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Diastereocontrolled synthesis of unit A of cryptophycin

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Abstract—Cryptophycin fragment A was prepared in 11 steps from protected methyl (*R*)-mandelate **4**. A diastereoselective addition of magnesium acetylide to methyl mandelate and a Sharpless epoxidation followed by regioselective opening of the resulting epoxide allowed the synthesis of this intermediate in high diastereomeric purity.

1. Introduction

Cryptophycins are cytotoxic, macrocyclic depsipeptides isolated in 1990 from blue-green algae.[1,2] Cryptophycin 1 **1** has been shown by Moore and co-workers to be a potent in vivo tumor-selective cytotoxin (Fig. 1).[2,3] Moreover, it was not an effective substrate for the P-glycoprotein efflux mechanism in multiple-drug resistant cells.[4] It presents a broad spectrum of antitumor activity and its exceptional antiproliferative effects are believed to be derived from reversible high affinity binding to microtubules.[5]

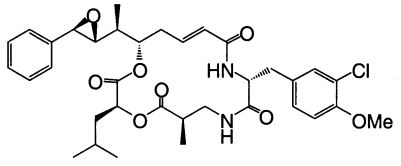
Following the first report on the synthesis of arenastatin (cryptophycin 24) in 1994[6] and cryptophycin 1 in 1995,[7] several syntheses of cryptophycin 1 itself or more stable analogues were reported.[8] A common strategy running through the majority of these syntheses has been the introduction of the epoxide pharmacophore in the last step of the synthesis by epoxidation of an ethylenic compound (cryptophycin 3). However, this reaction affords a 2:1 diastereoselectivity and necessitates a tedious HPLC separation for isolating the required major isomer. An alternative route using a Sharpless asymmetric dihydroxylation of the same compound was recently reported.[9]

This strategy allowed the preparation of a diol precursor of cryptophycin 1 with a good control of stereochemistry but in a rather moderate yield. However, it would be more efficient to introduce the diol moiety at the beginning of the synthesis. For this purpose, the protected triol **3** (Fig. 2) is a specially interesting synthon because, once incorporated in the final structure, it allows the access both to cryptophycin 1 **1** and to cryptophycin 8 **2** which contains a chlorhydrin unit[10] and shows an even better in vivo biological activity than cryptophycin 1 itself.[3,11]

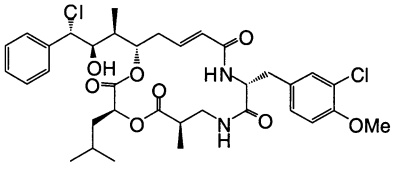
We wish to report here a method which allows the stereoselective synthesis of such a protected polyhydroxy unsaturated ester **3** with high enantiomerical purity by asymmetric epoxidation of an allylic alcohol derived from mandelic acid.

2. Results and discussion

We have previously reported that the condensation of a magnesium acetylide derived from a protected propargylic alcohol with the aluminium salt obtained by reaction at low temperature of Dibal-H with *O*-protected methyl mandelate



Cryptophycin 1 **1**



Cryptophycin 8 **2**

Figure 1.

Keywords: depsipeptide; diastereoselective epoxidation; polyol.

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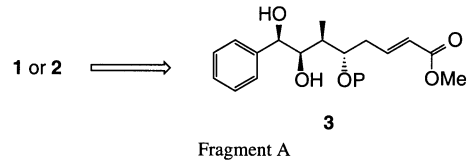
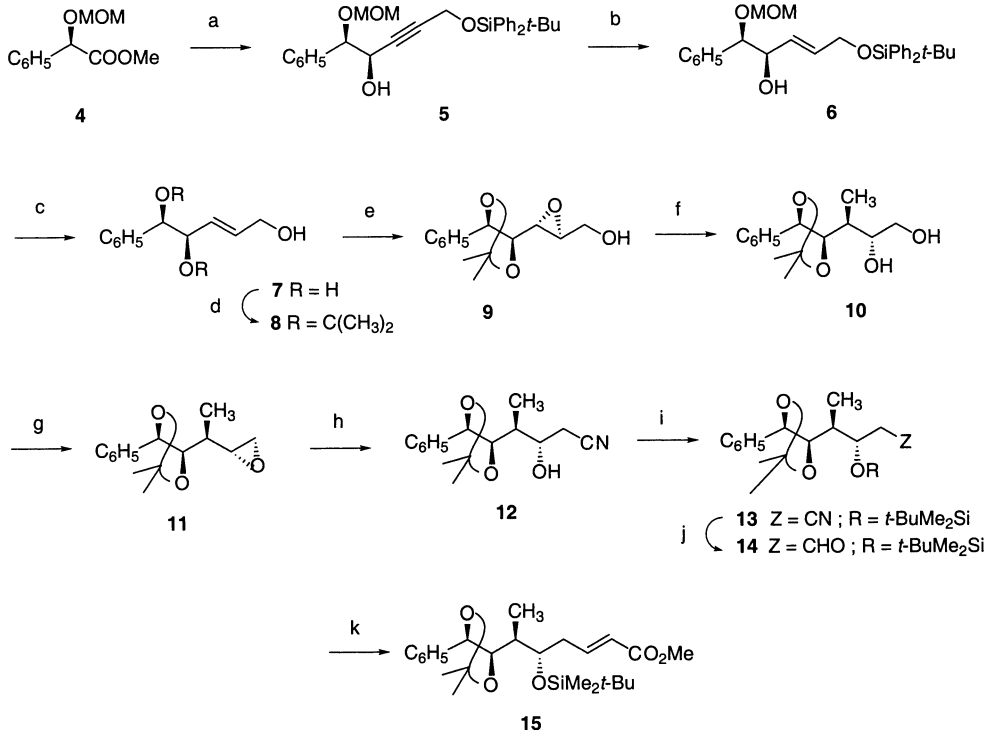


Figure 2.

4 allowed the obtention of the acetylenic protected triol **5** in high diasteomeric purity.[12] Further reduction of the triple bond under Denmark conditions[13] (Red-Al® at −20°C in order to prevent the O–Si bond cleavage) afforded the *E* allylic alcohol **6** stereospecifically. It appeared that such an allylic alcohol could be a good synthon for building the fragment A of cryptophycins. We envisaged introducing the methyl at position 3 via the regioselective opening of an epoxyalcohol of appropriate stereochemistry (in *anti* position vs diol moiety). Thus, we decided to investigate the epoxidation of **6**. We thought that the presence of a free hydroxy function would allow the obtention of the required *anti* epoxide stereoselectively. However, this secondary allylic alcohol was found unreactive towards the Sharpless epoxidation. Moreover, the reaction with *t*-butyl hydroperoxide in the presence of a catalytic amount of $VO(acac)_3$ afforded the required *anti* diastereomer in 40% diastereomeric excess only. As the opening reaction of this epoxide with dimethylcuprate was found very difficult probably because of steric hindrance, we decided to modify our strategy. In this order, compound **6** was completely deprotected in acidic medium and the resulting triol **7** was selectively reprotected as an acetonide to give the alcohol **8** (Scheme 1).

In contrast with the alcohol **6**, the alcohol **8** was easily epoxidised with *t*-butylhydroperoxide in the presence of (+)-diisopropyl L-tartrate to give as a 95:5 mixture of two diastereomers from which the compound **9** was isolated in 76% yield. This epoxide was then reacted with trimethylaluminium, a reagent which is known to favour the opening of 1-hydroxy-2,3-epoxides in 3 position[14] and we were pleased to isolate after hydrolysis, the 1-2 diol **10** exclusively. In order to access the unsaturated ester **15**, the aldehyde **14** was required. For this purpose, the diol **10** was converted to epoxide using the Sharpless conditions (trimethyl orthoacetate followed by trimethylsilyl chloride).[15] After cyclisation of the intermediate chlorhydrin with potassium carbonate, the resulting epoxide **11** was opened with potassium cyanide in the presence of lithium perchlorate[16] to give the hydroxy nitrile **12** (70% yield). This one was protected as a *t*-butyl-dimethylsilyl ether and the resulting nitrile **13** was reduced with DIBAL-H at low temperature to afford the aldehyde **14**. This intermediate was rather unstable and it was immediately reacted with trimethylphosphonoacetate in the presence of tetramethylguanidine as a base to give the required unsaturated ester **15** in 78% yield.

In conclusion, an efficient synthesis of cryptophycin unit A has been completed from mandelic acid. Introduction of the diol moiety in the benzylic position provides an efficient method for installing the epoxide pharmacophore.



Scheme 1. (a) Dibal-H hexane, −78°C then magnesium acetylide; (b) Red-Al®, Et_2O, −20°C, (c) 2 M HCl MeOH, 40°C; (d) acetone, $CuSO_4$, cat. APTS; (e) *t*-BuOOH, L-(+)-Diisopropyl-tartrate, $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2; (f) Me_3Al, hexane, rt; (g) $CH_3C(OMe)_3$, Me_3SiCl, CH_2Cl_2, 0°C, then K_2CO_3 MeOH, rt; (h) KCN, $LiClO_4$, CH_3CN, 70°C (i) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2; (j) Dibal-H toluene, −78°C; (k) trimethylphosphonoacetate, tetramethylguanidine, THF.

Experiments are currently underway for the total synthesis of cryptophycin 1 and analogues.

3. Experimental

3.1. General procedure

Products were purified by distillation or by medium pressure liquid chromatography on a Jobin–Yvon Modulprep (Kieselgel 60H Merck) or by flash chromatography (Kieselgel 60 Merck: 230–400 Mesh; solvent: cyclohexane/EtOAc) and analysed by GC (Chrompack BP5, 25 m capillary column) or by TLC (Merck silica gel 60F 254). Carbonated silica gel was obtained from Kieselgel Merck which was percolated with a 1 M aqueous solution of sodiumhydrogenocarbonate, washed with water until neutrality, then washed twice with methanol, dried and activated at 110°C for two days. NMR spectra were recorded on a Bruker AC at 200 MHz for ^{1}H- and 50 MHz for ^{13}C NMR or on a Bruker 400 Avance for ^{1}H. $CDCl_3$ was used as solvent with TMS as internal standard. IR spectra were recorded on a Perkin–Elmer 599 spectrophotometer. Mass spectra were recorded on a Ribermag R10-10C instrument at 70 eV ionising voltage; ammonia was used for chemical ionisation. Optical rotations were measured on a Jasco P-1010 polarimeter.

3.1.1. (1*R*,2*R*)-5-(*t*-Butyldiphenylsilyloxy)-1-methoxymethoxy-1-phenyl-pent-3-yn-2-ol (5). Compound **4** (3.15 g, 15 mmol) was dissolved in Et_2O/pentane (1:1, 60 mL) under an argon atmosphere, cooled to −78°C, and treated dropwise with 18 mL of DIBAL-H (1 M in hexanes). The mixture was stirred for 1 h before addition, through cannula, of a Grignard solution of magnesium acetylide, prepared as followed: an ethereal solution (30 mL) of protected propargyl alcohol (6.62 g, 22.5 mmol) was treated with 15.46 mL of *n*-BuLi (1.6 M in hexanes) at −20°C under an argon atmosphere; the mixture was stirred for 1 h at this temperature, warmed to 0°C, and recooled to −30°C; an ethereal magnesium bromide solution, obtained from magnesium (1.44 g, 60 mmol) and 1,2-dibromoethane (11.16 g, 60 mmol), was then cannulated and the reaction was allowed to reach 23°C, while stirring was continued overnight. The next day, the solution was cooled to −20°C and quenched by addition of a 10% HCl solution (30 mL) and diluted with water (50 mL). The organic extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) gave **5** (6.2 g, 87%) as an oil: $[\alpha]_D^{20}=-66$ (*c* 0.7, $CHCl_3$); IR (film) ν 3430 (br), 2955, 2930, 2890, 2860, 1425 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07 (s, 9H), 2.72 (d, *J*=5 Hz, 1H), 3.41 (s, 3H), 4.25–4.38 (m, 2H), 4.48–4.58 (m, 1H), 4.62–4.80 (m, 3H), 7.26–7.50 (m, 10H), 7.65–7.80 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.1, 26.6, 52.5, 55.8, 66.5, 80.8, 82.5, 84.9, 94.7, 127.6, 127.9, 128.2, 128.3, 129.7, 132.9, 135.6, 137.1; MS (CI, NH_3) *m/z* (relative intensity) 492 (M+NH_4^+, 22%), 198 (100%). Anal. Calcd for $C_{29}H_{34}SiO_4$: C, 73.38; H, 7.21. Found: C, 73.10; H, 7.29.

3.1.2. (1*R*,2*R*,3*E*)-5-(*t*-Butyldiphenylsilyloxy)-1-methoxymethoxy-1-phenyl-pent-3-ene-2-ol (6). In a four-necked, 500 mL, round-bottomed flask fitted with mechanical stirrer, thermometer, addition funnel, and argon inlet was placed the acetylenic alcohol **5** (4.75 g, 10 mmol) in 100 mL of anhydrous Et_2O. The solution was cooled to −25°C and treated via a syringe with a 3.2 M solution of bis(methoxyethoxy) aluminium hydride in toluene (4.8 mL, 15 mmol). The reaction, monitored by HPLC [column: Merck Lichrocart 250-4, 100RP-18.5 mm], was generally complete within 5 h. The solution was quenched by dropwise addition of 1 M H_2SO_4 (30 mL). The organic layer was separated and washed with H_2O (50 mL×2) and brine (50 mL). After drying ($MgSO_4$), the ethereal phase was concentrated under reduced pressure and the residual oil was chromatographed (cyclohexane/AcOEt 4:1) to afford the ethylenic compound **6** (3.43 g, 72%): $[\alpha]_D^{20}=-40.8$ (*c* 1.24, $CHCl_3$); IR (film) ν 3445, 2955, 2930, 2890, 2855, 1700, 1425 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (s, 9H), 3.16–3.24 (m, 1H), 3.48 (s, 3H), 4.18–4.52 (m, 3H), 4.58 (d, *J*=7.6 Hz, 1H), 4.71 (s, 2H), 5.71–6.01 (m, 2H), 7.33–7.56 (m, 10H), 7.65–7.82 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0, 26.6, 55.7, 63.3, 75.1, 82.3, 94.3, 126.8, 127.5, 127.8, 128.0, 128.2, 129.5, 131.2, 133.4, 135.3, 137.9; MS (CI, NH_3) *m/z* (relative intensity) 494 (M+NH_4^+, 18%), 342 (100%); Anal. Calcd for $C_{29}H_{36}SiO_4$: C, 73.07; H, 7.60. Found: C, 73.37; H, 7.75.

3.1.3. (1*R*,2*R*,3*E*)-1-Phenyl-pent-3-en-1,2,5-triol (7). Conc. HCl (0.2 mL) was added to a solution of **5** (7.2 g, 15 mmol) in methanol (50 mL) and stirred at 40°C for two days. Methanol was removed in vacuo and the residue was diluted in diethyl ether and washed with saturated aqueous $NaHCO_3$. After drying ($MgSO_4$), the ethereal phase was concentrated under reduced pressure and the residual oil was chromatographed (CH_2Cl_2/MeOH 9:1) to afford the triol **7** (2.7 g; 92%). $[\alpha]_D^{20}=+11.2$ (*c* 1.20, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.98 (m, 1H), 3.55–3.67 (m, 1H), 3.89–4.24 (m, 3H), 4.41–4.56 (m, 2H), 5.52 (dd, 1H, *J*=5.6, 15.7 Hz), 5.63–5.79 (m, 1H), 7.23–7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 62.1, 75.8, 77.1, 126.5, 126.9, 127.7, 128.1, 131.6, 132.3, 140.3; MS (CI, NH_3) *m/z* (relative intensity) 212 (M+NH_4^+, 100%), 194 (M, 4%).

3.1.4. (1*R*,2*R*,3*E*)-1,2-Di-*O*-isopropylidene-1-phenyl-pent-5-ene-1,3,5-triol (8). Anhydrous $CuSO_4$ (4.5 g, 28 mmol) and PTSA (30 mg) were added to a solution of **7** (2.7 g, 14 mmol) in acetone (100 mL). After stirring for two days at room temperature, acetone was evaporated in vacuo and the residue was dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). After concentration under reduced pressure 2.9 g of pure acetonide **8** was obtained as an oil (91%). $[\alpha]_D^{20}=+4.8$ (*c* 3.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.55 and 1.60 (2s, 2×3H), 2.46 (br s, 1H), 4.10 (br s, 2H), 4.25 (dd, 1H, *J*=5.6, 8.4 Hz), 4.69 (d, 1H, *J*=14.2 Hz), 5.74–5.88 (m, 2H), 7.32–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.9, 27.0, 62.5, 82.9, 83.6, 109.2, 126.4, 128.1, 128.4, 134.5, 136.7; MS (CI, NH_3) *m/z* (relative intensity) 252 (M+NH_4^+, 29%), 194 (100%). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.80; H, 7.74. Found: C, 71.56; H, 7.75.

3.1.5. (1*R*,2*R*,3*R*,4*R*)-1,2-Di-*O*-isopropylidene-3,4-epoxy-1-phenyl-pentan-1,2,5-triol (9). Ti(O-*i*-Pr)$_4$ (1.8 mL,

6 mmol) and L-(+)-diisopropyltartrate (1.3 mL, 6 mmol) were successively added to a −20°C cooled suspension of 4 Å molecular sieves (1.2 g) in CH_2Cl_2 (30 mL). After stirring for 10 min, a solution of the ethylenic compound **8** (1.00 g, 4.3 mmol) in CH_2Cl_2 (10 mL) was slowly added and stirred for 5 min at the same temperature. Anhydrous *t*-butylhydroperoxide (2 mL, 9 mmol) was then added and the resulting mixture was stirred for 4 days at −20°C. After hydrolysis with 2 M aqueous tartaric acid, the solution was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure; the residual oil was chromatographed (cyclohexane/AcOEt 6:4) to afford the epoxide **9** (812 mg, 76%): $[\alpha]_D^{20} = -33.4$ (*c* 1.90, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.55 and 1.58 (2s, 2×3H), 2.00 (s, 1H), 2.97–3.16 (m, 1H), 3.25–3.27 (dd, 1H, *J*=2.2, 5.1 Hz), 3.66–3.84 (m, 2H), 3.96 (dd, 1H, *J*=2.4, 10.4 Hz), 4.96 (d, 1H, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.6, 26.8, 54.5, 56.2, 60.8, 81.1, 81.6, 109.9, 126.5, 128.4, 137.4. MS (CI, NH_3) *m/z* (relative intensity) 268 ($M+NH_4^+$, 100%), 251 (15%). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.88; H, 7.19.

3.1.6. (1*R*,2*R*,3*S*,4*R*)-1,2-Di-*O*-isopropylidene-3-methyl-1-phenyl-pentan-1,2,4,5-tetrol (10). Compound **9** (550 mg, 2.2 mmol) was dissolved in a 5:1 mixture of hexane/CH_2Cl_2 (5 mL) and slowly added under an argon atmosphere to a solution of trimethylaluminium (6.6 mmol) in hexane (6 mL) cooled to −10°C. After one hour, the mixture was warmed up and stirred for 20 h at room temperature. After hydrolysis with 0.1 M aqueous tartaric acid, the reaction mixture was extracted with diethyl ether. The organic phase was washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure. After column chromatography on carbonated silica gel (cyclohexane/AcOEt 6:4), pure compound **10** was isolated as an oil (210 mg) in addition to 100 mg (18%) of the starting compound: 44% yield. $[\alpha]_D^{20} = -68.0$ (*c* 2.59, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (d, 3H, *J*=7.0 Hz), 1.52 and 1.58 (2s, 2×3H), 1.88–2.06 (m, 1H), 2.95 (br s, 1H), 3.45–3.55 (m, 1H), 3.87–3.92 (m, 1H), 4.09 (dd, 1H, *J*=2.2, 9.0 Hz), 4.83 (d, 1H, *J*=9.0 Hz), 7.35–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.1, 27.1, 30.1, 64.5, 74.6, 79.5, 83.1, 108.7, 126.7, 128.4, 128.5, 137.3; MS (CI, NH_3) *m/z* (relative intensity) 284 ($M+NH_4^+$, 100%), 267 (18%).

3.1.7. (1*R*,2*R*,3*S*,4*R*)-1,2-Di-*O*-isopropylidene-4,5-epoxy-3-methyl-1-phenyl-pentan-1,2-diol (11). Trimethylsilyl chloride (87 mg, 0.8 mmol) and trimethylorthoacetate (97 mg, 0.8 mmol) were added at 0°C to a solution of **10** (173 mg, 0.65 mmol) in CH_2Cl_2 (3 mL). The solution was stirred for one hour, concentrated under reduced pressure and dissolved in anhydrous methanol (5 mL). K_2CO_3 (225 mg, 1.6 mmol) was then added and the resulting suspension was vigorously stirred for 2 h before hydrolysis. The reaction mixture was extracted with diethyl ether and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 95:5 cyclohexane/AcOEt as eluent to give **11** as a colourless oil (105 mg, 65%). $[\alpha]_D^{20} = +10.9$ (*c* 2.57, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (d, 3H, *J*=7.0 Hz), 1.50 and 1.58 (2s, 2×3H), 1.55 (m, 1H), 2.47 (dd, 1H, *J*=2.6, 4.8 Hz), 2.74 (t, 1H, *J*=4.9 Hz), 2.80–2.88 (m, 1H), 4.04 (dd, 1H, *J*=4.0, 8.6 Hz), 4.84 (d, 1H, *J*=8.6 Hz), 7.29–7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.3, 26.8, 26.9, 37.0, 45.9, 57.3, 79.9, 83.8, 108.5, 126.7, 128.0, 128.2, 137.5; MS (CI, NH_3) *m/z* (relative intensity) 266 ($M+NH_4^+$, 100%), 249 (45%), 208 (90%). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.85; H, 8.19.

3.1.8. (2*S*,3*S*,4*R*,5*R*)-5-Cyano-1,2-di-*O*-isopropylidene-3-methyl-1-phenyl-pentan-1,2,4-triol (12). To a solution of epoxide **11** (124 mg, 0.5 mmol) in anhydrous acetonitrile (15 mL) was added anhydrous $LiClO_4$ (80 mg, 0.75 mmol) and KCN (49 mg, 0.75 mmol). The suspension was stirred at 70°C for 6 h and hydrolysed at room temperature with water. The reaction mixture was extracted with diethyl ether and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 7:3 cyclohexane/AcOEt as eluent to give **12** as a colorless oil (96 mg, 70% yield). $[\alpha]_D^{20} = -12.4$ (*c* 1.98, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, 3H, *J*=7.1 Hz), 1.51 and 1.58 (2d, 2×3H), 1.90–2.02 (m, 1H), 2.47 (dd, 1H, *J*=4.4, 16.8 Hz), 2.62 (dd, 1H, *J*=7.3, 16.8 Hz), 3.00 (d, 1H, *J*=6.1 Hz), 3.85–4.00 (m, 1H), 4.03 (dd, 1H, *J*=2.2, 8.8 Hz), 4.83 (d, 1H, *J*=8.9 Hz), 7.28–7.48 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.7, 23.7, 26.7, 27.1, 36.5, 70.7, 79.6, 82.4, 109.0, 117.8, 126.6, 128.6, 136.9; MS (CI, NH_3) *m/z* (relative intensity) 293 ($M+NH_4^+$, 100%), 276 (12%), 235 (95%). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.78; H, 7.68; N, 5.10. Found: C, 69.31; H, 8.03; N, 4.99.

3.1.9. (3*S*,4*S*,5*R*,6*R*)-3-*t*-Butyldimethylsilyloxy-5,6-di-*O*-isopropylidenedioxy-4-methyl-6-phenyl-hexanal (14). Under Argon, *t*-butyldimethylsilyltriflate (90 μL, 0.36 mmol) was added at 0°C to a solution of **12** (65 mg, 0.24 mmol) and 2,6-lutidine (60 μL, 5 mmol) in CH_2Cl_2 (5 mL). After stirring for 3 h, the reaction mixture was hydrolysed with water and the organic layer was extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 9:1 cyclohexane/AcOEt as eluent to give **13** (85 mg, 92% yield). This one was dissolved into anhydrous toluene (10 mL) and cooled to −78°C. 1 M DIBAL-H in toluene (450 μL, 0.45 mmol) was added and the resulting mixture was stirred for 2.5 h at the same temperature. The reaction was quenched with anhydrous methanol (0.8 mL) followed by 0.5N H_2SO_4 and vigorously stirred for 1 h. The reaction mixture was extracted with diethyl ether and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 92:8 cyclohexane/AcOEt as eluent to give **14** as an unstable compound (50 mg, 58%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.82 (s, 9H), 1.12 (d, 3H, *J*=7.0 Hz), 1.50 and 1.56 (2s, 2×3H), 1.80–1.92 (m, 1H), 2.46–2.55 (m, 2H), 3.86 (dd, 1H, *J*=2.4, 8.9 Hz), 4.07–4.15 (m, 1H), 4.70 (d, 1H, *J*=8.9 Hz), 7.29–7.39 (m, 5H), 9.75 (t, 1H, *J*=2.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.8, 7.8, 17.8, 25.6, 27.0, 27.1, 38.8, 47.3, 70.3, 80.5, 82.9, 108.9, 126.6, 128.3, 128.5, 137.6, 202.0.

3.1.10. (2*E*,5*S*,6*S*,7*R*,8*R*)-5-*t*-Butyldimethylsilyloxy-7,8-

di-*O*-isopropylidenedioxy-6-methyl-8-phenyl-octa-2-enoic acid methyl ester (15)Tetramethylguanidine (23 μL, 0.18 mmol) was added via a syringe to a stirred solution under argon at −78°C of aldehyde **13** (45 mg, 0.12 mmol) and trimethylphophonoacetate (33 mg, 0.18 mmol) in anhydrous THF (10 mL). Stirring was continued for 30 min at −78°C, then the solution was allowed to warm to room temperature for 4 h. The reaction was quenched with water (6 mL) and extracted with diethyl ether. The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 92:8 cyclohexane/AcOEt as eluent to give **15** (42 mg, 78%). $[\alpha]_D^{20} = +21.5$ (*c* 2.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ −0.04 and 0.03 (2s, 2×3H), 0.81 (s, 9H), 1.03 (d, 3H, *J*=6.9 Hz), 1.48 and 1.54 (2s, 2×3H), 1.72–1.76 (m, 1H), 2.23–2.32 (m, 2H), 3.62–3.68 (m, 1H), 3.73 (s, 3H), 3.95 (dd, 1H, *J*=2.7, 8.8 Hz), 4.66 (d, 1H, *J*=8.8 Hz), 5.68 (d, 1H, *J*=17.7 Hz), 6.82 (dt, 1H, *J*=7.0, 15.7 Hz), 7.26–7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.9, −0.1, 8.5, 17.8, 25.6, 26.8, 27.1, 36.3, 38.8, 51.2, 72.9, 80.7, 82.7, 108.7, 122.8, 126.8, 128.2, 128.5, 137.8, 146.1, 166.1; MS (CI, NH_3) *m/z* (relative intensity) 466 ($M+NH_4^+$, 100%). Anal. Calcd for $C_{25}H_{40}O_5Si$: C, 66.93; H, 8.98. Found: C, 67.09; H, 9.04.

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