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SYNTHESIS OF PHOSPHOLANE 1-OXIDE HAVING OXYGEN FUNCTIONAL GROUPS FROM A 4-BROMOBUTYLPHOSHINATE DERIVATIVE

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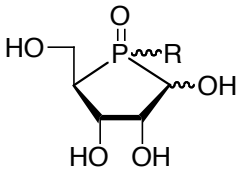
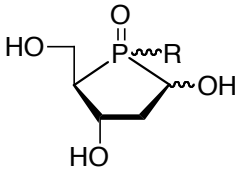
Abstract – Ethyl 4-bromo-2,3-dimethoxybutyl(phenyl)phosphinate (**10a**) was prepared from 2,3-di-*O*-methyl-L-threitol (**12**) in five steps. Reduction of **10a** with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by the action of hydrogen peroxide, afforded 3,4-dimethoxy-1-phenylphospholane 1-oxide (**3**), while the reaction of **10a** with magnesium in boiling THF resulted in the formation of ethyl 2-methoxy-3-butenyl(phenyl)phosphinate (**26**).

INTRODUCTION

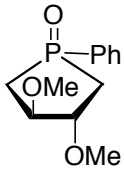
Various sugar analogs containing a heteroatom instead of oxygen in the ring have been prepared because of the wide interest in their chemical properties and potential biological activity.[1] In view of such a chemical modification by heteroatoms, we have prepared various sugar analogs having a phosphorus atom in the ring (phospha sugars).[2] Although some furanose-type phospha sugars having a phospholane oxide structure, *e.g.*, D-ribofuranose (**1**)[3] and 2-deoxy-D-ribofuranose analogs (**2**)[4] have been prepared, synthesis of such sugar analogs remains to be rather difficult, because it usually requires long reaction steps and only a few methods are available for stereoselective introduction of a phosphinoyl group into sugar moiety. This led us to explore a simpler preparative method for phospha furanoses by modification of the phospholane oxide in such a way as to attach oxygen functional groups to the ring carbons (*e.g.* **3**), followed by selective functionalization of the α-carbon of the ring phosphorus.[5,6]



1 (R = OH, Et, Ph)



2 (R = OH, Me)

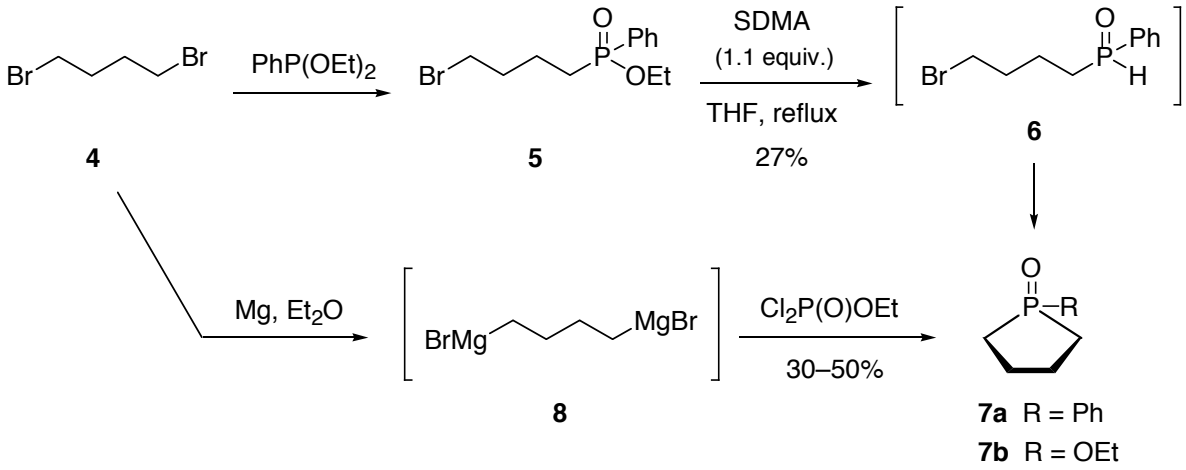


3

Among the reported synthetic procedures for phospholane oxides, the following two methods attracted our attention (Scheme 1). Namely, one method is the reductive cyclization of 4-bromobutylphosphinate

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

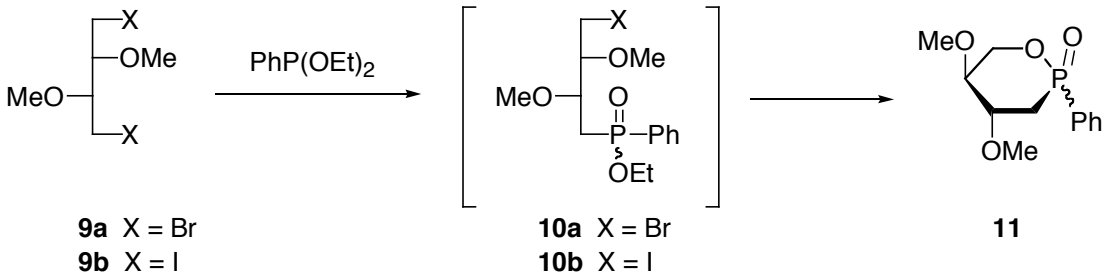
(**5**) [prepared from 1,4-dibromobutane (**4**)] with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA), to give 1-phenylphospholane 1-oxide (**7a**) *via* **6**.[7] The other method is the condensation of the di-Grignard reagent (**8**) (generated from **4**) with ethyl phosphorodichloridate, to give 1-ethoxyphospholane 1-oxide (**7b**).[5,8] We now describe synthetic studies on the phospholane oxide (**3**) having two methoxy groups as a model functional group by applying these two procedures to preparation of simple phospholane oxides.



Scheme 1

RESULTS AND DISCUSSION

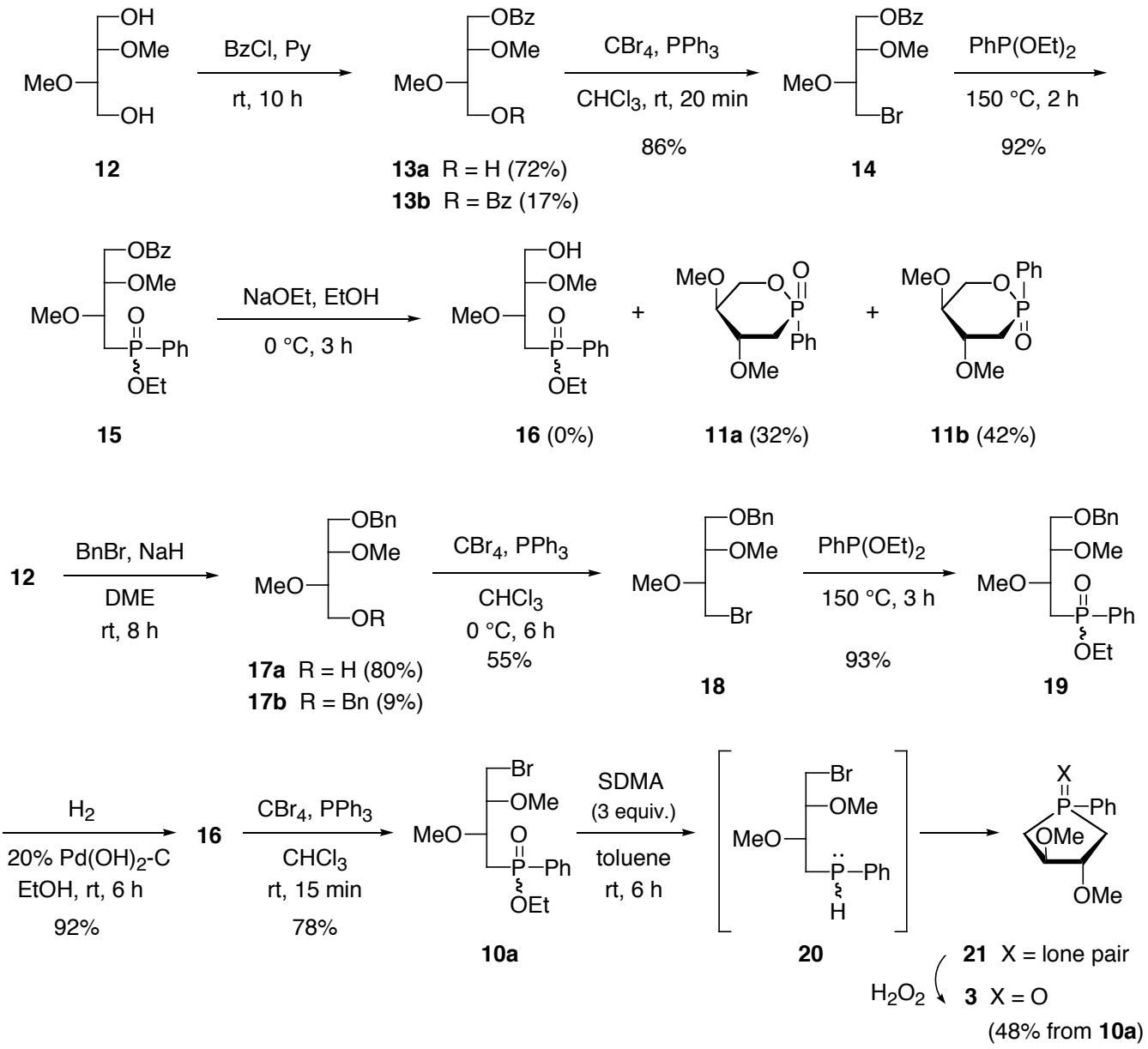
The 4-bromo-2,3-dimethoxybutylphosphinate derivative (**10a**) can be perceived as a key intermediate for the present study. In a previous paper,[9] we reported that Michaelis-Arubzov reaction of 1,4-dihalo-2,3-dimethoxybutanes (**9a,b**) with diethyl phenylphosphonite[10] afforded a cyclic phosphinate (**11**) and the isolation of the anticipated acyclic 4-halobutylphosphinates (**10a,b**) was not achieved (Scheme 2). Therefore we turned our attention to another approach for the preparation of **10**, namely, by the sequence of introduction of a phosphinoyl group and the subsequent halogenation of the terminal carbon.



Scheme 2

The starting material, 2,3-di-*O*-methyl-L-threitol (**12**)[11,12] was prepared from diethyl L-tartrate according to the reported method. For the mono-*O*-protection of 1,4-diol (**12**), we chose benzoyl group first (Scheme 3). Acylation of **11** with 1.1 mol equiv. of benzoyl chloride afforded 1-*O*-benzoyl-L-threitol

(**13a**) in 72% and 1,4-di-*O*-benzoyl derivative (**13b**) in 17%. Treatment of **13a** with carbon tetrabromide and triphenylphosphine at room temperature gave the corresponding bromide (**14**). Michaelis-Arbuzov reaction of **14** with diethyl phenylphosphonite afforded the 4-deoxy-4-[(*R* and *S*)-ethoxy(phenyl)-phosphinoyl]-L-threitol derivatives (**15**) as a 1:1 diastereomeric mixture concerning the phosphorus atom. Cleavage of benzoyl group of **16** with sodium ethoxide in ethanol resulted in the formation of cyclic phosphinates [**11a** (32%)] and [**11b** (42%)] instead of the desired acyclic phosphinate (**16**).



Scheme 3

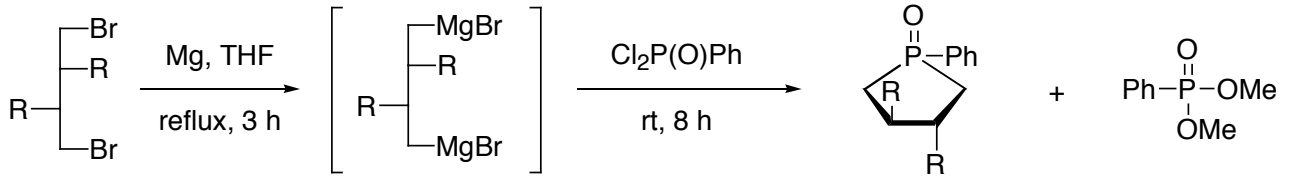
For an alternative protecting group for **12**, we then employed benzyl group. Thus, benzylation of **12** with 1.1 mol equiv. of benzyl bromide in the presence of sodium hydride afforded 1-*O*-benzyl-L-threitol (**17a**) in 80% and 1,4-di-*O*-benzyl derivative (**17b**) in 9%. It is known that benzyl ether having a leaving group at δ-position causes debenzylation in the presence of nucleophile to afford a tetrahydrofuran derivative.[13] To avoid such cyclization, bromination of **17a** with carbon tetrabromide and

triphenylphosphine was performed at 0 °C to give the 4-bromo-4-deoxy-L-threitol derivative (**18**) in 55% yield.[14] Michaelis-Arbuzov reaction of **18** with diethyl phenylphosphonite afforded the 4-deoxy-4-phosphinoyl derivative (**19**). Hydrogenolysis of **19** in the presence of 20% $Pd(OH)_2$–C provided the debenzylated product (**16**), which was coverted into the 1-bromo-1,4-dideoxy-4-phosphinoyl-L-threitol derivative (**10a**) by use of the same conditions as those employed for bromination of **13a**.

Compound (**10a**) was then reduced with 3 mol equiv. of SDMA at room temperature to the phosphine intermediate (**20**), which rendered cyclization to phospholane (**21**). The crude syrup of **21** was treated with hydrogen peroxide to afford the desired (3*R*,4*R*)-3,4-dimethoxy-1-phenylphospholane 1-oxide (**3**).[15] The phosphine and phosphine oxide structures of **21** and **3** were confirmed on the basis of the characteristic values of ^{31}P NMR spectral data (δ –30.9 for **21** and δ 52.0 for **3**).

Wetzel and Kenyon prepared phospholane oxide (**7a**) by reduction of phosphinate (**5**) with 1.1 mol equiv. of SDMA in boiling THF to 4-bromobutylphosphine oxide (**6**) and the subsequent cyclization in 27% yield[7] (Scheme 1). However, phosphine intermediates (such as **20**) are apparently more effective for cyclization than the corresponding phosphine oxides, in view of their nucleophilicities. Thus, phospholane oxide (**7a**) was prepared from **5** in an improved yield (51%), when our modified procedures were employed; namely, the reductive cyclization of phosphinate to phospholane (phosphine) and the following oxidation.

As the second approach to phospholane oxide (**3**), cyclization by use of Grignard reaction was investigated (Scheme 4). We confirmed that the treatment of 1,4-butanediyldimagnesium dibromide (**7**), generated from **4** with magnesium in THF, with phenylphosphonic dichloride afforded 1-phenyl-phospholane oxide (**6a**) in 40% yield with minor modification of reported procedures.[5,8] However, the same reaction of dibromide (**8a**) having two methoxy groups resulted in the formation of a considerable amount of dimethyl phenylphosphonate (**22**) instead of the anticipated phospholane oxide (**3**).

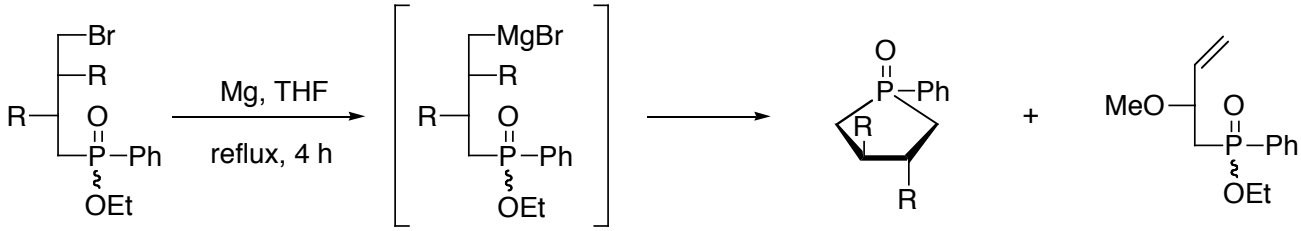


4 R = H
9a R = OMe

8 R = H
22 R = OMe

7a R = H (40% from **4**)
3 R = OMe (0% from **9a**)

23 (from **9a**)



5 R = H
10a R = OMe

24 R = H
25 R = OMe

7a R = H (54% from **5**)
3 R = OMe (2% from **10a**)

26 (59% from **10a**)

Scheme 4

We therefore attempted more effective intramolecular cyclization by Grignard reagent instead of intermolecular ring formation. As a comparative experiment, the reaction of the 4-bromobutyl-phosphinate (**5**) with magnesium was found to give **7a** (*via* **24**) in 54% yield, despite the fact that phosphinates are generally less reactive than the corresponding phosphinic chlorides for attack of nucleophiles. However, the same treatment of **10a** with magnesium resulted in the predominant formation of the 3-butenylphosphinate derivative (**26**) in 59% yield; the desired cyclic phosphine oxide (**3**) was obtained only in a small portion (2% yield).

Production of **26** can be perceived as the result of β-elimination of methoxy group from the intermediate (**25**), which took place faster than intramolecular nucleophilic attack to phosphorus by the terminal anion. The formation of **23** from **9a** supports this mechanism. Namely, methoxide anion derived from the intermediate (**22**) reacted with phenylphosphonic dichloride to afford **23**, whereas the resultant 1,3-butadiene must have been evaporated due to its volatility. Judging from these results, the use of Grignard reaction seems to be unsuitable for preparation of phospholane oxides having alkoxy groups.

The present work demonstrates a convenient way for preparation of phospholane oxide having oxygen functional groups. Extension of this work, including applications of these findings for preparation of phosphorinane oxide, as well as derivation of phospholane oxides into phospha sugars, is under investigation.

EXPERIMENTAL

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(*A*) 1:2, (*B*) 1:1, (*C*) 2:1 AcOEt–hexane, (*D*) AcOEt, and (*E*) 1:9 EtOH–AcOEt]. Column chromatography was performed with Daiso Silica Gel IR-60/210w. Components were detected by exposing the plates to UV light and/or spraying them with 20% sulfuric acid–ethanol (with subsequent heating). The NMR spectra were measured in $CDCl_3$ with Varian VXR-500 (500 MHz for ^1H) and Mercury 300 (121 MHz for ^{31}P) spectrometer at 23 °C. Chemical shifts are reported as δ values relative to $CHCl_3$ (7.26 ppm as an internal standard for ^1H) and 85% phosphoric acid (0 ppm as an external standard for ^{31}P).

1-*O*-Benzoyl-2,3-di-*O*-methyl-L-threitol (13a) and 1,4-di-*O*-benzoyl-2,3-di-*O*-methyl-L-threitol (13b).

To a solution of **12** (540 mg, 3.60 mmol) in dry DME (15 mL) was added benzoyl chloride (460 mg, 3.96 mmol) at 0 °C. The mixture was stirred at rt for 10 h and then water (1 mL) was added at 0 °C. The mixture was stirred at rt for 20 min and evaporated in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was separated by column chromatography with 1:2 AcOEt-hexane to give **13a** and **13b**.

13a: Colorless oil (660 mg, 72%); R_f = 0.12 (*A*), 0.27 (*B*); ^1H NMR δ = 2.28 (1H, br s, HO-4), 3.50 (1H, dt, $J_{3,4'}$ = 5.4, $J_{2,3}$ = $J_{3,4}$ = 4.6 Hz, H-3), 3.51, 3.53 (3H each, 2s, MeO-2,3), 3.73 (1H, dd, $J_{4,4'}$ = 11.7 Hz, H'-4), 3.75 (1H, dt, $J_{1',2}$ = 6.1, $J_{1,2}$ = 4.2 Hz, H-2), 3.87 (1H, dd, H-4), 4.40 (1H, dd, $J_{1,1'}$ = 11.7 Hz, H'-1),

4.59 (1H, dd, H-1), 7.44 [2H, t, $J_{o,m} = J_{m,p}$ = 7.5 Hz, Ph(*m*)], 7.56 [1H, tt, $J_{o,p}$ = 1.2 Hz, Ph(*p*)], 8.03 [2H, dd, Ph(*o*)]. *Anal*. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.54; H, 7.11.

13b: Colorless needles (218 mg, 17%); mp 53–55 °C; R_f = 0.52 (*A*); ^{1}H NMR δ = 3.57 (6H, s, MeO-2,3), 3.77 (2H, m, H-2,3), 4.51 (2H, dd, $J_{1,1'}$ = 11.7, $J_{1',2}$ = 5.9 Hz, H'-1,4), 4.62 (2H, dd, $J_{1,2}$ = 4.6 Hz, H-1,4), 7.44 [4H, t, $J_{o,m} = J_{m,p}$ = 7.5 Hz, Ph(*m*)], 7.57 [2H, tt, $J_{o,p}$ = 1.2 Hz, Ph(*p*)], 8.04 [4H, dd, Ph(*o*)]. *Anal*. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.15; H, 6.26.

1-*O*-Benzoyl-4-bromo-4-deoxy-2,3-di-*O*-methyl-L-threitol (14).

To a solution of **13a** (250 mg, 0.983 mmol) in $CHCl_3$ (5 mL) were added carbon tetrabromide (500 mg, 1.50 mmol) and triphenylphosphine (350 mg, 1.33 mmol) at 0 °C. The mixture was stirred at rt for 20 min, diluted with $CHCl_3$ (10 mL), washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:3 AcOEt-hexane to give **14** (268 mg, 86%) as a colorless oil: R_f = 0.61 (*A*); ^{1}H NMR δ = 3.51, 3.57 (3H each, 2s, MeO-2,3), 3.51 (1H, m, H-3), 3.61 (1H, dd, $J_{4,4'}$ = 7.3, $J_{3,4'}$ = 3.2 Hz, H'-4), 3.63 (1H, t, $J_{3,4}$ = 6.6 Hz, H-4), 3.89 (1H, ddd, $J_{1',2}$ = 5.9, $J_{1,2}$ = 5.4, $J_{2,3}$ = 2.9 Hz, H-2), 4.49 (1H, dd, $J_{1,1'}$ = 11.5 Hz, H'-1), 4.52 (1H, dd, H-1), 7.45 [2H, t, $J_{o,m} = J_{m,p}$ = 7.5 Hz, Ph(*m*)], 7.56 [1H, tt, $J_{o,p}$ = 1.2 Hz, Ph(*p*)], 8.04 [2H, dd, Ph(*o*)]. *Anal*. Calcd for $C_{13}H_{17}O_4Br$: C, 49.23; H, 5.40. Found: C, 49.29; H, 5.33.

1-*O*-Benzoyl-4-deoxy-4-[(*R* and *S*)-ethoxy(phenyl)phosphinoyl]-2,3-di-*O*-methyl-L-threitols (15).

A mixture of **14** (100 mg, 0.315 mmol) and diethyl phenylphosphonite[10] (0.300 mL, 1.56 mmol) was heated at 150 °C for 2 h under N_2 and concentrated in vacuo. The residue was purified by column chromatography with 2:1 AcOEt-hexane to give an inseparable diasteromeric mixture of **15** (118 mg, 92%) as a colorless syrup: R_f = 0.20 (*C*); ^{1}H NMR δ = 1.28, 1.29* (3H, 2t, J_{Et} = 7.1 Hz, C–CH_3), 2.22, 2.29* (1H, 2ddd, $J_{4,4'}$ = 15.4, 15.4*, $J_{4',P}$ = 12.2, 16.3*, $J_{3,4'}$ = 7.1, 6.4* Hz, H'-4), 2.38*, 2.46 (1H, 2ddd, $J_{4,P}$ = 12.0*, 18.1, $J_{3,4}$ = 6.3*, 5.9 Hz, H-4), 3.21, 3.32*, 3.40*, 3.55 (6H, 4s, MeO-2,3), 3.63, 3.75* (1H, 2ddd, $J_{1',2}$ = 5.9, 5.9*, $J_{1,2}$ = 4.9. 5.4*, $J_{2,3}$ = 3.2, 2.9* Hz, H-2), 3.79, 3.83* (1H, 2m, H–3), 3.85, 3.86* (1H, 2m, POCH'), 4.07, 4.08* (1H, 2dquint, $^2J_{H,H'}$ = 10.0, $J_{H,P}$ = 7.0 Hz, POCH), 4.405, 4.42* (1H, 2dd, $J_{1,1'}$ = 11.5, 11.7* Hz, H-1'), 4.44, 4.48* (1H, 2dd, H-1), 7.43, 7.43* [2H, t, $J_{o,m} = J_{m,p}$ = 7.5 Hz, C–Ph(*m*)], 7.46, 7.46* [2H, m, P–Ph(*m*)], 7.53, 7.53* [1H, m, P–Ph(*p*)], 7.56, 7.56* [1H, tt, $J_{o,p}$ = 1.2 Hz, C–Ph(*p*)], 7.79, 7.79* [2H, br dd, $J_{o,P}$ = 11.7, $J_{o,m}$ = 7.8 Hz, P–Ph(*o*)], 7.99, 8.01* [2H, 2br d, C–Ph(*o*)]; ^{31}P NMR δ = 41.9*, 42.6 (52:48* mixture, the assignment of some of the δ values may have to be interchanged). *Anal*. Calcd for $C_{21}H_{27}O_6P$: C, 62.06; H, 6.70. Found: C, 62.12; H, 6.78.

Debenzoylation of 15 with sodium ethoxide.

To a solution of **15** (60.0 mg, 0.148 mmol) in abs EtOH (1.0 mL) was added a 21% ethanolic solution of sodium ethoxide (0.02 mL, 0.05 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h and then

neutralized with Amberlite IR-120(H^+). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was separated by column chromatography with AcOEt to give (2*R*,4*R*,5*R*)-4,5-dimethoxy-2-oxo-2-phenyl-1,2-oxaphosphorinane (**11a**) and its (2*S*,4*R*,5*R*)-epimer (**11b**).

11a:[9] Colorless syrup (12.1 mg, 32%); R_f = 0.35 (*D*); ^{1}H NMR, see ref. 9.

11b:[9] Colorless needles (16.0 mg, 42%); mp 127–129 °C (from AcOEt-hexane) (lit.,[9] 128–129 °C); R_f = 0.22 (*D*); ^{1}H NMR, see ref. 9.

1-*O*-Benzyl-2,3-di-*O*-methyl-L-threitol (17a)[12] and 1,4-di-*O*-benzyl-2,3-di-*O*-methyl-L-threitol (17b).

To a solution of **12** (840 mg, 5.60 mmol) in dry DME (15 mL) was added sodium hydride (62% in mineral oil, 230 mg, 5.94 mmol) at 0 °C. After stirring at rt for 1 h, benzyl bromide (0.720 mL, 6.07 mol) was added. The mixture was stirred at rt for 8 h and saturated NH_4Cl aqueous solution (4 mL) was added. After distilling off most of DME in vacuo, the residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was separated by column chromatography to give **17a** and **17b**.

17a: Colorless oil (1.07 g, 80%) (lit.,[12] 73% yield using DMF as solvent); R_f = 0.27 (*B*); ^{1}H NMR δ = 2.12 (1H, br s, HO-4), 3.44 (1H, ddd, $J_{3,4'}$ = 4.9, $J_{2,3}$ = 4.8, $J_{3,4}$ = 4.4 Hz, H-3), 3.465, 3.47 (3H each, 2s, MeO-2,3), 3.54 (1H, ddd, $J_{1',2}$ = 4.9, $J_{1,2}$ = 4.6 Hz, H-2), 3.59 (1H, dd, $J_{1,1'}$ = 10.3 Hz, H'-1), 3.63 (1H, dd, $J_{4,4'}$ = 12.0 Hz, H'-4), 3.66 (1H, dd, H-1), 3.78 (1H, dd, H-4), 4.55 (2H, s, CH_2O-1), 7.29 [1H, m, Ph(*p*)], 7.32–7.36 [4H, m, Ph(*o,m*)].

17b: Colorless oil (166 mg, 9%); R_f = 0.52 (*A*), 0.77 (*B*); ^{1}H NMR δ = 3.46 (6H, s, MeO-2,3), 3.56 (4H, m, H_2-1,4), 3.65 (2H, m, H-2,3), 7.29 [2H, m, Ph(*p*)], 7.32–7.36 [8H, m, Ph(*o,m*)]. *Anal*. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.61; H, 8.02.

1-*O*-Benzyl-4-bromo-4-deoxy-2,3-di-*O*-methyl-L-threitol (18).

To a solution of **17a** (1.90 g, 7.91 mmol) in $CHCl_3$ (50 mL) were added carbon tetrabromide (4.00 g, 12.1 mmol) and triphenylphosphine (3.16 g, 12.1 mmol) at 0 °C. The mixture was stirred at 0–5 °C for 6 h, washed with saturated $NaHCO_3$ and then water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:3 AcOEt-hexane to give **18** (1.32 g, 55%) as a colorless oil: R_f = 0.64 (*A*); ^{1}H NMR δ = 3.45, 3.49 (3H each, 2s, MeO-2,3), 3.45 (1H, m, H-2), 3.58 (2H, m, H_2-1), 3.64 (2H, m, H_2-4), 3.68 (1H, m, H-3), 4.55 (2H, s, CH_2O-1), 7.27–7.37 (5H, m. Ph). *Anal*. Calcd for $C_{13}H_{19}O_3Br$: C, 51.50; H, 6.32. Found: C, 51.23; H, 6.39.

1-*O*-Benzyl-4-deoxy-4-[(*R* and *S*)-ethoxy(phenyl)phosphinoyl]-2,3-di-*O*-methyl-L-threitols (19).

A mixture of **18** (550 mg, 1.81 mmol) and diethyl phenylphosphonite (3.00 mL, 15.6 mmol) was heated at 150 °C for 3 h under N_2 and concentrated in vacuo. The residue was purified by column chromatography with 2:1 AcOEt-hexane to give an inseparable diasteromeric mixture of **19** (659 mg,

93%) as a colorless syrup: R_f = 0.12 (*B*); ^{1}H NMR δ = 1.275, 1.28* (3H, 2t, J_{Et} = 7.2 Hz, C–CH_3), 2.13, 2.19* (1H, 2ddd, $J_{4,4'}$ = 15.3, 15.3*, $J_{4',P}$ = 11.9, 16.5*, $J_{3,4'}$ = 7.6, 7.0* Hz, H'-4), 2.31*, 2.36 (1H, 2ddd, $J_{4,P}$ = 12.5*, 18.0, $J_{3,4}$ = 5.8*, 5.2 Hz, H-4), 3.16, 3.26*, 3.33*, 3.48 (6H, 4s, MeO-2,3), 3.45* (0.5H, ddd, $J_{1',2}$ = 5.8, $J_{1,2}$ = 4.9, $J_{2,3}$ = 3.4 Hz, H-2), 3.54* (0.5H, dd, $J_{1,1'}$ = 10.1 Hz, H'-1), 3.55–3.60 (1.5H, m, H_2-1,H-2), 3.63* (0.5H, dd, H-1), 3.77, 3.79* (1H, 2m, H-3), 3.81, 3.84* (1H, 2dquint, $^2J_{H,H'}$ = 10.0, $J_{H',P}$ = 7.0 Hz, POCH'), 4.06, 4.07* (1H, 2dquint, $J_{H,P}$ = 7.0 Hz, POCH), 4.48, 4.49*, 4.51, 4.52* (2H, 4d, ^2J = 11.9, 12.2* Hz, CH_2O-1), 7.26–7.32, 7.26–7.32* (5H, m, C–Ph), 7.46, 7.47* [2H, 2m, P–Ph(*m*)], 7.53, 7.54* [1H, 2m, P–Ph(*p*)], 7.77, 7.79* [2H, 2m, P–Ph(*o*)]; ^{31}P NMR δ = 42.4*, 43.0 (52:48* mixture, the assignment of some of the δ values may have to be interchanged). *Anal*. Calcd for $C_{21}H_{29}O_5P$: C, 64.27; H, 7.45. Found: C, 64.20; H, 7.51.

4-Deoxy-4-[(*R* and *S*)-ethoxy(phenyl)phosphinoyl]-2,3-di-*O*-methyl-L-threitols (16).

Compound (**19**) (550 mg, 1.40 mmol) was dissolved in ethanol (10 mL) and hydrogenated in the presence of 20% $Pd(OH)_2$–C (200 mg, 0.28 mmol) at rt. After 6 h, the catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was purified by short-path column chromatography with AcOEt to give **16** (389 mg, 92%) as a colorless syrup: R_f = 0.12 (*D*); ^{1}H NMR δ = 1.28*, 1.285 (3H, 2t, J_{Et} = 7.2 Hz, C–CH_3), 2.12, 2.23* (1H, 2ddd, $J_{4,4'}$ = 15.6, 15.6*, $J_{4',P}$ = 12.0, 16.8*, $J_{3,4'}$ = 7.1, 6.6* Hz, H'-4), 2.32*, 2.38 (1H, 2ddd, $J_{4,P}$ = 11.5*, 18.1, $J_{3,4}$ = 5.9*, 5.4 Hz, H-4), 2.55, 2.55* (1H, br s, HO-1), 3.16, 3.22*, 3.39*, 3.46 (6H, 4s, MeO-2,3), 3.30*, 3.42 (1H, 2ddd, $J_{1',2}$ = 4.4*, 4.9, $J_{1,2}$ = 4.4*, 4.6, $J_{2,3}$ = 4.1, 4.1* Hz, H-2), 3.65*, 3.67 (1H, dd, $J_{1,1'}$ = 11.7, 11.7* Hz, H'-1), 3.76*, 3.77 (1H, 2dd, H-1), 3.81, 3.82* (1H, 2m, H-3), 3.83, 3.89* (1H, 2m, POCH'), 4.055, 4.06* (1H, 2m, POCH), 7.49, 7.49* [2H, m, Ph(*m*)], 7.55, 7.55* [1H, m, Ph(*p*)], 7.79, 7.79* [2H, m, Ph(*o*)]; ^{31}P NMR δ = 42.5*, 43.0 (53:47* diastereomeric mixture, the assignment of some of the δ values may have to be interchanged). *Anal*. Calcd for $C_{14}H_{23}O_5P$: C, 55.62; H, 7.67. Found: C, 55.55; H, 7.71.

1-Bromo-1,4-dideoxy-4-[(*R* and *S*)-ethoxy(phenyl)phosphinoyl]-2,3-di-*O*-methyl-L-threitols (10a).

To a solution of **16** (300 mg, 0.992 mmol) in $CHCl_3$ (8 mL) were added carbon tetrabromide (500 mg, 1.50 mmol) and triphenylphosphine (350 mg, 1.33 mmol) at 0 °C. The mixture was stirred at rt for 15 min, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 4:1 AcOEt-$CHCl_3$ as an eluant to give an inseparable diastereomeric mixture (1:1) of **10a** (282 mg, 78%) as a colorless syrup: R_f = 0.35 (*D*); ^{1}H NMR δ = 1.29, 1.30* (3H, 2t, J_{Et} = 7.2 Hz, C–CH_3), 2.15, 2.23* (1H, 2ddd, $J_{4,4'}$ = 15.3, 15.3*, $J_{4',P}$ = 12.8, 16.8*, $J_{3,4'}$ = 6.4, 6.1* Hz, H'-4), 2.30*, 2.38 (1H, 2ddd, $J_{4,P}$ = 12.2*, 17.7, $J_{3,4}$ = 7.0*, 6.7 Hz, H-4), 3.21, 3.29*, 3.37*, 3.50 (6H, 4s, MeO-2,3), 3.49, 3.58* (1H, 2m, H-2), 3.52, 3.55* (1H, 2dd, $J_{1,1'}$ = 10.7, 9.2*, $J_{1',2}$ = 5.2, 5.2* Hz, H'-1), 3.63*, 3.67 (1H, 2dd, $J_{1,2}$ = 5.8, 6.7* Hz, H-1), 3.82, 3.85* (1H, 2dtd, $^2J_{H,H'}$ = 10.0, $J_{H',P}$ = 7.0 Hz, POCH'), 3.83, 3.92* (1H, 2m, H-3), 4.08, 4.09* (1H, 2dquint, $J_{H,P}$ = 7.0 Hz, POCH), 7.49, 7.50* [2H, 2m, Ph(*m*)], 7.56, 7.56*

[1H, m, Ph(*p*)], 7.78, 7.80* [2H, 2m, Ph(*o*)]; ^{31}P NMR δ = 41.6*, 42.2 (53:47* diastereomeric mixture, the assignment of some of the δ values may have to be interchanged). *Anal*. Calcd for $C_{14}H_{22}O_4BrP$: C, 46.04; H, 6.07. Found: C, 46.18; H, 6.01.

(3*R*,4*R*)-3,4-Dimethoxy-1-phenylphospholane 1-oxide (3).[15]

To a solution of **10a** (40.8 mg, 0.112 mmol) in dry toluene (0.8 mL) was added, with stirring, a solution of SDMA (3.4M toluene solution, 0.100 mL, 0.34 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then at rt for 6 h. The mixture was diluted with toluene (2 mL) and water (0.1 mL) was added to decompose excess SDMA. Then the mixture was passed through celite and the filtrate was evaporated in vacuo to give (3*R*,4*R*)-3,4-dimethoxy-1-phenylphospholane (**21**) as a colorless syrup: R_f = 0.56 (*A*); ^{31}P NMR δ = –30.9.

This syrup was dissolved in $CHCl_3$ (1 mL), treated with 30% H_2O_2 (0.2 mL, 2.0 mmol) at rt for 6 h. The mixture was diluted with $CHCl_3$ (10 mL), washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:19 EtOH-AcOEt to give **3** (13.0 mg, 48%) as colorless prisms: mp 76–77 °C (from AcOEt-hexane); R_f = 0.07 (*D*), 0.24 (*E*); ^{1}H NMR δ = 2.19 (1H, ddd, $J_{2,2'}$ = 15.9, $J_{2',P}$ = 4.4, $J_{2',3}$ = 3.5 Hz, H'-2), 2.22–2.31 (2H, m, H,H'-5), 2.46 (1H, ddd, $J_{2,P}$ = 18.9, $J_{2,3}$ = 6.1 Hz, H-2), 3.41, 3.45 (3H each, 2s, MeO-3,4), 4.06 (1H, dq, $J_{4,P}$ = 23.1, $J_{4,5}$ = $J_{4,5'}$ = 3.7, $J_{3,4}$ = 3.5 Hz, H-4), 4.17 (1H, ddt, $J_{3,P}$ = 23.7 Hz, H-3), 7.48–7.54 [3H, m, Ph(*m.p*)], 7.84 [2H, ddd, $J_{o,P}$ = 12.2, $J_{o,m}$ = 8.2, $J_{o,p}$ = 1.6 Hz, Ph(*o*)]; ^{31}P NMR δ = 52.0. *Anal*. Calcd for $C_{12}H_{17}O_3P$: C, 60.00; H, 7.13. Found: C, 59.97; H, 7.21.

1-Phenylphospholane 1-oxide (7a).[7,16]

A. Reductive cyclization of 5. By employing the same procedures as those described above, compound (**5**) was reduced with SDMA and then treated with H_2O_2 to give **7a** (51% yield) as a colorless syrup: R_f = 0.06 (*D*), 0.17 (*E*).

B. Grignard reaction of 4. The mixture of magnesium (120 mg, 4.94 mmol) and 1,2-dibromoethane (0.03 mL) in dry THF (3 mL) was stirred vigorously and a solution of **4** (0.300 mL, 2.54 mmol) in dry THF (2 mL) was added dropwise. The mixture was refluxed for 3 h and then cooled. To the mixture was added a solution of phenylphosphonic dichloride (0.360 mL, 2.54 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred at rt for 8 h and diluted with saturated NH_4Cl aqueous solution (5 mL). The mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:19 EtOH-AcOEt to give **7a** (182 mg, 40%).

C. Grignard reaction of 5. A mixture of magnesium (16 mg, 0.66 mmol) and 1,2-dibromoethane (0.01 mL) in dry THF (2 mL) was stirred vigorously and a solution of **5** (100 mg, 0.328 mmol) in dry THF (2 mL) was added dropwise. The mixture was refluxed for 4 h and neutralized with saturated NH_4Cl

aqueous solution (5 mL). The mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:19 EtOH-AcOEt to give **7a** (32.1 mg, 54%).

Grignard reaction of 9a.

Similar procedures to those for **7a** from **4** were employed. Compound (**9a**) (97.0 mg, 0.35 mmol) was treated with magnesium (25 mg, 1.03 mmol) in boiling THF and then phosphonic dichloride (0.050 mL, 0.35 mmol) at rt. Purification of the resulting mixture by column chromatography gave dimethyl phenylphosphonate (**23**) (32.0 mg, 49%) as a colorless oil: R_f = 0.43 (*D*); ^{1}H NMR δ = 3.75 (6H, d, J_{POMe} = 10.8 Hz, Me), 7.47 [2H, td, $J_{o,m} = J_{m,p}$ = 7.6, $J_{m,P}$ = 4.3 Hz, Ph(*m*)], 7.56 [1H, tq, $J_{o,p} = J_{p,P}$ = 1.4 Hz, Ph(*p*)], 7.79 [2H, ddd, $J_{o,P}$ = 13.2 Hz, Ph(*o*)]; ^{31}P NMR δ = 20.5.

Grignard reaction of 10a.

The mixture of magnesium (30 mg, 1.23 mmol) and 1,2-dibromoethane (0.01 mL) in dry THF (2 mL) was stirred vigorously and a solution of **10a** (230 mg, 0.623 mmol) in dry THF (3 mL) was added dropwise. The mixture was refluxed for 4 h and then diluted with saturated NH_4Cl aqueous solution (5 mL). The mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was separated by column chromatography with AcOEt to give ethyl (*R* and *S*)-[(2*R*)-2-methoxy-3-butenyl](phenyl)phosphinate (**26**) (93.8 mg, 59%) and **3** (3.0 mg, 2%).

26: Colorless syrup; R_f = 0.28 (*D*); ^{1}H NMR δ = 1.27, 1.29* (3H, 2t, J_{Et} = 7.2 Hz, C–CH_3), 2.07*, 2.13 (1H, 2ddd, $J_{1',P}$ = 12.8*, 18.3, $J_{1,1'}$ = 15.3*, 15.3, $J_{1',2}$ = 5.5*, 4.9 Hz, H'-1), 2.26, 2.25* (1H, 2ddd, $J_{1,P}$ = 11.3, 15.0*, $J_{1,2}$ = 8.5, 7.9* Hz, H-1), 3.07, 3.19* (3H, 2s, MeO), 3.83, 3.88* (1H, 2dquint, $^2J_{H,H'}$ = 10.4, $J_{H',P}$ = 7.0 Hz, POCH'), 3.93, 3.93* (1H, m, H-2), 4.04, 4.08* (1H, 2dquint, $J_{H,P}$ = 7.0 Hz, POCH), 5.09*, 5.165 [1H, 2ddd, $J_{3,4E}$ = 10.1, $J_{4E,4Z}$ = 1.5, $J_{2,4E}$ = 1.0 Hz, H-4(*E*)], 5.17*, 5.19 [1H, 2dt, $J_{3,4Z}$ = 17.1, $J_{2,4Z}$ = 1.0 Hz, H-4(*Z*)], 5.56*, 5.66 (1H, 2ddd, $J_{2,3}$ = 7.6 Hz, H-3), 7.45, 7.46* [2H, 2m, P–Ph(*m*)], 7.52, 7.52* [1H, m, P–Ph(*p*)], 7.76*, 7.77 [2H, 2m, P–Ph(*o*)]; ^{31}P NMR δ = 41.1, 42.3* (56:44* diastereomeric mixture, the assignment of some of the δ values may have to be interchanged). *Anal*. Calcd for $C_{14}H_{19}O_3P$: C, 63.15; H, 7.19. Found: C, 63.28; H, 7.09.

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14. Bromination of **17a** with same reagents at room temperature resulted in a lower yield (30%) of **18**.
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