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The Meinwald reaction of alkyl propionates. Synthesis of the C1–C9 fragment of aurisides

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Abstract—The C1–C9 northern fragment of aurisides **12a** was prepared in eight steps and 41% overall yield starting from Grieco's bicyclic lactone (+)-**4**. The synthesis features a key stereoselective Meinwald reaction of the lithium enolate of alkyl propionate with the functionalized δ-lactone **3**.

1. Introduction

Two marine natural products, aurisides A and B, were isolated in minute amounts from the Japanese sea hare *Dolabella auricularia* by Yamada and Kigoshi in 1996.[1] These halogenated macrolides showed potent cytotoxicity against HeLa S3 cell lines and large structural similarities to the macrolides isolated from the marine sponge Callipelta sp., callipeltosides A, B, and C.[2] Both aurisides and callipeltosides possess a rhamnose-derived glycoside attached to C5 of a 14-membered macrolactone. The macrocycle rings are bridged through a 6-membered hemiketal and possess a halogenated and unsaturated side-chain attached to C13. Yamada reported the first synthesis of the auriside aglycone in 1998.[3] Because of the small amounts isolated of these marine macrolides, their unique structure, and their interesting biological activity, we are engaged in a program toward their syntheses.[4,5]

In our synthetic strategy toward these marine macrolides, we proposed a general and highly convergent approach with main disconnections that provide two key intermediates as illustrated in Figure 1. We envision coupling of the northern fragment **1** with the southern fragment **2** via a chemoselective halogen–metal exchange of the vinylic iodide in **2** followed by condensation with the aldehyde moiety of fragment **1**. Further macrolactonization and allylic oxidation of the newly formed hydroxyl group should provide the auriside aglycone. We recently reported the stereoselective synthesis of the C10–C17 southern fragment **2**

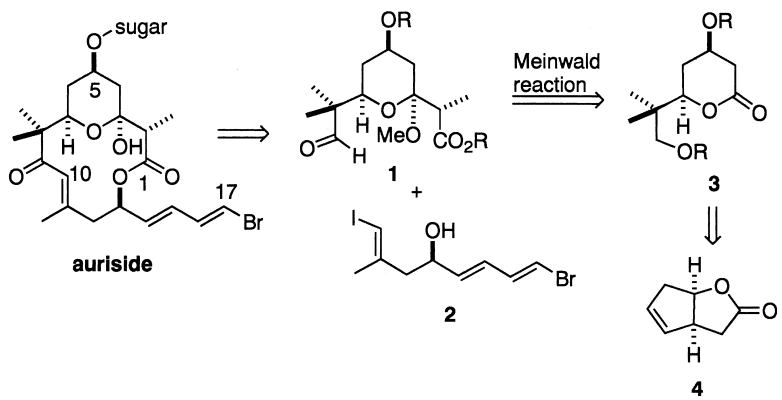

Figure 1. Retrosynthesis of the auriside aglycon.

Keywords: Meinwald reaction; alkyl propionates; aurisides.
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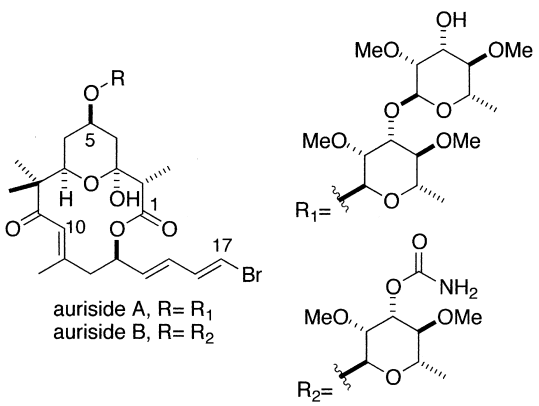
featuring a highly diastereoselective aldol condensation using a chiral *N*-acetyl 1,3-thiazolidine-2-thione.[5] In this article, we report the synthesis of the C1–C9 fragment of aurisides.



2. Discussion and results

Grieco's bicyclic lactone **4** is a valuable starting material for constructing functionalized δ-lactones.[6] We utilized bicyclic lactone **4** to efficiently construct the C1–C9 fragment of callipeltosides.[4a] Bicyclic lactone **4** can also be easily functionalized to provide δ-lactone **3** valuable for the synthesis of the northern fragment of aurisides. The Meinwald reaction, addition of the lithium enolate of ethyl acetate to a δ-lactone to give β-kemiketal esters,[7] has been employed in the synthesis of soraphen-A,[8] aplasmomycin-A,[9] elfemycins,[10] and by our group in the C1–C9 fragment of callipeltosides.[4a] For the synthesis of the C1–C9 fragment of aurisides, we envisioned a Meinwald reaction using a lithium enolate derived from an appropriate alkyl propionate to achieve stereocontrol in the formation of the C2 stereogenic center.

We began the synthesis of δ-lactone **3** starting from bicyclic lactone (+)-**4**, Fig. 2. Double methylation of bicyclic lactone **4** was accomplished in one flask in excellent yield. Stereoselective installation of the C5-hydroxyl group[11] was accomplished by oxymercuration–demercuration of lactone **5** delivering the *endo*-alcohol **6** in good yield. The *o*-bromobenzoate derivative **7** was prepared to confirm the structural assignments by X-ray single crystal analysis.[12] Protection of the hydroxyl group in **6** as the corresponding silylether followed by reduction with lithium aluminum hydride delivered diol **9**. Selective protection of the primary alcohol as the TBS ether gave cyclopentanol **10**. Cyclopentanol **10** was oxidized to cyclopentanone **11** using Ley's protocol in excellent yield.[13] Cyclopentanone **11** was subjected to Baeyer–Villiger oxidation to afford δ-lactone **3**.

Having δ-lactone **3** in hand, we investigated the Meinwald reaction using lithium enolates derived from alkyl propionates to form β-hemiketal esters, see Table 1. We observed that when LHMDS was used to generate the lithium enolates of alkyl propionates, only Claisen autocondensation products were isolated, and δ-lactone **3** was recovered unreacted.[14] However, when LDA was used to generate the corresponding enolates, and further addition to δ-lactone **3**, the desired β-hemiketal esters were obtained in good yields. Addition of the enolates occurred on the less hindered alpha-face of the δ-lactones giving initially the beta-hydroxy products. These intermediates tautomerized to the more stable anomeric hemiketals during the aqueous work-up.[15] The two epimeric products at C2 **12** and **13** were separated by column chromatography. We observed that the ratio of epimers on C2 changed during silica gel chromatography purification.[16] NOE experiments of the epimeric products to determine the configuration of C2 were not conclusive because of the free rotation of the propionate unit. Efforts to obtain crystals of compounds **12**, **13** and other derivatives were not successful. In contrast, a

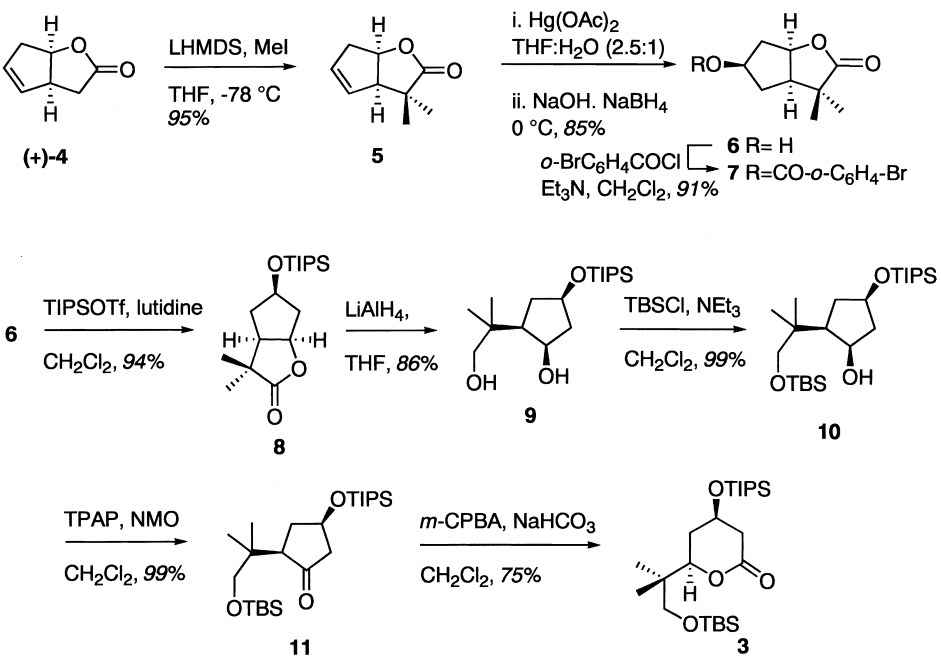
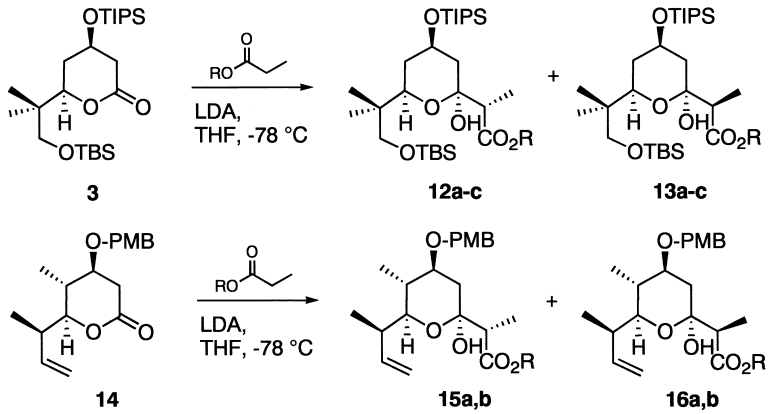


Figure 2. Preparation of δ-lactone **3**.

Table 1. The Meinwald reaction of δ-Lactones **3** and **14** with alkyl propionates



Entry	Lactone	R	Products	Diasterom. ratio	Yield (%)
1	**3**	Ethyl	**12a**:**13a**	4.4:1	85
2	**3**	Benzyl	**12b**:**13b**	3.3:1	82
3	**3**	*t*-butyl	**12c**:**13c**	1:2.3	99
4	**14**	Ethyl	**15a**:**16a**	5.4:1	65
5	**14**	Benzyl	**15b**:**16b**	4:1	90

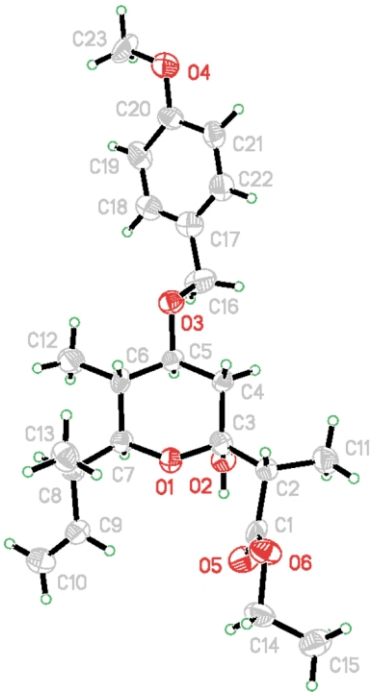


Figure 3. The X-ray crystal structure of **15a**.

crystalline product was formed in the Meinwald reaction in our synthesis of the C1–C9 fragment of callipeltosides.[4a] Thus, we expected that a Meinwald reaction of δ-lactone **14**, a key intermediate in our synthesis of callipeltosides, with the enolate of an alkyl propionate would deliver a hemiketal product that would be amenable for X-ray crystallographic analysis. Indeed, we were delighted to observe that a major crystalline product (**15a**) with the desired 2*S* configuration was formed as the major product in the addition of the ethyl propionate enolate to δ-lactone **14** (Fig. 3). Addition of the enolate of ethyl propionate to δ-lactone **3** gave hemiketal **12a** as the major product. Interestingly, we observed that addition of the enolate of *tert*-butyl propionate to δ-lactone **3** gave the C2 epimeric product **13c** preferentially.[16]

We noted that the H4 chemical shifts of the Meinwald products were valuable to assign the configuration at C2 (see Table 2).[17] The H4 equatorial hydrogen signal appeared down field in hemiketals with the 2*S* configuration (products **12** and **15**). Also, the difference in chemical shifts between the two H4 proton signals was larger for the (*S*)-C2 epimer ($\Delta\delta\sim1.0$ ppm) compared to the ones with the 2*R* configuration ($\Delta\delta\sim0.5$ ppm). Configuration of C2's were assigned to Meinwald products based on these observations.

3. Conclusions

In summary, we have efficiently prepared the C1–C9 fragment of aurisides from bicyclic lactone **4** in eight steps and more than 40% overall yield. Addition of the lithium enolate of ethyl propionate to δ-lactone **3** gave the β-hemiketal ester product with the functionality and stereochemistry required for the synthesis of aurisides. Efforts to couple the C1–C9 fragment with the C10–C17

Table 2. Comparison of ^{1}H NMR δ at C4 of Meinwald products

	Auriside-A	**12a**	**13a**	**15a**	**16a**
H-4a	1.03 td (*J*=11.7, 4.4)	1.23 ddd (*J*=12.2, 11.0, 2.7)	1.47 ddd (*J*=12.0, 10.7, 2.6)	1.16 m	1.57 m
H-4b	2.33 dd (*J*=11.7, 4.4)	2.33 ddd (*J*=12.0, 4.7, 1.5)	1.88 ddd (*J*=12.5, 4.7, 1.7)	2.40 dd (*J*=12.3, 4.6)	2.17 dd (*J*=12.0, 4.4)

fragment are currently undergoing in our laboratory and the synthesis of the auriside aglycon will be reported in due course.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded using Bruker AVANCE-300, WM-360 or AMX-400 spectrometers. Carbon multiplicities were determined using DEPT experiments. IR spectra were recorded using a Nicolet 210 spectrometer. Melting points were obtained in a Thomas Hoover melting point apparatus. Melting points reported here are uncorrected. Analytical TLC was performed using pre-coated silica gel 60 F_{254} Merck plates. Optical rotations were obtained using a Jasco P-1020 polarimeter.

4.1.1. (1*S*,5*R*)-4,4-Dimethyl-2-oxabicyclo[3.3.0]oct-6-en-3-one (5). LHMDS (1.0 M soln. in THF, 2.2 equiv., 33.48 mmol, 33.5 ml) was added by syringe over a period of 20 min to a well stirred solution of lactone **4** (15.22 mmol, 1.88 g) dissolved in dry THF and maintained at −78°C. After the addition was completed the reaction was stirred for further 90 min. Iodomethane (2.6 equiv., 39.57 mmol, 2.6 ml) was added by syringe over a period of 5 min to the enolate solution held at −60°C. Reaction was stirred at −60°C for 30 min and then at 0°C for 30 min. The reaction mixture was cooled to −78°C. LHMDS (soln. 1.0 M in THF, 1.1 equiv., 16.74 mmol, 16.75 ml) was added. After the addition was completed reaction was stirred for further 90 min. Methyliodide (1.3 equiv., 19.8 mmol, 1.3 ml) was added by syringe over a period of 5 min to the enolate solution held at −60°C. Reaction was stirred at −60°C for 30 min and then at 0°C for 30 min. The reaction mixture was diluted with diethyl ether (100 ml) and treated with sat. soln. NH_4Cl (60 ml). The organic phase was separated and the aqueous layer was extracted with diethyl ether (2×60 ml). Combined organic layers were washed with brine (2×40 ml) and with water (2×40 ml) and dried over Na_2SO_4. Solvent was removed under vacuum. The residue was purified by FCC and product was obtained as a yellow oil: 2.34 g (95% yield), TLC: R_f 0.3 (EtOAc–hexanes 1:4); $[\alpha]_D$=+61.7 (*c* 1.0, $CHCl_3$); IR: 2973, 2873, 1768, 1469, 1387, 1299, 1202, 1050, 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 5.81 (1H, dd, *J*=5.6, 2.3 Hz), 5.63 (1H, ddd, *J*=5.9, 4.2, 2.3 Hz), 5.06 (1H, ddd, *J*=5.9, 5.6, 3.5 Hz), 3.18 (1H, ddd, *J*=5.8, 3.7, 2.0 Hz), 2.68 (2H, bs), 1.36 (3H, s), 1.22 (3H, s); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 181.7 (C), 130.4 (CH), 128.6 (CH), 79.6 (CH), β (CH), 42.5 (C), 39.6 (CH_2), 26.9 (CH_3), 21.3 (CH_3).

4.1.2. 4,4-Dimethyl-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one (6). To a well stirred solution of mercuric diacetate (1.5 equiv., 22.7 mmol, 7.23 g) in THF/H_2O (2.5:1, 105 ml) cooled to 0°C (the solution acquired a yellow color and some perchloric acid was added dropwise until a colorless solution was obtained) was added a solution of lactone **11** (15.13 mmol, 2.3 g) in THF (7 ml). The reaction mixture was stirred at 0°C for 1 h. A solution of mercuric diacetate (0.5 equiv., 7.5 mmol, 2.4 g) in THF/H_2O (2.5:1, 35 ml) and perchloric acid were added dropwise. The reaction mixture was stirred at 0°C for 1 h. A solution of NaOH (5 ml) was added dropwise and the reaction mixture was stirred at rt for 30 min. The reaction mixture was cooled at 0°C and then $NaBH_4$ was added in small portions (the temperature should not above 0°C). The reaction was stirred at 0°C for 30 min. 1N HCl was added dropwise until pH 2 and then the reaction was stirred at 0°C for 30 min. The reaction mixture was saturated with NaCl. The organic phase was separated and the aqueous phase was extracted with AcOEt (3×30 ml). The aqueous phase was concentrated in rotary evaporator and extracted with AcOEt (3×15 ml). Combined organic phases were dried over Na_2SO_4 and filtered. Solvent was removed under vacuum to give an oil that was purified by FCC: 2.18 g (85% yield). Colorless oil, TLC: R_f 0.3 (EtOAc–hexanes 7:3); $[\alpha]_D$=+61.1 (*c* 1.0, $CHCl_3$); IR: 3447, 2971, 2935, 2863, 1752, 1455, 1383, 1342, 1198, 1081, 979 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 4.96 (1H, ddd, *J*=6.4, 5.2, 2.4 Hz), 4.37 (1H, q, *J*=4.8 Hz), 2.55 (1H, dt, *J*=8.8, 6.4 Hz), 2.10 (2H, m), 1.87 (2H, m, H-6), 1.31 (3H, s), 1.25 (3H, s); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 182.6 (C), 81.6 (CH), 72.7 (CH), 49.5 (CH), 43.3 (C), 41.2 (CH_2), 36.2 (CH_2), 27.8 (CH_3), 20.6 (CH_3).

4.1.3. 4,4-Dimethyl-7-(2′-bromobenzoyl)-2-oxabicyclo-[3.3.0]octan-3-one (7). To a well stirred solution of the alcohol **6** (0.2 mmol, 33.7 mg) in CH_2Cl_2 (5 ml) was added DMAP (cat.), 2-bromobenzoyl chloride (1.5 equiv., 0.3 mmol, 65 mg) and Et_3N (3.0 equiv., 0.3 mmol, 0.1 ml). The reaction mixture was stirred at rt for 2.5 h. Brine solution (5 ml) was added to the reaction mixture and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 ml). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC: 63.7 mg (91% yield). White crystals, TLC: R_f 0.33 (EtOAc–hexanes, 3:7); ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.78 (1H, dd, *J*=7.5, 1.5 Hz), 7.65 (1H, d, *J*=7.5 Hz), 7.41–7.20 (2H, m), 5.44 (1H, ddd, *J*=9.6, 5.5, 4.1 Hz), 5.02 (1H, dd, *J*=5.5, 5.5 Hz), 2.66 (1H, ddd, *J*=9.3, 6.5, 6.2 Hz), 2.37 (2H, m), 2.22 (1H, m), 2.05 (1H, m), 1.34 (3H, s), 1.22 (3H, s); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 181.6 (C), 165.6 (C), 134.5 (CH), 133.0 (CH), 131.7 (CH), 127.5 (CH), 127.3 (C), 122.0 (C), 81.2 (CH), 76.7 (CH), 49.8 (CH), 43.4 (CH_2), 38.8 (CH_2), 33.6 (CH_2), 27.7 (CH_3), 20.8 (CH_3). HRMS Calcd For $C_{16}H_{18}BrO_4$: 353.0395. Found: 353.0388.

4.1.4. 4,4-Dimethyl-7-(triisopropylsilyloxy)-2-oxabicyclo[3.3.0]octan-3-one (8). Anhydrous CH_2Cl_2 (60 ml) was placed under N_2 atmosphere and cooled to −50°C. TIPSOTf (1.5 equiv., 35.3 mmol, 9.5 ml) and 2,6-lutidine (1.5 equiv., 35.3 mmol, 4.2 ml) were added dropwise. Alcohol **7** (1.0 equiv., 23.5 mmol, 3.0 g) in anhydrous CH_2Cl_2 (20 ml) was added to the solution and the reaction was stirred at −50°C for 1 h. The reaction was treated with sat. $NaHCO_3$ soln. (50 ml). Organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×30 ml). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC: 5.4 g (94% yield). Colorless oil, TLC: R_f 0.3 (EtOAc–hexanes 15:85); $[\alpha]_D$=+35.2 (*c* 1.0, $CHCl_3$); IR: 2935, 2863, 1767, 1460, 1383, 1116, 1081, 1009, 881 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 4.81 (1H, ddd, *J*=6.8, 6.3, 2.0 Hz), 4.29 (1H, q, *J*=5.6 Hz), 2.40 (1H, dt, *J*=8.2, 6.8 Hz), 2.14 (1H, dt,

J=14.5, 6.9 Hz), 1.96 (1H, m), 1.84 (1H, m), 1.67 (1H, dt, J=14.0, 7.3 Hz), 1.21 (3H, s), 1.16 (3H, s); 0.98 (18H, s), 0.94 (3H, m); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 181.7 (C), 80.9 (CH), 73.6 (CH), 49.4 (CH), 43.1 (C), 41.8 (CH_2), 37.2 (CH_2), 27.5 (CH_3), 20.8 (CH_3), 18.1 ($6CH_3$), 12.2 (3CH). HRMS Calcd for $C_{18}H_{35}O_3Si$: 327.2355. Found: 327.2329.

4.1.5. 2-(2′-Hydroxy-1′,1′-dimethyl)-ethyl-4-triisopropylsilyloxy-cyclopentanol (9). To a well stirred solution of lactone **8** (1.0 equiv., 7.41 mmol, 2.417 g) dissolved in anhydrous THF (30 ml) and cooled to −20°C was added $LiAlH_4$ (1.0 equiv., 7.41 mmol, 281 mg) in small portions. The reaction mixture was stirred at −20°C for 30 min. MeOH (6 ml) was added to the reaction mixture and sat. sol. of Na_2SO_4 (10 ml) was also added. Reaction mixture was refluxed for 15 min and filtered through a bed of celite. Organic phase was concentrated under vacuum to give an oil that was purified by FCC: 2.08 g (86% yield). Colorless oil, TLC: R_f 0.3 (EtOAc–hexanes, 15:85); $[\alpha]_D$=−6.1 (c 1.0, $CHCl_3$); IR: 3273, 2945, 2868, 1465, 1362, 1112, 1009, 876 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 4.48 (1H, bt, J=5.8 Hz), 4.20 (1H, bd, J=3.3 Hz), 3.63 (1H, d, J=11.6 Hz), 3.12 (1H, d, J=11.6 Hz), 2.10 (1H, m), 1.89 (1H, m), 1.80 (1H, m), 1.73 (1H, m), 1.61 (1H, m), 1.21 (3H, s), 1.10 (3H, s,), 1.07 (18H, s), 1.02 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 74.0 (CH), 73.7 (CH), 68.0 (CH_2), 54.5 (CH), 44.6 (CH_2), 36.7 (C), 35.1 (CH_2), 26.8 (CH_3), 24.8 (CH_3), 17.9 ($6CH_3$), 11.8 (3CH). HRMS Calcd for $C_{18}H_{39}O_3Si$: 331.2668. Found: 331.2680.

4.1.6. 2-[2′-(*tert*-Butyldimethylsilyloxy)-1′,1′-dimethyl-ethyl]-4-triisopropylsilyloxy-cyclopentanol (10). To a well stirred solution of diol **9** (1.0 equiv., 1.17 mmol, 386.2 mg) in anhydrous CH_2Cl_2 (6 ml) at rt was added TBSCl (1.2 equiv., 1.4 mmol, 210 mg) and DMAP (0.2 equiv., 0.233 mmol, 27.6 mg). The reaction mixture was stirred and Et_3N (3.0 equiv., 3.51 mmol, 0.26 ml) was added dropwise. The reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with CH_2Cl_2 (20 ml) and treated with sat. $NaHCO_3$ soln. (10 ml). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 ml). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC: 517 mg (99% yield). Colorless oil, TLC: R_f 0.3 (EtOAc–hexanes 5:95); $[\alpha]_D$=−12.4 (c 1.0, $CHCl_3$); IR: 3518, 2950, 2868, 1465, 1357, 1091, 1004, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.40 (1H, m), 4.16 (1H, m), 3.43 (1H, d, J=9.6 Hz), 3.28 (1H, d, J=9.6 Hz), 1.95 (1H, m), 1.81 (1H, m), 1.75 (1H, m), 1.62 (1H, ddd, J=11.0, 8.8, 3.8 Hz), 1.38 (1H, m), 1.04 (18H, s), 1.03 (3H, s, CH), 0.98 (3H, s), 0.94 (3H, s), 0.87 (9H, s), 0.02 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 74.7 (CH), 74.0 (CH), 71.6 (CH_2), 51.4 (CH_2), 44.8 (CH_2), 37.0 (C), 35.3 (CH_2), 26.1 ($3CH_3$), 24.2 (CH_3), 23.9 (CH_3), 18.5 (C), 18.2 ($6CH_3$), 12.1 (3CH), −5.4 (CH_3), −4.2 (CH_3). HRMS Calcd for $C_{24}H_{53}O_3Si_2$: 445.3533. Found: 445.3539.

4.1.7. 2-[2′-(*tert*-Butyldimethylsilanyloxy)-1′,1′-dimethyl-ethyl]-4-triisopropylsilanyloxy-ciclopentanone (11). Alcohol **10** (1.0 equiv., 1.16 mmol, 517 mg) was dissolved in anhydrous CH_2Cl_2 (6 ml). Molecular sieves were added and the solution was stirred at rt. NMO (2.0 equiv., 2.33 mmol, 272.5 mg) and TPAP (0.1 equiv., 0.116 mmol, 40.86 mg) were added and the reaction mixture was stirred at rt for 24 h. Reaction mixture was filtered through celite and concentrated. The residue was purified by FCC: 508.2 mg (99% yield). Colorless oil, TLC: R_f 0.3 (EtOAc–hexanes 5:95); $[\alpha]_D$=+89.9 (c 1.0, $CHCl_3$); IR: 2945, 2863, 1742, 1470, 1358, 1250, 1112, 840, 774, 687 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.31 (1H, m), 3.43 (1H, d, J=9.8 Hz), 3.31 (1H, d, J=9.8 Hz), 2.56 (1H, dd, J=17.6, 7.0 Hz), 2.29 (1H, m), 2.22 (1H, m), 2.17 (1H, m), 1.76 (1H, m), 1.04 (18H, s), 1.03 (3H, s), 0.98 (3H, s), 0.86 (9H, s), 0.85 (3H, s), 0.00 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 216.8 (C), 70.7 (CH_2), 68.0 (CH), 54.3 (CH_2), 50.6 (CH), 37.7 (C), 36.1 (CH_2), 26.1 ($3CH_3$), 22.7 (CH_3), 22.2 (CH_3), 18.4 ($6CH_3$), 18.1 (C), 12.3 (3CH), −5.4 (CH_3), −5.4 (CH_3). HRMS Calcd For $C_{24}H_{51}O_3Si_2$: 443.3377. Found: 443.3377.

4.1.8. 6-[2′-(*tert*-Butyldimethylsilanyloxy)-1′,1′-dimethyl-ethyl]-4-triisopropylsilanyloxy-tetrahydropyran-2-one (3). Ketone **11** was dissolved in freshly distilled CH_2Cl_2 (10 ml). *m*CPBA (2.0 equiv., 2.33 mmol, 272.5 mg) and $NaHCO_3$ (2.0 equiv., 2.33 mmol, 272.5 mg) were added in small portions. The reaction was stirred at rt for 24 h. The reaction mixture was treated with sat. sol. $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 ml). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC: 395.8 mg (75% yield). Colorless oil, TLC: R_f 0.3 (EtOAc–hexanes 5:95); $[\alpha]_D$=−3.3 (c 1.0, $CHCl_3$); IR: 2955, 2868, 1736, 1475, 1465, 1244, 1091, 835, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 4.19 (1H, dddd, J=9.2, 8.3, 6.0, 5.5 Hz, H-4″), 4.11 (1H, dd, J=12.1, 2.9 Hz, H-6″), 3.44 (1H, d, J=9.8 Hz), 3.33 (1H, d, J=9.8 Hz), 2.83 (1H, ddd, J=17.1, 6.0, 1.5 Hz), 2.41 (1H, dd, J=17.1, 8.1 Hz), 2.13 (1H, dddd, J=13.5, 5.5, 3.0, 1.5 Hz), 1.60 (1H, ddd, J=13.5, 12.1, 9.2 Hz), 1.02 (18H, s), 1.02 (3H, s), 0.93 (3H, s), 0.85 (9H, s), 0.84 (3H, s), 0.01 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.9 (C), 80.3 (CH), 68.8 (CH_2), 65.0 (CH), 40.4 (CH_2), 38.9 (CH_2), 33.6 (C), 25.8 ($3CH_3$), 19.9 (CH_3), 18.1 (CH_3), 17.9 ($6CH_3$), 17.7 (C), 12.1 (3CH), −5.7 ($2CH_3$). HRMS Calcd for $C_{24}H_{51}O_4Si_2$: 459.3326. Found: 459.3323.

4.2. General procedure for the Meinwald addition of lithium enolates of alkyl propionates to δ-lactones

n-BuLi (0.869 mmol sol. 1.19 M, 0.73 ml) was added to a solution of diisopropylamine (0.910 mmol, 92.1 mg, 0.127 ml) in anhydrous THF (3 ml) at 0°C. The mixture was stirred at 0°C for 20 min and then cooled to −78°C. Alkyl propionate (2.0 equiv., 0.828 mmol) in THF (1 ml) was added over a period of 15 min. (syringe pump). The mixture was kept at −78°C and stirred for 30 min. followed by addition of δ-lactone (0.474 mmol) dissolved in THF (2 ml) over a period of 10 min. (syringe pump). The reaction mixture was stirred at −78°C for 1 h. Reaction was quenched at −78°C by addition of sat. NH_4Cl soln. (7 ml). The mixture was diluted with water (7 ml) and Et_2O (30 ml). Layers were separated and the aqueous layer was extracted with Et_2O (3×20 ml). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by FCC on silica gel.

4.2.1. 2*S*-Methyl-2-[6′*R*-[(1″,1″-dimethyl-2″-*tert*-butyl-dimethylsilyloxy)-eth-1′-yl]-4′*R*-triisopropylsilyloxy-2′*S*-hydroxy-tetrahydropyran-2′-yl]-propionic acid ethyl ester (12a). Colorless oil, TLC: R_f 0.35 (EtOAc–hexanes 5:95); $[\alpha]_D=-9.2$ (*c* 1.0, $CHCl_3$); IR: 3472, 2950, 2889, 2858, 1711, 1465, 1378, 1250, 1091, 855, 830, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.24 (1H, d, *J*=2.5 Hz), 4.12 (2H, q, *J*=7.1 Hz), 4.12 (1H, m), 3.70 (1H, dd, *J*=12.0, 1.7 Hz), 3.27 (1H, d, *J*=9.4 Hz), 3.22 (1H, d, *J*=9.4 Hz), 2.57 (1H, q, *J*=7.3 Hz), 2.09 (1H, ddd, *J*=12.0, 4.7, 1.5 Hz), 1.85 (1H, ddd, *J*=12.0, 4.7, 2.3 Hz), 1.25 (3H, t, *J*=7.0 Hz), 1.21 (1H, m), 1.18 (3H, d, *J*=7.3 Hz), 1.07 (1H, m), 1.04 (18H, s), 1.03 (3H, m), 0.86 (9H, s), 0.79 (3H, s), 0.75 (3H, s), −0.013 (3H, s), −0.021 (3H, s); ^1H NMR (C_6D_6, 360 MHz): δ 4.84 (1H, d, *J*=2.6 Hz), 4.48 (1H, m), 4.15 (1H, dd, *J*=12.0, 1.7 Hz), 4.11 (1H, dq, *J*=10.6, 7.1 Hz), 3.95 (1H, dq, *J*=10.6, 7.1 Hz), 3.48 (1H, d, *J*=9.2 Hz), 3.44 (1H, d, *J*=9.2 Hz), 2.65 (1H, q, *J*=7.2 Hz), 2.38 (1H, ddd, *J*=12.1, 4.6, 1.4 Hz), 2.16 (1H, ddd, *J*=12.1, 4.4, 1.6 Hz), 1.57 (1H, ddd, *J*=12.1, 12.2, 11.0 Hz), 1.23 (1H, ddd, *J*=12.2, 11.0, 2.7 Hz), 1.19 (3H, m), 1.17 (18H, s), 1.15 (3H, d, *J*=7.3 Hz), 1.04 (3H, s), 1.02 (9H, s), 1.00 (3H, t, *J*=7.2 Hz), 0.98 (3H, s), 0.13 (3H, s), 0.11 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.8 (C), 98.5 (C), 72.4 (CH), 69.4 (CH_2), 66.5 (CH), 60.7 (CH_2), 48.7 (CH), 42.1 (CH_2), 38.6 (C), 35.8 (CH_2), 26.1 ($3CH_3$), 20.7 (CH_3), 20.5 (CH_3), 18.4 ($6CH_3$), 18.3 (C), 14.4 (CH_3), 12.7 (CH_3), 12.5 (3CH), −5.4 (CH_3), −5.5 (CH_3).

4.2.2. 2*S*-Methyl-2-[6′*R*-[(1″,1″-dimethyl-2″-*tert*-butyl-dimethylsilyloxy)-eth-1′-yl]-4′*R*-triisopropylsilyloxy-2′*S*-hydroxy-tetrahydropyran-2′-yl]-propionic acid benzyl ester (12b). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37 (5H, m), 5.16 (1H, d, *J*=12.3 Hz), 5.13 (1H, d, *J*=12.2 Hz), 4.20 (1H, d, *J*=2.7 Hz), 4.17 (1H, m), 3.77 (1H, dd, *J*=12.0, 1.8 Hz), 3.30 (1H, d, *J*=9.5 Hz), 3.25 (1H, d, *J*=9.5 Hz), 2.70 (1H, q, *J*=7.3 Hz), 2.15 (1H, ddd, *J*=12.2, 4.7, 1.5 Hz), 1.89 (1H, ddt, *J*=12.2, 4.6, 1.7 Hz), 1.28 (1H, m), 1.24 (3H, d, *J*=7.2 Hz), 1.10 (1H, m), 1.08 (18H), 1.07 (3H, s), 0.90 (9H, s), 0.81 (3H, s), 0.77 (3H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.6 (C), 135.7 (C), 128.8 (2CH), 128.5 (CH), 128.3 (2CH), 98.6 (C), 72.4 (CH), 69.3 (CH_2), 66.6 (CH_2), 66.5 (CH), 48.8 (CH), 42.0 (CH_2), 38.5 (C), 35.8 (CH_2), 26.1 ($3CH_3$), 20.7 (CH_3), 20.6 (CH_3), 18.4 (C), 18.3 ($6CH_3$), 12.8 (CH_3), 12.5 (3CH), −5.4 (CH_3), −5.4 (CH_3).

4.2.3. 2*S*-Methyl-2-[6′*R*-[(1″,1″-dimethyl-2″-*tert*-butyl-dimethylsilyloxy)-eth-1′-yl]-4′*R*-triisopropylsilyloxy-2′*S*-hydroxy-tetrahydropyran-2′-yl]-propionic acid *tert*-butyl ester (12c). Colorless oil, TLC: R_f 0.35 (EtOAc–hexanes 5:95); $[\alpha]_D=-12.0$ (*c* 1.0, $CHCl_3$); IR: 3452, 2960, 2893, 2868, 1710, 1465, 1368, 1255, 1214, 1142, 1091, 845, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.53 (1H, d, *J*=2.6 Hz), 4.12 (H, m), 3.72 (1H, dd, *J*=12.0, 1.8 Hz), 3.31 (1H, d, *J*=9.3 Hz), 3.25 (1H, d, *J*=9.3 Hz), 2.44 (1H, q, *J*=7.2 Hz, H-2), 2.07 (1H, ddd, *J*=12.2, 4.8, 1.5 Hz), 1.85 (1H, m), 1.44 (9H, s), 1.21 (1H, dt, *J*=12.1, 11.0 Hz), 1.16 (3H, d, *J*=7.3 Hz), 1.04 (18H, s), 1.03 (3H, m), 1.01 (1H, m), 0.86 (9H, s), 0.82 (3H, s), 0.76 (3H, s), −0.010 (3H, s), −0.020 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.3 (C), 98.7 (C), 81.2 (C), 72.4 (CH), 69.3 (CH), 66.5 (CH_2), 49.2 (CH), 42.2 (CH_2), 38.6 (C), 35.9 (CH_2), 28.3 ($3CH_3$), 26.1 ($3CH_3$), 20.8 (C), 20.7 (C), 18.4 ($6CH_3$), 18.3 (C), 13.0 (C), 12.5 (CH), −5.3 (CH_3), −5.4 (CH_3).

4.2.4. 2*R*-Methyl-2-[6′*R*-[(1″,1″-dimethyl-2″-*tert*-butyl-dimethylsilyloxy)-eth-1′-yl]-4′*R*-triisopropylsilyloxy-2′*S*-hydroxy-tetrahydropyran-2′-yl]-propionic acid ethyl ester (13a). Colorless oil, TLC: R_f 0.38 (EtOAc-hexanes 5:95); $[\alpha]_D=-21.6$ (*c* 1.0, $CHCl_3$); IR: 3534, 3447, 2945, 2894, 2863, 1736, 1705, 1465, 1388, 1255, 1091, 855, 830, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.26 (1H, d, *J*=2.6 Hz), 4.19 (H, m), 4.14 (2H, q, *J*=7.0 Hz), 3.71 (1H, dd, *J*=12.0, 1.7 Hz), 3.30 (1H, d, *J*=9.4 Hz), 3.25 (1H, d, *J*=9.4 Hz), 2.60 (1H, q, *J*=7.3 Hz), 1.88 (1H, ddd, *J*=12.5, 4.7, 1.7 Hz), 1.84 (1H, ddd, *J*=12.5, 4.3, 1.7 Hz), 1.47 (1H, ddd, *J*=12.0, 10.7, 2.6 Hz), 1.25 (3H, t, *J*=7.0 Hz), 1.20 (3H, d, *J*=7.3 Hz), 1.19 (1H, m), 1.04 (18H, s), 1.03 (3H, m), 0.86 (9H, s), 0.80 (3H, s), 0.75 (3H, s), −0.014 (3H, s), −0.017 (3H, s); ^1HNMR (C_6D_6, 360 MHz): δ 4.80 (1H, d, *J*=2.4 Hz), 4.58 (H, m), 4.10 (1H, dd, *J*=12.3, 1.7 Hz), 3.95 (1H, dq, *J*=10.3, 7.0 Hz), 3.94 (1H, dq, *J*=10.3, 7.0 Hz), 3.44 (4H, s), 2.51 (1H, q, *J*=7.2 Hz), 2.17 (1H, ddd, *J*=12.2, 4.6, 1.4 Hz), 2.13 (1H, ddd, *J*=11.0, 4.0, 1.6 Hz), 1.73 (1H, ddd, *J*=12.2, 11.0, 2.4 Hz), 1.51 (1H, ddd, *J*=12.0, 12.0, 11.0 Hz), 1.20 (3H, m), 1.18 (18H, s), 1.16 (3H, d, *J*=7.3 Hz), 1.02 (3H, s), 1.09 (9H, s), 0.96 (3H, t, *J*=7.2 Hz), 0.10 (3H, s), 0.04 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.4 (C), 98.3 (C), 72.5 (CH), 69.4 (CH_2), 66.5 (CH), 61.0 (CH_2), 49.5 (CH), 41.6 (CH_2), 38.8 (C), 35.6 (CH_2), 26.1 ($3CH_3$), 20.6 (CH_3), 20.5 (CH_3), 18.4 ($6CH_3$), 18.3 (C), 14.4 (CH_3), 12.5 (3CH), 11.9 (CH_3), −5.4 (CH_3), −5.4 (CH_3).

4.2.5. 2*R*-Methyl-2-[6′*R*-[(1″,1″-dimethyl-2″-*tert*-butyl-dimethylsilyloxy)-eth-1′-yl]-4′*R*-triisopropylsilyloxy-2′*S*-hydroxy-tetrahydropyran-2′-yl]-propionic acid *tert*-butyl ester (13c). Colorless oil, TLC: R_f 0.38 (EtOAc–hexanes 5:95); $[\alpha]_D=-21.6$ (*c* 1.0, $CHCl_3$); IR: 3426, 2950, 2888, 2863, 1731, 1705, 1460, 1388, 1362, 1250, 1163, 1091, 845, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 4.41 (1H, d, *J*=2.2 Hz), 4.16 (1H, m), 3.72 (1H, dd, *J*=12.0, 1.9 Hz), 3.34 (1H, d, *J*=9.3 Hz), 3.27 (1H, d, *J*=9.3 Hz), 2.51 (1H, q, *J*=7.2 Hz), 1.84 (1H, dd, *J*=12.2, 4.8 Hz), 1.82 (1H, m), 1.44 (9H, s), 1.23 (1H, m), 1.21 (1H, m), 1.16 (3H, d, *J*=7.3 Hz), 1.04 (18H, s), 1.03 (3H, m), 0.86 (9H, s), 0.83 (3H, s), 0.77 (3H, s), −0.014 (6H, s); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 173.6 (C), 98.2 (C), 81.6 (C), 72.6 (CH), 69.5 (CH), 66.5 (CH_2), 50.0 (CH), 42.3 (CH_2), 38.9 (C), 35.7 (CH_2), 28.3 ($3CH_3$), 26.1 ($3CH_3$), 20.8 (CH_3), 20.7 (CH_3), 18.5 (C), 18.3 ($6CH_3$), 12.5 (3CH), 12.1 (C), −5.3 (CH_3), −5.4 (CH_3).

4.2.6. 2*S*-Methyl-2-[(2′*S*,4′*S*,5′*R*,6′*S*)-6′-[(1″*R*-methyl)-prop-2″-en-1″-yl)-5′-methyl-4′-(4-methoxybenzyloxy)-2′-hydroxy-tetrahydropyran-2′-yl]-propionic acid ethyl ester (15a). TLC: R_f 0.47 (EtOAc–hexanes 1:4); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.29 (1H, d, *J*=7.9 Hz), 6.89 (1H, d, *J*=8.7 Hz), 5.78 (1H, ddd, *J*=17.4, 10.4, 7.1 Hz), 4.94 (1H, m), 4.93 (1H, m), 4.59 (1H, d, *J*=10.8 Hz), 4.42 (1H, d, *J*=2.6 Hz), 4.38 (1H, d, *J*=10.8 Hz), 4.16 (2H, m), 3.81 (3H, s), 3.63 (1H, dd, *J*=10.5, 2.2 Hz), 3.50 (1H, ddd, *J*=10.7, 10.4, 4.7 Hz), 2.64 (1H, q, *J*=7.5 Hz), 2.40 (1H, dd, *J*=12.3, 4.6 Hz), 1.57 (1H, m), 1.29 (3H, t, *J*=7.0 Hz), 1.24 (3H, d, *J*=7.3 Hz), 1.16 (1H, m), 0.97 (3H, d, *J*=6.5 Hz), 0.93 (3H, d, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.8 (C), 159.3 (C), 143.2 (CH), 131.0 (C), 129.5 (2CH),

114.0 (2CH), 113.0 (CH_2), 98.3 (C), 77.6 (CH), 76.3 (CH), 71.1 (CH_2), 60.9 (CH_2), 55.5 (CH_3), 48.6 (CH), 39.0 (CH), 37.9 (CH), 37.7 (CH_2), 14.3 (CH_3), 12.7 (CH_3), 12.6 (CH_3), 12.0 (CH_3).

4.2.7. 2*S*-Methyl-2-[(2′*S*,4′*S*,5′*R*,6′*S*)-6′-[(1″*R*-methyl)-prop-2″-en-1″-yl)-5′-methyl-4′-(4-methoxybenzyloxy)-2′-hydroxy-tetrahydropyran-2′-yl]-propionic acid benzyl ester (15b). TLC: R_f 0.49 (EtOAc–hexanes 1:4); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (5H, m), 7.27 (2H, d, J=8.5 Hz), 6.87 (2H, d, J=8.5 Hz), 5.70 (1H, ddd, J=17.4, 10.3, 7.1 Hz), 5.14 (1H, m), 5.12 (1H, d, J=5.7 Hz), 4.96–4.86 (2H, m), 4.57 (1H, d, J=10.9 Hz), 4.36 (1H, d, J=10.9 Hz), 4.32 (1H, d, J=2.5 Hz), 3.79 (3H, s), 3.61 (1H, dd, J=10.7, 2.3 Hz), 3.48 (1H, dd, J=10.7, 10.4, 4.8 Hz), 2.71 (1H, q, J=7.3 Hz), 2.39 (1H, m), 2.37 (1H, m), 1.54 (1H, m), 1.24 (3H, d, J=7.3 Hz), 1.14 (1H, ddd, J=12.1, 11.0, 2.8 Hz), 0.94 (3H, d, J=6.7 Hz), 0.89 (3H, d, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.5 (C), 159.3 (C), 143.2 (CH), 135.6 (C), 130.9 (C), 129.6 (2CH), 128.8 (CH), 128.5 (2CH), 114.0 (2CH), 113.1 (C), 98.3 (C), 76.4 (CH), 71.1 (CH_2), 66.8 (CH_2), 55.5 (CH_3), 48.7 (CH), 39.0 (CH), 37.9 (CH), 37.7 (CH_2), 12.8 (CH_3), 12.5 (CH_3), 12.1 (CH_3).

4.2.8. 2*R*-Methyl-2-[(2′*S*,4′*S*,5′*R*,6′*S*)-6′-[(1″*R*-methyl)-prop-2″-en-1″-yl)-5′-methyl-4′-(4-methoxybenzyloxy)-2′-hydroxy-tetrahydropyran-2′-yl]-propionic acid ethyl ester (16a). TLC: R_f 0.35 (EtOAc–hexanes, 1:4); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (1H, d, J=7.9 Hz), 6.89 (1H, d, J=8.7 Hz), 5.83 (1H, ddd, J=17.4, 10.4, 7.1 Hz), 4.98 (1H, dt, J=17.3, 1.4 Hz), 4.92 (1H, d, J=10.1 Hz), 4.58 (1H, d, J=10.1 Hz), 4.39 (1H, d, J=11.0 Hz), 4.19 (2H, q, J=7.1 Hz), 3.80 (3H, s), 3.62 (1H, dd, J=10.5, 2.2 Hz), 3.56 (1H, ddd, J=10.9, 10.5, 4.6 Hz), 2.66 (1H, q, J=6.9 Hz), 2.41 (1H, m), 2.17 (1H, dd, J=12.0, 4.4 Hz), 1.57 (1H, m), 1.53 (1H, m), 1.30 (3H, t, J=6.9 Hz), 1.24 (3H, d, J=7.2 Hz), 0.97 (3H, d, J=6.5 Hz), 0.94 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.4 (C), 159.3 (C), 143.3 (CH), 131.0 (C), 129.6 (2CH), 113.0 (CH_2), 98.1 (C), 77.6 (CH), 76.6 (CH), 71.0 (CH_2), 61.2 (CH_2), 55.5 (CH_3), 49.4 (CH_2), 38.7 (CH), 38.1 (CH), 37.3 (CH_2), 14.3 (CH_3), 12.6 (CH_3), 12.1 (CH_3), 11.8 (CH_3).

4.2.9. C2*R*-Methyl-2-[(2′*S*,4′*S*,5′*R*,6′*S*)-6′-[(1″*R*-methyl)-prop-2″-en-1″-yl)-5′-methyl-4′-(4-methoxybenzyloxy)-2′-hydroxy-tetrahydropyran-2′-yl]-propionic acid benzyl ester (16b). TLC: R_f 0.27 (EtOAc–hexanes, 1:4); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (5H, bs), 7.27 (2H, d, J=8.8 Hz), 6.88 (2H, d, J=8.7 Hz), 5.79 (1H, ddd, J=17.4, 10.2, 7.1 Hz), 5.14 (1H, m), 5.15 (1H, d, J=2.3 Hz), 4.92 (2H, m), 4.55 (1H, d, J=10.7 Hz), 4.36 (1H, d, J=10.7 Hz), 4.34 (1H, m), 3.81 (3H, s), 3.61 (1H, dd, J=10.6, 2.1 Hz), 3.54 (1H, ddd, J=10.7, 10.7, 4.5 Hz), 2.73 (1H, q, J=7.1 Hz), 2.40 (1H, m), 2.15 (1H, dd, J=12.1, 4.5 Hz), 1.59 (1H, m), 1.53 (1H, m), 1.27 (3H, d, J=7.1 Hz), 0.96 (3H, d, J=6.4 Hz), 0.92 (3H, d, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.2 (C), 159.4 (C), 143.2 (CH), 135.7 (C), 131.0 (C), 129.6 (2CH), 128.8 (2CH), 128.5 (CH), 128.3 (2CH), 114.0 (2CH), 113.2 (C), 98.1 (C), 77.5 (CH), 71.0 (CH_2), 67.0 (CH_2), 55.5 (CH_3), 49.6 (CH), 38.7 (CH), 38.2 (CH), 37.3 (CH_2), 12.6 (CH_3), 12.1 (CH_3), 11.9 (CH_3).

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