and the ether removed. The residual yellow oil (180 g.) was boiled under reflux with ethyl alcohol (1 l.) and 2·5N-potassium hydroxide (500 c.c.) for 5 hours. The cooled solution was extracted with ether, and the aqueous layer acidified and extracted with ether. The ethereal solution was washed with water and dried (Na_2SO_4). The ether was distilled off and the residue treated with benzene (250 c.c.). The solvent was removed and the operation twice repeated. The crude γ-phenyl-γ-valerolactone was dissolved in ether and washed six times with 10% aqueous sodium carbonate. The ether was removed and the residue dissolved in hot 2·5N-potassium hydroxide. The solution was warmed with charcoal, cooled, filtered, and then gradually acidified with 5N-sulphuric acid. γ-Hydroxy-γ-phenylvaleric acid was obtained as a microcrystalline solid (48 g., 27%). Crystallisation from benzene gave plates, m. p. 105·5—106° (Found: C, 68·2; H, 7·4. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%) (Trivedi and Nargund, *J. Univ. Bombay*, 1941, **10**, 102, give m. p. 106°. Johnson, Peterson, and Schneider, *J. Amer. Chem. Soc.*, 1947, **69**, 74, give 104—106°).

Optical Resolution of γ-Hydroxy-γ-phenylvaleric Acid.—The acid (9·7 g., 0·05 g.-mol.) was dissolved in warm water (200 c.c.), and brucine tetrahydrate (23 g., 0·05 g.-mol.) added. The solution was filtered and cooled. Rosettes of needles separated (13·47 g.) which had m. p. 105—110° (decomp.), $[\alpha]_{5780}$ −49·6°, $[\alpha]_{5461}$ −58·2° in chloroform (*c*, 0·998). After five crystallisations from water brucine (+)-γ-hydroxy-γ-phenylvalerate was obtained as sheaves of needles, m. p. 107—108° (decomp.), $[\alpha]_{5780}$ −64·9° ± 0·5°, $[\alpha]_{5461}$ −75·9° ± 0·5° (*c*, 0·995 in chloroform) (Found: C, 64·3; H, 7·3. $C_{34}H_{40}O_7N_2,2\frac{1}{2}H_2O$ requires C, 64·4; H, 7·1%). The salt was treated with excess of warm sodium hydroxide solution, and the brucine removed by three extractions with chloroform. The aqueous layer, freed from chloroform, was acidified with hydrochloric acid at 0° and extracted with ether. The ethereal extract was washed with water and dried (Na_2SO_4). The ether was removed and the residue dissolved in the minimum amount of hot 2·5N-potassium hydroxide. The solution was cooled to 0° and acidified. The γ-hydroxy-γ-phenylvaleric acid which separated had m. p. 122—122·5°, $[\alpha]_{5780}$ +4·8° ± 0·2°, $[\alpha]_{5461}$ +5·7° ± 0·2° (*c*, 2·544 in absolute ethyl alcohol). Dissolution in alkali and reprecipitation by acid did not affect the specific rotation, nor did crystallisation from benzene. The lactone, prepared by repeated distillation with benzene, as described previously, had $[\alpha]_{5780}$ −54·8° ± 0·4°, $[\alpha]_{5461}$ −61·9° ± 0·4° (*c*, 1·214 in absolute ethyl alcohol) (Found: C, 67·9; H, 7·3. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%).

The mother-liquor from which the 13·37 g. of brucine salt had separated was concentrated to 35 c.c., and filtered warm. When the solution was kept, a mixture of needles and plates separated with $[\alpha]_{5461}$ −27·5° (*c*, 1·002 in chloroform). It was freed from brucine and then dissolved afresh in water with the equivalent of brucine. From the solution plates separated, m. p. 95·5—98°, with $[\alpha]_{5461}$ +6·5° ± 0·1° (*c*, 5·062 in chloroform). Recrystallisation from water gave a salt with $[\alpha]_{5461}$ +5·8° ± 0·1° (*c*, 3·441 in chloroform). The brucine was removed and the free acid lactonised. The lactone had $[\alpha]_{5461}$ +61·8° ± 0·5° (*c*, 0·955 in ethyl alcohol) (Found: C, 67·3; H, 7·1. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%).

Partial Asymmetric Synthesis of 5-Phenyl-5-hexanolactone.—An ethereal solution of phenylmagnesium bromide (0·1 g.-mol.) was added during 30 minutes to an ice-cooled solution of (−)-menthyl γ-acetylbutyrate (21·47 g., 0·08 g.-mol.) in ether (80 c.c.), with stirring. A thick oil separated and stirring was continued at 0° for a further hour. After being kept for 12 hours at 0° the mixture was treated with ice (50 g.) and 5N-sulphuric acid (100 c.c.). The aqueous layer was extracted four times with 50 c.c. of ether. The combined ethereal extracts were washed with water (3 × 50 c.c.), with 10% aqueous sodium carbonate (3 × 25 c.c.), and with water (3 × 25 c.c.) and finally dried (Na_2SO_4).

After removal of the ether, a yellow oil (26·3 g.) was obtained. This was boiled under reflux with 2·5N-aqueous potassium hydroxide (40 c.c.) and ethyl alcohol (80 c.c.) for 4 hours. The alcohol was removed by distillation and the residue was extracted with ether (2 × 75 c.c. and 5 × 50 c.c.) to remove neutral products. The aqueous layer was acidified with 5N-sulphuric acid, and the 5-hydroxy-5-phenylhexanoic acid which separated was extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated. Benzene (3 × 100 c.c.) was caused to distil from the residue and finally traces of benzene were removed by heating under diminished pressure at 100°. The yellow oily residue (10·26 g.) partly solidified when kept. Titration with alkali showed that it contained unchanged acid. Toluene was added and distilled off slowly. The residue was kept at 100°/5 mm. for 8 hours and was found to contain 90% of lactone and to have α_{5780}^{25} −0·08° ($l = 2$; c, 15·418 in ethyl alcohol). For analytical purposes, the crude lactone was purified by extracting its ethereal solution with aqueous sodium carbonate and drying (Na_2SO_4). Removal of the ether, followed by vacuum-drying over calcium chloride and paraffin wax, gave *5-phenyl-5-hexanolactone*, m. p. 62°, $[\alpha]_{5780}^{25}$ −0·22°, $[\alpha]_{5461}^{25}$ −0·24° ($l = 2$; c, 12·033 in ethyl alcohol) (Found: C, 75·2; H, 7·5. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%).

In two other experiments on ¼ of the above scale, the Grignard reagent was added to the ester solution at 0°. In the first, addition was effected (shaking) during 1 minute and in the second during ½ hour. When worked up as just described, the first gave a lactone, m. p. 70—72°, $[\alpha]_{5780}^{25}$ −2·21°, $[\alpha]_{5461}^{25}$ −2·52° (c, 5·626), and the second a lactone, m. p. 68—71°, $[\alpha]_{5780}^{25}$ −1·32°, $[\alpha]_{5461}^{25}$ −1·47°.

Partial Asymmetric Synthesis of 6-Hydroxy-6-phenylheptanoic Acid.—An ethereal solution of phenylmagnesium bromide (0·10 g.-mol.) was added to a solution of (−)-menthyl δ-acetylvalerate (22·6 g., 0·08 g.-mol.) in ether (80 c.c.) during 30 minutes, with ice-cooling and stirring. Cooling and stirring were continued for a further hour and the mixture was then kept at 0° for 12 hours. It was worked up by methods similar to those already described, *6-hydroxy-6-phenylheptanoic acid* being obtained (84% yield) as a pale yellow viscous oil (Found: C, 70·3; H, 8·2. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2%). The acid had α_{5780} +0·09° ($l = 2$; c, 50 in ethyl alcohol).

Interaction of (−)-Menthyl ω-Acetylpelargonate and Phenylmagnesium Bromide.—An ethereal solution of phenylmagnesium bromide (0·1 g.-mol.) was added during ½ hour to an ice-cooled solution of (−)-menthyl ω-acetylpelargonate (27·04 g., 0·08 g.-mol.) with stirring. After 12 hours (0°) the product was worked up as usual and gave 22 g. of impure 10-hydroxy-10-phenylundecanoic acid. Since the acid was optically inactive, the experiment was not further pursued.

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