Synthesis of Acetomycin Bislactone Analogues

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Dedicated to Prof. Mukaiyama on the occasion of his 77th birthday

Abstract: Bislactones **5** and **6** have been designed as esterase-resistant acetomycin analogues and prepared in 10 steps from methyl 2-methylacetoacetate. Consecutive quaternary and tertiary carbon centers at the C-3 and C-4 positions on the γ-lactone ring are constructed by Pd-catalyzed allylic alkylation in one step. The relative stereochemistry for **6** has been determined by X-ray crystallographic analysis.

Key word: bioorganic chemistry, palladium, esterase, stereoselective synthesis, γ-lactone

Introduction

Acetomycin (**1**) was isolated from *Streptomyces ramulosus sp.* in 1958 by Prelog et al.[1] The three-dimensional structures of the brominated derivative,[2] as well as that of acetomycin itself,[3] were determined by X-ray crystallographic analysis. Initially, only a weak antibacterial activity was known,[4] but Mamber et al. showed in 1987 that acetomycin possessed unique *anti*-cancer activity against L-1210 murine leukemia cells and HCT-8 human colon adenocarcinoma cells.[5] Although acetomycin has potent *anti*-cancer activity, it is not a useful medicine due to the rapid hydrolysis by esterase present in tissues.[6] We have been making efforts to design esterase-resistant analogues of acetomycin.[7] We reported the synthesis of 5-carbo and 5-ethoxy analogues, **3** and **4**,[8,9] which exhibited inactivity against esterase but unfortunately also insufficient *anti*-cancer activity. Since a γ-lactone ring was found to be stable to esterase, we have designed new acetomycin bislactone analogues, **5** and **6** (Figure 1). In their structures, C-5 acetoxy groups of **1** and 4,5-di*epi*-acetomycin (**2**) are connected to C-4 carbon to form an additional γ-lactone ring. *Endo*-bislactone (**5**) is structurally similar to **1**, and *exo*-bislactone (**6**) is structurally similar to **2**. Since the acetoxy group, which is prone to esterase attacks, is replaced with a γ-lactone ring in their specific structures, they are expected to be resistant to hydrolysis by esterase. Hopefully, they will indicate inhibition of the growth of cancer cells.

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Synthesis of Bislactones

The retro-synthetic analysis for **5** and **6** is shown in Figure 1. Recently, we have demonstrated that Pd-catalyzed allylic alkylation can be a powerful C-C bond-forming reaction to construct consecutive quaternary and tertiary carbons stereoselectively, and this reaction served the shortest synthesis of (–)-acetomycin.[10] Based on this method, we plan to connect the C-3 and C-4 carbons. Ozonolysis of an alkenyl bond gives aldehyde that corresponds to the C-5 carbon. Branched carbons at the C-4 position will lead to γ-lactone function.

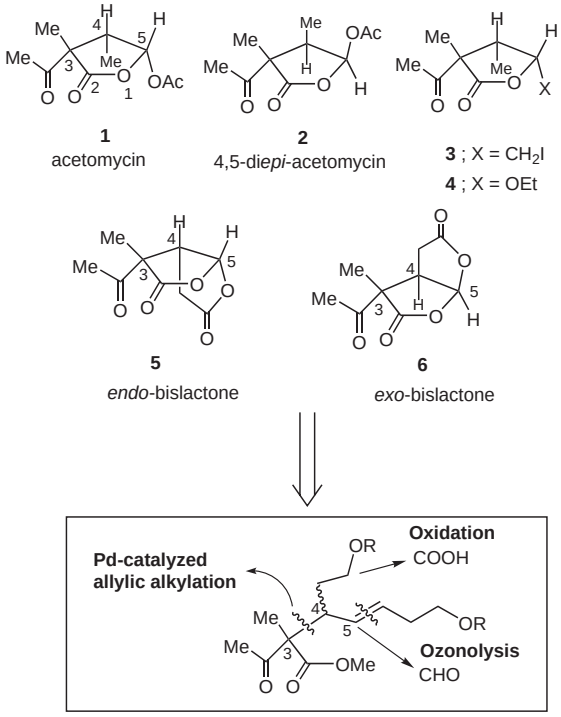
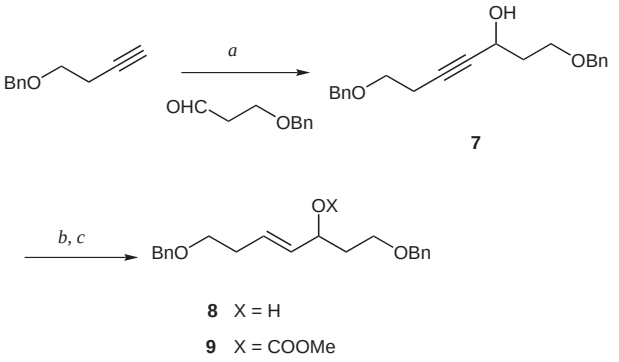


Figure 1 Structures of acetomycin and its analogues, and retrosynthetic analysis of bislactones.

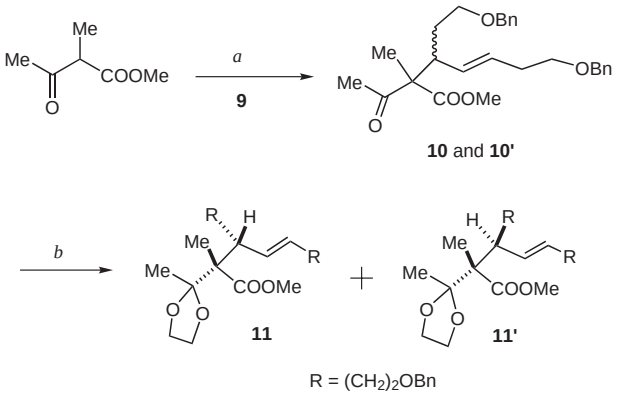
The coupling fragment **9** was prepared in three steps as shown in Scheme 1. The reaction of lithium salt of 4-benzyloxybutyne[11] with 3-benzyloxypropanal[12] gave propargyl alcohol **7** in 78% yield. Partial reduction of the triple bond by $LiAlH_4$ followed by carbonate formation with methyl chloroformate in the presence of DMAP gave **9** in 87% yield in two steps.

The key coupling reaction is shown in Scheme 2. The coupling of sodium salt of methyl 2-methylacetoacetate

with **9** was conducted in THF at room temperature in the presence of a Pd catalyst prepared in situ by $Pd(OAc)_2$ and PPh_3. A 6:5 mixture of diastereoisomers **10** and **10′** was obtained in 90% yield. Protection of ketone as a 1,3-dioxolane with ethylene glycol in the presence of *p*-TsOH gave **11** and **11′** in 92% yield, which were separable by chromatography. At a later stage, it was found that the polar isomer **11** leads to **5** and that the less polar isomer **11′** leads to **6**.



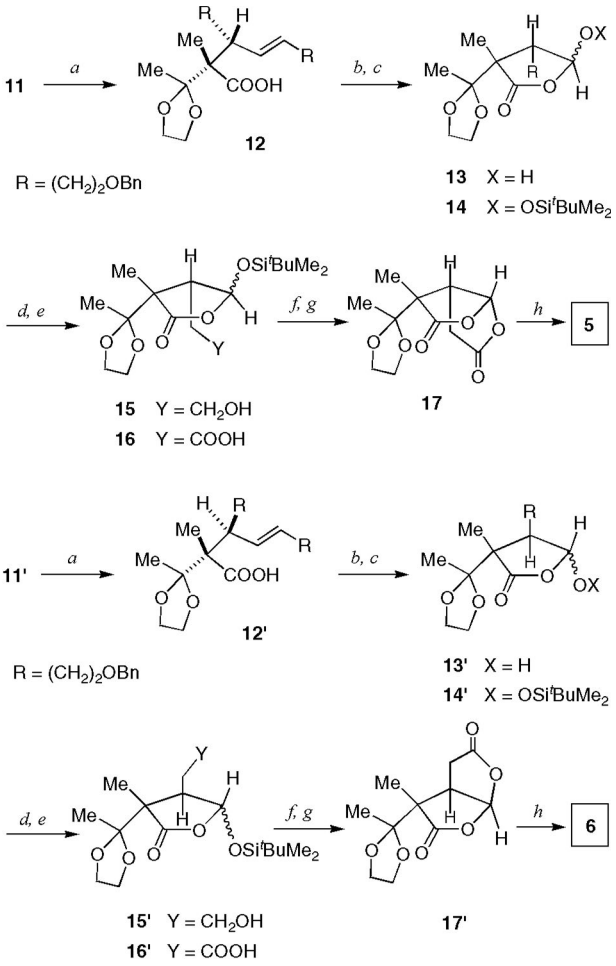
Scheme 1 *Reagents and conditions*: a) LDA, THF, –78 °C; b) $LiAlH_4$, THF, 0 °C; c) ClCOOMe, DMAP, CH_2Cl_2, r.t.



Scheme 2 *Reagents and conditions*: a) NaH, THF, r.t., then $Pd(OAc)_2$, PPh_3, 60 °C; b) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux.

The synthesis of **5** was achieved in 8 steps from the polar isomer **11** as shown in Scheme 3. First, we examined a basic hydrolysis of the methyl ester of **11**, but it totally failed because of steric hindrance of neopentyl carboxylate. However, a nucleophilic attack of lithium thiolate[13] on methyl carbon of the ester was successful in giving carboxylic acid **12** quantitatively. Ozonolysis of the alkenyl bond gave an aldehyde, which immediately cyclized to form 5-hydroxy-γ-lactone **13** as anomeric mixtures in 86% yield. The resulting hydroxy group at C-5 was then protected as a silyl ether in 94% yield. Deprotection of benzyl ether followed by oxidation with Jones reagent gave carboxylic acid **16** via **15** in 83% yield in two steps. Removal of the silyl group and successive acid treatment afforded bislactone **17** in 68% yield. Finally, deprotection of the 1,3-dioxolane function with BCl_3 gave the desired acetomycin bislactone analogue **5** in 73% yield.

The synthesis of the other isomer **6** was also accomplished from **11′** in exactly the same reaction sequences as those shown in Scheme 3. The total yield was 27% in 8 steps. Each yield is indicated in the experimental section.



Scheme 3 *Reagents and conditions*: a) $C_{12}H_{25}SLi$, HMPA, r.t.; b) Ozone, CH_2Cl_2, –78 °C, then Me_2S; c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; d) 10% Pd on charcoal, H_2, CH_2Cl_2:EtOH (1:1); e) Jones reagent, acetone, r.t.; f) HF/pyridine, THF–pyridine (4:1), r.t.; g) CSA, $CHCl_3$, r.t.; h) BCl_3, CH_2Cl_2, r.t.

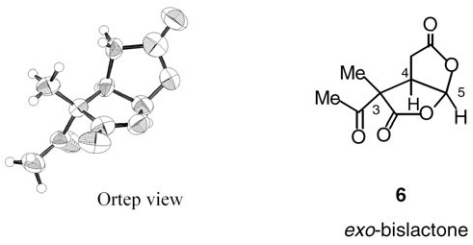


Figure 2 Crystal structure of **6**

Fortunately, a nice single crystal was obtained for **6**. X-ray crystallographic analysis of **6** confirmed the relative structure of the quaternary carbon center and bislactone rings. An ortep view of the *exo*-bislactone structure is shown in Figure 2. It can be clearly seen that one of the

lactone rings is located on the opposite side of the C-3 acetyl group.

No hydrolysis was observed when **5** or **6** was incubated with PLE (pig liver esterase) in buffer solution at room temperature even for two days. Since acetomycin was hydrolyzed with 2–3 hours under the same conditions, these bislactones were found to be resistant to esterase. Cytotoxicity against tumor cells will be reported elsewhere in due course.

Conclusion

Acetomycin bislactone analogues **5** and **6** were prepared in 10 steps from methyl 2-methylacetoacetate. The stereochemistry was determined by X-ray crystallographic analysis. They are completely resistant to esterase.

^{1}H NMR (300 MHz and 400 MHz) and ^{13}C NMR (75 MHz and 100 MHz) were recorded on JEOL LA-300 and Varian Unity spectrometers in $CDCl_3$ with TMS as an internal standard. Mass spectra were obtained on JMS-SX 102A QQ instruments. IR spectra were obtained on JASCO FT/IR-410 instruments. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under a N_2 atmosphere. CH_2Cl_2 was distilled fleshly over P_2O_5 under a N_2 atmosphere. THF was dried over benzophenone ketyl and was distilled before use. TLC was performed with Merck $60F_{254}$ precoated silica gel plates. Flash column chromatography was carried out using Merck silica gel 60 (230–410 mesh).

1,7-Dibenzyloxy-4-heptyn-3-ol (7); Typical Procedure

To a cooled solution of lithium diisopropylamide (23.5 mmol) in THF (25 mL) and hexane (15 mL) at –78 °C was added 4-benzyloxybutyne (3.6 g, 22.5 mmol) and the mixture was stirred for 10 min at the same temperature. Then a THF solution (20 mL) of aldehyde (3.6 g, 22.5 mmol) was dropped to the mixture at the same temperature and the mixture was stirred for 10 min at r.t. Saturated NH_4Cl was added at –78 °C and the mixture was extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel eluted with 20% EtOAc in hexane as eluent. The oily alcohol **7** (5.3 g) was obtained in 78% yield.

IR (neat): 3419 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.93 (dtd, *J* = 14.3, 6.2, 4.4 Hz, 1 H), 2.05 (dtd, *J* = 9.5, 8.1, 4.4 Hz, 2 H), 2.53 (td, *J* = 7.0, 1.8 Hz, 2 H), 3.01 (br s, 1 H), 3.57 (t, *J* = 7.0 Hz, 2 H), 3.66 (ddd, *J* = 9.5, 6.2, 4.7 Hz, 1 H), 3.83 (ddd, *J* = 14.3, 8.1, 4.7 Hz, 1 H), 4.52 (s, 2 H), 4.54 (s, 2 H), 4.59 (br s, 1 H), 7.26–7.38 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 36.9, 61.5, 67.7, 68.4, 72.9, 73.3, 81.6, 82.1, 127.7, 128.4, 137.9, 138.0.

MS (FAB): *m*/*z* = 325 [M$^+$ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}O_3$: 325.1804; found: 325.1807.

(*E*)-1,7-Dibenzyloxy-4-hepten-3-ol (8); Typical Procedure

To a suspension of $LiAlH_4$ (1.75 g, 15.4 mmol) in THF (100 mL) was dropped a THF solution of **7** (5.0 g, 15.4 mmol) at 0 °C, and the mixture was stirred for 2 h at r.t. The reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel with 20% EtOAc in hexane as eluent to give **8** (4.72 g) in 94% yield as a colorless oil.

IR (neat): 3434 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (td, *J* = 5.9, 5.5 Hz, 1 H), 2.36 (q, *J* = 6.6 Hz, 2 H), 2.76 (br s, 1 H), 3.51 (t, *J* = 6.6 Hz, 2 H), 3.62 (dt, *J* = 9.2, 6.1 Hz, 2 H), 3.69 (dt, *J* = 9.2, 5.5 Hz, 1 H), 4.30 (dt, *J* = 6.2, 5.9 Hz, 2 H), 4.51 (s, 4 H), 5.57 (dd, *J* = 15.4, 6.2 Hz, 1 H), 7.26–7.38 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.6, 36.6, 68.3, 69.7, 71.6, 72.9, 73.2, 127.5, 127.6, 127.6 (2 ×), 127.7 (2 ×), 128.3 (2 ×), 128.4 (2 ×), 134.3 (2 ×), 138.0, 138.4.

MS (FAB): *m*/*z* = 327 [M$^+$ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{27}O_3$: 327.1960; found: 327.1965.

(*E*)-1,7-Dibenzyloxy-3-methoxycarbonyloxy-4-heptene (9); Typical Procedure

To a stirred solution of **8** (4.6 g, 14.2 mmol) and DMAP (2.76 g, 22.6 mmol) in CH_2Cl_2 (180 mL) was added methyl chloroformate (8.0 g, 85 mmol) dropwise, and the mixture was stirred overnight at r.t. The mixture was diluted with EtOAc and washed with water and brine and dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel with 10% EtOAc in hexane as eluent to give carbonate **9** (5.1 g) in 93% yield as a colorless oil.

IR (neat): 1721 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89 (ddd, *J* = 12.8, 6.6, 6.2 Hz, 1 H), 2.02 (ddt, *J* = 7.7, 6.2, 5.9 Hz, 1 H), 2.63 (td, *J* = 7.0, 6.6 Hz, 2 H), 3.47–3.54 (m, 4 H), 3.75 (s, 3 H), 4.47 (s, 2 H), 4.50 (s, 2 H), 5.24 (dt, *J* = 7.3, 6.2 Hz, 1 H), 5.52 (ddt, *J* = 15.4, 7.7, 1.5 Hz, 1 H), 5.80 (dt, *J* = 15.4, 6.6 Hz, 1 H), 7.22–7.46 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.7, 34.6, 54.5, 66.0, 69.3, 72.9, 73.0, 76.4, 127.5 (2 ×), 127.6 (2 ×), 127.6 (2 ×), 128.3 (2 ×), 129.3 (2 ×), 131.5 (2 ×), 138.3 (2 ×), 155.0.

MS (FAB): *m*/*z* = 407 [M$^+$ + Na].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{28}O_5Na$: 407.1834; found: 407.1825.

Pd-Catalyzed Coupling Reaction of 9 and Methyl 2-Methylacetoacetate; Typical Procedure

To a solution of sodium salt of methyl 2-methylacetoacetate in THF (40 mL) prepared by NaH (239 mg, 9.96 mol) and methyl 2-methylacetoacetate (1.33 g, 10.3 mmol) was added a THF solution (40 mL) of **9** (3.18 g, 8.27 mmol), $Pd(OAc)_2$ (149 mg, 0.662 mmol) and PPh_3 (382 mg, 1.46 mmol). The mixture was heated at 60 °C for 30 min. After cooling, 10% aq HCl was added and the mixture was extracted with 20% EtOAc in hexane. The extract was washed with water and brine, and dried over $MgSO_4$. The crude oily product was purified by column chromatography on silica gel with 20% EtOAc in hexane as eluent to give **10** (3.28 g) in 90% yield as a 5:6 diastereomeric mixture.

IR (neat): 1738, 1714 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 5:6 mixture of diastereomers): δ = 1.30 (s, 5/11 × 3 H), 1.40 (s, 6/11 × 3 H), 1.41–1.56 (m, 2 H), 1.68 (m, 6/11 × 1 H), 1.82 (m, 5/11 × 1 H), 2.11 (s, 6/11 × 3 H), 2.17 (s, 5/11 × 3 H), 2.24–2.53 (m, 2 H), 3.37–3.57 (m, 4 H), 3.62 (s, 5/11 × 3 H), 3.70 (s, 6/11 × 3 H), 4.39–4.51 (m, 4 H), 5.16 (ddt, *J* = 15.2, 9.9, 1.3 Hz, 6/11 × 1 H), 5.31 (ddt, *J* = 15.0, 9.7, 1.2 Hz, 5/11 × 1 H), 4.48 (dt, *J* = 15.1, 6.9 Hz, 1 H), 7.24–7.36 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$, 5:6 mixture of diastereomers): δ = 12.9, 15.4, 16.4, 21.3, 26.6, 26.9, 29.9, 30.6, 33.0, 33.0, 43.9, 44.0, 47.8, 51.8, 52.2, 52.3, 63.6, 63.9, 64.8, 64.9, 68.0, 68.7, 69.9, 70.0, 72.7, 72.8, 72.8, 127.4 (2 ×), 127.5 (2 ×), 127.6 (4 ×), 127.6 (2 ×), 128.3 (4 ×), 128.3 (4 ×), 129.5 (2 ×), 130.2 (2 ×), 131.1 (2 ×), 131.4 (2 ×), 138.5, 138.6, 172.0, 172.5, 205.0, 205.2.

MS (FAB): *m*/*z* = 439 [M$^+$ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{35}O_5$: 439.2484; found: 439.2479.

Preparation of 11 and 11′; Typical Procedure

A mixture of **10** (1.94 g, 4.42 mmol) and ethylene glycol (0.55 g, 8.85 mmol) and *p*-toluenesulfonic acid (0.17 g, 0.88 mmol) was refluxed in benzene (50 mL) for 16 h and the resulting water was removed by Dean–Stark apparatus. After cooling, the mixture was diluted with EtOAc and washed with sat. aq $NaHCO_3$, water and brine. The organic layer was dried over $MgSO_4$ and condensed. The residue was purified by flash chromatography on silica gel with 10–30% EtOAc in hexane as eluent to give polar isomer **11** (0.99 g) in 46% yield and less polar isomer **11′** (0.98 g) in 46% yield.

11

Colorless oil; R_f = 0.42 (30% EtOAc in hexane).

IR (neat): 1721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 3 H), 1.35 (s, 3 H), 1.41–1.47 (m, 2 H), 2.33 (dt, *J* = 6.8, 5.7 Hz, 2 H), 2.88 (dt, *J* = 8.9, 4.2 Hz, 1 H), 3.34–3.49 (m, 4 H), 3.69 (s, 3 H), 3.78–3.93 (m, 4 H), 4.41 (ABq, *J* = 12.0 Hz, 2 H), 4.49 (s, 2 H), 5.30–5.42 (m, 2 H), 7.24–7.36 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 21.2, 30.9, 33.1, 42.4, 51.9, 58.7, 64.0, 65.3, 68.3, 70.2, 72.6, 72.9, 111.8, 127.4, 127.5, 127.6 (4 ×), 128.3 (2 ×), 128.3 (2 ×), 128.5, 131.4, 138.5, 138.7, 174.9.

MS (FAB): *m*/*z* = 483 [M$^+$ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{39}O_6$: 483.2747; found: 483.2754.

11′

Colorless oil; R_f = 0.49 (30% EtOAc in hexane).

IR (neat): 1737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H), 1.28–1.34 (m, 2 H), 1.53 (s, 3 H), 2.14–2.36 (m, 2 H), 2.81–2.86 (m, 1 H), 3.31–3.49 (m, 4 H), 3.57 (s, 3 H), 3.81–4.03 (m, 4 H), 4.44 (ABq, *J* = 12.1 Hz, 2 H), 4.47 (s, 2 H), 5.20 (dd, *J* = 9.5, 15.2 Hz, 1 H), 5.36–5.41 (m, 1 H), 7.22–7.36 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 21.2, 28.9, 33.0, 42.9, 47.8, 51.4, 64.0, 65.7, 68.3, 70.1, 72.8, 72.8, 112.0, 127.3, 127.4 (2 ×), 127.5, 127.6 (2 ×), 128.2 (2 ×), 128.3 (2 ×), 130.2, 131.2, 138.4, 138.8, 174.3.

MS (FAB): *m*/*z* = 483 [M$^+$ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{39}O_6$: 483.2747; found: 483.2752.

Demethylation of Methyl Esters 11 and 11′; Typical Procedure

The mixture of methyl ester (**11** or **11′,** 3 mmol) and lithium salt of dodecanethiol prepared by dodecanethiol (3.3 equiv) and BuLi (3 equiv) in HMPA (7 mL) was stirred for 3 h at r.t. To this mixture 10% HCl was added at 0 °C and the mixture was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel with 30–100% EtOAc in hexane as eluent to give carboxylic acids **12** quantitatively and **12′** in 96% yield.

12

Amorphous solid; R_f = 0.26 (50% EtOAc in hexane).

IR (KBr): 1699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3 H), 1.35 (s, 3 H), 1.43 (m, 1 H), 1.77 (m, 1 H), 2.32 (q, *J* = 6.6 Hz, 2 H), 2.79 (ddd, *J* = 11.2, 8.8, 2.0 Hz, 1 H), 3.35–3.50 (m, 4 H), 3.86–3.99 (m, 4 H), 4.41 (ABq, *J* = 12.1 Hz, 2 H), 4.48 (s, 2 H), 5.28–5.40 (m, 2 H), 7.23–7.36 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 20.7, 30.5, 33.1, 42.5, 58.0, 64.1, 64.8, 67.8, 70.1, 72.6, 72.9, 112.1, 127.4, 127.6, 127.7 (2 ×), 127.7 (2 ×), 128.3 (2 ×), 128.4 (2 ×), 129.1, 131.0, 138.4, 138.6, 176.3.

MS (FAB): *m*/*z* = 469 [M$^+$ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{37}O_6$: 469.2590; found: 469.2586.

12′

Amorphous solid; R_f = 0.35 (50% EtOAc in hexane).

IR (neat): 1697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (s, 3 H), 1.30 (m, 1 H), 1.48 (s, 3 H), 2.23 (m, 1 H), 2.27 (qd, *J* = 6.9, 1.2 Hz, 2 H), 2.78 (td, *J* = 9.6, 1.8 Hz, 1 H), 3.31–3.47 (m, 4 H), 3.83–4.03 (m, 4 H), 4.43 (ABq, *J* = 12.1 Hz, 2 H), 4.47 (s, 2 H), 5.24 (ddt, *J* = 14.1, 9.5, 1.3 Hz, 1 H), 5.45 (td, *J* = 7.0, 15.1 Hz, 1 H), 7.24–7.36 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 21.2, 29.2, 33.0, 42.4, 58.7, 64.1, 65.5, 68.2, 70.1, 72.8, 72.9, 112.1, 127.4, 127.5 (3 ×), 127.7 (2 ×), 128.3 (2 ×), 128.4 (2 ×), 130.6, 130.7, 138.5, 138.8, 176.6.

MS (FAB): *m*/*z* = 469 [M$^+$ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{37}O_6$: 469.2590; found: 469.2583.

Ozonolysis of Alkenes 12 and 12′; Typical Procedure

Through a CH_2Cl_2 solution (35 mL) of alkenyl substrate (**12** or **12′**, 3 mmol) ozone was bubbled at –78 °C until the substrate disappeared as indicated by TLC. After the excess of ozone gas was replaced with nitrogen gas, ozonide was decomposed with an excess of dimethyl sulfide. The mixture was diluted with EtOAc and washed with water, brine and dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel with 50% EtOAc in hexane as eluent to give lactone. Compound **13** was obtained as crystals in 86% yield and **13′** was obtained as an oil in 86% yield.

13

Colorless crystals; mp 96–98 °C (hexane); R_f = 0.40 (50% EtOAc in hexane).

IR (KBr): 3388, 1768 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 4:1 mixture of diastereomers): δ = 1.32 (s, 1/5 × 3 H), 1.37 (s, 1/5 × 3 H), 1.41 (s, 4/5 × 3 H), 1.43 (s, 4/5 × 3 H), 1.76 (m, 4/5 × 1 H), 1.86 (m, 1/5 × 1 H), 2.07 (m, 1 H), 2.57 (ddd, *J* = 10.3, 5.5, 4.6 Hz, 4/5 × 1 H), 2.70 (td, *J* = 6.0, 1.8 Hz, 1/5 × 1 H), 3.47–3.63 (m, 2 H), 3.93–4.15 (m, 4 H), 4.51 (ABq, *J* = 12.1 Hz, 4/5 × 2 H), 4.53 (ABq, *J* = 12.1 Hz, 1/5 × 2 H), 5.49 (d, *J* = 5.7 Hz, 4/5 × 1 H), 5.60 (s, 4/5 × 1 H), 5.66 (s, 1/5 × 1 H), 5.67 (d, *J* = 7.1 Hz, 1/5 × 1 H), 7.27–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 20.2, 20.3 20.8 21.0, 22.4, 25.3, 26.5, 43.8, 47.9, 50.7, 52.8, 55.2, 60.4, 62.9, 63.2, 63.8, 64.0, 64.2, 67.6, 68.9, 73.1, 73.2, 97.3, 101.5, 110.6, 111.3, 127.7 (2 ×), 127.8, 127.8, 128.5 (2 ×), 138.1, 171.2, 177.4.

MS (FAB): *m*/*z* = 337 [M$^+$ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}O_6$: 337.1651; found: 337.1647.

Anal. Calcd for $C_{18}H_{25}O_6$: C, 64.27; H, 7.19. Found: C, 64.06, H, 7.20.

13′

Colorless oil; R_f = 0.52 (50% EtOAc in hexane).

IR (neat): 3411, 1770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ = 1.26 (s, 1/2 × 3 H), 1.38 (s, 1/2 × 3 H), 1.44 (s, 1/2 × 3 H), 1.46 (s, 1/2 × 3 H), 1.61 (m, 1/2 × 1 H), 1.94 (m, 1 H), 2.25 (m, 1/2 × 1 H), 2.49 (dt, *J* = 11.5, 3.3 Hz, 1/2 × 1 H), 2.78 (ddd, *J* = 11.5, 5.7, 3.3 Hz, 1/2 × 1 H), 3.52–3.66 (m, 4 H), 3.85–4.06 (m, 4 H), 4.52 (ABq, *J* = 11.9 Hz, 1/2 × 2 H), 4.53 (s, 1/2 × 2 H), 4.95 (br s, 1 H), 5.39 (d, *J* = 3.1 Hz, 1/2 × 1 H), 5.72 (d, *J* = 5.7 Hz, 1/2 × 1 H), 7.26–7.37 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 16.6, 19.5, 19.8, 25.2, 28.9, 41.7, 45.5, 51.4, 53.9, 64.7, 65.0, 65.1, 65.2, 68.0, 68.6, 73.1, 73.2, 96.6, 101.2, 111.8, 112.1, 127.6 (2 ×), 127.6 (2 ×), 127.7 (2 ×), 128.4 (2 ×), 128.5 (2 ×), 137.9, 138.0, 176.8, 178.8.

MS (FAB): *m*/*z* = 337 [M^+ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}O_6$: 337.1651; found: 337.1647.

Silylation of 13 and 13′; Typical Procedure

To a solution of **13** or **13′′** (2.5 mmol) and 2,6-lutidine (5 equiv) in CH_2Cl_2 (20 mL) was added TBDMSOTf (2.5 equiv) at 0 °C. The mixture was stirred at r.t. for 2 h, diluted with Et_2O and washed with water and brine. The ethereal solution was dried over $MgSO_4$ and residual oil was purified by flash chromatography on silica gel with 15–20% EtOAc in hexane as eluent. Silyl ether **14** was obtained in 94% yield and **14′** was obtained in 93% yield.

14

Colorless oil; R_f = 0.58 (30% EtOAc in hexane).

IR (neat): 1774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 6 H), 0.92 (s, 9 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.77–1.87 (m, 1 H), 2.04–2.23 (m, 2 H), 3.49–3.63 (m, 2 H), 3.92–4.02 (m, 4 H), 4.51 (ABq, *J* = 11.9 Hz, 2 H), 5.62 (d, *J* = 6.8 Hz, 1 H), 7.26–7.37 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.58 (2 ×), 17.8, 20.8, 20.9, 25.6 (3 ×), 26.8, 53.0, 54.8, 63.3, 64.3, 69.1, 73.0, 102.0, 111.4, 127.6, 127.7 (2 ×), 128.4 (2 ×), 138.3, 176.4.

MS (FAB): *m*/*z* = 451 [M^+ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{39}O_6Si$: 451.2516; found: 451.2511.

14′

Colorless oil; R_f = 0.47 (30% EtOAc in hexane).

IR (neat): 1780 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3 H), 0.09 (s, 3 H), 0.86 (s, 9 H), 1.35 (s, 3 H), 1.47 (s, 3 H), 1.87–2.00 (m, 2 H), 2.80 (ddd, *J* = 11.0, 5.3, 3.8 Hz, 1 H), 3.39–3.52 (m, 2 H), 3.87–4.06 (m, 4 H), 4.49 (ABq, *J* = 12.0 Hz, 2 H), 5.59 (d, *J* = 5.3 Hz, 1 H), 7.26–7.37 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.8, –4.5, 16.3, 17.7, 19.7, 25.5, 25.5 (3 ×), 41.3, 51.4, 65.0, 65.2, 67.9, 73.0, 97.0, 112.2 (3 ×), 127.7 (2 ×), 128.4, 138.4, 178.7.

MS (FAB): *m*/*z* = 451 [M^+ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{39}O_6Si$: 451.2516; found: 451.2511.

Deprotection of Benzyl Ethers 15 and 15′; Typical Procedure

A solution of **14** or **14′** (2 mmol) in a 1:1 mixture of CH_2Cl_2 and EtOH (40 mL) was stirred in the presence of 10% Pd on charcoal under a hydrogen atmosphere. After the hydrogenation was completed, the reaction mixture was filtered and condensed. The pure product was obtained in quantitative yield.

15

Colorless oil; R_f = 0.38 (50% EtOAc in hexane).

IR (neat): 3502, 1770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.18 (s, 3 H), 0.20 (s, 3 H), 0.92 (s, 9 H), 1.33 (s, 3 H), 1.40 (s, 3 H), 1.77 (m, 1 H), 2.00–2.14 (m, 2 H), 3.74 (ddd, *J* = 12.5, 6.0, 1.6 Hz, 2 H), 3.94–4.04 (m, 4 H), 5.67 (d, *J* = 7.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1, –4.2, 17.7, 20.3, 20.8, 25.6 (3 ×), 29.3, 53.7, 54.8, 61.5, 63.2, 64.2, 101.7, 111.4, 176.1.

MS (FAB): *m*/*z* = 361 [M^+ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{33}O_6Si$: 361.2046; found: 361.2050.

15′

Amorphous solid; R_f = 0.33 (50% EtOAc in hexane).

IR (neat): 3504, 1777 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.15 (s, 3 H), 0.16 (s, 3 H), 0.90 (s, 9 H), 1.36 (s, 3 H), 1.47 (s, 3 H), 1.64 (br s, 1 H), 2.80 (ddd, *J* = 10.6, 5.3, 3.7 Hz, 1 H), 1.82–1.97 (m, 2 H), 3.60–3.76 (m, 2 H), 3.90–4.10 (m, 4 H), 5.75 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.7, –4.4, 16.3, 17.7, 19.6, 25.5 (3 ×), 28.2, 41.3, 51.4, 60.9, 65.0, 65.1, 97.1, 112.2, 178.7.

MS (FAB): *m*/*z* = 361 [M^+ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{33}O_6Si$: 361.2046; found: 361.2050.

Preparation of Carboxylic Acids 16 and 16′; Typical Procedure

To a stirred solution of alcohol (**16** or **16′**, 1 mmol) in acetone (18 mL) was added Jones reagent (2 M in H_2O, 1 mL) and the mixture was stirred for 2 h at r.t. After an excess of reagent was decomposed with *i*-PrOH, water and EtOAc were added. Organic layer was washed with water and brine, and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel with 50–100% EtOAc in hexane as eluent. Crystalline **16** was obtained in 83% yield and **16′** was obtained in 81% yield as an amorphous solid.

16

Colorless crystals; mp 149–151 °C (Et_2O); R_f = 0.40 (EtOAc).

IR (KBr): 3020, 1768, 1714 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.14 (s, 3 H), 0.17 (s, 3 H), 0.90 (s, 9 H), 1.34 (s, 3 H), 1.50 (s, 3 H), 2.50 (dd, *J* = 15.2, 5.5 Hz, 1 H), 2.57–2.62 (m, 1 H), 2.67 (dd, *J* = 15.2, 8.8 Hz, 1 H), 3.93–4.11 (m, 4 H), 5.53 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3, –4.4, 17.8, 19.5, 21.7, 25.5 (3 ×), 31.9, 51.6, 53.9, 62.5, 63.9, 100.9, 111.3, 175.9, 177.6.

MS (FAB): *m*/*z* = 375 [M^+ + H].

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{31}O_7Si$: 375.1839; found: 375.1843.

Anal. Calcd for $C_{17}H_{30}O_7Si$: C, 54.52; H, 8.07. Found: C, 54.29, H, 7.82.

16′

Amorphous solid; R_f = 0.35 (EtOAc).

IR (neat): 2955, 1782, 1711 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 3 H), 0.15 (s, 3 H), 0.89 (s, 9 H), 1.36 (s, 3 H), 1.49 (s, 3 H), 2.71–2.78 (m, 2 H), 3.06 (td, *J* = 8.8, 5.3 Hz, 1 H), 3.83–4.07 (m, 4 H), 5.85 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.8, –4.7, 16.7, 17.7, 19.1, 25.5 (3 ×), 30.4, 40.2, 51.0, 64.9, 65.1, 96.6, 112.0, 177.7, 178.5.

MS (FAB): *m*/*z* = 375 [M^+ + H].

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_{17}H_{31}O_7Si$: 375.1839; found: 375.1835.

Formation of Bislactone; Typical Procedure

A mixture of silyl ether (**16** or **16′**, 0.5 mmol), pyridinium poly(hydrogen fluoride) (250 mg) in a 4:1 mixture of THF and pyridine (6.5 mL) was stirred for 5 h at r.t. After the reaction completed, KCl–HCl buffer solution (pH 2.2) was added and extracted with EtOAc for several times. The combined organic extracts were dried over $MgSO_4$ and condensed. The resulting crude hydroxycarboxylic acid was dissolved in $CHCl_3$ (10 mL) and stirred for 3.5 h in the presence of CSA (0.25 mmol). The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$ and the crude product was purified by flash chromatography on silica gel with 40–50% EtOAc in hexane as eluent to give bislactone in 68% yield for **17** and in 55% for **17′**.

17

Colorless oil; R_f = 0.32 (50% EtOAc in hexane).

IR (neat): 1793 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.51 (s, 3 H), 2.61 (dd, *J* = 18.7, 10.0 Hz, 1 H), 3.06 (ddd, *J* = 10.0, 8.8, 5.5 Hz, 1 H), 3.47 (dd, *J* = 18.7, 8.8 Hz, 1 H), 3.95–4.21 (m, 4 H), 6.21 (d, *J* = 5.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.6, 28.5, 45.9, 54.1, 64.2, 64.5, 100.1, 109.8, 173.1, 174.5.

MS (FAB) *m/z* = 243 [M$^+$ + H].

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_{11}H_{15}O_6$: 243.0868; found: 243.0874.

17′

Colorless oil; R_f = 0.34 (50% EtOAc in hexane).

IR (neat): 1789 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.41 (s, 3 H), 2.55 (dd, *J* = 18.5, 7.7 Hz, 1 H), 2.71 (dd, *J* = 18.5, 10.3 Hz, 1 H), 3.38 (ddd, *J* = 10.3, 7.7, 5.9 Hz, 1 H), 4.01–4.05 (m, 4 H), 6.23 (d, *J* = 5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 19.3, 28.7, 41.4, 54.7, 64.9, 65.2, 102.1, 111.4, 173.6, 174.9.

MS (FAB): *m/z* = 243 [M$^+$ + H].

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_{11}H_{15}O_6$: 243.0869; found: 243.0874.

Deprotection of Cyclic Acetals 17 and 17′; Typical Procedure

To an ice cooled solution of **17** or **17′** (0.4 mmol) in CH_2Cl_2 (5.5 mL) was added BCl_3 (1.0 M in CH_2Cl_2 solution, 0.8 mL) and the mixture was stirred for 1 h at r.t. After the reaction completed, the mixture was diluted with CH_2Cl_2 and washed with aq $NaHCO_3$ and brine. The CH_2Cl_2 layer was dried over $MgSO_4$ and the crude product was purified by flash chromatography on silica gel with 40% EtOAc in hexane as eluent to give the desired product. Crystalline **5** and **6** were obtained in 73% and 78% yields, respectively.

5

Colorless crystals; mp 135–136 °C (MeOH); R_f = 0.24 (50% EtOAc in hexane).

IR (KBr): 1801, 1715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 3 H), 2.30 (dd, *J* = 18.9, 8.4 Hz, 1 H), 2.48 (s, 3 H), 2.99 (dd, *J* = 18.9, 9.7 Hz, 1 H), 3.21 (ddd, *J* = 9.7, 8.4, 5.3 Hz, 1 H), 6.26 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 27.6, 30.4, 45.0, 60.6, 100.1, 172.2, 173.0, 203.7.

MS (FAB): *m/z* = 199 [M$^+$ + H].

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_9H_{11}O_5$: 199.0607; found: 199.0609.

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.28, H, 5.21.

6

Colorless crystals; mp 127–128.5 °C (MeOH); R_f = 0.31 (50% EtOAc in hexane).

IR (neat): 1791, 1712 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (s, 3 H), 2.37 (s, 3 H), 2.48 (dd, *J* = 8.1, 18.5 Hz, 1 H), 2.74 (dd, *J* = 18.5, 10.3 Hz, 1 H), 3.90 (ddd, *J* = 10.3, 8.1, 5.7 Hz, 1 H), 6.21 (d, *J* = 5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1, 25.5, 28.0, 40.9, 61.3, 101.7, 171.9, 172.8, 201.4.

MS (FAB): *m/z* = 199 [M$^+$ + H].

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_9H_{11}O_5$: 199.0607; found: 199.0612.

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.35, H, 5.27.

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