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SYNTHESIS OF OPTICALLY ACTIVE DIETHER PHOSPHINATE ANALOGS OF LECITHIN

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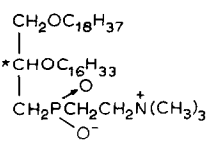
SUMMARY

Syntheses are described of the optically active diether phosphinate analogs of lecithin L-$ROCH_2CH(OR)CH_2CH_2P(O)(O^-)CH_2CH_2N^+(CH_3)_3$ and L-$ROCH_2CH(OR)CH_2CH_2P(O)(O^-)CH_2CH_2CH_2N^+(CH_3)_3$ ($R = C_{18}H_{37}$), which are respectively partially and completely isosteric, and of the same enantiomeric form, as the natural phospholipid. The following synthetic route was used: 1, 2, 5, 6-diisopropylidene D-mannitol → D-mannitol 3,4-di(*p*-methylbenzyl) ether → D-mannitol 1,2,5,6-tetraoctadecyl-3,4-di-(*p*-methylbenzyl) ether → D-mannitol 1,2,5,6-tetraoctadecyl ether → D-2,3-dioctadecoxyglyceraldehyde → L-3,4-dioctadecoxy-1-butene → L-3,4-dioctadecoxy-1-butanol → L-3,4-dioctadecoxy-1-bromobutane. From the L-bromo intermediate the lecithin analogs were prepared by procedures previously reported for the corresponding racemic compounds.

INTRODUCTION

Several diether phosphinic acid-containing analogs of lecithin have recently been synthesized in this laboratory[1–4]. These substances, which are the first known representatives of a new class of phospholipids, the phosphinate lipids, are noteworthy for their complete resistance to hydrolytic degradation. This property, as is obvious from the structures (I–IV), arises from their lack of either carboxylic or phosphorus ester bonds and their replacement by ether and phosphinate (C–P–C) moieties respectively. Phosphinate-containing lipids are not as yet known to be present, in nature.

The syntheses of I–IV previously reported involved only racemic compounds. Due to their introduction of the oxygen functions around the potentially asymmetric carbons (asterisks, I–IV) from olefinic intermediates[5,6], these syntheses are not readily adapted to the synthesis of the corresponding optically active analogs. Thus, an entirely new route was necessary for the synthesis of the intermediates required in the preparation of diether phosphinate lecithins of the same enantiomeric form as the



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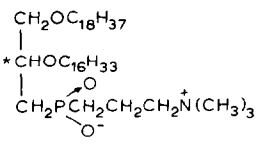

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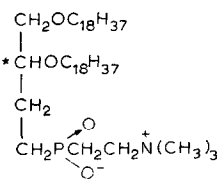

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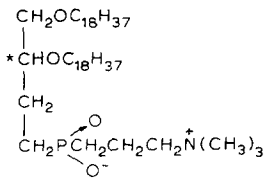


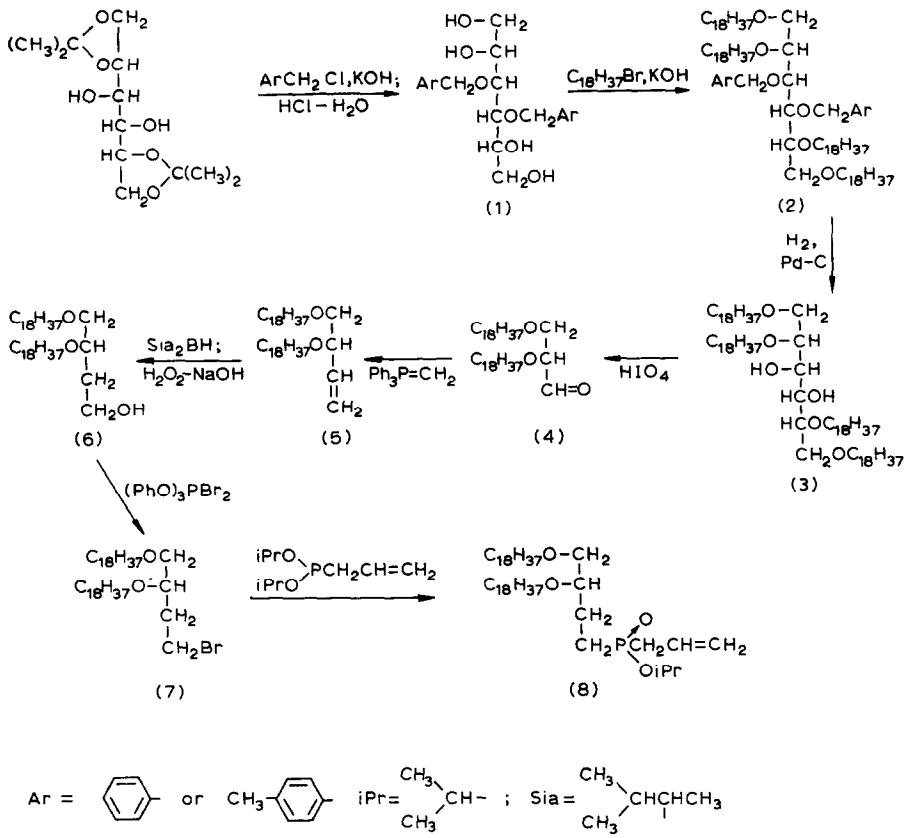
IV

natural phospholipids. Once these optically active intermediates were available, the introduction of the phosphorus function and succeeding steps utilized a synthetic route identical with that employed for the syntheses of the racemic analogs.

The present work was undertaken with the objective of synthesizing optically active diether phosphinate analogs of lecithin isosteric with the natural phospholipid on either or both sides of the phosphorus function (Analogs II, III and IV). For the synthesis of these 4-carbon (dialkoxybutyl) derivatives, chain lengthening of D-isopropylidene-D-glyceraldehyde was first considered. This substance, which has been used extensively by BAER and co-workers[7] for synthesis of optically active phospholipids, appeared particularly attractive in view of its facile preparation from diisopropylidene-D-mannitol[8] and its potential utilization in a Wittig-type chain elongation.

Reaction of 2,3-isopropylidene-D-glyceraldehyde (prepared either by lead tetraacetate[9] or sodium periodate oxidation of 1,2,5,6-diisopropylidene-D-mannitol) with methylenetriphenylphosphorane gave only very low yields of the expected D-3,4-isopropylidene-1-butene. Therefore, an alternative approach, the preparation of the long-chain ether groups prior to formation of the aldehyde moiety, was undertaken; *i.e.* the synthesis of a D-mannitol 1,2,5,6-tetraalkyl ether. For this purpose either D-mannitol 3,4-dibenzyl ether or D-mannitol 3,4-di (*p*-methylbenzyl) ether was first prepared from 1,2,5,6-diisopropylidene-D-mannitol; the latter diether was preferable, since the intermediates containing the *p*-methylbenzyl group had higher melting points and thus their isolation tended to be easier.

Periodic acid cleavage of the mannitol tetraalkyl ether readily gave the D-glyceraldehyde 2,3-diether, which was not isolated but was immediately reacted with methylenetriphenylphosphorane to give the desired L-3,4-dialkoxy-1-butene. Hydroboration with disiamylborane followed by alkaline peroxide oxidation gave the L-3,4-dialkoxybutanol; reaction with dibromotriphenoxyphosphorane then gave the expected L-3,4-dialkoxy-1-bromobutane. From this point onward the rest of the preparation was essentially identical to that of the corresponding racemic compounds[3,4]. By this route the diether phosphinate analogs III and IV were prepared in the same optical form as that of the natural glycerophospholipids, the latter analog also being completely isosteric with natural lecithin. The complete synthetic scheme is shown below.

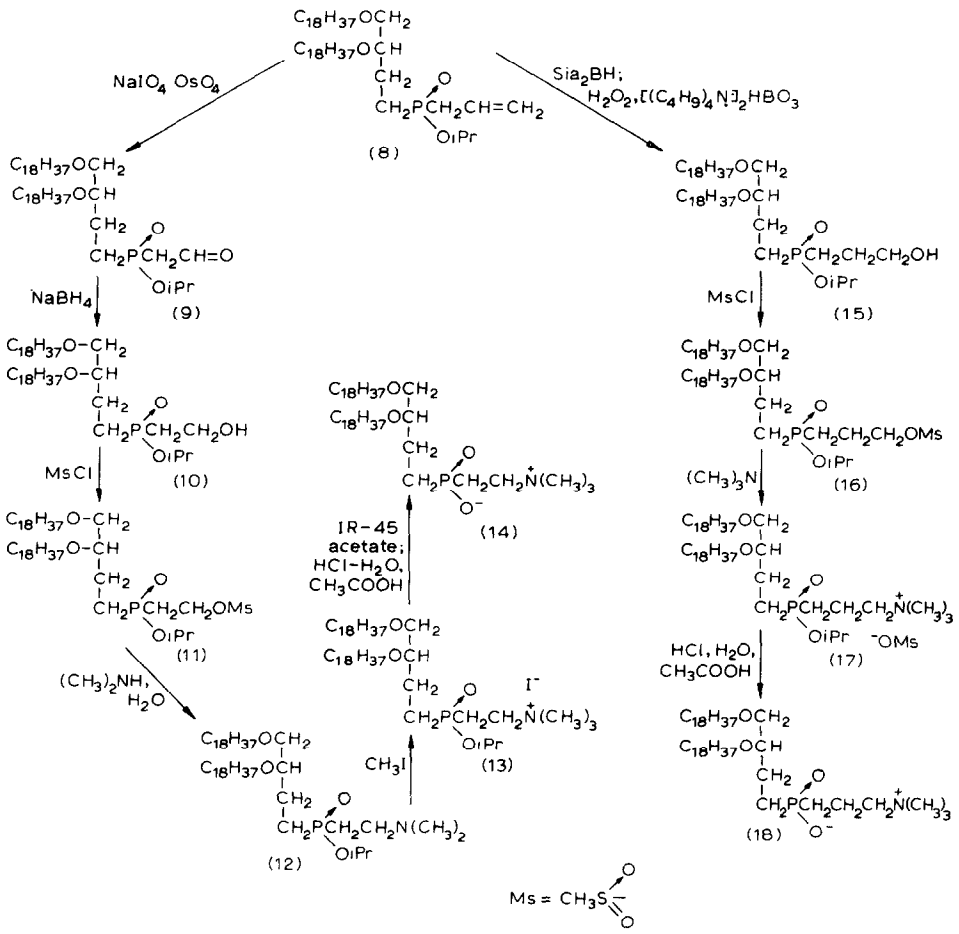


EXPERIMENTAL

Infrared spectra were taken in KBr pellets on a Perkin–Elmer 337 infrared spectrometer. Optical rotations were taken on a Bendix–Erickson 143 Automatic Polarimeter. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York 11377. Thin-layer chromatography was invariably performed on silica gel G-coated plates; solvent systems are indicated below. Organic compounds were visualized on these plates by spraying with 40% aqueous H_2SO_4 and charring over a hot plate.

D-*Mannitol 3,4-di(p-methylbenzyl) ether (1b)*

1,2,5,6-Diisopropylidene D-mannitol[9] (2.62 g, 10 mmoles) was dissolved in anhydrous redistilled tetrahydrofuran; *p*-methylbenzyl chloride (7 g, 50 mmoles) and finely-powdered dry KOH (5 g) were added, and the mixture was heated just below reflux with vigorous mechanical stirring for 17 h. The cooled mixture was filtered through celite and the precipitate washed thoroughly with tetrahydrofuran. The combined filtrate and washings were evaporated in *vacuo*. Thin-layer chromatography (10% ethyl acetate in hexane) indicated that the desired diether (R_F 0.36) was the main product and that practically no diisopropylidene mannitol (R_F 0.02) remained.



The oily mixture was hydrolyzed without further purification by dissolving it in 50 ml 95% ethanol, adding 6 M HCl and keeping the solution at room temperature overnight. After evaporation of solvent *in vacuo*, the residual oil was dehydrated by reevaporation 3 times with isopropanol. Thin-layer chromatography (15% methanol in chloroform) showed completeness of hydrolysis; the product was mainly the desired diether (R_F 0.58) containing a small amount of mannitol 3-*p*-methylbenzyl ether (R_F 0.12).

The oil was triturated with about 5 vol. of light petroleum (b.p. 40–60°) and a few drops of chloroform were added; the white crystalline product solidified immediately. After filtration the product was recrystallized from warm water (crystallization at 5°) and twice more from chloroform–hexane to give a homogeneous product; m.p. 91–92°, $[\alpha]_D^{23}+37.1°$ in tetrahydrofuran (*c*, 1.34 g/100 ml) or $[\alpha]_D^{20}+39.7°$ in methanol (*c*, 1.74 g/100 ml). Slightly less pure material was obtained by salting and cooling the aqueous filtrate and further cooling of the hexane–chloroform filtrates. Total yield, 3.02 g (75%). Calculated for $C_{22}H_{30}O_6$ (390.40): C, 67.62; H, 7.74; O, 24.58. Found: C, 67.59; H, 7.69; O, 24.43.

The infrared spectrum showed strong OH (H-bonded) at 3350 cm^{-1}; aromatic groups at 3030 cm^{-1} and strong ether absorptions 1060–1110 cm^{-1}.

When only the theoretical quantity of *p*-methylbenzyl chloride was employed, a major product was D-mannitol 3-(*p*-methylbenzyl) ether (m.p. 101–103°; R_F 0.25 in 15% methanol in chloroform), obtainable in analytically pure form by repeated crystallization of the product from chloroform. Calculated for $C_{14}H_{22}O_6$ (286.33): C, 58.72; H, 7.75; O, 33.52. Found: C, 58.48; H, 7.73; O, 33.38.

D-Mannitol 1,2,5,6-tetraoctadecyl 1-3,4-di(p-methylbenzyl) ether (2b)

To mannitol 3,4-di (*p*-methylbenzyl) ether (2.25 g, 5.7 mmoles) and 1-bromooctadecane (17.0 g, 50 mmoles) in 125 ml dioxan was added dry powdered KOH (10g) and powdered calcium hydride (5g). The mixture was heated under reflux with vigorous mechanical stirring. It was then filtered through celite while warm; the insoluble material was washed thoroughly with tetrahydrofuran. The combined filtrate and washings were evaporated to dryness; thin-layer chromatography (chloroform–acetone-acetic acid, 60:30:10, by vol.) indicated complete disappearance of mannitol di(*p*-methylbenzyl) ether (R_F 0.69).

The residue was dissolved in boiling acetone–ethyl acetate (3:1, v/v) and filtered from insoluble material at about 35°. A large precipitate of crude product formed by cooling the filtrate to 5° and was filtered off, most of the excess bromooctadecane remaining in the filtrate. The product was recrystallized in the same way. The yield of crude product at this point was 10.75 g. Material suitable for use in the next step was obtained by recrystallization from hexane–ethyl acetate (5°) and from acetone–ethyl acetate (3:1, v/v) (5°).

The considerable amount of dioctadecyl ether remaining in the product could not be removed by crystallization. Although this byproduct could be removed by chromatography on silicic acid, an analytical product could not thereby be obtained.

D-Mannitol 1,2,5,6,-tetraoctadecyl ether (3)

Recrystallized crude hexaether (5.61 g) containing considerable dioctadecyl ether was dissolved in 200 ml n-heptane and 10% palladium on charcoal (2g) was added. The mixture was continually shaken at room temperature in an atmosphere of pure H_2 at 50 lb/inch^2. Hydrogenation was slow under these conditions; the reaction proceeded at least for 45 h. (Subsequently, it was found that the hydrogenation could be completed within about 18 h when the concentration of hexaether was ten times that given above, with the quantities of solvent and catalyst remaining the same.) After evacuation of the hydrogenation vessel with degassing of the catalyst, atmospheric pressure was restored with N_2 and the mixture was filtered. After thorough washing of the catalyst with hexane the crude product was obtained by evaporation of the solvent *in vacuo*.

Fairly pure mannitol tetraoctadecyl ether could be obtained by crystallization from 3:1 acetone–ethyl acetate and then from hexane–ethyl acetate in the cold, but this procedure was accompanied by considerable loss of material. Thus, 2.0 g of product, m.p. 57–58°, was obtained by this method. The yield for the two steps from mannitol di(*p*-methylbenzyl) ether was estimated at approximately 37%. However, the crude product was found to be suitable for use in the next step, thus avoiding much of the loss involved in purifying the tetraether.

For analysis the material was recrystallized from acetone–ethyl acetate (3:1, v/v) and hexane–ethyl acetate at 2°, giving a product which was homogeneous by thin-layer chromatography in 10% ethyl acetate in hexane (R_F 0.54); m.p. 60–61°; $[\alpha]_D^{23} = -6.0°$ in hexane (*c.* 2.0 g/100 ml). Calculated for $C_{78}H_{158}O_6$ (1192.12): C, 78.59; H, 13.36; O, 8.05. Found: C, 78.67; H, 13.48; O, 8.02.

D-*Mannitol 3,4-dibenzyl ether (1a)*

Diisopropylidene D-mannitol[9] (2.62 g, 10 mmoles) was dissolved in 50 ml anhydrous peroxide-free tetrahydrofuran and benzyl chloride (5.1 g, 40 mmoles), finely-powdered dry KOH (11 g, 200 mmoles), and powdered calcium hydride (1.5 g) were added. The mixture was heated just below reflux for 24 h with vigorous mechanical stirring.

The reaction mixture was filtered through celite, the solids were thoroughly washed with dry tetrahydrofuran, and the filtrate and washings evaporated *in vacuo*. The residue was dissolved in a mixture of tetrahydrofuran (approx. 50 ml), 12 M HCl (2 ml) and water (5 ml). After standing overnight at room temperature, the mixture was evaporated to dryness.

The reaction mixture in 50 ml of chloroform was adsorbed onto a 20-cm diameter column of silicAR CC-7 (Mallinkrodt; 400 g). Chloroform (2 l) and chloroform–methanol (49:1 and 19:1, v/v 2 l of each) eluted only lower-polarity impurities. The product was eluted with 9:1 and 7.5:1 (v/v) chloroform–methanol to give an essentially homogeneous product, R_F 0.57 on thin-layer chromatography (solvent, 15% methanol in chloroform). The product solidified on being kept at −20° for several weeks, after thorough removal of solvents *in vacuo*; yield, 2.73 g (75%). Recrystallization from chloroform–hexane in the cold gave an analytically pure sample, m.p. 74–75°; $[\alpha]_D^{23} +48.4°$ (*c*, 0.1 g/100 ml in methanol). Calculated for $C_{20}H_{26}O_6$ (362.43): C, 66.28; H, 7.23; O, 26.49. Found: C, 66.07; H, 7.02; O, 26.40.

The infrared spectrum of this substance showed strong H-bonded OH at 3350 cm^{-1}, an aromatic peak at 3030 cm^{-1}, and a very strong ether absorption at 1075 cm^{-1}.

D-*Mannitol 1,2,5,6-tetraoctadecyl-3,4-dibenzyl ether (2a)*

D-Mannitol 3,4-dibenzyl ether (0.36 g, 1 mmole), 1-bromooctadecane (3.4 g, 10 mmoles), dry powdered KOH (2 g) and calcium hydride powder (1 g) in dioxan (25 ml) were heated just below reflux temperature with vigorous stirring for 16 h. The warm mixture was filtered through celite, the solids were washed with tetrahydrofuran, and the combined filtrate and washings were evaporated *in vacuo*.

The crude product was dissolved in warm acetone–ethyl acetate (3:1, v/v) and the mixture was allowed to stand at 24° for 2 h. Isothermal filtration gave a precipitate (mainly dioctadecyl ether) and a filtrate containing most of the desired hexaether. The filtrate was evaporated, and most of the unreacted bromooctadecane was removed by precipitating the product with 99% ethanol at 23°, the filtrate then containing the bulk of the bromide.

The precipitated product in hexane was applied to a column of 200 g silicAR CC7 (Mallinkrodt) and the product was eluted with 99:1 and 49:1 (v/v) ethyl acetate–hexane (200 ml each). A fairly pure middle fraction contained almost homogeneous product (R_F 0.24 in 2.5% ethyl acetate in hexane); it weighed 430 mg (31%), although impure fractions contained considerable product and no attempt was made at this

point to maximize the yield by rechromatography. An analytical fraction was obtained by recrystallization from ethyl acetate–acetone. This material had m.p. 34.5–35.5°; a completely satisfactory carbon analysis could not be obtained. Calculated for $C_{92}H_{170}O_6$ (1372.35): C, 80.52; H, 12.48. Found: C, 79.96; H, 12.39.

D-*Mannitol 1,2,5,6-tetraoctadecyl ether (3)*

This was prepared by hydrogenation of the hexaether using a palladium–charcoal catalyst by the procedure given above for the preferred route from D-mannitol 1,2,5,6-tetraoctadecyl-3,4-di(*p*-methylbenzyl) ether. The hydrogenation in the case of the dibenzyl hexaether was complete in 3–4 h. The product was identical with that obtained from the di(*p*-methylbenzyl) hexaether: m.p. 61.5–62.5°; calculated for $C_{78}H_{158}O_6$ (1192.1): C, 78.59; H, 13.36; O, 8.05; found: C, 78.37; H, 13.15; O, 8.20.

The infrared spectra of the compounds prepared from the two hexaethers were identical.

L-*3,4-Dioctadecoxy-1-butene (5)*

D-Mannitol 1,2,5,6-tetraoctadecyl ether (relatively crude material; 48 g, 0.04 mole on a pure basis) was dissolved in 500 ml anhydrous ether, and a solution of 20 g (0.08 mole) of paraperiodic acid in a mixture of 1200 ml ether and 50 ml tetrahydrofuran was added dropwise with stirring during 1 h. The mixture was kept at 5° for 3 h and 20 g more periodic acid in ether–tetrahydrofuran was added and the mixture again kept at 5° for 2 h. The mixture, containing precipitated iodic acid, was washed three times with relatively large volumes of water; the last wash was neutral. The ethereal solution was dried over $MgSO_4$, filtered, and the filtrate evaporated *in vacuo*. The white residual solid was dissolved in 200 ml tetrahydrofuran. The infrared spectrum of the crude product showed a strong aldehyde band at 1725 cm^{-1}.

Under dry N_2 56 g (0.50 mole) of potassium *tert.*-butoxide was dissolved in 1.5 l of anhydrous freshly-distilled tetrahydrofuran. Methyl(triphenyl)phosphonium bromide (215 g, 0.60 mole) was added portionwise with vigorous mechanical stirring, which was then continued for 3 h more.

The solution of aldehyde in tetrahydrofuran was added dropwise during 2 h to the Wittig reagent with stirring in a static N_2 atmosphere at 5°. The mixture was gradually allowed to reach room temperature and then stirred for 17 h longer. Finally, the mixture was heated under reflux for 2 h; the yellow color of excess Wittig reagent remained.

The mixture was filtered through glass wool and the filtrate evaporated to dryness *in vacuo*. The residue was extracted with ether and water, and the ethereal layer was dried over $MgSO_4$, filtered, and evaporated.

The residual yellowish-brown material was fractionally crystallized from acetone–ethyl acetate (3:1, v/v). At 24° the crystallized material (10.7 g) contained the bulk of the dioctadecyl ether impurity as well as a small amount of desired product and a considerable quantity of more polar impurities. The material obtained by cooling the filtrate to 18° was largely the desired olefin (R_F 0.44 in 3% ethyl acetate in hexane) with a minor amount of dioctadecyl ether (R_F 0.60). Another crop of product of similar purity was obtained by cooling the filtrate to 3°. The second and third crops were combined, dissolved in ethyl acetate, and reprecipitated with acetonitrile, a process which removed residual triphenylphosphine oxide. The yield at this point was 32.7 g

(68%). Although most of the remaining impurities could be removed by column chromatography, an analytically pure material could not be obtained. The best fraction had m.p. 42.5–44°; $[\alpha]_D^{28} = +0.74°$. The infrared spectrum was relatively simple and showed small olefinic absorptions at 3065 cm^{-1} and 1620 cm^{-1}, as well as a large ether doublet at 1128 cm^{-1} and 1105 cm^{-1}.

L-3,4-Dioctadecoxybutanol (6)

A solution of disiamylborane was prepared by dropwise addition of 2-methyl-2-butene (2.4 g, 0.034 mole) to 20 ml 0.85 M borane in tetrahydrofuran with stirring under N_2 at 10° and then for 1 h at room temperature. The borane solution was added during 10 min to a solution of 3.3 g (0.0056 mole) L-3,4-dioctadecoxy-1-butene in 30 ml anhydrous tetrahydrofuran and the solution was kept overnight at room temperature.

Volatile materials were removed *in vacuo* and about 5 ml methanol was carefully added to decompose excess borane. The residue was dissolved in tetrahydrofuran (25 ml), and to the solution at 5° was added 1 ml 10% NaOH in methanol followed by 10 ml 15% aqueous H_2O_2 with vigorous stirring dropwise during 30 min. The mixture was then stirred overnight at room temperature.

The reaction mixture was evaporated to half its volume *in vacuo* and poured into a solution of 30 ml 12 M HCl in 800 ml ice water. After standing overnight the mixture was filtered to give 3.2 g of white product (94%), consisting of the desired alcohol (R_F 0.83, 2% methanol in chloroform) but containing small amounts of more polar and less polar impurities; m.p. 56–57°. The material could be purified to complete homogeneity by crystallization several times from ethyl acetate acetone or by elution from a silicic acid column with 10% ethyl acetate in hexane; m.p. 56–57°; $[\alpha]_D^{23} = -9.1°$ in tetrahydrofuran (*c*, 1.85 g/100 ml). Calculated for $C_{40}H_{82}O_3$ (611.098): C, 78.62; H, 13.53; O, 7.85. Found: C, 78.65; H, 13.67: O, 7.60. The infrared spectrum showed an alcohol band at 3300 cm^{-1} in addition to a well-resolved ether doublet at 1119 cm^{-1} and 1140 cm^{-1}.

L-1-Bromo-3,4-dioctadecoxybutane (7)

The procedure used was identical to that employed for the corresponding racemic compound[5]. The product was obtained in 99% yield in a fairly pure state; R_F 0.66 in ethyl acetate–hexane (1:19, v/v)or R_F 0.85 in hexane–methylene chloride (1:1, v/v), the latter solvent system being more effective in separating the product from impurities.

To obtain an analytically pure material, the product (45 mg) in hexane was applied to a 4-mm diameter column of SilicAR cc-7 (20 g), which was washed successively with hexane (25 ml), 19:1, v/v hexane–methylene chloride (25 ml) and 9:1, v/v hexane–methylene chloride (25 ml), all of which eluted trace impurities. The product was eluted with 1:1, v/v hexane–methylene chloride (50 ml); yield of pure product, 39 mg (87%). The product was finally precipitated from chloroform solution with acetonitrile; m.p. 41–41.5°; $[\alpha]_D^{25}$ had the surprisingly high value of −21.9° (concn., 0.39 g/100 ml in tetrahydrofuran). Calculated for $C_{40}H_{81}O_2Br$ (641.00): C, 71.28; H, 12.11; Br, 11.86. Found: C, 70.98; H, 12.06; Br, 11.94. The infrared spectrum was quite simple, and indicated an absence of –OH. A band at 658 cm^{-1} possibly represented a C–Br mode, but this could not be definitively assigned.

Further synthetic steps

The succeeding steps were essentially identical with those used for the synthesis of the racemic forms of Analogs III and IV, and are thus given only in summary form.

L-*Isopropyl 3,4-dioctadecoxybutyl(allyl)phosphinate (8)*. This intermediate was prepared from L-3,4-dioctadecoxybutyl bromide and diisopropyl allylphosphinate according to the procedure given for the DL-compound.[3] The compound was obtained in 90% yield but was not purified to an analytically pure form. A fraction of m.p. 37–38° had $[\alpha]_D^{25}$ of −6.1° in tetrahydrofuran; the infrared spectrum was very similar to that of the DL-allylphosphinate.

L-*Isopropyl 3,4-dioctadecoxybutyl (2'-acetaldo) phsophinate (9)* was prepared, like the DL-aldehydo phosphinate, by cleavage of the allyl compound with osmate–periodate[3]. The crude aldehyde was reduced directly by $NaBH_4$ in ethanol in the same manner as the corresponding racemic compound[3] to give L-*isopropyl 3,4-dioctadecoxybutyl(2'-hydroxyethyl) phosphinate (10)*. For use in succeeding steps it was necessary to purify the hydroxyethylphosphinate chromatographically[3]. Fairly pure material was thus obtained from the column in 47% overall yield for the two steps from the allylphosphinate.

L-*Isopropyl 3,4-dioctadecoxybutyl(2'-mesyloxyethyl) phosphinate (11)* was prepared by the same procedure used for the synthesis of the DL-mesylate[3]. Similarly, reaction with aqueous dimethylamine followed by quaternization with iodomethane gave L-*isopropyl 3,4-dioctadecoxybutyl [2'-(trimethylammonium)ethyl] phosphinate iodide (13)*. After conversion of the iodide to the acetate salt, hydrolysis by HCl in acetic acid solution gave the L-diether phosphinate lecithin Analog 14 in 88% yield from the phosphinate alcohol 10, according to the procedure used for the DL-analog[3]. Recrystallization from chloroform–acetone at room temperature gave the L-lecithin analog in analytically pure form as a sesquihydrate in 63% yield from 10. The white crystalline material had m.p. 203–205°.(decompn.); $[\alpha]_D^{23} = -2.7°$ (*c*, 1.1 g/100 ml in 4:1, v/v chloroform–isopropanol); R_F 0.47 in chloroform–methanol–water (65:25:4, by vol.). Calculated for $C_{45}H_{94}NO_4P \cdot 1\frac{1}{2}H_2O$ (771.24):C, 70.08; H, 12.68; N, 1.81; P, 4.02. Found: C, 70.23; H, 12.90; N, 2.01; P, 3.72.

Like the DL-lecithin analog III, the optically active analog can be interconverted into two forms which differ in their infrared spectra[3]. The spectrum of one of these forms is shown in Fig. 1; it is essentially identical with the corresponding form of the DL-compound.

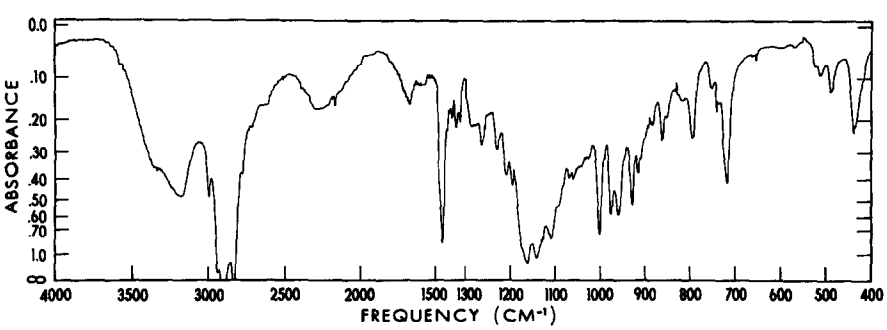


Fig. 1. Infrared spectrum of L3,4-dioctadecoxybutyl[2'-(trimethylammonium)ethyl] phosphinate.

L-*Isopropyl 3,4-dioctadecoxybutyl(3'-hydroxypropyl) phosphinate (15)* was prepared by reaction of the allyl phosphinate (8) with disiamylborane followed by alkaline peroxide oxidation, according to the procedure used for the corresponding racemic compound[4]. The product was purified by column chromatography; a 30% yield of almost pure product was obtained from the column, together with a number of impure fractions also containing the product. Methanesulfonyl chloride gave L-*isopropyl 3,4-dioctadecoxybutyl(3'-mesyloxypropyl) phosphinate (16)*, which on reaction with aqueous trimethylamine gave L-*isopropyl 3,4-dioctadecoxybutyl [3'-(trimethylammonium)propyl] phosphinate methanesulfonate salt (17)*. Finally, hydrolysis in HCl-acetic acid gave the completely isosteric lecithin analog of the L-configuration. The product was deionized by passage through Amberlites IR-120(H^+) and IR-45 (base), and finally purified on a silicic acid column according to the previous procedure[4]. Chromatographically homogeneous product (R_F 0.43 in chloroform methanol–water 65:25:4, by vol.) was thus obtained in 58% yield from the alcohol 15. The product melted with decomposition at 184–186°; $[\alpha]_D^{23} = +1.7°$ (*c*, 1 g/100 ml in chloroform–isopropanol 4:1, v/v). A final crystallization from chloroform gave an analytical sample. After careful drying at 120° in a stream of N_2 the substance gave a correct analysis for *anhydrous* L-*3,4-dioctadecoxybutyl[3'-(trimethylammonium)propyl] phosphinate (18)*. Calculated for $C_{46}H_{96}NO_4P$(758.251): C, 72.86; H, 12.76; N, 1.85; P, 4.08. Found: C, 72.65; H, 12.91; N, 2.18; P, 3.84.

Like the corresponding DL-compound, the L-analog showed the phenomenon of interconversion into at least two (possibly three) forms which differ markedly in their infrared spectra[4]. The interconversion is not as easily performed as in the case of the 2'-(trimethylammonium)ethyl analog, however; *i.e.* longer reaction times are necessary to complete each step[3].

The infrared spectrum of the form opposite to that shown in Fig. 1 for Analog 14 is given in Fig. 2.

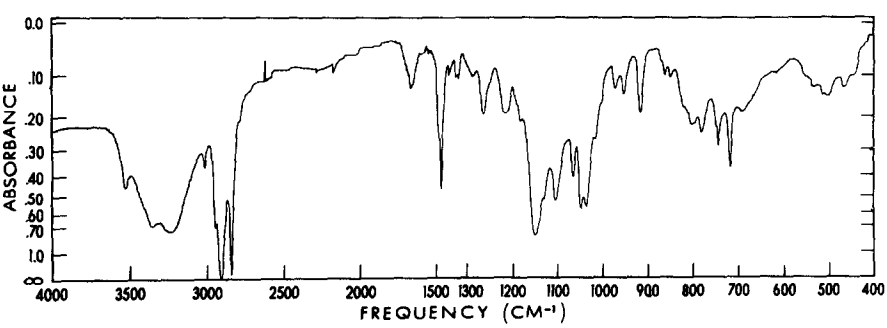


Fig. 2. Infrared spectrum of L-3,4-dioctadecoxybutyl[3'-(trimethylammonium) propyl] phosphinate.

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