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Formal total synthesis of (+)-methynolide

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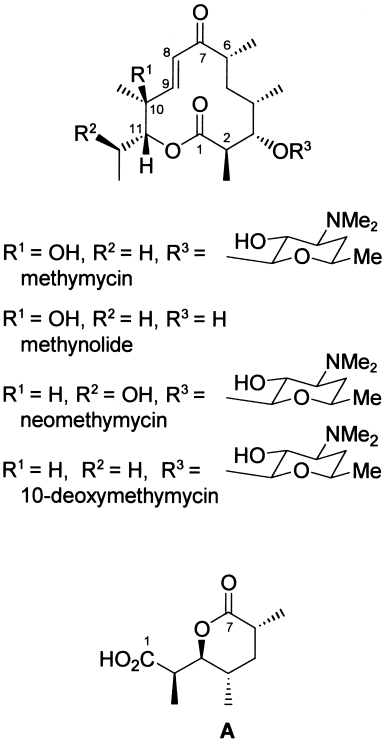
Abstract—A formal total synthesis of (+)-methynolide was achieved in 23 steps highlighted by a crotylboration, a ring-closing metathesis, a Sharpless kinetic resolution of an allylic alcohol and a Takai reaction.

Complex molecules like macrolide antibiotics with multiple stereocenters have received much attention over the past 50 years due to their potent biological activities.[1] The methymycin family of antibiotics comprises three 12-membered macrolides isolated from *Streptomyces* species (methymycin,[2] neomethymycin,[2] 10-deoxymethymycin[3]) and shown to display antibiotic activity against Gram-positive bacteria. Their structures were established through chemical degradation,[3] spectroscopic studies,[4] and total synthesis.[5] Efforts directed towards the total synthesis of methymycin have evolved around the Prelog-Djerassi lactone **A**,[6] a key degradation product retaining the original four stereocenters present in the C_1–C_7 segment of methynolide, the aglycone of methymycin (Scheme 1).



Scheme 1.

Since the first synthesis of methymycin from lactone **A**, by Masamune,[5] eight additional syntheses of methynolide or its corresponding *seco*-acid have appeared. The groups of Grieco,[7] Yamaguchi,[8] White,[9] Yonemitsu,[10] and Ditrich[11] combined two chiral fragments giving an open-chain precursor which was cyclized by intramolecular esterification[5,7,8,11] or an intramolecular Wittig type reaction.[10] Three of these syntheses combined the chiral C_1–C_8 fragment with the C_9–C_{11} fragment[5,10,11] and three of them combined the C_1–C_7 with the C_8–C_{11} fragment.[7–9] Linear strategies were also reported by Ireland,[12] Vedejs[13] and Bartlett.[14]

In this communication we report our work on the synthesis of (+)-methynolide from the previously synthesized intermediate (+)-**31** (Scheme 2).[7,9] The retrosynthetic analysis of this intermediate suggested a convergent approach, i.e. the assemblage of (+)-**31** from two chiral fragments **B** (C_1–C_7) and **C** (C_8–C_{11}). These two fragments would be linked by addition of a vinyllithium reagent, derived from the vinyl iodide **C** to the amide functionality of fragment **B** (Scheme 2). The synthesis of the C_1–C_7 fragment of methynolide was envisaged either from lactones **E** or **E′** both of which would be obtained respectively from dienes **F** or **F′** by using a ring-closing metathesis reaction (RCM). The common precursor of these two dienes would be the commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate (+)-**1**. The second fragment **C** would be obtained through a Takai[15] reaction applied to an aldehyde that could be prepared by dihydroxylation and subsequent oxidation of the optically active allylic alcohol (+)-**22**. Alcohol (+)-**22** would be synthesized from methacrolein **21** by using a Sharpless kinetic resolution of an allylic alcohol (Scheme 2).[16]

Keywords: macrolactone; metathesis; crotylboronate; Takai reaction; Sharpless kinetic resolution.

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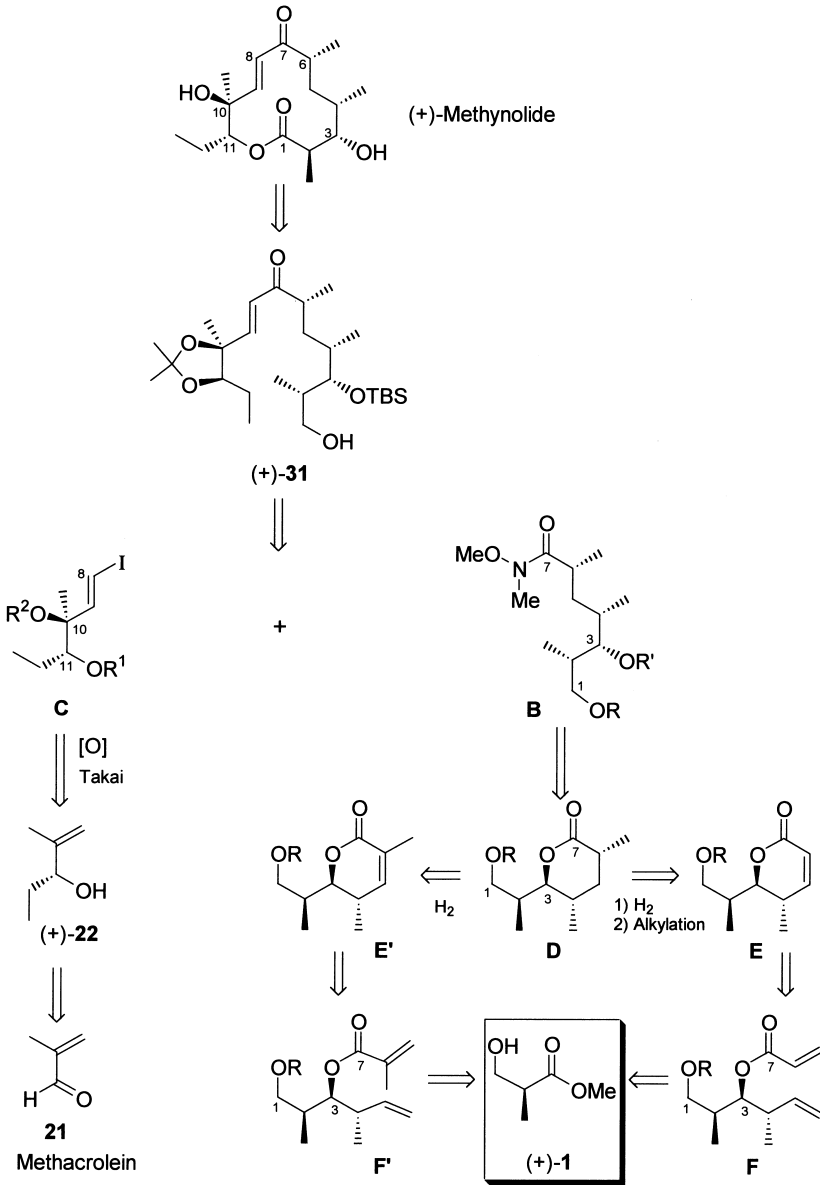
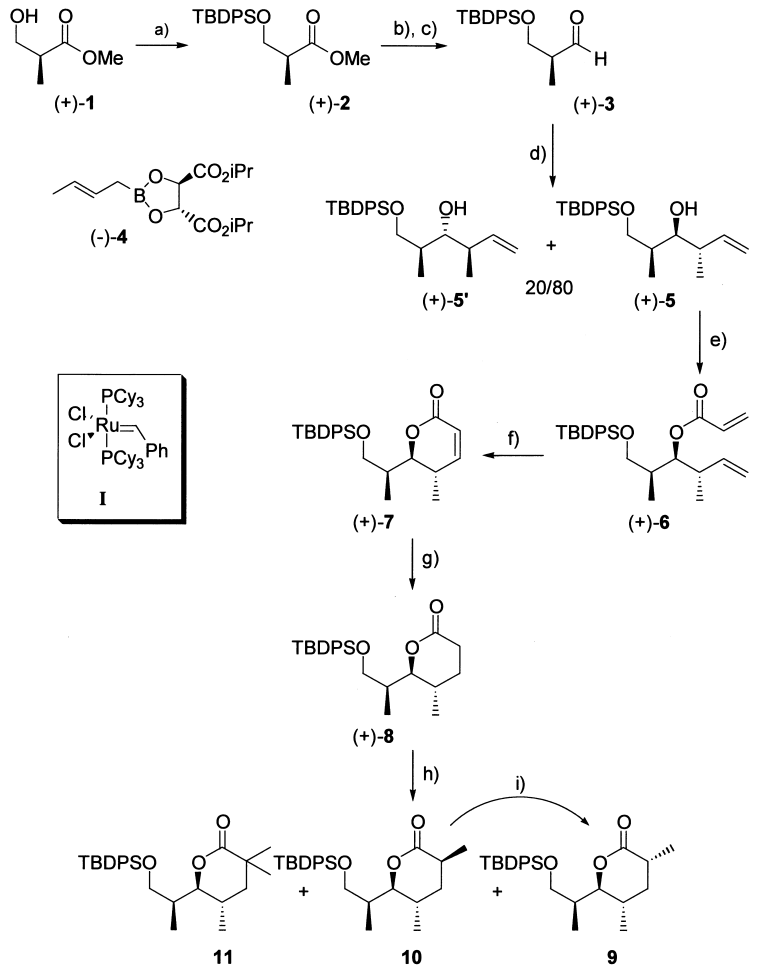


Scheme 2. Retrosynthetic analysis of (+)-methynolide.

The synthesis of the C_1–C_7 fragment was achieved from methyl (2*S*)-3-hydroxy-2-methyl propionate (+)-**1** via lactone **7** or lactone **16** (Scheme 3). To attain lactone (+)-**7**, the β-hydroxy ester (+)-**1** was transformed to the *t*-butyldiphenylsilyl ether (+)-**2** (*t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2) in quantitative yield, and (+)-**2** was converted to aldehyde (+)-**3** in two steps by reduction of the ester with DIBAL-H followed by a Swern oxidation. The overall yield for this latter transformation was 98%. Control of the stereogenic centers at C_3 and C_4 was achieved by addition of crotylboronate (−)-**4** to aldehyde (+)-**3**.[17] Compounds (+)-**5** and (+)-**5′** were obtained in 77% yield in the ratio 80/20[17]and the desired adduct (+)-**5** was isolated in 62% yield after chromatography. The next step was the transformation of (+)-**5** to the precursor of the unsaturated lactone (+)-**7**. When compound (+)-**5** was treated with acryloyl chloride at 0°C in the presence of triethylamine and a catalytic amount of DMAP, the unsaturated ester (+)-**6** was isolated in 54% yield. The yield of (+)-**6** was increased to 80% when (+)-**5** was treated with diisopropylethylamine at −78°C in CH_2Cl_2. To transform the diene ester (+)-**6** to the corresponding unsaturated lactone (+)-**7** a RCM reaction, induced by the Grubbs' catalyst **I** (15 mol%) was used in the presence of a catalytic amount of titanium(IV) isopropoxide [$Ti(OiPr)_4$, 30 mol%] in refluxing CH_2Cl_2.[18] Under these conditions, lactone (+)-**7** was isolated in 96% yield and then hydrogenated on $Pd(OH)_2$ in AcOEt, to produce the saturated lactone (+)-**8** in 92% yield. The following step was the introduction of the methyl at C_6. When lactone (+)-**8** was treated with LDA (1.5 equiv.) at −78°C and the enolate was quenched with MeI (50 equiv.) in the presence of HMPA (3 equiv.), a mixture of the monoalkylated products **9** and **10**, and the dialkylated compound **11** was obtained in 76% yield in the ratio 1/1/2. The formation of the dialkylated product **11** was circumvented by adding a solution of the enolate of (+)-**8** slowly to a solution of iodomethane/HMPA at −78°C. Under these conditions, the lactones **9** and **10** were the only isolated products

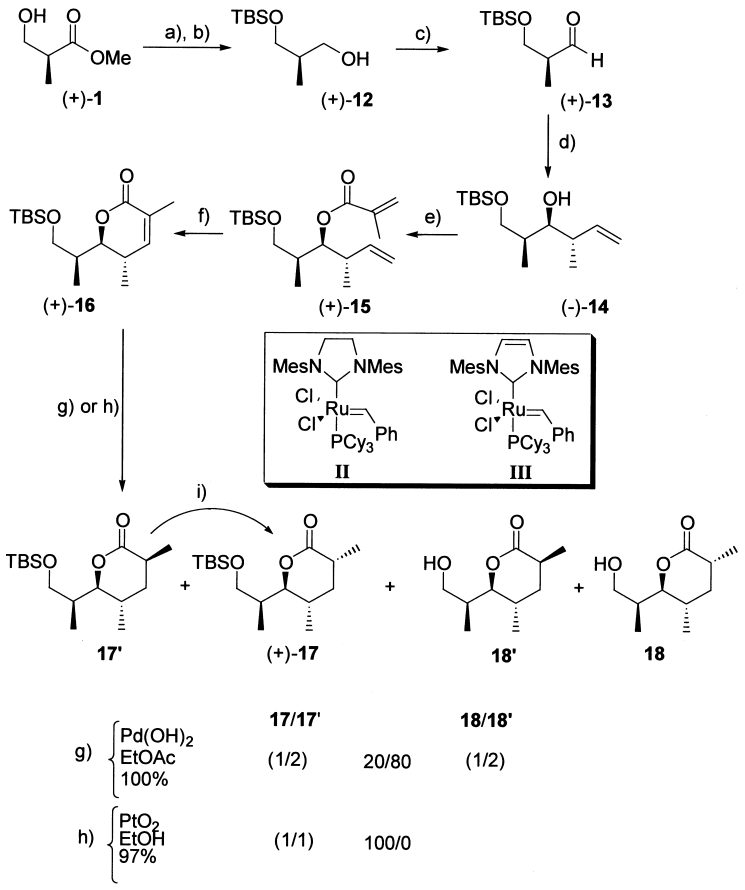


Scheme 3. Synthesis of lactones **7** and **16**. *Reagents and conditions*: (a) TBDPSCl, imidazole, CH_2Cl_2, quantitative yield. (b) DIBAL-H, CH_2Cl_2, 98%. (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, quantitative yield. (d) (−)-**4**, 4 Å MS, toluene, 77%. (e) acryloyl chloride, diisopropylethylamine, cat. DMAP, −78°C, CH_2Cl_2, 80%. (f) **I** (15 mol%), $Ti(Oi\text{-}Pr)_4$ (30 mol%), CH_2Cl_2, 96%. (g) H_2, $Pd(OH)_2$, EtOAc, 92%. (h) LDA, MeI, HMPA, THF, −78°C, **9/10**=1/1. (i) *t*-BuOK, *t*-BuOH, 50°C, **9/10**=4/1, 62% yield (two steps).

(70% yield) as a 1 to 1 mixture. As the three substituents of the desired lactone are equatorial, the mixture of **9** and **10** was treated under basic conditions to favor the formation of the thermodynamically more stable isomer. This was accomplished by treating lactones **9** and **10** at 50°C in the presence of *t*-BuOK/*t*-BuOH, affording compounds **9** and **10** as a 4 to 1 mixture in 62% yield. Lactone **9** was thus obtained from methyl (2*S*)-3-hydroxy-2-methyl propionate (+)-**1** in nine steps with an overall yield of 21% (Scheme 3).

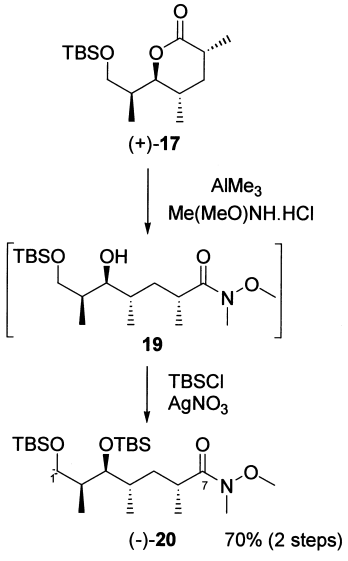
With the aim of increasing the yield of the precursor of the C_1–C_7 fragment via the synthesis of the Prelog-Djerassi lactone derivative, a second strategy was examined. Instead of introducing the methyl at C_6 by alkylation of the lactone, the methyl group was introduced by using a RCM reaction applied to diene (+)-**15** (Scheme 4). The synthesis of diene (+)-**15** was achieved in four steps from methyl (2*S*)-3-hydroxy-2-methyl propionate (+)-**1**. The β-hydroxy ester (+)-**1** was transformed to compound (−)-**14**[17] (dr≥97/3) which was then condensed with methacryloyl chloride in the presence of Et_3N at 0°C to produce (+)-**15** in 79% yield. The RCM reaction was then performed in the presence of catalyst **II**[19] (15 mol%, CH_2Cl_2, reflux, 14 h) and the unsaturated lactone (+)-**16** was isolated in 77% yield for a conversion of 80%. A better result was obtained in the presence of catalyst **III**,[20] as compound (+)-**15** was totally converted, after 14 h in refluxing CH_2Cl_2, to the unsaturated lactone (+)-**16** in 98% yield. When lactone (+)-**16** was hydrogenated on $Pd(OH)_2$, a mixture of lactones **17/17′** in a 1 to 2 ratio and deprotected lactones **18/18′** was formed in quantitative yield. The ratio (**17**+**17′**)/(**18**+**18′**) was 20/80 (Scheme 4).

To avoid the formation of **18/18′**, the hydrogenation of (+)-**16** was performed over PtO_2 in EtOH. The use of this catalyst led to lactones **17** and **17′** in a 1 to 1 ratio in 97% yield. After treatment of **17/17′** under basic conditions (*t*-BuOK/*t*-BuOH, 55°C, 14 h) a 2/1 mixture of **17** and **17′** was obtained. This ratio was increased to 2.3/1 by kinetic protonation of the enolate (LDA, −78°C then 10% citric acid),[7] and lactone (+)-**17** was isolated in 65% yield. This second pathway for obtaining the C_1–C_7 fragment is shorter than the first one and the overall yield is better (33% versus 21%) (Scheme 4). It is worth noting that replacement of the TBDPS protecting group by a TBS group led to a higher diastereoselectivity in the crotylboration step and an increase of the overall yield of (+)-**17**.



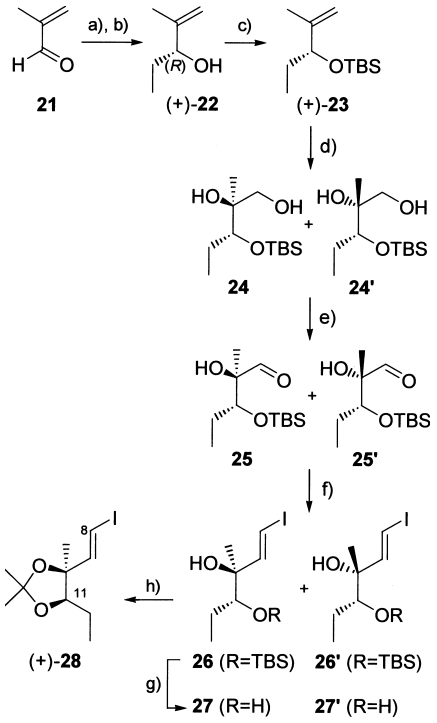
Scheme 4. *Reagents and conditions*: (a) TBSCl, imidazole, DMF. (b) DIBAL-H, THF. (c) pyr.SO_3, DMSO, Et_3N, CH_2Cl_2, 0°C, 82% (three steps). (d) (−)-**4**, 4 Å MS, toluene, 81%. (e) methacryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, 0°C, 79%. (f) **II** or **III** (15 mol%), CH_2Cl_2, reflux, 96–98%. (g) H_2, $Pd(OH)_2$, EtOAc, **17**+**17′**/**18**+**18′**=20/80, 100%. (h) H_2 (4 atm), PtO_2, EtOH, **17**/**17′**=1/1, 97%. (i) LDA, −78°C, 1.5 h; then 10% aqueous citric acid, −78°C, **17** (65% yield, two steps) and **17′** (32% yield, two steps).

Lactone (+)-**17** was transformed to the Weinreb amide (−)-**20** in two steps. After treatment of lactone (+)-**17** with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminium,[21] methoxyamide (+)-**19** was obtained. Due to the sensitivity of (+)-**19** to acidic and basic conditions, this compound was not purified but directly protected under mild conditions ($AgNO_3$, TBSCl, DMF)[22,23] and transformed to compound (−)-**20** with an overall yield of 70% for the two steps (Scheme 5).



Scheme 5. Synthesis of fragment **B**.

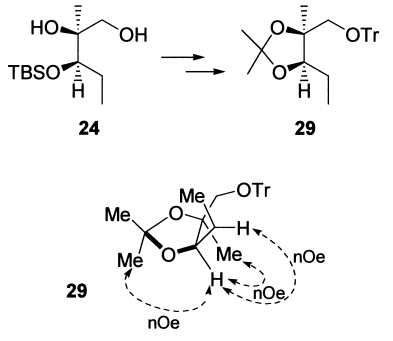
The C_8–C_{11} fragment, was synthesized from methacrolein **21**. When methacrolein was treated with ethylmagnesium bromide in ether, the corresponding alcohol (±)-**22** was isolated in 68% yield. This was converted to alcohol (+)-**22** of 90% enantiomeric excess by using a Sharpless kinetic resolution [$Ti(OiPr)_4$, (+)-DIPT, *t*-BuOOH, MS 4 Å].[16,24] The diasteroselectivity and the (*R*) absolute configuration were determined by using Trost's mandelic ester method.[25] Interestingly when the kinetic resolution of (±)-**22** was achieved at −20°C without stirring, the diastereomeric ratio was 85/15 but with stirring this ratio was increased to 95/5. After protection of the secondary alcohol of (+)-**22** (*t*-$BuMe_2SiCl$, imidazole), the obtained silyl ether (+)-**23** was treated with OsO_4 in the presence of NMO to produce the monoprotected triols **24** and **24′** in 92% yield as a mixture of two inseparable diastereomers in a 5.5/1 ratio (Scheme 6). The relative stereochemistry at C_2 and C_3 in the major isomer was determined by the nOe of compound **29** derived from compound **24** (Scheme 7). The relative *cis*-stereochemistry of the hydroxy groups in **29** showed that the osmylation of compound **23** was diastereoselective[26] in accord with Vedejs',[27] Houk's,[28] or Kishi's[29] models.



Scheme 6. Synthesis of the C_8–C_{11} fragment. *Reagents and conditions*: (a) EtMgBr, Et_2O, 68%. (b) Ti(O*i*-Pr)$_4$, (+)-DIPT, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −20°C, 91% (90% ee). (c) TBSCl, imidazole, DMF, 81%. (d) OsO_4, NMO, acetone, H_2O, **24/24′**=5.5/1, 92%. (e) pyr.SO_3, DMSO, Et_3N, CH_2Cl_2, 0°C, quantitative yield. (f) $CrCl_2$, CHI_3, THF, 78%. (g) TBAF, THF, 87%. (h) 2,2-dimethoxypropane, PPTS, acetone, **28/28′**=5.5/1, quantitative yield; Separation of the two diastereomers.

After oxidation of the mixture of **24/24′** (pyr.SO_3, DMSO, Et_3N), the resulting aldehydes **25/25′** were transformed to vinyl iodides **26/26′** in 78% yield by using a Takai reaction (HCI_3, $CrCl_2$). The stereoselectivity $E/Z \geq 97/3$ was determined by ^{1}H NMR analysis. Compounds **26** and **26′** were then deprotected (TBAF), the resulting diols **27/27′** were treated with 2,2-dimethoxypropane (PPTS, acetone) to afford ketals **28/28′** as a 5.5/1 mixture of diastereomers which were separated by flash chromatography on silica gel. The desired ketal (+)-**28** was isolated in 74% overall yield from **26/26′** (Scheme 6). The transformation of methacrolein **21** to (+)-**28** was achieved in eight steps with an overall yield of 27%.

With both building blocks (−)-**20** and (+)-**28** in hand, we next completed the carbon skeleton of methynolide by addition of vinyllithium reagent **28′**, obtained from the corresponding vinyl iodide by lithiation (*t*-BuLi, ether, −78°C), to the previously obtained amide (−)-**20**. The coupling product (+)-**30** was isolated in quantitative yield (for a 66% conversion of (−)-**20**). Selective deprotection of (+)-**30** with HF.pyridine in a mixture of pyridine/THF afforded the known compound (+)-**31**[7,9] in 69% isolated yield. As (+)-**31** was previously converted to methynolide in three steps,[7,5b] a formal total synthesis of methynolide has been achieved in 23 steps (Scheme 8).



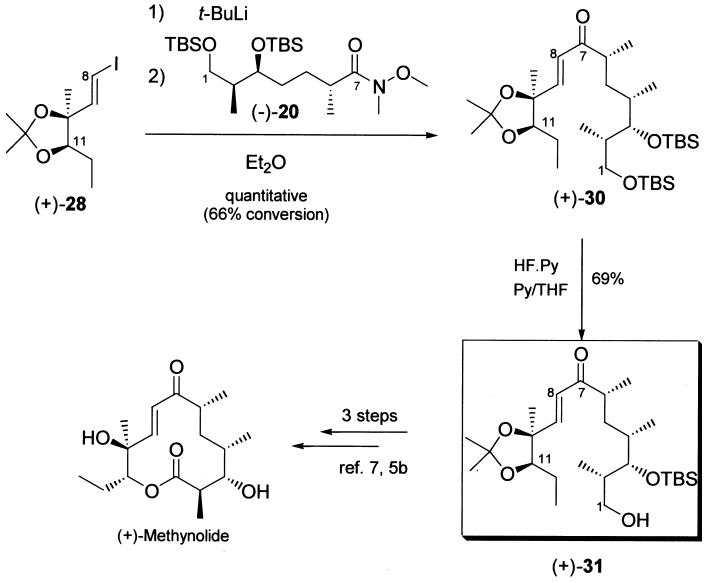
Scheme 7. Determination of the relative stereochemistry of **24**.

1. Experimental

1.1. General procedures

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium/benzophenone ketyl immediatly before use. CH_2Cl_2, DMF, DMSO, Et_3N, diisopropylethylamine and diisopropylamine were distilled from CaH_2 under argon. Moisture sensitive reactions were conducted in oven or flame-dried glassware under an argon atmosphere. Flash chromatography was carried out on Kieselgel 60 (230–400 mesh, Merck) and analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}). Melting points are uncorrected. Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie in Paris. Mass spectra were obtained by GC/MS with electron impact ionization by using a 5971 Hewlett Packard instrument at 70 eV: only selected ions are reported. HRMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure in Paris. Optical rotations were measured on a Perkin–Elmer 343 polarimeter. ^{1}H and ^{13}C spectra were respectively recorded on a Bruker AC 300 spectrometer at 300 and 75 MHz. Spectra were recorded in $CDCl_3$ as solvent, and chemical shifts (δ) are expressed in ppm relative to residual $CHCl_3$ at δ=7.27 for ^{1}H and to $CDCl_3$ at δ=77.1 for ^{13}C. ^{1}H NMR *J* values are given in Hz. IR spectra were recorded as neat films (NaCl cell) and KBr pellets for solids on a Perkin–Elmer 298 or FT-IR 1600.

1.1.1. Methyl (2*S*)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropionate (+)-2.[30] To a solution of commercially available (+)-**1** (2.00 g, 16.9 mmol, 1.87 mL, 1 equiv.) and imidazole (1.50 g, 22.1 mmol, 1.3 equiv.) in CH_2Cl_2 (20 mL) at 0°C, *tert*-butyldiphenylsilyl chloride (4.42 mL, 16.9 mmol, 1 equiv.) was slowly added. After 20 h at rt, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford (+)-**2** (6.02 g, 16.9 mmol) quantitatively. R_f: 0.80 (Et_2O/petroleum ether: 1/1); $[\alpha]_D^{20}$=+12.5 (*c* 2.6, EtOAc); IR (neat) 1740, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80–7.30 (m, 10H), 3.86 (dd, *J*=10.1 and 7.1 Hz, 1H), 3.75 (dd, *J*=10.1 and 5.8 Hz, 1H), 3.72 (s, 3H), 2.75 (m, 1H), 1.18 (d, *J*=7.1 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.2 (s), 135.4 (4d), 133.4 (2s), 129.5 (2d), 127.7 (4d), 65.8 (t), 51.4 (q), 42.3 (d), 26.6 (3q), 18.8 (s), 13.3 (q); EI MS *m/z* (relative intensity) 341 (M−Me, 1), 325 (M−OMe, 2), 299



Scheme 8. Synthesis of fragment C_1–C_{11} from the C_1–C_7 and C_8–C_{11} fragments.

(M−*t*-Bu, 60), 214 (20), 213 (100), 199 (16), 197 (16), 105 (25), 91 (11), 59 (13), 57 (32).

1.1.2. (2*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-2-methylpropanal[17,31] **(+)-3.** To a solution of (+)-**2** (6.02 g, 16.9 mmol, 1 equiv.) in CH_2Cl_2 (100 mL) at −78°C, DIBAL-H (37.0 mL, 1 M in hexanes, 37.0 mmol, 2.2 equiv.) was added dropwise. The cooling bath was removed and after 2 h at rt, an aqueous 10% HCl solution (50 mL) was slowly added at 0°C. The aqueous phase was extracted with CH_2Cl_2 (3×80 mL) and the combined extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give (2*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropan-1-ol[30] (5.46 g, 16.7 mmol) as a colorless oil in 98% yield. R_f: 0.90 (Et_2O/petroleum ether: 1/1); $[\alpha]_D^{20}$=+18.0 (*c* 3.3, EtOAc); IR (neat) 3400, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.80–7.40 (m, 10H), 3.78 (dd, *J*=10.2 and 4.6 Hz, 1H), 3.75–3.69 (m, 2H), 3.65 (dd, *J*=10.2 and 7.6 Hz, 1H), 2.49 (t, *J*=5.8 Hz, 1H), 2.05 (m, 1H), 1.10 (s, 9H), 0.89 (d, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.6 (4d), 133.4 (2s), 129.5 (2d), 126.7 (4d), 67.8 (t), 65.8 (t), 39.5 (d), 26.6 (3q), 18.8 (s), 13.4 (q); EI MS *m/z* (relative intensity) 271 (M−*t*-Bu, 9), 229 (4), 200 (18), 199 (100), 193 (17), 181 (13), 139 (18), 77 (12), 57 (15).

To a solution of oxalyl chloride (3.81 mL, 43.6 mmol, 2.2 equiv.) in CH_2Cl_2 (300 mL) at −78°C was slowly added DMSO (3.92 mL, 54.6 mmol, 2.8 equiv.). After 30 min at −78°C, a solution of (2*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropan-1-ol (6.50 g, 19.8 mmol, 1 equiv.) in CH_2Cl_2 (75 mL) was added, and after 20 min at −78°C Et_3N (13 mL) was introduced. After 15 min at −78°C and 10 min at 0°C, the reaction mixture was diluted with pentane (60 mL) and brine (60 mL) was added. The aqueous layer was extracted with pentane. The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford (+)-**3** (6.45 g, 19.8 mmol, quantitative yield) which was used in the next step without further purification. R_f: 0.5 (Et_2O/petroleum ether: 1/1); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.70 (s, 1H), 7.80–7.30 (m, 10H), 3.92 (dd, *J*=10.3 and 5.0 Hz, 1H), 3.86 (dd, *J*=10.3 and 6.5 Hz, 1H), 2.60 (m, 1H), 1.12 (d, *J*=5.8 Hz, 3H), 1.07 (s, 9H); EI MS *m/z* (relative intensity) 269 (M−*t*-Bu, 64), 239 (67), 211 (25), 199 (100), 183 (87), 181 (22).

1.1.3. (2*S*, 3*S*, 4*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2,4-dimethylhex-5-en-3-ol[17] **(+)-5 and (2*S*, 3*R*, 4*R*)-1-[(*tert*-butyldiphenylsilyl)oxy]-2,4-dimethylhex-5-en-3-ol**[17] **(+)-5′.** A solution of (−)-**4**[32] (1.40 mL, 1 M in toluene, 1.40 mmol, 1.5 equiv.) was added to a slurry of 4 Å flame-dried powdered molecular sieves (20 mg). After being stirred for 10 min at rt, the mixture was cooled to −78°C. A solution of aldehyde (+)-**3** (0.305 g, 0.935 mmol, 1 equiv.) in dry toluene (1 mL) was then introduced dropwise via cannula. After the addition was complete, the solution was maintained at −78°C overnight. Excess ethanolic $NaBH_4$ (0.1 mL, 2 mol/L, 0.2 mmol, 0.2 equiv.) was then added dropwise and the solution warmed to 0°C. The mixture was then diluted with 1N aqueous NaOH solution and stirred vigorously for 2 h. During this stirring, the reaction temperature was allowed to warm to rt. The aqueous layer was extracted with Et_2O (5×5 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel of the crude residue (hexanes/Et_2O: 9/1) afforded (+)-**5** (0.220 g, 0.576 mmol) and (+)-**5′** (55 mg, 0.144 mmol) in a total yield of 77%. Compound (+)-**5**: R_f: 0.22 (hexanes/Et_2O: 9/1); IR (neat) 3500, 1640, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72–7.65 (m, 4H), 7.45–7.35 (m, 6H), 5.83 (m, 1H), 5.14–5.06 (m, 2H), 3.73 (d, *J*=5.2 Hz, 2H), 3.59 (dd, *J*=8.5 and 2.6 Hz, 1H), 2.44 (bs, 1H), 2.29 (m, 1H), 1.83 (m, 1H), 1.07 (s, 9H), 0.96 (d, *J*=7.0 Hz, 3H), 0.95 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8 (d), 135.5 (4d), 133.3 (s), 133.2 (s), 129.8 (2d), 127.6 (4d), 115.3 (t), 76 (d), 68.3 (t), 41.7 (d), 36.7 (d), 26.8 (3q), 19.2 (s), 16.7 (q), 9.6 (q); EI MS *m/z* (relative intensity) 325 (M−*t*-Bu, 3), 269 (18), 239 (7), 229 (15), 200 (19), 199 (100), 135 (15), 109 (55); Anal. calcd for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96. Found: C, 75.24; H, 9.04. Compound (+)-**5′**: R_f: 0.33 (hexanes/Et_2O: 9/1); ^1H NMR

($CDCl_3$, 300 MHz) δ 7.72–7.66 (m, 4H), 7.50–7.35 (m, 6H), 5.96 (ddd, J=16.9, 10.7 and 8.5 Hz, 1H), 5.13–5.03 (m, 2H), 3.75 (dd, J=10.3 and 4.4 Hz, 1H), 3.69 (dd, J=10.3 and 7.4 Hz, 1H), 3.54 (bs, 1H), 3.45 (bdd, J=7.9 and 3.1 Hz, 1H), 2.39 (m, 1H), 1.85 (m, 1H), 1.12 (d, J=7.0 Hz, 3H), 1.06 (s, 9H), 0.82 (d, J=7.0 Hz, 3H).

1.1.4. (1*S*, 2*S*)-1-{(1*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-1-methylethyl}-2-methylbut-3-enyl prop-2-enoate (+)-6. To a stirred solution of (+)-**5** (0.150 g, 0.39 mmol, 1 equiv.) in dry CH_2Cl_2 (1 mL), a catalytic amount of DMAP (~15 mg) was added at rt. The reaction mixture was cooled to −78°C. Hünig's base (0.21 mL, 1.21 mmol, 3.1 equiv.) was added dropwise, immediatly followed by acryloyl chloride (0.04 mL, 0.49 mmol, 1.25 equiv.). After 2 h of stirring at −78°C, the reaction mixture was diluted with CH_2Cl_2 (5 mL), quenched with brine (1 mL) and warmed rapidly to rt. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (hexanes/Et_2O: 100/0 to 90/10) provided (+)-**6** (0.136 g, 0.31 mmol, 80% yield). R_f: 0.52 (hexanes/Et_2O: 95/5); $[\alpha]_D^{20}$=+18.0 (c 1.0, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.75–7.67 (m, 4H), 7.50–7.37 (m, 6H), 6.42 (dd, J=17.3 and 1.8 Hz, 1H), 6.14 (dd, J=17.3 and 10.3 Hz, 1H), 5.83 (dd, J=10.3 and 1.8 Hz, 1H), 5.77 (ddd, J=17.3, 10.3 and 8.8 Hz, 1H), 5.17 (dd, apparent t, J=5.9 Hz, 1H), 5.03–4.89 (m, 2H), 3.61 (dd, J=10.1 and 6.1 Hz, 1H), 3.53 (dd, J=10.1 and 6.1 Hz, 1H), 2.48 (m, 1H), 2.04 (m, 1H), 1.12 (s, 9H), 1.02 (d, J=7.0 Hz, 3H), 0.99 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7 (s), 139.8 (d), 135.5 (4d), 133.6 (2s), 130.1 (t), 129.5 (2d), 128.5 (d), 127.5 (4d), 115.2 (t), 76.9 (d), 65.6 (t), 40.4 (d), 37.2 (d), 26.8 (3q), 19.2 (s), 17.3 (q), 11.8 (q); EI MS m/z (relative intensity) 379 (M−t-Bu, 1), 269 (3), 253 (100), 239 (6), 223 (6), 199 (36), 193 (31), 183 (15), 135 (9), 109 (42).

1.1.5. (5*S*, 6*S*)-6-{(1*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-1-methylethyl}-5-methyl-5,6-dihydro 2*H*-pyran-2-one (+)-7. To a stirred solution of diene (+)-**6** (0.460 g, 1.06 mmol, 1 equiv.) in dry CH_2Cl_2 (104 mL) was added $Ti(OiPr)_4$ (0.09 mL, 0.32 mmol, 0.3 equiv.). The reaction mixture was refluxed 1 h before the addition in three portions of Grubbs' catalyst **I** (3×29 mg, 0.16 mmol, 0.15 equiv.) in CH_2Cl_2 (3×1 mL) over 1 h. The reaction mixture was refluxed overnight, cooled to rt, filtered over a pad of silica gel (rinsing with EtOAc) and concentrated in vacuo. Flash chromatography on silica gel (hexanes/EtOAc: 90/10 to 70/30) afforded (+)-**7** (0.417 g, 1.02 mmol, 96% yield). R_f: 0.22 (hexanes/EtOAc: 80/20); $[\alpha]_D^{20}$=+24 (c 1.0, $CHCl_3$); IR (neat) 1730, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.64–7.48 (m, 4H), 7.37–7.20 (m, 6H), 6.58 (dd, J=9.7 and 2.0 Hz, 1H), 5.87 (dd, J=9.7 and 2.5 Hz, 1H), 4.33 (dd, J=11.0 and 2.2 Hz, 1H), 3.73 (dd, J=10.0 and 8.4 Hz, 1H), 3.51 (dd, J=10.0 and 5.7 Hz, 1H), 2.55 (m, 1H), 1.91 (m, 1H), 1.01 (d, J=7.2 Hz, 3H), 0.97 (s, 9H), 0.80 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.8 (s), 152.6 (d), 135.9 (4d), 134.0 (2s), 130.1 (2d), 128.1 (4d), 120.6 (d), 82.8 (d), 63.4 (t), 37.3 (d), 30.6 (d), 27.3 (3q), 19.7 (s), 16.5 (q) 10.3 (q); EI MS m/z (relative intensity) 376 (3), 374 (3), 363 (1), 351 (M−t-Bu, 80), 321 (64), 269 (17), 239 (20), 199 (100), 191 (30), 183 (50), 135 (14), 105 (14); HRMS (CI^+, NH_3) calcd for $C_{25}H_{36}O_3NSi$ ($M+NH_4^+$): 426.2464, found 426.2447.

1.1.6. (5*S*, 6*S*)-6-{(1*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-1-methylethyl}-5-methyltetrahydro-2*H*-pyran-2-one (+)-8. A mixture of lactone (+)-**7** (164 mg, 0.40 mmol, 1 equiv.) and $Pd(OH)_2$ (40 mg) in EtOAc (1.5 mL) was stirred overnight under a hydrogen atmosphere at rt. The reaction mixture was filtered through Celite (rinsing with EtOAc) and the solvent evaporated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc: 100/0 to 70/30) to provide (+)-**8** (151 mg, 0.37 mmol, 92% yield). R_f: 0.22 (hexanes/EtOAc: 70/30); $[\alpha]_D^{20}$=+31.0 (c 1.0, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71–7.64 (m, 4H), 7.45–7.36 (m, 6H), 4.30 (dd, J=10.3 and 1.5 Hz, 1H), 3.81 (dd, apparent t, J=9.9 Hz, 1H), 3.59 (dd, J=9.9 and 5.9 Hz, 1H), 2.61 (ddd, J=17.7, 7.0 and 4.0 Hz, 1H), 2.45 (ddd, J=17.7, 10.2 and 7.1 Hz, 1H), 2.07–1.77 (m, 3H), 1.56 (m, 1H), 1.07 (s, 9H), 0.98 (d, J=6.3 Hz, 3H), 0.83 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8 (s), 135.4 (4d), 133.6 (2s), 129.5 (2d), 127.5 (4d), 84.0 (d), 65.2 (t), 37.1 (d), 29.5 (t), 29.4 (d), 27.9 (t), 26.8 (3q), 19.1 (q), 17.1 (q), 8.8 (q); EI MS m/z (relative intensity) 365 (1), 353 (M−t-Bu, 21), 323 (78), 275 (89), 253 (9), 199 (100), 183 (18), 181 (15), 139 (13), 135 (10); HRMS (CI^+, CH_4) calcd for $C_{25}H_{35}O_3Si$ ($M+H^+$): 411.2355, found 411.2353.

1.1.7. (3*R*, 5*S*, 6*S*)-6-{(1*S*)-2-[(*tert*-Butyldiphenylsilyl)-oxy]-1-methylethyl}-3,5-dimethyl-tetrahydro-2*H*-pyran-2-one (9) and (3*S*, 5*S*, 6*S*)-6-{(1*S*)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-methylethyl}-3,5-dimethyltetrahydro-2*H*-pyran-2-one (10). A solution of LDA was generated at 0°C by dropwise addition of n-BuLi (0.09 mL, 2.5 M solution in hexanes, 0.23 mmol, 1.0 equiv.) to a solution of diisopropylamine (0.03 mL, 0.23 mmol, 1.0 equiv.) in THF (1.1 mL). A solution of lactone (+)-**8** (0.092 g, 0.23 mmol, 1 equiv.) in THF (1.1 mL) was then added via cannula at −78°C. After 2 h of stirring at −78°C, the solution of enolate was added dropwise via cannula to a precooled (−78°C) solution of methyl iodide (0.14 mL, 2.23 mmol, 10 equiv.) and HMPA (0.12 mL, 0.67 mmol, 3 equiv.) in THF (1 mL). After 20 min at −78°C, the reaction mixture was diluted with Et_2O (7 mL) and quenched by addition of aqueous 2% HCl solution (2 mL). The cooling bath was removed. The aqueous layer was extracted with EtOAc (3×15 mL), dried over $MgSO_4$, filtered and evaporated. Purification by TLC (hexanes/EtOAc: 9/1) afforded a 1:1 mixture of the two epimers **9** and **10** (0.068 g, 0.16 mmol, 70% yield). R_f: 0.50 (**9**) and 0.56 (**10**) (hexanes/Et_2O: 80/20); IR (neat) (**9**+**10**) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (**9**+**10**) δ 7.71–7.63 (m, 4H, **9** and **10**), 7.47–7.36 (m, 6H, **9** and **10**), 4.30 (dd, J=10.5 and 1.3 Hz, 1H, **9**), 4.27 (dd, J=10.5 and 1.5 Hz, 1H, **10**), 3.81 (dd, J=9.9 and 8.8 Hz, 1H, **9** or **10**), 3.78 (apparent t, J=9.9 Hz, 1H, **9** or **10**), 3.61 (dd, J=9.9 and 5.5 Hz, 1H, **9** or **10**), 3.57 (dd, J=9.9 and 5.9 Hz, 1H, **9** or **10**), 2.53 (m, 1H, **9** and **10**), 2.05–1.85 (m, 2H, **9** and **10**), 1.73 (m, 1H, **9** and **10**), 1.69 (m, 1H, **10**), 1.35 (m, 1H, **9**), 1.30 (d, J=7.0 Hz, 3H, **9**), 1.21 (d, J=7.0 Hz, 3H, **10**), 1.07 (s, 9H, **9** and **10**), 0.98 (d, J=6.6 Hz, 3H, **10**), 0.96 (d, J=6.2 Hz, 3H, **9**), 0.84 (d, J=7.0 Hz, 3H, **10**), 0.81 (d, J=7.3 Hz, 3H, **9**); ^{13}C NMR ($CDCl_3$, 75 MHz) (**9**+**10**) δ 176.4, 174.4 (s), 135.4, 135.4 (d), 133.7–133.5 (s), 129.6, 129.5, 127.6, 127.5 (d), 85.3, 81.2 (d), 65.3 (t),

37.6 (t), 37.3, 36.9, 36.2, 36.1 (d), 35.3 (t), 32.2, 30.5, 28.0 (d), 26.8 (q), 19.1 (s), 17.5, 17.2, 17.1, 16.2, 8.8, 8.7 (q); EI MS (**9**+**10**) *m*/*z* (relative intensity) 391 (1), 379 (1), 367 (M−*t*-Bu, 21), 337 (65), 289 (92), 267 (14), 199 (100), 183 (25), 181 (16), 139 (15), 135 (14), 123 (10).

1.2. Equilibration with *t*-BuOK

A solution of the 1/1 mixture of lactones **9** and **10** (0.105 g, 0.25 mmol, 1 equiv.) and *t*-BuOK (0.014 g, 0.13 mmol, 0.5 equiv.) in *tert*-butanol (2 mL) was heated at 50°C overnight, cooled to rt, diluted with EtOAc (5 mL) and quenched by addition of H_2O (2 mL). The aqueous phase was extracted with EtOAc (3×20 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (hexanes/EtOAc: 100/0 to 90/10) afforded a 4/1 mixture of **9** and **10** (0.065 g, 0.16 mmol, 62% yield).

1.2.1. (5*S*, 6*S*)-6-{(1*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-1-methylethyl}-3,3,5-trimethyl-tetrahydro-2*H*-pyran-2-one (11). A solution of LDA was generated at 0°C by dropwise addition of *n*-BuLi (0.16 mL, 2.5 M solution in hexanes, 0.40 mmol, 1.0 equiv.) to a solution of diisopropylamine (0.06 mL, 0.41 mmol, 1.5 equiv.) in THF (1.3 mL). A solution of lactone (+)-**8** (0.106 g, 0.26 mmol, 1 equiv.) in THF (1.3 mL) was then added via cannula at −78°C. After 2 h of stirring at −78°C, a solution of methyl iodide (0.80 mL, 20 mmol, 50 equiv.) and HMPA (0.21 mL, 1.20 mmol, 3 equiv.) in THF (1 mL) was added dropwise. After 1 h at −78°C, the reaction mixture was diluted with Et_2O (7 mL) and quenched by addition of an aqueous 2% HCl solution (2 mL). The cooling bath was removed. The aqueous layer was extracted with EtOAc (3×15 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (hexanes/EtOAc: 100/0 to 90/10) afforded **11** (0.044 g, 0.10 mmol, 38% yield) and a 1:1 mixture of the two epimers **9** and **10** (0.042 g, 0.10 mmol, 38% yield). Compound **11**: R_f: 0.62 (hexanes/Et_2O: 80/20); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62–7.47 (m, 4H), 7.36–7.17 (m, 6H), 4.17 (m, 1H), 3.71 (m, 1H), 3.49 (m, 1H), 2.00–1.80 (m, 2H), 1.61–1.43 (m, 2H), 1.20 (s, 6H), 0.97 (s, 9H), 0.86 (d, *J*=7.0 Hz, 3H), 0.71 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.7 (s), 137.6 (4d), 135.7 (2s), 131.7 (2d), 129.7 (4d), 87.4 (d), 67.4 (t), 46.3 (t), 40.6 (s), 39.3 (q), 30.2 (q), 30.1 (d), 29.1 (d), 29.0 (3q), 21.3 (s), 19.2 (q), 10.9 (q); EI MS *m*/*z* (relative intensity) 381 (M−*t*-Bu, 17), 351 (30), 337 (22), 303 (42), 289 (33), 199 (100), 183 (24), 135 (17), 95 (11).

1.2.2. (2*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropan-1-ol (+)-12.[33] To a stirred solution of (*S*)-(+)-methyl-3-hydroxy-2-methylpropionate (+)-**1** (6.08 g, 51.5 mmol, 1 equiv.) in DMF (100 mL), imidazole (6.31 g, 92.6 mmol, 1.8 equiv.) and *tert*-butyldimethylsilyl chloride (10.9 g, 72.1 mmol, 1.4 equiv.) were added at rt. The reaction mixture was allowed to stir 5 h at rt and was then quenched by a saturated aqueous sodium bicarbonate solution (100 mL). The reaction mixture was extracted with hexane (3×150 mL). The organic layer was washed with water (2×100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to provide methyl (2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropionate (14.1 g). To a stirred solution of this crude product in THF (200 mL) at 0°C, DIBAL-H (118 mL, 1 M solution in hexanes, 118 mmol, 2.3 equiv.) was added via cannula. The cooling bath was removed and the reaction mixture was stirred overnight at rt and then added to a well-stirred mixture of sodium potassium tartrate (150 g) in water (500 mL) and hexanes (500 mL). The resulting slurry was stirred until two clear layers separated (approximately 1 h). The layers were separated and the aqueous layer was extracted with diethyl ether (3×300 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (CH_2Cl_2) or by distillation (bp: 92°C, 20 mmHg) provided (+)-**12** (8.61 g, 42.2 mmol, 82% yield). R_f: 0.33 (dichloromethane, TLC stain: $KMnO_4$); $[\alpha]_D^{20}$=+9.79 (*c* 2.38, CH_2Cl_2) [lit.[33]: $[\alpha]_D^{20}$=+9.44 (*c* 1.97, CH_2Cl_2)]; IR (neat) 3360 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.70 (dd, *J*=9.7 and 4.6 Hz, 1H), 3.63–3.56 (m, 2H), 3.53 (dd, *J*=9.7 and 7.9 Hz, 1H), 3.04 (bs, 1H), 1.91 (m, 1H), 0.88 (s, 9H), 0.82 (d, *J*=7.0 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.4 (t), 67.8 (t), 36.9 (d), 25.7 (3q), 18.0 (s), 12.9 (q), −5.7 (q), −5.8 (q); EI MS *m*/*z* (relative intensity) 203 (1), 189 (1), 171 (1), 155 (1), 147 (M−*t*-Bu, 25), 105 (45), 75 (100).

1.2.3. (2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropanal (+)-13.[34] To a stirred solution of (2*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropan-1-ol (2.00 g, 9.80 mmol, 1 equiv.), dry DMSO (7.50 mL), CH_2Cl_2 (37 mL), and Et_3N (6.80 mL, 48.8 mmol, 5 equiv.) at 0°C, pyr.SO_3 complex (6.24 g, 39.1 mmol, 4 equiv.) was added in small portions over a 3 min period. After 2 h at 0°C, the reaction mixture was diluted with Et_2O (120 mL) and washed with H_2O (2×25 mL) and brine (25 mL). Drying ($MgSO_4$) followed by solvent removal in vacuo afforded aldehyde (+)-**13** (1.98 g, 9.89 mmol, quantitative yield) which was used in the next step without further purification. R_f: 0.32 (hexanes/Et_2O: 80/20); IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.72 (bs, 1H), 3.85 (dd, *J*=9.9 and 5.1 Hz, 1H), 3.79 (dd, *J*=9.9 and 6.4 Hz, 1H), 2.51 (m, 1H), 1.08 (d, *J*=7.0 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.4 (d), 63.3 (t), 48.7 (d), 25.6 (3q), 18.0 (s), 10.1 (q), −5.7 (2q); EI MS *m*/*z* (relative intensity) 187 (M−Me, 1), 145 (M−*t*-Bu, 100), 115 (85), 101 (19), 85 (14), 75 (30).

1.2.4. (2*S*, 3*S*, 4*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-2,4-dimethylhex-5-en-3-ol (−)-14.[17] To a slurry of flame-dried powdered 4 Å molecular sieves (0.14 g) in anhydrous toluene (6.4 mL) under argon at rt, (−)-**4**[32] (10.9 mL, 10.9 mmol, 1 M solution in toluene, 1.5 equiv.) was added. After being stirred for 10 min at rt, the mixture was cooled to −78°C. A solution of aldehyde (+)-**13** (crude, theoretically 7.25 mmol, 1 equiv.) in dry toluene (6.4 mL) was then introduced dropwise via cannula. After the addition was complete, the solution was maintained at −78°C overnight. Excess ethanolic $NaBH_4$ [1 mL of a solution of $NaBH_4$ (0.75 g) in absolute EtOH (10 mL)] was then added dropwise. The cooling bath was removed and the solution warmed to 0°C. The mixture was then diluted with an 1N aqueous NaOH solution (19 mL) and stirred vigorously for 2 h. The layers were then separated and the aqueous layer was extracted with Et_2O (5×60 mL). The organic extracts were dried over $MgSO_4$, filtrated and concentrated in vacuo. NMR analysis of the crude product

revealed that (−)-**14** was present with the *anti–anti* diastereomer in a ratio greater than 97/3. Purification by flash chromatography (hexanes/Et_2O: 100/0 to 95/5) provided (−)-**14** (1.51 g, 5.87 mmol, 81% yield). R_f: 0.33 (hexanes/Et_2O: 9/1); $[\alpha]_D^{20}=-1.02$ (*c* 2.55, $CHCl_3$) [lit.[17]: $[\alpha]_D^{20}=-3.9$ (*c* 2.6, $CHCl_3$)]; IR (neat) 3500, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.85 (ddd, *J*=17.3, 10.3 and 8.1 Hz, 1H), 5.17–5.06 (m, 2H), 3.74 (dd, *J*=9.6 and 4.4 Hz, 1H), 3.70 (dd, *J*=9.6 and 4.8 Hz, 1H), 3.54 (ddd apparent dt, *J*=8.8 and 2.2 Hz, 1H), 2.80 (d, *J*=1.8 Hz, 1H), 2.28 (m, 1H), 1.81 (m, 1H), 0.96 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=7.0 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.0 (d), 114.9 (t), 76.6 (d), 68.2 (t), 41.7 (d), 36.2 (d), 25.7 (3q), 18.1 (s), 16.5 (q), 9.2 (q), −5.7 (2q); EI MS *m/z* (relative intensity) 243 (M–Me, 1), 225 (M–H_2O–Me, 1), 203 (29), 145 (55), 115 (27), 109 (93), 105 (49), 89 (48), 75 (100); Anal. calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 65.02; H, 11.52.

1.2.5. (1*S*, 2*S*)-1-{(1S)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-methylethyl}-2-methylbut-3-enyl 2-methylprop-2-enoate (+)-15. To a stirred solution of (−)-**14** (5.31 g, 20.6 mmol, 1 equiv.) in dry CH_2Cl_2 (55 mL) at 0°C was slowly added Et_3N (8.00 mL, 59.7 mmol, 2.9 equiv.) and a catalytic amount of DMAP (0.37 g, 3 mmol, 0.15 equiv.). Methacryloyl chloride (4.10 mL, 44.3 mmol, 2.15 equiv.) was then added dropwise. After removal of the cooling bath, the mixture was stirred overnight at rt, and then quenched by the addition of a saturated aqueous NH_4Cl solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The organic layers were combined, washed with a saturated aqueous NaCl solution (30 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by flash chromatography (hexanes/Et_2O: 100/0 to 95/5) to provide (+)-**15** (5.30 g, 16.3 mmol, 79% yield). R_f: 0.68 (hexanes/Et_2O: 96/4); $[\alpha]_D^{20}=+16.5$ (*c* 1.5, $CHCl_3$); IR (neat) 1730, 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.08 (bs, 1H), 5.75 (ddd, *J*=17.1, 10.1 and 8.6 Hz, 1H), 5.52 (quint, *J*=1.7 Hz, 1H), 5.05–4.96 (m, 3H), 3.51 (dd, *J*=9.9 and 5.7 Hz, 1H), 3.43 (dd, *J*=9.9 and 6.3 Hz, 1H), 2.53 (m, 1H), 1.97 (m, 1H), 1.94 (bs, 3H), 1.02 (d, *J*=7.0 Hz, 3H), 0.93 (d, *J*=7.0 Hz, 3H), 0.90 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7 (s), 140.0 (d), 135.5 (s), 128.7 (t), 115.0 (t), 76.8 (d), 65.3 (t), 40.6 (d), 37.3 (d), 25.7 (3q), 18.2 (q), 17.7 (q), 11.5 (q), 18.1 (s), −5.6 (q), −5.7 (q); EI MS *m/z* (relative intensity) 271 (4), 241 (9), 185 (5), 145 (11), 144 (12), 143 (100), 115 (8), 109 (42), 69 (30); HRMS (CI^+, CH_4) calcd for $C_{18}H_{35}O_3Si$ ($M+H^+$): 327.2355, found 327.2346; Anal. calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.49. Found: C, 66.36; H, 10.61.

1.2.6. (5*S*, 6*S*)-6-{(1*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-methylethyl}-3,5-dimethyl-5,6-dihydro-2*H*-pyran-2-one (+)-16. (4,5-DihydroIMES)(PCy_3)Cl_2Ru=CHPh **II**[19b] (0.121 g, 0.145 mmol, 0.15 equiv.) was added in one portion at rt to a stirred solution of (+)-**15** (0.300 g, 0.95 mmol, 1 equiv.) in dry CH_2Cl_2 (46 mL). The reaction mixture was refluxed overnight (oil bath temperature: 58°C), cooled to rt, concentrated in vacuo and purified by flash chromatography (hexanes/Et_2O: 100/0 to 80/20) to provide the starting material (+)-**15** (0.060 g, 0.19 mmol, 20%) and (+)-**16** (0.219 g, 0.73 mmol, 77% yield, 96% yield based on recovered material). R_f: 0.38 (hexanes/Et_2O: 80/20, TLC stain: $KMnO_4$); $[\alpha]_D^{20}=+51.6$ (*c* 1.35, $CHCl_3$); IR (neat) 1730, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.34 (bs, 1H), 4.22 (bd, *J*=11.2 Hz, 1H), 3.68 (dd, apparent t, *J*=9.6 Hz, 1H), 3.52 (dd, *J*=9.6 and 5.9 Hz, 1H), 2.62 (m, 1H), 1.92 (m, 1H), 1.89 (bs, 3H), 1.04 (d, *J*=7.4 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.9 (s), 146.3 (d), 126.9 (s), 82.3 (d), 64.3 (t), 36.7 (d), 30.6 (d), 25.7 (3q), 18.1 (s), 16.7 (q), 16.0 (q), 9.7 (q), −5.5 (q), −5.6 (q); EI MS *m/z* (relative intensity) 297 (M-1, 1), 283 (M−Me, 1), 253 (5), 241 (M−*t*-Bu, 63), 223 (11), 211 (100), 167 (10), 149 (16), 145 (27), 129 (13), 121 (28), 115 (22), 75 (54); Anal. calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.51; H, 10.17.

1.2.7. (3*R*, 5*S*, 6*S*)-6-{(1*S*)-2-[(*tert*-Butyldimethylsilyl)-oxy]-1-methylethyl}-3,5-dimethyl-tetrahydro-2*H*-pyran-2-one (+)-17[35] and (3*S*, 5*S*, 6*S*)-6-{(1*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-methylethyl}-3,5-dimethyltetrahydro-2*H*-pyran-2-one 17′. A mixture of lactone (+)-**16** (0.720 g, 2.40 mmol, 1 equiv.) and PtO_2 (41 mg) in EtOH (7 mL) was stirred under a hydrogen atmosphere (4 atm) at rt overnight. The reaction mixture was filtered through Celite (rinsing with EtOAc) and the solvent evaporated in vacuo to afford a mixture of epimers (+)-**17** and **17′** (0.698 g, 2.33 mmol) in a 1/1 ratio (measured by ^1H NMR).

A solution of LDA was generated at 0°C by dropwise addition of *n*-BuLi (1.15 mL, 2.5 M solution in hexanes, 2.88 mmol, 1.2 equiv.) to a solution of diisopropylamine (0.40 mL, 2.88 mmol, 1.2 equiv.) in THF (3 mL). A solution of the crude reaction mixture containing (+)-**17** and **17′** in THF (6 mL) was added via cannula at −78°C to the solution of LDA previously formed. After 1.5 h at −78°C the reaction mixture was quenched by addition of an aqueous 10% citric acid solution (1.5 mL). The cooling bath was removed. The aqueous layer was extracted with Et_2O (3×15 mL), dried over $MgSO_4$ and concentrated in vacuo. NMR analysis of the crude mixture revealed that (+)-**17** and **17′** were present in a 2.3/1 ratio. Purification by flash chromatography (hexanes/Et_2O: 95/5) afforded **17′** (0.23 g, 0.77 mmol, 32% yield two steps) and (+)-**17** (0.468 g, 1.56 mmol, 65% yield two steps). Compound (+)-**17**: R_f: 0.47 (hexanes/Et_2O: 70/30); $[\alpha]_D^{20}=+44.8$ (*c* 2.7, $CHCl_3$) [lit.[35]: $[\alpha]_D^{20}=+55.5$ (*c* 2.7, $CHCl_3$)]; IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.14 (dd, *J*=10.3 and 1.1 Hz, 1H), 3.66 (apparent t, *J*=9.9 Hz, 1H), 3.48 (dd, *J*=9.9 and 6.3 Hz, 1H), 2.46 (m, 1H), 1.98–1.84 (m, 3H), 1.36 (m, 1H), 1.27 (d, *J*=7.0 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H), 0.88 (s, 9H), 0.83 (d, *J*=7.0 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5 (s), 85.4 (d), 64.5 (t), 37.6 (t), 37.4 (d), 36.1 (d), 30.5 (d), 25.7 (3q), 18.1 (s), 17.2 (q), 17.0 (q), 8.8 (q), −5.5 (2q); EI MS *m/z* (relative intensity) 299 (1), 285 (M−Me, 1), 255 (5), 243 (M−*t*-Bu, 25), 225 (26), 213 (100), 185 (10), 151 (27), 143 (31), 123 (49), 115 (16), 95 (12), 75 (66); HRMS (CI^+, CH_4) calcd for $C_{16}H_{33}O_3Si$ ($M+H^+$): 301.2199, found 301.2203. Compound **17′**: R_f: 0.51 (hexanes/Et_2O: 70/30); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.19 (dd, *J*=10.5 and 1.7 Hz, 1H), 3.65 (dd, *J*=9.9 and 9.0 Hz, 1H), 3.49 (dd, *J*=9.9 and 5.9 Hz, 1H), 2.61 (m, 1H), 2.06–1.83 (m, 2H), 1.68 (m, 2H), 1.20 (d, *J*=7.0 Hz, 3H), 0.96 (d, *J*=6.6 Hz, 3H), 0.87 (s, 9H), 0.85 (d, *J*=7.0 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.4 (s), 81.3 (d), 64.5 (t), 36.8 (d), 35.3 (t), 32.3 (d), 28.0 (d), 25.7 (3q), 18.1 (s), 17.4 (q), 16.2 (q), 8.7 (q), −5.5 (2q).

1.2.8. (3*R*, 5*S*, 6*S*)-6-((1*S*)-2-Hydroxy-1-methylethyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (18)[36] and (3*S*, 5*S*, 6*S*)-6-((1*S*)-2-hydroxy-1-methylethyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (18′).[36] A mixture of lactone (+)-**16** (0.208 g, 0.70 mmol, 1 equiv.) and $Pd(OH)_2$ (70 mg) in EtOAc (4 mL) was stirred under a hydrogen atmosphere at rt overnight. The reaction mixture was filtered through Celite (rinsing with EtOAc) and the solvent evaporated in vacuo. Purification by flash chromatography (hexanes/EtOAc: 70/30 to 30/70) afforded a mixture of epimers (+)-**17** and **17′** (0.041 g, 0.14 mmol, 20% yield) in a 1/2 ratio and epimers **18** and **18′** (0.103 g, 0.55 mmol, 80% yield) in a 1/2 ratio (measured by ^{1}H NMR). R_f: 0.25 (hexanes/EtOAc: 40/60); ^{1}H NMR ($CDCl_3$, 300 MHz) (compound **18**) δ 4.22 (dd, J=10.3 and 1.8 Hz, 1H), 3.69 (m, 1H), 3.56 (m, 1H), 2.74 (bs, 1H), 2.47 (m, 1H), 2.05–1.85 (m, 3H), 1.39 (m, 1H), 1.18 (d, J=7.0 Hz, 3H), 0.94 (d, J=6.2 Hz, 3H), 0.85 (d, J=7.0 Hz, 3H); (compound **18′**) δ 4.24 (dd, J=10.3 and 1.8 Hz, 1H), 3.69 (m, 1H), 3.56 (m, 1H), 2.74 (bs, 1H), 2.65 (m, 1H), 2.05–1.85 (m, 3H), 1.67 (m, 1H), 1.24 (d, J=7.4 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H), 0.87 (d, J=7.0 Hz, 3H).

1.2.9. (2*R*, 4*S*, 5*S*, 6*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-*N*-methoxy-*N*,2,4,6-tetramethylheptanamide (19). Trimethylaluminium (2.18 mL, 2 M solution in toluene, 4.36 mmol, 3 equiv.) was very slowly added to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (0.427 g, 4.36 mmol, 3 equiv.) in CH_2Cl_2 (2.5 mL) at −78°C (*Caution*: Strong CH_4 release occured). The cooling bath was removed and the clear colorless resulting solution was allowed to stir for 2 h at rt. After cooling the solution to 0°C, a solution of lactone (+)-**17** (0.436 g, 1.45 mmol, 1 equiv.) in CH_2Cl_2 (3 mL) was added via cannula. The cooling bath was removed and the reaction mixture was stirred at rt overnight. The solution was cooled to 0°C, diluted with CH_2Cl_2 (10 mL) and Rochelle's salt (~0.5 g) in water (1 mL) was added (very slowly at first). The mixture was filtered through Celite and washed several times with CH_2Cl_2. Drying the solution over $MgSO_4$, concentration in vacuo and flash chromatography provided alcohol **19** which was used in the next step without further purification. R_f: 0.38 (hexanes/Et_2O: 50/50); IR (neat) 3460, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 3H), 3.66 (bd, J=4.8 Hz, 2H), 3.41 (dd, J=8.5 and 2.6 Hz, 1H), 3.17 (s, 3H), 3.05 (m, 1H) 2.89 (m, 1H), 2.16 (m, 1H), 1.75 (m, 1H), 1.39 (m, 1H), 1.12 (d, J=6.6 Hz, 3H), 1.08 (m, 1H), 0.87 (s, 9H), 0.86 (d, J=6.6 Hz, 3H), 0.82 (d, J=6.6 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.8 (s), 77.7 (d), 68.0 (t), 61.3 (q), 37.4 (t), 36.5 (d), 34.5 (d), 33.1 (bd), 32.2 (q), 25.7 (3q), 18.6 (s), 18.1 (q), 16.6 (q), 9.38 (q), −5.6 (q), −5.7 (q); EI MS *m*/*z* (relative intensity) 346 (M−Me, 1), 274 (5), 255 (5), 243 (28), 225 (29), 213 (100), 188 (12), 169 (15), 151 (37), 145 (14), 143 (29), 123 (68), 75 (88).

1.2.10. (2*R*, 4*S*, 5*S*, 6*S*)-5,7-bis[(*tert*-Butyldimethylsilyl)-oxy]-*N*-methoxy-*N*,2,4,6-tetramethylheptanamide (−)-20. To a solution of crude alcohol **19** (theoretically 1.45 mmol, 1 equiv.) in DMF (10 mL) at 0°C was added $AgNO_3$ (0.493 g, 2.90 mmol, 2 equiv.). When $AgNO_3$ was dissolved (about 2 min), *tert*-butyldimethylsilyl chloride (0.437 g, 2.90 mmol, 2 equiv.) was added. A white precipitate appeared immediatly. After 1 h of stirring at 0°C, the reaction mixture was diluted with Et_2O (50 mL) and filtered into a cold (0°C) aqueous 5% $NaHCO_3$ solution (40 mL). The organic phase was separated and the aqueous layer was extracted with Et_2O (3×40 mL). The combined organic phases were washed with H_2O (2×20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (hexanes/Et_2O: 100/0 to 70/30) afforded (−)-**20** (0.482 g, 1.02 mmol, 70% yield for two steps). R_f: 0.35 (hexanes/Et_2O: 70/30); $[\alpha]_D^{20}$=−1.00 (*c* 0.99, $CHCl_3$); IR (neat) 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 3H), 3.59 (dd, J=4.4 and 3.3 Hz, 1H), 3.44 (dd, J=9.7 and 6.8 Hz, 1H), 3.36 (dd, J=9.7 and 6.8 Hz, 1H), 3.17 (s, 3H), 3.02 (m, 1H), 1.91–1.71 (m, 2H), 1.52 (m, 1H), 1.12 (d, J=6.6 Hz, 3H), 1.09 (m, 1H), 0.92 (d, J=7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.85 (d, J=7.0 Hz, 3H), 0.03 (bs, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.7 (s), 75.2 (d), 66.5 (t), 61.3 (q), 37.9 (d), 37.2 (t), 36.5 (d), 32.8 (d), 32.2 (q), 25.8 (3q), 25.9 (3q), 18.5 (q), 18.2 (s), 18.1 (s), 16.0 (q), 12.1 (q), −4.1 (q), −4.5 (q), −5.1 (q), −5.5 (q); EI MS *m*/*z* (relative intensity) 460 (M−Me, 1), 418 (M−*t*-Bu, 100), 388 (5), 317 (25), 302 (19), 283 (6), 259 (6), 241 (7), 225 (6), 212 (5), 185 (17), 147 (36), 123 (18), 89 (40), 73 (57); HRMS (CI^+, CH_4) calcd for $C_{24}H_{54}NO_4Si_2$ ($M+H^+$): 476.3591, found 476.3599.

1.2.11. (±)-2-Methylpent-1-en-3-ol (±)-22.[24] To a stirred solution of freshly distilled methacrolein **21** (24.5 mL, 300 mmol, 1 equiv.) in Et_2O (120 mL) at −20°C was added EtMgBr (100 mL, 3 M solution in Et_2O, 300 mmol, 1 equiv.) via cannula over 20 min. The reaction was quenched with a saturated aqueous NH_4Cl solution (120 mL), extracted with Et_2O (3×150 mL) and dried over $MgSO_4$. Distillation of Et_2O (atmospheric pressure), followed by distillation under reduced pressure (bp 54°C, 20 mmHg) gave (±)-**22** as a colorless liquid (20.4 g, 204 mmol, 68% yield). R_f: 0.38 (CH_2Cl_2/Et_2O: 95/5); IR 3360, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.90 (m, 1H), 4.81 (m, 1H), 3.95 (t, J=6.4 Hz, 1H), 2.06 (bs, 1H), 1.69 (bs, 3H), 1.60–1.49 (m, 2H), 0.86 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.1 (s), 110.9 (t), 77.1 (d), 27.5 (t), 17.2 (q), 9.6 (q).

1.2.12. (+)-(*R*)-2-Methylpent-1-en-3-ol (+)-22.[24] To a stirred solution of (±)-**22** (8.12 g, 81.1 mmol, 1 equiv.) in dry CH_2Cl_2 (300 mL) were added diisopropyl tartrate (2.60 mL, 12.2 mmol, 0.15 equiv.) and powdered molecular sieves (2.50 g). The reaction mixture was cooled to −20°C and $Ti(OiPr)_4$ (2.35 mL, 7.90 mmol, 0.10 equiv.) was added. After 30 min, *tert*-butyl hydroperoxide (8.5 mL, 5.5 M in decane, 46.7 mmol) was added and stirring was continued for 48 h. The reaction mixture was quenched by addition of a precooled (0°C) aqueous $FeSO_4$/citric acid solution (33 g of $FeSO_4$ and 11 g of citric acid in 100 mL of H_2O). The cooling bath was removed and the mixture was vigorously stirred for 40 min. The organic layer was dried over $MgSO_4$ and concentrated under atmospheric pressure to give a mixture of tartrate, epoxide, and resolved alcohol.

Purification by flash chromatography on silica gel (CH_2Cl_2) gave the resolved alkene (*R*)-**22** (3.69 g, 36.9 mmol, 91% based on the *R*-enantiomer) as a colorless liquid. ^{1}H NMR analysis of their mandelic ester indicated a 90% ee.[25] (+)-**22**: $[\alpha]_D^{20}$=+4.1 (*c* 1.0, CH_2Cl_2) [lit.[24]: $[\alpha]_D^{20}$=+5.6 (*c* 1.6, $CHCl_3$)].

1.2.13. (3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpent-1-ene (+)-23.[37,38] To a stirred solution of alcohol (+)-**22** (5.00 g, 50.0 mmol, 1 equiv.) in dry DMF (100 mL) and imidazole (6.12 g, 90.0 mmol, 1.8 equiv.) was added *tert*-butyldimethylsilyl chloride (10.5 g, 70.0 mmol, 1.4 equiv.) in one portion at rt. After 5 h, 100 mL of saturated aqueous sodium bicarbonate were added. The aqueous layer was extracted with hexanes (3×150 mL). The organic layers were washed with H_2O (2×100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (hexanes) to provide (+)-**23** (8.63 g, 40.3 mmol, 81% yield) as a colorless oil. R_f: 0.67 (hexanes); $[\alpha]_D^{20}$=+5.30 (*c* 1.85, $CHCl_3$) [lit.[38]: $[\alpha]_D^{20}$=+6.9 (*c* 2.65, $CDCl_3$)]; IR (neat) 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.86 (m, 1H), 4.77 (m, 1H), 3.96 (t, *J*=6.2 Hz, 1H), 1.67 (bs, 3H), 1.51 (m, 2H), 0.91 (s, 9H), 0.84 (t, *J*=7.3 Hz, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.5 (s), 110.3 (t), 77.9 (d), 28.8 (t), 25.5 (3q), 18.1 (s), 17.0 (q), 9.7 (q), −4.9 (q), −5.2 (q); EI MS *m/z* (relative intensity) 214 (M, 1), 199 (M−Me, 4), 185 (M-Et, 27), 157 (M−*t*-Bu, 100), 129 (5), 115 (M−*t*-BuMe$_2$Si, 12), 75 (98).

1.2.14. (2*S*, 3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpentane-1,2-diol (24) and (2*R*, 3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpentane-1,2-diol (24′). To a stirred solution of NMO (1.21 g, 10.3 mmol, 1.01 equiv.) in acetone (68 mL) and H_2O (11 mL) at 0°C was added OsO_4 (3.2 mL, 4% solution in H_2O, 0.51 mmol, 0.05 equiv.). After 5 min, a solution of olefin (+)-**23** (2.19 g, 10.2 mmol, 1 equiv.) in acetone (29 mL) was added via cannula. The brown mixture was allowed to warm to rt overnight. A mixture of $Na_2S_2O_3$ (1.80 g), Florisil (6.81 g) and H_2O (3 mL) was added. After 45 min, the mixture was filtered and volatiles were removed in vacuo. The residue was diluted with saturated aqueous NaCl (3 mL) and extracted with EtOAc (3×100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc: 100/0 to 90/10) provided diols **24** and **24′** (2.34 g, 9.44 mmol, 92% yield) as an inseparable mixture of two diastereomers in a 5.5/1 ratio (measured by ^{1}H NMR). R_f: 0.37 (CH_2Cl_2/EtOAc: 90/10); IR (neat) 3420 cm^{-1}. Major diastereomer (**24**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.83 (bd, *J*=11.0 Hz, 1H), 3.57 (dd, *J*=7.5 and 3.5 Hz, 1H), 3.36 (dd, apparent t, *J*=11.0 Hz, 1H), 2.80 (bs, 1H), 2.71 (bd, *J*=8.5 Hz, 1H), 1.64 (m, 1H), 1.46 (m, 1H), 1.08 (s, 3H), 1.00 (t, *J*=7.5 Hz, 3H), 0.92 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 81.4 (d), 73.8 (s), 67.6 (t), 25.9 (3q), 25.8 (t), 20.9 (q), 18.1 (s), 11.4 (q), −4.4 (2q); EI MS *m/z* (relative intensity) 247 (M−1, 1), 233 (M−Me, 1), 201 (11), 173 (M−*t*-Bu-H_2O, 100), 159 (5), 143 (5), 133 (30), 131 (6), 129 (8), 117 (19), 115 (33), 75 (57). Minor diastereomer (**24′**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64 (dd, *J*=6.2 and 4.4 Hz, 1H), 3.47 (m, 2H), 2.46 (bs, 1H), 2.13 (bs, 1H), 1.68 (m, 1H), 1.47 (m, 1H), 1.13 (s, 3H), 0.98 (t, *J*=7.3 Hz, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H); HRMS (CI^+, CH_4) calcd for $C_{12}H_{29}O_3Si$ ($M+H^+$): 249.1886, found 249.1891.

1.2.15. (2*R*, 3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-2-methylpentanal (25) and (2*S*, 3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-2-methylpentanal (25′). To a stirred solution of diols **24** and **24′** (in a ratio of 5.5/1) (2.17 g, 8.75 mmol, 1 equiv.) in dry DMSO (6.70 mL), CH_2Cl_2 (34 mL), and Et_3N (6.10 mL, 43.8 mmol, 5 equiv.) at 0°C was added pyr.SO_3 complex (5.58 g, 35.0 mmol, 4 equiv.) in small portions over a 3 min period. After 2 h at 0°C, the reaction mixture was diluted with Et_2O (100 mL) and washed with H_2O (2×20 mL) and brine (20 mL). Drying ($MgSO_4$) followed by filtration and by removal of the solvent in vacuo afforded a 5.5/1 mixture of aldehydes **25** and **25′** (2.15 g, 8.75 mmol, quantitative yield) which was used in the next step without further purification. R_f: 0.35 (hexanes/Et_2O: 85/15); IR (neat) (**25**+**25′**) 3420, 1730 cm^{-1}; Major diastereomer **25**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.70 (s, 1H), 3.60 (dd, *J*=7.5 and 4.2 Hz, 1H), 3.35 (bs, 1H), 1.73 (m, 1H), 1.57 (m, 1H), 1.27 (s, 3H), 0.96 (t, *J*=7.5 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.0 (d), 80.0 (s), 79.2 (d), 25.9 (t), 25.7 (3q), 18.8 (q), 18.0 (s), 11.0 (q), −4.4 (q), −4.5 (q); Minor diastereomer **25′**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (s, 1H), 3.84 (dd, apparent t, *J*=5.0 Hz, 1H), 3.42 (bs, 1H), 1.76 (m, 1H), 1.54 (m, 1H), 1.23 (s, 3H), 0.95 (t, *J*=7.5 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.5 (d), 80.2 (s), 76.7 (d), 25.7 (3q), 24.9 (t), 19.5 (q), 17.9 (s), 10.0 (q), −4.2 (q), −4.7 (q); EI MS (**25**+**25′**) *m/z* (relative intensity) 245 (M-1, 1), 231 (M−Me, 1), 217 (M−Et, 3), 201 (5), 189 (M−*t*-Bu, 3), 173 (29), 145 (9), 131 (100), 117 (11), 115 (13), 75 (67), 73 (50).

1.2.16. (3*S*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-iodo-3-methylhex-1-en-3-ol (26) and (3*R*,4*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-iodo-3-methylhex-1-en-3-ol (26′). Anhydrous $CrCl_2$ (flame-dried under argon, 10.4 g, 85.8 mmol, 10 equiv.) and freshly distilled THF (170 mL) were stirred together for 30 min at rt, generating a creamy gray-green suspension. After cooling at 0°C, a solution of crude aldehydes **25** and **25′** in a ratio of 5.5/1 (2.11 g, 8.58 mmol, 1 equiv.) and iodoform (6.76 g, 17.2 mmol, 2 equiv.) in THF (34 mL) was introduced via cannula. The resulting dark red reaction mixture was stirred for 3 h at 0°C, filtered through Celite and the solid residue was washed with Et_2O (2×150 mL). The filtrate was washed with H_2O (3×100 mL), saturated aqueous $Na_2S_2O_3$, H_2O and brine (50 mL each), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes/Et_2O: 100/0 to 95/5) provided a 5.5/1 mixture of **26** and **26′** (2.47 g, 6.69 mmol, 78% yield). R_f: 0.36 (hexanes/Et_2O: 95/5); IR (neat) 3460, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) (major epimer **26**) δ 6.59 (d, *J*=14.5 Hz, 1H), 6.35 (d, *J*=14.5 Hz, 1H), 3.42 (dd, *J*=5.9 and 4.4 Hz, 1H), 2.40 (bs, 1H), 1.61 (m, 1H), 1.42 (m, 1H), 1.22 (s, 3H), 0.93 (s, 9H), 0.94–0.90 (m, 3H), 0.11 (2s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) (major epimer **26**) δ 148.8 (d), 79.5 (d), 78.1 (s), 75.8 (d), 26.6 (3q), 25.8 (t), 24.7 (q), 18.1 (s), 10.8 (q), −4.0 (q), −4.5 (q); EI MS (**26**+**26′**) *m/z* (relative intensity) 355

(M−Me, 1), 313 (M−*t*-Bu, 9), 255 (6), 197 (5), 186 (53), 173 (100), 127 (7), 117 (18), 115 (18), 75 (87), 73 (80).

1.2.17. (3*S*, 4*R*)-1-Iodohex-1-ene-3,4-diol (27) and (3*R*, 4*R*)-1-iodohex-1-ene-3,4-diol (27′). To a stirred solution of the 5.5/1 mixture of vinyl iodides **26** and **26′** (0.483 g, 1.31 mmol, 1 equiv.) in THF (4 mL) was added *n*-Bu_4NF (4 mL, 1 M solution in THF, 4 mmol, 3 equiv.) at rt. After 1 h of stirring, the reaction mixture was concentrated under reduced pressure. The residue was immediatly purified by flash chromatography (CH_2Cl_2/Et_2O: 90/10) to afford a 5.5/1 mixture of diols **27** and **27′** (0.291 g, 1.14 mmol, 87% yield). R_f: 0.28 (CH_2Cl_2/Et_2O: 90/10); IR (neat) (**27**+**27′**) 3400, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major epimer **27**) δ 6.60 (d, J=14.5 Hz, 1H), 6.38 (d, J=14.5 Hz, 1H), 3.28 (dd, J=10.5 and 2.4 Hz, 1H), 2.82 (bs, 2H), 1.55 (m, 1H), 1.29 (m, 1H), 1.25 (s, 3H), 1.00 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) (major epimer **27**) δ 148.0 (d), 79.5 (d), 78.2 (s), 77.1 (d), 24.8 (t), 24.2 (q), 10.9 (q); EI MS (major epimer **27**) *m*/*z* (relative intensity) 241 (M−Me, 1), 223 (1), 197 (61), 179 (8), 111 (5), 82 (6), 71 (100).

1.2.18. (4*S*, 5*R*)-5-Ethyl-4-(2-iodoethenyl)-2,2,4-trimethyl-1,3-dioxolane (+)-28 and (4*R*, 5*R*)-5-ethyl-4-(2-iodoethenyl)-2,2,4-trimethyl-1,3-dioxolane (28′). To a stirred solution of the 5.5/1 mixture of diols **27** and **27′** (0.289 g, 1.13 mmol, 1 equiv.) in acetone (6 mL) were added 2,2-dimethoxypropane (0.41 mL, 3.39 mmol, 3 equiv.) and a catalytic amount of PPTS (15 mg, 0.06 mmol, 5 mol%) at rt. After 2 days stirring, additional 2,2-dimethoxypropane was introduced (0.41 mL, 3.39 mmol, 3 equiv.). After 1 day, the reaction mixture was concentrated in vacuo and immediatly purified by flash chromatography (hexanes/Et_2O: 100/0 to 90/10) to give (+)-**28** (0.283 g, 0.96 mmol, 85% yield) and **28′** (0.050 g, 0.17 mmol, 15% yield). Compound (+)-**28**: R_f: 0.56 (hexanes/Et_2O: 90/10); $[\alpha]_D^{20}$=+2.24 (*c* 1.03, $CHCl_3$); IR (neat) 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.49 (d, J=14.3 Hz, 1H), 6.32 (d, J=14.3 Hz, 1H), 3.69 (dd, J=8.6 and 4.6 Hz, 1H), 1.59–1.42 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.01 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.2 (d), 107.7 (s), 85.5 (d), 85.4 (s), 76.5 (d), 28.0 (q), 26.3 (q), 24.0 (q), 23.0 (t), 11.0 (q); EI MS *m*/*z* (relative intensity) 296 (M, 1), 281 (M−Me, 16), 238 (26), 181 (7), 111 (100); HRMS (EI) calcd for $C_9H_{14}IO_2$ (M−Me): 281.0039, found 281.0033.

1.2.19. (±)-(4*SR*,5*RS*)-5-Ethyl-2,2,4-trimethyl-4-[(trityloxy)methyl]-1,3-dioxolane (±)-29. A 5.5/1 mixture of diols (±)-**24** and (±)-**24′** (0.50 g, 2.02 mmol, 1 equiv.) was dissolved in pyridine (21 mL), and a catalytic amount of DMAP (37 mg, 0.30 mmol, 0.15 equiv.) was added at rt followed by the addition of triphenylmethyl chloride (2.24 g, 8.08 mmol, 4 equiv.). After three days, a small amount of water and EtOH (21 mL) were added. The mixture was concentrated in vacuo, treated with hexanes (13 mL), filtered and the residue was extracted with hexanes (25 mL). The hexanes solution was dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (hexanes/AcOEt: 100/0 to 96/4) afforded an inseparable 5.5/1 mixture of (±)-(2*SR*,3*RS*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-1-(trityloxy)pentan-2-ol **32** and its C_2 epimer **32′** (0.73 g, 1.49 mmol, 74% yield). R_f: 0.30 (hexanes/EtOAc: 96/4); IR (neat) 3580, 1600, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major diastereomer **32**) δ 7.51–7.45 (m, 6H), 7.37–7.23 (m, 9H), 3.51 (bdd, J=7.5 and 4.2 Hz, 1H), 3.17 (s, 2H), 2.55 (bs, 1H), 1.63 (m, 1H), 1.34 (m, 1H), 1.33 (s, 3H), 0.91 (t, J=7.5 Hz, 3H), 0.83 (s, 9H), 0.07 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) (major diastereomer **32**) δ 143.8 (3s), 128.7 (6d), 127.7 (6d), 126.9 (3d), 86.5 (s), 78.8 (d), 74.9 (s), 67.8 (t), 25.9 (3q), 25.1 (t), 21.9 (q), 18.1 (s), 11.3 (q), −4.0, −4.5 (q); EI MS (**32**+**32′**) *m*/*z* (relative intensity) 281 (1), 259 ($OCPh_3$, 1), 243 (CPh_3, 100), 228 (3), 217 (4), 201 (6),173 (16), 165 (20), 73 (9).

To a stirred solution of the 5.5/1 mixture of alcohols (±)-**32** and (±)-**32′** (0.73 g, 1.49 mmol, 1 equiv.) in THF (4 mL) at 0°C was added TBAF (1 M solution in THF, 2.30 mL, 1.5 equiv.). The cooling bath was removed and the reaction mixture was stirred at rt overnight. Concentration in vacuo and flash chromatography (CH_2Cl_2/EtOAc: 100/0 to 90/10) afforded an inseparable 5.5/1 mixture of (±)-(2*SR*,3*RS*)-2-methyl-1-(trityloxy)pentan-2,3-diol (±)-**33** and of its epimer at C_2 (±)-**33′** (0.54 g, 1.44 mmol, 96% yield) as a white powder. Mp 120°C; R_f: 0.42 (CH_2Cl_2/EtOAc: 90/10); IR (KBr) (**33**+**33′**) 3450, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major diastereomer **33**) δ 7.56–7.49 (m, 6H), 7.40–7.25 (m, 9H), 3.43 (m, 1H), 3.35 (m, 1H), 3.32 (d, J=9.2 Hz, 1H), 3.20 (d, J=9.2 Hz, 1H), 2.64 (bs, 1H), 1.46 (m, 1H), 1.16 (s, 3H), 1.10 (m, 1H), 1.05–0.98 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) (major diastereomer **33**) δ 143.5 (3s), 128.5 (6d), 127.9 (6d), 127.1 (3d), 87.1 (s), 79.4 (d), 73.9 (s), 68.2 (t), 24.3 (t), 21.5 (q), 11.3 (q).

To a stirred solution of diols (±)-**33** and (±)-**33′** (ratio: 5.5/1) (0.187 g, 0.50 mmol, 1 equiv.) in dry acetone (4 mL) was added 2,2-dimethoxypropane (0.18 mL, 1.50 mmol, 3 equiv.) and a catalytic amount of PPTS. After 2 days of stirring at rt, the reaction mixture was concentrated in vacuo and purified by flash chromatography (CH_2Cl_2/EtOAc: 100/0 to 95/5) to afford (±)-**29** (0.188 g, 0.45 mmol, 90% yield) and (±)-**29′** (epimer at C_2) in a ratio of 93/7. R_f: 0.69 (CH_2Cl_2); IR (neat) 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (compound **29**) δ 7.65–7.57 (m, 6H), 7.44–7.29 (m, 9H), 3.80 (dd, J=8.8 and 4.4 Hz, 1H), 3.13 (AB syst, J=9.2 Hz, 2H), 1.64–1.48 (m, 2H), 1.51 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.05 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) (compound **29**) δ 143.9 (3s), 128.8 (6d), 127.6 (6d), 126.9 (3d), 106.8 (s), 86.5 (s), 85.2 (d), 81.6 (s), 65.7 (t), 28.2 (q), 26.5 (q), 22.6 (q), 21.7 (t), 11.6 (q); EI MS [(±)-**29**] *m*/*z* (relative intensity) 401 (M−Me, 3), 339 (1), 274 (3), 259 ($OCPh_3$, 1), 243 (CPh_3, 86), 228 (6), 165 (40), 143 (100), 101 (8), 85 (17).

1.2.20. (4*R*, 6*S*, 7*S*, 8*S*)-7,9-Bis[(*tert*-Butyldimethylsilyl)oxy]-1-((4*S*, 5*R*)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)-4,6,8-trimethylnon-1-en-3-one (+)-30. To a stirred solution of vinyl iodide (+)-**28** (0.193 g, 0.65 mmol, 1 equiv.) in Et_2O (4 mL) at −78°C, *t*-BuLi (0.80 mL, 1.7 M solution in pentane, 1.36 mmol, 2.1 equiv.) was added dropwise, resulting in a yellow-pink colored solution. After 20 min of stirring, a solution of amide (−)-**20** (0.124 g, 0.26 mmol, 0.4 equiv.) in Et_2O (2 mL) was added via cannula. The reaction mixture was allowed to

warm to 0°C over 4 h, diluted with Et_2O (5 mL) and quenched with H_2O (3 mL). The aqueous layer was extracted with Et_2O (3×20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (hexanes/Et_2O: 100/0 to 90/10) afforded (+)-**30** (0.100 g, 0.17 mmol, 66% yield) and recovered starting material (−)-**20** (0.043 g, 0.09 mmol, 33% yield). R_f: 0.41 (hexanes/Et_2O: 90/10); $[\alpha]_D^{20}$=+13.5 (*c* 1.00, $CHCl_3$); IR (neat) 1700, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.79 (d, *J*=15.4 Hz, 1H), 6.44 (d, *J*=15.4 Hz, 1H), 3.81 (apparent bt, *J*=6.6 Hz, 1H), 3.63 (dd, *J*=5.2 and 2.6 Hz, 1H), 3.41 (dd, *J*=9.8 Hz and 7.5 Hz, 1H), 3.35 (dd, *J*=9.8 Hz and 6.6 Hz, 1H), 2.82 (m, 1H), 1.90–0.86 (m, 24H), 0.90 (s, 9H), 0.89 (s, 9H), 0.81 (d, *J*=6.6 Hz, 3H), 0.03 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.3 (s), 146.8 (d), 126.8 (d), 107.8 (s), 86.0 (d), 81.8 (s), 74.5 (d), 66.2 (t), 42.6 (d), 37.8 (d), 36.7 (t), 36.1 (d), 28.0 (q), 26.3 (q), 26.0 (q), 25.7 (3q), 24.5 (3q), 23.2 (t), 18.2 (s), 18.1 (s), 17.5 (q), 16.0 (q), 11.6 (q), 11.1 (q), −4.0 (q), −4.5 (q), −5.5 (2q); EI MS *m*/*z* (relative intensity) 527 (M−*t*-Bu, 2), 469 (10), 411 (6), 377 (5), 337 (6), 317 (100), 301 (8), 259 (11), 225 (27), 185 (60), 147 (63), 122 (24), 89 (52), 73 (85); HRMS (CI^+, CH_4) calcd for $C_{32}H_{65}O_5Si_2$ ($M+H^+$): 585.4371, found 585.4370.

1.2.21. (4*R*, 6*S*, 7*S*, 8*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-1-((4*S*, 5*R*)-5-ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)-9-hydroxy-4,6,8-trimethylnon-1-en-3-one (+)-31. To a solution of (+)-**30** (0.100 g, 0.17 mmol, 1 equiv.) in dry THF (2 mL) at 0°C was added a freshly prepared solution of pyridinium hydrofluoride (0.8 mL) [solution prepared from commercially available HF.Py (0.5 mL), THF (2.5 mL) and pyridine (1 mL)]. The cooling bath was removed. After 7 h of stirring at rt, the reaction mixture was quenched by addition of aqueous saturated $NaHCO_3$ solution (1 mL), stirred for 15 min at rt and diluted with CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (hexanes/Et_2O: 80/20 to 50/50) afforded diol (+)-**31** (0.055 g, 0.12 mmol, 69% yield). R_f: 0.16 (hexanes/Et_2O: 70/30); $[\alpha]_D^{20}$=+27.3 (*c* 0.86, $CHCl_3$); IR (neat) 3460, 1690, 1630 $cm^{-1;}$ ^1H NMR ($CDCl_3$, 300 MHz) δ 6.80 (d, *J*=15.4 Hz, 1H), 6.44 (d, *J*=15.4 Hz, 1H), 3.82 (apparent t, *J*=6.6 Hz, 1H), 3.65–3.40 (m, 3H), 2.82 (m, 1H), 1.94–0.84 (m, 22H), 1.12 (d, *J*=7.0 Hz, 3H), 1.03 (t, *J*=7.4 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.5 (s), 154.5 (d), 126.9 (d), 107.9 (s), 85.9 (d), 81.8 (s), 76.2 (d), 66.3 (t), 42.4 (d), 38.3 (d), 36.3 (t), 35.4 (d), 28.0 (q), 26.3 (t), 25.9 (3q), 24.5 (q), 23.1 (t), 18.1 (s), 17.8 (q), 16.1 (q), 12.4 (q), 11.1 (q), −4.1 (q), −4.5 (q); EI MS *m*/*z* (relative intensity) 455 (M−Me, 1), 411 (7), 355 (8), 263 (23), 239 (12), 225 (13), 213 (16), 203 (100), 145 (33), 123 (51), 109 (52), 95 (46), 75 (97).

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