Pergamon

Tetrahedron Vol. 51, No. 7, pp. 2099-2108, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01083-8

Synthesis of Pyrophosphonic Acid Analogues of Farnesyl Pyrophosphate

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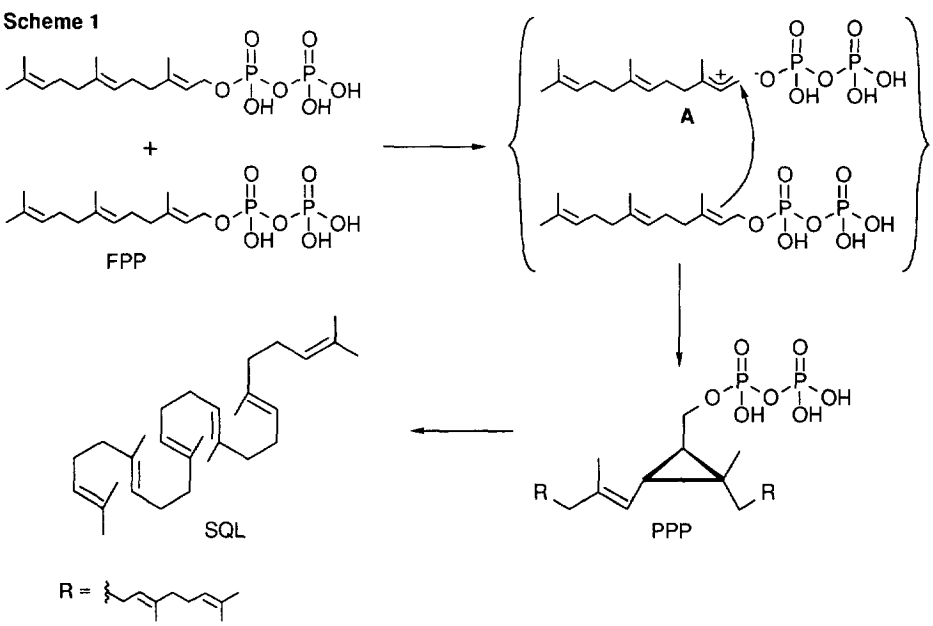
Abstract: The synthesis of four new analogues (*i.e.* **3-6**) of farnesyl pyrophosphate (FPP), which may function as inhibitor of squalene synthase, is described. Compounds **3** and **4** were readily accessible by reaction of farnesal with diethyl phosphite or dimethyl lithiomethylphosphonate, respectively, followed by condensation of the resulting alcohols with diethyl phosphonomethyl triflate. The preparation of **5** and **6** was accomplished by alkylation of bis(diethyl phosphonomethyl) ether or tetraethyl methylenebisphosphonate, respectively, with farnesyl bromide.

Introduction

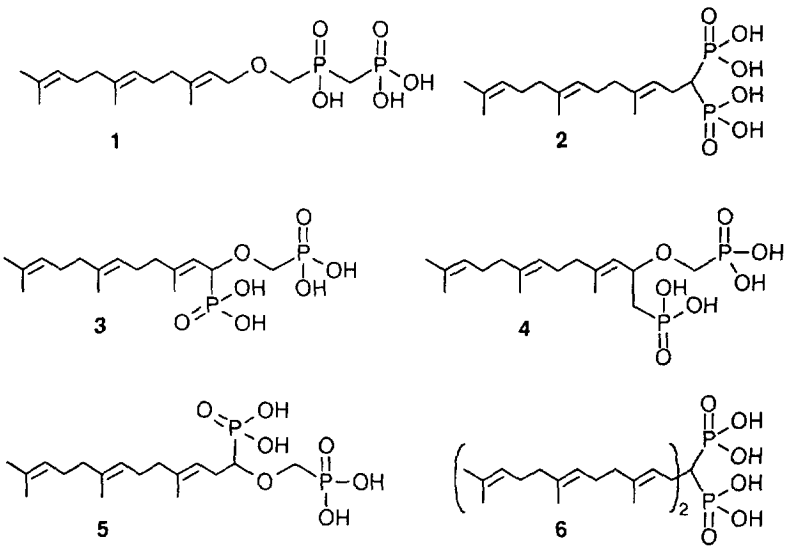
The enzyme squalene synthase (SS) catalyses (see Scheme 1) the head-to-head condensation of two farnesyl pyrophosphate (FPP) molecules to give squalene (SQL) *via* the intermediate presqualene pyrophosphate (PPP). The SS-mediated reductive dimerization of two FPP-units, which is the first

Scheme 1



biosynthetic step leading exclusively to sterols, presents an attractive target for inhibition of the cholesterol biosynthesis. Thusfar, several mechanisms have been proposed[1] for the enzymic conversion of FPP into SQL. Recently, Mookhtiar *et al.*[2] postulated that sequential occupation of the donor and acceptor sites of SS by two individual FPP molecules is followed by cleavage of the carbon-oxygen bond of the donor FPP to give an intimate ion pair (see **A** in Scheme 1) of the allylic carbocation and inorganic pyrophosphate. In the next step, an insertion reaction takes place between the C1 of the cation and the C2-C3 double bond of the acceptor FPP to produce PPP, which is further processed to SQL.

The first potent inhibitor of SS (*i.e.* **1**) was reported by Biller *et al.*[3] and contains an oxy-methylphosphinylmethylphosphonate moiety instead of the naturally occurring pyrophosphate function. The allylic oxygen in this analogue is believed to be involved in binding to the donor-site of SS. Later on,



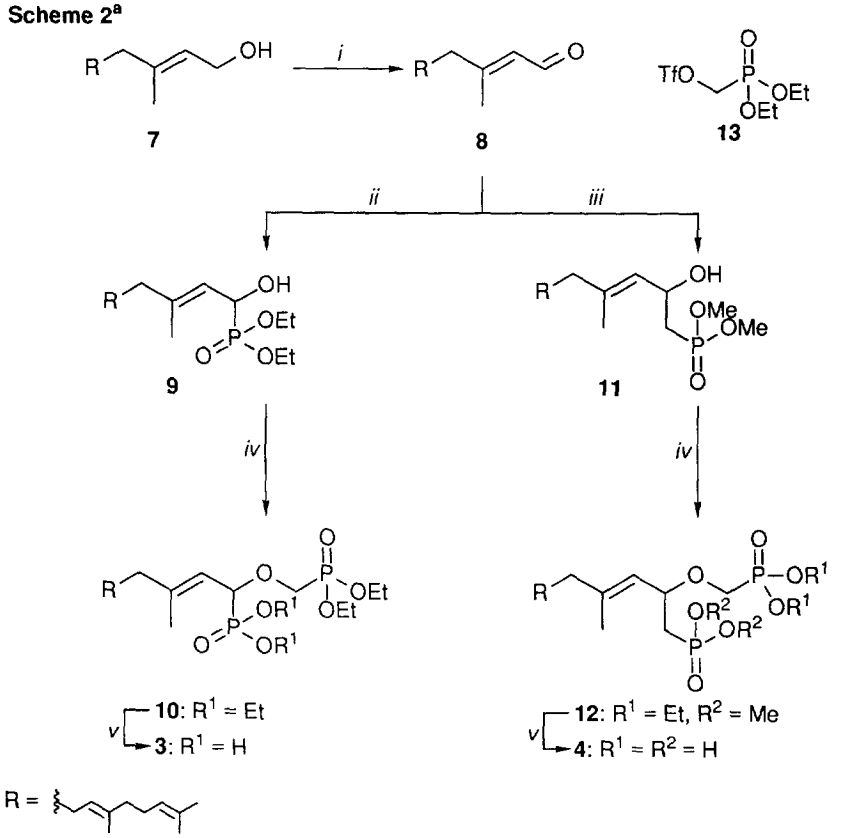
Ciosek *et al.*[4] showed that 1,1-bisphosphonate analogues of FPP (*e.g.* compound **2**) are even more potent inhibitors of SS. The latter class of compounds may mimic the proposed[2] tight-ion pair of the allylic cation and the inorganic pyrophosphate.

As part of an ongoing[5] program directed towards the design and synthesis of SS-inhibitors, we here report the preparation of four new analogues of FPP (*i.e.* **3**, **4**, **5** and **6**) containing the same phosphonic acid structural elements as the earlier mentioned 1,1-bisphosphonic acid inhibitors. Apart from this, compounds **3**-**5** also contain an allylic (as in **3** and **4**) or homoallylic (as in **5**) oxygen, either of which seems to be essential for binding to SS.[3]

Results and Discussion

Retrosynthetic analysis reveals (see Scheme 2) that farnesal (**8**) is an appropriate starting compound in the synthesis of target compounds **3** and **4**. Aldehyde **8** was obtained in nearly quantitative yield by Swern oxidation of farnesol (**7**). The synthesis route to **3** proceeded further with the preparation of α-hydroxy farnesylphosphonate **9**. Initially, treatment of **8** with diethyl phosphite in diethyl ether and sodium hydride, led to an intractable mixture of products. Fortunately, **9** could be synthesized in 50% yield according to the procedure of Pompliano *et al.*.[6] In the following step, protected bisphosphonate **10** was readily accessible by addition of diethyl phosphonomethyltriflate (**13**)[7] to the lithium alcoholate of **9**, generated *in situ* with *n*-butyllithium in tetrahydrofuran at -78°C. Removal of the phosphonate protecting groups of **10** occurred smoothly by the following two-step procedure. Thus, reaction of **10** with trimethylsilyl bromide (TMS-Br) in the presence of the acid scavenger *sym*-collidine, and subsequent basic hydrolysis of the resulting TMS-ester with aqueous KOH, yielded crude bisphosphonic acid **3**. Purification of the crude reaction mixture by CHP20P-gel chromatography[8] afforded homogeneous **3** (K^+-salt) in 65% yield.

Scheme 2[a]



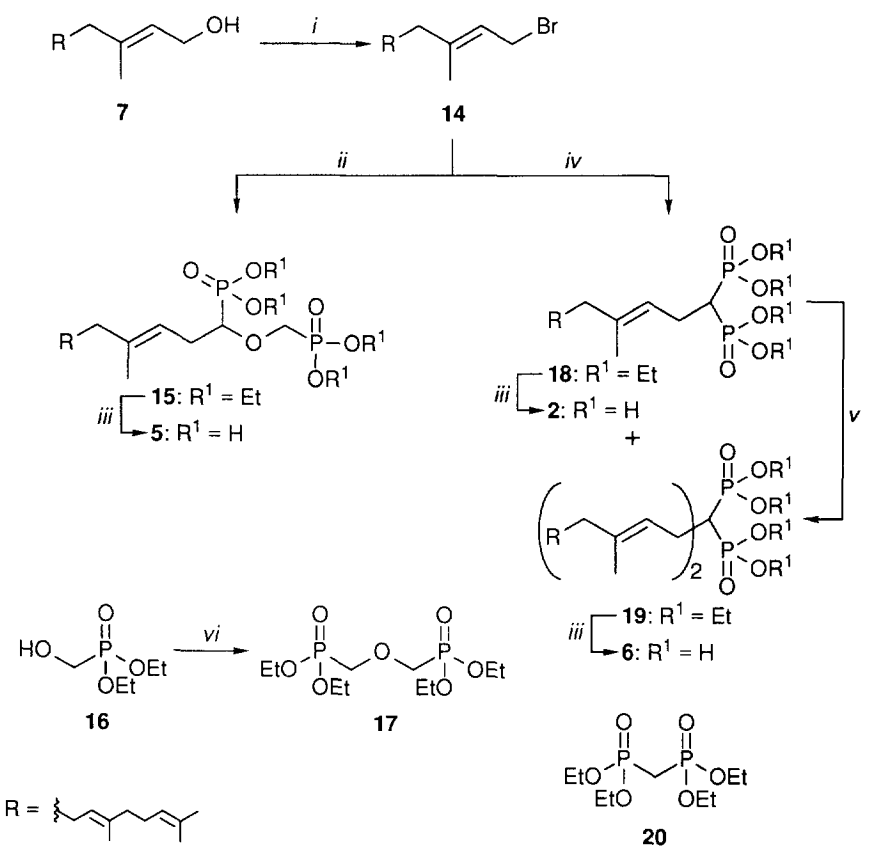
[a] **Reagents and conditions**

i: Swern oxydation; *ii*: $HP(O)(OEt)_2$, NEt_3; *iii*: $LiCH_2P(O)(OMe)_2$, THF, -78 to 0°C; *iv*: *n*-BuLi, 2) **13**, THF, -78 to 0°C; *v*: 1) TMS-Br, *sym*-collidine, CH_2Cl_2, 2) N KOH.

A similar route was followed to the synthesis of FPP-analogue **4**. Thus, condensation of farnesal **8** with dimethyl lithiomethylphosphonate gave the requisite β-hydroxy phosphonate **11** in 75% yield. Transformation of **11** into **4** was achieved by the same sequence of reactions as mentioned earlier for the conversion of **9**→**3**. Hence, condensation of the lithium salt of **11** with triflate **13** furnished bisphosphonate **12**. Transesterification of **12** followed by saponification of the resulting TMS-ester with N KOH provided bisphosphonic acid **4** in a satisfactory yield.

In principle, analogue **5** could be prepared in a similar fashion. However, the latter would entail a three-step homologation sequence of farnesal to homofarnesal[9] prior to the introduction of the two phosphonic acids. A more direct route to compound **5** is delineated in Scheme 3 and comprises alkylation of bis(diethyl phosphonomethyl) ether (**17**) with farnesyl bromide (**14**). Reagent **17**, previously prepared[10] by nucleophilic displacement of the bromine atoms in bis(bromomethyl) ether with the potassium anion of

Scheme 3[a]



[a]**Reagents and conditions**

i: NBS, dimethyl sulfide, CH_2Cl_2, -40 to 0°C; *ii*: **17**, LDA, THF, -78°C; *iii*: 1) TMS-Br, *sym*-collidine, CH_2Cl_2, 2) N KOH; *iv*: **20**, NaH, THF; *v*: NaH, **14**, THF; *vi*: *n*-BuLi, **13**, THF, -78°C.

diethyl phosphite, was readily accessible by treatment of **13** with the lithium salt of diethyl hydroxymethylphosphonate (**16**). Addition of farnesyl bromide (**14**) to the lithiated species of **17** gave protected analogue **15** in 48% yield. The low yield of the alkylation reaction may be ascribed to the destabilizing effect of the neighbouring ether-oxygen on the carbanion of **17**. Deprotection of **15** to give **5** proceeded analogous to the transformation of **10→3**.

In order to compare the biological activity of the new FPP-analogues **3-5** with a known inhibitor of Ciosek *et al.*,[4] we prepared farnesylmethylbisphosphonic acid **2** starting from farnesyl bromide (**14**)[11] and commercially available tetraethyl methylenebisphosphonate (**20**). Thus, alkylation of **20** with **14** in the presence of sodium hydride gave major **18** and minor **19** (10%), as gauged by ^{31}P-NMR spectroscopy of the crude reaction mixture. In this respect, it is interesting to note that Sulsky *et al.*[12] reported that alkylation of **20** with allylic halides yielded mainly the disubstituted products. Further processing of **18**, as described earlier, resulted in the isolation of **2** in good yield. At this stage, we reasoned that the disubstituted product **6** may also function as potential inhibitor of SS. Preparation of bisfarnesylmethylenebisphosphonic acid **6** was readily accomplished by alkylation of **18** with bromide **14** in the presence of sodium hydride to afford **19**. Deblocking of **19** proceeded smoothly to give, after purification, homogeneous **6**.

In conclusion, the results presented in this paper show that four new analogues of FPP were readily accessible by a simple and straightforward methodology. These analogues are valuable tools to get a better insight into the structure-activity relationship between FPP-analogues and the enzyme squalene synthase.

Experimental Section

General procedures

(E,E)-Farnesol was purchased from Aldrich and distilled. Toluene, dichloromethane and ether were dried by refluxing with P_2O_5 for 2 hours and then distilled. Toluene and ether were stored over sodium wire. Dichloromethane was stored over molecular sieves (0.4 nm). THF and acetonitrile were dried by refluxing with CaH_2 for 16 h, distilled and stored over molecular sieves (0.4 nm). THF and ether were redistilled from $LiAlH_4$ directly before use. All reactions were carried out under a blanket of argon. TLC-analysis was performed on silicagel (Schleicher & Schull, F 1500 LS 254). Compounds were visualised by spraying the TLC-plates with $KMnO_4$ (1%) in aqueous Na_2CO_3 (2%). Column chromatography was performed on Merck Kieselgel (230-400 Mesh ASTM). Evaporations were carried out below 40°C under reduced pressure (15 mm Hg). ^{1}H, ^{13}C and ^{31}P NMR spectra were measured at 199.99, 50.1 and 80.7 MHz, respectively, using a JEOL JNM-FX 200 spectrometer on line with a JEC 980 B computer. ^{1}H and ^{13}C chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS) as internal standard and ^{31}P chemical shifts are given in ppm (δ) relative to 85% H_3PO_4 as external standard.

(E,E)-Diethyl 1-hydroxy-farnesylphosphonate (9)

To a solution of (E,E)-farnesal (**8**) (1 g, 4.5 mmol) in acetonitrile (5 mL) were added triethylamine (1.25 mL) and diethylphosphite (0.9 mL, 7 mmol). After stirring for 5 days TLC-analysis (ethyl acetate/acetone 9/1 v/v) indicated that no further conversion of farnesal into the target compound took place and the reaction mixture was taken up in ether and washed with water. The organic layer was dried ($MgSO_4$) and evaporated to dryness. Purification of the crude product was effected by chromatography over silica gel (EtOAc/acetone 1/0 to 9/1 v/v) to give the title compound as a colourless oil in 50% yield.

$^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 15.5 (C14); 16.1 (OCH_2CH_3); 16.6 (C13); 17.2 (C15); 25.2 (C12); 26.1 (C5); 26.5 (C9); 39.5 (C4 and C8); 62.2 (OCH_2CH_3); 65.4 (C1, $J_{C\text{-}P}$ = 165.3 Hz); 120.4 (C2); 123.5 (C6); 124.1 (C10); 140.4 (C3, $J_{C\text{-}P}$ = 14.6 Hz); 134.8 (C7); 130.6 (C11).

^1H NMR ($CDCl_3$): δ 1.26 (t, 6 H, OCH_2CH_3); 1.59, 1.68, 1.72 (3 x s, 12 H, H12, H13, H14, H15); 1.98-2.24 (m, 8 H, H4, H5, H8, H9); 4.07-4.23 (m, 5 H, H1, OCH_2CH_3); 5.02-5.15 and 5.26-5.32 (2 x m, 3 H, H2, H6, H10).

$^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 23.8.

(E,E)-Diethyl 1-(diethyl phosphonomethoxy)-farnesylphosphonate (10)

A cooled (-78°C) solution of **9** (358 mg, 1 mmol) in THF (5 mL) was treated with *n*-BuLi (625 µL, 1.6M in hexane, 1 mmol) and stirring was continued for 40 min. Then diethyl phosphonomethyltriflate (330 mg, 1 mmol) in THF (1 mL) was added and the reaction mixture was stirred for 30 min at -78°C and 2h at 0°C. The reaction was diluted with ether (10 mL), washed with saturated NH_4Cl (5 mL) and dried over $MgSO_4$. Concentration of the organic layer under reduced pressure and purification of the residue by silica gel chromatography (EtOAc/acetone 1/0 to 9/1 v/v) gave 95% of the title compound.

$^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 15.6 (C14); 16.1 (OCH_2CH_3); 16.7 (C13); 17.3 (C15); 25.3 (C12); 25.9 (C5); 26.4 (C9); 39.4 (C8); 39.5 (C4); 62.0 (OCH_2CH_3 and OCH_2P, $^1J_{C\text{-}P}$ = 165.3 Hz, $^3J_{C\text{-}P}$ = 14.6 Hz); 74.0 (C1, $^1J_{C\text{-}P}$ = 172.6 Hz, $^3J_{C\text{-}P}$ = 10.2 Hz); 123.9 (C2); 125.2 (C6); 125.6 (C10); 145.6 (C3, $J_{C\text{-}P}$ = 13.1 Hz); 137.2 (C7); 135.2 (C11).

$^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 20.4, 21.4.

(E,E)-Dimethyl 2-hydroxy-4,8,12-trimethyl-3,7,11-tridecatrienylphosphonate (11)

A cooled (-78°C) solution of dimethyl methylphosphonate (0.46 mL, 4.2 mmol) in THF (15 mL) was treated with *n*-BuLi (2.6 mL, 1.6M in hexane, 4.16 mmol). After 40 min farnesal (440 mg, 2 mmol) in THF (5 mL) was added dropwise and stirring was continued until TLC analysis (ethyl acetate/acetone 9/1 v/v) showed complete disappearance of the starting material. The reaction was quenched with saturated NH_4Cl and diluted with ether. The organic layer was washed twice with water and dried over $MgSO_4$. After evaporation of the solvent the crude material was purified by column chromatography over silica gel (ethyl acetate/methanol 100/0 to 95/5 v/v) to give the title compound in 75% yield.

$^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 15.5 (C15); 16.1 (C14); 17.1 (C16); 25.2 (C13); 25.8 (C6); 26.2 (C10); 32.9 (C1, $J_{C\text{-}P}$ = 136.3 Hz); 39.0 (C9); 39.2 (C5); 51.8 (OCH_3); 62.8 (C2, $J_{C\text{-}P}$ = 2.9 Hz); 123.3 (C7); 123.8 (C11); 126.7 (C3, $J_{C\text{-}P}$ = 14.7 Hz); 131.7 (C12); 134.7 (C8); 137.5 (C4).

^{31}P NMR ($CDCl_3$) δ 32.5.

(E,E)-Dimethyl 2-(diethyl phosphonomethoxy)-4,8,12-trimethyl-3,7,11-tridecatrienyl-phosphonate (12)
A cooled (-78°C) solution of **11** (512 mg, 1.5 mmol) in THF (5 mL) was treated with *n*-BuLi (0.94 mL, 1.6M in hexane, 1.5 mmol) and stirred for 40 min. Then diethyl phosphonomethyltriflate (480 mg, 1.5 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78°C followed by 2 h at 0°C. The reaction was quenched with saturated NH_4Cl and the mixture was diluted with ether and washed with water. The organic layer was dried over $MgSO_4$ and concentrated. Purification of the crude reaction mixture by silica gel chromatography (ether/acetone 1/0 to 9/1 v/v) afforded 86% of the title compound.
$^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 14.5 (OCH_2CH_3); 15.7 (C15); 16.0 (C14); 17.1 (C16); 24.9 (C13); 25.5 (C6); 26.0 (C10); 30.8 (C1, J_{C-P} = 139.2 Hz); 39.0 (C9); 39.0 (C5); 51.6 (OCH_3); 60.2 (OCH_2P, J_{C-P} = 170.0 Hz); 62.1 (OCH_2CH_3); 72.0 (C2, J_{C-P} = 14.6 Hz); 122.6 (C7); 122.8 (C11); 122.5 (C3, J_{C-P} = 11.7 Hz); 130.3 (C12); 134.7 (C8); 142.0 (C4).
^{31}P NMR ($CDCl_3$) δ 31.5, 22.7.

(E,E)-Diethyl 1-(diethyl phosphonomethoxy)-4,8,12-trimethyl-3,7,11-tridecatrienyl-phosphonate (15)
A cooled (-78°C) solution of bis(diethyl phosphonomethyl) ether (600 mg, 2 mmol) in THF (2 mL) was treated with LDA (2 mmol) and stirred for 30 min. Then farnesyl bromide (1.2 mmol) in THF (2 mL) was added and stirring was continued for another hour. When TLC analysis showed no further conversion of the starting compound the reaction was quenched by addition of saturated NH_4Cl. The mixture was diluted with ether and the organic layer was washed with saturated NH_4Cl and brine, dried over $MgSO_4$ and concentrated. Purification of the crude oil over silica gel (EtOAc/acetone 1/0 to 9/1 v/v) yielded 48% of the title compound as a colourless oil.
$^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 15.8 (C15); 15.9 (C14); 16.0 (OCH_2CH_3); 16.1 (C16); 25.2 (C13); 26.1 (C6); 26.3 (C10); 28.6 (C2); 39.3 (C9); 39.4 (C5); 62.0 (OCH_2CH_3); 65.1 (OCH_2P, J_{C-P} = 165.3 Hz); 77.9 (C1, J_{C-P} = 160.9 and 13.1 Hz); 118.7 (C3, J_{C-P} = 11.7 Hz); 123.6 (C7); 123.9 (C11); 130.7 (C12); 134.6 (C8); 137.6 (C4).
^1H NMR ($CDCl_3$) δ 1.34 (t, 12 H, OCH_2CH_3); 1.60, 1.64, 1.68 (3 x s, 12 H, H13, H14, H15, H16); 1.93-2.16 (m, 8 H, H5, H6, H9, H10); 2.40-2.53 (m, 2 H, H2); 3.61-3.72 (m, 1 H, H1); 5.10-5.33 (m, 3 H, H3, H7, H11).
$^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 20.6, 22.3

(E,E)-Tetraethyl farnesylmethylene-1,1-bisphosphonate (18)
To a cooled (0°C) suspension of NaH (67 mg, 2.8 mmol) in THF (2 mL) was added dropwise a solution of tetraethylmethylene bisphosphonate (746 µL, 3 mmol) in THF (2 mL). After stirring for 30 min farnesyl bromide (2 mmol) in THF (2 mL) was added and stirring was continued for 2 hours. When TLC analysis showed complete conversion of the starting material, the reaction was stopped by addition of ethanol. The reaction mixture was diluted with ether and washed with saturated NH_4Cl and brine and dried over $MgSO_4$. Purification of the crude mixture by silica gel chromatography (EtOAc/acetone 1/0 to 9/1 v/v) afforded pure **18** in 62% yield.

$^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 15.3 (C15); 15.6 (C14); 15.7 (OCH_2CH_3); 17.2 (C16); 23.4 (t, C2, J_{C-P} = 4.4 Hz); 24.9 (C13); 25.8 (C10); 26.0 (C6); 36.9 (t, C1, J_{C-P} = 134 Hz); 39.0 (C5 and C9); 121.3 (t, C3, J_{C-P} = 7.3 Hz); 123.3 (C7); 123.7 (C11); 130.2 (C12); 134.1 (C8); 135.8 (C4).
$^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 24.2.

(E,E,E,E)-Tetraethyl bis(farnesyl)methylene-1,1-bisphosphonate (19)

To a cooled (0°C) suspension of NaH (240 mg, 10 mmol) in THF (5 mL) was added dropwise a solution of compound **15** (4 mmol) in THF (5 mL). After stirring for 30 min farnesyl bromide (5 mmol) in THF (5 mL) was added and stirring was continued for 2 hours. When TLC analysis showed complete conversion of the starting material, the reaction was stopped by addition of ethanol. The reaction mixture was diluted with ether and washed with saturated NH_4Cl and brine and dried over $MgSO_4$. Purification of the crude mixture by silica gel chromatography (EtOAc/acetone 1/0 to 9/1 v/v) afforded homogeneous **19** in 64% yield.

$^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 15.2, 15.6, 15.9 (C14, C15, C16); 15.8 (OCH_2CH_3); 24.9 (C13); 25.9, 26.0 (C6, C10); 28.5 (C2); 39.0, 39.4 (C5, C9); 45.2 (t, C1, J_{C-P} = 130 Hz); 118.7 (C3); 123.5, 123.7 (C7, C11); 130.1 (C12); 134.0 (C8); 136.1 (C4).
^1H NMR ($CDCl_3$) δ 1.32 (t, 12 H, OCH_2CH_3); 1.59, 1.62, 1.68 (3xs, 24 H, H13, H14, H15, H16); 1.99-2.17 (m, 16 H, H5, H6, H9, H10); 2.60 (dt(b), 4 H, H2); 4.17 (quin., 8H, OCH_2CH_3); 5.01-5.19 and 5.31-5.47 (2xm, 6 H, H3, H7, H11).
$^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 27.0.

Bis(diethyl phosphonomethyl) ether (17)

A cooled (-78°C) solution of diethyl hydroxymethylphosphonate (840 mg, 5 mmol) in THF (5 mL) was treated with *n*-BuLi (1.6 M, 3.1 mL, 5 mmol) and the reactionmixture was stirred for 40 min at -78°C. Then diethyl phosphonomethyltriflate (1.5 g, 5 mmol) in THF (5 mL) was added and the reaction mixture was allowed to warm to 0°C in 2 h. The reaction was stopped by addition of saturated NH_4Cl, the mixture was diluted with ether, washed with brine and dried over $MgSO_4$. After removal of the solvent the crude oil was purified by silica gel chromatography (EtOAc/acetone 100/0 to 9/1 v/v) to give 69% of **17**.
$^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 16.2 (OCH_2CH_3); 60.1 (dd, OCH_2P, $^1J_{C-P}$ = 164 Hz, $^3J_{C-P}$ = 15 Hz); 62.3 (OCH_2CH_3);
$^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 20.0.
Anal. calcd. for $C_{10}H_{24}O_7P_2$: P 19.5; found P 19.65%

General procedure for the deprotection of compounds 10, 12, 15, 18 and 19

The starting material (1 mmol) was dissolved in a mixture of dichloromethane (5 mL) and *sym*-collidine (0.7 mL, 5 mmol). Then TMS-Br (0.85 mL, 6.25 mmol) was added and the reaction mixture was stirred for 16 h at RT. The volatiles were removed by evaporation and the residue was treated with aqueous KOH (0.5M, 10 mL). The mixture was stirred for 30 min at RT and then concentrated under reduced pressure. The crude compound was purified on a CHP20P column that was eluted with a linear gradient of 80%

acetonitrile/water in 5% methanol/water. Freeze drying of the appropriate fractions yielded the deprotected compounds **2-6** as amorphous white solids.

2: Yield: 68%. $^{13}C\{^1H\}$ NMR (D_2O) δ 16.2 (C14, C15); 18.0 (C16); 25.0 (C2); 25.9 (C13); 27.0, 27.3 (C6, C10); 40.0, 40.2 (C5, C9); 40.8 (t, C1, J_{C-P} = 112 Hz); 125.1 (C3); 125.5 (C7, C11); 133.0 (C12); 136.5 (C8); 136.6 (C4).

^1H NMR (D_2O) δ 1.56, 1.59, 1.64 (3xs, 12 H, H13, H14, H15, H16); 1.77 (tt, 1 H, H1, J_{H-P} = 21 Hz, $J_{H1,H2}$ = 7 Hz); 1.93-2.10 (m, 8 H, H5, H6, H9, H10); 2.47 (tt, 2 H, H2, $J_{H1,H2} = J_{H2,H3}$ = 6.9 Hz, J_{H-P} = 15.4 Hz); 5.10 (t, 1 H, H3, $J_{H2,H3}$ = 6.8 Hz); 5.18, 5.47 (2xt, 2 H, H7, H11).

$^{31}P\{^1H\}$ NMR (D_2O) δ 20.7.

3: Yield: 65%. $^{13}C\{^1H\}$ NMR (D_2O) δ 16.1 (C14); 17.1 (C13); 17.9 (C15); 25.8 (C12); 26.8 (C5); 27.0 (C9); 39.8 (C8); 40.3 (C4); 121.0 (C2); 125.2 (C6); 125.4 (C10); 133.6 (C11); 136.9 (C7); 143.7 (C3, J_{C-P} = 9 Hz).

^1H NMR (D_2O) δ 1.58, 1.60, 1.65, 1.71 (4 x s, 12 H, H12, H13,H14, H15); 1.95-2.19, (m, 8 H, H4, H5, H8, H9); 3.11-3.26 (m (b), 1 H, H_A OCH_2P); 3.56-3.69 (m (b), 1 H, H_B OCH_2P); 4.07-4.18 (m (b), 1 H, H1); 5.11-5.21 (m, 3 H, H2, H6, H10).

$^{31}P\{^1H\}$ NMR (D_2O) δ 16.1, 17.0.

Anal. calcd. for $C_{16}H_{30}O_7P_2$: P 15.6; found P 15.49%

4: Yield: 63%. $^{13}C\{^1H\}$ NMR (D_2O) δ 16.4 (C15); 17.0 (C14); 18.1 (C16); 26.1 (C13); 27.1 (C6); 27.2 (C10); 35.6 (C1, J_{C-P} = 130.0 Hz); 40.2 (C9); 40.2 (C5); 65.3 (OCH_2P, J_{C-P} = 155.0 Hz); 75.5 (C2); 124.9 (C7); 125.2 (C11); 125.7 (C3, J_{C-P} = 15.3 Hz); 132.4 (C12); 136.3 (C8); 141.0 (C4).

^1H NMR (D_2O) δ 1.58 (s, 3 H, H16); 1.59 (s, 3 H, H15); 1.65 (s, 3 H, H13); 1.72 (s, 3 H, H14); 1.95-2.12 (m, 8 H, H5, H6, H9, H10); 3.34 (ABX, 1 H, $H_A(OCH_2P)$, J_{H-P} = 8.6 Hz, J_{AB} = 13.2 Hz); 3.60 (ABX, 1 H, $H_B(OCH_2P)$, J_{H-P} = 7.5 Hz, J_{BA} = 13.2 Hz); 4.54 (q, 1 H, H2); 5.08-5.14 (m, 3 H, H3, H7, H11).

^{31}P NMR (D_2O) δ 20.79, 15.93.

Anal. calcd. for $C_{17}H_{32}O_7P_2$: P 15.1; found P 14.94%

5: Yield: 70%. $^{13}C\{^1H\}$ NMR (D_2O) δ 16.2 (C15); 16.5 (C14); 17.9 (C16); 25.9 (C13); 26.9 (C6); 27.2 (C10); 30.6 (C2); 39.9 (C9); 40.1 (C5); 70.7 (OCH_2P, J_{C-P} = 149.6 and 7.0 Hz); 82.5 (C1, J_{C-P} = 152.5 and 13.7 Hz); 124.1 (C3, J_{C-P} = 11.5 Hz); 125.2 (C7); 125.6 (C11); 133.7 (C12); 136.9 (C8); 137.4 (C4).

^1H NMR (D_20) δ 1.64, 1.65, 1.71 (3 x s, 12 H, H13, H14, H15, H16); 2.01-2.17 (m, 8 H, H5, H6, H9, H10); 2.40 and 2.55-2.60 (6 lines and m, 2 H, H2); 3.31 (dt, 1 H, H1, J_{H-P} = 4.0 Hz, $J_{1,2}$ = 8.8 Hz); 3.64 (ABX, 2 H, OCH_2P, J_{A-B} = 11.6 Hz, J_{H-P} = 9.2 Hz); 5.19, (t (b), 1 H, H7, $J_{6,7}$ = 7.0 Hz); 5.25 (t (b), 1 H, H11, $J_{10,11}$ = 6.3 Hz); 5.51 (t (b), 1 H, H3, $J_{2,3}$ = 6.8 Hz);

$^{31}P\{^1H\}$ NMR (D_2O) δ 15.0, 17.6.

Anal. calcd. for $C_{17}H_{32}O_7P_2$: P 15.1; found P 15.17%

6: Yield: 67%. $^{13}C\{^1H\}$ NMR (D_2O) δ 16.4, 16.7, 18.1 (C14, C15, C16); 26.1 (C13); 27.5, 27.6 (C6, C10); 28.5 (C2); 40.4, 40.7 (C5, C9); 122.2 (C3); 125.3, 125.5 (C7, C11); 131.7 (C12); 135.7 (C8); 136.6 (C4).

^1H NMR ($CDCl_3$) δ 1.57, 1.60, 1.64, 1.65 (4xs, 24 H, H13, H14, H15, H16); 1.95-2.10 (m, 16 H, H5, H6, H9, H10); 2.58-2.66 (m, 4 H, H2); 5.09, 5.17, 5.57 (3xt(b), 6 H, H3, H7, H11).

$^{31}P\{^1H\}$ NMR (D_2O) δ 25.8.

Anal. calcd. for $C_{31}H_{55}O_6P_2$: P 10.6; found P 10.49%

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(*Received in UK* 11 *August* 1994; *revised* 8 *December* 1994; *accepted* 9 *December* 1994)