Diastereo- and Enantioselective Total Synthesis of Stigmatellin A

Dieter Enders,* Gunter Geibel, and Simon Osborne[a]

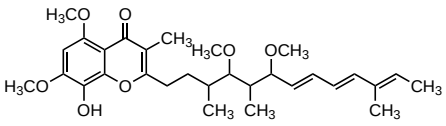
Dedicated to Professor Gerhard Höfle on the occasion of his 60th birthday

Abstract: Stigmatellin A (**1**) isolated from the myxobacterium *Stigmatella aurantiaca* is a powerful inhibitor of electron transport in mitochondria and chloroplasts. The first highly diastereo- and enantioselective total synthesis of this important natural product is described. Key steps in the synthesis are the alkylation of the SAMP-hydrazone (*S*)-**13**, a titanium mediated *syn*-diastereoselective aldol reaction, the *anti*-diastereoselective triacetoxyborohydride reduction of the aldol adduct (*R*,*R*,*S*)-**16**, formation of the chromone system via Baker–Venkataraman rearrangement and exclusive (*E*) C=C double bond formation via Horner–Wadsworth–Emmons reaction.

Keywords: aldol reactions · asymmetric synthesis · hydrazones · natural products · total synthesis

Introduction

Stigmatellin A (**1**) was first isolated by Höfle et al. in 1984[1] together with the geometric isomer stigmatellin B (**2**) from the gliding bacterium *Stigmatella aurantiaca*.[2] As one of the most powerful inhibitors known for the electron transport chain in chloroplasts and mitochondria,[3] its importance in elucidating the mode of action of these two vitally fundamental processes has been considerable.[4] Point of attack is on the one hand the cytochrome bc_1-segment of the respiratory chain[5] and on the other hand the reducing side of photosystem II and the cytochrome b_6/f-complex.[6] Investigations with derivatives of stigmatellin have shown that the chromone system is responsible for the inhibition reaction.[3, 5] Thierbach et al. demonstrated that the concentrations required for 50% inhibition of NADH oxidation in submitochondrial particles increase considerably when either the 4-oxo or the 8-hydroxy function of the chromone part are changed. The structure of the side chain not only imposes the necessary polarity to the molecule, but also contains functionality essential for biological activity. Jagow et al. proved that alterations in the side chain, that is shift of a methoxy group, loss of the methyl groups, or saturation of the C=C double bonds drastically affect the binding characteristics of stigmatellin A.[7] Thus, the side chain is not only necessary for partitioning the molecule into the hydrophobic phase but also makes an essential contribution to the binding energy.



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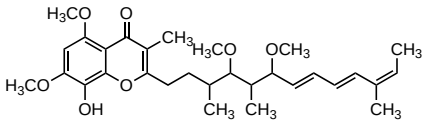

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The structure of stigmatellin A was elucidated from ^{1}H-NMR, ^{13}C-NMR, MS, IR, UV and CHN analysis data, although there was no information obtained on the relative or absolute configuration until it was determined as (*S*,*S*,*S*,*S*) through chemical correlation by employing a combination of our SAMP/RAMP-hydrazone method and the Evans *syn*-aldol protocol.[8] In this paper we report on the first highly diastereo- and enantioselective synthesis of stigmatellin A from achiral starting materials employing our well established SAMP/RAMP-hydrazone methodology to create the stereogenic centres of the chain.

Results and Discussion

The retrosynthetic analysis of stigmatellin A (Scheme 1) led to the three subunits **A**, **B** and **C**. Fragment **3** (**A**) had already been synthesized by Höfle et al.[1] without the protecting group on one of the hydroxyl groups. This protecting group is

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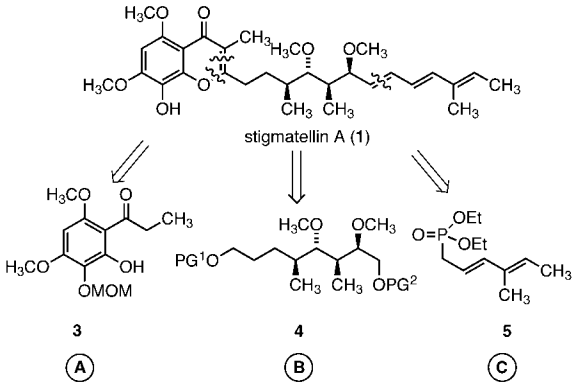
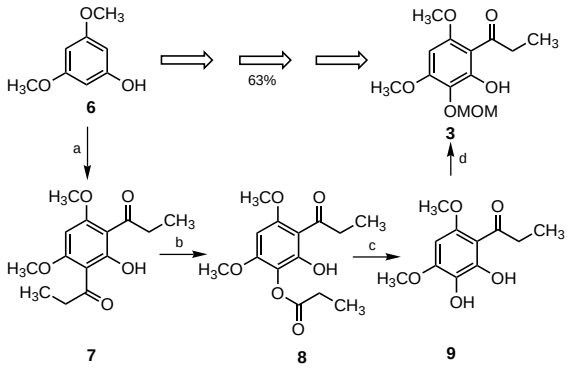


Scheme 1. Retrosynthetic analysis of stigmatellin A.

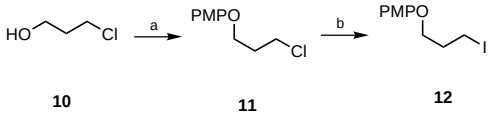


Scheme 2. Synthesis of the aromatic ketone **3**. a) Propionic acid, P_4O_{10}, H_3PO_4 (73%); b) TFA, *m*-CPBA, CH_2Cl_2 (87%); c) MeOH, HCl (99%); d) MOMCl, DIPEA, CH_2Cl_2 (98%).

essential to target the right hydroxy group when coupling with the chiral fragment **B**. This subunit **4** (**B**), the most complicated building block, could be synthesized by employing the SAMP/RAMP-hydrazone methodology[9] and a *syn*-selective aldol reaction.[10] It is necessary to protect the two ends of the chain in a different manner, so that it is possible to deprotect them selectively. We decided to use the benzyl group on one side and the *p*-methoxyphenyl group on the other. It should be possible to remove the benzyl group easily with hydrogen and the acid and base stable *p*-methoxyphenyl group with ceric ammonium nitrate. Subunit **5** (**C**) should be available starting from tiglinaldehyde and then coupled to the chain by a Horner–Wadsworth–Emmons reaction. As this olefination takes place under very mild conditions, we planned to complete the fragments **3** and **4** first.

The synthesis of ketone **9** (already synthesized by Höfle et al.) caused several problems in the beginning, however, by careful modification of the original reaction conditions the overall yield for the three step process starting from 3,5-dimethoxyphenol (**6**) has been considerable improved to 64% (Scheme 2). The first step is a straightforward diacylation of 3,5-dimethoxyphenol with propionic acid in the presence of P_4O_{10}. This reaction generates several side products, notably the two possible mono-acylated ketones, if the reaction is not homogeneous. The second step is a Baeyer–Villiger conversion of ketone **7** to ester **8**. This step is the most sensible part of the synthesis of **3**. The reaction can be performed at 0 °C only with purified *meta*-chloroperbenzoic acid (technical *m*-CPBA washed with pH 7 buffer)[11] and gives an excellent yield of 87%. If the reaction is unsuccessful (by TLC), the best method is to immediately resubmit **7** to the reaction conditions. The next step is a straightforward ester hydrolysis. The final protection of one hydroxyl group with chloromethyl-methylether (MOMCl) gives fragment **3** quantitatively and completely chemoselective. The second hydroxyl group is blocked by a hydrogen bond to the carbonyl function in *ortho*-position. This was entirely consistent with the ^{1}H-NMR chemical shift of the hydroxyl group $\delta = 13.93$.

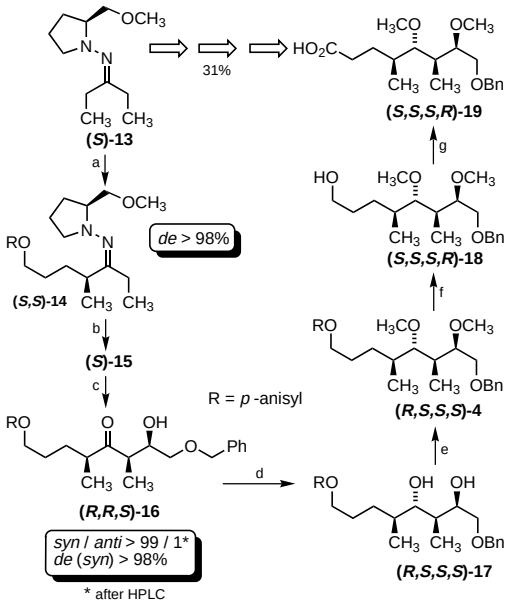
The synthesis of the central portion **4** (**B**) of stigmatellin A required a modified version of the synthesis of the degradation products reported earlier[8] (see Scheme 4). The main question was how to protect and differentiate the two ends of the molecule. We started with the alkylation[12] of the SAMP-hydrazone (*S*)-**13** with the iodide **12**, which was efficiently synthesized in two steps from 1-chloropropan-3-ol: protection of the hydroxyl group (*p*-methoxyphenol, diethyl azodicarboxylate (DEAD), Ph_3P, 95%)[13] followed by displacement of the chloride with iodide in a simple Finkelstein reaction (Scheme 3).[14] The alkylation product (*S*,*S*)-**14** was obtained with virtually complete asymmetric induction (*de* > 98%) and



Scheme 3. Synthesis of the protected iodoalcohol **12**. a) *p*-Methoxyphenol, DEAD, Ph_3P (95%); b) NaI, acetone (83%).

was oxidatively cleaved to give the corresponding ketone (*S*)-**15**.[15] The ketone was then subjected to a *syn*-selective titanium-mediated aldol reaction according to Evans et al.[10] with benzyl protected glycol aldehyde to give the aldol adduct **16** in quantitative yield with a *syn*/*anti* selectivity of 2:1. The two isomers could easily be separated by HPLC to afford the needed product (*R*,*R*,*S*)-**16** in 64% yield. The protected glycol aldehyde was efficiently synthesized in three steps from (*R*,*S*)-α,β-isopropylidene glycerol. Protection of the hydroxyl group with benzyl bromide followed by removal of the acetonide group and Criegee cleavage of the diol[16] with an overall yield of 63%.

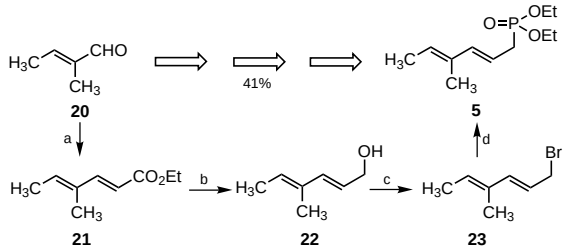
Abstract in German: *Stigmatellin A (**1**), isoliert aus dem Myxobakterium Stigmatella aurantiaca, ist ein starker Inhibitor des Elektronentransports in Mitochondrien und Chloroplasten. Die erste hoch diastereo- und enantioselektive Totalsynthese dieses wichtigen Naturstoffs wird beschrieben. Schlüsselschritte der Synthese sind die Alkylierung des SAMP-Hydrazons (S)-**13**, eine Titan-unterstützte syn-diastereoselektive Aldol-Reaktion, die anti-diastereoselektive Triacetoxyborhydrid-Reduktion des Aldol-Addukts (R,R,S)-**16**, Aufbau des Chromonsystems durch Baker–Venkataraman-Umlagerung und (E)-selektive C=C-Doppelbindungsbildung über eine Horner–Wadsworth–Emmons-Reaktion.*



Scheme 4. Diastereo- and enantioselective synthesis of the chain. a) LDA, Et_2O, $PMPO(CH_2)_3I$ (80%); b) MMPP, MeOH, pH 7 buffer (87%); c) $TiCl_4$, CH_2Cl_2, *i*$PrNEt_2$, $BnOCH_2CHO$ (64% after HPLC); d) Me_4NH-$B(OAc)_3$, CH_3CN, CH_3CO_2H (99%); e) KH, THF, 18-crown-6, MeI (77%); f) CAN, CH_3CN, H_2O (90%); g) PDC, DMF (100%).

anti-Selective reduction of the ketone group of the aldol product (*R*,*R*,*S*)-**16** with tetramethylammonium triacetoxyborohydride according to Evans et al.[17] gave the diol (*R*,*S*,*S*,*S*)-**17** in excellent 99% yield and with complete induction at the new hydroxyl centre. The now following conversion of the diol to the corresponding diether was problematic. The reaction with diazomethane only led to monomethylated product. The method of choice was the reaction with potassium hydride/methyliodide in the presence of 18-crown-6,[18] which gave the diastereomerically pure diether (*R*,*S*,*S*,*S*)-**4** in good yield (77%). In order to couple this fragment with the aromatic ketone **3** it was neccessary to remove the *p*-methoxyphenyl group. This could easily be achieved with ceric ammonium nitrate (CAN)[19] in high yield (90%). Finally, oxidation of the hydroxy group with pyridinium dichromate PDC[20] gave the acid (*S*,*S*,*S*,*R*)-**19** in quantitative yield.

In order to synthesize the diene subunit **5** of stigmatellin A (Scheme 5) we started from the commercially available tiglinaldehyde **20**, which was used in a simple Horner-olefination to give diene ester **21**. The ester was then



Scheme 5. Synthesis of the diene. a) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF (71%); b) DIBAH, Et_2O (99%); c) PBr_3, Et_2O (93%); d) $(EtO)_3P$ (63%).

selectively reduced with two equivalents of diisobutylaluminum hydride (DIBAH) to afford the known alcohol **22** as a modification of a known procedure.[21] According to Corey et al.[22] the alcohol was converted into the bromide **23** by stirring with PBr_3 in diethyl ether at 0 °C. It was neccessary to use the bromide directly in the next reaction. Each attempt to purify and isolate the bromide failed, because the compound starts to decompose in seconds. The phosphonate **5** was synthesized by a Michaelis–Arbuzov rearrangement,[23] where bromide **23** was heated with triethylphosphite. The ethylbromide formed during the reaction was removed continuously by distilling with a reflux condenser filled with warm water. Distillation gives the phosphonate **5** in good yield (41%, starting from tiglinaldehyde).

We started the coupling of the three building blocks **A**, **B**, and **C** with the formation of the chromone system, a well known reaction in the literature. The most common methods are the Kostanecki–Robinson reaction, the Claisen condensation and the Baker–Venkataraman rearrangement.[24] Höfle et al. used the Kostanecki–Robinson reaction to build up chromone systems with the substitution pattern of stigmatellin A. This reaction did not seem suitable in our case, because a large excess of the valuable enantiopure acid (*S*,*S*,*S*,*R*)-**19** would be needed and the reaction needs drastic conditions so that a large amount of side products could be predicted. The method of choice to generate chromone systems with a long chain in 2- or 3-position is the Baker–Venkataraman rearrangement.[25]

In the first step (Scheme 6) the ester **24** was synthesized by converting the acid **19** in situ into the corresponding mixed anhydride with pivaloylchloride, which then reacted with the aromatic ketone **3** to give ester **24** in 57% yield. The success of the reaction could easily be monitored by a down field shift of the resonance of the aromatic proton in the ^{1}H-NMR spectrum from 5.97 to 6.37 ppm. Baker–Venkataraman rearrangement of the ester gave the chromone **25** in good yield (75%). Deprotection of the hydroxyl group with Pd/C under atmospheric pressure led to alcohol **26**. This step must carefully be controlled by TLC to avoid undesired hydration of the carbonyl function or the chromone system. The corresponding aldehyd **27** was prepared under modified Swern conditions. A solution of the product in methylene chloride was stirred with 5 N HCl to remove the MOM protection group. Because of the sensitivity of the aldehyde it was directly used in the final Horner–Wadsworth–Emmons reaction according to Nicolaou et al., who used this olefination in the total synthesis of amphoteronolid B.[26] Starting from acid **19** we achieved an overall yield of 24%; starting from the SAMP-hydrazone **13** the yield is 7.4%. The synthetic stigmatellin A showed an optical rotation of $[\alpha]_D^{21} = +37.7$ ($c = 0.70$ in methanol), which is in perfect correlation with the natural product $[\alpha]_D^{20} = +38.5$ ($c = 2.3$ in methanol).[1]

In summary, the first diastereo- and enantioselective total synthesis of stigmatellin A from readily available achiral starting materials employing the SAMP/RAMP-hydrazone methodology to create the first stereocenter with virtually complete asymmetric induction has been reported.

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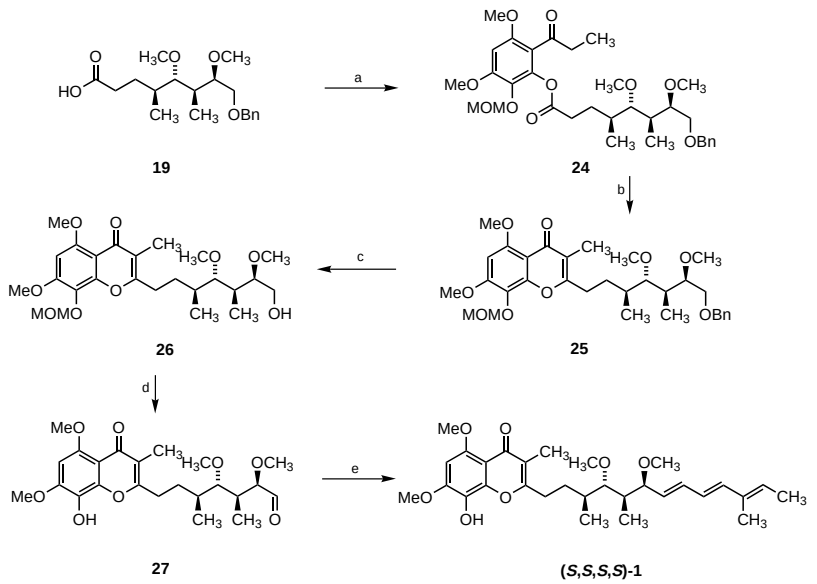

Scheme 6. The final steps. a) 1) CH_2Cl_2, *i*PrNEt$_2$, *t*BuCOCl, RT; 2) CH_2Cl_2, **3**, DMAP, RT (57%); b) MeOH, Na (75%); c) MeOH, Pd/C, H_2 (74%); d) CH_2Cl_2, oxalyl chloride, DMSO, *i*PrNEt$_2$; e) 1) LDA, THF, $-78\,^{\circ}C$; 2) **5**, 16 h, $-78\,^{\circ}C \rightarrow$RT (77%, two steps).

Experimental Section

Solvents were dried and purified prior to use. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from potassium under argon. Dichloromethane, acetonitrile, dimethyl sulphoxide (DMSO), dimethylformamide (DMF), diisopropylamine, and diisopropylethylamine (DIPEA) were distilled from CaH_2 and stored under argon. Methanol was distilled from the corresponding magnesium alkoxide. Acetone was distilled from P_4O_{10}. Ethyl acetate was distilled from potassium carbonate. Diethyl ether, light petroleum (fraction with b.p. 40–80 °C) and pentane were distilled prior to use. Analytical glass-backed TLC plates (silica gel 60 F_{254}) and silica gel (230–400 mesh) were purchased from Merck, Darmstadt. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. Melting points are uncorrected. Optical rotations were measured using a Perkin–Elmer P241 polarimeter and solvents of Merck UVASOL quality. Microanalyses were obtained with a CHN-O-RAPID or Vario EL elemental analyser. ^{1}H- and ^{13}C-NMR spectra were measured on a Varian VXR 300, Gemini 300 (300 and 75 MHz) or Varian Unity 500 (500 and 125 MHz) in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on Perkin–Elmer FT/IR 1750 and 1720X spectrophotometers as films. Mass spectra were obtained on a Varian MAT 212 or a Finnigan MAT SSQ 7000, EI 70 eV or CI 100 eV (relative intensities in parantheses). High-resolution mass spectra were measured on a Finnigan MAT, MAT 95. Melting points were recorded on a Büchi apparatus (system Dr. Tottoli) and are uncorrected.

1-(2-Hydroxy-4,6-dimethoxy-3-propionylphenyl)-1-propanone (7): P_4O_{10} (35 g) was slowly added to conc. H_3PO_4 (20 mL) in a 100 mL flask with stirring bar (**Warning**! The reaction is strongly exothermic). After a clear solution formed, 3,5-dimethoxyphenol (**6**) (5 g, 32 mmol) followed by propionic acid (6 g, 80 mmol) were added. The reaction mixture was heated under stirring to 70 °C for 1 h. After the reaction mixture was allowed to cool for 30 min., ice (60 g) and water (20 mL) were carefully added and extracted with methylene chloride (3×120 mL). The remaining aqueous solution was then carefully quenched with saturated sodium carbonate solution to pH 4–5, whereupon the aqueous phase was again extracted with CH_2Cl_2 (3×120 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting red oil was then dissolved in a small amount of CH_2Cl_2 and purified by column chromatography (silica gel, light petroleum/diethyl ether 1:1 (1 L) followed by light petroleum/diethyl ether 1:3) to give a white solid (6.2 g, 73%); analytical data as reported in the literature.[1a]

Propionic acid-(2-hydroxy-4,6-dimethoxy-3-propionylphenyl)ester (8): Trifluoroacetic acid (1 mL, 13 mmol) was added dropwise to a cooled solution of diketone **7** (3.5 g, 13 mmol) and *m*-CPBA (100%) (3.7 g, 21 mmol) in CH_2Cl_2 (35 mL) in a 100 mL flask with stirring bar (temperature was kept below 5 °C). The reaction mixture was stirred 16 h and allowed to warm up to room temperature. The reaction mixture was concentrated, dissolved in ethyl acetate (150 mL) and washed with saturated $NaHCO_3$ solution. The aqueous solution was extracted with ethyl acetate (150 mL). The combined organic solvents were dried, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, light petroleum/diethyl ether 1:2) to give a white solid (3.2 g, 87%); analytical data as reported in the literature.[1a]

1-(2,3-Dihydroxy-4,6-dimethoxyphenyl)propan-1-one (9): A solution of ketoester **8** (1.1 g, 4 mmol) in MeOH (15 mL) and 6N HCl (3.2 mL) was heated under reflux for 2 h, allowed to cool, diluted with CH_2Cl_2 (100 mL), and concentrated. The resulting oil was purified by column chromatography (silica gel, CH_2Cl_2) to give a yellow solid (0.88 g, 99%); analytical data as reported in the literature.[1a]

1-(2-Hydroxy-4,6-dimethoxy-3-methoxymethoxyphenyl)propan-1-one (3): A solution of ketodiol **9** (2.4 g, 10.6 mmol) and diisopropylethylamine (12 mL, 68.9 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C whereupon MOMCl (0.94 g, 11.7 mmol) was added. The reaction mixture was allowed to warm up to room temperature overnight. pH 7 buffer (20 mL) was added. The aqueous solution was then extracted with CH_2Cl_2 (3×50 mL); the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography (silica gel, ethyl acetate) to give a yellow solid (2.82 g, 98%); ^{1}H NMR (300 MHz): $\delta = 1.15$ (t, $^3J(H,H) = 7.2$ Hz, 3H, CH_3), 3.02 (q, $^3J(H,H) = 7.2$ Hz, 2H, CH_2), 3.61 (s, 3H, CH_2OCH_3), 3.89, 3.92 (2s, 2×3H, $2 \times OCH_3$), 5.09 (s, 2H, OCH_2O), 5.97 (s, 1H, Ar-H), 13.93 (s, 1H, OH); ^{13}C NMR (75 MHz): $\delta = 8.53$, 37.72, 55.57, 55.82, 57.25, 86.39, 97.98, 106.04, 126.84, 158.29, 158.79, 159.22, 207.01; IR (KBr): $\tilde{\nu} = 3428$, 2984, 2942, 2902, 2847, 2826, 2370, 1702, 1625, 1597, 1506, 1473, 1422, 1373, 1348, 1286, 1251, 1220, 1155, 1122, 1080, 1050, 1001, 967, 918, 821, 788, 763, 733, 695, 620, 589 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 271 (5.2) $[M+1]^+$, 270 (35) $[M]^+$, 239 (9), 225 (16), 211 (20), 209 (30), 197 (55), 193 (9), 183 (17), 182 (100), 179 (18), 153 (13), 150 (8), 136 (19), 69 (9), 57 (8), 45 (45); $C_{13}H_{16}O_6$ (270.28): calcd C 57.77, H 6.71; found C 57.69, H 6.69.

1-(3-Chloropropoxy)-4-methoxybenzene (11): DEAD (16.42 g, 100 mmol) was slowly added at 0 °C to a mixture of 3-chloro-1-propanol (**10**) (9.44 g, 100 mmol), 4-methoxyphenol (12.42 g, 100 mmol) and triphenylphosphine (26.2 g, 100 mmol) in CH_2Cl_2 (200 mL). After 0.5 h the reaction mixture was allowed to warm up to room temperature and stirred for 72 h and then concentrated. The residue was thoroughly washed with 10:1 light petroleum/diethyl ether (150 mL) and the solution then filtered through silica ($6 \times$). After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, light petroleum/diethyl ether 12:1) to give the product as a colorless oil (19.06 g, 95%); ^{1}H NMR (300 MHz): $\delta =$ 2.19 (tt, $^3J(H,H) = 6.4$ Hz, $^3J(H,H) = 5.7$ Hz, 2H, $2 \times$ H-2), 3.75 (s, 3H, OCH_3), 3.77 (t, $^3J(H,H) = 6.4$ Hz, 2H, CH_2Cl), 4.04 (t, $^3J(H,H) = 5.7$ Hz, 2H, OCH_2), 6.83 (s, 4H, $4 \times$ Ar-H); ^{13}C NMR (75 MHz): $\delta = 32.40$, 41.59, 55.70, 64.99, 114.68, 115.53, 152.88, 153.99; IR (KBr): $\tilde{\nu} = 2953$, 2933, 2877, 2834, 2474, 2062, 1853, 1593, 1509, 1469, 1442, 1290, 1233, 1181, 1041, 826, 743 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 200 (30.4) $[M]^+$, 124 (100), 123 (45), 109 (78), 95 (20), 92 (7), 81 (11), 77 (10), 65 (10), 64 (10), 63 (10), 52 (7), 51 (8), 49 (6); $C_{10}H_{13}ClO_2$ (200.66): calcd C 59.84, H 6.53; found C 59.97, H 6.24.

1-(3-Iodopropoxy)-4-methoxybenzene (12): A solution of chloride **11** (12.88 g, 64 mmol) in dry acetone (125 mL) was added to a solution of NaI (21.08 g, 141 mmol) in dry acetone (250 mL). The solution was heated under reflux for 5 d, allowed to cool and then filtered through silica. The

silica was washed with diethyl ether (200 mL) and the organic phases were washed with saturated $Na_2S_2O_3$ solution. After drying and evaporation, the product was purified by column chromatography (silica gel, light petroleum/diethyl ether 12:1) to give a colorless oil, which sets as a colorless solid in the freezer (15.59 g, 83 %); ^{1}H NMR (300 MHz): $\delta = 2.22$ (tt, $^3J(H,H) = 6.7$ Hz, $^3J(H,H) = 5.7$ Hz, 2H, 2 × H-2), 3.14 (t, $^3J(H,H) = 6.7$ Hz, 2H, CH_2I), 3.75 (s, 3H, OCH_3), 3.96 (t, $^3J(H,H) = 5.7$ Hz, 2H, OCH_2), 6.83 (s, 4H, Ar-H); ^{13}C NMR (75 MHz): $\delta = 2.74$, 33.06, 55.68, 67.94, 114.63, 115.54, 152.77, 153.95; IR (KBr): $\tilde{\nu} = 2949$, 2870, 2832, 2472, 2057, 1852, 1592, 1508, 1467, 1441, 1290, 1230, 1180, 1039, 825, 795, 739, 614 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 292 (64.5) $[M]^+$, 169 (11), 165 (12), 137 (18), 124 (81), 123 (100), 109 (58), 107 (10), 95 (32), 92 (12), 81 (9), 80 (6), 79 (6), 77 (15), 65 (11), 64 (13), 63 (11), 54 (6), 53 (7), 52 (8), 51 (6); $C_{10}H_{13}IO_2$ (292.11): calcd C 41.12, H 4.49; found C 41.38, H 4.42.

(2′*S*,2*S*)-(+)-[1-Ethyl-5-(4″-methoxyphenoxy)-2-methylpentylidene]-(2′-methoxy-methylpyrrolidin-1′-yl)-amine [(*S*,*S*)-14]: *n*-Butyllithium (1.6 M solution in hexane, 27.5 mL, 44 mmol, 1.1 equiv) was added slowly at 0 °C under an atmosphere of argon to a stirred solution of diisopropylamine (6.2 mL, 44 mmol, 1.1 equiv) in diethyl ether (50 mL). After stirring for 15 min, hydrazone (*S*)-**13** (7.9 g, 40 mmol, 1 equiv) was added dropwise. The solution was stirred for 5 h at 0 °C and then cooled to −100 °C. The iodide **12** (8.2 g, 44 mmol, 1.1 equiv) was added very slowly and the reaction mixture was stirred for 2 h at −100 °C, slowly allowed to warm to room temperature overnight, then poured into water and extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil. Purification by flash chromatography (silica gel, light petroleum/diethyl ether 4:1) afforded the product as a colorless oil (6.09 g, 80 %). $\alpha_D^{22} = +157.9°$ (neat); ^{1}H NMR (300 MHz): $\delta =$ 1.06 (d, $^3J(H,H) = 7.1$ Hz, 3H, $CHCH_3$), 1.13 (t, $^3J(H,H) = 7.4$ Hz, 3H, CH_2CH_3), 1.45 – 1.85 (m, 4H, 2 × H-3, 2 × H-4), 1.67 (m, 1H, NCHC*H*H), 1.80 (m, 2H, NCH_2CH_2), 2.00 (m, 1H, NCHCH*H*), 2.15 (q, $^3J(H,H) =$ 7.4 Hz, 2H, CH_2CH_3), 2.38 (q, $J(H,H) = 8.4$ Hz, 1H, NCH*H*), 2.99 (m, 1H, H-2), 3.16 (m, 1H, NC*H*H), 3.28 (s, 3H, OCH_3), 3.31 – 3.60 (m, 3H, $CHCH_2OCH_3$), 3.75 (s, 3H, Ar-OCH_3), 3.89 (t, $^3J(H,H) = 6.2$ Hz, 2H, 2 × H-5), 6.81 (s, 4H, Ar-H); ^{13}C NMR (75 MHz): $\delta = 12.32$, 18.22, 21.89, 23.51, 26.64, 27.29, 30.79, 34.21, 55.21, 55.70, 59.02, 66.12, 68.29, 75.64, 114.61, 115.35, 153.28, 153.70, 175.03; IR (film): $\tilde{\nu} = 2965$, 2934, 2872, 2831, 1627, 1592, 1509, 1462, 1385, 1352, 1288, 1233, 1182, 1126, 1109, 1042, 918, 825, 792, 745, 725, 524; MS (70 eV, EI): *m*/*z* (%): 362 (8.2) $[M]^+$, 318 (17), 317 (79), 193 (8), 159 (7), 151 (7), 137 (54), 125 (19), 124 (37), 123 (18), 110 (10), 109 (32), 107 (10), 96 (9), 95 (11), 82 (7), 81 (7), 77 (12), 70 (28), 69 (100), 68 (8), 67 (7), 56 (27), 55 (16), 54 (7), 53 (9), 45 (10); $C_{21}H_{34}N_2O_3$ (362.51): calcd C 69.58, H 9.45, N 7.73; found C 69.59, H 9.15, N 7.85.

(*S*)-(+)-7-(4′-Methoxyphenoxy)-4-methylheptan-3-one [(*S*)-15]: Hydrazone (*S*,*S*)-**14** (4.8 g, 13.2 mmol, 1 equiv) was added slowly at −15 °C to a suspension of MMPP (8.2 g, 16.6 mmol, 1.25 equiv) in methanol (65 mL) and pH 7 buffer (65 mL). The reaction mixture was stirred until completion (TLC control, about 15 min) and poured into diethyl ether (100 mL). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give a slight yellow oil. Purification by flash column chromatography (silica gel, light petroleum/diethyl ether 1:1) afforded the ketone (*S*)-**15** as colorless oil (2.89 g, 87 %). $\alpha_D^{23} = +12.3°$ (neat); ^{1}H NMR (300 MHz): $\delta =$ 1.04 (t, $^3J(H,H) = 7.3$ Hz, 3H, $CHCH_3$), 1.10 (d, $^3J(H,H) = 7.0$ Hz, 3H, CH_2CH_3), 1.45 – 1.88 (m, 4H, 2 × H-5, 2 × H-6), 2.46 (q, $^3J(H,H) = 7.3$ Hz, 1H, H-2), 2.48 (q, $^3J(H,H) = 7.3$ Hz, 1H, H-2), 2.60 (sext, $^3J(H,H) = 7.0$ Hz, 1H, H-4), 3.75 (s, 3H, OCH_3), 3.87 (t, $^3J(H,H) = 6.2$ Hz, 2H, OCH_2), 6.81 (s, 4H, Ar-H); ^{13}C NMR (75 MHz): $\delta = 7.79$, 16.64, 27.15, 29.48, 34.25, 45.73, 55.69, 68.34, 114.64, 115.40, 153.17, 153.80, 215.05; IR (film): $\tilde{\nu} =$ 3045, 2969, 2937, 2875, 2834, 1712, 1592, 1509, 1462, 1378, 1289, 1232, 1181, 1151, 1107, 1040, 976, 875, 826, 801, 746, 726, 525 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 350 (2.3) $[M]^+$, 127 (54), 126 (11), 124 (20), 123 (6), 109 (23), 95 (8), 85 (11), 81 (7), 77 (6), 71 (7), 69 (7), 57 (100), 55 (11), 53 (9); $C_{15}H_{22}O_3$ (250.34): calcd C 71.97, H 8.86; found C 71.74, H 8.75.

(2*R*,3*R*,5*S*)-(−)-1-Benzyloxy-hydroxy-8-(4′-methoxyphenoxy)-3,5-dimethyloctan-4-one [(*R*,*R*,*S*)-16]: Titanium tetrachloride (0.45 mL, 4 mmol, 1.1 equiv) was added dropwise to a solution of ketone (*S*)-**15** (0.9 g, 3.6 mmol, 1 equiv) in CH_2Cl_2 (20 mL) at −78 °C under an atmosphere of argon to give a red solution. After 5 min diisopropylethylamine (0.9 mL, 5 mmol 1.4 equiv) was added very slowly and the color changed to a black dark red. The resulting solution was stirred at −78 °C for a further 1.5 h, whereupon 2-benzyloxyacetaldehyde (1.08 g, 7.2 mmol, 2 equiv) was added and stirring continued for a further 2 h. After the reaction mixture was allowed to warm to room temperature saturated ammonium fluoride solution (20 mL) and then water (10 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil. Purification by flash chromatography (silica gel, light petroleum/diethyl ether 1:1) and separation of the diastereomers by HPLC afforded the aldol product (*R*,*R*,*S*)-**16** as colorless oil (0.93 g, 64 % after HPLC). $[\alpha]_D^{28} = -2.4$ ($c = 1.03$ in chloroform); ^{1}H NMR (300 MHz): $\delta = 1.09$ (d, $^3J(H,H) =$ 6.7 Hz, 3H, CH_3-5), 1.14 (d, $^3J(H,H) = 7.1$ Hz, 3H, CH_3-3), 1.38 – 1.87 (m, 4H, 2 × H-6, 2 × H-7), 2.74 (q, $^3J(H,H) = 6.7$ Hz, 1H, H-5), 2.82 (d, $^3J(H,H) = 3.4$ Hz, 1H, OH), 2.94 (qd, $^3J(H,H) = 7.1$ Hz, $^3J(H,H) = 5.4$ Hz, 1H, H-3), 3.45 (t, $^3J(H,H) = 6.4$ Hz, 2H, 2 × H-8), 3.74 (s, 3H, OCH_3), 3.83 (t, $^3J(H,H) = 6.2$ Hz, 1H, H-15), 3.84 (t, $^3J(H,H) = 6.2$ Hz, 1H, H-15), 4.05 (m, 1H, H-2), 4.48 (d, $^2J(H,H) = 11.8$ Hz, 1H, Ar-CH*H*), 4.52 (d, $^2J(H,H) = 11.8$ Hz, 1H, Ar-C*H*H), 6.80 (s, 4H, Ar-H), 7.24 – 7.34 (m, 5H, Ar-H); ^{13}C NMR (75 MHz): $\delta = 11.79$, 16.25, 27.01, 29.15, 45.31, 46.73, 55.69, 68.32, 70.62, 71.64, 73.40, 114.64, 115.41, 127.77, 127.79, 128.44, 137.85, 153.09, 153.78, 217.85; IR (film): $\tilde{\nu} = 3484$, 3063, 3031, 2934, 2872, 2835, 1704, 1592, 1560, 1509, 1455, 1376, 1306, 1289, 1232, 1181, 1107, 1039, 997, 917, 826, 795, 741, 700, 524 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 400 (3.7) $[M]^+$, 277 (7), 259 (9), 151 (13), 127 (8), 125 (6), 124 (15), 109 (8), 107 (6), 99 (6), 97 (6), 92 (9), 91 (100), 85 (6), 77 (5), 69 (15), 65 (5), 57 (7), 44 (66), 43 (9), 41 (14); $C_{24}H_{32}O_5$ (400.51): calcd C 71.97, H 8.05; found C 71.77, H 8.20.

(2*R*,3*S*,4*S*,5*S*)-(−)-1-Benzyloxy-8-(4′-methoxyphenoxy)-3,5-dimethyloctan-2,4-diol [(*R*,*S*,*S*,*S*)-17]: Acetic acid (6 mL) was slowly added at −40 °C to a suspension of tetramethyl ammonium triacetoxyborohydride (1.58 g, 6 mmol) in acetonitrile (4 mL) and after 5 min aldol (*R*,*R*,*S*)-**16** (2.2 g, 5.5 mmol) in acetonitrile (5 mL). After stirring for 15 min at −40 °C the reaction mixture was kept in the freezer (−25 °C) for 72 h, whereupon it was quenched with a 0.5 N solution of Na/K-tartrate (10 mL). After warming to room temperature the mixture was diluted with CH_2Cl_2 (25 mL) and washed with sat. $NaHCO_3$ solution (25 mL). The aqueous solution was reextracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were then once more washed with $NaHCO_3$ solution (30 mL) and the aqueous solution once again reextracted with CH_2Cl_2 (3 × 25 mL). After drying ($MgSO_4$), filtration, and concentration, the crude mixture was purified by flash column chromatography (silica gel, light petroleum/diethyl ether 1:1) to give the pure diol (*R*,*S*,*S*,*S*)-**17** as colorless liquid (2.2 g, 99 %). $[\alpha]_D^{24} = -23.6$ ($c = 1.73$ in chloroform); ^{1}H NMR (300 MHz): $\delta =$ 0.92 (d, $^3J(H,H) = 6.7$ Hz, 3H, CH_3-5), 0.95 (d, $^3J(H,H) = 7.4$ Hz, 3H, CH_3-3), 1.65 – 1.95 (m, 4H, 2 × H-6, 2 × H-7), 2.98 (s, 1H, OH-2), 3.07 (m, 1H, H-3), 3.51 (m, 2H, 2 × H-8), 3.55 (m, 1H, H-5), 3.74 (s, 3H, OCH_3), 3.88 (m, 2H, 2 × H-1), 3.90 (m, 1H, H-4), 4.19 (m, 1H, H-2), 4.53 (d, $^2J(H,H) =$ 11.8 Hz, 1H, Ar-CH*H*), 4.54 (s, 1H, OH-4), 4.59 (d, $^2J(H,H) = 11.8$ Hz, 1H, Ar-C*H*H), 6.18 (s, 4H, Ar-H), 7.26 – 7.36 (m, 5H, Ar-H); ^{13}C NMR (75 MHz): $\delta = 11.89$, 16.46, 26.91, 27.42, 35.84, 36.06, 55.67, 68.94, 71.06, 72.67, 73.40, 79.96, 114.61, 115.46, 127.59 – 128.45 (3C), 137.97, 153.23, 153.69; IR (film): $\tilde{\nu} = 3452$, 3063, 3030, 2934, 2871, 2834, 1591, 1509, 1466, 1454, 1419, 1329, 1289, 1232, 1180, 1107, 1041, 917, 825, 741, 700, 662, 616, 524 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 402 (4.6) $[M]^+$, 223 (9), 222 (10), 171 (33), 153 (8), 139 (6), 137 (11), 125 (26), 124 (100), 123 (14), 121 (6), 110 (5), 109 (36), 107 (13), 101 (17), 99 (42), 95 (11), 92 (26), 91 (95), 85 (6), 83 (5), 81 (10), 79 (5), 77 (7), 71 (6), 69 (20), 65 (11), 57 (14), 55 (11); $C_{24}H_{34}O_5$ (402.53): calcd C 71.61, H 8.51; found C 71.34, H 8.55.

(2*R*,3*S*,4*S*,5*S*)-(+)-1-Benzyloxy-2,4-dimethoxy-8-(4′-methoxyphenoxy)-3,5-dimethyloctane [(*R*,*S*,*S*,*S*)-4]: Potassium hydride (1.02 g, 25.5 mmol) was added to a solution of 18-crown-6 (1.88 g, 7.2 mmol) in 40 mL THF at 0 °C under an atmosphere of argon. After 5 min methyl iodide (1.25 mL, 20.4 mmol) was added and the reaction mixture stirred for further 5 min, whereupon diol (*R*,*S*,*S*,*S*)-**17** (1.45 g, 3.6 mmol) in THF (20 mL) was added dropwise. After stirring for 12 h at 0 °C and further 36 h at room temperature the reaction mixture was carefully quenched with brine (20 mL). The aqueous solution was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (silica gel, light petroleum/diethyl ether 4:1) to give the diether (*R*,*S*,*S*,*S*)-**4** as colorless oil (1.19 g, 77 %). $[\alpha]_D^{26} = +1.0$ ($c =$ 0.84 in chloroform); ^{1}H NMR (300 MHz): $\delta = 0.81$ (d, $^3J(H,H) = 7.1$ Hz, 3H, CH_3-3), 1.06 (d, $^3J(H,H) = 6.7$ Hz, 3H, CH_3-5), 1.20 – 1.95 (m, 6H, H-3, H-5, 2 × H-6, 2 × H-7), 3.04 (dd, $^3J(H,H) = 9.4$ Hz, $^3J(H,H) = 2.7$ Hz, 1H,

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H-4), 3.38–3.75 (m, 3H, H-2, 2 × H-1), 3.48 (s, 6H, OCH_3-2, OCH_3-4), 3.75 (s, 3H, Ar-OCH_3), 3.88 (t, ^3J(H,H) = 6.7 Hz, 2H, 2 × H-8), 4.50 (d, ^2J(H,H) = 12.1 Hz, 1H, Ar-CH*H*), 4.56 (d, ^2J(H,H) = 12.1 Hz, 1H, Ar-C*H*H), 6.81 (s, 4H, Ar-H), 7.24–7.36 (m, 5H, Ar-H); ^{13}C NMR (75 MHz): δ = 10.46, 17.78, 25.84, 27.46, 34.65, 38.39, 55.68, 58.48, 61.33, 68.84, 72.67, 73.27, 78.87, 87.29, 114.56, 115.41, 127.52, 127.58, 128.35, 138.39, 153.23, 153.64; IR (film): $\tilde{\nu}$ = 3063, 3030, 2935, 2832, 1745, 1591, 1509, 1466, 1455, 1382, 1368, 1288, 1233, 1181, 1144, 1096, 1040, 967, 940, 920, 825, 793, 738, 699, 612, 524 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 430 (3.4) $[M]^+$, 237 (10), 205 (16), 185 (11), 177 (5), 163 (9), 137 (10), 135 (15), 124 (20), 123 (15), 118 (7), 115 (28), 113 (9), 109 (17), 107 (9), 95 (9), 92 (10), 91 (100), 85 (19), 83 (10), 81 (15), 79 (6), 77 (7), 71 (9), 59 (7), 55 (13), 45 (8); $C_{26}H_{38}O_5$ (430.58): calcd C 72.53, H 8.89; found C 72.43, H 9.26.

(4*S*,5*S*,6*S*,7*R*)-(+)-1-Benzyloxy-5,7-dimethoxy-4,6-dimethyloctan-1-ol [(*S*,*S*,*S*,*R*)-18]: Ceric ammonium nitrate (1.36 g, 2.5 mmol) was added at 0 °C, in small portions, to a solution of diether (*R*,*S*,*S*,*S*)-**4** (310 mg, 0.72 mmol) in acetonitrile/water 4:1 (50 mL). After 6 min the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (40 mL) and water (40 mL). After drying ($MgSO_4$), filtration and concentration, flash column chromatography (silica gel, light petroleum/diethyl ether 3:2) gave the product as an orange oil (210 mg, 90%). $[\alpha]_D^{21}$ = +2.1 (*c* = 1.09 in chloroform); ^{1}H NMR (300 MHz): δ = 0.77 (d, ^3J(H,H) = 7.1 Hz, 3H, CH_3-6), 0.86 (m, 1H, H-4), 1.03 (d, ^3J(H,H) = 6.7 Hz, 3H, CH_3-4), 1.24 (m, 1H, H-6), 1.39–1.83 (m, 4H, 2 × H-2, 2 × H-3), 3.02 (dd, ^3J(H,H) = 9.3 Hz, ^3J(H,H) = 2.5 Hz, 1H, H-5), 3.48 (s, 6H, OCH_3-2, OCH_3-5), 3.56–3.67 (m, 4H, 2 × H-1, 2 × H-8), 3.72 (ddd, ^3J(H,H) = 6.4 Hz, ^3J(H,H) = 4.7 Hz, ^3J(H,H) = 2.0 Hz, 1H, H-7), 4.51 (d, ^2J(H,H) = 12.1 Hz, 1H, Ar-CH*H*), 4.56 (d, ^2J(H,H) = 12.1 Hz, 1H, Ar-C*H*H), 7.26–7.36 (m, 5H, Ar-H); ^{13}C NMR (75 MHz): δ = 10.51, 17.86, 25.68, 30.90, 34.73, 38.39, 58.50, 61.32, 63.34, 72.65, 73.31, 78.91, 87.40, 127.57, 127.63, 128.38, 138.41; IR (film): $\tilde{\nu}$ = 3412, 3088, 3063, 3030, 2935, 2877, 2832, 2346, 1951, 1809, 1701, 1658, 1587, 1497, 1455, 1381, 1367, 1256, 1196, 1096, 1029, 966, 941, 906, 850, 738, 699, 615, 488 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 324 (0.2) $[M]^+$, 171 (22), 131 (35), 115 (47), 100 (6), 99 (92), 98 (7), 92 (10), 91 (100), 85 (16), 83 (13), 81 (40), 73 (6), 72 (12), 71 (8), 69 (8), 65 (8), 57 (11), 55 (13), 45 (7).

(4*S*,5*S*,6*S*,7*R*)-(+)-1-Benzyloxy-5,7-dimethoxy-4,6-dimethyloctanic acid [(*S*,*S*,*S*,*R*)-19]: PDC (1.46 g, 3.9 mmol) was added to a solution of alcohol (*S*,*S*,*S*,*R*)-**18** (210 mg, 0.65 mmol) in DMF (5 mL) at room temperature. The resulting mixture was stirred overnight and then poured into diethyl ether (100 mL). The mixture was washed with sat. NH_4Cl solution (3 ×) and the aqueous solution was extracted with diethyl ether. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. Flash column chromatography (silica gel, diethyl ether/acetic acid 99:1) gave the pure acid (*S*,*S*,*S*,*R*)-**19** as colorless oil (220 mg, 100%). $[\alpha]_D^{23}$ = +1.0 (*c* = 1.11 in chloroform); ^{1}H NMR (300 MHz): δ = 0.77 (d, ^3J(H,H) = 7.1 Hz, 3H, CH_3-6), 1.04 (d, ^3J(H,H) = 6.7 Hz, 3H, CH_3-4), 1.42–1.86 (m, 4H, 2 × H-2, H-4, H-6), 2.30 (m, 1H, H-3), 2.45 (m, 1H, H-3), 3.05 (dd, ^3J(H,H) = 9.4 Hz, ^3J(H,H) = 2.4 Hz, 1H, H-5), 3.40–3.70 (m, 2H, 2 × H-8), 3.48 (s, 6H, OCH_3-5, OCH_3-7), 3.74 (ddd, ^3J(H,H) = 6.4 Hz, ^3J(H,H) = 4.7 Hz, ^3J(H,H) = 2.0 Hz, 1H, H-7), 4.51 (d, ^2J(H,H) = 12.1 Hz, 1H, Ar-CH*H*), 4.56 (d, ^2J(H,H) = 12.1 Hz, 1H, Ar-C*H*H), 7.26–7.36 (m, 5H, Ar-H), 11.33 (s, 1H, COOH); ^{13}C NMR (75 MHz): δ = 10.31, 17.42, 24.67, 32.01, 34.10, 38.35, 58.45, 61.35, 72.55, 73.30, 78.95, 87.30, 127.61, 127.69, 128.40, 138.31, 180.36; IR (film): $\tilde{\nu}$ = 3600–2600, 3088, 3064, 3031, 2973, 2934, 2832, 1954, 1734, 1709, 1605, 1496, 1454, 1422, 1384, 1367, 1250, 1199, 1176, 1158, 1096, 1028, 946, 874, 852, 738, 699, 617, 479 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 306 (5.4) $[M - CH_3OH]^+$, 237 (9), 185 (11), 146 (8), 145 (91), 131 (8), 127 (5), 115 (51), 114 (6), 113 (69), 99 (8), 92 (11), 91 (100), 85 (42), 83 (21), 72 (9), 71 (13), 65 (8), 57 (9), 55 (17). $C_{26}H_{38}O_5$ (338.44): calcd C 67.43, H 8.93; found C 66.98, H 8.59.

(2*E*,4*E*)-4-Methylhexa-2,4-dienacid ethylester (21): Diethoxyphosphoryl acetic acid ethylester (11.2 g, 50 mmol) was slowly added at 0 °C under an atmosphere of argon (total time for addition: 15 min) to a suspension of sodium hydride (1.6 g, 67 mmol) in dry THF (50 mL). After further stirring for 2 h (by which time the suspension had turned into a translucent solution), the mixture was cooled to −78 °C and tiglinaldehyde **20** (4.8 mL, 50 mmol) was added, neat, dropwise (total time for addition: 15 min). The reaction was then left and allowed to warm to room temperature overnight. The resulting mixture was diluted with diethyl ether (100 mL) and washed with water (50 mL). The water was extracted with diethyl ether (3 × 100 mL) and the combined organic phases washed with brine (80 mL). After drying ($MgSO_4$), filtration, and concentration, the mixture was purified by flash column chromatography (silica gel, light petroleum/diethyl ether 5:1) to give the product as a colorless oil (11.1 g, 71%). ^{1}H NMR (300 MHz): δ = 1.30 (t, ^3J(H,H) = 7.1 Hz, 3H, OCH_2CH_3), 1.77 (s, 3H, CH_3-4), 1.81 (d, ^3J(H,H) = 7.1 Hz, 3H, CH_3-6), 4.20 (q, ^3J(H,H) = 7.1 Hz, 2H, CH_2), 5.78 (d, ^3J(H,H) = 15.7 Hz, 1H, H-2), 5.98 (q, ^3J(H,H) = 7.1 Hz, 1H, H-5), 7.32 (d, ^3J(H,H) = 15.7 Hz, 1H, H-3); ^{13}C NMR (75 MHz): δ = 11.78, 14.36, 14.55, 60.13, 115.31, 133.79, 136.28, 149.47, 167.63; IR (film): $\tilde{\nu}$ = 2975, 2920, 2860, 1710, 1620, 1440, 1395, 1365, 1300, 1260, 1225, 1165, 1095, 1030, 975, 860, 815, 790, 715, 695 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 155 (3.0) $[M+1]^+$, 154 (30.0) $[M]^+$, 139 (31), 125 (5), 112 (5), 111 (76), 109 (35), 97 (6), 83 (8), 82 (7), 81 (100), 80 (25), 79 (58), 77 (13), 67 (8), 66 (6), 65 (9), 55 (18), 53 (37), 52 (5), 51 (14); $C_9H_{14}O_2$ (154.21): calcd C 70.10, H 9.15; found C 69.84, H 9.38.

(2*E*,4*E*)-4-Methylhexa-2,4-dien-1-ol (22): A solution of DIBAL (1.5 M in toluene, 38.6 mL) was added dropwise at −78 °C under an atmosphere of argon to a solution of ester **21** (4.25 g, 27.6 mmol) in dry diethyl ether (100 mL). After 1 h TLC showed no starting material and the reaction was quenched with sat. NH_4Cl solution (60 mL), warmed to room temperature, diluted with water (40 mL) and extracted with diethyl ether (5 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the product as a colorless oil, which was used directly in the next step without further purification (3.05 g, 99%). ^{1}H NMR (300 MHz): δ = 1.70 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 3.03 (s,1H, OH), 4.14 (d, ^3J(H,H) = 6.1 Hz, 2H, CH_2), 5.54 (q, ^3J(H,H) = 6.4 Hz, 1H, H-5), 5.67 (dt, ^3J(H,H) = 15.7 Hz, ^3J(H,H) = 6.4 Hz, 1H, H-2), 6.22 (d, ^3J(H,H) = 15.7 Hz, 1H, H-3); ^{13}C NMR (75 MHz): δ = 12.02, 13.82, 63.58, 125.05, 127.13, 133.99, 136.34; IR (film): $\tilde{\nu}$ = 3450, 3020, 2980, 2910, 2850, 1710, 1690, 1645, 1620, 1440, 1380, 1300, 1270, 1225, 1180, 1100, 1075, 1035, 1000, 960, 910, 840, 800, 790, 760, 730, 690 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 112 (24.0) $[M]^+$, 97 (23), 95 (8), 94 (34), 91 (6), 84 (9), 83 (27), 81 (5), 79 (43), 77 (24), 70 (22), 69 (27), 68 (14), 67 (30), 65 (12), 57 (9), 56 (19), 55 (100), 53 (34), 51 (18), 50 (7).

(2*E*,4*E*)-1-Bromo-4-methylhexa-2,4-dien (23): PBr_3 (3.27 mL, 18 mmol) was added dropwise at 0 °C to a solution of alcohol **22** (5.05 g, 45 mmol) in diethyl ether (400 mL). The reaction mixture was stirred at 0 °C overnight and was then poured into water (400 mL). After extraction with diethyl ether (5 × 150 mL), the combined organic phases were washed with water, sat. K_2CO_3 solution and brine. Drying (Na_2SO_4), filtration, and concentration gave the crude product as slight yellow oil. The product must be used directly into the next reaction, since after a few minutes strong decomposition occurs (7.33 g, 93%).

(2*E*,4*E*)-4-Methylhexa-2,4-dienylphosphonic acid diethylester (5): Triethylphosphite (12.2 g, 71 mmol) was stirred in a two-necked flask fitted with a dropping funnel and a reflux condensor (water, 50–60 °C) with a distillation bridge. Bromide **23** (9 g, 51 mmol) was added dropwise and the reaction mixture stirred overnight at 160 °C until no more ethyl bromide was formed. The crude product was purified by distillation at 0.05 mbar to give the phosphonate **5** as colorless liquid, b.p. 86 °C/0.05 mbar (7.46 g, 63%). ^{1}H NMR (300 MHz): δ = 1.30 (t, ^3J(H,H) = 6.9 Hz, 6H, 2 × CH_2CH_3), 1.70 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.63 (dd, ^2J(H,P) = 19.0 Hz, ^3J(H,H) = 7.5 Hz, 2H, 2 × H-7), 4.10 (m, 4H, 2 × CH_2CH_3), 5.37–5.57 (m, 2H, H-2, H-5), 6.16 (dd, ^4J(H,P) = 15.0 Hz, ^3J(H,H) = 5.0 Hz, 1H, H-3); ^{13}C NMR (75 MHz): δ = 12.00, 13.74, 16.49 (d, ^3J(C,P) = 5.7 Hz), 30.80 (d, ^1J(C,P) = 140.3 Hz), 61.89 (d, ^2J(C,P) = 7.1 Hz), 114.63 (d, ^5J(C,P) = 12.1 Hz), 126.60 (d, ^5J(C,P) = 4.0 Hz), 134.02 (d, ^4J(C,P) = 4.0 Hz), 139.72 (d, ^3J(C,P) = 14.4 Hz); IR (film): $\tilde{\nu}$ = 3479, 3039, 2982, 2931, 2912, 2867, 1715, 1647, 1479, 1445, 1392, 1369, 1295, 1251, 1164, 1098, 1056, 1028, 964, 869, 853, 786, 713, 594, 549, 483 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 233 (5.3) $[M+1]^+$, 232 (37.4) $[M]^+$, 152 (5), 139 (7), 138 (9), 125 (12), 111 (16), 107 (5), 97 (9), 95 (36), 94 (100), 93 (31), 91 (6), 81 (8), 80 (5), 79 (38), 77 (8), 67 (13), 55 (10), 41 (8); $C_{11}H_{21}O_3P$ (232.26): HRMS: calcd 232.1228; found 232.1228.

(4*S*,5*S*,6*S*,7*R*)-8-Benzyloxy-5,7-dimethoxy-4,6-dimethyloctanic acid-3,5-dimethoxy-2-methoxymethoxy-6-propionylphenylester [(*S*,*S*,*S*,*R*)-24]: Diisopropylethylamine (0.25 mL, 1.42 mmol) was added to a stirred solution of acid (*S*,*S*,*S*,*R*)-**19** (0.24 g, 0.71 mmol) in CH_2Cl_2 (5 mL) at room temperature. The solution was stirred at this temperature for 5 min and pivaloylchloride (0.09 mL, 0.72 mmol) was added dropwise. After additional stirring for 30 min phenol **3** (192 mg, 0.71 mmol) and a catalytical amount of DMAP was added. The reaction mixture was left at room

temperature for 3 h, then poured into water and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (silica gel, diethyl ether/light petroleum 3:1) afforded ester (*S*,*S*,*S*,*R*)-**24** as a colorless oil (240 mg, 57%).^{1}H NMR (300 MHz): $\delta = 0.79$ (d, ^3J(H,H) = 7.1 Hz, 3H, CH_3-6), 1.06 (d, ^3J(H,H) = 6.6 Hz, 3H, CH_3-4), 1.09 (t, ^3J(H,H) = 7.3 Hz, 3H, CH_2CH_3), 1.54–1.94 (m, 4H, 2 × H-3, H-4, H-6), 2.50 (m, 1H, H-2), 2.62 (m, 1H, H-2), 2.77 (q, ^3J(H,H) = 7.3 Hz, 2H, CH_2CH_3), 3.05 (dd, ^3J(H,H) = 9.3 Hz, ^3J(H,H) = 2.2 Hz, 1H, H-5), 3.40–3.70 (m, 2H, 2 × H-8), 3.48 (2s, 6H, OCH_3-5, OCH_3-7), 3.53 (s, 3H, CH_2OCH_3), 3.74 (ddd, ^3J(H,H) = 6.4 Hz, ^3J(H,H) = 4.8 Hz, ^3J(H,H) = 2.1 Hz, 1H, H-7), 3.79 (s, 3H, Ar-OCH_3), 3.85 (s, 3H, Ar-OCH_3), 4.50 (d, ^2J(H,H) = 12.0 Hz, 1H, Ar-CH*H*), 4.55 (d, ^2J(H,H) = 12.0 Hz, 1H, Ar-C*H*H), 4.99 (s, 2H, OCH_2O), 6.37 (s, 1H, Ar-H), 7.20–7.40 (m, 5H, Ar-H); ^{13}C NMR (75 MHz): $\delta = 8.15$, 10.34, 17.35, 24.45, 31.50, 33.97, 37.44, 38.46, 56.09, 57.19 (2C), 58.44, 61.33, 72.83, 73.30, 78.91, 87.16, 94.35, 98.56, 117.35, 127.59, 127.62, 128.36, 132.06, 138.41, 142.26, 153.83, 154.81, 171.55, 202.57; IR (film): $\tilde{\nu} = 3063$, 2970, 2938, 2844, 2250, 1766, 1693, 1608, 1581, 1497, 1461, 1439, 1425, 1398, 1375, 1343, 1287, 1242, 1208, 1160, 1102, 1029, 999, 957, 813, 734, 700, 648, 598 cm^{-1}; MS (100 eV, CI, methane): *m*/*z* (%): 619 (8.9) $[M+C_2H_5]^+$, 590 (1.0) $[M]^+$, 397 (18), 361 (20), 321 (46), 289 (49), 272 (15), 271 (100), 270 (28), 239 (63), 227 (25), 226 (20), 213 (21), 211 (15), 199 (38), 197 (55), 183 (82), 182 (18), 181 (50), 167 (18), 91 (46); $C_{20}H_{29}O_8$ [M − PhCH$_2$OCH$_2$CH(OCH$_3$)-CH(CH$_3$)]$^+$: HRMS: calcd 397.1862; found 397.1863.

2-[(3*S*,4*S*,5*S*,6*R*)-7-Benzyloxy-4,6-dimethoxy-4,6-dimethylheptyl]-5,7-dimethoxy-8-methoxymethoxy-3-methyl-4*H*-1-benzopyran-4-one [(*S*,*S*,*S*,*R*)-25]: Sodium (0.21 g, 9.1 mmol) was added carefully to dry methanol (15 mL). The reaction mixture was allowed to cool down to room temperature and ester (*S*,*S*,*S*,*R*)-**24** (71 mg, 0.12 mmol) in dry methanol (6 mL) was added. The resulting mixture was heated under reflux for 2 h and concentrated. The residue was dissolved in ethyl acetate (20 mL) and washed with 1N HCl (2 ×) and 15% NH_3 solution. The organic phase was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, CH_2Cl_2/acetone/methanol 90:8:2) to give the product as a colorless oil (51 mg, 75%).^{1}H NMR (300 MHz): $\delta = 0.70$ (d, ^3J(H,H) = 7.1 Hz, 3H, CH_3-5), 1.12 (d, ^3J(H,H) = 6.9 Hz, 3H, CH_3-3), 1.58–1.84 (m, 4H, 2 × H-2, H-3, H-5), 1.99 (s, 3H, CH_3), 2.57 (m, 1H, H-1), 2.75 (m, 1H, H-1), 3.04 (dd, ^3J(H,H) = 9.3 Hz, ^3J(H,H) = 2.5 Hz, 1H, H-4), 3.34–3.66 (m, 2H, 2 × H-7), 3.46 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.62 (s, 3H, CH_2OCH_3), 3.70 (ddd, ^3J(H,H) = 6.3 Hz, ^3J(H,H) = 4.7 Hz, ^3J(H,H) = 2.1 Hz, 1H, H-6), 3.95 (2s, 6H, 2 × Ar-OCH_3), 4.50 (d, ^3J(H,H) = 12.1 Hz, 1H, Ar-CH*H*), 4.54 (d, ^3J(H,H) = 12.1 Hz, 1H, Ar-C*H*H), 5.08 (s, 2H, OCH_2O), 6.38 (s, 1H, Ar-H), 7.24–7.36 (m, 5H, Ar-H); ^{13}C NMR (75 MHz): $\delta = 9.72$, 10.34, 17.75, 27.47, 30.02, 34.59, 38.52, 56.14, 56.48, 57.24, 58.42, 61.42, 72.59, 73.32, 78.83, 87.07, 92.02, 98.69, 108.04, 117.02, 126.80, 127.57, 127.62, 128.38, 138.36, 155.81, 156.59, 162.57, 177.36.

(2*R*,3*S*,4*S*,5*S*)-7-[5,7-Dimethoxy-8-methoxymethoxy-3-methyl-4-oxo-4*H*-2-chromenyl]-2,4-dimethoxy-3,5-dimethylheptanol [(*R*,*S*,*S*,*S*)-26]: Hydrogen was bubbled through a solution of chromone (*S*,*S*,*S*,*R*)-**25** (51 mg) in dry methanol (10 mL) until the reaction mixture was saturated (2 min). After the addition of a catalytical amount of palladium coal (10% Pd/C) hydrogen was bubbled through the solution until completion (TLC control, about 4 min). The reaction mixture was directly purified by flash column chromatography (silica gel, CH_2Cl_2/acteone/methanol 90:8:2) to give the product as a colorless oil (31.6 mg, 74%).^{1}H NMR (300 MHz): $\delta = 0.77$ (d, ^3J(H,H) = 7.1 Hz, 3H, CH_3-3), 1.11 (d, ^3J(H,H) = 6.6 Hz, 3H, CH_3-5), 1.50–1.86 (m, 4H, H-3, H-5, 2 × H-6), 1.99 (s, 3H, CH_3), 2.58 (m, 1H, H-7), 2.74 (m, 1H, H-7), 2.99 (dd, ^3J(H,H) = 8.5 Hz, ^3J(H,H) = 3.6 Hz, 1H, H-4), 3.37–3.72 (m, 3H, 2 × H-1, H-2), 3.45 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.65 (s, 3H, CH_2OCH_3), 3.95 (s, 3H, Ar-OCH_3), 3.96 (s, 3H, Ar-OCH_3), 5.09 (s, 2H, OCH_2O), 6.38 (s, 1H, Ar-H).

(2*R*,3*S*,4*S*,5*S*)-7-[8-Hydroxy-5,7-dimethoxy-methyl-4-oxo-4*H*-2-chromenyl]-2,4-dimethoxy-3,5-dimethylheptanal [(*R*,*S*,*S*,*S*)-27]: Dimethyl sulfoxide (11.2 mg, 0.143 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of oxalyl chloride (9.3 mg, 0.072 mmol) in dry CH_2Cl_2 (1 mL) at −78 °C under an atmosphere of argon. After 15 min a solution of alcohol (*R*,*S*,*S*,*S*)-**26** (31.6 mg, 0.065 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the resultant colorless mixture was stirred at −78 °C for 30 min. Diisopropylethylamine (42.8 mg, 0.325 mmol) was added. After 5 min at −78 °C the reaction mixture was allowed to warm to room temperature, then poured into water (4 mL) and extracted with CH_2Cl_2 (3 ×). The combined organic solvents are stirred for 30 min with 1N HCl (10 mL), washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated to give the crude product which was directly used in the next reaction step without further purification.

2-[(3*S*,4*S*,5*S*,6*S*,7*E*,9*E*,11*E*)-4,6-Dimethoxy-3,5,11-methyl-7,9,11-tridecatrienyl]-8-hydroxy-5,7-dimethoxy-3-methyl-4*H*-1-benzopyran-4-one [(*S*,*S*,*S*,*S*)-1]: *n*-BuLi (1.5 M solution in *n*-hexane, 0.05 mL) was added dropwise at 0 °C under an atmosphere of argon to a stirred solution of freshly distilled diisopropylamine (7 mg, 0.07 mmol) in dry THF (1 mL). After 5 min the mixture was cooled to −78 °C and phosphonate **5** (16 mg, 0.07 mmol) in dry THF (1 mL) was added dropwise. After 15 min at −78 °C, aldehyde (*R*,*S*,*S*,*S*)-**27** (0.035 mmol) in dry THF (1 mL) was added dropwise to the stirred phosphonate anion solution. The reaction mixture was stirred and allowed to warm up to room temperature overnight before it was quenched with sat. NH_4Cl solution (4 mL). The product was extracted with diethyl ether (20 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash column chromatography (silica gel, CH_2Cl_2/acetone/methanol 90:8:2) gave the product as slightly yellow oil (13.9 mg, 77%). $[\alpha]_D^{21} = +37.7$ ($c = 0.70$ in methanol); ^{1}H NMR (500 MHz): $\delta = 0.79$ (d, ^3J(H,H) = 7.3 Hz, 3H, CH_3-5), 1.11 (d, ^3J(H,H) = 7.0 Hz, 3H, CH_3-3), 1.53 (m, 1H, H-2), 1.69 (m, 1H, H-5), 1.74 (d, ^3J(H,H) = 6.7 Hz, 3H, 3 × H-13), 1.75 (s, 3H, CH_3-11), 1.76 (m, 1H, H-3), 1.91 (m, 1H, H-2),1.98 (s, 3H, CH_3), 2.61 (ddd, ^2J(H,H) = 14.6 Hz, ^3J(H,H) = 8.5 Hz, ^3J(H,H) = 7.5 Hz, 1H, H-1), 2.79 (ddd, ^2J(H,H) = 14.6 Hz, ^3J(H,H) = 8.9 Hz, ^3J(H,H) = 4.9 Hz, 1H, H-1), 3.10 (dd, ^3J(H,H) = 9.2 Hz, ^3J(H,H) = 3.2 Hz, 1H, H-4), 3.24 (s, 3H, OCH_3-6), 3.49 (s, 3H, OCH_3-4), 3.90 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 2.8 Hz, 1H, H-6), 3.92 (s, 3H, Ar-OCH_3), 3.98 (s, 3H, Ar-OCH_3), 5.47 (s, 1H, OH), 5.58 (q, ^3J(H,H) = 7.0 Hz, 1H, H-12), 5.58 (dd, ^3J(H,H) = 15.5 Hz, ^3J(H,H) = 7.6 Hz, 1H, H-7), 6.13 (dd, ^3J(H,H) = 15.5 Hz, ^3J(H,H) = 9.6 Hz, 1H, H-9), 6.21 (d, ^3J(H,H) = 15.5 Hz, 1H, H-10), 6.22 (dd, ^3J(H,H) = 15.5 Hz, ^3J(H,H) = 9.6 Hz, 1H, H-8), 6.42 (s, 1H, Ar-H); ^{13}C NMR (125 MHz): $\delta = 9.73$, 10.35, 11.94, 14.06, 17.59, 27.02, 29.53, 34.67, 41.69, 56.23, 56.38, 56.81, 61.36, 81.29, 87.28, 92.36, 108.1, 116.9, 125.2, 127.3, 127.9, 131.7, 133.3, 134.6, 137.8, 146.0, 149.2, 153.1, 162.4, 177.4.

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