Preparation of Carboxylic Esters and Phosphoric Esters by the Activation of Alcohols[1)]

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The reaction of dibenzyl hydrogen phosphate with alcohols in the presence of diethyl azodicarboxylate and triphenylphosphine, followed by catalytic hydrogenation, resulted in the formation of the corresponding alkyl dihydrogen phosphates. When *p*-tolyl dihydrogen phosphate and ethanol were allowed to react with diethyl azodicarboxylate and triphenylphosphine, ethyl *p*-tolyl hydrogen phosphate and diethyl *p*-tolyl phosphate were obtained. On the other hand, dipyridinium *p*-tolyl phosphate gave ethyl *p*-tolyl hydrogen phosphate and di-*p*-tolyl pyrophosphate. The reaction of alkyl *N,N'*-tetraethylphosphorodiamidites with carboxylic acids in the presence of diethyl azodicarboxylate resulted in the formation of corresponding carboxylic esters. When these reactions (benzoylation) were carried out with the use of optically active 2-octanol, 2-octyl benzoate was obtained with inverted configuration.

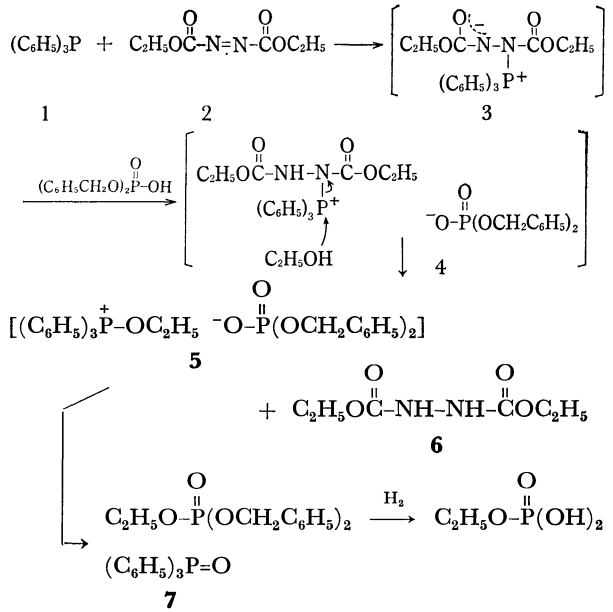
A number of phosphorylating systems have been devised with a view to preparing phosphate and pyrophosphate diesters by intermolecular dehydration between phosphate monoesters and either an alcohol or a phosphate monoester. In order to bring the phosphate into reaction with an alcohol, most systems employed initial activation of phosphate monoesters by organic dehydrating reagents such as dicyclohexylcarbodiimide,[2)] trichloroacetonitrile[3)] or ketene dimer.[4)] There are, however, few reports on phosphorylation of alcohols which involves initial activation of alcohols.[5-7)]

The present study was carried out with a view to producing esters of phosphoric acid and carboxylic acid *via* activation of alcohols.

Results and Discussion

Preparation of Esters of Phosphoric Acid. Recently, preparation of symmetrical pyrophosphate diesters by means of quinonedibenzimide and tri-*n*-butylphosphine has been reported.[8)] A successful method for the preparation of esters of carboxylic acid by means of triphenylphosphine (**1**) and diethyl azodicarboxylate (**2**) was reported.[9)] The reaction was applied to the phosphorylation of alcohols.

When dibenzyl hydrogen phosphate was treated with a small excess of ethanol in the presence of **1** and **2** at room temperature, followed by catalytic hydrogenation, ethyl dihydrogen phosphate was isolated as its anilinium salt in 92% yield. An exothermic reaction set in as soon as **1** was added to a solution of **2**, dibenzyl hydrogen phosphate and ethanol. It may be reasonable to assume that the reaction intermediate, a quaternary phosphonium salt (**3**),[10)] is protonated to give a second phosphonium salt (**4**). Since ethanol is a



more reactive nucleophile than phosphate anion, **4** primarily undergoes nucleophilic attack by the ethanol to give triphenyl ethoxy phosphonium salt (**5**) and diethyl hydrazodicarboxylate (**6**). The phosphonium salt decomposes into dibenzyl ethyl phosphate and triphenylphosphine oxide (**7**).

When *p*-tolyl dihydrogen phosphate was used in place of dibenzyl hydrogen phosphate in the above reaction, ethyl *p*-tolyl hydrogen phosphate was obtained in a 48% yield along with an undesirable side product, diethyl *p*-tolyl phosphate (23%). Twenty-four percent of *p*-tolyl dihydrogen phsophate was recovered unchanged. The results are summarized in Table 1.

The reaction of dipyridinium *p*-tolyl phsophate with ethanol in the presence of **1** and **2** resulted in the formation of ethyl *p*-tolyl hydrogen phosphate and di-*p*-

1) Presented at the 20th (April 1967) and 23rd (April 1970) meetings of the Chemical Society of Japan.

2) H. G. Khorana and A. R. Todd, *J. Chem. Soc.*, **1953**, 2257.

3) F. Cramer and G. Weimann, *Chem. Ber.*, **91**, 996 (1961).

4) T. Mukaiyama, T. Hata, and O. Mitsunobu, *J. Org. Chem.*, **27**, 1815 (1962).

5) H. G. Khorana, *Can. J. Chem.*, **32**, 227 (1954).

6) F. Cramer, K. Pawelzik, and F. W. Lichtenthaler, *Chem. Ber.*, **91**, 1555 (1958).

7) R. J. W. Cremlyn, *J. Chem. Soc.*, **1961**, 1805.

8) I. Kuwajima and T. Mukaiyama, *J. Org. Chem.*, **29**, 1385 (1964).

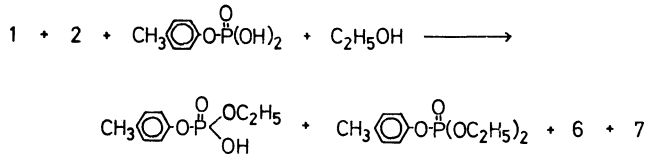
9) O. Mitsunobu and M. Yamada, This Bulletin, **40**, 2380 (1967).

10) E. Brunn and R, Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **8**, 513 (1969).

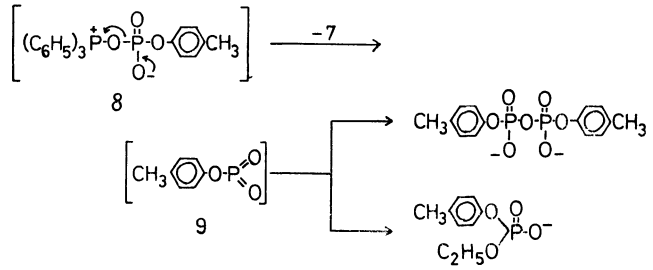
Table 1. Phosphorylation of alcohols by means of diethyl azodicarboxylate and triphenyl phosphine

Starting materials			Products						
$RO\overset{O}{\overset{\|}{}}\!>\!P\text{-}OH$ $R'O$		R″OH	$RO\overset{O}{\overset{\|}{}}\!>\!P\text{-}O^{-}\ H_3\overset{+}{N}C_6H_5$ $R''O$		Yield (%)	MP °C	Anal. %		
R	R′	R″	R	R″				C	H	N
C_6H_5–	H–	C_2H_5–	C_6H_5–	C_2H_5–	41	97—99	Found	56.70	6.27	4.76
							Calcd	56.94	6.15	4.74
C_6H_5–	H–	n-C_3H_7–	C_6H_5–	n-C_3H_7–	59	116—119	Found	57.85	6.54	4.79
							Calcd	58.24	6.53	4.53
p-$CH_3C_6H_4$–	H–	C_2H_5–	p-$CH_3C_6H_4$–	C_2H_5–	48[a]	103	Found	57.84	6.52	4.89
							Calcd	58.24	6.53	4.53
p-$CH_3C_6H_4$–	H–	n-C_3H_7–	p-$CH_3C_6H_4$–	n-C_3H_7–	30	122	Found	59.04	6.97	4.46
							Calcd	59.43	6.86	4.34
$C_6H_5CH_2$–	$C_6H_5CH_2$–	C_2H_5–	H–	C_2H_5–	92	167—170	Found	43.88	6.58	6.80
							Calcd	43.83	6.45	6.39
$C_6H_5CH_2$–	$C_6H_5CH_2$–	n-C_3H_7–	H–	n-C_3H_7–	96	155—157	Found	46.74	7.26	6.34
							Calcd	46.35	6.92	6.01

a) 23.1% of diethyl p-tolyl phosphate was isolated.



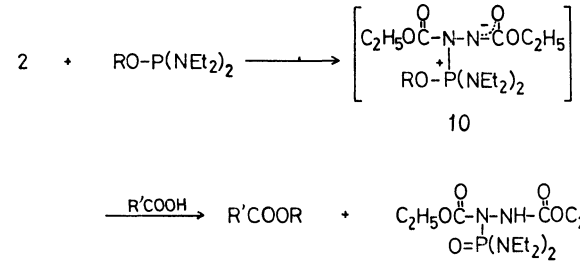
tolyl pyrophosphate as indicated by paper chromatography. Since metaphosphates are generally believed to be reactive intermediates for the phosphorylation of alcohols by means of phosphoric monoesters and dehydrating reagents,[11-14] the result might be explained as follows. The nucleophilic reactivity of the phosphate anion is enhanced by the presence of pyridine[4,15] and the formation of dipolar ion (**8**) takes place. The dipolar ion subsequently decomposed into metaphosphate (**9**) or the trimetaphosphate which gave the phosphate diester and the pyrophosphate diester.



Preparation of Esters of Carboxylic Acid. The above phosphorylation method could not be applied to the phosphorylation and acylation of 2′ and/or 3′-hydroxy groups of nucleosides.[16] Thus, alkyl N,N'-tetraethylphosphorodiamidites prepared from alcohols and N,N'-tetraethylphosphorodiamidous chloride were allowed to react with **2** and carboxylic acids.

When n-propyl N,N'-tetraethylphosphorodiamidite was treated with equimolar amounts of **2** and benzoic acid at room temperature for 3 hr, n-propyl benzoate and diethyl N-(bisdiethylaminophosphoryl) hydrazodicarboxylate were obtained in 78% and 62% yields, respectively. The fact that no rearranged product, isopropyl benzoate, could be detected by NMR spectra indicates the exclusion of a carbonium ion mechanism.

Similarly, various alkyl benzoate and alkyl caproate were obtained. The results are summarized in Table 2.



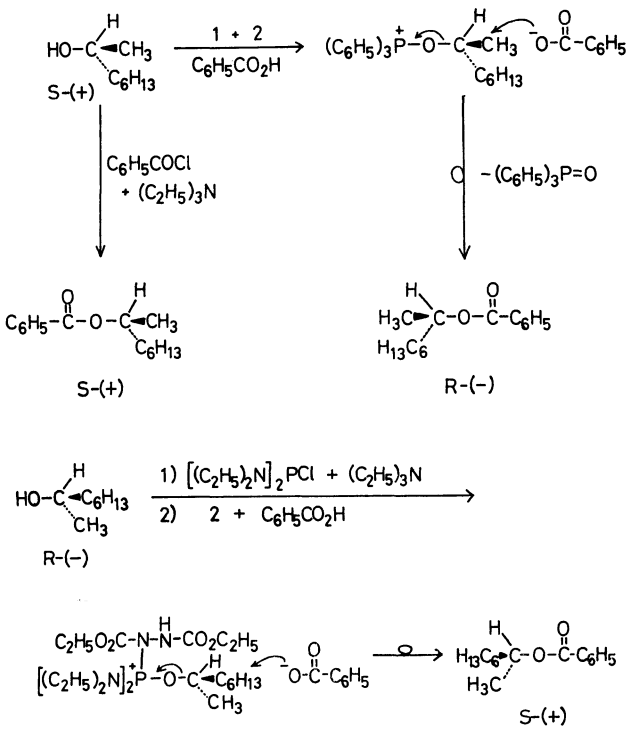
Steric Course of the Reactions. Dealkylation of alkoxyphosphonium salt is generally a simple bimolecular displacement at saturated carbon. Gerrard and Green[17] have shown that the phosphite derived from (+)-2-octanol reacts with ethyl iodide to give octyl iodide with inverted configuration.

In order to clarify the formation of alkoxyphosphonium salts (**5** and **10**) as intermediates in the present reactions, acylation of an optically active alcohol was attempted.

When S-(+)-2-octanol was allowed to react with **1**, **2**, and benzoic acid at room temperature, 2-octyl benzoate was obtained with a specific rotation of $[\alpha]_D$ −39.5°. The reaction of **2** and benzoic acid with R-(−)-2-octyl N,N'-tetraethylphosphorodiamidite derived from R-(−)-2-octanol resulted in the formation of 2-octyl benzoate with a specific rotation of $[\alpha]_D$+32.3°. As the 2-octyl benzoate prepared from S-(+)-2-octanol

11) A. R. Todd, *Proc. Chem. Soc.*, **1962**, 199.
12) P. T. Gilham and H. G. Khorana, *J. Amer. Chem. Soc.*, **80**, 6212 (1958).
13) G. Weimann and H. G. Khorana, *ibid.*, **84**, 4329 (1962).
14) D. M. Brown, J. A. Flint, and N. K. Hamer, *J. Chem. Soc.*, **1964**, 326.
15) F. Cramer and M. Winter, *Chem. Ber.* **92**, 2761 (1959).
16) O. Mitsunobu, K. Kato, and J. Kimura, *J. Amer. Chem. Soc.*, **91**, 6510 (1969).
17) W. Gerrard and W. J. Green, *J. Chem. Soc.*, **1951**, 2550.

and benzoyl chloride showed a specific rotation of $[\alpha]_D$ +38.9°, the present reactions proceeded stereospecifically with inversion of configuration at the alkyl group.



The result can be best explained by assuming the formation of alkoxyphosphonium salts (**5** and **10**). Inversion of the cofiguration takes place on dealkylation. Thus it can be concluded that acylation of alcohols by the present methods involves initial acitvation of alcohols and not of carboxylic acids. Phosphorylation of alcohols may also proceed through an analogous activation process.

Experimental

The IR spectra were measured on a Nippon Bunko IR-G spectrophotometer. The NMR spectra were obtained on a Hitachi Perkin-Elmer R-20 high-resolution spectrometer at 60 MHz, using tetramethylsilane as an internal standard. Optical rotations were measured with JASCO ORD/UV-5.

Reagents. Diethyl azodicarboxylate,[18] dibenzyl hydrogen phosphate,[19] aryl dihydrogen phosphate,[4,20] and S-(+)- and R-(−)-2-octanols[21] were prepared by known procedures. Alkyl *N,N'*-tetraethylphosphorodiamidites were prepared from *N,N'*-tetraethylphosphorodiamidous chloride and alcohols. The alcohols, carboxylic acids, and solvents were purified by ordinary procedures.

Phosphorylation of Ethanol by Means of Dibenzyl Hydrogen Phosphate, Diethyl Azodicarboxylate and Triphenylphosphine. A solution of **1** (1.31 g; 0.005 mol) in 5 m*l* of tetrahydrofuran (THF) was added dropwise to a solution of **2** (0.87 g; 0.005 mol), dibenzyl hydrogen phosphate (1.39 g; 0.005 mol) and ethanol (0.5 m*l*) in 10 m*l* of THF at room temperature under stirring. After the solution was kept standing over night at room temperature, the solvent was removed under reduced pressure. Ethanol (5 m*l*) was added to the residue and undissolved precipitate (mp 128—134°C; 0.42 g) was removed by filtration. Ethanol-water (1: 1; 30 m*l*) was added to the filtrate and the solution was hydrogenated over Pd-C (500 mg) at room temperature and atmospheric pressure. After absorption of hydrogen ceased, the catalyst was filtered off and the solvent was removed under reduced pressure. Water (5 m*l*) and aniline (0.47 g) were added to the residue and undissolved white precipitate, a mixture of **6** and **7** (mp 125—149°C; 1.63 g), was removed by filtration and washed with water. The filtrate and washings were evaporated to dryness to give anilinium ethyl hydrogen phosphate (1.01 g; 91.7%; mp 130—156°C). An analytical sample was obtained by recrystallization from acetonitrile containing a few drops of water, mp 168—170°C. Found: C, 43.88; H, 6.58; N, 6.80. Calcd for $C_8H_{14}NO_4P$: C, 43.83; H, 6.45; N, 6.39.

Phosphorylation of Ethanol by Means of p-*Tolyl Dihydrogen Phosphate, Diethyl Azodicarboxylate, and Triphenylphosphine.* A solution of **1** (10.48 g; 0.04 mol) in 30 m*l* of THF was added dropwise to a solution of **2** (6.96 g; 0.04 mol), *p*-tolyl dihydrogen phosphate (7.52 g; 0.04 mol) and ethanol (5 m*l*) in 50 m*l* of THF at room temperature under stirring. After the solution was kept standing overnight at room temperature, aniline (3.72 g) was added. Paper chromatogram of the reaction mixture showed the existence of a trace of di-*p*-toly pyrophosphate which could not be isolated. Precipitated anilinium *p*-tolyl hydrogen phosphate (2.34 g; 20.8% recovered, mp 176—182°C) was filtered off and the solvent was removed under reduced pressure. Benzene (30 m*l*) was added to the residue and heated to dissolve it. After cooling the solution in a refrigerator, **6** (5.66 g, 80.4%; mp 134—137°C; a mixed melting point with an authentic sample was not depressed) was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was taken up in 20 m*l* of ether and the undissolved precipitate was removed by filtration. The filtrate was washed with water (10 m*l*×5), dried (Na_2SO_4) and distilled to give diethyl *p*-tolyl phosphate (bp 97—100°C at 0.1—0.2 mmHg; 2.26 g; 23.1%; redistillation gave bp 92—95°C at 0.1 mmHg). The diethyl *p*-tolyl phosphate was shown to be identical with the authentic sample by comparison of the infrared spectra (IR (liquid) 1167 (P–OEt), 1280 cm^{-1} (P=O)). From the residue of the fractionation, **7** (mp 145—154°C, after recrystallization from CCl_4) was obtained. The white crystalline compound undissolved in the ether in the above procedure was washed with warm water (100 m*l*) giving **7** (mp 153—156°C; 9.78 g; 88.0%). The washings were evaporated to dryness to give anilinium ethyl *p*-tolyl phosphate (mp 95—120°C; 6.31 g), which was washed with ether and recrystallized from ethyl acetate, mp 103—105°C. A small amount of anilinium *p*-tolyl hydrogen phosphate (0.42 g; 3.7%, mp 175—182°C) was removed by this procedure because it was not soluble in hot ethyl acetate. The yield of the anilinium ethyl *p*-tolyl phosphate was 47.7%.

Found: C, 57.84; H, 6.52; N, 4.89. Calcd for $C_{15}H_{20}NO_4P$: C, 58.24; H, 6.53; N, 4.53.

Ethyl phenyl, phenyl *n*-propyl, and *p*-tolyl *n*-propyl hydrogen phosphates were prepared in an analogous way. They are summarized in Table 1. The corresponding dialkyl aryl phosphates were not isolated.

Reaction of ethyl N,N'-*tetraethylphosphorodiamidite with* n-*caproic acid and diethyl azodicarboxylate.* A solution of ethyl *N, N'*-tetraethylphosphorodiamidite (2.20 g, 0.01 mol) in 15 m*l* of THF was added dropwise to **2** (1.74 g, 0.01 mol) and *n*-

18) N. Rabjohn, "Organic Syntheses." Coll. Vol. III, p. 375 (1955).
19) V. M. Clark and A. R. Todd, *J. Chem. Soc.*, **1950**, 2030.
20) F. Cramer and M. Winter, *Chem. Ber.*, **92**, 2761 (1959).
21) A. W. Ingersoll, "Organic Reactions," Vol. II, ed. by R. Adams, John Wiley and Sons, Inc., New York (1960), p. 376.

Table 2. Preparation of esters of carboxylic acid by means of alkyl *N,N'*-tetraethylphosphorodiamidites and diethyl azodicarboxylate

$(Et_2N)_2P$–OR	Products: $R'-\overset{O}{\overset{\|}{C}}-OR$			$C_2H_5OCON(O=P(NEt_2)_2)NHCOOC_2H_5$	
R	R'	Bp °C/mmHg	Yield (%)	Bp °C/mmHg (mp °C)	Yield (%)
CH_3CH_2–	*n*-C_5H_{11}–	58—59/15	54.5	(112—114)	50.8
$CH_3CH_2CH_2$–	*n*-C_5H_{11}–	76—78/16	63.0	(109—111)	51.3
CH_3CH_2–	C_6H_5–	94—96/15	90.5	140—142/0.25	49.6
$CH_3CH_2CH_2$–	C_6H_5–	108—110/18.5	77.5	136—142/0.003	62.4
$(CH_3)_2CH$–	C_6H_5–	42—50/2	70.2	128—162/0.32	39.0
$CH_3(CH_2)_2CH_2$–	C_6H_5–	66—68/1	85.3	129—142/0.0025	15.1
$CH_3\underset{\|}{C}H(CH_2)_5CH_3$	C_6H_5–	108—113/1	80.0	(110—113)	25.7
$CH_3\underset{\|}{C}H(CH_2)_5CH_3$ [a]	C_6H_5–	98—100/0.35	54.1 [b]	(110—113)	59.0

a) R-(−) b) S-(+)

caproic acid (1.16 g, 0.01 mol) in 30 m*l* of THF at room temperature. The solution was stirred for 3 hr and concentrated to a sirup. After the sirup was kept standing in a refrigerator overnight, diethyl *N*-(bisdiethylaminophosphoryl)-hydrazodicarboxylate was obtained by filtration: 1.86 g, 50.8%, mp 102—104°C. An analytical sample was obtained by recrystallization from petroleum ether, mp 112—114°C.

Found: C, 45.96; H, 8.39%. Calcd for $C_{14}H_{31}N_4O_5P$: C, 45.89; H, 8.53%. IR(KBr) cm^{-1}: 3170(N–H), 1760, 1730(C=O), 1240(P=O).

The filtrate was distilled to give ethyl caproate, 54.5%, bp 58—59°C/15 mmHg.

Reaction of Ethyl N,N'-*Tetraethylphosphorodiamidite with Benzoic Acid and Diethyl Azodicarboxylate.* A solution of ethyl *N,N'*-tetraethylphosphorodiamidite (2.20 g, 0.01 mol) in 10 m*l* of THF was added dropwise to **2** (1.74 g, 0.01 mol) and benzoic acid (1.22 g, 0.01 mol) in 20 m*l* of THF at room temperature and stirred for 3 hr followed by concentration. After the residue was kept standing overnight in a refrigerator, ethyl benzoate (1.36 g, 90.7%, bp 95—97°C/17 mmHg) and diethyl *N*-(bisdiethylaminophosphoryl)hydrazodicarboxylate (2.29 g, 62.6%, bp 140—142°C/0.25 mmHg) were obtained by distillation.

Similarly, various alkyl benzoates were prepared in good yields as summarized in Table 2. Satisfactory NMR and IR data were obtained for all these esters.

Preparation of R-(−)-2-Octyl N,N'-*Tetraethylphosphorodiamidite.* R-(−)-2-octanol (8.97 g, 0.069 mol) and triethylamine (6.97g, 0.069 mol) in 150 m*l* of benzene were added dropwise to an ice cooled solution of *N,N'*-tetraethylphosphorodiamidous chloride (14.53 g, 0.069 mol) in 150 m*l* of benzene and the mixture was stirred for additional 7 hr. After the mixture was kept standing 2 days, water was added and the benzene layer was separated. The aqueous phase was extracted with benzene. The organic layer was dried by sodium sulfate. The benzene was removed and the residue was distilled to give a 77.5% yield of R-(−)-2-octyl *N,N'*-tetraethylphosphorodiamidite (bp 112—133°C/2 mmHg) which upon redistillation had bp 125—132°C/2 mmHg, $[\alpha]_D$−15.0° (60.6 mg/cc in ethanol).

Reaction of R-(−)-2-Octyl N,N'-*tetraethylphosphorodiamidite with Benzoic Acid and Diethyl Azodicarboxylate.* A solution of R-(−)-2-octyl *N,N'*-tetraethylphosphorodiamidite (3.05 g, 0.01 mol) in 15 m*l* of THF was added dropwise to a solution of benzoic acid (1.22 g, 0.01 mol) and **2** (1.74 g, 0.01 mol) in 30 m*l* of THF at room temperature. After stirring for 3 hr, the solvent was removed and the residue was kept standing overnight in a refrigerator. A white crystalline compound was collected by filtration and washed with petroleum ether giving diethyl *N*-(bisdiethylaminophosphoryl)hydrazodicarboxylate (2.16 g, 59.0%, mp 110—113°C). The filtrate was distilled to afford S-(+)-2-octyl benzoate (54.1%, bp 96—113°C/0.35 mmHg) which upon redistillation had bp 98—100°C/0.35 mmHg, $[\alpha]_D$+33.4° (62.0 mg/cc in ethanol).

Reaction of S-(+)-2-Octanol with Benzoic Acid, Diethyl Azodicarboxylate, and Triphenylphosphine. Diethyl azodicarboxylate (0.871 g, 0.005 mol) in 5 m*l* of THF was added dropwise to a solution of **1** (1.31 g, 0.005 mol), S-(+)-2-octanol (0.652 g, 0.005 mol) and benzoic acid (0.611 g, 0.005 mol) in 5 m*l* of THF at room temperature. After the solution was kept standing overnight, the slovent was removed. Ether (5 m*l*) was added to the residue and undissolved white crystalline compound was filtered off. The filtrate was distilled to give a 20.2% yield of 2-octyl benzoate with $[\alpha]_D$−39.5° (0.032 mol/*l* in THF); bp 114°C/1.5 mmHg.

Preparation of S-(+)-2-Octyl Benzoate. Benzoyl chloride (35.1 mg, 0.0025 mol) in benzene (2 m*l*) was added dropwise to a solution of S-(+)-2-octanol (32.5 mg, 0.0025 mol) and triethylamine (25.2 mg, 0.0025 mol) in benzene (2 m*l*) at room temperature. After removal of triethylammonium chloride by filtration, the residue was distilled to give S-(+)-2-octyl benzoate (380 mg, 65%, bp 97—100°C/0.4 mmHg). Redistillation gave a pure sample, bp 98°C/1 mmHg, $[\alpha]_D$+38.9° (0.081 mol/*l* in THF).

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