Stereospecific Synthesis from Carbohydrate Precurors of (*R*)- and (*S*)-Ethyl Isopropyl Methyl Phosphate and Other Optically Active Neutral Phosphorus Esters

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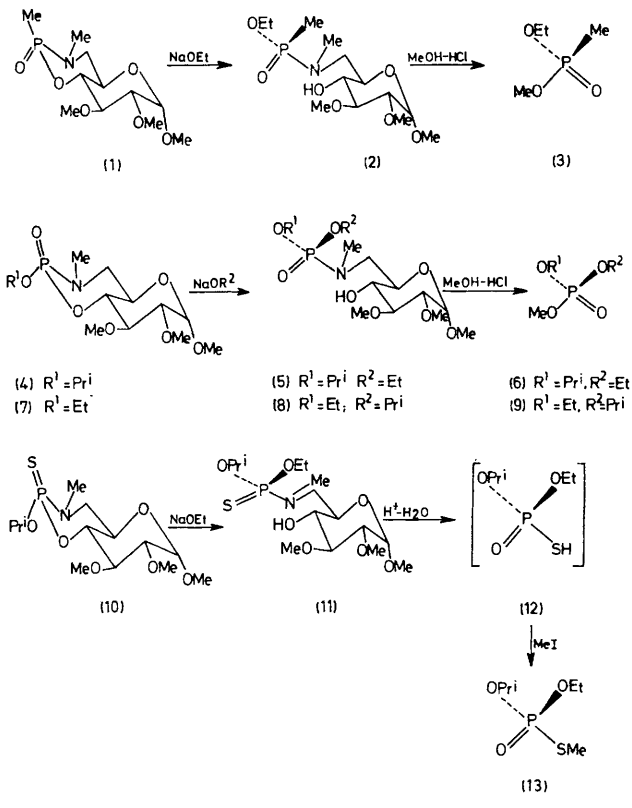
Summary Stereospecific syntheses starting from carbohydrate precursors of (+)-(*R*) and (−)-(*S*)-ethyl isopropyl methyl phosphates, (+)-(*R*)-*O*-ethyl *O*,*S*-dimethyl phosphorothioate, and (+)-(*R*)-ethyl methyl methylphosphonate are described; the enantiomeric purity of these compounds was determined by an n.m.r. method involving the use of tris-[3-(heptafluoro-n-propylhydroxymethylene)-(+)-camphorato]europium(III).

WE have previously shown the value of cyclic phosphorus esters derived from carbohydrates for the stereospecific synthesis and configurational assignments of optically active phosphine oxides[1] and phosphonothioacids.[2] We now report that optically active dialkyl methylphosphonates, trialkyl phosphates, and dialkyl *S*-alkyl phosphorothioates may be obtained in high states of optical purity from appropriate cyclic phosphoramidates derived from carbohydrates.

Compound (**2**) [prepared[2] from (**1**)] on treatment with MeOH–HCl gave (*R*)-ethyl methyl methylphosphonate† (**3**), which following purification by chromatography over silica (R_f 0·8 in $CHCl_3$–MeOH, 10:1) and distillation [b.p. 80 °C (bath) at 15 mmHg] had $[\alpha]_D$ + 1·9° (*c* 1·2 in $CHCl_3$). Compound (**3**) was also prepared by treatment with bromine in methanol of *O*-ethyl *S*-alkyl methylphosphonothioates derived from the corresponding thioacids with known configurations.[3]

The equatorial isopropyl derivative (**4**) (prepared by treating the corresponding axial chloro-derivative[2] with sodium in Pr^iOH) was converted into (**5**) in 22% yield on treatment with hot 2M NaOEt in EtOH [t.l.c. in light petroleum–acetone 1:1; R_f 0·5 for (**4**); 0·6 for (**5**)].



† Configurational assignments for sequences (**1**) to (**3**), (**4**) to (**6**), (**7**) to (**9**), and (**10**) to (**13**) are based on previous observations that ring opening of the cyclic phosphoramidate occurs by P–O bond cleavage with inversion of configuration at phosphorus and that acid-catalysed acyclic P–N bond cleavage also occurs with inversion of configuration.[2]

(*S*)-Ethyl isopropyl methyl phosphate (**6**) was obtained by treatment of (**5**) with MeOH–HCl overnight. Compound (**6**), following chromatography over silica (R_f 0·6 in C_6H_6–Me_2CO–MeOH, 8:1:1) and distillation [b.p. 60° (bath) at 2 mmHg] had $[\alpha]_D$ −0·2° (*c* 5·9 in $CHCl_3$). Similarly (*R*)-ethyl isopropyl methyl phosphate (**9**), $[\alpha]_D$ + 0·2° (*c* 6·8), was prepared from (**7**)[2] *via* (**8**).

The cyclic phosphoramidothioate derivative (**10**) on treatment with boiling 4M NaOEt in EtOH afforded (**11**) [t.l.c. light petroleum–acetone 3:1, R_f 0·6 for (**10**), 0·55 for (**11**)] in 30% yield. Acidic aqueous hydrolysis of (**11**) afforded the phosphorothioacid (**12**) which was not isolated directly. Instead the hydrolysis mixture was made alkaline and treated with MeI to form (*S*)-*O*-ethyl *O*-isopropyl *S*-methyl phosphorothioate (**13**). Following purification by chromatography over silica (R_f 0·4 in light petroleum–acetone, 5:1) and distillation [b.p. 130—140° (bath) at 14 mmHg] (**13**) had $[\alpha]_D$ + 3·6° (*c* 1·9 in $CHCl_3$).

Traditional difficulties associated with the assessment of the enantiomeric purity of compounds with low optical rotations for which no standards are available were circumvented by n.m.r. comparison at 60 MHz in $CDCl_3$ of enantiomers and racemates in the presence of the optical active shift reagent tris-[3-(heptafluoro-n-propylhydroxymethylene)-(+)-camphorato]europium(III) [hereafter Eu(hfc)$_3$].‡ In the presence of this shift reagent the P–OMe signal in racemic ethyl methyl methylphosphonate appeared as a pair of doublets. Satisfactory shift differences (3—6 Hz) were obtained by adding *ca.* 100 mg of shift reagent to the phosphorus ester (30—40 mg) in $CDCl_3$ (0·5 ml). In the presence of Eu(hfc)$_3$ compound (**3**) gave only one P–OMe doublet which was shown to correspond to the higher field P–OMe doublet in the racemate by addition of a little racemate to (**3**). This result showed that (**3**) was essentially a single enantiomer. {In another preparation of (**3**) a product with $[\alpha]_D$ + 1·1° was obtained. This sample by the n.m.r. method was shown to be a 4:1 mixture of the (*R*) and (*S*) isomers, a result quite consistent with the rotational data.} Similarly, the (*S*)- and (*R*)-ethyl isopropyl methyl phosphates (**6**) and (**9**) respectively were shown to be essentially single enantiomers by n.m.r. spectroscopy. The P–OMe doublet of (**6**) was at higher field than the corresponding doublet in (**9**) in the presence of Eu(hfc)$_3$. The n.m.r. procedure for measuring enantiomeric purity was less satisfactory for the (*S*)-*O*-ethyl *O*-isopropyl *S*-methyl phosphorothioate (**13**) since the racemate of this compound only gave a small shift difference (*ca.* 1 Hz) between enantiomers for the P–S–Me signal. However, on treatment with Br_2 in MeOH, (**13**) was converted, with inversion of configuration, into essentially pure (**6**). Thus (**13**) was essentially a single enantiomer.

The above results are important for studies of phosphorus stereochemistry for the following reasons. (i) The synthesis of (+)-(*R*)-ethyl methyl methylphosphonate is the first synthesis of a compound of this type which does not involve an alkylphosphonothioic acid as an intermediate. (ii) The configuration assignments for (**6**), (**9**), and (**13**) are the first recorded for phosphorus esters which do not contain a C–P bond. Hitherto only a very limited number of optically active phosphates have been prepared.[4] (iii) The use of the optically active europium shift reagent for assessment of the enantiomeric purity of small quantities of optically active phosphorus esters has greatly facilitated the above work and the work described in the following paper.[5] Unfortunately satisfactory complex formation is dependent on the presence of a P=O group and commonly available optically active shift reagents do not give satisfactory results with compounds containing a P=S group.

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‡ Chiral shift reagent supplied by Ryvan Chemicals Co. Ltd., Southampton.

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