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Stereoselective synthesis of (+)-IKD-8344

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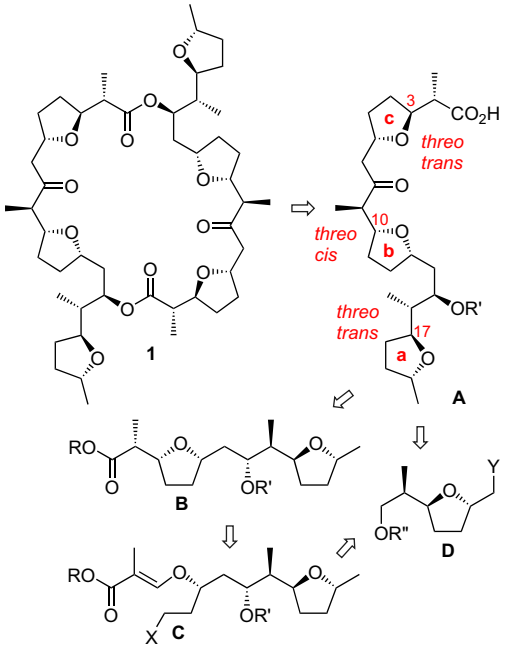
Abstract—Total synthesis of IKD-8344 was accomplished via stepwise cyclodimerization of the monomeric seco acid under Yamaguchi conditions. In the synthesis of the monomeric seco acid, Wittig olefination reaction was employed for an efficient bond formation at C7–C8. The *threo-trans* oxolane unit for the rings **a** and **c** was prepared via intramolecular Williamson ether synthesis of the hydroxyl mesylate prepared via asymmetric aldol reaction. Radical cyclization of a β-alkoxymethacrylate intermediate furnished the *threo-cis* oxolane unit for the **b** ring fragment.

1. Introduction

In 1992, Minami and co-workers reported a novel 28-membered ring macrodiolide[1] antibiotic IKD-8344 (**1**) from an unidentified alkalophilic Actinomycete, strain No. 8344, which exhibits potent anthelmintic activity against *Trichinella spiralis* and strong cytotoxicity against L5178Y mouse leukemia cells with IC_{50} of 0.54 ng mL^{-1}.[2a] They also reported X-ray crystal structure of **1** in 1994, which enabled full stereochemical assignment of this intriguing natural product.[2b] More recently, it was also isolated from *Streptomyces* sp. A6792 and selective antifungal activities against the mycelial form of *Candida albicans* were noted.[3] The unique bioactivity profile of the molecule makes it an attractive target for synthetic investigations.

IKD-8344 (**1**) is a dimer of a monomeric seco acid **A**. The monomeric seco acid **A** contains three methyl branches and three oxolane units: a *threo* (C2–C3)-*trans* (C3–C6) array (ring **c**) is connected to a *threo* (C9–C10)-*cis* (C10–C13) arrangement (ring **b**), which is flanked by another *threo* (C16–C17)-*trans* (C17–C20) unit (ring **a**). Efficient and stereoselective construction of these structural units is the prerequisite to a successful total synthesis of **1**, and Fuchs and co-workers reported in 2000 a viable solution to this problem starting from Jacobsen catalytic epoxidation of cycloheptadienyl sulfones.[4] More serious problems are encountered at the assemblage stage; it is difficult to couple these units and the difficulty therein is manifested by the absence of reports on the total synthesis of **1** in the literature prior to our communication in 2006.[5] In this paper, we describe a full account of our efforts in the successful synthesis of **1**.

In the retrosynthetic analysis, synthesis of **1** would be accomplished via dimerization of the monomeric seco acid **A**, which may be prepared by coupling of the fragments **B** and **D**. The fragment **B** may be obtained via radical cyclization of the β-alkoxymethacrylate derivative **C**, which incorporates the *threo*-cis ring **b** element. The intermediate **C** should be accessible from the fragment **D** (Scheme 1). A successful total synthesis of **1** would then require development of a reliable and efficient route to the *threo*-trans fragment **D**, which serves as a precursor for both rings **a** and **c**.



Scheme 1. Retrosynthetic analysis.

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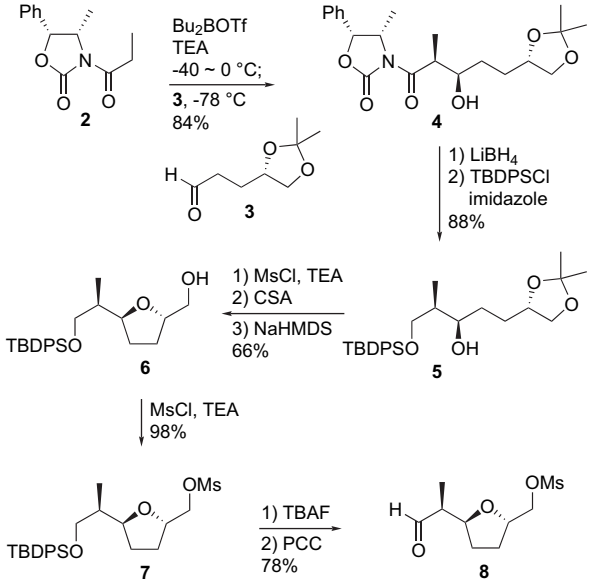
2. Results and discussion

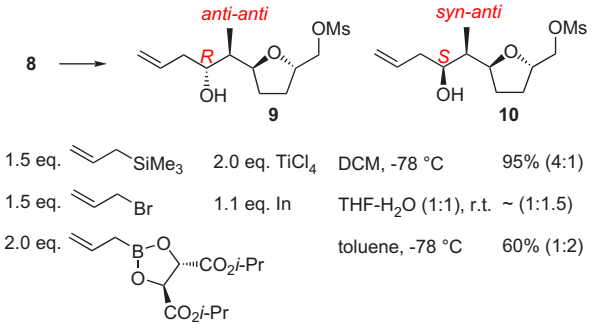
Efficacy of the known[6] and new procedures was examined in search of an efficient synthesis of the fragment **D**, and satisfactory results were obtained following the protocol involving asymmetric aldol reaction and intramolecular hydroxyl substitution. In practice, aldol reaction of aldehyde **3**[7] with the boron enolate of the chiral imide **2**[8] yielded the imide aldol **4**. Lithium borohydride reduction of **4** and selective TBDPS protection of the primary hydroxyl group of the diol product afforded the secondary alcohol **5**. The *threo-trans* oxolane derivative **6** was obtained via mesylation of the hydroxyl group in **5**, acetonide deprotection, and treatment with sodium hexamethyldisilazide. The push toward **1** started in earnest at this point as a reliable supply of the fragment **D** was realized following the above reaction sequence. The primary mesylate **7** prepared from **6** was converted into aldehyde **8** via TBDPS deprotection and PCC oxidation (Scheme 2).



Scheme 2. Synthesis of the fragment **D**.

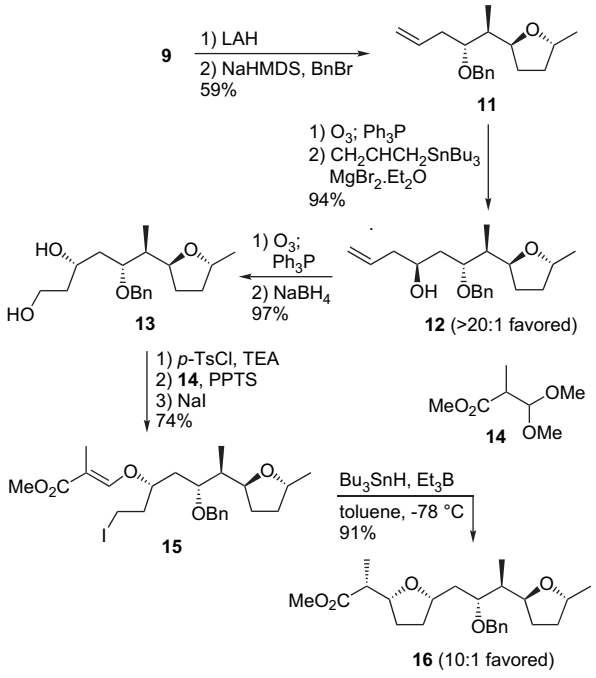
Next, conditions for stereoselective allylation reactions were explored. For preparation of the anti-anti homoallylic alcohol **9**, introduction of the (15*R*) configuration was required, and this was problematic.[9] For example, Roush allylation using allyl boronate prepared from isopropyl (*S*,*S*)-tartrate yielded a mixture of the products favoring (1:2) the wrong isomer **10**. Little stereoselectivity materialized when allyl bromide and indium were employed. Finally, reaction of **8** with allyltrimethylsilane in the presence of titanium chloride led to a 4:1 mixture of the homoallylic alcohols favoring the correct isomer **9** (Scheme 3).

At this point, the mesyloxy group in **9** was removed via LAH reduction,[10] and the homoallylic ether **11** was obtained after benzyl protection. Ozonolysis of **11** provided the corresponding aldehyde, which was converted stereoselectively into the homoallylic alcohol **12** by reaction with allyltributylstannane in the presence of magnesium bromide etherate.[11] Sodium borohydride reduction of the aldehyde obtained from **12** via ozonolysis provided diol **13**. Iodide **15** was obtained via



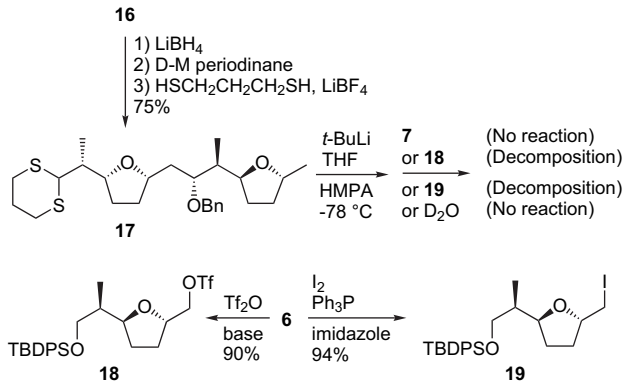
Scheme 3. Allylation studies.

tosylation of the primary hydroxyl group of **13**, reaction with the dimethyl acetal **14**,[12] and iodide substitution. Radical cyclization[13] of β-alkoxymethacrylate **15** proceeded smoothly to produce selectively (10:1) the *threo-cis* oxolane product **16** in good yield[14] (Scheme 4).



Scheme 4. Synthesis of the fragment **B**.

With fragments **B** and **D** in hand, ways were explored for the efficient coupling of these fragments at C7–C8. First, the dithiane derivative **17** was prepared from ester **16** in three steps, and it was allowed to react with mesylate **7** after exposure to *t*-BuLi at −78 °C. The reaction did not proceed. Triflate **18** and iodide **19** decomposed under the same reaction conditions. There was little evidence of deuterium exchange when a sample of **17** was allowed to react with *t*-BuLi at −78 °C, and then with D_2O, which suggested that the desired lithiation of **17** did not occur at low temperature (Scheme 5). When a sample of **17** was allowed to react with *n*-BuLi at room temperature[15] and then with mesylate **7**, the coupling reaction did not proceed. Instead, a low yield of an olefinic product was obtained, which was the product of benzyl alcohol elimination from **17**. Benzyloxy elimination upon lithiation has already been reported in literature.[15,16]



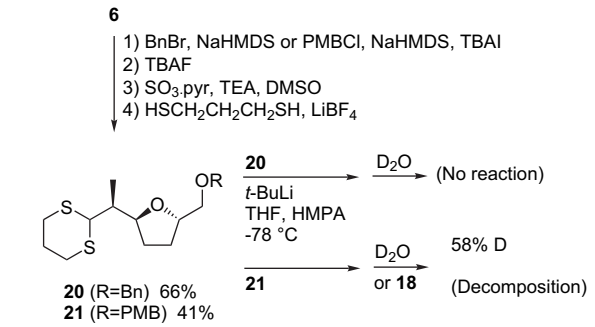
Scheme 5. Attempted dithiane coupling reactions of the fragments **B** and **D**.

For more detailed studies on lithiation, the model dithiane **20** was prepared from **6** via benzylation, TBDPS deprotection, oxidation, and dithiane formation. As in the case of **17**, there was little evidence of deuterium exchange for **20** when it was allowed to react with *t*-BuLi at −78 °C, and then with D_2O. The situation changed when the corresponding PMB ether **21** was employed;[17] a reasonable degree (58%) of deuterium exchange was noted upon sequential exposure to *t*-BuLi at −78 °C and then D_2O. Unfortunately, the lithiated sample of **21** did not react with triflate **18** (Scheme 6).

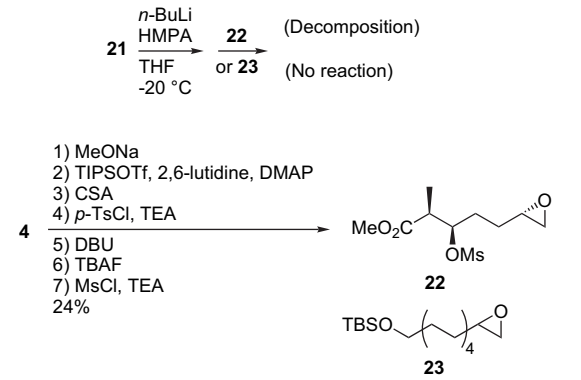
Epoxides were considered to be viable partners in these coupling reactions as the desired reaction product would be obtained via epoxide alkylation followed by intramolecular hydroxyl substitution. The candidate epoxide **22** was prepared from aldol **4**, but the mesyloxy elimination in **22** was the only reaction observed from the reaction between the lithiated sample of **21** and epoxide **22**. The reaction with epoxide **23** was also fruitless (Scheme 7). From these reaction results, it was concluded that dithiane alkylation is untenable for coupling reactions of substrates like **17**, **20**, and **21** due to steric reasons.

The cyanohydrin derivative **25** was prepared from (+)-methyl 8-*epi*-nonactate benzyl ether (**24**)[18] for further model studies. Unfortunately, the lithiated sample of **25** reacted with neither iodide **19** nor epoxide **26** prepared from acetonide alcohol **5** (Scheme 8). It was concluded that cyanohydrin derivatives like **25** also suffer from fatal steric hindrance problems in the proposed coupling reactions.

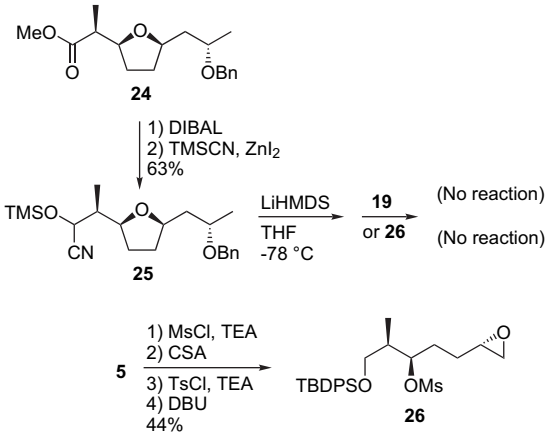
Next, the sulfone derivative **27** was prepared from alcohol **6** for potential use in the coupling reaction. It did not react with



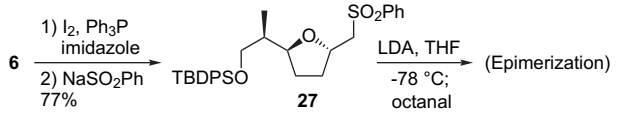
Scheme 6. Attempted model dithiane lithiation and triflate alkylation reactions.



Scheme 7. Attempted model dithiane lithiation and epoxide alkylation reactions.



Scheme 8. Attempted model cyanohydrin TMS ether alkylation reactions.

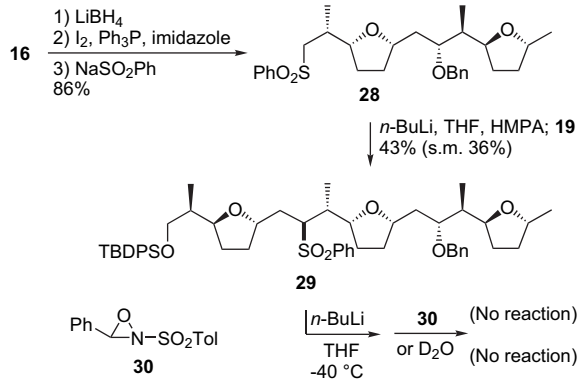


Scheme 9. Attempted model Julia coupling reaction of the fragment **D**.

octanal upon lithiation, and the partial epimerization was the only reaction observed (Scheme 9).

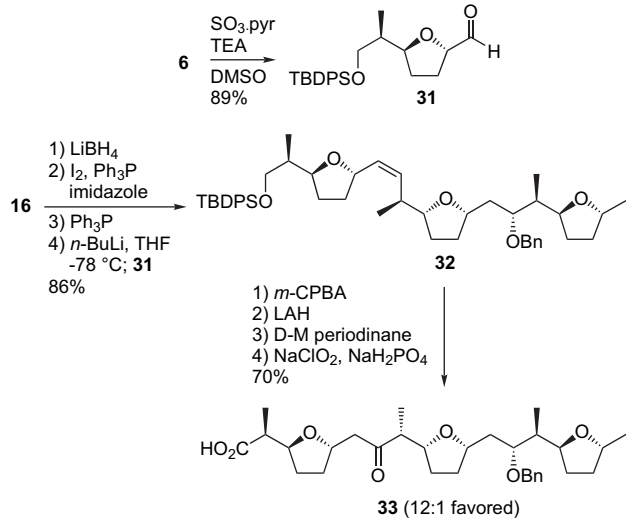
Reaction of the alternative sulfone **28**, prepared from the **B** fragment **16**, yielded more promising results. After lithiation, it reacted with iodide **19**, and the desired product **29** was obtained in 43% yield. Unfortunately, the usual lithiation–oxidation protocol using oxaziridine **30** did not proceed, and it was not possible to obtain the desired ketone product. Little evidence of deuterium exchange for **29** was noted when it was allowed to react with *n*-BuLi, and then with D_2O, which implied that there were fundamental problems in the lithiation step (Scheme 10).

After considerable exploration, it was found that the crucial coupling at C7–C8 was possible employing Wittig olefination reaction. Aldehyde **31** was prepared from the primary alcohol **6**. Ester **16** was converted into the corresponding phosphonium salt via lithium borohydride reduction, iodide substitution, and reaction with triphenylphosphine, and the ylide obtained from the phosphonium salt reacted with



Scheme 10. Attempted sulfone alkylation and oxidation reactions of the fragments **B** and **D**.

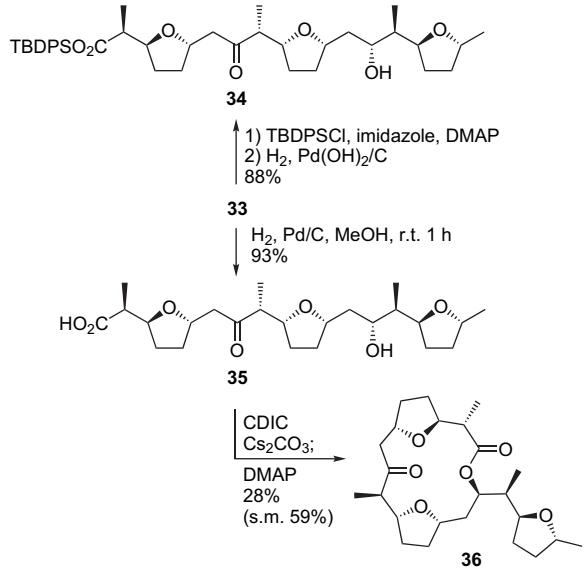
aldehyde **31** in good yield to produce olefin **32**. A mixture of epoxides was obtained from **32** via oxidation with *m*-CPBA. Reaction of the mixture with excess lithium aluminum hydride produced diol products resulting from concomitant TBDPS deprotection. Dess–Martin oxidation of the diol mixture, and sodium chlorite oxidation of the aldehyde functionality provided regioselectively (~12:1) the correct keto carboxlylic acid **33**. Use of DIBAL as the reducing agent eventually produced the alternative ketone as the major product (Scheme 11).



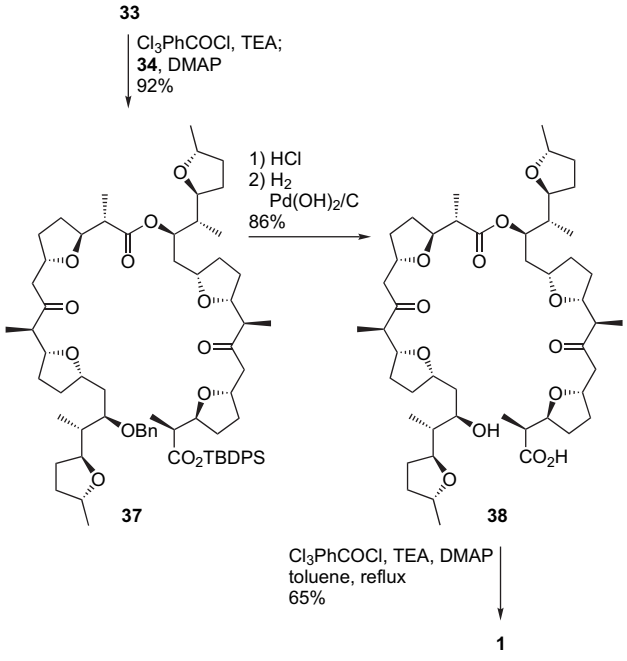
Scheme 11. Wittig coupling reactions of the fragments **B** and **D**.

The secondary alcohol **34** was obtained from **33** via TBDPS protection and hydrogenolysis. The monomeric seco acid **35** was prepared via hydrogenolysis. The direct macrodiolide formation of the monomeric seco acid **35** did not proceed. A relatively low yield of the macrolide product **36** was obtained in the presence of 2-chloro-1,3-dimethylimidazolinium chloride (CDIC) and Cs_2CO_3[19] (Scheme 12).

Coupling reaction of **33** and **34** proceeded efficiently under standard Yamaguchi conditions to afford ester **37**. The dimeric seco acid **38** was obtained efficiently via TBDPS deprotection and hydrogenolysis. IKD-8344 (**1**)[20] was finally obtained upon lactonization of **38** under modified Yamaguchi conditions[21] (Scheme 13).

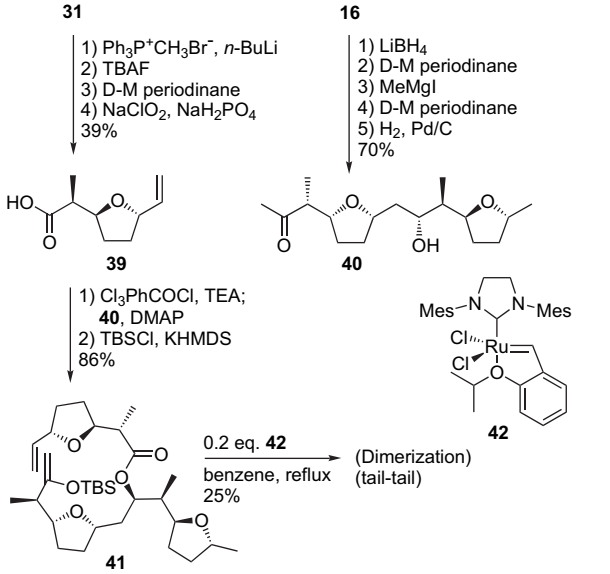


Scheme 12. Synthesis of the monomeric seco acid and attempted cyclodimerization.



Scheme 13. Synthesis of IKD-8344.

Efficacy of the ring-forming olefin metathesis reaction was investigated for the crucial C7–C8 coupling in the synthesis of the monomeric seco acid. The unsaturated carboxylic acid **39** was prepared from aldehyde **31** in four steps, and the keto alcohol **40** was obtained from the **B** fragment **16**. Coupling reaction of **39** and **40** proceeded efficiently under Yamaguchi conditions and the resulting keto ester was converted into the silyl enol ether **41**. In the presence of the second generation Grubbs–Hoveyda catalyst,[22] no trace of the product resulting from olefin-silyl enol ether ring-forming metathesis reaction[23] was found in the reaction mixture. The low-yield products from the reaction were tentatively identified as the tail–tail dimers (Scheme 14).



Scheme 14. Attempted synthesis of the seco acid unit via ring-forming metathesis reaction.

3. Conclusions

In the present synthesis, radical cyclization of a β-alkoxymethacrylate intermediate furnished the *threo-cis* oxolane unit. The *threo-trans* oxolane unit was prepared via intramolecular Williamson ether synthesis of the hydroxyl mesylate prepared via asymmetric aldol reaction. The crucial C7–C8 bond formation was accomplished via Wittig olefination, epoxidation, regioselective reduction by lithium aluminum hydride, and Dess–Martin oxidation. The present synthesis presents another example of application of β-alkoxymethacrylate radical cyclization reactions for stereoselective construction of complex oxacyclic natural products.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained on the 300, 400, 500, and 600 MHz spectrometer. Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants as hertz. Mass spectra were recorded using electron impact (EI), chemical ionization (CI), and fast atom bombardment (FAB) method. Significant fragments are reported as *m/z* (relative intensity). Optical rotation data were obtained on a automatic polarimeter.

The progress of reaction was checked on TLC plates, and the spots were visualized under 254 nm UV light and/or charring after dipping the TLC plate into vanillin solution (9.0 g of vanillin and 1.5 mL of concentrated sulfuric acid in 300 mL of methanol), $KMnO_4$ solution (3 g of $KMnO_4$, 20 g of K_2CO_3, and 5 mL of 5% NaOH solution in 300 mL of water), or phosphomolybdic acid solution (250 mg phosphomolybdic acid in 50 mL ethanol). Column chromatography was performed on silica gel using hexane–EtOAc (v/v). The solvents were simple distilled unless otherwise noted.

Unless otherwise specified, all reactions were conducted under a slight positive pressure of dry nitrogen. The usual work-up refers to washing the quenched reaction mixture with brine, drying the organic extracts over anhydrous $MgSO_4$, and evaporating under reduced pressure using a rotary evaporator.

All solvents used in the reactions were dried under nitrogen atmosphere. THF was distilled from Na-benzophenone and CH_2Cl_2 was distilled from P_2O_5. Benzene was washed with concd H_2SO_4, distilled from Na-benzophenone, and stored over 4 Å molecular sieves. Et_2O was distilled from LAH. CH_3CN was distilled from CaH_2 and stored over 4 Å molecular sieves. Pyridine and TEA was distilled over KOH and stored over 4 Å molecular sieves.

4.1.1. Alcohol 5. *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 10.7 mL) was added to a solution of imide **2** (3.25 g, 13.9 mmol) in CH_2Cl_2 (14 mL) at −40 °C, followed within 1 min by TEA (1.78 mL, 12.7 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 30 min at this temperature. Upon cooling to −78 °C, a solution of aldehyde **3** (1.47 g, 9.29 mmol) in CH_2Cl_2 (5 mL) was introduced over 3 min. The reaction mixture was stirred for 1 h at −78 °C, warmed to 0 °C over 15 min, and stirred at 0 °C for 3.5 h. The reaction was quenched by addition of water (10 mL). The reaction mixture was extracted with CH_2Cl_2 (15 mL×3) and the organic extracts were washed with saturated NH_4Cl solution (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The boron containing compounds in the residue was azeotroped off a few times with CH_3OH. Purification of the residue by flash column chromatography (Hex–EtOAc, 3:1) yielded aldol **4** (3.05 g, 84%). R_f 0.25 (Hex–EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.30 (m, 5H), 5.70 (d, 1H, J=7.2 Hz), 4.85–4.76 (m, 1H), 4.13–4.03 (m, 2H), 4.01–3.95 (m, 1H), 3.84–3.79 (m, 1H), 3.56–3.51 (m, 1H), 3.21 (d, 1H, J=3.1 Hz), 1.88–1.49 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H), 1.25 (d, 3H, J=6.9 Hz), 0.89 (d, 3H, J=6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 152.5, 133.0, 128.64, 128.55, 125.4, 108.6, 78.7, 75.9, 71.3, 69.2, 54.6, 42.4, 30.3, 30.0, 26.8, 25.6, 14.2, 10.4. MS *m/z* (CI, relative intensity): 392 (M^++1, 10), 334 (100), 234 (39), 178 (28), 101 (45). HRMS (CI) calcd for $C_{21}H_{30}O_6N$ (M^++1) 392.2073, found 392.2075. $[\alpha]_D^{28}$ −3.2 (*c* 3.74, $CHCl_3$).

$LiBH_4$ (2.0 M in THF, 8.9 mL) was added to a suspension of aldol **4** (3.50 g, 8.94 mmol) in Et_2O (89 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 30 min, the reaction was quenched by addition of saturated NH_4Cl solution (50 mL). The reaction mixture was extracted with EtOAc (50 mL×2) and the organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave the corresponding diol. R_f 0.20 (Hex–EtOAc, 1:1).

Imidazole (0.910 g, 13.4 mmol) and TBDPSCl (2.74 mL, 10.7 mmol) were added to a solution of the diol in CH_2Cl_2 (30 mL) at room temperature. After 1 h, the reaction was quenched by addition of saturated NH_4Cl solution (20 mL). The reaction mixture was extracted with CH_2Cl_2 (20 mL×3), and the organic extracts were washed with brine

(20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) provided alcohol **5** (3.59 g, 88% for two steps). R_f 0.72 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.65 (m, 4H), 7.47–7.37 (m, 6H), 4.14–4.03 (m, 2H), 3.90–3.83 (m, 1H), 3.75 and 3.67 (ABX, 2H, J_{AB}=10.0 Hz, J_{AX}=4.1 Hz, J_{BX}=6.0 Hz), 3.60–3.51 (m, 1H), 2.95 (d, 1H, J=4.0 Hz), 1.85–1.74 (m, 2H), 1.68–1.45 (m, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.06 (s, 9H), 0.92 (d, 3H, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 135.5, 132.8, 129.9, 129.8, 127.8, 108.8, 76.4, 74.1, 69.6, 68.5, 39.3, 30.7, 30.6, 27.0, 26.8, 25.8, 19.1, 10.4. IR (neat): ν_{max}=3500, 3070, 3048, 2931, 2859, 1471, 1427, 1369, 1216, 1157, 1110, 1066, 823, 703, 613, 505 cm^{-1}. MS *m/z* (CI, relative intensity): 457 (M^++1, 38), 399 (29), 341 (100), 321 (36), 303 (28), 269 (15), 263 (39), 243 (49), 199 (49). HRMS (CI) calcd for $C_{27}H_{41}O_4Si$ (M^++1) 457.2774, found 457.2773. $[\alpha]_D^{23}$ +9.1 (*c* 0.53, $CHCl_3$).

4.1.2. Alcohol 6. TEA (1.12 mL, 8.03 mmol) and MsCl (0.540 mL, 6.89 mmol) were added to a solution of alcohol **5** (2.62 g, 5.74 mmol) in CH_2Cl_2 (12 mL) at 0 °C, and then the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 1 h, and the reaction was quenched by addition of saturated NH_4Cl solution (6 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3), and the organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) provided the corresponding mesylate (3.01 g, 98%). R_f 0.53 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67–7.62 (m, 4H), 7.46–7.25 (m, 6H), 5.00–4.94 (m, 1H), 4.07–4.00 (m, 2H), 3.61–3.51 (m, 3H), 2.94 (s, 3H), 1.96–1.80 (m, 3H), 1.62–1.59 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H), 1.07 (s, 9H), 0.91 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.53, 135.49, 133.3, 133.2, 129.8, 127.7, 108.8, 83.6, 75.6, 69.2, 64.8, 38.8, 38.3, 29.7, 28.9, 26.9, 26.8, 25.6, 19.1, 10.9. IR (neat): ν_{max}= 3072, 3046, 2987, 2956, 2933, 2857, 1471, 1427, 1359, 1176, 1112, 908, 742, 703, 615, 505 cm^{-1}. MS *m/z* (FAB, relative intensity): 535 (M^++1, 4), 323 (18), 303 (14), 277 (56), 269 (14), 239 (19), 217 (22), 199 (41), 183 (24), 135 (100), 125 (61). HRMS (FAB) calcd for $C_{28}H_{43}O_6SiS$ (M^++1) 535.2549, found 535.2546. $[\alpha]_D^{23}$ −11.5 (*c* 0.39, $CHCl_3$).

CSA (59.9 mg, 0.260 mmol) was added to a solution of the mesylate (2.76 g, 5.16 mmol) in CH_3OH (52 mL) at room temperature. After stirring for 2 h, the reaction was quenched by addition of TEA (0.036 mL) and the reaction mixture was concentrated. Purification of the residue by flash column chromatography (EtOAc) afforded the corresponding diol (2.14 g, 84%). R_f 0.55 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.62 (m, 4H), 7.46–7.37 (m, 6H), 5.02–4.97 (m, 1H), 3.70–3.58 (m, 4H), 3.46–3.44 (m, 1H), 2.94 (s, 3H), 2.85 (s, 2H), 1.95–1.85 (m, 3H), 1.51–1.46 (m, 2H), 1.07 (s, 9H), 0.91 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.59, 135.55, 133.4, 133.3, 129.8, 127.8, 127.6, 83.7, 71.7, 66.6, 64.9, 38.8, 38.3, 29.7, 28.6, 26.9, 19.2, 10.8. IR (neat): ν_{max}=3390, 3072, 2931, 2857, 1471, 1427, 1390, 1336, 1172, 1112, 908, 823, 740, 615, 505 cm^{-1}. MS *m/z* (CI, relative intensity): 495 (M^++1, 0.6), 377 (8), 257 (15), 239 (31), 199 (100), 179 (79), 137 (14), 75 (35). HRMS (CI) calcd for $C_{25}H_{39}O_6SiS$ (M^++1) 495.2236, found 495.2230. $[\alpha]_D^{23}$ +1.9 (*c* 0.65, $CHCl_3$).

NaHMDS (1.0 M in THF, 1.4 mL) was added to a solution of the diol (0.34 g, 0.69 mmol) in THF (7 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature. After 2 h, the reaction was quenched by addition of saturated NH_4Cl solution (5 mL). The reaction mixture was extracted with Et_2O (5 mL×2) and the organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave alcohol **6** (0.22 g, 80%). R_f 0.52 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.69 (m, 4H), 7.45–7.36 (m, 6H), 4.06–3.98 (m, 1H), 3.95–3.90 (m, 1H), 3.77–3.67 (m, 2H), 3.59 and 3.46 (ABX, 2H, J_{AB}=11.4 Hz, J_{AX}=2.9 Hz, J_{BX}=6.3 Hz), 2.03–1.54 (m, 5H), 1.07 (s, 9H), 0.97 (d, 3H, J=6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.9, 129.5, 127.6, 80.3, 79.0, 66.1, 65.1, 40.8, 29.8, 27.6, 26.9, 19.4, 13.1. IR (neat): ν_{max}=3444, 3070, 3048, 2929, 1471, 1427, 1390, 1361, 1187, 1112, 823, 701, 613 cm^{-1}. MS *m/z* (CI, relative intensity): 399 (M^++1, 33), 341 (53), 321 (45), 303 (44), 291 (24), 243 (100), 95 (54). HRMS (CI) calcd for $C_{24}H_{35}O_3Si$ (M^++1) 399.2355, found 399.2353. $[\alpha]_D^{23}$ +6.2 (*c* 0.35, $CHCl_3$).

4.1.3. Mesylate 7. TEA (0.160 mL, 1.16 mmol) and MsCl (0.078 mL, 0.99 mmol) were added to a solution of alcohol **6** (0.33 g, 0.83 mmol) in CH_2Cl_2 (2 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 1 h, and the reaction was quenched by addition of saturated NH_4Cl solution (2 mL). The reaction mixture was extracted with CH_2Cl_2 (5 mL×3). The organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave mesylate **7** (0.387 g, 98%). R_f 0.53 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.64 (m, 4H), 7.44–7.32 (m, 6H), 4.20–4.14 (m, 3H), 3.92–3.90 (m, 1H), 3.69 and 3.63 (ABX, 2H, J_{AB}=9.8 Hz, J_{AX}=4.4 Hz, J_{BX}=6.0 Hz), 2.90 (s, 3H), 2.02–1.97 (m, 2H), 1.81–1.62 (m, 3H), 1.05 (s, 9H), 0.96 (d, 3H, J=6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.64, 135.63, 133.8, 129.6, 127.6, 80.9, 76.1, 72.0, 66.1, 40.8, 37.6, 29.5, 28.1, 26.9, 19.4, 13.1. IR (neat): ν_{max}=2931, 2867, 2827, 1359, 1176, 1112, 958, 823, 742, 703, 615, 505 cm^{-1}. MS *m/z* (CI, relative intensity): 477 (M^++1, 63), 419 (92), 399 (48), 381 (39), 277 (42), 125 (86), 95 (100). HRMS (CI) calcd for $C_{25}H_{37}O_5SiS$ (M^++1) 477.2131, found 477.2134. $[\alpha]_D^{23}$ +1.9 (*c* 2.88, $CHCl_3$).

4.1.4. Aldehyde 8. TBAF (1.0 M in THF, 2.9 mL) was added to a solution of mesylate **7** (1.3 g, 2.7 mmol) in THF (27 mL) at room temperature and the reaction mixture was stirred for 2 h. After evaporation of the solvent, the residue was purified by flash column chromatography (EtOAc) to give the corresponding primary alcohol (0.60 g, 95%). R_f 0.53 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.35–4.15 (m, 3H), 3.87–3.75 (m, 1H), 3.61–3.56 (m, 2H), 3.06 (s, 3H), 3.03–2.99 (m, 1H), 2.21–2.02 (m, 2H), 1.82–1.16 (m, 3H), 0.83 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 85.1, 76.4, 71.1, 67.9, 40.6, 37.6, 31.1, 27.3, 13.3. IR (neat): ν_{max}=3419, 3018, 2967, 2935, 2884, 1351, 1174, 1087, 954, 528 cm^{-1}. MS *m/z* (CI, relative intensity): 239

(M^++1, 87), 221 (100), 179 (38), 125 (57), 107 (42), 83 (30). HRMS (CI) calcd for $C_9H_{19}O_5S$ (M^++1) 239.0953, found 239.0953. $[\alpha]_D^{24}$ +0.5 (*c* 1.08, $CHCl_3$).

A solution of the alcohol (0.940 g, 3.94 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of PCC (1.70 g, 7.89 mmol) and 4 Å molecular sieve (1.70 g) in CH_2Cl_2 (40 mL) at room temperature. After stirring for 2 h, the reaction mixture was diluted with hexane (50 mL) and filtered through a short pad of silica gel. Concentration of the filtrate and purification of the residue by flash column chromatography (Hex–EtOAc, 1:2) gave aldehyde **8** (0.764 g, 82%). R_f 0.47 (Hex–EtOAc, 1:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (d, 1H, J=2.4 Hz), 4.35–4.25 (m, 1H), 4.22–4.10 (m, 3H), 3.06 (s, 3H), 2.54–2.44 (m, 1H), 2.17–2.09 (m, 2H), 1.77–1.58 (m, 2H), 1.07 (d, 3H, J=3.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 79.8, 76.6, 71.3, 51.2, 37.6, 30.0, 27.4, 10.3. IR (neat): ν_{max}=2969, 2938, 2728, 1725, 1353, 1174, 954, 821, 528 cm^{-1}. $[\alpha]_D^{24}$ +26.8 (*c* 1.16, $CHCl_3$).

4.1.5. Homoallylic alcohols 9 and 10. $TiCl_4$ (1.0 M in CH_2Cl_2, 1.4 mL) was added to a solution of aldehyde **8** (0.17 g, 0.72 mmol) in CH_2Cl_2 (36 mL) at −78 °C under N_2. After 15 min, allyltrimethylsilane (0.17 mL, 1.1 mmol) was added to the solution, and the resulting solution was stirred for 30 min at −78 °C. The reaction was quenched by addition of saturated $NaHCO_3$ solution (20 mL). The reaction mixture was extracted with CH_2Cl_2 (30 mL×3), and the organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave a mixture (4:1) of the homoallylic alcohols **9** and **10**. R_f 0.34 (Hex–EtOAc, 1:1).

4.1.6. Homoallylic alcohol 12. A mixture of the homoallylic alcohols **9** and **10** (0.730 g, 2.62 mmol) in Et_2O (10 mL) was added dropwise to a suspension of LAH (498 mg, 13.1 mmol) in Et_2O (26 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of water (2 mL) and 15% aqueous NaOH solution (0.5 mL). Filtration, concentration, and purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave the homoallylic alcohols **9A** (0.319 g, 66%) and **10A** (0.077 g, 16%). Compound **9A**: R_f 0.70 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.02–5.88 (m, 1H), 5.09 (dd, 2H, J=7.6, 13.2 Hz), 4.76 (s, 1H), 4.15–4.07 (m, 1H), 3.90–3.82 (m, 1H), 3.66–3.60 (m, 1H), 2.41–2.63 (m, 1H), 2.18–2.09 (m, 2H), 2.04–1.95 (m, 1H), 1.66–1.34 (m, 3H), 1.20 (d, 3H, J=6.0 Hz), 0.75 (d, 3H, J=6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.3, 116.6, 84.5, 75.6, 75.5, 43.4, 38.7, 33.4, 32.5, 21.0, 12.6. IR (neat): ν_{max}=3465, 3073, 2969, 2931, 1639, 1459, 1432, 1378, 1083, 1000, 908, 873 cm^{-1}. MS *m*/*z* (CI, relative intensity): 185 (M^++1, 3), 177 (12), 167 (49), 149 (100), 113 (43), 85 (11). HRMS (CI) calcd for $C_{11}H_{21}O_2$ (M^++1) 185.1541, found 185.1541. $[\alpha]_D^{26}$ −27.6 (*c* 0.65, $CHCl_3$). Compound **10A**: R_f 0.61 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96–5.87 (m, 1H), 5.15–5.06 (m, 2H), 4.15–4.08 (m, 1H), 4.01–3.94 (m, 1H), 3.81–3.76 (m, 1H), 3.19 (d, 1H, J=6.8 Hz), 2.28–2.21 (m, 2H), 2.08–2.00 (m, 2H), 1.76–1.60 (m, 2H), 1.52–1.42 (m, 1H), 1.21 (d, 3H, J=6.1 Hz), 0.87 (d, 3H, J=7.1 Hz).

NaHMDS (1.0 M in THF, 0.49 mL), BnBr (0.060 mL, 0.49 mmol) were added to a solution of the homoallylic alcohol **9A** (75 mg, 0.41 mmol) in THF–DMF (5:1, 5.8 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction was quenched by addition of 2 N HCl (2 mL). The reaction mixture was extracted with Et_2O (10 mL×2). The organic extracts were washed with brine (10 mL×3), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 8:1) gave benzyl ether **11** (0.10 g, 90%). R_f 0.56 (Hex–EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.27 (m, 5H), 5.98–5.87 (m, 1H), 5.13–5.02 (m, 2H), 4.53–4.50 (ABq, 2H, J_{AB}=11.7 Hz), 4.07–4.01 (m, 1H), 3.97–3.89 (m, 1H), 3.67–3.62 (m, 1H), 2.38–2.23 (m, 2H), 2.07–1.88 (m, 3H), 1.61–1.39 (m, 2H), 1.20 (d, 3H, J=6.0 Hz), 0.85 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 136.1, 128.2, 127.6, 127.3, 116.3, 80.1, 79.5, 74.7, 71.3, 40.4, 34.3, 33.9, 30.1, 21.4, 10.2. IR (neat): ν_{max}=3066, 3029, 2967, 2933, 1641, 1496, 1454, 1376, 1070, 1027, 910, 734, 696 cm^{-1}. MS *m*/*z* (CI, relative intensity): 275 (M^++1, 42), 233 (55), 167 (22), 125 (15), 91 (49), 85 (100). HRMS (CI) calcd for $C_{18}H_{27}O_2$ (M^++1) 275.2011, found 275.2016. $[\alpha]_D^{26}$ −8.9 (*c* 0.83, $CHCl_3$).

O_3 was introduced to a stirred solution of the benzyl ether **11** (183 mg, 0.670 mmol) in CH_2Cl_2 (7 mL) over a period of 10 min at −78 °C. Following the addition of PPh_3 (525 mg, 2.00 mmol), the reaction mixture was allowed to warm to room temperature. After stirring for 3 h, the solvent was evaporated and the residue was purified by flash column chromatography (Hex–EtOAc, 4:1) to give the corresponding aldehyde (179 mg, 97%). R_f 0.31 (Hex–EtOAc, 4:1).

$MgBr_2 \cdot Et_2O$ (751 mg, 2.91 mmol) and allyltributylstannane (0.450 mL, 1.45 mmol) were added to a solution of the aldehyde (268 mg, 0.970 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 1 h, the reaction was quenched by addition of 2 N HCl (3 mL). The reaction mixture was extracted with CH_2Cl_2 (5 mL×3), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 4:1) gave the homoallylic alcohol **12** (300 mg, 97%). R_f 0.19 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.27 (m, 5H), 5.92–5.78 (m, 1H), 5.09 (dd, 2H, J=13.6, 6.5 Hz), 4.56 and 4.49 (ABq, 2H, J_{AB}=11.4 Hz), 4.13–4.03 (m, 1H), 3.99–3.93 (m, 1H), 3.90–3.78 (m, 2H), 2.92 (d, 1H, J=4.2 Hz), 2.27–2.23 (m, 2H), 2.11–1.96 (m, 3H), 1.70–1.38 (m, 4H), 1.19 (d, 3H, J=6.1 Hz), 0.84 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 135.2, 128.4, 127.8, 127.6, 117.3, 79.7, 77.8, 74.9, 71.1, 69.1, 42.2, 40.1, 35.6, 33.8, 31.0, 21.4, 10.0. IR (neat): ν_{max}=3419, 3066, 3029, 2967, 2929, 1454, 1376, 1068, 1027, 997, 734, 698 cm^{-1}. MS *m*/*z* (CI, relative intensity): 319 (M^++1, 38), 301 (10), 277 (10), 233 (10), 211 (29), 193 (15), 169 (19), 107 (18), 91 (28), 85 (100). HRMS (CI) calcd for $C_{20}H_{31}O_3$ (M^++1) 319.2273, found 319.2276. $[\alpha]_D^{25}$ +28.6 (*c* 0.87, $CHCl_3$).

4.1.7. Iodide 15. O_3 was introduced to a stirred solution of the homoallylic alcohol **12** (867 mg, 2.72 mmol) in CH_2Cl_2 (54 mL) over a period of 15 min at −78 °C. Following addition of PPh_3 (2.14 g, 8.17 mmol), the reaction

mixture was allowed to warm to room temperature. After stirring for 3 h, concentration of the solvent gave the crude aldehyde. R_f 0.47 (Hex–EtOAc, 1:1).

$NaBH_4$ (124 mg, 3.27 mmol) was added slowly to a solution of the crude aldehyde in CH_3OH (27 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 30 min, the reaction mixture was diluted with Et_2O (30 mL). The reaction was quenched by addition of saturated NH_4Cl solution (30 mL). The reaction mixture was extracted with EtOAc (40 mL×3). The organic extracts were washed with brine (80 mL) and dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (EtOAc) afforded diol **13** (851 mg, 97% for two steps). R_f 0.5 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 4.57 and 4.48 (ABq, 2H, J_{AB}=11.3 Hz), 4.15–4.03 (m, 2H), 4.00–3.94 (m, 1H), 3.85–3.75 (m, 3H), 3.57 (d, 1H, J=4.0 Hz), 2.93 (t, 1H, J=5.4 Hz), 2.13–2.00 (m, 3H), 1.82–1.37 (m, 6H), 1.19 (d, 3H, J=6.1 Hz), 0.85 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 132.1, 128.4, 127.8, 127.6, 79.8, 77.4, 75.0, 71.0, 70.4, 61.8, 40.0, 38.7, 36.3, 33.7, 31.2, 21.3, 9.9. IR (neat): ν_{max}=3390, 3062, 3029, 2965, 2935, 2875, 1666, 1646, 1496, 1454, 1438, 1378, 1120, 1027 cm^{-1}. MS *m/z* (CI, relative intensity): 323 (M^++1, 44), 305 (14), 279 (26), 215 (36), 197 (44), 107 (28), 85 (100). HRMS (CI) calcd for $C_{19}H_{31}O_4$ (M^++1) 323.2222, found 323.2223. $[\alpha]_D^{27}$ +15.9 (*c* 4.46, $CHCl_3$).

TEA (0.740 mL, 5.28 mmol) and *p*-TsCl (755 mg, 3.96 mmol) were added to a solution of the diol (851 mg, 2.64 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at 0 °C for 14 h, the resulting solution was diluted with CH_2Cl_2 (5 mL), and poured into saturated NH_4Cl solution (4 mL). The reaction mixture was extracted with CH_2Cl_2 (5 mL×2), and the organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave the corresponding tosylate (1.16 g, 92%). R_f 0.5 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, 2H, J=8.3 Hz), 7.37–7.26 (m, 6H), 4.54 and 4.42 (ABq, 2H, J_{AB}=11.4 Hz), 4.23–4.15 (m, 2H), 4.10–4.04 (m, 1H), 3.94–3.88 (m, 2H), 3.78–3.70 (m, 1H), 3.03 (s, 1H), 2.43 (s, 3H), 2.10–1.97 (m, 3H), 1.86–1.68 (m, 2H), 1.64–1.37 (m, 4H), 1.18 (d, 3H, J=6.1 Hz), 0.82 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 138.4, 133.1, 129.8, 128.4, 127.9, 127.8, 127.7, 79.7, 77.3, 74.9, 70.8, 68.1, 66.0, 39.9, 36.5, 35.8, 33.7, 31.3, 21.6, 21.3, 10.0. IR (neat): ν_{max}=3419, 3031, 2965, 2929, 2875, 1598, 1454, 1359, 1176, 1068, 960, 917 cm^{-1}. MS *m/z* (CI, relative intensity): 477 (M^++1, 44), 369 (11), 351 (11), 215 (12), 197 (23), 101 (11), 91 (63), 85 (100). HRMS (CI) calcd for $C_{26}H_{37}O_6S$ (M^++1) 477.2311, found 477.2310. $[\alpha]_D^{27}$ +9.1 (*c* 1.10, $CHCl_3$).

Methyl 3,3-dimethoxy-2-methylpropionate (**14**, 48 mg, 0.29 mmol) was added to a solution of the tosylate (28 mg, 0.060 mmol) and PPTS (3.0 mg, 0.010 mmol) in benzene (1 mL). The reaction mixture was heated under reflux for 2 h. After removal of the solvent, purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) afforded the β-alkoxymethacrylate derivative (30 mg, 89%). R_f 0.45 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 2H, J=8.2 Hz), 7.38–7.08 (m, 8H), 4.52 and 4.28 (ABq, 2H, J_{AB}=11.1 Hz), 4.24–4.15 (m, 1H), 4.13–3.99 (m, 3H), 3.83–3.79 (m, 1H), 3.70–3.62 (m, 1H), 3.65 (s, 3H), 2.41 (s, 3H), 2.06–1.90 (m, 5H), 1.74–1.70 (m, 1H), 1.64 (s, 3H), 1.59–1.39 (m, 3H), 1.16 (d, 3H, J=6.1 Hz), 0.80 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 157.2, 144.8, 138.5, 132.6, 129.8, 128.3, 127.8, 127.7, 127.5, 105.5, 79.6, 78.2, 75.2, 74.5, 70.4, 66.3, 51.0, 39.1, 34.8, 34.7, 33.7, 31.7, 21.5, 21.2, 9.6, 9.0. IR (neat): ν_{max}=3064, 3031, 2965, 2923, 2867, 1704, 1644, 1598, 1454, 1361, 1294, 1178, 1122 cm^{-1}. $[\alpha]_D^{26}$ +43.4 (*c* 3.46, $CHCl_3$).

NaI (69 mg, 0.46 mmol) was added to a solution of the β-alkoxymethacrylate derivative (0.10 g, 0.18 mmol) in acetone (5 mL) at room temperature, and then the solution was heated under reflux for 2 h. The reaction mixture was washed with brine (5 mL). The reaction mixture was extracted with Et_2O (10 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 4:1) gave iodide **15** (87 mg, 90%). R_f 0.41 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.25 (m, 6H), 4.54 and 4.33 (ABq, 2H, J_{AB}=11.3 Hz), 4.24–4.16 (m, 1H), 4.08–4.00 (m, 1H), 3.86 (dt, 1H, J=10.6, 2.9 Hz), 3.73–3.61 (m, 1H), 3.65 (s, 3H), 3.25–3.07 (m, 2H), 2.19–1.98 (m, 3H), 1.84–1.79 (m, 1H), 1.75 (d, 3H, J=0.4 Hz), 1.66–1.37 (m, 3H), 1.17 (d, 3H, J=6.1 Hz), 0.83 (d, 3H, J=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 157.6, 138.6, 128.4, 127.9, 127.6, 105.5, 82.0, 79.8, 75.5, 74.7, 70.7, 51.1, 39.8, 39.3, 34.6, 33.8, 31.7, 21.4, 9.8, 9.3.

4.1.8. Ester 16. *n*-Bu_3SnH (0.018 mL, 0.070 mmol) and Et_3B (1.0 M in hexane, 0.088 mL) were added to a solution of iodide **15** (31 mg, 0.058 mmol) in toluene (6 mL) at −78 °C. The resulting solution was stirred for 1 h under air at −78 °C. Concentration and purification of the residue by flash column chromatography (Hex–EtOAc, 4:1) furnished ester **16** (22 mg, 91%). R_f 0.31 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.24 (m, 5H), 4.53 and 4.47 (ABq, 2H, J_{AB}=11.3 Hz), 4.08–3.99 (m, 3H), 3.86–3.78 (m, 2H), 3.69 (s, 3H), 2.60–2.55 (m, 1H), 2.05–1.90 (m, 6H), 1.70–1.39 (m, 5H), 1.19 (d, 3H, J=6.0 Hz), 1.11 (d, 3H, J=7.0 Hz), 0.82 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 139.2, 128.2, 127.7, 127.2, 80.0, 79.6, 77.9, 77.2, 74.6, 71.6, 51.6, 45.2, 40.6, 36.5, 33.9, 31.6, 30.7, 28.4, 21.4, 13.1, 10.0. IR (neat): ν_{max}=3029, 2967, 2877, 1739, 1455, 1376, 1197, 1068, 736, 698 cm^{-1}. MS *m/z* (CI, relative intensity): 405 (M^++1, 81), 297 (100), 295 (28), 279 (11), 213 (63), 183 (31), 157 (42), 91 (23). HRMS (CI) calcd for $C_{24}H_{37}O_5$ (M^++1) 405.2641, found 405.2641. $[\alpha]_D^{27}$ +14.0 (*c* 1.16, $CHCl_3$).

4.1.9. Dithiane 17. $LiBH_4$ (2.0 M in THF, 0.050 mL) was added to a solution of ester **16** (19 mg, 0.050 mmol) in Et_2O (1 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction was quenched by addition of saturated NH_4Cl solution (1 mL). The reaction mixture was extracted with Et_2O (2 mL×4) and the organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column

chromatography (Hex–EtOAc, 1:1) gave the corresponding alcohol (18 mg, 100%). R_f 0.52 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.23 (m, 5H), 4.57 and 4.45 (ABq, 2H, J_{AB}=11.4 Hz), 4.10–4.01 (m, 2H), 3.93–3.87 (m, 1H), 3.81–3.73 (m, 1H), 3.66–3.45 (m, 4H), 2.04–1.92 (m, 5H), 1.73–1.39 (m, 7H), 1.20 (d, 3H, J=6.1 Hz), 0.83–0.79 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 128.2, 127.8, 127.3, 85.3, 79.7, 77.6, 77.3, 74.6, 71.5, 68.5, 41.3, 40.2, 36.0, 33.8, 30.95, 30.92, 30.6, 21.3, 13.9, 9.9. IR (neat): ν_{max}=3444, 3064, 3029, 2964, 2875, 1455, 1376, 1070, 894, 863, 734, 698 cm^{-1}. MS m/z (CI, relative intensity): 377 (M^++1, 100), 269 (35), 185 (33), 129 (18), 107 (11), 91 (15), 85 (41). HRMS (CI) calcd for $C_{23}H_{37}O_4$ (M^++1) 377.2692, found 377.2693. $[\alpha]_D^{27}$ +39.4 (c 2.56, $CHCl_3$).

Dess–Martin periodinane (676 mg, 1.59 mmol) was added to a solution of the alcohol (400 mg, 1.06 mmol) in CH_2Cl_2 (70 mL). The reaction mixture was stirred at room temperature for 1 h and the reaction was quenched by addition of saturated $Na_2S_2O_3$ solution (50 mL). The reaction mixture was extracted with CH_2Cl_2 (40 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave the corresponding aldehyde (394 mg, 99%). R_f 0.66 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.83 (d, 1H, J=1.9 Hz), 7.34–7.26 (m, 5H), 4.47 and 4.56 (ABq, 2H, J_{AB}=11.4 Hz), 4.14–4.11 (m, 1H), 4.08–4.01 (m, 1H), 3.96–3.90 (m, 2H), 3.78–3.73 (m, 1H), 2.52–2.42 (m, 1H), 2.03–1.95 (m, 6H), 1.73–1.51 (m, 4H), 1.49–1.39 (m, 1H), 1.17 (d, 3H, J=6.1 Hz), 1.05 (d, 3H, J=7.0 Hz), 0.83 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.3, 139.2, 128.2, 127.7, 127.3, 79.8, 79.6, 77.5, 77.1, 74.6, 71.6, 51.8, 40.4, 36.3, 33.9, 31.3, 31.1, 29.6, 21.4, 10.4, 10.0. IR (neat): ν_{max}=3087, 3062, 3030, 2966, 2933, 2871, 2725, 1726, 1496, 1456, 1377, 1070, 893, 737, 698 cm^{-1}. $[\alpha]_D^{29}$ −6.0 (c 0.45, $CHCl_3$).

A mixture of the aldehyde (25 mg, 0.070 mmol), 1,3-propanedithiol (0.010 mL, 0.10 mmol), and $LiBF_4$ (0.63 mg, 0.0070 mmol) in CH_3CN (0.1 mL) was stirred at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (0.5 mL) and extracted with CH_2Cl_2 (2 mL×2). The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (Hex–EtOAc, 4:1) to afford dithiane **17** (25 mg, 81%). R_f 0.64 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.23 (m, 5H), 4.63 (d, 1H, J=3.2 Hz), 4.56 and 4.52 (ABq, 2H, J_{AB}=11.3 Hz), 4.13–4.03 (m, 2H), 3.92–3.80 (m, 3H), 3.05–2.80 (m, 4H), 2.13–1.78 (m, 9H), 1.77–1.26 (m, 5H), 1.20 (d, 3H, J=6.1 Hz), 1.03 (d, 3H, J=7.0 Hz), 0.84 (d, 3H, J=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 128.2, 127.7, 127.3, 79.6, 79.4, 78.1, 74.6, 71.7, 52.6, 44.7, 40.6, 36.6, 33.9, 31.7, 31.3, 30.7, 30.6, 29.5, 26.5, 21.5, 12.6, 10.0.

4.1.10. Triflate 18. Triflic anhydride (0.030 mL, 0.20 mmol) was added dropwise to a solution of alcohol **6** (65 mg, 0.16 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (50 mg, 0.24 mmol) in CH_2Cl_2 (6 mL) at −78 °C. After 15 min, the mixture was diluted with ether (3 mL) and the mixture was allowed to warm to 0 °C and filtered. The filtrate was washed with 1 N HCl (2 mL) and brine (2 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified immediately by flash column chromatography (Hex–EtOAc, 10:1) to afford the triflate **18** (78 mg, 90%). R_f 0.50 (Hex–EtOAc, 10:1).

4.1.11. Iodide 19. PPh_3 (88 mg, 0.34 mmol), imidazole (45 mg, 0.67 mmol), and I_2 (85 mg, 0.34 mmol) were added to a solution of alcohol **6** (89 mg, 0.22 mmol) in THF (2 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was diluted with Et_2O (4 mL) and poured into saturated $Na_2S_2O_3$ solution (2 mL), and the reaction mixture was extracted with Et_2O (3 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 12:1) gave iodide **19** (101 mg, 94%). R_f 0.68 (Hex–EtOAc, 12:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71–7.66 (m, 4H), 7.45–7.36 (m, 6H), 4.06–3.99 (m, 2H), 3.68–3.66 (m, 2H), 3.26 and 3.14 (ABX, 2H, J_{AB}=9.7 Hz, J_{AX}=4.5 Hz, J_{BX}=7.7 Hz), 2.22–2.10 (m, 1H), 2.05–1.94 (m, 1H), 1.81–1.58 (m, 3H), 0.95 (s, 9H), 0.94 (d, 3H, J=6.8 Hz).

4.1.12. Attempted coupling reaction of dithiane 17 with triflate 18. *t*-BuLi (1.7 M in pentane, 0.019 mL) and HMPA (0.010 mL) were added sequentially to a solution of dithiane **17** (10 mg, 0.022 mmol) in THF (0.10 mL) at −78 °C. After 5 min, a solution of triflate **18** (17 mg, 0.032 mmol) in THF (0.10 mL) was added to the solution at −78 °C. The reaction mixture was allowed to warm to −50 °C. After 1 h, TLC analysis indicated that triflate **18** decomposed.

4.1.13. Attempted coupling reaction of dithiane 17 with iodide 19. *t*-BuLi (1.7 M in pentane, 0.025 mL) and HMPA (0.010 mL) were added sequentially to a solution of dithiane **17** (10 mg, 0.022 mmol) in THF (0.10 mL) at −78 °C. After 5 min, a solution of iodide **19** (16 mg, 0.032 mmol) in THF (0.10 mL) was added to the solution at −78 °C. The reaction mixture was allowed to warm to −50 °C. After 1 h, TLC analysis indicated that iodide **19** decomposed.

4.1.14. Attempted deuterium exchange reaction of dithiane 17. *t*-BuLi (1.7 M in pentane, 0.013 mL) and HMPA (0.010 mL) were added sequentially to a solution of dithiane **17** (8.7 mg, 0.019 mmol) in THF (0.10 mL) at −78 °C. After 5 min, the reaction was quenched by addition of D_2O. ^{1}H NMR analysis indicated that deuterium exchange did not proceed at all.

4.1.15. Dithiane 20. NaHMDS (1.0 M in THF, 2.0 mL), BnBr (0.24 mL, 2.0 mmol) were added to a solution of alcohol **6** (0.63 g, 1.6 mmol) in DMF (7 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction was quenched by addition of 2 N HCl (5 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 4:1) gave the corresponding benzyl ether (0.70 g, 91%). R_f 0.67 (Hex–EtOAc, 4:1). ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.68–7.65 (m, 4H), 7.42–7.18 (m, 11H), 4.57 and 4.53 (ABq, 2H, J_{AB}=12.3 Hz), 4.15–4.05 (m, 1H), 3.96–3.89 (m, 1H), 3.72 and 3.65 (ABX, 2H, J_{AB}=9.8 Hz, J_{AX}=4.7 Hz, J_{BX}=6.1 Hz), 2.02–1.80 (m, 3H), 1.71–1.57 (m, 2H), 1.05 (s, 9H), 0.93 (d, 3H, J=6.8 Hz).

TBAF (1.0 M in THF, 0.46 mL) was added to a solution of the benzyl ether (0.15 g, 0.31 mmol) in THF (10 mL) at room temperature and the reaction mixture was stirred for 12 h. After evaporation of the solvent, the residue was purified by flash column chromatography (Hex–EtOAc, 1:1) to give the corresponding alcohol (0.60 g, 92%). R_f 0.25 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 4.60 (s, 2H), 4.27–4.19 (m, 1H), 3.81 (td, 1H, J=8.7, 5.9 Hz), 3.66–3.51 (m, 3H), 3.48 (d, 2H, J=5.0 Hz), 2.14–1.97 (m, 2H), 1.79–1.54 (m, 3H), 0.80 (d, 3H, J=6.9 Hz).

TEA (0.290 mL, 2.07 mmol) and SO_3·pyridine (198 mg, 1.24 mmol) were added to a solution of the alcohol (165 mg, 0.659 mmol) in DMSO–CH_2Cl_2 (1:1, 2.60 mL) at room temperature. The reaction mixture was stirred for 30 min, and the reaction was quenched by addition of saturated NH_4Cl solution (5 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave the corresponding aldehyde (150 mg, 92%). R_f 0.68 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (d, 1H, J=2.3 Hz), 7.38–7.22 (m, 5H), 4.59 and 4.57 (ABq, 2H, J_{AB}=12.3 Hz), 4.28–4.20 (m, 1H), 4.14 (td, 1H, J=8.0, 5.8 Hz), 3.47 (d, 2H, J=4.9 Hz), 2.56–2.45 (m, 1H), 2.12–1.97 (m, 2H), 1.79–1.61 (m, 2H), 1.06 (d, 3H, J=7.0 Hz).

A mixture of the aldehyde (53 mg, 0.21 mmol), 1,3-propanedithiol (0.030 mL, 0.26 mmol), and $LiBF_4$ (2.0 mg, 0.020 mmol) in CH_3CN (0.21 mL) was stirred at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (1 mL) and extracted with CH_2Cl_2 (3 mL×2). The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (Hex–EtOAc, 4:1) to afford dithiane **20** (62 mg, 86%). R_f 0.61 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 4.66–4.56 (m, 3H), 4.23–4.15 (m, 1H), 4.03 (td, 1H, J=8.7, 5.4 Hz), 3.51 and 3.44 (ABX, 2H, J_{AB}=10.1 Hz, J_{AX}=6.0 Hz, J_{BX}=4.5 Hz), 3.06–2.80 (m, 4H), 2.16–1.76 (m, 5H), 1.72–1.47 (m, 2H), 1.02 (d, 3H, J=7.0 Hz).

4.1.16. Attempted deuterium exchange reaction of dithiane 20. *t*-BuLi (1.7 M in pentane, 0.047 mL) and HMPA (0.032 mL) were added sequentially to a solution of dithiane **20** (18 mg, 0.053 mmol) in THF (1 mL) at −78 °C. After 20 min, the reaction mixture was allowed to warm to −20 °C and stirred for 2.5 h. The reaction was quenched by addition of D_2O. ^{1}H NMR analysis confirmed that deuterium exchange reaction did not proceed at all.

4.1.17. Dithiane 21. NaHMDS (1.0 M in THF, 0.50 mL), PMBCl (0.080 mL, 0.62 mmol), and TBAI (15 mg, 0.040 mmol) were added to a solution of alcohol **6** (0.17 g, 0.41 mmol) in THF–DMF (5:1, 6.0 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction was quenched by addition of 2 N HCl (5 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 4:1) gave the corresponding PMB ether (0.14 g, 67%). R_f 0.56 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.65 (m, 4H), 7.42–7.23 (m, 6H), 7.24 (d, 2H, J=7.6 Hz), 6.85 (d, 2H, J=7.7 Hz), 4.51 and 4.46 (ABq, 2H, J_{AB}=11.8 Hz), 4.11–4.08 (m, 1H), 3.94–3.92 (m, 1H), 3.79 (s, 3H), 3.70 and 3.65 (ABX, 2H, J_{AB}=9.3 Hz, J_{AX}=4.5 Hz, J_{BX}=6.2 Hz), 3.43–3.36 (m, 2H), 1.96–1.83 (m, 3H), 1.63–1.56 (m, 2H), 1.04 (s, 9H), 0.93 (d, 3H, J=6.8 Hz).

TBAF (1.0 M in THF, 0.42 mL) was added to a solution of the PMB ether (0.14 g, 0.29 mmol) in THF (10 mL) at room temperature and the reaction mixture was stirred for 12 h. After evaporation of the solvent, the residue was purified by flash column chromatography (Hex–EtOAc, 1:2) to give the corresponding alcohol (72 mg, 93%). R_f 0.41 (Hex–EtOAc, 1:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, 2H, J=8.5 Hz), 6.88 (d, 2H, J=8.6 Hz), 4.49 (s, 2H), 4.22–4.18 (m, 1H), 3.83–3.76 (m, 4H), 3.66–3.54 (m, 3H), 3.44 (d, 2H, J=4.9 Hz), 2.11–1.97 (m, 2H), 1.76–1.59 (m, 3H), 0.79 (d, 3H, J=6.9 Hz).

TEA (0.180 mL, 1.28 mmol) and SO_3·pyridine (123 mg, 0.770 mmol) were added to a solution of the alcohol (72.0 mg, 0.260 mmol) in DMSO–CH_2Cl_2 (1:1, 1.00 mL) at room temperature. The reaction mixture was stirred for 30 min, and the reaction was quenched by addition of saturated NH_4Cl solution (5 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave the corresponding aldehyde (56.0 mg, 78%). R_f 0.51 (Hex–EtOAc, 2:1).

A mixture of the aldehyde (72 mg, 0.26 mmol), 1,3-propanedithiol (0.040 mL, 0.39 mmol), and $LiBF_4$ (2.4 mg, 0.030 mmol) in CH_3CN (0.3 mL) was stirred at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (1 mL) and extracted with CH_2Cl_2 (3 mL×2). The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (Hex–EtOAc, 4:1) to afford dithiane **21** (80 mg, 84%). R_f 0.61 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, 2H, J=8.6 Hz), 6.88 (d, 2H, J=8.6 Hz), 4.60 (d, 1H, J=3.1 Hz), 4.56 and 4.52 (ABq, 2H, J_{AB}=11.8 Hz), 4.22–4.12 (m, 1H), 4.03 (td, 1H, J=8.7, 5.4 Hz), 3.81 (s, 3H), 3.48 and 3.40 (ABX, 2H, J_{AB}=10.1 Hz, J_{AX}=6.0 Hz, J_{BX}=4.6 Hz), 3.06–2.79 (m, 4H), 2.15–1.81 (m, 5H), 1.69–1.41 (m, 2H), 1.01 (d, 3H, J=7.0 Hz).

4.1.18. Deuterium exchange reaction of dithiane 21. *t*-BuLi (1.7 M in pentane, 0.067 mL) and HMPA (0.040 mL) were added sequentially to a solution of dithiane **21** (28 mg, 0.076 mmol) in THF (1 mL) at −78 °C. After 5 min, the reaction was quenched by addition of D_2O. ^{1}H NMR analysis confirmed 58% deuterium exchange.

4.1.19. Attempted coupling reaction of dithiane 21 with triflate 18. *t*-BuLi (1.7 M in pentane, 0.040 mL) and HMPA (0.043 mL) were added sequentially to a solution of dithiane **21** (23 mg, 0.062 mmol) in THF (1 mL) at −78 °C. After 20 min, the reaction mixture was allowed to warm to −20 °C and stirred for 2 h. A solution of triflate **18** (40 mg, 0.075 mmol) in THF (0.5 mL) was added to the solution at −78 °C. The reaction mixture was allowed to warm to −50 °C. After 2 h, TLC analysis indicated that triflate **18** decomposed.

4.1.20. Epoxide 22. A solution of Na (129 mg, 5.60 mmol) in CH_3OH (10 mL) was added dropwise to a solution of the aldol imide **4** (2.00 g, 5.10 mmol) in CH_3OH (10 mL) at 0 °C. After 10 min, the reaction was quenched by addition of saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×2) and the resulting extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave the corresponding hydroxy methyl ester (850 mg, 68%). R_f 0.47 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14–4.03 (m, 2H), 3.96–3.76 (m, 1H), 3.71 (s, 3H), 3.53 (t, 1H, J=7.1 Hz), 2.77 (d, 1H, J=4.7 Hz), 2.56 (qd, 1H, J=7.2, 3.8 Hz), 1.85–1.70 (m, 1H), 1.68–1.44 (m, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.21 (d, 3H, J=7.2 Hz).

2,6-Lutidine (2.00 mL, 17.3 mmol), DMAP (2.10 g, 17.3 mmol), and TIPSOTf (2.80 mL, 10.4 mmol) were added sequentially to a solution of the hydroxyl methyl ester (850 mg, 3.45 mmol) in CH_2Cl_2 (10 mL) at room temperature. After 12 h, the reaction was quenched by addition of saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash column chromatography (Hex–EtOAc, 6:1) to give the corresponding TIPS derivative (1.30 g, 94%). R_f 0.57 (Hex–EtOAc, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.37–4.25 (m, 1H), 4.14–4.01 (m, 2H), 3.66 (s, 3H), 3.55–3.41 (m, 1H), 2.56 (qd, 1H, J=7.0, 4.0 Hz), 1.77–1.65 (m, 1H), 1.64–1.40 (m, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.15 (d, 3H, J=7.0 Hz), 1.04 (s, 21H).

CSA (6.9 mg, 0.030 mmol) was added to a solution of the TIPS derivative (0.240 g, 0.060 mmol) in CH_3OH (10 mL) at room temperature. After stirring for 2 h, the reaction was quenched by addition of TEA (1 mL) and the reaction mixture was concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) afforded the corresponding diol (0.170 g, 80%). R_f 0.27 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.28–4.23 (m, 1H), 3.69–3.64 (m, 1H), 3.47–3.41 (m, 1H), 2.63–2.55 (m, 1H), 2.34 (br s, 1H), 1.95 (br s, 1H), 1.83–1.54 (m, 2H), 1.48–1.38 (m, 2H), 1.16 (d, 3H, J=7.0 Hz), 1.05 (s, 21H).

TEA (0.250 mL, 1.78 mmol) and *p*-TsCl (270 mg, 1.42 mmol) were added to a solution of the diol (430 mg, 1.19 mmol) in CH_2Cl_2 (1.19 mL). The reaction mixture was stirred at 0 °C for 14 h, and the resulting solution was diluted with CH_2Cl_2 (2 mL) and poured into saturated NH_4Cl solution (2 mL). The reaction mixture was extracted with CH_2Cl_2 (3 mL×2), and the organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 3:1) gave the corresponding tosylate (440 mg, 72%). R_f 0.47 (Hex–EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 2H, J=8.3 Hz), 7.36 (d, 2H, J=8.0 Hz), 4.20 (td, 1H, J=4.4, 7.7 Hz), 4.00 (dd, 1H, J=9.6, 3.0 Hz), 3.91–3.73 (m, 2H), 3.65 (s, 3H), 2.52 (qd, 1H, J=6.9, 4.5 Hz), 2.45 (s, 3H), 2.26 (d, 1H, J=4.1 Hz), 1.70–1.28 (m, 4H), 1.13 (d, 3H, J=7.0 Hz), 1.02 (s, 21H).

DBU (0.060 mL, 0.41 mmol) was added to a solution of the tosylate (0.10 g, 0.19 mmol) in THF (6 mL) and the reaction mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was subjected to flash column chromatography (Hex–EtOAc, 8:1) to give the corresponding epoxide (54 mg, 81%). R_f 0.43 (Hex–EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.28 (td, 1H, J=4.5, 7.8 Hz), 3.67 (s, 3H), 2.94–2.88 (m, 1H), 2.76 (t, 1H, J=4.1 Hz), 2.55 (qd, 1H, J=7.0, 4.1 Hz), 2.48–2.46 (m, 1H), 1.84–1.41 (m, 4H), 1.16 (d, 3H, J=7.0 Hz), 1.05 (s, 21H).

TBAF (1.0 M in THF, 0.85 mL) was added to a solution of the epoxide (0.23 g, 0.65 mmol) in THF (10 mL) at room temperature and the reaction mixture was stirred for 12 h. After evaporation of the solvent, the residue was purified by flash column chromatography (Hex–EtOAc, 1:1) to give the corresponding alcohol (0.12 g, 95%). R_f 0.20 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97–3.90 (m, 1H), 3.72 (s, 3H), 2.99–2.93 (m, 1H), 2.78 (t, 1H, J=4.2 Hz), 2.70 (d, 1H, J=4.7 Hz), 2.62–2.50 (m, 2H), 1.98–1.87 (m, 1H), 1.64–1.39 (m, 3H), 1.21 (d, 3H, J=7.2 Hz).

TEA (0.12 mL, 0.87 mmol) and MsCl (0.080 mL, 0.75 mmol) were added to a solution of the alcohol (0.12 g, 0.62 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 1 h, and the reaction was quenched by addition of saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave epoxide **22** (0.14 g, 85%). R_f 0.25 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.05–5.01 (m, 1H), 3.73 (s, 3H), 3.04 (s, 3H), 2.96–2.93 (m, 1H), 2.82–2.77 (m, 2H), 2.53–2.51 (m, 1H), 1.98–1.87 (m, 3H), 1.50–1.44 (m, 1H), 1.26 (d, 3H, J=7.1 Hz).

4.1.21. Epoxide 23. Imidazole (1.22 g, 0.0180 mol) and TBSCl (2.50 g, 0.0170 mol) were added to a solution of 10-undecen-1-ol (2.35 g, 0.0140 mol) in CH_2Cl_2 (50 mL) at room temperature. After 1 h, the reaction was quenched by addition of saturated NH_4Cl solution (15 mL). The reaction mixture was extracted with CH_2Cl_2 (15 mL×3). The organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated to give the crude TBS ether. R_f 0.80 (Hex–EtOAc, 6:1).

m-CPBA (4.76 g, 0.0170 mol) was added to a solution of the crude TBS ether obtained above in CH_2Cl_2 (30 mL) at room temperature. After 1 h, the reaction mixture was washed

with saturated $NaHCO_3$ solution (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 6:1) afforded epoxide **23** (3.50 g, 84% for two steps) R_f 0.61 (Hex–EtOAc, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (t, 2H, J=6.6 Hz), 2.93–2.87 (m, 1H), 2.76–2.73 (m, 1H), 2.47–2.44 (m, 1H), 1.56–1.38 (m, 6H), 1.38–1.09 (m, 11H), 0.88 (s, 9H), 0.04 (s, 6H).

4.1.22. Attempted coupling reaction of dithiane 21 with epoxide 22. *n*-BuLi (2.5 M in hexane, 0.026 mL) and HMPA (0.038 mL) were added sequentially to a solution of dithiane **21** (20 mg, 0.054 mmol) in THF (1 mL) at −78 °C. After 20 min, the reaction mixture was allowed to warm to −20 °C and stirred for 2 h. A solution of epoxide **22** (17 mg, 0.065 mmol) in THF (0.5 mL) was added to the solution at −78 °C. The reaction mixture was allowed to warm to −20 °C. After 2 h, the reaction was quenched by addition of saturated NH_4Cl solution (5 mL). The reaction mixture was extracted with Et_2O (5 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave only a trace amount of mesyloxy elimination product. R_f 0.25 (Hex–EtOAc, 2:1).

4.1.23. Attempted coupling reaction of dithiane 21 with epoxide 23. *n*-BuLi (2.5 M in hexane, 0.050 mL) and HMPA (0.072 mL) were added sequentially to a solution of dithiane **21** (38 mg, 0.103 mmol) in THF (1 mL) at −20 °C. After 1.5 h, a solution of epoxide **23** (59 mg, 0.124 mmol) in THF (0.5 mL) was added to the solution at 0 °C and the reaction mixture was stirred for 2 h. TLC analysis indicated that the coupling reaction did not proceed at all.

4.1.24. Cyanohydrin derivatives 25 and 25′. DIBAL (1.0 M in toluene, 0.13 mL) was added to a solution of ester **24** (39 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) at −78 °C. After 30 min, the reaction was quenched by addition of CH_3OH (0.4 mL) at −78 °C and the reaction mixture was diluted with EtOAc (5 mL). Saturated sodium potassium tartrate (5 mL) was added to the mixture at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and extracted with EtOAc (5 mL×3). The extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave the corresponding aldehyde (30 mg, 85%). R_f 0.65 (Hex–EtOAc, 2:1).

TMSCN (0.010 mL, 0.090 mmol) and ZnI_2 (3.0 mg, 0.010 mmol) were added to a solution of the aldehyde (20 mg, 0.070 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 8 h, the reaction was quenched by addition of saturated $NaHCO_3$ solution and the reaction mixture was extracted with CH_2Cl_2 (5 mL×3). The extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 4:1) gave a mixture of cyanohydrin derivatives **25** and **25′** (20 mg, 74%). R_f 0.60 (Hex–EtOAc, 4:1).

4.1.25. Epoxide 26. TEA (0.360 mL, 2.56 mmol) and *p*-TsCl (366 mg, 1.92 mmol) were added to a solution of the diol obtained from **4** (634 mg, 1.28 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 0 °C for 14 h, the resulting solution was diluted with CH_2Cl_2 (5 mL) and poured into saturated NH_4Cl solution (7 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×2), and the organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave the corresponding tosylate (530 mg, 65%). R_f 0.63 (Hex–EtOAc, 1:1).

DBU (0.260 mL, 1.72 mmol) was added to a solution of the tosylate (530 mg, 0.820 mmol) in THF (40 mL) and the reaction mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was subjected to flash column chromatography (Hex–EtOAc, 4:1) to give epoxide **26** (295 mg, 73%). R_f 0.31 (Hex–EtOAc, 4:1).

4.1.26. Attempted coupling reaction of 25/25′ with iodide 19. LiHMDS (1.0 M in THF, 0.058 mL) was added dropwise to a solution of the mixture of **25** and **25′** in THF (2 mL) at −78 °C. After 40 min, a solution of iodide **19** (80 mg, 0.16 mmol) in THF (1 mL) was added to the solution and the reaction mixture was allowed to warm to 0 °C over 2 h. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. TLC analysis indicated that the coupling reaction did not proceed at all.

4.1.27. Attempted coupling reaction of 25/25′ with epoxide 26. LiHMDS (1.0 M in THF, 0.032 mL) was added dropwise to a solution of the mixture of **25** and **25′** in THF (1 mL) at −78 °C. After 40 min, a solution of epoxide **26** (21 mg, 0.044 mmol) in THF (1 mL) was added to the solution and the reaction mixture was allowed to warm to 0 °C over 2 h. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. TLC analysis indicated that the coupling reaction did not proceed at all.

4.1.28. Sulfone 27. $NaSO_2Ph$ (944 mg, 5.75 mmol) was added to a solution of iodide **19** (585 mg, 1.15 mmol) in DMF (6 mL) at room temperature. After stirring at 50 °C for 1 day, the reaction mixture was diluted with EtOAc (6 mL), and washed with water (10 mL×2) and brine (10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 4:1) gave sulfone **27** (490 mg, 82%). R_f 0.32 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 2H, J=14.5 Hz), 7.81–7.64 (m, 4H), 7.43–7.40 (m, 6H), 7.36–7.28 (m, 3H), 4.30 (m, 1H), 3.64 (m, 1H), 3.54 and 3.18 (ABX, 2H, J_{AB}=24.0 Hz, J_{AX}=9.1 Hz, J_{BX}=11.3 Hz), 3.35 (m, 2H), 2.18–2.12 (m, 1H), 1.93–1.85 (m, 1H), 1.69–1.59 (m, 3H), 1.02 (s, 9H), 0.86 (d, 3H, J=6.8 Hz).

4.1.29. Sulfone 28. PPh_3 (0.15 g, 0.57 mmol), imidazole (78 mg, 1.2 mmol), and I_2 (0.15 g, 0.57 mmol) were added to a solution of the alcohol obtained from **16** (0.14 g, 0.38 mmol) in THF (0.8 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was diluted with Et_2O (2 mL) and poured into saturated $Na_2S_2O_3$ solution (2 mL), and the reaction mixture was extracted with Et_2O (3 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 8:1) gave the corresponding

iodide (0.18 g, 99%). R_f 0.44 (Hex–EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H), 4.58 and 4.52 (ABq, 2H, J_{AB}=11.3 Hz), 4.13–4.04 (m, 2H), 3.97–3.92 (m, 1H), 3.80–3.77 (m, 1H), 3.57–3.54 (m, 1H), 3.47–3.38 (m, 2H), 2.05–1.94 (m, 5H), 1.64–1.50 (m, 5H), 1.48–1.38 (m, 2H), 1.20 (d, 3H, J=6.1 Hz), 0.95 (d, 3H, J=6.6 Hz), 0.83 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 128.2, 127.7, 127.2, 81.9, 79.7, 77.5, 76.6, 74.5, 71.7, 40.6, 40.5, 36.4, 33.8, 31.7, 31.0, 29.2, 21.5, 17.5, 16.0, 10.0.

$NaSO_2Ph$ (133 mg, 0.810 mmol) was added to a solution of the iodide (79.0 mg, 0.160 mmol) in DMF (2 mL) at room temperature. After stirring for 6 h at room temperature, the reaction mixture was diluted with EtOAc (2 mL), washed with brine (2 mL), and dried over Na_2SO_4. Filtration, concentration, and purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) furnished sulfone **28** (74.0 mg, 91%). R_f 0.42 (Hex–EtOAc, 2:1).

4.1.30. Sulfones 29/29′. *n*-BuLi (2.5 M in hexane, 0.05 mL, 0.12 mmol) was added dropwise to a solution of sulfone **28** (56 mg, 0.11 mmol) in THF (0.6 mL) at −40 °C and the slurry was stirred for 20 min. The mixture was warmed to room temperature and stirred for 10 min. The mixture was cooled to −40 °C. HMPA (0.20 mL) was added followed by a solution of iodide **19** in THF (0.9 mL). The mixture was stirred at −40 °C for 1 h and then at room temperature for 1 h. The reaction was quenched by addition of saturated NH_4Cl solution (3 mL) and the reaction mixture was extracted with EtOAc (4 mL×3). The organic extracts were dried over $MgSO_4$, and purified by flash chromatography (Hex–EtOAc, 4:1) to give the mixture of sulfones **29** and **29′** (42 mg, 43%). R_f 0.31 (Hex–EtOAc, 4:1).

4.1.31. Attempted oxidation of 29/29′. *n*-BuLi (2.5 M in hexane, 0.0060 mL) was added to a solution of the mixture of **29** and **29′** (9.0 mg, 0.010 mmol) in THF (0.1 mL) at −40 °C. After 1 h, a solution of oxaziridine **30** (5.6 mg, 0.020 mmol) in THF (0.1 mL) was added to the solution at −40 °C. The reaction mixture was allowed to warm to 0 °C over 1 h. TLC analysis indicated that the oxidation reaction did not proceed at all.

4.1.32. Attempted deuterium exchange reaction of 29/29′. *n*-BuLi (2.5 M in hexane, 0.016 mL) was added to a solution of the mixture of **29** and **29′** (10 mg, 0.020 mmol) in THF (0.1 mL) at −40 °C. The reaction mixture was stirred for 1 h and HMPA (0.010 mL) was added to the mixture. After 2 h, the reaction was quenched by addition of D_2O. ^{1}H NMR analysis confirmed that deuterium exchange reaction did not proceed at all.

4.1.33. Aldehyde 31. TEA (1.58 mL, 11.4 mmol) and SO_3·pyridine (1.09 g, 6.80 mmol) were added to a solution of alcohol **6** (905 mg, 2.27 mmol) in DMSO–CH_2Cl_2 (1:1, 4.50 mL) at room temperature. The reaction mixture was stirred for 30 min, and the reaction was quenched by addition of saturated NH_4Cl solution (3 mL). The reaction mixture was extracted with CH_2Cl_2 (5 mL×3). The organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave aldehyde **31** (801 mg, 89%). R_f 0.69 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.61 (d, 1H, J=1.9 Hz), 7.71–7.66 (m, 4H), 7.43–7.34 (m, 6H), 4.23–4.18 (m, 1H), 4.04–3.96 (m, 1H), 3.78–3.69 (m, 2H), 2.19–2.07 (m, 1H), 1.99–1.78 (m, 3H), 1.66–1.52 (m, 1H), 1.07 (s, 9H), 0.98 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.1, 135.5, 133.8, 133.7, 129.5, 127.5, 82.4, 82.0, 65.8, 40.5, 28.9, 27.3, 26.8, 19.3, 13.1. IR (neat): ν_{max}=3070, 3048, 2960, 2931, 2857, 1733, 1471, 1427, 1390, 1112, 1070, 823, 703, 505 cm^{-1}. $[\alpha]_D^{28}$ −7.2 (*c* 1.90, $CHCl_3$).

4.1.34. Olefin 32. PPh_3 (275 mg, 1.05 mmol) was added to a solution of the iodide obtained from **16** (340 mg, 0.700 mmol) in CH_3CN (7 mL). The resulting solution was heated under reflux for 14 h. The reaction mixture was diluted with CH_3CN (7 mL) and washed with hexane (10 mL×10). Evaporation of the solvent afforded the corresponding phosphonium salt (487 mg, 93%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95–7.89 (m, 6H), 7.81–7.77 (m, 3H), 7.74–7.68 (m, 6H), 7.34–7.30 (m, 5H), 4.56 and 4.42 (ABq, 2H, J_{AB}=11.5 Hz), 4.02–3.87 (m, 3H), 3.76–3.70 (m, 4H), 2.08–1.98 (m, 6H), 1.69–1.60 (m, 3H), 1.51–1.06 (m, 3H), 0.94 (d, 3H, J=6.0 Hz), 0.83 (d, 3H, J=6.9 Hz), 0.74 (d, 3H, J=6.7 Hz). $[\alpha]_D^{27}$ +50.9 (*c* 0.39, $CHCl_3$).

n-BuLi (2.5 M in hexane, 0.48 mL) was added dropwise to a solution of the phosphonium salt (600 mg, 0.800 mmol) in THF (4 mL) at −78 °C. The resulting orange solution was stirred at −78 °C for 30 min. A solution of aldehyde **31** (381 mg, 0.960 mmol) in THF (4 mL) was added dropwise to the solution at −78 °C. After 1 h, the mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched by addition of acetone (0.8 mL) and water (16 mL), and the reaction mixture was extracted with Et_2O (20 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–Acetone, 4:1) gave olefin **32** (557 mg, 94%). R_f 0.66 (Hex–Acetone, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.66 (m, 4H), 7.39–7.22 (m, 11H), 5.49–5.33 (m, 2H), 4.67–4.60 (m, 1H), 4.55 and 4.49 (ABq, 2H, J_{AB}=11.4 Hz), 4.07–3.94 (m, 3H), 3.88–3.84 (m, 1H), 3.82–3.73 (m, 2H), 3.66–3.60 (m, 2H), 2.65–2.57 (m, 1H), 2.07–1.92 (m, 7H), 1.87–1.67 (m, 3H), 1.63–1.45 (m, 5H), 1.44–1.38 (m, 1H), 1.17 (d, 3H, J=6.0 Hz), 1.05 (s, 9H), 0.99 (d, 3H, J=6.7 Hz), 0.94 (d, 3H, J=6.8 Hz), 0.83 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 135.60, 135.57, 134.2, 133.9, 131.3, 129.38, 129.36, 128.1, 127.6, 127.5, 127.2, 82.5, 80.2, 79.6, 78.0, 76.7, 74.7, 74.6, 71.5, 66.4, 40.9, 40.7, 36.9, 36.4, 33.9, 33.7, 31.8, 30.8, 29.9, 28.2, 26.9, 21.5, 19.3, 17.1, 12.9, 10.0. IR (neat): ν_{max}=3066, 2962, 2931, 2861, 1457, 1428, 1375, 1108, 1058, 740, 701, 505 cm^{-1}. MS *m*/*z* (FAB, relative intensity): 739 (M^++1, 3), 307 (19), 282 (19), 154 (100), 137 (64), 107 (31). HRMS (FAB) calcd for $C_{47}H_{67}O_5Si$ (M^++1) 739.4758, found 739.4760. $[\alpha]_D^{27}$ +18.9 (*c* 5.15, $CHCl_3$).

4.1.35. Keto carboxylic acid 33. *m*-CPBA (327 mg, 1.46 mmol) was added to a solution of olefin **32** (540 mg, 0.730 mmol) in CH_2Cl_2 (8 mL) at 0 °C. After 3 h, the reaction mixture was washed with saturated $NaHCO_3$ solution (5 mL×2). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash

column chromatography (Hex–EtOAc, 3:1) afforded a mixture of epoxides **32A** (238 mg, 43%) and **32A′** (230 mg, 42%). Epoxide **32A**: R_f 0.41 (Hex–EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.64 (m, 4H), 7.43–7.25 (m, 11H), 4.56 and 4.52 (ABq, 2H, J_{AB}=11.4 Hz), 4.10–4.02 (m, 2H), 3.96–3.87 (m, 3H), 3.85–3.67 (m, 2H), 3.65–3.61 (m, 2H), 2.93 (dd, 1H, J=9.2, 4.2 Hz), 2.77 (dd, 1H, J=8.2, 4.2 Hz), 2.17–2.13 (m, 1H), 2.03–1.67 (m, 10H), 1.64–1.57 (m, 5H), 1.43–1.34 (m, 1H), 1.14 (d, 3H, J=6.1 Hz), 1.05 (s, 9H), 0.97 (d, 3H, J=6.3 Hz), 0.95 (d, 3H, J=6.4 Hz), 0.83 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 135.60, 135.57, 134.1, 134.0, 129.5, 129.4, 128.2, 127.7, 127.5, 127.2, 81.6, 81.1, 79.6, 78.1, 76.7, 75.8, 74.6, 71.7, 66.2, 58.8, 57.1, 41.1, 40.7, 36.5, 36.4, 34.0, 31.9, 31.3, 30.8, 29.7, 27.7, 26.9, 21.5, 19.4, 13.1, 12.7, 10.0. $[\alpha]_D^{28}$ +15.5 (c 1.90, $CHCl_3$). Epoxide **32A′**: R_f 0.36 (Hex–EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71–7.65 (m, 4H), 7.40–7.22 (m, 11H), 4.56 and 4.46 (ABq, 2H, J_{AB}=11.5 Hz), 4.10–3.93 (m, 3H), 3.87–3.62 (m, 5H), 3.57–3.52 (m, 1H), 2.95 (dd, 1H, J=7.8, 4.2 Hz), 2.82 (dd, 1H, J=9.4, 4.2 Hz), 2.17–2.11 (m, 1H), 2.03–1.72 (m, 9H), 1.71–1.35 (m, 7H), 1.17 (d, 3H, J=6.1 Hz), 1.04 (s, 12H), 0.94 (d, 3H, J=6.8 Hz), 0.83 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 135.7, 135.6, 134.1, 134.0, 129.4, 128.2, 127.7, 127.6, 127.3, 81.3, 80.5, 79.6, 78.1, 77.8, 77.2, 74.7, 71.5, 66.3, 60.7, 60.0, 40.7, 40.6, 37.4, 36.1, 34.0, 31.5, 30.8, 29.4, 29.3, 29.1, 26.9, 21.5, 19.4, 14.1, 12.9, 9.9. $[\alpha]_D^{27}$ +15.2 (c 0.85, $CHCl_3$).

A solution of the mixture of **32A** and **32A′** (300 mg, 0.400 mmol) in Et_2O (1.3 mL) was added dropwise to a suspension of LAH (90.0 mg, 2.38 mmol) in Et_2O (3 mL) at 0 °C. After 12 h, the reaction was quenched by addition of water (3.6 mL) and 15% aqueous NaOH solution (0.9 mL). Drying the organic layer over $MgSO_4$, filtration, and concentration gave a crude mixture of diols **32B** and **32B′**.

Dess–Martin periodinane (84 mg, 0.20 mmol) was added to a solution of **32B/32B′** (34 mg, 0.07 mmol) in CH_2Cl_2 (4.4 mL). The reaction mixture was stirred at room temperature for 1 h and the reaction was quenched by addition of saturated $Na_2S_2O_3$ solution (3 mL). The reaction mixture was extracted with CH_2Cl_2 (4 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave the corresponding keto aldehyde (30 mg, 88%). R_f 0.5 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (d, 1H, J=2.3 Hz), 7.38–7.21 (m, 5H), 4.53 and 4.44 (ABq, 2H, J_{AB}=11.3 Hz), 4.48–4.38 (m, 1H), 4.10–3.96 (m, 3H), 3.91–3.68 (m, 3H), 2.97–2.90 (m, 1H), 2.71–2.62 (m, 2H), 2.48–2.38 (m, 1H), 2.24–1.90 (m, 8H), 1.68–1.36 (m, 7H), 1.18 (d, 3H, J=6.1 Hz), 1.02 (d, 3H, J=6.9 Hz), 1.00 (d, 3H, J=6.8 Hz), 0.82 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8, 204.4, 139.2, 128.2, 127.6, 127.3, 80.8, 79.7, 79.1, 77.8, 76.9, 75.3, 74.6, 71.7, 52.1, 51.5, 48.4, 40.5, 36.4, 33.9, 31.8, 31.3, 30.8, 30.4, 29.4, 21.5, 12.8, 10.2, 10.0. IR (neat): ν_{max}=3089, 3066, 3029, 2967, 2935, 1714, 1455, 1375, 1070, 892 cm^{-1}. $[\alpha]_D^{27}$ +16.2 (c 0.65, $CHCl_3$).

A solution of $NaClO_2$ (2.7 mg, 0.030 mmol) and NaH_2PO_4 (3.6 mg, 0.030 mmol) in water (0.15 mL) was added to a solution of the keto aldehyde (24 mg, 0.050 mmol) in t-BuOH (3.1 mL) and 2-methyl-2-butene (1.5 mL). The reaction mixture was stirred for 1 h at room temperature and then an additional equivalent of $NaClO_2$ and NaH_2PO_4 in water was added to the solution. After 1 h, the reaction mixture was concentrated and the residue was dissolved in Et_2O (3 mL) and water (1 mL). The solution was acidified (pH 2) by addition of 2 N HCl solution. The aqueous layer was extracted with Et_2O (3 mL×3) and the organic extracts were dried over $MgSO_4$. Filtration, concentration, and purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave keto carboxylic acid **33** (25 mg, 99%). R_f 0.1 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.24 (m, 5H), 4.54 and 4.43 (ABq, 2H, J_{AB}=11.4 Hz), 4.47–4.38 (m, 1H), 4.15–4.00 (m, 3H), 3.88–3.78 (m, 3H), 3.09–2.98 (m, 1H), 2.70–2.56 (m, 2H), 2.51–2.41 (m, 1H), 2.25–1.88 (m, 8H), 1.70–1.39 (m, 8H), 1.20 (d, 3H, J=6.1 Hz), 1.13 (d, 3H, J=7.0 Hz), 1.00 (d, 3H, J=6.9 Hz), 0.83 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8, 177.4, 139.2, 128.2, 127.6, 127.3, 80.8, 79.74, 79.66, 77.8, 75.4, 74.7, 71.6, 52.2, 48.1, 44.6, 40.4, 36.3, 33.8, 32.1, 31.3, 30.7, 30.2, 29.4, 21.3, 12.9, 12.8, 9.9. IR (neat): ν_{max}=3066, 3027, 2969, 2938, 2877, 1733, 1712, 1455, 1376, 1193, 1068 cm^{-1}. MS m/z (FAB, relative intensity): 531 (M^++1, 20), 339 (7), 283 (4), 209 (9), 143 (22), 125 (23), 85 (100). HRMS (FAB) calcd for $C_{31}H_{47}O_7$ (M^++1) 531.3322, found 531.3328. $[\alpha]_D^{24}$ +9.7 (c 0.60, $CHCl_3$).

4.1.36. The monomeric seco acid 35. Keto carboxylic acid **33** (26 mg, 0.048 mmol) was dissolved in MeOH (1 mL) and palladium on activated carbon (10% w/w, 100 mg) was added. The reaction mixture was stirred under hydrogen atmosphere for 1 h and then filtered through a filter paper. After solvent evaporation, flash column chromatography (EtOAc) yielded the monomeric seco acid **35** (20 mg, 93%). R_f 0.20 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.48–4.41 (m, 1H), 4.12–4.00 (m, 3H), 3.96–3.90 (m, 2H), 3.78–3.72 (m, 1H), 3.04–2.96 (m, 1H), 2.71–2.55 (m, 2H), 2.50–2.42 (m, 1H), 2.28–1.90 (m, 6H), 1.75–1.39 (m, 9H), 1.22 (d, 3H, J=6.0 Hz), 1.15 (d, 3H, J=7.0 Hz), 1.01 (d, 3H, J=6.9 Hz), 0.76 (d, 3H, J=6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.6, 177.646, 83.9, 80.5, 79.8, 76.6, 75.5, 75.3, 73.2, 52.3, 47.7, 44.7, 44.3, 40.1, 33.4, 32.08, 32.05, 31.1, 30.1, 29.2, 21.0, 13.0, 12.7, 12.5.

4.1.37. Secondary alcohol 34. Imidazole (52 mg, 0.77 mmol), TBDPSCl (0.10 mL, 0.45 mmol), and DMAP (7.0 mg, 0.060 mmol) were added to a solution of keto carboxylic acid **33** (60 mg, 0.11 mmol) in CH_2Cl_2 (4 mL) at room temperature. The reaction mixture was stirred for 2 h. After evaporation of the solvent, flash column chromatography (Hex–EtOAc, 3:1) gave the corresponding TBDPS ester (80 mg, 95%). R_f (Hex–EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, 4H, J=7.3 Hz), 7.54–7.23 (m, 11H), 4.53 and 4.44 (ABq, 2H, J_{AB}=11.3 Hz), 4.48–4.39 (m, 1H), 4.31–4.23 (m, 1H), 4.08–4.00 (m, 2H), 3.92–3.74 (m, 3H), 2.97–2.91 (m, 1H), 2.79–2.59 (m, 3H), 2.21–2.15 (m, 1H), 2.06–1.86 (m, 6H), 1.70–1.37 (m, 8H), 1.17 (d, 6H, J=6.0 Hz), 0.93 (s, 9H), 0.97 (d, 3H, J=6.9 Hz), 0.82 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8, 173.6, 139.1, 135.2, 131.96, 131.90, 129.9, 129.8, 128.2, 127.61, 127.59, 127.2, 80.5, 80.0, 79.6, 77.8, 75.2, 74.6,

71.6, 52.1, 48.1, 47.0, 40.5, 36.4, 33.9, 32.1, 31.3, 30.8, 29.22, 29.17, 26.8, 21.5, 19.1, 13.0, 12.8, 10.0.

The TBDPS ester (80 mg, 0.10 mmol) was dissolved in EtOAc (5 mL) and palladium hydroxide on activated carbon (20% w/w, 35 mg) was added. The reaction mixture was stirred under hydrogen atmosphere for 1 h and then filtered through a filter paper. After solvent evaporation, flash column chromatography (Hex–EtOAc, 3:1) yielded the secondary alcohol **34** (63 mg, 93%). R_f 0.28 (Hex–EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, 4H, J=6.8 Hz), 7.42–7.27 (m, 6H), 4.74 (s, 1H), 4.47–4.39 (m, 1H), 4.34–4.22 (m, 1H), 4.19–4.01 (m, 2H), 3.97–3.78 (m, 2H), 3.72–3.66 (m, 1H), 2.93–2.85 (m, 1H), 2.75–2.56 (m, 3H), 2.20–1.96 (m, 6H), 1.73–1.37 (m, 9H), 1.20–1.17 (m, 6H), 1.10 (s, 9H), 0.98 (d, 3H, J=6.9 Hz), 0.73 (d, 3H, J=6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.5, 173.6, 135.2, 131.95, 131.89, 129.87, 129.84, 127.60, 127.57, 84.1, 80.4, 80.0, 76.8, 75.4, 75.1, 73.5, 52.4, 47.6, 47.0, 44.4, 40.5, 33.4, 32.2, 32.1, 31.3, 29.3, 29.1, 26.8, 21.1, 19.1, 13.0, 12.8, 12.6. IR (neat): ν_{max}=3462, 3072, 3049, 2966, 2933, 2881, 2862, 1728, 1462, 1429, 1377, 1254, 1190, 1115, 1068, 742, 700 cm^{-1}. $[\alpha]_D^{23}$ −4.8 (c 0.55, $CHCl_3$).

4.1.38. Ester 37. To a mixture of the keto carboxylic acid **33** (33 mg, 0.062 mmol) and TEA (0.0220 mL, 0.155 mmol) in THF (2.5 mL) was added 2,4,6-trichlorobenzoyl chloride (0.016 mL, 0.105 mmol). The reaction mixture was stirred for 2 h at room temperature. The white precipitate that had formed was removed by filtration under N_2 via cannula transfer to a glass pipette equipped with a septum and a plug of glass wool. The THF filtrate was evaporated by a stream of N_2. The residue was diluted with benzene (3 mL) and DMAP (23 mg, 0.186 mmol) was added. To this mixture was added the secondary alcohol **34** (55 mg, 0.081 mmol) in benzene (1 mL). The reaction mixture was stirred for 2 h at room temperature and the reaction was quenched by addition of saturated NH_4Cl solution (3 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave ester **37** (68 mg, 92%). R_f 0.63 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, 4H, J=6.6 Hz), 7.42–7.26 (m, 10H), 5.19–5.16 (m, 1H), 4.53 and 4.44 (ABq, 2H, J_{AB}=11.3 Hz), 4.45–4.33 (m, 2H), 4.30–4.23 (m, 1H), 4.15–4.04 (m, 4H), 3.90–3.75 (m, 6H), 2.89–2.80 (m, 2H), 2.72–2.49 (m, 6H), 2.18–2.04 (m, 2H), 1.99–1.81 (m, 13H), 1.70–1.28 (m, 15H), 1.19–1.16 (m, 9H), 1.09 (s, 9H), 1.09–1.05 (m, 3H), 1.00 (d, 3H, J=6.9 Hz), 0.95 (d, 3H, J=6.9 Hz), 0.82 (d, 3H, J=7.0 Hz), 0.80 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.7, 211.6, 173.7, 173.6, 139.2, 135.2, 131.9, 129.9, 128.2, 127.63, 127.60, 127.3, 80.5, 80.1, 79.7, 79.6, 79.3, 77.8, 75.2, 75.1, 74.7, 74.6, 71.6, 52.1, 48.1, 47.8, 47.1, 45.5, 41.0, 40.5, 36.3, 36.1, 33.9, 32.2, 32.1, 31.4, 31.1, 30.8, 30.1, 29.3, 29.1, 26.8, 21.5, 21.3, 19.2, 13.0, 12.8, 10.6, 10.0. $[\alpha]_D^{22}$ +5.0 (c 0.16, $CHCl_3$).

4.1.39. IKD-8344 (1). Concd HCl (0.090 mL) was added to a solution of ester **37** (34 mg, 0.028 mmol) in CH_3OH (3 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature. After 3 h, the reaction was quenched by addition of TEA (0.16 mL) and the reaction mixture was concentrated. Purification of the residue by flash column chromatography (EtOAc) gave the corresponding acid (25 mg, 92%). R_f 0.4 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.31 (m, 5H), 5.25–5.22 (m, 1H), 4.52 and 4.44 (ABq, 2H, J_{AB}=11.3 Hz), 4.45–4.31 (m, 2H), 4.17–4.02 (m, 5H), 3.92–3.75 (m, 6H), 3.04–3.00 (m, 1H), 2.84–2.80 (m, 1H), 2.66–2.58 (m, 4H), 2.54–2.47 (m, 2H), 2.23–2.13 (m, 3H), 2.01–1.94 (m, 13H), 1.79–1.76 (m, 2H), 1.72–1.40 (m, 13H), 1.20 (d, 3H, J=5.9 Hz), 1.18 (d, 3H, J=5.9 Hz), 1.14 (d, 3H, J=7.0 Hz), 1.07 (d, 3H, J=7.0 Hz), 1.00 (d, 3H, J=6.0 Hz), 0.98 (d, 3H, J=6.4 Hz), 0.82 (d, 3H, J=6.6 Hz), 0.80 (d, 3H, J=6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8, 173.9, 139.1, 128.2, 127.7, 127.3, 80.6, 80.4, 79.7, 79.4, 77.8, 77.2, 75.4, 75.1, 74.8, 74.6, 73.0, 71.6, 65.8, 52.2, 52.1, 47.9, 47.7, 45.5, 44.6, 40.9, 40.5, 36.3, 36.0, 33.9, 33.8, 32.1, 32.0, 31.4, 31.1, 30.8, 30.6, 30.0, 29.3, 29.1, 21.4, 21.2, 15.2, 12.9, 12.73, 12.67, 10.5, 10.0. IR (neat): ν_{max}=2967, 2877, 1731, 1712, 1457, 1376, 1189, 1070, 889, 736, 698 cm^{-1}. MS m/z (FAB, relative intensity): 953 (M^++1, 4), 423 (10), 307 (28), 289 (14), 154 (100), 136 (65), 91 (30). HRMS (FAB) calcd for $C_{55}H_{85}O_{13}$ (M^++1) 953.5990, found 953.6002. $[\alpha]_D^{26}$ +6.3 (c 0.6, $CHCl_3$).

The carboxylic acid (10 mg, 0.010 mmol) was dissolved in EtOAc (1 mL) and palladium hydroxide on activated carbon (20% w/w, 22 mg) was added. The reaction mixture was stirred under hydrogen atmosphere for 1 h and then filtered through a filter paper. After solvent evaporation, flash column chromatography (EtOAc) yielded the dimeric seco acid **38** (8.4 mg, 93%). R_f 0.2 (EtOAc). MS m/z (FAB, relative intensity): 863 (M^++1, 9), 423 (24), 339 (11), 227 (7), 209 (18), 154 (32), 136 (26), 85 (100), 69 (19). HRMS (FAB) calcd for $C_{48}H_{79}O_{13}$ (M^++1) 863.5520, found 863.5516.

The dimeric seco acid **38** (15 mg, 0.017 mmol) was dissolved in toluene (113 mL). TEA (0.15 mL, 1.04 mmol), 2,4,6-trichlorobenzoyl chloride (0.11 mL, 0.70 mmol), and DMAP (42 mg, 0.35 mmol) were added to the solution at room temperature, and then the solution was heated under reflux for 4 h. The reaction was quenched by addition of saturated NH_4Cl solution (100 mL) and the reaction mixture was extracted with CH_2Cl_2 (150 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave IKD-8344 (**1**, 9.5 mg, 65%). R_f 0.28 (Hex–EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32–5.28 (m, 2H), 4.38–4.31 (m, 2H), 4.15–4.01 (m, 4H), 3.96–3.87 (m, 4H), 3.82–3.76 (m, 2H), 2.95–2.83 (m, 4H), 2.46–2.26 (m, 6H), 2.19–2.13 (m, 2H), 2.03–1.90 (m, 9H), 1.81–1.73 (m, 3H), 1.68–1.59 (m, 5H), 1.51–1.38 (m, 9H), 1.18 (d, 6H, J=6.0 Hz), 1.09 (d, 6H, J=7.4 Hz), 1.00 (d, 6H, J=7.3 Hz), 0.83 (d, 6H, J=7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.0, 175.1, 80.5, 80.0, 79.5, 75.2, 74.9, 74.8, 72.2, 53.4, 45.6, 45.6, 41.1, 36.2, 33.9, 32.1, 30.9, 30.7, 29.6, 29.4, 21.2, 14.4, 13.7, 10.9. MS m/z (FAB, relative intensity): 867 (M^++Na, 58), 883 (45), 845 (14), 423 (12), 307 (22), 289 (11), 209 (43), 154 (83), 85 (100). HRMS (FAB) calcd for $C_{48}H_{76}O_{12}Na$ (M^++Na) 867.5235, found 867.5239. $[\alpha]_D^{15}$ +39.7 (c 0.25, $CHCl_3$).

4.1.40. Keto alcohol 40. MeMgI (3.0 M in Et_2O, 0.24 mL) was added dropwise to a solution of the aldehyde obtained from **16** (90 mg, 0.24 mmol) in THF (0.5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and the reaction was quenched by addition of saturated NH_4Cl solution (8 mL). The reaction mixture was extracted with Et_2O (5 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave a mixture of alcohols. R_f 0.50 (Hex–EtOAc, 2:1).

Dess–Martin periodinane (153 mg, 0.361 mmol) was added to a solution of the mixture of the alcohols in CH_2Cl_2 (16 mL). The reaction mixture was stirred at room temperature for 1 h and the reaction was quenched by addition of saturated $Na_2S_2O_3$ solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (15 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave the corresponding ketone (68.0 mg, 73% for two steps). R_f 0.56 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.25 (m, 5H), 4.45 and 4.54 (ABq, 2H, J_{AB}=11.4 Hz), 4.06–4.00 (m, 2H), 3.94–3.84 (m, 2H), 3.82–3.76 (m, 1H), 2.67–2.57 (m, 1H), 2.24 (s, 3H), 2.01–1.97 (m, 5H), 1.66–1.55 (m, 5H), 1.49–1.36 (m, 1H), 1.17 (d, 3H, J=6.0 Hz), 1.01 (d, 3H, J=6.9 Hz), 0.82 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.3, 139.2, 128.2, 127.7, 127.3, 80.9, 79.7, 77.4, 76.7, 74.5, 71.6, 52.5, 40.5, 36.3, 33.9, 31.3, 31.0, 30.4, 29.5, 21.4, 12.9, 9.9. IR (neat): ν_{max}=3091, 3064, 3030, 2968, 2937, 2877, 1712, 1456, 1375, 1358, 1090, 1072, 737, 698 cm^{-1}. MS *m*/*z* (CI, relative intensity): 389 (M^++1, 100), 281 (53), 197 (22), 167 (17), 141 (17), 85 (53). HRMS (CI) calcd for $C_{24}H_{37}O_4$ (M^++1) 389.2692, found 389.2689. $[\alpha]_D^{26}$ +11.0 (*c* 0.26, $CHCl_3$).

The ketone (196 mg, 0.504 mmol) was dissolved in CH_3OH (9 mL) and palladium on activated carbon (10% w/w, 268 mg) was added. The reaction mixture was stirred under hydrogen atmosphere for 4 h and then filtered through a filter paper. After solvent evaporation, flash column chromatography (Hex–EtOAc, 2:1) yielded the keto alcohol **40** (147 mg, 98%). R_f 0.22 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (s, 1H), 4.13–4.08 (m, 2H), 3.99–3.84 (m, 2H), 3.76–3.70 (m, 1H), 2.62–2.55 (m, 1H), 2.20 (s, 3H), 2.16–2.08 (m, 1H), 2.03–1.99 (m, 3H), 1.77–1.70 (m, 1H), 1.66–1.35 (m, 6H), 1.20 (d, 3H, J=6.0 Hz), 1.03 (d, 3H, J=6.9 Hz), 0.76 (d, 3H, J=6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.6, 84.0, 80.5, 76.8, 75.4, 73.4, 52.8, 44.4, 40.4, 33.4, 32.2, 31.3, 29.2, 29.1, 21.1, 12.8, 12.5. IR (neat): ν_{max}=3458, 2968, 2933, 2877, 1712, 1460, 1444, 1377, 1356, 1095, 1066, 876, 820 cm^{-1}. MS *m*/*z* (CI, relative intensity): 299 (M^++1, 100), 281 (20), 227 (11), 197 (8), 185 (11), 141 (14), 85 (43). HRMS (CI) calcd for $C_{17}H_{31}O_4$ (M^++1) 299.2222, found 299.2222. $[\alpha]_D^{26}$ −3.7 (*c* 0.25, $CHCl_3$).

4.1.41. Acid 39. *n*-BuLi (2.5 M in hexane, 1.6 mL) was added dropwise to a solution of $MePPh_3Br$ (1.4 g, 4.0 mmol) in THF (20 mL) at −78 °C. The resulting orange solution was stirred at −78 °C for 30 min. A solution of aldehyde **31** (1.6 g, 4.0 mmol) in THF (20 mL) was added dropwise to the solution at −78 °C. After 1 h, the mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched by addition of acetone (4 mL) and water (80 mL), and the reaction mixture was extracted with Et_2O (50 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–Et_2O, 8:1) gave the corresponding olefin (0.91 g, 61%). R_f 0.56 (Hex–Et_2O, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.66 (m, 4H), 7.43–7.34 (m, 6H), 5.88–5.77 (m, 1H), 5.20 (d, 1H, J=17.1 Hz), 5.05 (d, 1H, J=10.3 Hz), 4.34–4.26 (m, 1H), 4.02–3.94 (m, 1H), 3.75–3.63 (m, 2H), 2.09–2.01 (m, 1H), 2.00–1.93 (m, 1H), 1.90–1.79 (m, 1H), 1.66–1.54 (m, 2H), 1.05 (s, 9H), 0.95 (d, 3H, J=6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.7, 135.6, 134.0, 133.9, 129.44, 129.40, 127.53, 127.52, 114.6, 80.3, 79.7, 66.2, 40.8, 32.7, 29.5, 26.9, 19.3, 12.9. IR (neat): ν_{max}=3070, 3051, 2962, 2931, 2858, 1469, 1427, 1111, 1057, 702, 505 cm^{-1}. MS *m*/*z* (CI, relative intensity): 395 (M^++1, 44), 337 (53), 317 (100), 303 (34), 209 (16), 199 (11), 121 (81), 107 (28). HRMS (CI) calcd for $C_{25}H_{35}O_2Si$ (M^++1) 395.2406, found 395.2409. $[\alpha]_D^{25}$ +5.6 (*c* 0.36, $CHCl_3$).

TBAF (1.0 M in THF, 3.5 mL) was added to a solution of the olefin (0.91 g, 2.3 mmol) in THF (23 mL) at room temperature and the reaction mixture was stirred for 2 h. After evaporation of the solvent, the residue was purified by flash column chromatography (Hex–EtOAc, 4:1) to give the corresponding alcohol (0.36 g, 99%). R_f 0.22 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88–5.77 (m, 1H), 5.22 (d, 1H, J=17.1 Hz), 5.08 (d, 1H, J=10.3 Hz), 4.47–4.40 (m, 1H), 3.88–3.81 (m, 1H), 3.67–3.59 (m, 3H), 2.17–2.02 (m, 2H), 1.80–1.71 (m, 1H), 1.70–1.56 (m, 2H), 0.80 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 115.1, 85.5, 80.1, 68.7, 40.7, 32.0, 31.7, 13.3. IR (neat): ν_{max}=3402, 3070, 2958, 2931, 2858, 1466, 1427, 1111, 1034, 872, 706, 505 cm^{-1}. $[\alpha]_D^{25}$ −0.9 (*c* 0.75, $CHCl_3$).

Dess–Martin periodinane (1.16 g, 2.75 mmol) was added to a solution of the alcohol (358 mg, 2.29 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was stirred at room temperature for 1.5 h and the reaction was quenched by addition of saturated $Na_2S_2O_3$ solution (80 mL). The reaction mixture was extracted with CH_2Cl_2 (50 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 4:1) gave the corresponding aldehyde (291 mg, 82%). R_f 0.51 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (d, 1H, J=2.1 Hz), 5.88–5.77 (m, 1H), 5.23 (d, 1H, J=17.1 Hz), 5.10 (d, 1H, J=10.3 Hz), 4.46–4.41 (m, 1H), 4.21–4.14 (m, 1H), 2.54–2.45 (m, 1H), 2.17–2.08 (m, 2H), 1.72–1.63 (m, 2H), 1.07 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.3, 138.8, 115.2, 80.2, 79.4, 51.5, 32.0, 30.2, 10.3.

A solution of $NaClO_2$ (111 mg, 1.23 mmol) and NaH_2PO_4 (147 mg, 1.23 mmol) in water (5.50 mL) was added to a solution of the aldehyde (291 mg, 1.89 mmol) in *t*-BuOH (110 mL) and 2-methyl-2-butene (55.0 mL). The reaction mixture was stirred for 1 h at room temperature and then an additional equivalent of $NaClO_2$ and NaH_2PO_4 in water was added to the solution. After 1 h, the reaction mixture was concentrated and the residue was dissolved in Et_2O (80 mL) and water (50 mL). The solution was acidified

(pH 2) by addition of 2 N HCl solution. The aqueous layer was extracted with Et_2O (50 mL×3) and the organic extracts were dried over $MgSO_4$. Filtration, concentration, and purification of the residue by flash column chromatography ($CHCl_3$–MeOH, 5:1) gave acid **39** (255 mg, 79%). R_f 0.19 ($CHCl_3$–MeOH, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88–5.77 (m, 1H), 5.24 (d, 1H, J=17.1 Hz), 5.09 (d, 1H, J=10.3 Hz), 4.50–4.34 (m, 1H), 4.24–4.11 (m, 1H), 2.62–2.53 (m, 1H), 2.17–2.06 (m, 2H), 1.76–1.60 (m, 2H), 1.17 (d, 3H, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.8, 138.6, 115.4, 80.3, 80.0, 44.9, 32.2, 29.6, 13.0. IR (neat): ν_{max}=3084, 2978, 2941, 2883, 2636, 1712, 1462, 1425, 1227, 1057, 928, 889, 854 cm^{-1}. MS *m/z* (CI, relative intensity): 171 (M^++1, 37), 153 (93), 125 (14), 101 (38), 97 (100), 83 (15), 59 (37). HRMS (CI) calcd for $C_9H_{15}O_3$ (M^++1) 171.1021, found 171.1022. $[\alpha]_D^{26}$ +15.3 (*c* 0.44, $CHCl_3$).

4.1.42. Silyl enol ether 41. To a mixture of acid **39** (30 mg, 0.174 mmol) and TEA (0.0620 mL, 0.442 mmol) in THF (5 mL) was added 2,4,6-trichlorobenzoyl chloride (0.0460 mL, 0.295 mmol). The reaction mixture was stirred for 2 h at room temperature. The white precipitate that had formed was removed by filtration under N_2 via cannula transfer to a glass pipette equipped with a septum and a plug of glass wool. The THF filtrate was evaporated by a stream of N_2. The residue was diluted with benzene (4 mL) and DMAP (49 mg, 0.402 mmol) was added. To this mixture was added alcohol **40** (40.0 mg, 0.134 mmol) in benzene (3 mL). The reaction mixture was stirred for 2 h at room temperature and the reaction was quenched by addition of saturated NH_4Cl solution (4 mL). The reaction mixture was extracted with CH_2Cl_2 (8 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave the corresponding ester (55 mg, 92%). R_f 0.47 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86–5.74 (m, 1H), 5.28–5.23 (m, 1H), 5.19 (d, 1H, J=17.1 Hz), 5.04 (d, 1H, J=10.3 Hz), 4.42–4.35 (m, 1H), 4.22–4.15 (m, 1H), 4.13–4.02 (m, 1H), 3.88–3.80 (m, 3H), 2.64–2.50 (m, 2H), 2.23 (s, 3H), 2.14–1.88 (m, 8H), 1.85–1.80 (m, 1H), 1.71–1.35 (m, 6H), 1.18 (d, 3H, J=6.0 Hz), 1.10 (d, 3H, J=7.0 Hz), 1.00 (d, 3H, J=6.9 Hz), 0.83 (d, 3H, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.1, 173.9, 139.2, 114.6, 80.5, 80.3, 79.9, 79.4, 76.5, 74.6, 73.1, 52.5, 45.6, 41.0, 36.2, 33.8, 32.4, 31.1, 29.9, 29.6, 29.3, 29.2, 21.3, 13.0, 12.8, 10.6. IR (neat): ν_{max}=2970, 2933, 2877, 1732, 1714, 1460, 1377, 1356, 1254, 1190, 1057, 951, 891 cm^{-1}. MS *m/z* (CI, relative intensity): 451 (M^++1, 47), 379 (19), 281 (100), 197 (27), 141 (14), 85 (37). HRMS (CI) calcd for $C_{26}H_{43}O_6$ (M^++1) 451.3059, found 451.3058. $[\alpha]_D^{28}$ +5.4 (*c* 1.15, $CHCl_3$).

KHMDS (0.50 M in toluene, 0.20 mL) was added to a solution of TBSCl (50 mg, 0.33 mmol) in THF (1 mL) at −78 °C. To the resulting mixture was added dropwise a solution of the ester (30 mg, 0.070 mmol) in THF (1 mL) at −78 °C over 30 min. After stirring for 1 h at −78 °C, TEA (0.050 mL, 0.33 mmol) was added followed by saturated $NaHCO_3$ solution (3 mL). The reaction mixture was stirred at 23 °C for 20 min and extracted with petroleum ether (5 mL×3). The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (Hex–EtOAc, 4:1) on neutral alumina to afford the TBS enol ether **41** (34 mg, 93%). R_f 0.50 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85–5.74 (m, 1H), 5.25–5.16 (m, 2H), 5.03 (d, 1H, J=10.3 Hz), 4.41–4.35 (m, 1H), 4.24–4.16 (m, 1H), 4.13–4.00 (m, 3H), 3.93–3.79 (m, 3H), 2.58–2.53 (m, 1H), 2.35–2.29 (m, 1H), 2.09–1.93 (m, 9H), 1.79–1.56 (m, 3H), 1.46–1.37 (m, 3H), 1.17 (d, 3H, J=6.0 Hz), 1.11 (d, 3H, J=7.0 Hz), 0.95 (d, 3H, J=6.9 Hz), 0.91 (s, 9H), 0.83 (d, 3H, J=6.9 Hz), 0.16 (d, 6H, J=4.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 161.2, 139.2, 130.9, 128.8, 114.7, 89.1, 80.2, 79.9, 79.3, 74.7, 73.6, 45.6, 44.7, 41.0, 36.3, 33.9, 32.5, 31.8, 29.8, 29.2, 27.7, 27.4, 25.7, 21.3, 19.1, 18.1, 13.2, 13.0, 10.7, −4.7, −4.8.

4.1.43. Attempted ring-forming metathesis reaction of the silyl enol ether 41. A suspension of catalyst **42** (6.0 mg, 0.0090 mmol) and 4 Å molecular sieves (0.40 g) in benzene (8 mL) was heated under reflux. A solution of the silyl enol ether **41** (25 mg, 0.044 mmol) in benzene (2 mL) was added slowly to the suspension over 30 min. After 30 min, the reaction mixture was allowed to cool to room temperature and the solvent was removed. Purification of the residue by flash column chromatography (Hex–EtOAc, 4:1) provided the starting material **41** (9.9 mg, 40%) and a product tentatively assigned as the tail–tail dimer (12 mg, 25%). R_f 0.19 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.58–5.66 (m, 2H), 5.24–5.19 (m, 2H), 4.37 (br s, 2H), 4.25–4.18 (m, 2H), 4.13–4.06 (m, 2H), 4.06 (s, 2H), 4.01 (s, 2H), 3.93–3.80 (m, 6H), 2.60–2.55 (m, 2H), 2.34–2.30 (m, 2H), 2.05–1.87 (m, 18H), 1.78–1.52 (m, 8H), 1.47–1.37 (m, 4H), 1.17 (d, 6H, J=6.0 Hz), 1.10 (d, 6H, J=7.0 Hz), 0.96 (d, 6H, J=6.9 Hz), 0.92 (s, 18H), 0.83 (d, 6H, J=6.9 Hz), 0.16 (d, 12H, J=4.2 Hz).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.005.

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