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Iterative Deoxypropionate Synthesis Based on a Copper-Mediated Directed Allylic Substitution: Formal Total Synthesis of Borrelidin (C3–C11 Fragment)**

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Abstract: A new iterative strategy for the flexible preparation of any oligodeoxypropionate stereoisomer is presented which relies on an *o*-DPPB-directed copper mediated allylic substitution employing enantiomerically pure Grignard reagents; the reaction is working with perfect control over all aspects of the reaction selectivity. This key C–C bond-forming step features reversed polarity compared with established enolate alkylation methodology. It thus avoids existing problems of enolate alkylation strategies such as enolate reactivity as well as costs and problems associated with the chiral auxiliary. Practicability of this new method is demonstrated through application in natural product syntheses. Thus, an efficient synthesis of the northern part of the angiogenesis inhibitor borrelidin (**28**), the deoxypropionate building block **27**, could be devised, representing a formal total synthesis.

Keywords: allylation · asymmetric synthesis · diastereoselectivity · Grignard reagents · polyketides

Introduction

Many biologically interesting natural products of polyketide origin contain a fully reduced, "skip" 1,3,5,*n* (odd number)-polymethyl-substituted carbon chain.[1] These deoxypropionate structures are usually constructed relying on iterative asymmetric enolate alkylations as originally introduced by Evans[2] in the early 1990s. Significant improvements have been achieved employing pseudoephedrine amide enolates[3] and azaenolates derived from RAMP-hydrazones,[4] respectively. Despite these advances, efficiency of this methodology frequently suffers from either low enolate reactivity or removability and costs of the chiral auxiliary, drawbacks which are prohibitive for large scale applications. As a consequence, during the last years many efforts have been devoted to explore alternative strategies for iterative and stereoselective deoxypropionate construction. Among those are methodologies relying on diastereoselective conjugate addition of organometallics.[5] More recently an enantioselective catalytic conjugate addition variant employing a chiral diphosphine copper catalyst was reported.[6] Furthermore, catalytic enantioselective carboalumination has been used as an elegant key step for iterative deoxypropionate construction.[7]

We herein report in full detail on an alternative iterative strategy relying on our recently developed stereospecific directed copper-mediated allylic substitution reaction.[8] Our approach allows a flexible preparation of any desired oligodeoxypropionate stereoisomer of interest in a stereospecific manner and has been used in order to prepare the northern hemisphere of the angiogenesis inhibitor borrelidin.

Results and Discussion

The general strategy of our approach to deoxypropionates is outlined in Scheme 1. Key step is a S_N2' reaction of the chiral organometallic reagent **3** with the chiral allyl electrophile **2** providing dideoxypropionate **1**. Iteration would be feasible via oxidative alkene cleavage and transformation to the corresponding organometallic reagent **4**. Subsequent stereospecific allylic substitution with **2** furnishes the deoxypropionate building block **5** of each given stereostructure. This approach is complementary to the known enolate alkylation, since the growing propionate chain is introduced as a nucleophile and not as an electrophile ("Umpolung"). This may avoid some of the problems associated with the fre-

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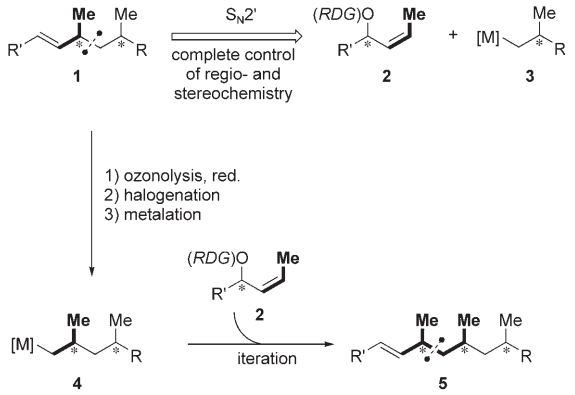
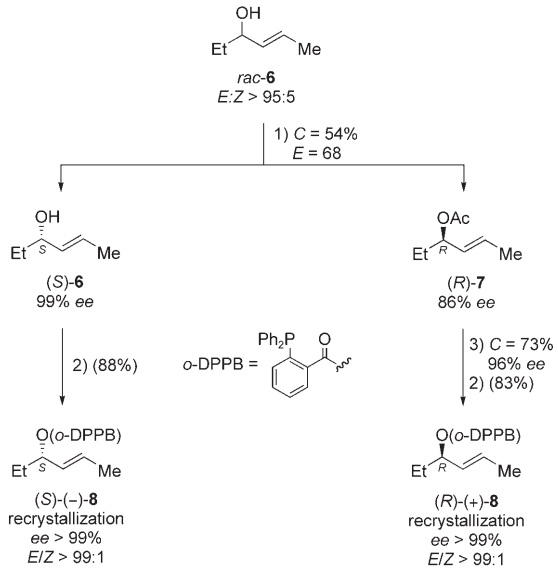
quently observed sluggish reactivity of enolates towards β-branched alkyl electrophiles. However, key to success of this strategy is the availability of an allylic substitution reaction that occurs with complete chemo-, regio- and stereoselectivity, as well as complete 1,3-chirality transfer. Our recently developed "directed" copper-mediated allylic substitution employing the *ortho*-diphenylphosphanylbenzoate (*o*-DPPB) function as a reagent-directing leaving group meets these requirements. However, compatibility with enantiomerically pure β-branched Grignard reagents **3** was at that time unknown. Furthermore, practical and scalable access to enantiomerically pure building blocks **2** and **3** was mandatory.



Scheme 1. Iterative strategy for the enantioselective construction of deoxypropionate structures relying on a directed copper-mediated allylic substitution (RDG = Reagent-Directing Group).

Enzyme catalysis was chosen as a convenient method to produce larger quantities of both optical antipodes of allylic alcohols **6** (Scheme 2). Thus, enzymatic kinetic resolution of readily available *rac*-**6** was achieved with Novozym 435.[9] Best results were obtained by shaking the reaction mixture at 30 °C in *n*-pentane as the solvent. At a conversion of 54 % the remaining alcohol (*S*)-**6** was obtained in enantiomerically pure form (>99 % *ee*) which gives a selectivity factor of $E = 68$.[10] Subjecting scalemic acetate (*R*)-**7** to enzymatic ester hydrolysis, employing the same enzyme (Novozym 435) again, furnished (*R*)-**6** (96 % *ee*). Both optical antipodes of **6** were transformed through esterification using the Steglich protocol to the corresponding *ortho*-diphenylphosphanylbenzoates **8** which were purified by recrystallization. According to this procedure, gram quantities of both optical antipodes of allyl electrophile **8** could be prepared in enantiomerically pure form. Allylic *o*-DPPB esters **8** could be stored in crystalline form for months without notable decomposition or oxidation to the corresponding phosphane oxide.

For the chiral organometallic reagent we chose the Grignard reagent **12** derived from the known bromide **10** (Scheme 3).[11] Both enantiomers of this bromide are readily accessible either from the commercially available Roche esters (**9**)[12] or through enzymatic esterification processes



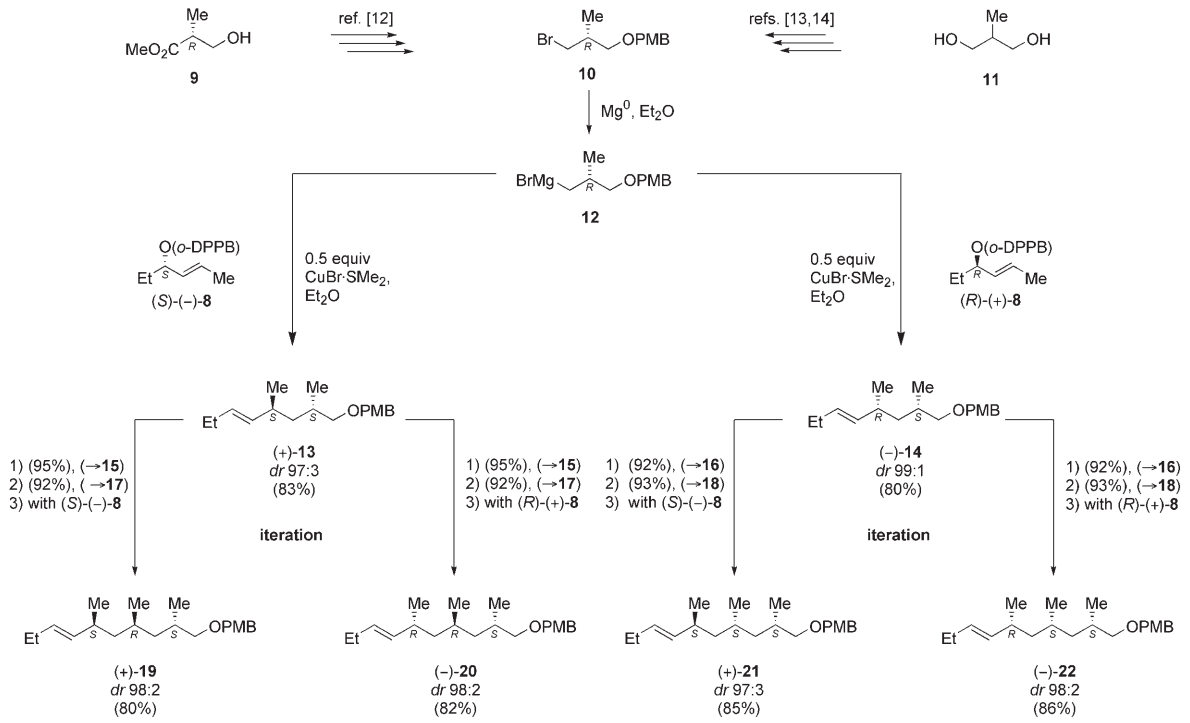
Scheme 2. Preparation of enantiomerically pure *o*-DPPB allylic esters **8**. 1) Novozym 435, vinylacetate, *n*-pentane, 30 °C; 2) *o*-DPPBA, DCC, DMAP, CH_2Cl_2; 3) Novozym 435, pH 7 buffer, 5 °C; DCC: dicyclohexylcarbodiimide.

starting from 2-methylpropane-1,3-diol (**11**)[13] or a derivative thereof.[14]

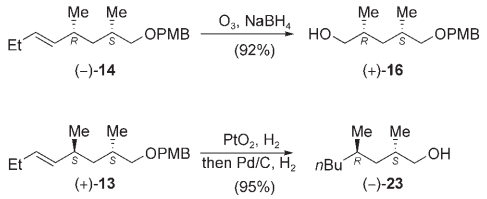
First, bromide **10** was converted to the corresponding Grignard reagent **12**. It proved mandatory to employ magnesium activated according to the dry stir method[15,16] in order to assure a smooth magnesiation. Thus, addition of one equivalent of a freshly prepared ethereal solution of Grignard reagent **12** to the allylic electrophile (*S*)-(−)-**8** in the presence of 0.5 equiv $CuBr{\cdot}SMe_2$ initiated a clean allylic substitution to give in perfect regio- (>99:1) and excellent stereoselectivity (*dr* 97:3) the dideoxypropionate (+)-**13** in good isolated yield. Even better stereoselectivity was noted upon reaction of Grignard **12** with the (*R*)-allyl electrophile (+)-**8** (*dr* 99:1). Thus, reactions producing the *syn*-relative configuration appear to represent a matched case while those producing the *anti*-configuration represent a mismatched case. However, it should be emphasized that even in the mismatched case high selectivity is observed.

Relative and absolute configuration of the dideoxypropionates (+)-**13** and (−)-**14** was determined through derivatization to the known alcohols (+)-**16**[17] and (−)-**23**,[18] respectively (Scheme 4).

In order to demonstrate practicability as well as stereochemical flexibility of our strategy, we decided to prepare all possible diastereomers of a series of trideoxypropionates in enantiomerically pure form (Scheme 3). The iteration of this sequence started with oxidative alkene cleavage of dideoxypropionate derivatives (+)-**13** and (−)-**14** through ozonolysis and reductive work up with $NaBH_4$ to give the corresponding alcohols in excellent yields (Scheme 3, step 1). At this stage we decided to explore an alternative method for Grignard generation relying on halogen–metal exchange. This procedure turned out to be operationally more conven-



Scheme 3. Enantioselective construction of di- and trideoxypropionate building blocks based on iterative *o*-DPPB-directed copper-mediated allylic substitution. 1) O_3, $NaBH_4$; 2) PPh_3I_2, Im; 3) 2 equiv *t*BuLi, $MgBr_2{\cdot}OEt_2$, then (*S*)-(−)-**8**, $CuBr{\cdot}SMe_2$, Et_2O.

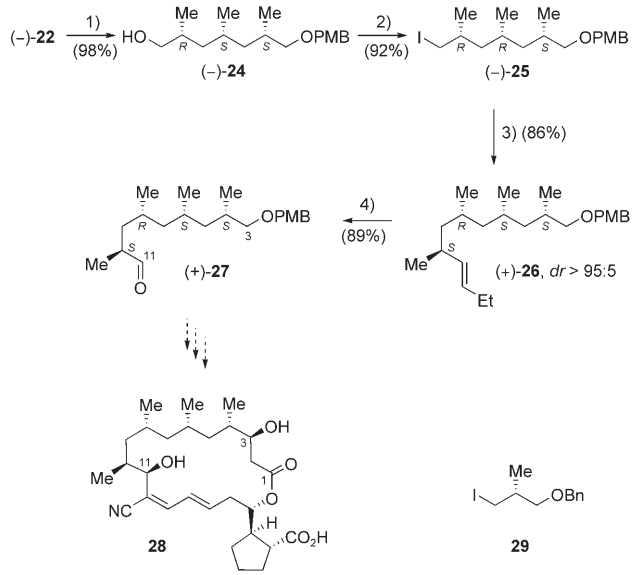


Scheme 4. Proof of relative and absolute configuration.

ient for small scale reactions. For this purpose the above-derived primary alcohols **15**, **16** were converted to the corresponding iodides **17**, **18** (Scheme 3, step 2). Halogen–metal exchange proceeded cleanly upon treatment with *tert*-butyllithium followed by transmetallation to magnesium. Directed allylic substitution with allyl electrophiles (*S*)-(−)-**8** and (*R*)-(+)-**8**, respectively, in the presence of 0.5 equiv copper(I) salt proceeded cleanly to give all four possible diastereomeric trideoxypropionate building blocks **19**–**22** in good yield, perfect regio- and excellent stereoselectivity as essentially single stereoisomers.

Formal total synthesis of borrelidin (C3–C11 fragment): Borrelidin (**28**) is a biologically intriguing and structurally unique macrolide antibiotic first isolated from *Streptomyces rochei* in 1949 by Berger and co-workers.[1b] The compound shows broad antiviral and antibacterial activity which presumably arises from its inhibition of threonyl-tRNA synthetase and protein biosynthesis.[19] In addition to its recently described CDK inhibitory activity,[20] borrelidin was found to inhibit angiogenesis in rat aorta models at subnanomolar concentrations ($IC_{50} = 0.4\ ng\,mL^{-1}$) through a so far unknown mechanism of action.[21] These results render this macrolide an attractive synthetic target for the development of novel antiangiogenetic drugs. Very recently, four elegant total syntheses have been reported[22] among which the synthesis of Theodorakis[22c] became of particular interest to us. Thus, in his synthesis the key building block for the northern hemisphere of borrelidin, aldehyde (+)-**27**, which is a tetradeoxypropionate derivative, was prepared employing the iterative enolate alkylation strategy developed by Myers et al.[3] in 13 steps starting from iodide **29** in 36% overall yield.[22c]

Our synthesis of the aldehyde (+)-**27** commenced from the all-*syn* trideoxypropionate (−)-**22** which was subjected to ozonolysis followed by reductive workup with $NaBH_4$ to give after Mukaiyama redox condensation the iodide (−)-**25** in excellent yields. Transformation of (−)-**25** to the corresponding Grignard reagent and subjection to the conditions of the directed allylic substitution with (*S*)-(−)-**8** gave the tetradeoxypropionate (+)-**26** in excellent yield and stereoselectivity (Scheme 5). Ozonolysis followed by reductive workup with triphenylphosphine furnished the known aldehyde (+)-**27**,[22c] thus representing a formal total synthesis of borrelidin. Our synthesis required eight steps from bromide **10** in a global yield of 41% and thus compares favorably with the approach towards (+)-**27** reported by Theodorakis.



Scheme 5. Formal total synthesis (C3–C11 fragment) of borrelidin **28** via iterative directed allylic substitution. 1) O_3, $NaBH_4$, (→**24**); 2) PPh_3I_2, Im; 3) 2 equiv *t*BuLi, $MgBr_2{\cdot}OEt_2$, then (*S*)-(−)-**8**, $CuBr{\cdot}SMe_2$, Et_2O; 4) O_3, PPh_3.

Conclusion

A new iterative strategy for the flexible preparation of any possible oligodeoxypropionate stereoisomer at will has been developed. Key to success was an *o*-DPPB-directed copper mediated allylic substitution employing enantiomerically pure Grignard reagents, which occurs with perfect control over all aspects of reaction selectivity. This fragment coupling step features reversed polarity compared to established enolate alkylation methodology. It thus avoids existing problems of enolate alkylation strategies such as enolate reactivity as well as costs of chiral auxiliary and problems with its removal. Practicality and applicability in natural product syntheses could be shown by the efficient synthesis of the northern part of the angiogenesis inhibitor borrelidin **28**, the deoxypropionate building block **27**, representing a formal total synthesis.

Experimental Section

General remarks: Reactions were performed in flame-dried glassware under argon (purity > 99.998%). The solvents were dried by standard procedures, distilled, and stored under argon. All temperatures quoted are not corrected. ^1H, ^{13}C NMR spectra: Bruker AM-400, Bruker DRX-500 with tetramethylsilane (TMS), chloroform ($CHCl_3$), or benzene (C_6H_6) as internal standards. ^{31}P NMR spectra: Varian Mercury 300 with 85% H_3PO_4 as external standard. Melting points: Melting point apparatus by Dr. Tottoli (Büchi). Elemental analyses: Elementar Vario EL. Flash chromatography: Silica gel Si 60, E. Merck AG, Darmstadt, 40–63 μm. Reversed phase silica gel Polygoprep 100–50 C18, Macherey-Nagel. *tert*-Butyllithium was purchased from Aldrich.

Resolution of *rac-trans*-hex-4-en-3-ol (6): Novozym 435[23] (800 mg) was added at 30°C to a solution of *rac*-**6** (8.0 g, 80 mmol) in *n*-pentane (40 mL) and vinyl acetate (7.6 g, 88 mmol, 1.1 equiv). The reaction mixture was shaken at this temperature until a conversion of 54% (NMR control) was reached (typically 21 h). After filtration and washing with *n*-pentane, the solution was poured directly on a flash column. Purification by flash chromatography (*n*-pentane/diethyl ether 20:1→1:2) and removing the solvents under atmospheric pressure provided (*R*)-*trans*-hex-4-en-3-yl acetate [(+)-**7**] (40 mmol, 50%, 86% *ee* determined after saponification to the corresponding alcohol **6**. $[\alpha]_D^{20} = +47.6$ ($c = 5.80$ in $CHCl_3$) and (*S*)-*trans*-hex-4-en-3-ol [(−)-**6**] (34 mmol, 42%, >99% *ee*, $[\alpha]_D^{20} = -2.0$, $c = 0.93$ in $CHCl_3$) as colorless liquids. GC (CP-Chirasil-Dex-CB, 25 m × 0.25 mm, 85°C isothermal, 5 psi H_2, t_R[(*R*)-**6**] = 7.6 min, t_R[(*S*)-**6**] = 7.9 min). The analytical and spectroscopic data correspond to those reported previously.[24]

Resolution of (*R*)-*trans*-hex-4-en-3-yl acetate [(+)-7]: Novozym 435 (1184 mg) was added at 5°C to a solution of (+)-**7** (8.42 g, 59.2 mmol, 86% *ee*) in diethyl ether (118 mL) and phosphate buffer pH 7 (178 mL) and stirred at this temperature until a conversion of 73% was reached (4 d). After filtration and washing with diethyl ether, the mixture was saturated with NaCl, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with conc. K_2CO_3 solution and dried over Na_2SO_4. The solvents were removed through distillation under atmospheric pressure. Flash chromatography with *n*-pentane/diethyl ether 20:1 furnished the alcohol (*R*)-**6** (26.3 mmol, 44%, 96% *ee*) as a colorless liquid. $[\alpha]_D^{20} = +2.1$ ($c = 0.85$ in $CHCl_3$). The analytical and spectroscopic data correspond to those reported previously.[24]

(3*S*,*E*)-3-[2-(Diphenylphosphanyl)benzoyloxy]-4-hexene [(−)-8]: Alcohol (*S*)-**6** (2.00 g, 20.0 mmol) was added dropwise at room temperature to a solution of *o*-DPPBA[25] (6.13 g, 20.0 mmol, 1.0 equiv), DCC (4.13 g, 20.0 mmol, 1.0 equiv) and DMAP (2.45 g, 20.0, 1.0 equiv) in CH_2Cl_2 (80 mL). After 24 h the reaction mixture was filtered through a plug of CH_2Cl_2-wetted Celite and washed with additional CH_2Cl_2. An appropriate amount of silica gel was added to the filtrate, which was then concentrated to dryness. Flash chromatography (petroleum ether/*tert*-butyl methyl ether 40:1) furnished after recrystallization first at 5°C and then at −20°C (−)-**8** (6.84 g, 17.6 mmol, 88%, >99% *ee*, >99:1 *E*/*Z*) as colorless crystals. $[\alpha]_D^{20} = -16.5$ ($c = 1.75$ in $CHCl_3$); m.p. 41°C; HPLC (DAICEL Chiralpak AD, 0.46 × 25 cm, 0.8 mL min^{-1}, *n*-heptane/isopropanol 99:1, 15°C, 260 nm, t_R[(*R*,*Z*)-**8**] = 10.3 min, t_R[(*S*,*Z*)-**8**] = 11.2 min, t_R[(*R*,*E*)-**8**] = 12.3 min, t_R[(*S*,*E*)-**8**] = 17.5 min); ^1H NMR (500.003 MHz, $CDCl_3$): $\delta = 0.81$ (t, $^3J = 7.5$ Hz, 3H; 1-CH_3), 1.50–1.65 (m, 2H; 2-CH_2), 1.63 (dd, $^3J = 6.7$, $^4J = 1.6$ Hz, 3H; 6-CH_3), 5.21–5.32 (m, 2H; 3- and 4-CH), 5.64 (dq, $^3J_{trans} = 14.6$, $^3J = 6.6$ Hz, 1H; 5-CH), 6.88–6.91 (m, 1H; Ar-H), 7.24–7.40 (m, 12H; Ar-H), 8.05–8.08 (m, 1H; Ar-H); ^{13}C NMR (125.741 MHz, $CDCl_3$): $\delta = 9.6$ (C-1), 17.7 (C-6), 27.4 (C-2), 77.3 (C-3), 128.1(C-5), 128.4 (d, J(C,P) = 7.0 Hz, 2C), 128.5 (d, J(C,P) = 1.7 Hz, 2C), 129.1 (2C), 129.2 (C-4), 130.6 (d, J(C,P) = 2.7 Hz, 2C), 131.7, 133.9 (d, J(C,P) = 9.7 Hz, 2C), 134.0 (d, J(C,P) = 10.0 Hz, 2C), 134.3, 135.1 (d, J(C,P) = 19.4 Hz), 138.2 (d, J(C,P) = 11.8 Hz), 138.3 (d, J(C,P) = 11.5 Hz), 140.1 (d, J(C,P) = 27.0 Hz), 166.2 (d, J(C,P) = 2.4 Hz, C=O); ^{31}P NMR (125.741 MHz, $CDCl_3$): $\delta = -3.63$; elemental analysis calcd (%) for $C_{25}H_{25}O_2P$ (388.44): C 77.30, H 6.49; found: C 77.25, H 6.67.

(3*R*,*E*)-3-[2-(Diphenylphosphanyl)benzoyloxy]-4-hexene [(+)-8]: The procedure was analogous to that used for the preparation of (−)-**8**. From alcohol (*R*)-**6** (1.46 g, 14.6 mmol), *o*-DPPBA (4.47 g, 14.6 mmol, 1.0 equiv), DCC (3.01 g, 14.6 mmol, 1.0 equiv) and DMAP (1.78 g, 14.6 mmol, 1.0 equiv) was obtained *o*-DPPB ester (+)-**8** (4.71 g, 12.1 mmol, 83%, >99% *ee*, >99:1 *E*/*Z*) as colorless crystals. The spectroscopic data correspond to those of (−)-**8**. $[\alpha]_D^{20} = +16.8$ ($c = 1.88$ in $CHCl_3$); m.p. 41°C; elemental analysis calcd (%) for $C_{25}H_{25}O_2P$ (388.44): C 77.30, H 6.49; found: C 77.21, H 6.60.

(2*S*,4*S*)-Dimethyl-1-(4′-methoxybenzyloxy)-oct-(5*E*)-ene [(+)-13]: $CuBr{\cdot}SMe_2$ (21 mg, 0.10 mmol, 0.5 equiv) was added at RT to a solution of (−)-**8** (78 mg, 0.20 mmol) in diethyl ether (4 mL) and the mixture was stirred for 5 min at RT. The Grignard reagent **12** (2.4 mL, 0.24 mmol, 0.1 M solution in diethyl ether, 1.2 equiv) was added dropwise at RT to the yellow solution. After stirring for 2 h the suspension was quenched by adding saturated aqueous NH_4Cl solution (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL).

The combined organic phases were dried (Na_2SO_4) and the solvents were removed in vacuo. Flash chromatography of the residue with petroleum ether/*tert*-butyl methyl ether 50:1 yielded the title compound (+)-**13** as a colorless oil (46 mg, 83%, *dr* 97:3). HPLC (Macherey-Nagel EC 250/4 Nucleosil 100-5, 0.4×25 cm, 0.8 mL min^{-1}, *n*-heptane/ethyl acetate 200:0.3, 25°C, 275 nm): t_R[(−)-**14**] = 52.4 min (2.8%), t_R[(+)-**13**] = 55.0 min (97.2%). $[\alpha]_D^{20}$ = +18.2 (*c* = 0.68 in $CHCl_3$); ^{1}H NMR (499.873 MHz, $CDCl_3$): δ = 0.91 (d, ^3J = 6.8 Hz, 3H; CH_3), 0.92 (d, ^3J = 6.8 Hz, 3H; CH_3), 0.95 (t, ^3J = 7.5 Hz, 3H; CH_3), 1.08 (dt, ^2J = 13.5, ^3J = 7.5 Hz, 1H; CH_2), 1.29 (m, 1H; CH_2), 1.81 (m, 1H; CH), 1.98 (m, 2H; CH_2), 2.14 (m, 1H; CH), 3.18 (dd, ^2J = 9.1, ^3J = 7.1 Hz, 1H; CH_2), 3.32 (dd, ^2J = 9.1, ^3J = 5.4 Hz, 1H; CH_2), 3.80 (s, 3H; O-CH_3), 4.41 (d, ^2J = 11.7 Hz, 1H; CH_2-Ar), 4.44 (d, ^2J = 11.7 Hz, 1H; CH_2-Ar), 5.25 (ddt, ^3J = 15.3, 7.6, ^4J = 1.4 Hz, 1H; CH), 5.38 (dtd, ^3J = 15.3, 6.2, ^4J = 0.9 Hz, 1H; CH), 6.87 (m, 2H; Ar-H), 7.26 (m, 2H; Ar-H); ^{13}C NMR (125.709 MHz, $CDCl_3$): δ = 14.0, 17.7, 20.7, 25.5, 31.0, 34.0, 41.2, 55.3, 72.6, 75.6, 113.7 (2C), 129.1 (2C), 129.9, 131.0, 135.6, 159.0; elemental analysis calcd (%) for $C_{18}H_{28}O_2$ (276.41): C 78.21, H 10.21; found C 77.90, H 10.32.

(2*S*,4*R*)-Dimethyl-1-(4′-methoxybenzyloxy)-oct-(5*E*)-ene [(−)-14]: The procedure was analogous to that used for the preparation of (+)-**13**. From *o*-DPPB ester (+)-**8** (78 mg, 0.20 mmol), CuBr·SMe_2 (21 mg, 0.10 mmol, 0.5 equiv) and Grignard reagent **12** (2.4 mL, 0.24 mmol, 0.1 M solution in diethyl ether, 1.2 equiv) was obtained alkene (−)-**14** (44 mg, 0.16 mmol, 80%, *dr* 99:1) as a colorless oil. $[\alpha]_D^{20}$ = −3.9 (*c* = 0.41 in $CHCl_3$); ^{1}H NMR (499.873 MHz, $CDCl_3$): δ = 0.89 (d, ^3J = 6.8 Hz, 3H; CH_3), 0.91 (d, ^3J = 6.8 Hz, 3H; CH_3), 0.95 (t, ^3J = 7.5 Hz, 3H; 8-CH_3), 1.01 (m, 1H; 3-CH_2), 1.33 (m, 1H; 3-CH_2), 1.79 (m, 1H; 2-CH), 1.98 (m, 2H; 7-CH_2), 2.17 (m, 1H; 4-CH), 3.18 (dd, ^2J = 9.1, ^3J = 7.1 Hz, 1H; 1-CH_2), 3.27 (dd, ^2J = 9.1, ^3J = 5.8 Hz, 1H; 1-CH_2), 3.80 (s, 3H; -O-CH_3), 4.42 (pt, ^2J = 12.2 Hz, 2H; -O-CH_2), 5.17 (ddt, ^3J = 15.2, ^3J = 8.3, ^4J = 1.3 Hz, 1H; 5-CH), 5.40 (dtd, ^3J = 15.2, ^3J = 6.3, ^4J = 0.6 Hz 1H; 6-CH), 6.87 (m, 2H; 3′-CH), 7.26 (m, 2H; 2′-CH); ^{13}C NMR (125.741 MHz, $CDCl_3$): δ = 14.0 (CH_3), 16.9 (CH_3), 22.0 (CH_3), 25.5 (C-7), 31.0 (C-2), 34.2 (C-4), 41.3 (C-3), 55.2 (O-CH_3), 72.5 (O-CH_2), 76.2 (C-1), 113.7 (2× C-3′), 129.0 (2×C-2′), 130.5 (C-6), 130.9 (C-1′), 134.9 (C-5), 159.0 (C-4′); elemental analysis calcd (%) for $C_{18}H_{28}O_2$ (276.41): C 78.21, H 10.21; found C 78.36, H 10.44.

(2*S*,4*S*)-Dimethyl-5-(4′-methoxybenzyloxy)-pentan-1-ol [(−)-15]: Through a solution of (+)-**13** (276 mg, 1.00 mmol) in MeOH (10 mL) at −78°C was bubbled a stream of ozone (one bubble per s) until a quantitative conversion was observed by TLC. Subsequently, the ozone was removed by bubbling argon through this solution. $NaBH_4$ (189 mg, 5.00 mmol, 5.0 equiv) was added at −78°C and then the mixture was slowly warmed to RT. NH_4Cl solution (10 mL) was added, the solution was extracted with ethyl acetate (3×10 mL) and dried (Na_2SO_4). An appropriate amount of silica gel was added to the filtrate, which was then concentrated to dryness. Flash chromatography (petroleum ether/*tert*-butyl methyl ether 20:1) furnished alcohol (−)-**15** (240 mg, 0.950 mmol, 95%) as a colorless oil. $[\alpha]_D^{20}$ = −11.9 (*c* = 1.78 in $CHCl_3$); ^{1}H NMR (499.873 MHz, $CDCl_3$): δ = 0.89 (pt, *J* = 6.2 Hz, 6H; CH_3), 1.21 (m, 2H; 3-CH_2), 1.60 (br t, 1H; OH), 1.74 (m, 1H; 2- or 4-CH), 1.88 (m, 1H; 2- or 4-CH), 3.24 (dd, ^2J = 9.0, ^3J = 6.4 Hz, 1H; CH_2), 3.27 (dd, ^2J = 8.9, ^3J = 6.4 Hz, 1H; CH_2), 3.42 (m, 2H; CH_2), 3.80 (s, 3H; O-CH_3), 4.43 (pt, *J* = 11.9 Hz, 2H; CH_2-Ar), 6.88 (m, 2H; 3′-CH), 7.25 (m, 2H; 2′-CH); ^{13}C NMR (125.709 MHz, $CDCl_3$): δ = 16.3 (CH_3), 17.0 (CH_3), 30.5 (CH), 33.0 (CH), 37.3 (C-3), 55.2 (O-CH_3), 68.8 (C-1), 72.7 (CH_2-Ar), 76.3 (C-5), 113.7 (2× C-3′), 129.1 (2×C-2′), 130.7 (C-1′), 159.1 (C-4′); elemental analysis calcd (%) for $C_{15}H_{24}O_3$ (252.35): C 71.39, H 9.59; found C 71.45, H 9.75.

(2*R*,4*S*)-Dimethyl-5-(4′-methoxybenzyloxy)-pentan-1-ol [(+)-16]: The procedure was analogous to that used for the preparation of (−)-**15**. From alkene (−)-**14** (470 mg, 1.70 mmol) and $NaBH_4$ (322 mg, 8.51 mmol, 5.0 equiv) was obtained alcohol (+)-**16** (394 mg, 1.56 mmol, 92%) as a colorless oil. $[\alpha]_D^{20}$ = +2.5 (*c* = 2.97 in $CHCl_3$); ^{1}H NMR (400.136 MHz, $CDCl_3$): δ = 0.87–0.98 (m, 1H), 0.93 (d, ^3J = 6.5 Hz, 3H; CH_3), 0.94 (d, ^3J = 6.9 Hz, 3H; CH_3), 1.42–1.50 (m, 1H), 1.64–1.74 (m, 2H), 1.80–1.90 (m, 1H), 3.21 (dd, ^2J = 9.0, ^3J = 6.4 Hz, 1H; CH_2), 3.28 (dd, ^2J = 9.0, ^3J = 5.6 Hz, 1H; CH_2), 3.39 (dd, ^2J = 10.7, ^3J = 6.2 Hz, 1H; CH_2), 3.47 (dd, ^2J = 10.7, ^3J = 5.2 Hz, 1H; CH_2), 3.80 (s, 3H; O-CH_3), 4.42 (pt, *J* = 12.5 Hz, 2H; CH_2-Ar), 6.87 (m, 2H; 3′-CH), 7.25 (m, 2H; 2′-CH); ^{13}C NMR (100.624 MHz, $CDCl_3$): δ = 17.6 (CH_3), 18.2 (CH_3), 31.0 (CH), 33.3 (CH), 37.7 (C-3), 55.2 (O-CH_3), 67.9 (C-1), 72.7 (CH_2-Ar), 75.6 (C-5), 113.7 (2×C-3′), 129.1 (2×C-2′), 130.7 (C-1′), 159.1 (C-4′). The analytical and spectroscopic data correspond to those reported previously.[17]

Triphenyliodophosphonium iodide: A solution of triphenylphosphine (13.1 g, 50.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0°C to iodine (12.8 g, 50.5 mol, 1.01 equiv) in CH_2Cl_2 (50 mL). The resulting suspension was stirred for 30 min. A complete consumption of triphenylphosphine was detected via TLC. The suspension was filtered, the filtrate was concentrated in vacuo and the resulting solid was suspended in petroleum ether (100 mL) and filtered. The combined solids were washed with petroleum ether (100 mL) and dried in vacuo yielding the title compound PPh_3I_2 (24.5 g, 47.5 mmol, 95%) as a yellow solid which was stored at −20°C under exclusion of light. Elemental analysis calcd (%) for $C_{18}H_{15}I_2$ (516.09): C 41.89, H 2.93; found C 41.92, H 2.96. The spectroscopic data correspond to those reported previously.[26]

5-Iodo-1-(4′-methoxybenzyloxy)-(2*S*,4*S*)-dimethylpentane [(−)-17]: A solution of alcohol (−)-**15** (530 mg, 2.10 mmol) in CH_2Cl_2 (4 mL) was added dropwise at RT under exclusion of light to PPh_3I_2 (1.30 g, 2.52 mmol, 1.2 equiv) and imidazole (345 mg, 5.07 mmol, 2.4 equiv) in CH_2Cl_2 (9 mL). The suspension was stirred overnight. TLC showed a quantitative conversion of the starting material. The suspension was concentrated in vacuo. Flash chromatography (petroleum ether/*tert*-butyl methyl ether 20:1) furnished the title compound (−)-**17** (699 mg, 1.93 mmol, 92%) as a colorless oil which was stored at −20°C under exclusion of light. $[\alpha]_D^{20}$ = −6.5 (*c* = 1.79 in $CHCl_3$); ^{1}H NMR (400.136 MHz, $CDCl_3$): δ = 0.91 (d, ^3J = 6.9 Hz, 3H; CH_3), 0.95 (d, ^3J = 6.4 Hz, 3H; CH_3), 1.16–1.33 (m, 2H; 3-CH_2), 1.61 (m, 1H; CH), 1.82 (m, 1H; CH), 3.14 (dd, ^2J = 9.5, ^3J = 6.0 Hz, 1H; 5-CH_2), 3.18–3.25 (m, 2H; CH_2), 3.27 (dd, ^2J = 9.0, ^3J = 6.0 Hz, 1H; 1-CH_2), 3.80 (s, 3H; O-CH_3), 4.42 (pt, *J* = 12.3 Hz, 2H; CH_2-Ar), 6.87 (m, 2H; 3′-CH), 7.25 (m, 2H; 2′-CH); ^{13}C NMR (100.624 MHz, $CDCl_3$): δ = 17.1 (CH_3), 18.3 (CH_3), 20.3 (C-5), 31.1 (CH), 32.3 (CH), 40.8 (C-3), 55.3 (O-CH_3), 72.7 (CH_2-Ar), 75.9 (C-1), 113.8 (2×C-3′), 129.1 (2×C-2′), 130.8 (C-1′), 159.1 (C-4′); elemental analysis calcd (%) for $C_{15}H_{23}IO_2$ (362.25): C 49.73, H 6.40; found C 49.76, H 6.30.

5-Iodo-1-(4′-methoxybenzyloxy)-(2*S*,4*R*)-dimethylpentane [(+)-18]: The procedure was analogous to that used for the preparation of (−)-**17**. From the alcohol (+)-**16** (631 mg, 2.50 mmol), PPh_3I_2 (1.55 g, 3.00 mmol, 1.2 equiv) and imidazole (408 mg, 6.00 mmol, 2.4 equiv) was obtained iodide (+)-**18** (844 mg, 2.33 mmol, 93%) as a colorless oil. $[\alpha]_D^{20}$ = +1.1 (*c* = 2.77 in $CHCl_3$); ^{1}H NMR (400.136 MHz, $CDCl_3$): δ = 0.94 (d, ^3J = 6.9 Hz, 3H; CH_3), 0.98 (d, ^3J = 6.4 Hz, 3H; CH_3), 0.98–1.07 (m, 1H; 3-CH_2), 1.43 (m, 1H; 3-CH_2), 1.53 (m, 1H; CH), 1.80 (m, 1H; CH), 3.10 (dd, ^2J = 9.5, ^3J = 6.0 Hz, 1H; CH_2), 3.21–3.25 (m, 2H; CH_2), 3.30 (dd, ^2J = 9.0, ^3J = 5.6 Hz, 1H; CH_2), 3.80 (s, 3H; O-CH_3), 4.42 (pt, ^2J = 12.0 Hz, 2H; CH_2-Ar), 6.87 (m, 2H; 3′-CH), 7.25 (m, 2H; 2′-CH); ^{13}C NMR (100.624 MHz, $CDCl_3$): δ = 17.6 (CH_3), 17.8 (CH_3), 21.4 (C-5), 31.0 (CH), 32.0 (CH), 40.8 (C-3), 55.2 (O-CH_3), 72.6 (CH_2-Ar), 75.4 (C-1), 113.7 (2× C-3′), 129.0 (2×C-2′), 130.8 (C-1′), 159.1 (C-4′); elemental analysis calcd (%) for $C_{15}H_{23}IO_2$ (362.25): C 49.73, H 6.40; found C 50.06, H 6.35.

(2*S*,4*R*,6*S*)-Trimethyl-1-(4′-methoxybenzyloxy)-dec-(7*E*)-ene [(+)-19]: *t*BuLi (0.6 mL, 1.66 M in pentane, 1.0 mmol, 2.0 equiv) was added dropwise at −100°C to a solution of the iodide (−)-**17** (181 mg, 0.500 mmol) in diethyl ether (1.0 mL). After 15 min TLC showed complete conversion of the starting material. Then a freshly prepared ethereal solution of $MgBr_2$·OEt_2 (from 1.00 mmol Mg,[27] 0.65 mmol dibromoethane, 0.7 mL diethyl ether) was added and the solution was slowly warmed to RT (30 min). The resulting colorless Grignard solution was added dropwise at RT via a transfer needle within 30 min to a solution of the *o*-DPPB ester (−)-**8** (214 mg, 0.550 mmol, 1.1 equiv), CuBr·SMe_2 (56 mg, 0.275 mmol, 0.55 equiv) in diethyl ether (11 mL). The resulting suspension was stirred overnight. Then saturated NH_4Cl solution (3.5 mL), aqueous NH_3 solution (12.5%, 1.3 mL), and CH_2Cl_2 (11 mL) were added and the mixture stirred until two clear phases were obtained. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×

5 mL). The combined organic phases were dried (Na_2SO_4). An appropriate amount of silica gel was added to the filtrate, which was then concentrated to dryness. Flash chromatography (petrolether/*tert*-butyl methyl ether 50:1) followed by reversed phase chromatography (acetonitrile/water 75:25→80:20, the product fractions were first concentrated in vacuo, then extracted with CH_2Cl_2 and dried over $CaCl_2$) furnished the alkene (+)-**19** (127 mg, 0.40 mmol, 80%, *dr* 98:2) as a colorless oil. GC (CP-SIL 5 Lowbleed/MS; 30 m × 0.32 mm × 0.25 μm: 50 °C (5 min isothermal), → 150 °C (25 °C min^{-1}, 10 min isothermal), → 170 °C (25 °C min^{-1}, 30.2 min isothermal), 2.5 mL min^{-1} He, t_R[(−)-**22**] = 36.9 min, t_R[(+)-**21**] = 37.5 min, t_R[(−)-**20**] = 38.5 min, t_R[(+)-**19**] = 40.4 min); $[\alpha]_D^{20} = +1.7$ ($c = 1.14$ in $CHCl_3$); ^{1}H NMR (499.873 MHz, $CDCl_3$): $\delta = 0.81$ (d, $^3J = 6.5$ Hz, 3H; CH_3), 0.88 (d, $^3J = 6.6$ Hz, 3H; CH_3), 0.92 (d, $^3J = 6.6$ Hz, 3H; CH_3), 0.95 (t, $^3J = 7.5$ Hz, 3H; 10-CH_3), 0.99–1.06 (m, 2H; 3- and 5-CH_2), 1.16 (m, 2H; 3- and 5-CH_2), 1.53 (m, 1H; 4-CH), 1.84 (m, 1H; 2-CH), 1.98 (m, 2H; 9-CH_2), 2.15 (m, 1H; 6-CH), 3.16 (dd, $^2J = 9.1$, $^3J = 7.1$ Hz, 1H; 1-CH_2), 3.27 (dd, $^2J = 9.1$, $^3J = 5.5$ Hz, 1H; 1-CH_2), 3.80 (s, 3H; O-CH_3), 4.41 (d, $^2J = 11.7$ Hz, 1H; CH_2-Ar), 4.44 (d, $^2J = 11.7$ Hz, 1H; CH_2-Ar), 5.17 (ddt, $^3J = 15.3$ Hz, 8.1, $^4J = 1.5$ Hz, 1H; 7-CH), 5.38 (dtd, $^3J = 15.3$, 6.4, $^4J = 0.8$ Hz, 1H; 8-CH), 6.87 (m, 2H; 3′-CH), 7.25 (m, 2H; 2′-CH); ^{13}C NMR (125.709 MHz, $CDCl_3$): $\delta = 14.1$ (C-10), 17.0 (CH_3), 19.3 (CH_3), 21.7 (CH_3), 25.6 (C-9), 27.3 (C-4), 30.8 (C-2), 34.2 (C-6), 41.5 (C-3), 45.6 (C-5), 55.2 (O-CH_3), 72.6 (CH_2-Ar), 76.3 (C-1), 113.7 (2 × C-3′), 129.1 (2 × C-2′), 130.1 (C-8), 131.0 (C-1′), 135.3 (C-7), 159.0 (C-4′); elemental analysis calcd (%) for $C_{21}H_{34}O_2$ (318.49): C 79.19, H 10.76; found C 79.04, H 10.73.

(2*S*,4*R*,6*R*)-Trimethyl-1-(4′-methoxybenzyloxy)-dec-(7*E*)-ene [(−)-20]: The procedure was analogous to that used for the preparation of (+)-**19**. From *o*-DPPB ester (+)-**8** (214 mg, 0.550 mmol, 1.1 equiv), CuBr·SMe_2 (56 mg, 0.275 mmol, 0.55 equiv) and iodide (−)-**17** (181 mg, 0.500 mmol) was obtained alkene (−)-**20** (131 mg, 0.410 mmol, 82%, *dr* 98:2) as a colorless oil. $[\alpha]_D^{20} = -26.0$ ($c = 1.71$ in $CHCl_3$); ^{1}H NMR (499.873 MHz, $CDCl_3$): $\delta = 0.82$ (d, $^3J = 6.6$ Hz, 3H; CH_3), 0.87 (d, $^3J = 6.6$ Hz, 3H; CH_3), 0.91 (d, $^3J = 6.6$ Hz, 3H; CH_3), 0.95 (t, $^3J = 7.4$ Hz, 3H; 10-CH_3), 1.07–1.13 (m, 4H; 3- and 5-CH_2), 1.54 (m, 1H; 4-CH), 1.84 (m, 1H; 2-CH), 1.98 (m, 2H; 9-CH_2), 2.16 (m, 1H; 6-CH), 3.18 (dd, $^2J = 9.0$, $^3J = 6.9$ Hz, 1H; 1-CH_2), 3.26 (dd, $^2J = 9.1$, $^3J = 5.9$ Hz, 1H; 1-CH_2), 3.79 (s, 3H; O-CH_3), 4.41 (d, $^2J = 11.7$ Hz, 1H; CH_2-Ar), 4.44 (d, $^2J = 11.7$ Hz, 1H; CH_2-Ar), 5.21 (ddt, $^3J = 15.3$, 7.9, $^4J = 1.4$ Hz, 1H; 7-CH), 5.38 (dtd, $^3J = 15.3$, 6.3, $^4J = 0.8$ Hz, 1H; 8-CH), 6.87 (m, 2H; 3′-CH), 7.26 (m, 2H; 2′-CH); ^{13}C NMR (125.709 MHz, $CDCl_3$): $\delta = 14.1$ (C-10), 16.8 (CH_3), 19.8 (CH_3), 21.0 (CH_3), 25.6 (C-9), 27.3 (C-4), 30.9 (C-2), 34.0 (C-6), 40.7 (C-3), 45.7 (C-5), 55.2 (O-CH_3), 72.6 (CH_2-Ar), 76.5 (C-1), 113.7 (2 × C-3′), 129.1 (2 × C-2′), 129.9 (C-8), 131.0 (C-1′), 135.6 (C-7), 159.0 (C-4′); elemental analysis calcd (%) for $C_{21}H_{34}O_2$ (318.49): C 79.19, H 10.76; found C 79.15, H 10.81.

(2*S*,4*S*,6*S*)-Trimethyl-1-(4′-methoxybenzyloxy)-dec-(7*E*)-ene [(+)-21]: The procedure was analogous to that used for the preparation of (+)-**19**. From *o*-DPPB ester (−)-**8** (214 mg, 0.550 mmol, 1.1 equiv), CuBr·SMe_2 (56 mg, 0.275 mmol, 0.55 equiv) and iodide (+)-**18** (181 mg, 0.500 mmol) was obtained alkene (+)-**21** (135 mg, 0.425 mmol, 85%, *dr* 97:3) as a colorless oil. $[\alpha]_D^{20} = +12.1$ ($c = 2.11$ in $CHCl_3$); ^{1}H NMR (499.873 MHz, $CDCl_3$): $\delta = 0.84$ (d, $^3J = 6.6$ Hz, 3H; CH_3), 0.86–0.92 (m, 1H; CH_2), 0.89 (d, $^3J = 6.6$ Hz, 3H; CH_3), 0.91 (d, $^3J = 6.6$ Hz, 3H; CH_3), 0.94 (t, $^3J = 7.4$ Hz, 3H; 10-CH_3), 0.99–1.06 (m, 1H; CH_2), 1.15 (m, 1H; CH_2), 1.30 (m, 1H; CH_2), 1.51 (m, 1H; 4-CH), 1.83 (m, 1H; 2-CH), 1.96 (m, 2H; 9-CH_2), 2.13 (m, 1H; 6-CH), 3.11 (dd, $^2J = 9.1$, $^3J = 7.4$ Hz, 1H; 1-CH_2), 3.31 (dd, $^2J = 9.1$, $^3J = 5.1$ Hz, 1H; 1-CH_2), 3.79 (s, 3H; O-CH_3), 4.38 (d, $^2J = 11.7$ Hz, 1H; CH_2-Ar), 4.42 (d, $^2J = 11.7$ Hz, 1H; CH_2-Ar), 5.23 (ddt, $^3J = 15.3$, 7.5, $^4J = 1.4$ Hz, 1H; 7-CH), 5.36 (dtd, $^3J = 15.4$, 6.3, $^4J = 0.8$ Hz, 1H; 8-CH), 6.86 (m, 2H; 3′-CH), 7.24 (m, 2H; 2′-CH); ^{13}C NMR (125.709 MHz, $CDCl_3$): $\delta = 14.1$ (C-10), 18.2 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 25.6 (C-9), 27.7 (C-4), 30.9 (C-2), 33.9 (C-6), 41.7 (C-3), 44.7 (C-5), 55.2 (O-CH_3), 72.6 (CH_2-Ar), 75.8 (C-1), 113.7 (2 × C-3′), 129.0 (2 × C-2′), 129.6 (C-8), 131.0 (C-1′), 135.9 (C-7), 159.0 (C-4′); elemental analysis calcd (%) for $C_{21}H_{34}O_2$ (318.49): C 79.19, H 10.76; found C 78.97, H 10.85.

(2*S*,4*S*,6*R*)-Trimethyl-1-(4′-methoxybenzyloxy)-dec-(7*E*)-ene [(−)-22]: The procedure was analogous to that used for the preparation of (+)-**19**. From *o*-DPPB ester (+)-**8** (1.50 g, 3.85 mmol, 1.1 equiv), CuBr·SMe_2 (397 mg, 1.93 mmol, 0.55 equiv) and iodide (+)-**18** (1.27 g, 3.50 mmol) was obtained alkene (−)-**22** (959 mg, 3.01 mmol, 86%, *dr* 98:2) as a colorless oil. $[\alpha]_D^{20} = -7.9$ ($c = 1.66$ in $CHCl_3$); ^{1}H NMR (499.873 MHz, $CDCl_3$): $\delta = 0.83$ (d, $^3J = 6.5$ Hz, 3H; CH_3), 0.89 (d, $^3J = 6.6$ Hz, 3H; CH_3), 0.90–0.95 (m, 2H; 3- and 5-CH_2), 0.92 (d, $^3J = 6.8$ Hz, 3H; CH_3), 0.94 (t, $^3J = 7.5$ Hz, 3H; 10-CH_3), 1.19–1.29 (m, 2H; 3- and 5-CH_2), 1.51 (m, 1H; 4-CH), 1.82 (m, 1H; 2-CH), 1.97 (m, 2H; 9-CH_2), 2.14 (m, 1H; 6-CH), 3.15 (dd, $^2J = 9.1$, $^3J = 7.2$ Hz, 1H; 1-CH_2), 3.28 (dd, $^2J = 9.0$, $^3J = 5.4$ Hz, 1H; 1-CH_2), 3.79 (s, 3H; O-CH_3), 4.39 (d, $^2J = 11.7$ Hz, 1H; CH_2-Ar), 4.43 (d, $^2J = 11.7$ Hz, 1H; CH_2-Ar), 5.14 (ddt, $^3J = 15.3$, 8.2, $^4J = 1.5$ Hz, 1H; 7-CH), 5.38 (dtd, $^3J = 15.3$, 6.4, $^4J = 0.7$ Hz, 1H; 8-CH), 6.86 (m, 2H; 3′-CH), 7.24 (m, 2H; 2′-CH); ^{13}C NMR (125.709 MHz, $CDCl_3$): $\delta = 14.1$ (C-10), 17.8 (CH_3), 20.4 (CH_3), 22.1 (CH_3), 25.5 (C-9), 27.5 (C-4), 30.8 (C-2), 34.3 (C-6), 42.1 (C-3), 44.5 (C-5), 55.2 (O-CH_3), 72.6 (CH_2-Ar), 76.0 (C-1), 113.7 (2 × C-3′), 129.0 (2 × C-2′), 130.3 (C-8), 131.0 (C-1′), 135.1 (C-7), 159.0 (C-4′); elemental analysis calcd (%) for $C_{21}H_{34}O_2$ (318.49): C 79.19, H 10.76; found C 78.99, H 10.86.

(2*S*,4*R*)-Dimethyloctan-1-ol [(−)-23]: PtO_2 (1.8 mg) was degassed in vacuo. Under an atmosphere of hydrogen (balloon) was then added a degassed solution of (+)-**13** (36.8 mg, 0.133 mmol, *dr* 97:3) in diethyl ether (1.8 mL) and the suspension was stirred overnight. GC-MS analysis showed complete reduction of the double bond. Then Pd/C (10%, 14 mg) was added and the suspension was stirred for further 3 h. TLC analysis showed complete conversion of the starting material. The suspension was filtrated, washed with diethyl ether and concentrated carefully through distillation under ambient pressure. Flash chromatography (pentane/diethyl ether 5:1) yielded alcohol (−)-**23** (19.9 mg, 0.126 mmol, 95%) as a colorless oil. $[\alpha]_D^{20} = -23.6$ ($c = 0.83$ in $CHCl_3$, *dr* 97:3, lit.[18] = −26.1 $c = 0.97$ in $CHCl_3$); ^{1}H NMR (400.136 MHz, $CDCl_3$): $\delta = 0.82$ (d, $^3J = 6.9$ Hz, 3H; CH_3), 0.87 (d, $^3J = 6.9$ Hz, 3H; CH_3), 0.87 (t, $^3J = 6.9$ Hz, 3H; 8-CH_3), 1.00–1.75 (m, 11H), 3.38 (dd, $^2J = 10.3$, $^3J = 6.4$ Hz, 1H; 1-CH_2), 3.46 (dd, $^2J = 10.5$, $^3J = 5.8$ Hz, 1H; 1-CH_2); ^{13}C NMR (100.624 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 16.4 (CH_3), 19.4 (CH_3), 23.0 (CH_2), 29.3 (CH_2), 29.9 (CH), 33.3 (CH), 37.7 (CH_2), 40.7 (CH_2), 69.1 (C-1). The analytical and spectroscopic data correspond to those reported previously.[18]

7-(4′-Methoxybenzyloxy)-(2*S*,4*S*,6*R*)-trimethyl-1-heptanol [(+)-24]: The procedure was analogous to that used for the preparation of (−)-**15**. From alkene (−)-**22** (181 mg, 0.569 mmol) and $NaBH_4$ (106 mg, 2.79 mmol, 5.0 equiv) was obtained alcohol (+)-**24** (164 mg, 0.558 mmol, 98%) as a colorless oil. $[\alpha]_D^{20} = +8.4$ ($c = 1.43$ in $CHCl_3$); ^{1}H NMR (400.136 MHz, $CDCl_3$): $\delta = 0.84$–0.92 (m, 2H; CH_2), 0.87 (d, $^3J = 6.5$ Hz, 3H; CH_3), 0.89 (d, $^3J = 6.9$ Hz, 3H; CH_3), 0.91 (d, $^3J = 7.3$ Hz, 3H; CH_3), 1.24–1.37 (m, 2H; CH_2), 1.43 (br s, 1H; OH), 1.56 (m, 1H; CH), 1.68 (m, 1H; CH), 1.82 (m, 1H; CH), 3.16 (dd, $^2J = 9.0$, $^3J = 6.9$ Hz, 1H; 7-CH_2), 3.29 (dd, $^2J = 9.0$, $^3J = 5.2$ Hz, 1H; 7-CH_2), 3.33 (dd, $^2J = 10.5$, $^3J = 6.7$ Hz, 1H; 1-CH_2), 3.49 (dd, $^2J = 10.5$, $^3J = 4.9$ Hz, 1H; 1-CH_2), 3.78 (s, 3H; O-CH_3), 4.38 (d, $^2J = 11.6$ Hz, 1H; CH_2-Ar), 4.42 (d, $^2J = 11.6$ Hz, 1H; CH_2-Ar), 6.85 (m, 2H; 3′-CH), 7.25 (m, 2H; 2′-CH); ^{13}C NMR (100.624 MHz, $CDCl_3$): $\delta = 17.6$ (CH_3), 18.3 (CH_3), 21.0 (CH_3), 27.8 (CH), 30.9 (CH), 33.1 (CH), 41.2 (CH_2), 41.7 (CH_2), 55.2 (O-CH_3), 68.1 (C-1), 72.6 (CH_2-Ar), 75.5 (C-7), 113.7 (2 × C-3′), 129.0 (2 × C-2′), 130.9 (C-1′), 159.0 (C-4′); elemental analysis calcd (%) for $C_{18}H_{30}O_3$ (294.43): C 73.43, H 10.27; found C 73.36, H 10.23.

7-Iodo-1-(4′-methoxybenzyloxy)-(2*S*,4*R*,6*R*)-trimethyl-1-heptane [(−)-25]: The procedure was analogous to that used for the preparation of (−)-**17**. From alcohol (+)-**24** (199 mg, 0.676 mmol), PPh_3I_2 (419 mg, 0.811 mmol, 1.2 equiv) and imidazole (110 mg, 1.62 mmol, 2.4 equiv) was obtained iodide (−)-**25** (252 mg, 0.624 mmol, 92%) as a colorless oil. $[\alpha]_D^{20} = -8.2$ ($c = 0.77$ in $CHCl_3$); ^{1}H NMR (400.136 MHz, C_6D_6): $\delta = 0.73$ (d, $^3J = 6.5$ Hz, 3H; CH_3), 0.79 (d, $^3J = 6.4$ Hz, 3H; CH_3), 0.73–0.89 (m, 2H; CH_2), 1.02 (d, $^3J = 6.9$ Hz, 3H; CH_3), 1.13–1.25 (m, 2H; CH_2), 1.28–1.45 (m, 2H; CH), 1.88 (m, 1H; CH), 2.79 (dd, $^2J = 9.7$, $^3J = 5.4$ Hz, 1H; 7-CH_2), 2.88 (dd, $^2J = 9.5$, $^3J = 3.4$ Hz, 1H; 7-CH_2), 3.17 (dd, $^2J = 8.8$, $^3J = 6.2$ Hz, 1H; 1-CH_2), 3.23 (dd, $^2J = 8.8$, $^3J = 5.4$ Hz, 1H; 1-CH_2), 3.32 (s,

3H; O-CH_3), 4.34 (d, ^2J=11.6 Hz, 1H; CH_2-Ar), 4.38 (d, ^2J=12.0 Hz, 1H; CH_2-Ar), 6.83 (m, 2H; 3′-CH), 7.25 (m, 2H; 2′-CH); ^{13}C NMR (100.624 MHz, C_6D_6): δ=17.9 (CH_3), 18.5 (CH_3), 20.5 (CH_3), 21.6 (C-7), 27.7 (CH), 31.3 (CH), 31.6 (CH), 42.2 (CH_2), 44.1 (CH_2), 54.8 (O-CH_3), 73.0 (CH_2-Ar), 75.6 (C-1), 114.1 (2×C-3′), 129.3 (2×C-2′), 131.5 (C-1′), 159.7 (C-4′); elemental analysis calcd (%) for $C_{18}H_{30}O_3$ (404.33): C 53.47, H 7.23; found C 53.70, H 7.27.

(2*S*,4*S*,6*R*,8*S*)-Tetramethyl-1-(4′-methoxybenzyloxy)-dodec-(9*E*)-ene [(+)-26]: The procedure was analogous to that used for the preparation of (+)-**19**. From *o*-DPPB ester (−)-**8** (274 mg, 0.706 mmol, 1.2 equiv), CuBr·SMe_2 (73.0 mg, 0.355 mmol, 0.6 equiv) and iodide (−)-**25** (238 mg, 0.588 mmol) was obtained alkene (+)-**26** (182 mg, 0.505 mmol, 86%, *dr* > 95:5) as a colorless oil. $[\alpha]_D^{20}$=+8.3 (*c*=1.11 in $CHCl_3$); ^{1}H NMR (499.873 MHz, $CDCl_3$): δ=0.81 (d, ^3J=6.5 Hz, 3H; CH_3), 0.84 (d, ^3J=6.6 Hz, 3H; CH_3), 0.90 (d, ^3J=6.6 Hz, 3H; CH_3), 0.92 (d, ^3J=6.8 Hz, 3H; CH_3), 0.95 (t, ^3J=7.5 Hz, 3H; 12-CH_3), 0.81–1.03 (m, 3H; 3-, 5- and 7-CH_2), 1.12–1.23 (m, 2H; 5- and 7-CH_2), 1.27–1.33 (m, 1H; 3-CH_2), 1.48–1.59 (m, 2H; 4- and 6-CH), 1.83 (m, 1H; 2-CH), 1.97 (m, 2H; 11-CH_2), 2.15 (m, 1H; 8-CH), 3.14 (dd, ^2J=9.1, ^3J=7.2 Hz, 1H; 1-CH_2), 3.31 (dd, ^2J=9.1, ^3J=5.1 Hz, 1H; 1-CH_2), 3.79 (s, 3H; -O-CH_3), 4.39 (d, ^2J=11.7 Hz, 1H; CH_2-Ar), 4.43 (d, ^2J=11.7 Hz, 1H; CH_2-Ar), 5.24 (ddt, ^3J=15.3, 7.6, ^4J=1.4 Hz, 1H; 9-CH), 5.37 (dtd, ^3J=15.3, 6.3, ^4J=0.8 Hz, 1H; 10-CH), 6.86 (m, 2H; 3′-CH), 7.24 (m, 2H; 2′-CH); ^{13}C NMR (125.709 MHz, $CDCl_3$): δ=14.1 (C-12), 18.4 (CH_3), 20.4 (CH_3), 20.7 (CH_3), 21.0 (CH_3), 25.6 (C-11), 27.6 (C-4 and C-6), 30.9 (C-2), 34.0 (C-8), 41.7 (C-3), 44.7, 45.4 (C-5 and C-7), 55.2 (O-CH_3), 72.6 (CH_2-Ar), 75.7 (C-1), 113.7 (2×C-3′), 129.0 (2×C-2′), 129.6 (C-10), 131.0 (C-1′), 136.0 (C-9), 159.0 (C-4′); elemental analysis calcd (%) for $C_{18}H_{30}O_3$ (360.57): C 79.94, H 11.18; found C 79.91, H 11.03.

9-(4′-Methoxybenzyloxy)-(2*S*,4*R*,6*S*,8*S*)-tetramethylnonanal [(+)-27]: Through a solution of (+)-**26** (72 mg, 0.20 mmol) in MeOH (3 mL) at −78 °C was bubbled a stream of ozone (one bubble per s) until quantitative conversion was monitored by TLC. Subsequently, the ozone was removed by bubbling argon through this solution. Triphenylphosphine (63 mg, 0.24 mmol, 1.2 equiv) and CH_2Cl_2 (2 mL) were added at −78 °C and then the mixture was slowly warmed to RT. Water (3 mL) was added, the solution was extracted with *tert*-butyl methyl ether (3×5 mL) and dried (Na_2SO_4). An appropriate amount of silica gel was added to the filtrate, which was then concentrated to dryness. Flash chromatography (petroleum ether/*tert*-butyl methyl ether 100:1) yielded the aldehyde (+)-**27** (59.6 mg, 0.178 mmol, 89%) as a colorless oil. $[\alpha]_D^{20}$=+5.0 (*c*=1.09 in CH_2Cl_2, lit.[22c]=+5.4, *c*=0.5 in CH_2Cl_2); ^{1}H NMR (499.873 MHz, $CDCl_3$): δ=0.83 (d, ^3J=6.5 Hz, 3H; CH_3), 0.84 (d, ^3J=6.6 Hz, 3H; CH_3), 0.90 (d, ^3J=6.8 Hz, 3H; CH_3), 1.04 (d, ^3J=6.9 Hz, 3H; 2-CH-CH_3), 0.90–1.00 (m, 1H), 1.19–1.33 (m, 4H), 1.36–1.43 (m, 1H), 1.50–1.65 (m, 2H), 1.78–1.85 (m, 1H), 2.35–2.44 (m, 1H; 2-CH), 3.16 (dd, ^2J=8.9, ^3J=6.9 Hz, 1H; 9-CH_2), 3.29 (dd, ^2J=9.1, ^3J=5.2 Hz, 1H; 9-CH_2), 3.78 (s, 3H; O-CH_3), 4.38 (d, ^2J=11.7 Hz, 1H; CH_2-Ar), 4.42 (d, ^2J=11.7 Hz, 1H; CH_2-Ar), 6.85 (m, 2H; 3′-CH), 7.23 (m, 2H; 2′-CH), 9.59 (d, ^3J=1.9 Hz, 1H; -C(O)H); ^{13}C NMR (125.709 MHz, $CDCl_3$): δ=13.1 (CH_3), 18.3 (CH_3), 20.0 (CH_3), 20.7 (CH_3), 27.4, 27.5, 30.9, 37.0, 41.7, 44.2, 45.5, 55.3 (O-CH_3), 72.7 (CH_2-Ar), 75.6 (C-9), 113.7 (2×C-3′), 129.0 (2×C-2′), 130.9 (C-1′), 159.0 (C-4′), 205.3 (C-1). The analytical data correspond to those reported previously.[22c]

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