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SYNTHESIS OF MOENOCINOL [1]

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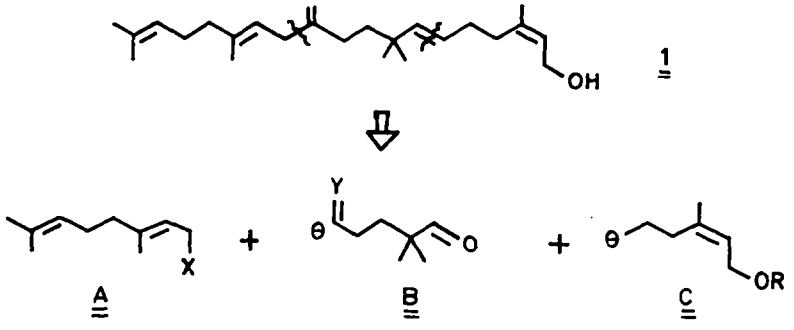
Abstract - 3-Benzyloxy-3,3-dimethylpropanal (2) is converted in eight convenient steps into C_{18}-aldehyde intermediate 10. Main steps in the synthesis of the missing C_7-unit 18 were γ-alkoxyethylation of methyl acetoacetate and cis-selective methylation of the phosphate derivative 13. Intermediates 10 and 18 are converted to moenocinol (1) via a known procedure.

Glycosylphosphates and glycophospholipids occur as important compounds in the intermediary metabolism and as integral constituents of membranes. Not surprisingly, microorganisms developed modified derivatives with antibiotic properties. [2] Moenomycin A, the main constituent of Flavomycin® is such a glycophospholipidic antibiotic; [2,3] it inhibits effectively the peptidoglycan biosynthesis of bacterial cell walls. [3,4]

Moenomycin A is composed of a complex pentasaccharide unit, a phosphorylated glycerate moiety, and a lipidic alcohol called moenocinol of structure 1. Moenocinol (1) has been synthesized recently by several groups. [5-9] Our interest in glycophospholipids [10] has prompted us to develop an efficient synthesis of alcohol 1 for further studies. The retrosynthetic analysis is delineated in Scheme 1; it refers partly to the straightforward synthesis of Coates and Johnson. [8]

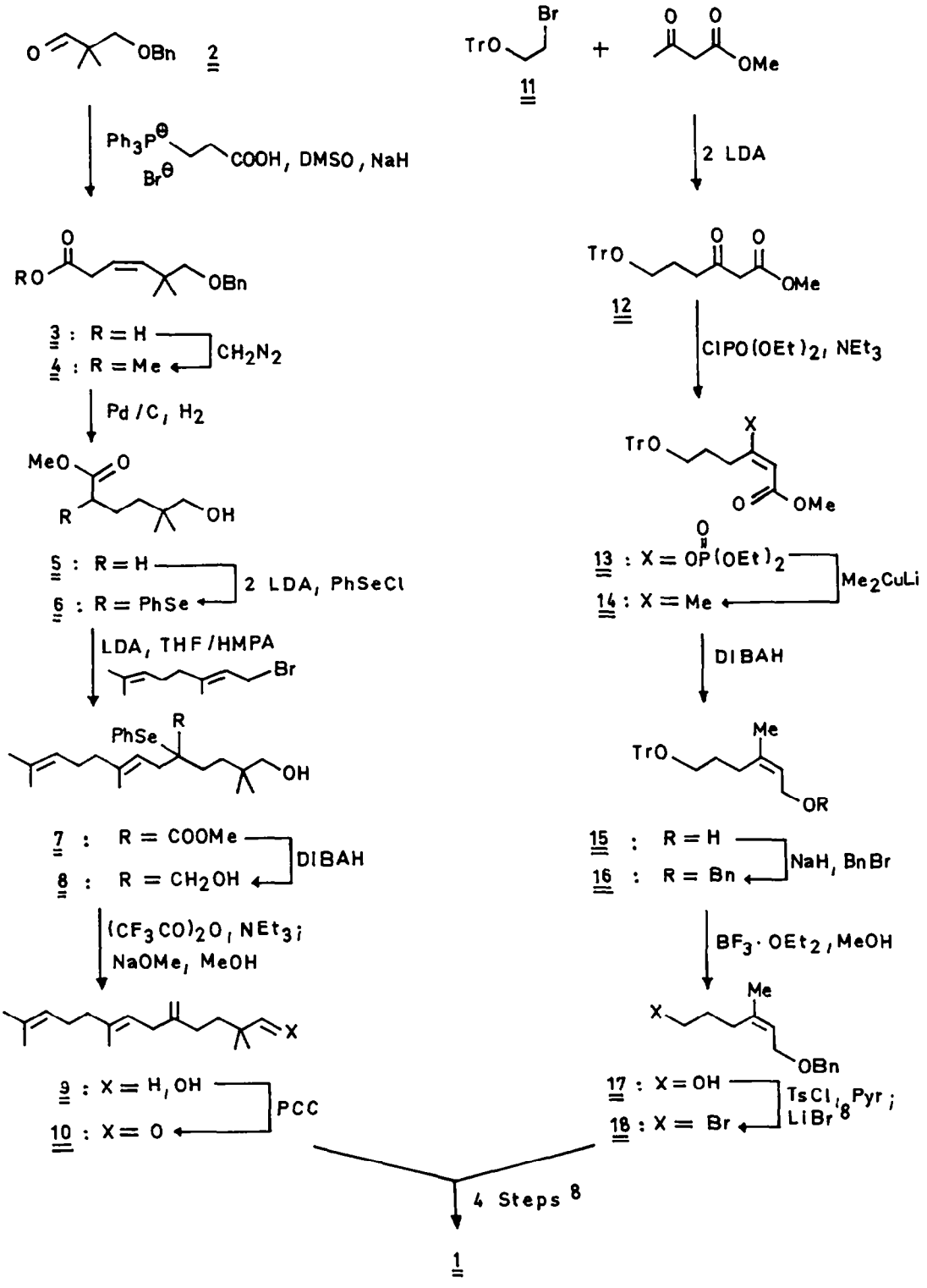
Scheme 1



As described for other syntheses of moenocinol (1) geranyl bromide is used as part A (X = Br). It is connected with moiety B as outlined in Scheme 2. 3-Benzyloxy-2,2-dimethylpropionaldehyde (2), readily available from 2,2-dimethyl-1,3-propanediol, [11] is transformed via a Wittig reaction into cis-hexenoate 3. Subsequent treatment with diazomethane afforded the methyl ester 4. Hydrogenation with palladium on carbon led to concomitant removal of the benzyl protecting group and of

the CC-double bond. The 6-hydroxy-5,5-dimethyl-hexanoate 5 obtained gave upon phenylselenylation the derivative 6 which was alkylated with geranyl bromide in α-position to the carboxylate group providing compound 7. Subsequent diisobutyl aluminumhydride (DIBAH) reduction afforded the diol 8 in almost quantitative yield. The exo-methylene group was then introduced cleanly by reductive elimination according to a method of Krief [12] which consists of a trifluoroacetic anhydride/triethylamine

Scheme 2



treatment of phenylselenylated diol 8. This reaction was associated with trifluoroacetylation of the primary hydroxy group; therefore subsequent sodium methoxide/methanol treatment was required to afford the primary alcohol 9. This compound and the aldehyde 10 obtained after oxidation with pyridinium chlorochromate (PCC) in dichloromethane (overall yield from 2 ≈28 %) are in all physical data identical to material received by Coates and Johnson [8] in thirteen steps (overall yield 5 %).

Nerol was selected as a starting material for short syntheses of moiety C (Scheme 1). [5-9] However, this approach lacks high chemoselectivity in the required cleavage of the Δ^6-CC-double bond of nerol. Therefore we developed a different access to moiety C which is outlined in Scheme 2. The dianion of methyl acetoacetate is alkylated in γ-position with ß-trityloxyethyl bromide 11 affording hexanoate derivative 12. Stereocontrolled phosphorylation applying a method of Weiler and coworkers [13] gave exclusively the (E)-2-hexenoate 13. Subsequent phosphate/methyl exchange with dimethylcuprate in ether was diastereoselective (cis:trans = 5:1) and afforded the required (Z)-2-hexenoate 14 with a C_7 carbon skeleton. Reduction of the ester group with DIBAH in toluene afforded (Z)-2-hexenol 15. Benzyl protection of the newly formed hydroxy group led to compound 16 which was smoothly detritylated by the method of Weidmann et al. [14] using borontrifluoride ether in presence of methanol. The hydroxy compound 17 obtained was converted by the procedure of Coates and Johnson [8] into bromide 18 which can be transformed with AB moiety 10 in four convenient steps into moenocinol 1. [8]

EXPERIMENTAL

General Procedures:

^{1}H n.m.r. spectra were recorded in the solvents noted (Me_4Si, 0.00 ppm) with a Bruker CP 80 CW and a Bruker WM 250 Cryospec. - I.r. spectra were recorded with a Perkin Elmer Model 621. - R_F values refer to t.l.c. performed on silica gel (Merck) with the solvent systems noted. Column chromatography was performed under normal pressure with silica gel (Merck, 70-325 mesh) and under medium pressure with silica gel (Merck, "LiChroprep" Si 60, 40-60 µm) with the solvent systems noted.

3-Benzyloxy-2,2-dimethyl-propanal (2)

To a solution of commercially available 2,2-dimethylpropanediol [7] (104 g, 1 mol) in dry N,N-dimethyl formamide (500 ml) was added solid sodium hydride (25 g, 1 mol) at -5°C within 20 min. After 30 min benzyl bromide (171 g, 1 mol) was added slowly to this solution. The reaction mixture was kept at room temperature overnight; then it was treated with methanol (200 ml) and subsequently with ice water (1 l). The organic material was extracted with dichloromethane (3 x 500 ml); the extract was dried with sodium sulfate, and evaporated to yield an oil, which was dissolved in ether (1 l). The ether solution was washed with water (3 x 200 ml) and then the product was chromatographed on silica gel (toluene/acetone, 2:1) to yield 155.5 g (80 %) 1-benzyloxy-2,2-dimethyl-propan-3-ol (b.p. 149-150°C, 11 torr) which was used for the synthesis of compound 2.

To a stirred suspension of pyridinium chlorochromate (9.7 g, 0.05 mol) in dry dichloromethane (45 ml) was added 1-benzyloxy-2,2-dimethyl-propan-3-ol (5.8 g, 0.03 mol) in dichloromethane (40 ml) at room temperature. The reaction mixture was diluted after 2 h with dry ether (100 ml), it was filtrated and the sirupy residue washed with ether (3 x 30 ml). The ether phases were combined, dried over sodium sulfate, evaporated and the residue distilled. Yield 5.19 g (90 %) of compound 2 as colourless oil, b.p. (11 torr) 130°C; - t.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.73; - ^{1}H n.m.r. (80 MHz, $CDCl_3$) δ = 9.55 (s, 1H, CHO), 7.25 (m, 5H, C_6H_5), 4.47 (s, 2H, $C\underline{H}_2$-Ph), 3.43 (s, 2H, $C\underline{H}_2$-O), 1.10 (s, 6H, 2 CH_3).

Anal.Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.04; H, 8.39.

(Z)-6-Benzyloxy-5,5-dimethyl-3-hexenoic acid (3)

Dry dimethylsulfoxide (200 ml) was added under nitrogen to sodium hydride (4.8 g, 0.2 mol). This mixture was heated to 80°C until hydrogen formation had ceased (~3 h). Then it was cooled to 0°C and 3-triphenylphosphonio-propionic acid bromide (41.5 g, 0.1 mol), obtained from triphenylphosphine and 3-bromo-propionic acid) dissolved in dimethyl sulfoxide (200 ml) was added. Subsequently to the red solution obtained, compound 2 (19.2 g, 0.1 mol) was introduced at room temperature; after 10 min the reaction mixture was warmed for 6 h to 60°C and then it was quenched with hydrochloric acid (10 %, 1 l) at 0°C, extracted with ether (3 x 200 ml), the ether extracts washed with water (3 x 100 ml) and then evaporated. The oily residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 4:1). Yield 17.88 g (72 %), colourless oil which was directly used for the synthesis of compound 4; - t.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.33; - ^{1}H n.m.r. (80 MHz, $CDCl_3$) δ = 10.5 (sb, 1H, COOH), 7.33 (mc, 5H, C_6H_5), 5.51 (mc, 2H, CH = CH), 4.51 (s, 2H, $C\underline{H}_2$-Ph), 3.50-3.25 (m, 4H, $C\underline{H}_2$-O, $C\underline{H}_2$-COOH), 1.15 (s, 6, 2 CH_3).

Methyl (Z)-6-benzyloxy-5,5-dimethyl-3-hexenoate (4)

To a solution of acid 3 (5 g, 20 mmol) in ether (20 ml) was added diazomethane (0.1 M solution in ether) under nitrogen formation ceased. Then the solvent was evaporated and the residue chromatographed on silica gel (n-pentane/ethyl acetate, 3:2). Yield 4.98 (95 %), colourless oil; t.l.c. (n-pentane/ethyl acetate, 3:2) R_F 0.75. - ^{1}H n.m.r. (80 MHz, $CDCl_3$) δ = 7.35 (mc, 5H, C_6H_5), 5.55 (mc, 2H, CH=CH, J = 2 Hz), 4.53 (s, 2H, $C\underline{H}_2$-Ph), 3.68 (s, 3H, OCH_3), 3.33-3.20 (m, 4H, $C\underline{H}_2$-O, CO-CH_2), 1.15 (s, 6H, 2 CH_3).

Anal.Calcd. for $C_{16}H_{23}O_3$: C, 73.25; H, 8.45. Found: C, 73.49; H, 8.45.

Methyl 6-hydroxy-5,5-dimethyl-hexanoate (5)

A solution of compound 4 (5 g, 19 mmol) in ethyl acetate (100 ml) was hydrogenated with palladium on carbon (10 %) for 45 min. T.l.c. indicated that all starting material was converted into a new product. The catalyst was filtered off and the filtrate evaporated. The residue was chromatographed on silica gel (n-pentane/ethyl acetate, 3:2). Yield 3.15 g (95 %), colourless oil; - t.l.c. (n-pentane/ethyl acetate, 3:2) R_F 0.37; - ^{1}H n.m.r. (80 MHz, $CDCl_3$) δ = 3.70 (s, 3H, OCH_3), 3.33 (s, 2H, $C\underline{H}_2$-OH), 2.40-2.10 (m, 3H, CO-$C\underline{H}_2$, OH), 1.75-1.10 (m, 4H, CH_2-CH_2), 0.88 (s, 6H, 2 CH_3).

Anal.Calcd. for $C_{15}H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.83; H, 10.47.

Methyl 6-hydroxy-5,5-dimethyl-2-phenylseleno-hexanoate (6)

To a solution of lithium diisopropylamide (35.33 mmol, prepared from diisopropylamine and 1.4 M tert.-butyllithium in n-pentane) in dry tetrahydrofuran (80 ml) was added at -80°C a solution of ester 5 (2.8 g, 9.52 mmol) in dry tetrahydrofuran (10 ml). After 2 hexamethylphosphoric triamide (5 ml) was added and 10 min later phenyl selenylchloride (4 g, 20.9 mmol) in tetrahydrofuran (5 ml). The reaction mixture was poured after 2 h on hydrochloric acid (10 %, 200 ml), ether (200 ml) was added, and this mixture washed with water (3 x 100 ml). The solvent was evaporated and the residue chromatographed on silica gel (n-pentane/ethyl acetate, 3:2). Yield 3.7 g (70 %), colourless oil; - t.l.c. (n-pentane/ethyl acetate, 3:2) R_F 0.60; - ^{1}H n.m.r. (80 MHz, $CDCl_3$) δ = 7.7-7.25 (m, 5H, C_6H_5); 3.74 (s, 3H, OCH_3), 3.70 (mc, 1H, CH-Se), 3.30 (s, 2H, $C\underline{H}_2$-OH), 1.90-1.10 (m, 5H, CH_2-CH_2, OH), 0.9 (s, 6H, $2CH_3$).

Anal.Calcd. for $C_{15}H_{22}O_3Se$: C, 54.71; H, 6.73. Found:, C, 54,95; H, 6.86.

(7E)-1-Hydroxy-5-methyloxycarbonyl-2,2,8,12-tetramethyl-5-phenylseleno-7,11,-tridecadiene (7)

To a solution of lithium diisopropylamide (13.34 mmol, prepared from equivalent

amounts of diisopropylamine and 1.4 M tert.-butyllithium in n-pentane) in dry tetrahydrofuran (80 ml) was added at -78°C compound 6 (2.09 g, 6.35 mmol) dissolved in dry tetrahydrofuran (5 ml). After 3 h hexamethylphosphoric triamide (7 ml) was added and then geranyl bromide (2.6 g, 12 mmol) dissolved in dry tetrahydrofuran (5 ml). The reaction mixture was poured after 12 h on hydrochloric acid (1 %, 200 ml), the organic material extracted with ether (3 x 100 ml), the ether extract washed with water, dried over sodium sulfate, and then evaporated. The residue was chromatographed on silica gel (n-pentane/ethyl acetate, 7:3). Yield 2.47 g (85 %), colourless oil, which was directly used for the synthesis of compound 8. - T.l.c. (n-pentane/ethyl acetate, 7:3) R_F 0.62; - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.57-7.25 (m, 5H, C_6H_5), 5.23 (t, 1H, C = CH), 5.11 (t, 1H, C = CH), 3.61 (s, 3H, OCH_3), 3.32 (d, 1H, CH-OH), 3.23 (d, 1H, CH-OH), 2.51 (mc, 2H, CH-CH_2-C-Se), 2.06 (mc, 4H, =CH-CH_2-CH_2-CH), 1.69 (s, 3H, CH_3), 1.61 (2s, 6H, 2 CH_3), 1.6-1.1 (m, 4H, -CH_2-CH_2), 0.83 (s, 3H, CH_3), 0.81 (s, 3H, CH_3).

(7E)-1-Hydroxy-5-hydroxymethyl-2,2,8,12-tetramethyl-5-phenylseleno-7,11-tridecadiene (8)

To a solution of compound 7 (2.28 g, 5.2 mmol) in dry toluene (20 ml) was added at -3°C diisobutyl aluminum hydride (10.4 ml of a 1.5 M solution in toluene). The reaction mixture was stirred for 40 min at 0°C. The reaction was quenched with ethanol (0.5 ml) and then with saturated sodium carbonate solution (0.3 ml). After 20 min sodium sulfate (3 g) was added at 0°C to remove excess water. The mixture was filtered, the solid material washed with ether and the ether phase evaporated. The residue was chromatographed on silica gel (n-pentane/ethyl acetate, 3:2). Yield 2.11 g (96 %), colourless oil; - t.l.c. (n-pentane/ethyl acetate, 3:2) R_F 0.57; - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.61-7.26 (m, 5H, C_6H_5), 5.32 (dd, 1H, C = CH-CH_2-C-Se), 5.10 (dd, 1H, C=CH-CH_2-CH_2), 3.32 (m, 4H, 2 CH_2-OH), 2.53 (mc, 1H, =CH-CH-C-Se), 2.30 (dd, 1H, =CH-CH-C-Se) 2.10 (m, 5H, =CH-CH_2-CH_2-CO=, OH), 1.70-1.30 (m, 14 H, 3 CH_3, CH_2-CH_2, OH), 0.86 (s, 3H, CH_3), 0.85 (s, 3H, CH_3).

Anal.Calcd. for $C_{24}H_{38}O_2Se$: C, 59.15; H, 7.09. Found: C, 59.39; H, 7.19.

Reduction of compound 7 with lithium aluminum hydride in tetrahydrofuran afforded compound 8 in 65 % yield. [1]

(7E)-1-Hydroxy-2,2,8,12-tetramethyl-5-methylen-7,11-tridecadiene (9)

To a solution of compound 8 (90 mg, 0.2 mmol) in dry dichloromethane (3 ml) was added triethylamine (8 ml of a 0.2 M solution in dichloromethane) and subsequently trifluoroacetic anhydride (16 ml of a 0.2 M solution in dichloromethane). The reaction mixture was kept for 15 min at room temperature, then it was quenched with saturated sodium hydrogencarbonate solution (10 ml), the organic material extracted with dichloromethane, the extract dried over magnesium sulfate, and the solvent evaporated. Yield 54 mg (84 %); - t.l.c. (petroleum ether/acetone, 9:1) R_F = 0.78.

Dissolution of this material in methanol (3 ml) and addition of sodium methoxide (5 ml of a 0.1 M solution in methanol) led to complete removal of the trifluoroacetyl group within 15 min. The mixture was treated with acidic ion exchange resin to remove sodium ions. The solvent was evaporated and the residue chromatographed on silica gel (n-pentane/ethyl acetate, 3:2). Yield 42 mg (qu) colourless oil; - t.l.c. (n-pentane/ethyl acetate, 3:2) R_F 0.72. - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 5.18 (t, 1H, C = CH), 5.10 (t, 1H, C=CH), 4.72 (s, 2H, $=CH_2$), 3.34 (s, 2H, CH_2-OH), 2.72 (d, 2H, =CH-CH_2-C=), 2.10-1.90 (m, 5H, CH_2-CH_2, OH), 1.68 (s, 3H, CH_3), 1.60 (s, 6H, 2CH_3), 1.40-1.20 (m, 4H, CH_2-CH_2), 0.89 (s, 6H, 2 CH_3).

The ^{1}H n.m.r. data are in agreement with published data for this compound. [8]

(7E)-2,2,8,12-Tetramethyl-5-methylen-7,11-tridecadienal (10)

To a solution of compound 9 (50 mg, 0.2 mmol) in dichloromethane (5 ml) was added pyridinium chlorochromate (65 mg, 0.3 mmol) at room temperature. After 24 h

dry ether (10 ml) was added, the solid material was filtered off, thoroughly washed with dry ether, and the filtrate evaporated. The residue was purified as described in lit. [8]. Yield 45 mg (91 %) of the aldehyde 10, colourless oil. - The ^{1}H n.m.r. and i.r. data were in agreement with the published data. [8]

1-Bromo-2-triphenylmethyloxy-ethane (11)

To a solution of triphenylmethyl chloride (139 g, 0.5 mol) in dry pyridine (400 ml) was added at 0°C 1,2-dihydroxy-ethane (31 g, 0.5 mol). After 30 min the reaction mixture was stirred for 2.5 h at room temperature. The reaction was quenched by addition of ice water (1 l). The organic material was extracted with ether (3 x 300 ml), the ether phase was thoroughly washed with water (4 x 100 ml), dried over sodium sulfate, and then the solvent evaporated. The residue was flash chromatographed on silica gel (toluene/acetone, 9:1). Yield 129.4 g (85 %) of 2-triphenylmethyloxyethanol, amorphous material; - t.l.c. (toluene/acetone, 9:1) R_F 0.37.

This compound (8.5 g, 28 mmol) was dissolved in dry pyridine (100 ml) and to the solution p-toluene-sulfonylchloride (5.33 g, 28 mmol) added at 0°C. After 10 min the reaction mixture was kept for 3.5 h at room temperature. The reaction was quenched by addition of water (300 ml). The organic material was extracted with ether (3 x 100 ml), the ether phase was thoroughly washed with water (4 x 50 ml), dried over sodium sulfate, and then the solvent evaporated. The residue was filtered through silica gel (dichloromethane). Yield 12 g (94 %) of 1-tosyloxy-2-triphenylmethyloxy-ethane, colourless crystals; m.p. 137°C; - t.l.c. (dichloromethane) R_F 0.77.

To the solution of this compound (4.58 g, 10 mmol) in dry acetone (50 ml) was added lithium bromide (4.34 g, 50 mmol). The reaction mixture was heated under reflux for 3 h. Then the solvent was evaporated and the residue treated with a dichloromethane/water mixture. The dichloromethane phase was dried over magnesium sulfate and the solvent evaporated. The residue was chromatographed on silica gel (n-pentane/dichloromethane, 3:2). Yield 3.6 g (98 %), colourless crystals, m.p. 121°C; - t.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.73; - ^{1}H n.m.r. (80 MHz, $CDCl_3$) δ = 7.41-7.20 (m, 15 H, 3 C_6H_5), 3.36-3.29 (mc, 4H, CH_2-CH_2).

Anal.Calcd. for $C_{21}H_{19}BrO$: C, 68.67; H, 5.21. Found: C, 68.56; H, 5.28.

Methyl 3-oxo-6-triphenylmethyloxy-hexanoate (12)

To a solution of lithium diisopropylamide (7.08 mmol, prepared from equivalent amounts of diisopropylamine and 1.6 M tert.-butyllithium in n-pentane) in dry tetrahydrofuran (50 ml) was added a solution of methyl acetoacetate (0.382 ml, 3.54 mmol) in dry tetrahydrofuran (2 ml) at -78°C. The temperature was raised to 0°C within 1 h and then hexamethylphosphoric triamide (2 ml) and subsequently a solution of compound 11 (1.3 g, 3.54 mmol) in dry tetrahydrofuran (5 ml) was added. The reaction mixture was kept for 1 h at 0°C and then for 3 h at room temperature. It was quenched with hydrochloric acid (10 %, 100 ml), the organic material was extracted with dichloromethane (3 x 100 ml), the extract was washed with water (3 x 50 ml), dried over sodium sulfate, and the solvent evaporated. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 4:1). Yield 1.14 g (80 %), colourless crystals, m.p. 60°C; - t.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.31; - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.44-7.20 (m, 15H, 3 C_6H_5), 3.71 (s, 3H, OCH_3), 3.43 (s, 2H, CO-CH_2), 3.09 (t, 2H, CH_2-O, J = 6.4 Hz), 2.64 (t, 2H, CO-CH_2, J = 7.3 Hz), 1.90 (m, 2H, CH_2-CH_2-CH_2).

Anal.Calcd. for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.38; H, 6.58.

Diethyl 3-[methyl (2E)-6-triphenylmethyloxy-2-hexenoate]yl phosphate (13)

To a solution of triethylamine (3 ml), 22 mmol) in hexamethylphosphoric triamide (10 ml) was added diethyl phosphoric chloride (3 ml, 15 mmol) at 0°C. To this mixture was added after 10 min a solution of compound 12 (403 mg, 1 mmol) in tetrahy-

drofuran (1 ml). The reaction mixture was stirred for 1 h and then quenched with saturated ammonium chloride solution (20 ml). The organic material was extracted with dichloromethane (3 x 50 ml), the extract was washed with water (3 x 20 ml), dired over magnesium sulfate, and the solvent evaporated. The residue was chromatographed on silica gel (toluene/ethyl acetate, 4:1). Yield 440 mg (82 %), colourless oil; this material was immediately used for the synthesis of compound 14. - T.l.c. (toluene/ethyl acetate, 4:1) R_F 0.44; - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.40-7.12 (m, 15 H, 3 C_6H_5), 5.85 (d, 1H, C = CH, J < 1 Hz), 4.16 (mc, 4H, $P(OCH_2-)_2$), 3.66 (s, 3H, OCH_3), 3.12 (t, 2H, $O-CH_2$, J = 6.4 Hz), 2.92 (t, 2H, $=C-CH_2$, J = 4.5 Hz), 1.90 (m, 2H, CH_2-CH_2), 1.34 (mc, 6H, $P(OCH_2-CH_3)_2$).

Methyl (2Z)-3-methyl-6-triphenylmethyloxy-2-hexenoate (14)

To a suspension of copper(I) iodide (120 mg, 1.12 mmol) in dry and oxygen free ether (10 ml) was added at 0°C methyllithium (2 ml of a 1.5 M solution). The mixture was cooled to -78°C and a solution of compound 13 (300 mg, 0.56 mmol) in dry ether (10 ml) added. The reaction mixture was kept for 2 h at -78°C and then for 2 h at -45°C. It was quenched with saturated ammonium chloride solution (10 ml), the organic material was extracted with ether (3 x 50 ml), the extract was washed with water (3 x 20 ml), dried over magnesium sulfate, and the solvent evaporated. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 4:1). Yield 160 mg (71 %) of compound 14, colourless oil (and 32 mg (14 %) of the corresponding (E)-isomer). - T.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.57; - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.45-7.20 (m, 15H, 3 C_6H_5), 5.64 (s, 1H, C = CH), 3.64 (s, 3H, OCH_3), 3.11 (t, 2H, $O-CH_2$, J = 6.4 Hz), 2.69 (t, 2H, $=C-CH_2$, J = 8 Hz), 1.87 (d, 3H, $=C-CH_3$, J = 1 Hz), 1.81 (mc, 2H, $CH_2-CH_2-CH_2$).

Anal.Calcd. for $C_{27}H_{28}O_3$: C, 80.79; H, 7.05. Found: C, 80.89; H, 7.03.

(E)-Isomer: ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.45-7.20 (m, 15H, 3 C_6H_5), 5.64 (d, 1H, C=CH, J = 1 Hz), 3.67 (s, 3H, OCH_3), 3.07 (t, 2H, $O-CH_2$, J = 6.1 Hz), 2.24 (t, 2H, $=C-CH_2$, J = 7 Hz), 2.13 (d, 3H, $=C-CH_3$, J = 1 Hz), 1.79 (m, 2H, $CH_2-CH_2-CH_2$).

(2Z)-1-Hydroxy-3-methyl-6-triphenylmethyloxy-2-hexene (15)

To a solution of compound 14 (140 mg, 0.35 mmol) in dry toluene (4 ml) was added under nitrogen a solution of diisobutyl aluminumhydride (0.66 ml of a 1.5 M solution in toluene) at 0°C. The reaction was quenched after 30 min with ethanol (0.5 ml) and saturated sodium sulfate (1 ml). Ether (5 ml) was added after 10 min and then magnesium sulfate (3 g). The mixture was stirred for 2 h at room temperature, the solid material was filtered off and the solvent evaporated from the filtrate. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 3:1). Yield 117 mg (90 %), colourless oil; - t.l.c. (n-pentane/ethyl acetate, 3:2) R_F 0.57; - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.38-7.12 (m, 15H, 3 C_6H_5), 5.28 (dt, 1H, $C=CH-CH_2-O$, J = 1,2, 7.0 Hz), 4.00 (d, 2H, $=C-CH_2-O$, J = 7.0 Hz), 2.97 (t, 2H, $O-CH_2-CH_2-CH_2$, J = 6.4 Hz), 2.04 (t, 2H, $CH_2-C=C$, J = 7.0 Hz), 1.65 (m, 2H, $CH_2-CH_2-CH_2$), 1.57 (s, 3H, CH_3), 1.15 (sb, 1H, OH).

Anal.Calcd. for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.71; H, 7.53.

(2Z)-1-Benzyloxy-3-methyl-6-triphenylmethyloxy-2-hexene (16)

To a solution of compound 15 (100 mg, 0.268 mmol) in dry dimethylformamide (10 ml) was added sodium hydride (24 mg, 1 mmol). This mixture was heated to 60°C for 30 min. Then benzyl bromide (0.1 ml) was added and the reaction kept at 60°C for 3 h. Then the same procedure was repeated with sodium hydride and benzyl bromide addition. The reaction was stopped with methanol (0.5 ml), this mixture dissolved in dichloromethane (100 ml) and washed with water (4 x 20 ml). The solvent was evaporated and the residue chromatographed on silica gel (petroleum ether/ethyl acetate, 4:1). Yield 118 mg (95 %), colourless oil; - t.l.c. (petroleum ether/ethyl acetate, 4:1) R_F 0.70; - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.50-7.15 (m, 20 H,

4 C_6H_5), 5.36 (dt, 1H, C=C<u>H</u>-CH_2-O, J = 7 Hz, 1.2 Hz), 4.43 (s, 2H, O$C\underline{H}_2$-Ph), 3.96 (d, 2H, =C-CH_2-O, J = 7 Hz), 3.05 (t, 2H, O-$C\underline{H}_2$-CH_2-CH_2, J = 6.5 Hz), 2.09 (m, 2H, CH_2-C=C), 1.80-1.60 (m, 2H, CH_2-$C\underline{H}_2$-CH_2), 1.56 (s, 3H, CH_3).

Anal.Calcd. for $C_{33}H_{34}O_2$: C, 85.67; H, 7.40. Found: C, 85.47; H, 7.35.

(2Z)-1-Benzyloxy-6-hydroxy-3-methyl-2-hexene (17)

To a solution of compound 16 (60 mg, 0.13 mmol) in dry tetrahydrofuran (1 ml) and methanol (0.1 ml) was added a solution of boron trifluoride·ether (1.3 ml of a 0.1 M solution in dichloromethane) at room temperature. The reaction was quenched after 2 h by addition of water (10 ml). The organic material was extracted with dichloromethane (2 x 30 ml), the extract was washed with water (2 x 20 ml) and the solvent evaporated. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate, 3:2). Yield 22 mg (75 %), colourless oil; - t.l.c. (petroleum ether/ethyl acetate, 3:2) R_F 0.30; - ^{1}H n.m.r. (250 MHz, $CDCl_3$) δ = 7.34 (m, 5H, C_6H_5), 5.44 (dt, 1H, =C<u>H</u>-CH_2-O, J = 7.5, 1 Hz), 4.51 (s, 2H, O$C\underline{H}_2$-Ph), 4.02 (d, 2H, =C-CH_2-O, J = 6.7 Hz), 3.65 (t, 2H, O-CH_2, J = 6.4 Hz), 2.12 (t, 2H, CH_2-C=, J = 7.6 Hz), 1.71 (m, 2H, CH_2-$C\underline{H}_2$-CH_2), 1.66 (s, 3H, CH_3), 1.54 (bs, 1H, OH).

The ^{1}H n.m.r. data are in agreement with the published data for this compound. [8]

(2Z)-1-Benzyloxy-6-bromo-3-methyl-2-hexene (18)

To a solution of compound 17 (22 mg, 0.1 mmol) in dry pyridine (1 ml) was added p-toluenesulfonyl chloride (38 mg, 0.2 mmol) at 0°C. After 10 min the reaction mixture was kept for 4 h at room temperature. Workup followed essentially the procedure described in lit. [8]. Yield 37 mg (qu) of the corresponding tosylate.

To a solution of this material in dry acetone (3 ml) was added lithium bromide (44 mg, 0.5 mmol). The reaction mixture was heated under reflux for 3 h and then worked up as described in lit. [8]. Yield 26 mg (92 %). The ^{1}H n.m.r. and IR data were in agreement with the published data. [8]

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