230. Approaches to the Synthesis of Cytochalasans

Part 7[1])

Synthesis of Some Building Blocks for the Construction of the Macrocyclic Moiety

by **Daniel Wallach, Ivan G. Csendes, Peter E. Burckhardt, Tibur Schmidlin** and **Christoph Tamm***

Institut für Organische Chemie der Universität, St. Johanns-Ring 19, CH-4056 Basel

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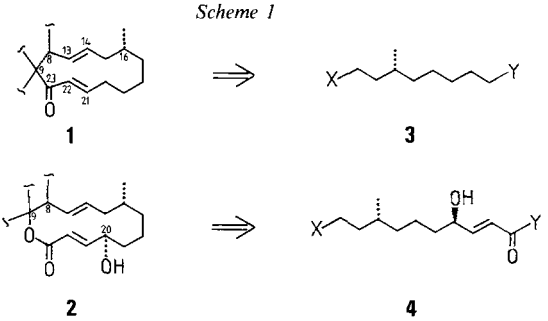
Summary

The synthesis of ethyl(2*E*,4*E*,8*R*)-8-methyl-10-[(2*H*-tetrahydropyran-2-yl)oxy]-2,4-decadienoate (**11**), methyl (2*E*,8*R*)-8-methyl-10-[(2*H*-tetrahydropyran-2-yl)oxy]-2-decenoate (**16**), synthons for the construction of the macrocyclic moieties of the cytochalasins A, B and F, and of (3*R*)-[7-(1,3-dioxolan-2-yl)-3-methylheptyl]triphenylphosphonium bromide (**24**), a C_8-building block for deoxaphomin, proxiphomin and protophomin is described. In all instances (+)-(*R*)-pulegone (**5**) served as starting material.

The structural pattern of the macrocyclic moiety **1** or **2** of several cytochalasans[2]) exhibits striking similarity due to the presence of the CH_3-group at chiral C-atom C(16) and due to the position of two double bonds between C(13),C(14) and C(21),C(22), respectively[3]). In the macrolides of type **2**, the location of the O-bridge represents an additional common feature. Dissection of the strategic bonds led to a synthetic scheme [3] according to which building blocks of type **3** and **4**, consisting of 8 or 10 C-atoms, respectively, are required *(Scheme 1)*.

Scheme 1



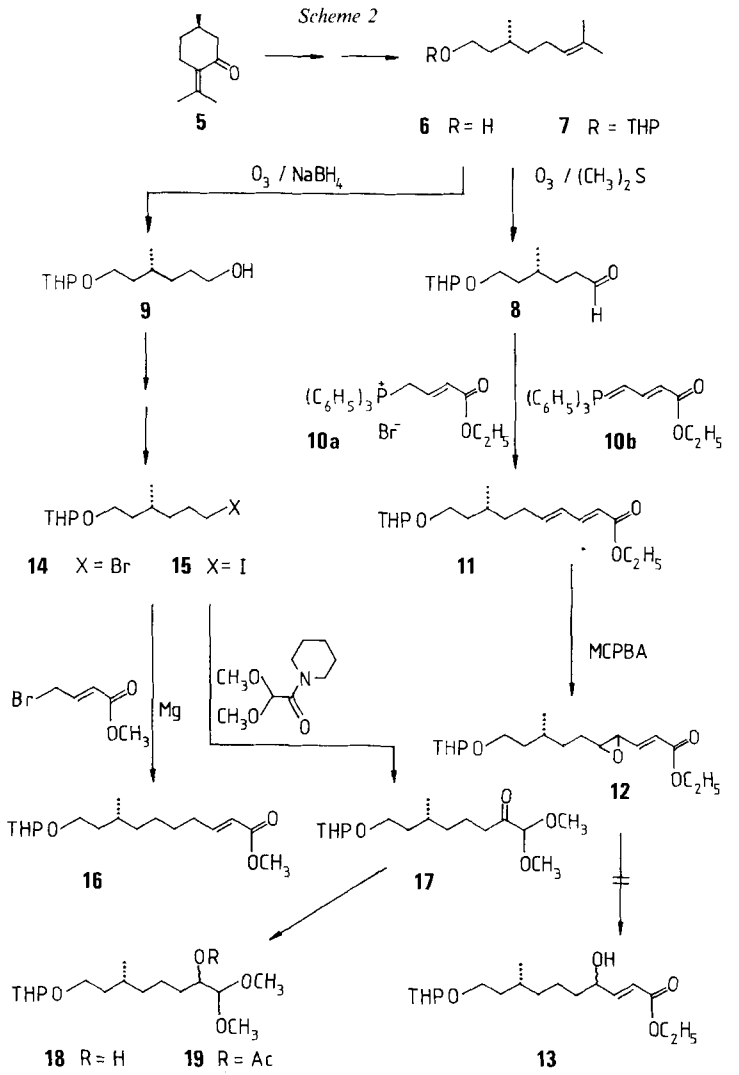
[1]) Part 6: [1].

[2]) These comprise the cytochalasins A, B, and F, deoxaphomin, proxiphomin and protophomin.

[3]) For convenience, the numbering used in this communication corresponds to that used for the cytochalasans [2].

Any attempt to prepare synthons such as **3** and **4** faces the problem of the stereo control at C(16). In principal, the same is valid for an additional chiral centre to be introduced into the target molecules bearing a OH-group at C(20). To solve this problem, we decided to use (+)-(*R*)-pulegone (**5**) as starting material because the secondary CH_3-group of this monoterpene possesses the same absolute configuration as in 3-methylpimelic acid as shown by interrelation of both compounds. (3*R*)-3-methylpimelic acid has been obtained by degradation of cytochalasin B in the course of its structure elucidation. In the first part of this communication, we report attempts to prepare a C_{10}-chain as required for the macrolide type. In the second part, the synthesis of a C_8-chain suitable for the construction of macro-carbocyclic proxiphomin and protophomin is described.

Scheme 2



For the synthesis of the C_{10}-building block, a C_6-unit was joined with a C_4-moiety. Starting from (*R*)-pulegone (**5**), citronellol (**6**) was prepared according to *Plesek* [5]. Protection of the OH-group in **6** was achieved by acid-catalyzed addition of dihydropyrane [6] to give compound **7** in good yield *(Scheme 2)*. In the next step, the olefin **7** was degradated by ozonolysis. Depending on the workup conditions, either aldehyde **8** or alcohol **9** were obtained. Extension of the chain was achieved by the reaction of **8** with the ylide **10b** [7], which was prepared from ethyl 4-bromocrotonate, leading to the diene-carboxylate **11**. For the introduction of an O-function in the γ-position, **11** was treated with *m*-chloroperbenzoic acid. Selective oxidation of the C(γ),C(δ)-double bond took place. However, several attempts to convert the epoxide **12** into the desired OH-derivative **13** have failed.

Starting from alcohol **9**, two key building blocks, bromide **14** and iodide **15**, were prepared in high yield *via* tosylation or mesylation followed by exchange of halide. Cross coupling [8] of the *Grignard* compound of **14** with methyl 4-bromocrotonate gave the C_{10}-synthon **16** in *ca.* 60% yield. Although compound **16** still lacks the O-function at C(4) furnishing the final functionality at C(20) in structure **2**[4]), it meets the requirements needed for the transformation into a phosphorane. The latter could operate as a building block like compound **4**.

Introduction of an additional O-function into a C_8-synthon required for the synthesis of deoxaphomin was achieved by starting from bromide **14**. For this purpose the *Grignard* compound of **14** was reacted with 1-(dimethoxyacetyl)piperidine [9] to give the α-ketoacetal **17** (yield 19%). The latter was easily reduced by $NaBH_4$ to the epimeric α-hydroxyacetals **18**. For selective deprotection of the primary OH-group, the acetyl derivative **19** was prepared.

Another goal of this investigation was the synthesis of the C_8-unit of type **3** required for the construction of proxiphomin and protophomin. It has been achieved by three different routes by the linking of a C_6- with a C_2-unit, whereby the overall yields were gradually increased. The first sequence started from bromide **14**, which by reaction of its *Grignard* compound with ethylene oxide yielded about 40% of the extended alcohol **20** *(Scheme 3)*. Oxidation of **20** to the aldehyde **21** was accomplished by pyridinium dichromate (PDC) in 65% yield. Treatment of **21** with EtOH and catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) resulted in a transetherification. Thus, the aldehyde group of **21** was protected as an acetal by simultaneous deprotection of the primary OH-group. The resulting hydroxy-acetal **22** was obtained in 85% yield. The primary OH-group of **22** was replaced by Br using the mesylate as intermediate. After reacetalization, the ethylene acetal **23** was obtained in a total yield of 86%. On heating **23** with Ph_3P in benzene, the phosphonium bromide **24** was obtained in 70% yield. The product was very hygroscopic and difficult to purify.

Bromide **14** did not react smoothly with Mg. The addition of the resulting *Grignard* reagent to ethylene oxide was always accompanied by some reduction of **14** to the corresponding alkane, thus decreasing the yield. Therefore the use of 2-(lithiomethyl)-4-dihydro-1,3-thioazole (**25**) [10] was investigated as an alternative route for

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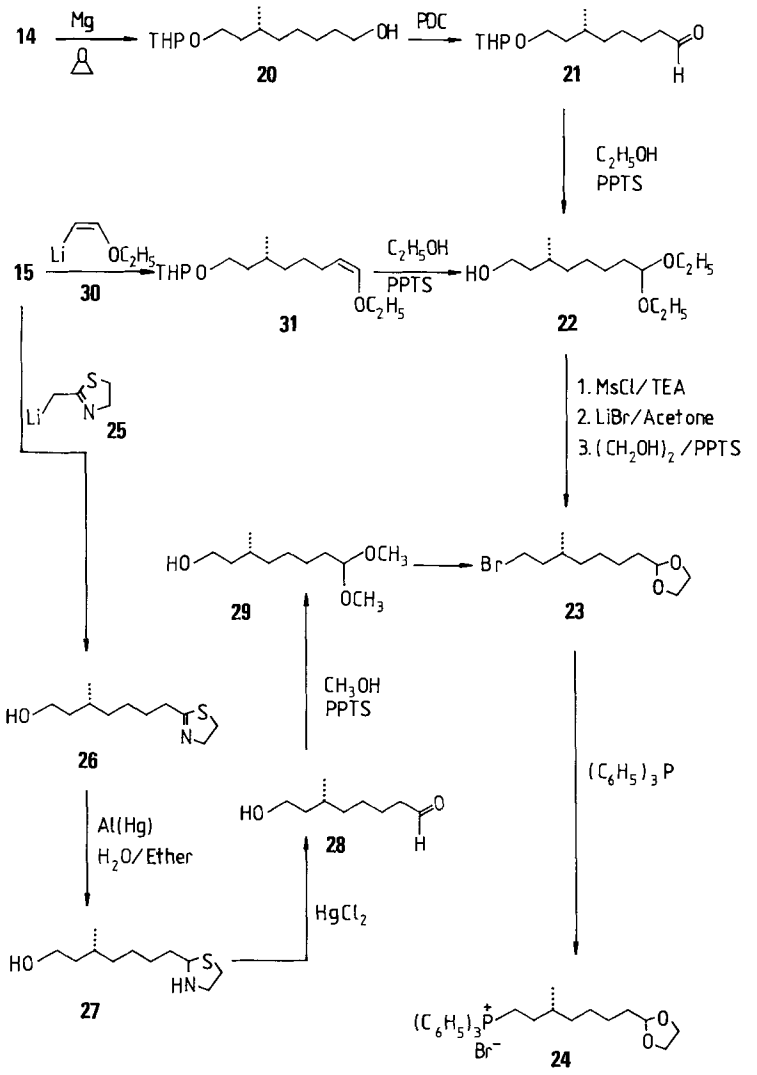
[4]) Since epimerization may easily occur at C(20), it is advisable to introduce chirality in a final reduction step. A synthesis, yet by a different strategy, of the synthon **4** needed for the construction of the cytochalasins B and F has been reported recently [1].

Scheme 3



the C_2-extension. The alkylated thiazole **26**, in which the 2*H*-tetrahydropyran-2-yl group has been lost by the workup with acid, was hydrogenated by Al(Hg) in wet Et_2O to give thiazolidine **27** in 57% (calculated on the basis of the iodide **15**). Desulfurization by $HgCl_2$ led to the hydroxy aldehyde **28**. It showed a high tendency to form polymeric acetals. However, by treatment with MeOH and PPTS again a monomeric species, *i.e.* compound **29**, was obtained from the polymeric product. The phosphonium bromide **24** was prepared from **29** by the same sequence as outlined already for the conversion of **22** to **24**. Since iodide **15** is accessible in higher yield than bromide **14** and the yields of the remaining steps range from 60 to 80% each, an improvement had

been achieved as compared to the ethylene-oxide procedure. Nevertheless, the use of mercury may be regarded as a disadvantage. Therefore, a third route was studied.

(*Z*)-2-Ethoxyvinyllithium (**30**) is a useful equivalent of acetaldehyde for a chain extension [11]. If this reagent is alkylated by iodide **15**, an enol ether is expected to be formed, which should add EtOH to give compound **22**. In fact, we converted **15** into the enol ether **31** in good yield, but only in the presence of 5 equiv. of hexamethylphosphoric triamide. This observation is in contrast to the conditions quoted in [11]. Acid-catalyzed addition of EtOH to **31** yielded the acetal **22**, whose conversion to the target molecule **24** has already been carried out (see above). Taking advantage of the sequence using (*Z*)-2-ethoxyvinyllithium (**30**), the optically active phosphonium bromide **24**[5]) may now be easily obtained from (*R*)-citronellol (**6**) in seven steps.

The support of these investigations by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* is gratefully acknowledged.

Experimental Part

General. See [13]. 90-MHz ^{1}H-NMR spectra and IR spectra were recorded on a *Varian EM 390* and a *Perkin-Elmer* model *177* grating spectrometer, respectively. Air- and water-sensitive reactions were carried out in a dry Ar atmosphere. All solvents were adequately dried before use.

Abbreviations. CC = column chromatography on silica gel, HMPT = hexamethylphosphoric triamide, MCPBA = *m*-chloroperbenzoic acid, PDC = pyridinium dichromate, PPTS = pyridinium *p*-toluenesulfonate.

(3R)-3,7-Dimethyl-6-octen-1-ol (Citronellol) (**6**). Following the procedure described in [5], 74.1 g (79%) of **6** were obtained, starting from 92.1 g (0.60 mol) of (+)-(*R*)-pulegone (**5**). The physical data of **6** were in agreement with the reported values [5].

(6R)-2,6-Dimethyl-8-[(2H-tetrahydropyran-2-yl)oxy]-2-octene (**7**). To a solution of **6** (27.4 ml, 0.15 mol) and 3,4-dihydro-2H-pyran (27.2 ml, 0.30 mol) in benzene (50 ml) some drops of $SOCl_2$ were added. After some min. the mixture began to warm up. It was stopped by cooling down to 10°. The mixture was kept at r.t. for 15 h. Evaporation *i.v.* left a residue, which was diluted with Et_2O (400 ml) and washed with 2M $KHCO_3$ (1 × 75 and 2 × 25 ml) and H_2O (2 × 50 ml). The org. layer yielded after evaporation of the solvents *i.v.* 38.41 g of crude **7**, which was purified by destillation to give 32.30 g (90%) of **7**, b.p. 109–112° (0.65 Torr). $[\alpha]_D^{22} = 4° \pm 0.5°$ (c = 2, CH_2Cl_2). IR (film): 2950, 2880, 1130, 1080, 1040, 870, 815. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.90 (*d*, J = 6, CH_3–C(6)); 1.1–2.1 (*m*, 19H); 3.2–4.2 (*m*, 2H–C(8), 2H–C(6')); 4.58 (br., H–C(2')); 5.12 (*m*, H–C(3)). MS: 240 (M^+), 156, 154, 123, 109, 95, 85.

(4R)-4-Methyl-6-[(2H-tetrahydropyran-2-yl)oxy]hexanal (**8**). An O_3/O_2 mixture was bubbled through a solution of **7** (12.0 g, 50 mmol) in MeOH (100 ml) at −50° until 50 mmol of O_3 had been absorbed. 4.5 ml of $(CH_3)_2S$ were added and the mixture was stirred at −10° for 2 h. After evaporation of the solvents *i.v.* the residue was diluted with Et_2O (250 ml) and washed with H_2O. On evaporation *i.v.* the org. layer gave 9.50 g of crude product. It was purified by CC (CH_2Cl_2/EtOH gradient) to give 6.00 g (56%) of pure **8** as colourless oil. $[\alpha]_D^{22} = 4° \pm 1°$ (c = 2, $CHCl_3$). IR (film): 2950, 2880, 1730, 1125, 1080, 1035. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.90 (*d*, J = 5, H_3C–C(4)); 1.2–1.9 (*m*, 11H); 2.4 (br., 2H–C(2)); 3.2–3.8 (*m*, 2H–C(6), 2H–C(6')); 4.6 (br., H–C(2')); 9.8 (br., H–C(1)). MS: 213 ($M^+ - 1$), 185, 170, 129, 85.

(4R)-4-Methyl-6-[(2H-tetrahydropyran-2-yl)oxy]hexan-1-ol (**9**). A stirred solution of **7** (25.45 g, 106 mmol) in MeOH (260 ml) was cooled to −65° and treated with O_3 (6.04 g, 126 mmol). The solution has to remain colourless. To the still cold solution, $NaBH_4$ (14.0 g, 370 mmol) was added in small portions. After having reached r.t. the mixture was kept stirring for an additional 2.5 h. The product was extracted by Et_2O (1 × 800 and 2 × 200 ml), which was washed with H_2O (3 × 80 ml). Evaporation of the solvents *i.v.* gave 22.40 g (98%) of **9**, pure according to TLC, as a colourless oil. $[\alpha]_D^{22} = 2° \pm 0.5°$ (c = 2.5, CH_2Cl_2). IR (film): 3410 br., 2940, 2870, 1140, 1125, 1075, 1030. ^{1}H-NMR (60 MHz, CCl_4): 0.95 (*d*, J = 5, CH_3–C(4)); 1.0–1.9 (*m*, 13H); 2.8

[5]) This compound, but in its racemic form, has independently been synthesized by *Kim et al.* [12].

(br. *s*, HO–C(1)); 3.1–3.9 (*m*, 2H–C(1), 2H–C(6), 2H–C(6')); 4.5 (br., H–C(2')). MS: 216 (M^+), 143, 131, 115, 101, 97, 85.

*Ethyl (2*E*,4*E*,8*R*)-8-Methyl-10-[(2*H*-tetrahydropyran-2-yl)oxy]-2,4-decadienoate* (**11**). A solution of **8** (1.30 g, 6.0 mmol) in 5 ml of THF was added to a solution of 0.48 g of NaOEt and phosphonium bromide **10a** [7] (2.80 g, 6.1 mmol) in 10 ml of EtOH at r.t. After 12 h the mixture was filtered. The concentrated filtrate was diluted with Et_2O (500 ml) and washed with H_2O. On evaporation of the solvents *i.v.*, 2.05 g of crude **11** were obtained. Purification of the latter by CC (CH_2Cl_2/MeOH gradient) yielded 0.95 g (51%) of pure **11** as a colourless oil. IR (film): 2940, 1720, 1640, 1260, 1080, 1035. UV (EtOH): 206.5 (3.82), 213 (3.76), 261 (4.20). ^{1}H-NMR (60 MHz, $CDCl_3$): 0.95 (*d*, *J* = 6, CH_3–C(8)); 1.2–1.9 (*m*, 11H); 1.35 (*t*, *J* = 7, CH_3CH_2O); 2.3 (*m*, 2H–C(6)); 3.2–3.8 (*m*, 2H–C(10), 2H–C(6')); 4.25 (*q*, *J* = 7, CH_3CH_2O); 4.6 (br., H–C(2')); 5.7 (br., H–C(5)); 5.95 (*d*, *J* = 15, H–C(2)); 6.2 (br., H–C(4)); 7.4 (br., H–C(3)). MS: 310 (M^+), 309, 265, 237, 195, 85.

*Ethyl (2*E*,4*RS*,5*RS*,8*R*)-4,5-Epoxy-8-methyl-10-[(2*H*-tetrahydropyran-2-yl)oxy]-2-decenoate* (**12**). A solution of **11** (650 mg, 2.0 mmol) in $CHCl_3$ (25 ml) was treated at r.t. with MCPBA (430 mg, 2.5 mmol) for 3 d. Excess of peracid was destroyed by addition of 2N Na_2SO_3 (5 ml). The mixture was washed consecutively with 2N Na_2CO_3 and H_2O. Evaporation of the solvent *i.v.* left 550 mg of residue, which was purified by CC (CH_2Cl_2/MeOH gradient) to yield 360 mg (55%) of pure **12**. $[\alpha]_D^{20} = 5° \pm 1°$ (*c* = 1.85, $CHCl_3$). IR (film): 2975, 1720, 1655, 1080, 1040, 875. UV (EtOH): 218 (4.10). ^{1}H-NMR (60 MHz, $CDCl_3$): 0.90 (*d*, *J* = 6, CH_3–C(8)); 1.2–1.9 (*m*, 13H); 1.25 (*t*, *J* = 7, CH_3CH_2O); 3.2–3.8 (*m*, H–C(4), H–C(5), 2H–C(10), 2H–C(6')); 4.18 (*q*, *J* = 7, CH_3CH_2O); 4.6 (br., H–C(2')); 6.10 (*d*, *J* = 15, H–C(2)); 6.80 (*dd*, *J* = 15, *J'* = 6, H–C(3)). MS: 325 ($M^+ - 1$), 281, 85.

*(4*R*)-1-Bromo-4-methyl-6-[(2*H*-tetrahydropyran-2-yl)oxy]hexane* (**14**). To a stirred solution of **9** (22.4 g, 103 mmol) in pyridine (270 ml), TsCl (37.0 g, 194 mmol) were added at 0°. After 1 h a white precipitate was formed. The mixture was kept for 1 d at 0°, then toluene (200 ml) was added and the suspension was filtered by rinsing with toluene (4 × 50 ml). Evaporation of the filtrate *i.v.* gave 53.3 g of an oil, which was purified by CC (CH_2Cl_2/Et_2O gradient) to yield 27.97 g (73%) of pure tosylate. The latter was dissolved in acetone (195 ml) and LiBr (25.99 g, 299 mmol) were added. The mixture was stirred at r.t. for 1 d. The suspension obtained was filtered using acetone/Et_2O 1:3 (in total 440 ml), the filtrate was concentrated to 80 ml and taken up in Et_2O (650 and 2 × 215 ml). The org. layers were washed with H_2O (4 × 60 ml), dried and evaporated *i.v.* to yield 20.14 g (96% based on tosylate) of **14** as a TLC-pure, colourless oil. $[\alpha]_D^{22} = 4° \pm 0.5°$ (*c* = 3, CH_2Cl_2). IR (film): 2940, 2870, 1200, 1140, 1120, 1080, 1030. ^{1}H-NMR (60 MHz, CCl_4): 0.95 (*d*, *J* = 6, CH_3–C(4)); 1.1–2.1 (*m*, 13H); 3.2–3.9 (*m*, 2H–C(1), 2H–C(6), 2H–C(6')); 4.48 (br., H–C(2')). MS: 279 (M^+), 277, 179, 177, 150, 97, 85.

*(4*R*)-1-Iodo-4-methyl-6-[(2*H*-tetrahydropyran-2-yl)oxy]hexane* (**15**). To a solution of **9** (6.75 g, 31.2 mmol) and Et_3N (7.0 ml, 50 mmol) in 150 ml of CH_2Cl_2, MsCl (2.8 ml, 36 mmol) was added dropwise at 0°. After stirring for 15 min at 0°, the mixture was extracted with ice-cold H_2O, sat. NH_4Cl, sat. $KHCO_3$ and brine. Evaporation of the solvents *i.v.* gave 8.68 g (95%) of mesylate, pure according to TLC, as a yellowish oil. To a solution of the latter (8.6 g, 29.2 mmol) in 30 ml of acetone, NaI (6.0 g, 40 mmol) was added. The mixture was stirred for 17 h at r.t., then taken up in Et_2O and washed successively with $Na_2S_2O_3$ and brine. On evaporation *i.v.*, the org. phases gave a yellowish oil, which was further purified by CC (CH_2Cl_2) to yield 8.9 g (93%) of pure **15**. IR (film): 2930, 2865. ^{1}H-NMR (60 MHz, CCl_4): 0.95 (*d*, *J* = 6, CH_3–C(4)); 1.05–2.15 (*m*, 13H); 3.10 (*t*, *J* = 7, 2H–C(1)); 2.95–3.95 (*m*, 2H–C(6), 2H–C(6')); 4.37–4.55 (br., H–C(2')).

*Methyl (2*E*,8*R*-8-Methyl-10-[(2*H*-tetrahydropyran-2-yl)oxy]-2-decenoate* (**16**). To a suspension of Mg (0.61 g, 25 mg-atom) in 5 ml of Et_2O, bromoethane (0.4 ml) were added to start an auxilary *Grignard* reaction. To the proceeding reaction mixture, a solution of **14** (2.79 g, 10.0 mmol) in THF (20 ml) was added within 1 h, the mixture being kept at 75° for 2 h. The resulting *Grignard* compound was then added dropwise to a well-stirred and chilled solution of methyl 4-bromocrotonate (2.77 ml, 20.0 mmol) in THF (15 ml) within 1.5 h. The mixture was kept at 15° for 14 h. Hydrolysis by 0.2M NH_4Cl (150 ml) and evaporation of the solvent *i.v.* gave a residue, which was taken up in Et_2O (100 ml). The org. solution was washed with 0.1M NH_4Cl (10 ml) and brine (2 × 10 ml), the aq. layers being re-extracted by Et_2O (3 × 40 ml). The combined org. phases yielded 3.0 g of crude **16**, which was purified by CC (CH_2Cl_2/Et_2O gradient) to give 1.74 g (58%) of **16** as a yellowish oil. ^{1}H-NMR (60 MHz, CCl_4): 0.93 (*d*, *J* = 6, CH_3–C(8)); 1.1–2.5 (*m*, 17H); 3.1–4.2 (*m*, 2H–C(10), 2H–C(6')); 3.6 (*s*, CH_3O–C(1)); 4.4 (br., H–C(2')); 5.92 (*d*, *J* = 15, H–C(2)); 6.9 (*dt*, *J* = 15, *J'* = 7, H–C(3)).

*(6*R*)-1,1-Dimethoxy-6-methyl-8-[(2*H*-tetrahydropyran-2-yl)oxy]octan-2-one* (**17**). To a suspension of Mg (3.5 g, 144 mg-atom) in 100 ml of Et_2O, bromoethane (2.1 g) was added dropwise to start a *Grignard* reaction. To this mixture, a solution of **14** (5.00 g, 17.9 mmol) in Et_2O (100 ml) was added slowly under reflux. Refluxing was continued for 5 h. After addition of 1-(dimethoxyacetyl)piperidine [9] (10.00 g, 53.5 mmol), dissolved in

Et_2O (75 ml), refluxing was continued for 4 h. The mixture was hydrolyzed by 50% of NH_4Cl (60 ml). The Et_2O-layer was separated, the aq. phase extracted with Et_2O (2 × 100 ml) and the combined org. phases were washed with H_2O, dried and evaporated *i.v.* to give crude **17**. Purification of the latter by CC (CH_2Cl_2/acetone gradient) yielded 1.04 g (19%) of **17** as a colourless oil. IR (CH_2Cl_2): 2975, 1725, 1120, 1070, 1030. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.90 (*d*, $J = 6$, CH_3–C(6)); 1.2–1.9 (*m*, 13H); 2.55 (*t*, $J = 7$, 2H–C(3)); 3.4 (*s*, 2 CH_3O–C(1)); 3.6–3.9 (*m*, 2H–C(8), 2H–C(6′)); 4.45 (*s*, H–C(1)); 4.6 (br., H–C(2′)). MS: 302 (M^+), 301, 271, 227, 85.

(2RS,6R)-1,1-Dimethoxy-6-methyl-8-[(2H-tetrahydropyran-2-yl)oxy]octan-2-ol (**18**). A solution of **17** (1.70 g, 5.20 mmol) in 100 ml of MeOH was treated with $NaBH_4$ (2.00 g) at r.t. for 12 h. Workup as described for the preparation of **17** from **14** yielded 1.62 g of crude product, which was purified by CC (benzene/MeOH gradient) to give 1.48 (87%) of **18** as a colourless oil. IR (CH_2Cl_2): 3560, 2940, 2880, 1120, 1075, 1030. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.90 (*d*, $J = 6$, CH_3–C(6)); 1.2–1.9 (*m*, 15H); 2.1 (br., HO–C(2)); 3.4 (*s*, 2 CH_3O–C(1)); 3.6–3.9 (*m*, H–C(2), 2H–C(8), 2H–C(6′)); 4.1 (*d*, $J = 7$, H–C(1)); 4.55 (br., H–C(2′)). MS: 304 (M^+), 303, 272, 229, 75.

(2RS,6R)-1,1-Dimethoxy-6-methyl-8-[(2H-tetrahydropyran-2-yl)oxy]oct-2-yl Acetate (**19**). A mixture of **18** (1.30 g, 4.27 mmol), pyridine (20 ml) and Ac_2O (14 ml) was kept at r.t. for 24 h. Evaporation of the solvents left a residue, which was diluted with Et_2O (150 ml) and washed with 0.1N HCl and H_2O. After removal of the solvent *i.v.* 1.42 g of a yellowish oil were obtained. Purification of the latter by CC (CH_2Cl_2/MeOH gradient) yielded 1.30 g (88%) of **19** as a colourless oil. IR (CH_2Cl_2): 2950, 2880, 1735, 1230, 1130, 1075, 1030. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.90 (*d*, $J = 6$, CH_3–C(6)); 1.2–1.9 (*m*, 15H); 2.05 (*s*, CH_3COO–C(2)); 3.40 (*s*, 2 CH_3O–C(1)); 3.6–3.9 (*m*, 2H–C(8), 2H–C(6′)); 4.25 (*d*, $J = 7$, H–C(1)); 4.60 (br., H–C(2′)); 5.05 (br., H–C(2)).

(6R)-6-Methyl-8-[(2H-tetrahydropyran-2-yl)oxy]-1-octanol (**20**). The *Grignard* reagent of **14** (5.58 g, 20.0 mmol), which was prepared in the same way as described for **16** from **14**, was added dropwise to a solution of ethylene oxide (1.5 ml, 30.0 mmol) in 7.5 ml of Et_2O at −5° within 1 h. The milky suspension obtained was allowed to warm up and was refluxed for 1 h. Hydrolysis with 4M NH_4Cl (50 ml) was followed by extraction with Et_2O (125 and 2 × 75 ml). The org. phases were washed with ice-water (3 × 25 g + 25 ml), dried and evaporated *i.v.* to yield 7.00 g of a yellow oil. Purification of the latter by CC (CH_2Cl_2/Et_2O gradient) gave 1.84 g (38%) of pure **20** as a colourless oil. $[\alpha]_D^{23} = 16° \pm 0.5°$ ($c = 2.3$, CH_2Cl_2). IR (film): 3420, 2950, 2880. ^{1}H-NMR (60 MHz, CCl_4): 0.90 (*d*, $J = 6$, CH_3–C(6)); 1.1–2.0 (*m*, 17H); 2.5 (br. *d*, HO–C(1)); 3.1–4.0 (*m*, 2H–C(1), 2H–C(8), 2H–C(6′)); 4.5 (br., H–C(2′)). MS: 244 (M^+), 171, 101, 85.

(6R)-6-Methyl-8-[(2H-tetrahydropyran-2-yl)oxy]-1-octanal (**21**). To a solution of **20** (1.27 g, 5.2 mmol) in 20 ml of CH_2Cl_2, PDC (3.2 g, 8.5 mmol) was added. The suspension was stirred at r.t. for 1 d. After dilution with Et_2O (30 ml), the mixture was filtered through a short column of *Florisil*. Evaporation of the filtrate gave a residue, which was purified by CC (Et_2O) to yield 825 mg (65%) of pure **21**. IR (film): 2940, 2870, 2720, 1725. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.89 (*d*, $J = 6$, CH_3–C(6)); 1.1–2.0 (*m*, 15H); 2.45 (*td*, $J = 7$, $J' = 1.8$, 2H–C(2)); 3.27–4.10 (*m*, 2H–C(8), 2H–C(6′)); 4.51–4.68 (br. *s*, H–C(2′)); 9.76 (*t*, $J = 1.8$, H–C(1)). MS: 241 ($M^+ - 1$), 169, 101, 85.

(3R)-3-Methyl-8,8-diethoxy-1-octanol (**22**). *a*) A solution of **21** (380 mg, 1.6 mmol) and PPTS (40 mg) in 15 ml of EtOH was stirred at 55° for 3 h. The mixture was taken up in Et_2O and washed with Na_2CO_3 and brine. The org. phase gave on evaporation of the solvent *i.v.* a colourless oil, which was purified by CC (Et_2O) to yield 314 mg (85%) of pure **22**. *b*) Analogous treatment of **31** (4.5 g, 16.6 mmol) gave 3.58 g (93%) of pure **22**. IR (film): 3420, 2940, 2880, 1135, 1070. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.89 (*d*, $J = 6$, CH_3–C(3)); 1.12–1.74 (*m*, 12H); 1.20 (*t*, $J = 7$, 2 CH_3CH_2O); 3.39–3.82 (*m*, 2H–C(1)); 3.60 (*qa*, $J = 7$, 2 × CH_3CH_2O); 4.48 (*t*, $J = 5$, H–C(8)). MS: 232 (M^+), 231, 187, 157, 141, 123, 103, 75.

2-[(5′R)-7′-bromo-5′-methylheptyl]-1,3-dioxolane (**23**). *a*) To a solution of **22** (3.5 g, 15.0 mmol) and Et_3N (10 ml, 72 mmol) in 100 ml of CH_2Cl_2 MsCl (2.3 ml, 30.0 mmol) was added dropwise at 0°. After stirring for 15 min at 0°, the mixture was extracted with ice-water, sat. NH_4Cl, sat. $KHCO_3$, and brine. On evaporation *i.v.* the org. phase yielded 4.4 g (94%) of mesylate as a yellowish oil, which was pure according to TLC. To a solution of this mesylate (4.4 g, 14.1 mmol) in 35 ml of acetone was added LiBr (5 g, 57 mmol) and the mixture was stirred at r.t. for 13 h. After concentration *i.v.* it was diluted with Et_2O and washed with brine. Evaporation of the solvent *i.v.* left 3.7 g of residue, which was dissolved in 100 ml of benzene. After addition of ethylene glycol (10 ml) and PPTS (370 mg) the mixture was refluxed for 3 h. The product was extracted with Et_2O. The org. layers were washed with sat. $KHCO_3$ and brine, dried and evaporated to give crude **23**. The latter was purified by CC (CH_2Cl_2) followed by bulb-to-bulb destillation to yield 3.4 g (91% based on the mesylate) of pure **23**. *b*) In the same manner as described above, **29** (400 mg, 1.95 mmol) yielded 460 mg (88%) of **23**.

$[\alpha]_D^{25} = -2.5° \pm 0.5°$ (c = 19.2, $CHCl_3$). IR (film): 2920, 2860, 1360, 1180. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.88 (*d*, J = 6, CH_3–C(5′)); 1.00–2.05 (*m*, 11H); 3.43 (*t*, J = 7, 2H–C(7′)); 3.88–4.10 (*m*, 2H–C(4), 2H–C(5)); 4.84 (*t*, J = 4, H–C(2)). MS: 266, 264, 251, 249, 185, 73.

*(3*R*)-[7-(1′,3′-dioxolan-2′-yl)-3-methylheptyl]triphenylphosphonium Bromide* (**24**). A solution of **23** (6.0 g, 22.6 mmol) and Ph_3P (6.55 g, 25 mmol) in 10 ml of benzene was refluxed for 3 d. The solvent was evaporated to give a brown oil, which was purified by CC (CH_2Cl_2/MeOH 9:1) to yield 9 g (75%) of pure, hygroscopic salt **24**. IR (CH_2Cl_2): 3050, 2940, 2860, 1590, 1435, 1115, 730, 695. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.99 (*d*, J = 6, CH_3–C(3)); 1.10–2.00 (*m*, 11H); 3.40–4.07 (*m*, 2H–C(1), 2H–C(4′), 2H–C(5′)); 4.81 (*t*, J = 4, H–C(2′)); 7.65–8.05 (*m*, 15H). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 19.1 (*q*, CH_3–C(3)); 20.8 (*td*, J(C,P) = 53, C(1)); 24.0 (*t*, C(6)); 26.5 (*t*, C(5)); 29.2 (*td*, J(C,P) = 4, C(2)); 33.4 (*dd*, J(C,P) = 14, C(3)); 33.7 (*t*, C(4)); 36.0 (*t*, C(7)); 64.7 (*t*, C(4′), C(5′)); 104.3 (*d*, C(2′)); 118.2 (*sd*, J(C,P) = 86, *ipso*-C arom.); 130.6 (*dd*, J(C,P) = 12, *meta*-C arom.); 133.6 (*dd* J(C,P) = 9, *ortho*-C arom.); 135.1 (*dd*, J(C,P) = 3, *para*-C arom.). MS: 447 (M^+ – 79/81 (Br)). Anal. calc. for $C_{20}H_{36}BrO_2P$ (527.50): C 66.03, H 6.87; found: C 65.28, H 6.90.

*(3*R*)-3-Methyl-7-(4′-dihydro-1′,3′-thiazol-2′-yl)-1-heptanol* (**26**). To a solution of 2-methyl-4-dihydro-1,3-thiazol (6.3 ml, 66.6 mmol) in 80 ml of THF, BuLi (49 ml, 73.5 mmol) was added at –78° over a period of 20 min. The mixture was stirred at –78° for 3 h. Then, a solution of **15** (23.9 g, 73 mmol) in 15 ml of THF was added dropwise over a period of 10 min. The mixture was stirred for an additional 1.5 h at –78°, before it was allowed to warm slowly to r.t. over night. The reaction was quenched by addition of 150 g of ice-water, and the pH was adjusted to 2 by adding 6N HCl. After stirring for 2 h at r.t., the org. layer was separated and the aq. layer was extracted with pentane. The org. layer was washed with brine, dried and evaporated *i.v.* to give a residue, which was purified by CC (CH_2Cl_2); 5.58 g of **15** were recovered. The aq. layer was adjusted to pH = 10 by addition of 8N KOH, saturated with NaCl and extracted with Et_2O. Removal of the solvent *i.v.* yielded crude **26**. After purification by bulb-to-bulb destillation 8.89 g (62% based on 2-methyl-4-dihydro-1,3-thiazole) of pure **26** were obtained. IR (film): 3330, 2930, 2860, 1625. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.89 (*d*, J = 6, CH_3–C(3)); 1.12–1.88 (*m*, 10H); 2.52 (*t*, J = 8, 2H–C(7)); 3.27 (*td*, J = 8, J' = 1, 2H–C(5′)); 3.66 (*t*, J = 6, 2H–C(1)); 4.21 (*td*, J = 8, J' = 1, 2H–C(4)). MS: 215 (M^+), 200, 114, 101.

*(3*R*)-3-Methyl-7-(1′,3′-thiazolidin-2-yl)-1-heptanol* (**27**). To Al(Hg) [10] prepared starting from 11 g of Al, a solution of **26** (8.89 g, 43.3 mmol) in 600 ml of Et_2O (previously shaken with H_2O) was added and the mixture was refluxed for 2.5 h. After it had been kept for an additional 2.5 h at r.t., the mixture was filtered and the filtrate evaporated *i.v.* to give 8.26 g (92%) of **27** as a colourless oil, pure according to TLC. IR (film): 3340, 3270, 2935, 2860. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.90 (*d*, J = 6, CH_3–C(3)); 1.07–2.00 (*m*, 11H); 2.15–2.45 (br., OH, NH); 2.70–2.80 (*m*, 2H–C(4′), 2H–C(5′)); 3.60 (*t*, J = 6, 2H–C(1)); 4.41 (*t*, J = 6, H–C(2)).

*(6*R*)-8-Hydroxy-6-methyloctanal* (**28**). To a solution of $HgCl_2$ (21 g) in 90 ml of acetonitrile/H_2O 4:1, a solution of **27** (8.26 g, 38 mmol) in 10 ml of CH_3CN was added dropwise within 15 min. The mixture was stirred at r.t. for 2 h. 75 ml of H_2O were added prior to filtration of the mixture. The extraction of the filtrate by Et_2O gave 5.33 g (88%) of crude aldehyde **28**, which immediately formed a polymeric product. The latter was used in the next step without purification.

*(3*R*)-8,8-Dimethoxy-3-methyl-1-octanol* (**29**). A solution of **28** (5.33 g, 33 mmol) and PPTS (100 mg) in 50 ml of MeOH was refluxed for 1 h. The mixture was diluted with Et_2O, which was washed with Na_2CO_3 and brine. Evaporation of the solvent *i.v.* left a colourless oil, which was purified by CC (Et_2O) to yield 5.37 g (80%) of pure **29**. IR (film): 3400, 2940, 2880, 1130, 1055. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.89 (*d*, J = 6, CH_3–C(3)); 1.20–1.70 (*m*, 12H); 3.31 (*s*, 2 CH_3O–C(8)); 3.68 (*t*, J = 7, 2H–C(1)); 4.36 (*t*, J = 5, H–C(8)). MS: 203 (M^+ – 1), 173, 123, 75.

*(1*Z*,6*R*)-1-Ethoxy-6-methyl-8-[(2*H*-tetrahydropyran-2-yl)oxy]-1-octene* (**31**). To a solution of (*Z*)-2-ethoxyvinyl bromide (7.1 g, 47 mmol) in 50 ml of THF *t*-BuLi (50 ml, 95 mmol) was added dropwise at –78°. After stirring for 1 h at –78°, HMPT (19.25 ml, 110 mmol) followed by a solution of **15** (7.5 g, 22.9 mmol) in 20 ml of THF was added. The mixture was kept at –78° for 12 h and at r.t. for 8 h before working up. The reaction was quenched by addition of H_2O and the product was extracted with Et_2O. The crude product obtained was purified by CC (CH_2Cl_2) to yield 4.58 g (74%) of **31**. IR (film): 3030, 2930, 2865, 1665. ^{1}H-NMR (60 MHz, CCl_4): 0.90 (*d*, J = 6, CH_3–C(6)); 1.10–2.15 (*m*, 15H); 1.22 (*t*, J = 7, CH_3CH_2O); 3.15–3.90 (*m*, 2H–C(8), 2H–C(6′)); 3.70 (*q*, J = 7, CH_3CH_2O); 4.20 (*dt*, J = 6, J' = 6, H–C(2)); 4.40–4.58 (br., H–C(2′)); 5.77 (*dt*, J = 6, J' = 1, H–C(1)). MS: 270 (M^+), 241, 225, 123, 101, 85.

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