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Enantioselective total synthesis of the proposed structure of macrolide iriomoteolide-1b

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ABSTRACT

An enantioselective total synthesis of the proposed structure of macrolide iriomoteolide-1b has been achieved by a convergent protocol, which was featured by an enantioselective organocatalytic transfer hydrogenation of enal, a Julia–Kocienski olefination to establish the C15–C16 *E*-olefin moiety, a Kulinkovich reaction associated with cyclopropyl-allyl rearrangement to produce allyl stannane and ytterbium triflate and carboxylic acid promoted allylation between allyl stannane and aldehyde with tertiary alcohol at the α-position. The construction of macrolide **2** was realized by the successful implementation of RCM utilizing 5 mol % Grubbs's second generation catalyst at room temperature with *E*-isomer as a single product.

1. Introduction

Iriomoteolide-1a and 1b, two novel 20-membered macrolactones bearing almost the same carbon skeleton and chiral centers, were isolated from a benthic dinoflagellate *Amphidinium* species, respectively, in 2007 by Tsuda and co-workers.[1] The major difference between these two analogues is that iriomoteolide-1a (**1**) was featured a terminal double bond, which was isomerized to the *Z*-internal alkene and herein a stable enone was formed instead of hemiketal in iriomoteolide-1b (**2**).[1b] Iriomoteolide-1a exhibits significant cytotoxicity against Epstein–Barr virus (EBV)-infected human B lymphocyte Raji cells (IC_{50}: 3 ng/mL) and human B lymphocyte DG-75 cells (IC_{50}: 2 ng/mL),[1a] which was more potent than iriomoteolide-1b against DG-75 cells (IC_{50}: 0.9 μg/mL).[1b] Considering their similar structure and distinct cytotoxicity, iriomoteolide-1a and 1b have became attractive target moleculars of many organic chemists.[2–4] Horne and co-workers firstly accomplished the proposed structure of iriomoteolide-1a (**1**) employing a Yamaguchi esterification and ring-closing metathesis (RCM) reaction.[3a] Meanwhile, Xu and Ye group reported the synthesis of the macrolactone core using Hoveyda-Grubbs' second generation catalyst to provide the product with sole *E*-configuration at C15=C16.[3b] Then Ghosh and Yuan fulfilled the syntheses of the proposed structures of iriomoteolide-1a and iriomoteolide-1b with a Sakurai reaction, Julia–Kocienski olefinations and a Yamaguchi esterification as the key steps.[3c] Besides the synthesis of the proposed structures, a (2*E*)-diastereomer of iriomoteolide-1a was also described by Yang and co-workers.[4] But unfortunately, none of their final products were matched with the naturally occurring iromoteolide-1a and iromoteolide-1b by comparison of their NMR spectral data.[3,4] In our efforts directed toward the total synthesis of these macrolides, we have previously presented an efficient route to the synthesis of the C15–C16 *E*-olefin moiety via a Julia–Kocienski olefination.[5] Herein, we would like to disclose a concise, convergent and executable approach for preparing the proposed structure of iriomoteolide-1b featured by the allylation between allyl stannane and aldehyde promoted by both ytterbium triflate and carboxylic acid, and Yamaguchi esterification accompanying with an unexpected double bond migration (Fig. 1).

2. Results and discussion

We have previously reported the synthesis of aldehyde **12** through stereoselective reduction of the double bond in **8** with the $NaBH_4$/$NiCl_2 \cdot 6H_2O$ system to give the product in moderate selectivity (dr>5:1).[5] However, a more efficient and stereoselective protocol to obtain saturated aldehyde **12** is still required and will be intriguing to synthetic chemists. Inspired by the organocatalytic transfer hydrogenation developed by Macmillan and List,[6] α,β-unsaturated ester **8** was firstly reduced with diisobutylaluminumhydride (DIBAL-H)

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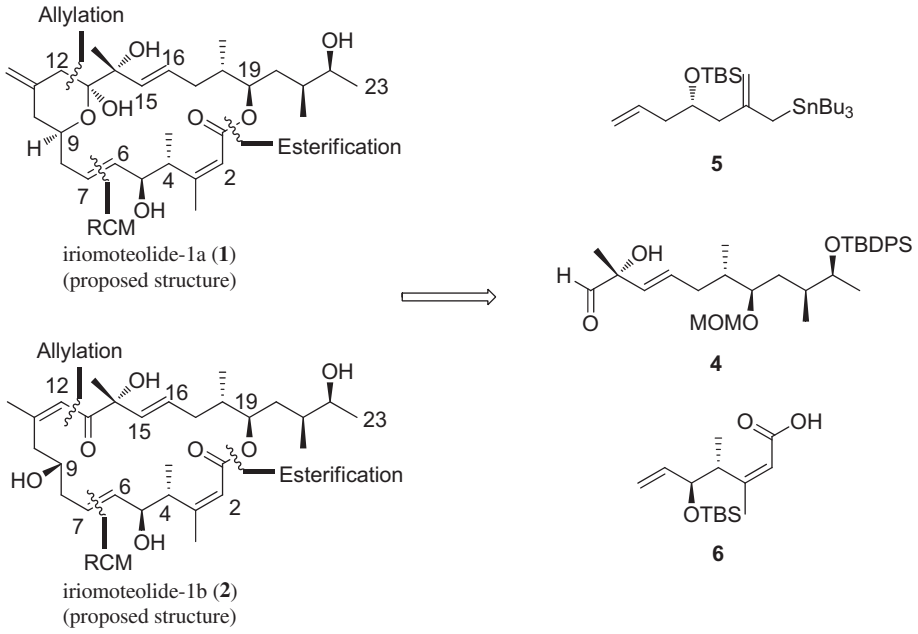
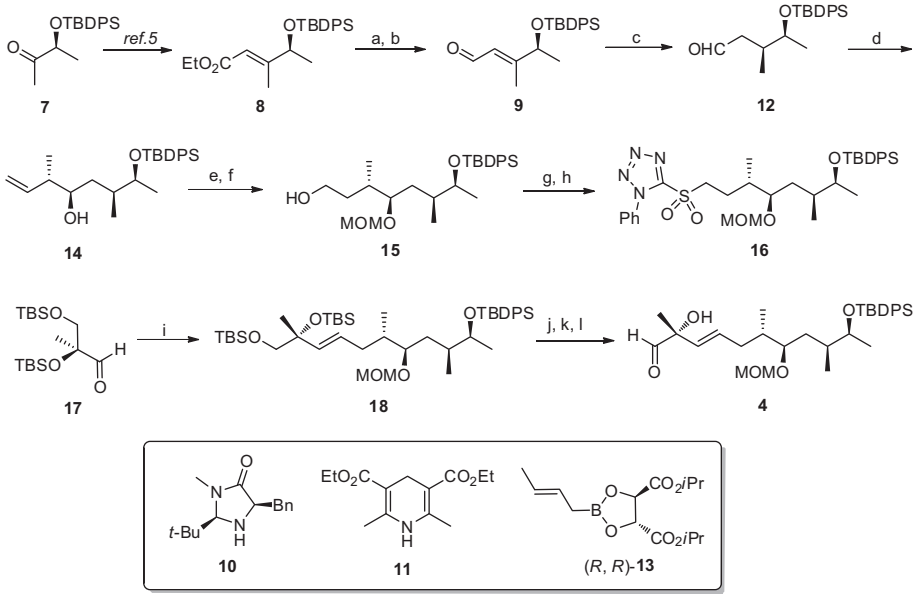


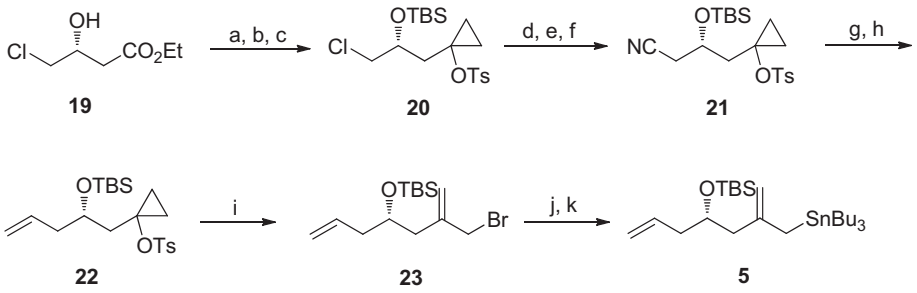
Fig. 1. Retroanalysis of the proposed iriomoteolide-1a (**1**) and 1b (**2**).

followed by Swern oxidation to give enal **9**, in which the double bond was successfully hydrogenated by the ethyl Hantzsch ester **11** in the presence of imidazolidinone catalyst **10**. As expected, the desired aldehyde **12** could be obtained in 94% yield and with high selectivity (dr>20:1). With the chiral aldehyde **12** in hand, the further synthesis of fragment **4** was outlined in Scheme 1. Asymmetric Roush crotylation of the aldehyde **12** using the chiral *trans*-crotylboronate **13** proceeded smoothly to provide the corresponding alcohol **14** in 95% yield with good diastereoselectivity (dr>10:1).[5,7] Protection of hydroxyl group as a MOM ether followed by hydroboration–oxidation led to the primary alcohol **15** in 78% yield. Subsequently, conversion of **15** to Kocienski-type sulfone **16** was carried out smoothly by a two-step sequence including a Mitsunobu reaction[8] and an oxidation using ammonium molybdate and hydrogen peroxide. Then Julia–Kocienski olefinaton was carried out between sulfone **16** and the pre-prepared aldehyde **17**[5] affording the desired *E*-isomer **18** almost exclusively (dr>20:1) in 91% yield. The high selectivity for *E*-olefin could be ascribed to the steric hindrance from the adjacent protected tertiary alcohol.[9] Next, a primary TBS group in **18** was selectively removed in the presence of HF·Py and pyridine. Subsequent oxidation of the resulting alcohol using DMP[10] as an oxidant and removal of a tertiary alcohol TBS group with TBAF at room temperature in 10–15 min afforded aldehyde **4** in 60% yield over the three steps from **18**. It should be noted that TBS group on the tertiary alcohol of **4** was detrimental to the following allylation of the aldehyde due to the large steric hindrance, so it was favored to be removed before an allylation.

The synthesis of allyl stannane **5** (Scheme 2) commenced with the known chiral ethyl (*R*)-(+)-4-chloro-3-hydroxybutyrate **19**,



Scheme 1. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C, 97%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 92%; (c) **10** (20 mol %), **11** (1.5 equiv), TFA (20 mol %), $CHCl_3$, −30 °C, 94%, dr>20:1; (d) (*R*,*R*)-**13**, 4 Å MS, toluene, −78 °C, 95%; (e) DIPEA, MOMCl, TBAI, CH_2Cl_2, 40 °C, 98%; (f) $BH_3{\cdot}SMe_2$, THF, rt; then EtOH, 2.5 M NaOH, 30% H_2O_2, rt, 80%; (g) PTSH, DIAD, PPh_3, THF, rt, 96%; (h) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 30% H_2O_2, EtOH, rt, 92%; (i) **16**, LiHMDS, DMF/HMPA, −40 °C, 10 min; then **17**, −40 °C to rt, 91%; (j) HF·Py, Py, THF, rt, 80%; (k) DMP, $NaHCO_3$, CH_2Cl_2, 90%; (l) TBAF, THF, rt, 50–84%. PTSH=1-phenyl-1*H*-tetrazole-5-thiol, DMP=Dess–Martin periodinane.

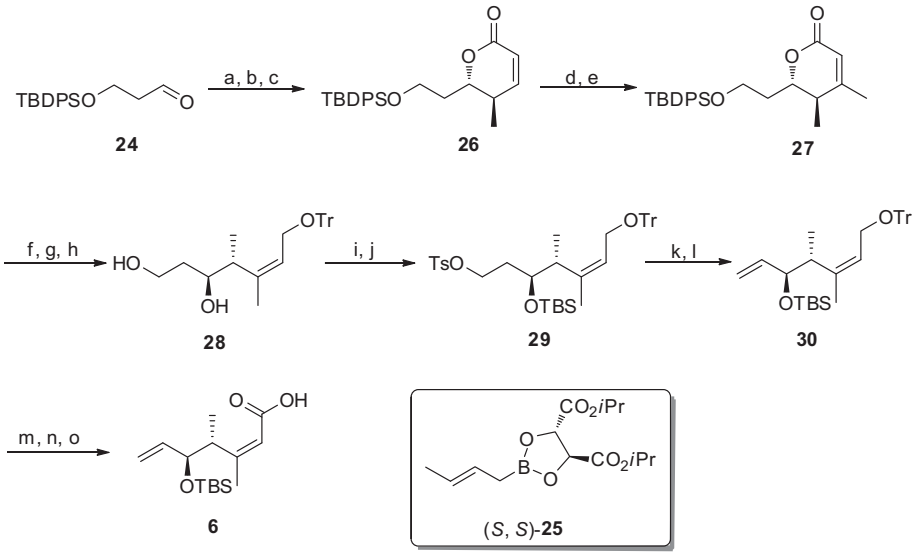


Scheme 2. Reagents and conditions: (a) imidazole, DMAP, TBSCl, CH_2Cl_2, rt, 83%; (b) Ti(O*i*-Pr)$_4$, EtMgBr, Et_2O, 94%; (c) imidazole, DMAP, TsCl, CH_2Cl_2, reflux, 95%; (d) TBAF, THF, rt, 80%; (e) NaCN, $LiClO_4$, CH_3CN, 70–75 °C, 93%; (f) imidazole, DMAP, TBSCl, CH_2Cl_2, 40 °C, 89%; (g) DIBAL-H, CH_2Cl_2, −78 °C, 74%; (h) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C, 98%; (i) $MgBr_2\cdot Et_2O$, CH_2Cl_2, reflux, 1 h, 88%; (j) NaI, acetone, rt, 90%; (k) $Bu_3SnSnBu_3$, Pd_2dba_3 (5 mol %), THF, 55 °C, 3 h, 100% conversion. NaHMDS=sodium bis(trimethylsilyl)amide, Pd_2dba_3=tris(dibenzylideneacetone)dipalladium(0).

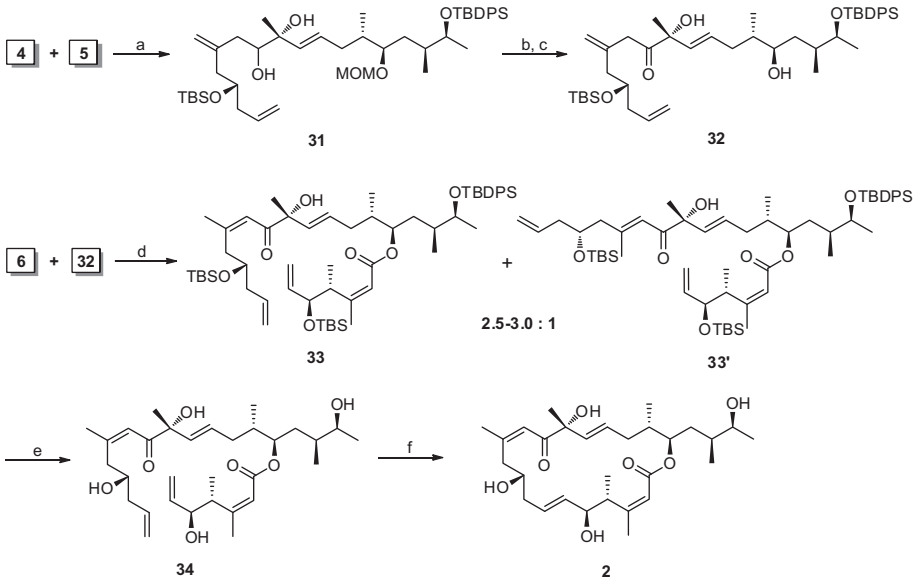
which was firstly transformed to TBS ether under basic conditions. Then according to the method developed by Kulinkovich and Meijere,[11] 1-substituted cyclopropanol was obtained followed by treating with tosyl chloride to provide **20** in 89% yield over the two steps. A TBAF promoted deprotection–epoxidation gave the epoxide in 80% yield, which initially was supposed to be opened through a copper-catalyzed addition of ethylmagnesium bromide to the epoxy. However, no desired product was obtained with several copper salts evaluated.[12a] Another method using NaCN as the nucleophile in the presence of $LiClO_4$ was herein introduced. Gratifyingly, it proceeded successfully followed by protection of the resulting alcohol with TBSCl providing cyanide **21** in 83% yield over the two steps.[12b] Reduction of cyanide **21** with DIBAL-H and subsequent undergoing Wittig methylenation using $Ph_3P^+CH_3Br^-$ provided an olefin **22** in 76% yield in two steps. Displacement of the sulfonate group with bromide accompanying with a cyclopropylallyl rearrangement of **22** took place efficiently to afford an allyl bromide **23** in 88% yield,[13] which was finally transformed to the allyl stannane **5** through cross-coupling of the corresponding allyl iodide with bis(tributyltin) using a catalytic amount of $Pd_2dba_3\cdot CHCl_3$ (5 mol %). Due to the easy decomposition in the silica gel column, the allyl stannane **5** was used as the crude product for the following allylation without further purification.[14]

Synthesis of the last fragment (*Z*)-diene acid **6** was depicted in Scheme 3. Asymmetric crotylation of the aldehyde **24** produced alcohol (not shown) in 91% yield with excellent diastereoselectivity (dr>19:1), which was converted to the α,β-unsaturated lactone **26** via acylation and subsequent ring-closing metathesis in 79% yield over the three steps.[15] The C3 methyl group in lactone **27** was then introduced through 1,4-addition of Me_2CuLi and PhSeCl mediated dehydrogenation in 72% yield.[16] After reductively opening of lactone **27** under Luche's conditions,[17] the primary alcohol of the resulted diol was selectively protected as a trityl ether and then treated with TBAF to remove TBDPS group providing the novel diol **28** in 73% yield over three steps. Diol **28** was converted to the corresponding olefin **30** in 88% yield in a four-step consequence involving tosylation of the primary alcohol, formation of TBS silyl ether, Finkelstein-type iodination and *t*-BuOK mediated β-elimination.[18] Acid **6** was finally obtained through trityl removal of **30**,[19] oxidation of the allyl alcohol with DMP, and further oxidation of the resulting aldehyde with sodium chlorite in 74% yield over the three steps.

With all the building blocks in hand, development of a reliable assembly process became the next goal. The completion of the synthesis of the proposed structure of iriomoteolide-1b (**2**) was shown in Scheme 4. Since the Barbier reaction between the allyl bromide **23** and aldehyde **4** has been proved to be fruitless, a careful survey of the conditions for the crucial coupling reaction between allyl stannane **5** and aldehyde **4** was carried out. It was found that the allylation did not proceed in the presence of ytterbium triflate



Scheme 3. Reagents and conditions: (a) (*S*,*S*)-**25**, 4 Å MS, toluene, −78 °C, 91%; (b) Acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, rt, 95%; (c) Grubbs Cat. second (5 mol %), CH_2Cl_2, reflux, 91%; (d) $(CH_3)_2CuLi$, Et_2O, −20 °C to 0 °C, 85%; (e) LDA, TMSCl, PhSeCl, THF, −78 °C, 3 h; then $NaHCO_3$, 30% H_2O_2, THF/EtOAc (v/v, 1:2), 3 h, 85%; (f) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, 0 °C to rt, overnight, 54% (81% br s, m); (g) TrCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 90%; (h) TBAF, THF, rt, 100%; (i) TsCl, Et_3N, DMAP, CH_2Cl_2, 99%; (j) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%; (k) NaI, acetone, rt, 97%; (l) *t*-BuOK, THF, 0 °C to rt, 97%; (m) 1.0 M HCl (saturated with NaCl), $CHCl_3$, rt, 2 days, 86%; (n) DMP, $NaHCO_3$, CH_2Cl_2, rt, 93%; (o) $NaClO_2$, Na_2HPO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 0 °C, 40 min, 92%.



Scheme 4. Reagents and conditions: (a) $Yb(OTf)_3$ (20 mol %), *p*-NO_2PhCO_2H (2 equiv), THF, rt, 91%; (b) IBX, DMSO, rt, 90%; (c) *B*-Bromocatecholborane, CH_2Cl_2, −78 °C, 10–15 min, 78%; (d) **6**, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, 0 °C to rt, 2 h; then **32**, DMAP, toluene, 0 °C to rt, 23 h, 90%; (e) HF·Py, THF, rt, 6 days, 60–70%; (f) Grubbs Cat. second (5 mol %), CH_2Cl_2, rt, overnight, 90%. IBX=2-iodoxybenzoicacid.

or carboxylic acid,[20b] respectively, and aldehyde **4** was prone to decomposing under above conditions. However, by the combination of ytterbium triflate and carboxylic acid in the reaction, the allylation proceeded smoothly at room temperature to give **31** as a pair of diastereoisomers up to 91% yield.[20a] although 20 mol % of ytterbium triflate was required. Critical to our success was the development of this mild and convergent method for the allylation of allyl stannane **5** with aldehyde **4** with tertiary alcohol at the α-position of the carbonyl group. Oxidation of **31** using IBX and subsequent removal of MOM group with *B*-Bromocatecholborane at −78 °C delivered the key intermediate **32** in 70% yield over the two steps. Next, Yamaguchi esterification was employed to combination of the key intermediate **32** and acid **6**. However, an unexpected migration of the double bond occurred and we got the enone products *Z*-**33** and *E*-**33′** as mixtures with a ratio of 2.5–3.0:1.[21] The Mukaiyama and Corey–Nicolaou esterification conditions were also investigated to avoid the migration of the double bond but both proved to be unsuccessful.[22] Ultimately, after global deprotection of α,β-unsaturated ketone **33** with excess HF·Py (200 equiv) at room temperature for about 6 days, the macrolide **2** was assembled by the RCM reaction using 5 mol % Grubbs's second generation catalyst at room temperature with *E*-isomer as a sole product[23] in 63% yield over the two steps. However, the spectral data of synthetic iriomoteolide-1b (**2**) did not match with that reported for natural iriomoteolide-1b.[1b] That the major difference of ^1H and ^{13}C shifts at C4 (3.80 ppm and 40.5 ppm for synthetic iriomoteolide-1b compared to 2.62 ppm and 48.7 ppm for the natural product), along with many other minor inconsistencies throughout the spectra, suggests that the structure of natural iriomoteolide-1b has been assigned incorrectly.[24]

3. Conclusion

In summary, we have presented herein a concise, efficient, and highly stereoselective total synthesis of the proposed structure of iriomoteolide-1b (**2**). The macrolide **2** was synthesized successfully in 19 steps from the known methyl ketone **7** with 10.2% overall yield. This convergent route was featured an organocatalytic enantioselective transfer hydrogenation, ytterbium triflate and carboxylic acid promoted allylation between allyl stannane and aldehyde with tertiary alcohol at the α-position. Efforts directed toward the total synthesis of iriomoteolide-1a in order to correct the proposed structure are currently ongoing in our laboratory.

4. Experimental section

4.1. General

All reactions were conducted under Ar atmosphere unless stated otherwise and monitored by TLC on precoated silica gel HSGF254 plates (Yantai Chemical Co., Ltd). Column chromatography was performed on silica gel 300–400 mesh (Yantai Chemical Co., Ltd) and eluted with hexanes and diethyl ether or ethyl acetate mixtures. All solvents were refluxed and distilled from sodium benzophenone ketyl (THF, Et_2O, toluene) or CaH_2 (CH_2Cl_2, DMF, DMSO). The NMR spectra (^1H: 400 MHz, ^{13}C: 100 MHz) are reported in δ units (parts per million) and *J* values (hertz) with Me_4Si as the internal standard. Infrared (IR) spectra are reported in wave numbers (cm^{-1}). Optical rotations are reported in units of 10^{-1} deg cm^3 g^{-1}.

4.2. (*S*,*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylpent-2-enal (9)

To a solution of α,β-unsaturated ester **8** (1.68 g, 4.24 mmol) in CH_2Cl_2 (20 mL) was added DIBAL-H (1.0 M in toluene, 10.6 mL, 10.6 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h before it was quenched by aqueous Rochelle salt solution and stirred at room temperature for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification on silica gel (EtOAc/hexanes 1:20) provided allyl alcohol (1.46 g, 97%) as a colorless oil.

$[\alpha]_D^{25}$ −13.3 (*c* 3.45, $CHCl_3$); IR (film): 3375, 3071, 2931, 2890, 2858, 1589, 1367, 1188, 838, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.46–7.34 (m, 6H), 5.33 (t, *J*=6.8 Hz, 1H), 4.22 (t, *J*=6.3 Hz, 1H), 4.07–3.98 (m, 2H), 1.64 (s, 3H), 1.19 (d, *J*=6.5 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 136.0, 135.9, 134.5, 134.4, 129.6, 129.6, 127.5, 127.4, 123.1, 74.3, 59.1, 27.0, 23.0, 19.2, 11.5; MS (ESI): *m*/*z* 377.2, $[M+Na]^+$; HRMS (MALDI) calcd for $C_{22}H_{30}O_2SiNa^+$ $[M+Na]^+$: 377.1907, found: 377.1921.

To a cooled (−78 °C) flask containing 10 mL of CH_2Cl_2 was added oxallylchloride (0.70 mL, 8.21 mmol) under argon, followed by dropwise addition of DMSO (1.17 mL, 16.4 mmol) dissolved in 5 mL of CH_2Cl_2. After 15 min, the above allyl alcohol dissolved in 5 mL of CH_2Cl_2 was added to the reaction solution at −78 °C. After 1 h, Et_3N (9.8 mL, 70.1 mmol) was added, and the reaction vessel was maintained at −78 °C for 20 min before the cooling bath was removed. After the reaction had warmed to room temperature for 20 min, aq $NaHCO_3$ was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4. After filtration, the organic phase was concentrated and purified by flash chromatography (Et_2O/hexanes 1:20) to afford enal **9** (1.34 g, 92%) as a colorless oil.

$[\alpha]_D^{25}$ −41.6 (*c* 1.55, $CHCl_3$); IR (film): 3071, 2931, 2893, 2858, 1679, 1472, 1428, 1112, 822, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (d, *J*=8.1 Hz, 1H), 7.68–7.66 (m, 2H), 7.60–7.59 (m, 2H), 7.47–7.33 (m, 6H), 6.02 (d, *J*=8.0 Hz, 1H), 4.24 (t, *J*=6.5 Hz, 1H), 2.01 (s, 3H), 1.19 (d, *J*=6.5 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 165.2, 135.8, 135.8, 133.8, 133.3, 129.9, 129.9, 127.7, 125.0, 73.4, 27.0, 22.8, 19.2, 13.4; MS (ESI): *m*/*z* 375.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{28}O_2SiNa^+$ $[M+Na]^+$: 375.1751, found: 375.1751.

4.3. (3*S*,4*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylpentanal (12)

A colorless solution of enal **9** (905 mg, 2.57 mmol) dissolved in 10 mL of chloroform was cooled to −30 °C. To this solution was added (2*R*,5*R*)-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one **10** (126 mg, 0.51 mmol), the ethyl Hantzsch ester **11** (975 mg, 3.85 mmol) and trifluoroacetic acid (58 mg, 0.51 mmol). The resulting yellow suspension was stirred at −30 °C for 3 days. The reaction mixture was then diluted with Et_2O and passed though a short pad of silica gel. The solution was concentrated and purified by flash chromatography (Et_2O/hexanes 1:20) to afford aldehyde **12** (856 mg, 94%) as a colorless oil.

$[\alpha]_D^{28}$ +3.6 (*c* 1.25, $CHCl_3$); IR (film): 3071, 3049, 2961, 2931, 2889, 2858, 2715, 1726, 1587, 1472, 1427, 1382, 1110, 1043, 822, 740, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72(t, *J*=2.2 Hz, 1H), 7.68–7.66 (m, 4H), 7.45–7.36 (m, 6H), 3.86–3.81 (m, 1H), 2.71–2.64 (m, 1H), 2.25–2.18 (m, 2H), 1.06 (s, 9H), 0.96 (d, *J*=6.3 Hz, 3H), 0.85 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 135.9, 135.9, 134.5, 134.0, 129.7, 129.6, 127.7, 127.5, 72.2, 46.3, 35.0, 27.1, 19.3, 18.5, 15.7; MS (ESI): *m*/*z* 409.2, $[M+MeOH+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{30}O_2SiNa^+$ $[M+Na]^+$: 377.1904, found: 377.1907.

4.4. (3*S*,4*R*,6*S*,7*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-3,6-dimethyloct-1-en-4-ol (14)[5]

A solution of aldehyde **12** (1.23 g, 3.47 mmol) in toluene (5 mL) was added dropwise to a mixture of crotylboronate (*R*,*R*)-**13** (0.80 M stock solution in toluene, 6.5 mL, 5.20 mmol) and powdered activated 4 Å MS (600 mg) in toluene (25 mL) at −78 °C. After 3 h at −78 °C, the reaction mixture was quenched by satd K_2CO_3 solution and stirred at room temperature for 2 h. The layers were separated and the aqueous phase was extracted with EtOAc and washed with brine. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Et_2O/hexanes 1:20) to afford 1.35 g (95%) of **14** as a colorless oil.

$[\alpha]_D^{29}$ −8.1 (*c* 1.50, $CHCl_3$); IR (film): 3405, 3070, 2957, 2926, 2855, 1462, 1419, 1371, 1110, 1026, 958, 821, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.67 (m, 4H), 7.44–7.37 (m, 6H), 5.82–5.73 (m, 1H), 5.11–5.06 (m, 2H), 3.90–3.84 (m, 1H), 3.50 (m, 1H), 2.20–2.12 (m, 1H), 1.87–1.74 (m, 2H), 1.39–1.07 (m, 2H), 1.07 (s, 9H), 1.02 (d, *J*=6.8 Hz, 3H), 0.95 (d, *J*=6.3 Hz, 3H), 0.89 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 136.0, 136.0, 135.9, 134.8, 134.1, 129.6, 129.5, 127.6, 127.4, 115.9, 73.3, 72.5, 44.2, 37.1, 36.8, 27.1, 19.3, 19.1, 16.6, 16.4; MS (ESI): *m*/*z* 411.0, $[M+H]^+$; HRMS (MALDI) calcd for $C_{26}H_{38}O_2SiNa^+$ $[M+Na]^+$: 433.2544, found: 433.2533.

4.5. (3*S*,4*R*,6*S*,7*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-4-(methoxymethoxy)-3,6-di methyloctan-1-ol (15)

To a solution of the above alcohol **14** (808 mg, 1.97 mmol) and TBAI (363 mg, 0.984 mmol) in CH_2Cl_2 (12 mL) was added DIPEA (2.74 mL, 15.73 mmol) and the mixture was cooled to 0 °C. MOMCl (0.60 mL, 7.87 mmol) was added dropwise, and the mixture was warmed to 40 °C and stirred for 24 h. The reaction was quenched by satd $NaHCO_3$, extracted with CH_2Cl_2 and washed with brine. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Et_2O/hexanes 1:40) to afford MOM ether (880 mg, 98%) as a colorless oil.

$[\alpha]_D^{24}$ −20.7 (*c* 1.50, $CHCl_3$); IR (film): 3071, 2930, 2822, 1462, 1428, 1379, 1104, 1038, 955, 822, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.67 (m, 4H), 7.43–7.35 (m, 6H), 5.86–5.69 (m, 1H), 5.04–4.99 (m, 2H), 4.59 (s, 2H), 3.84–3.78 (m, 1H), 3.49–3.44 (m, 1H), 3.34 (s, 3H), 2.42–2.37 (m, 1H), 1.77–1.71 (m, 1H), 1.64–1.58 (m, 1H), 1.37–1.33 (m, 1H), 1.05 (s, 9H), 1.04 (d, *J*=7.7 Hz, 3H), 0.94 (d, *J*=6.3 Hz, 3H), 0.91 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 136.0, 136.0, 135.1, 134.3, 129.5, 129.4, 127.5, 127.3, 115.0, 96.1, 80.5, 72.5, 55.7, 40.9, 37.0, 33.8, 27.1, 20.0, 19.4, 15.4, 15.3; MS (ESI): *m*/*z* 477.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{28}H_{42}O_3SiNa^+$ $[M+Na]^+$: 477.2795, found: 477.2782.

A solution of borane-dimethyl sulfide (2.0 M solution in THF, 3.52 mL, 7.04 mmol) was added to a solution of the above MOM ether (200 mg, 0.38 mmol) in dry THF (15 mL) at 0 °C. After being warmed to room temperature and stirred for 6 h, the mixture was again cooled to 0 °C and carefully quenched by successively addition of EtOH (2 mL), aq NaOH (2 mL, 2.5 M), and 30% H_2O_2 (2 mL). The mixture was stirred for 2 h at room temperature. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:10) to afford alcohol **15** (665 mg, 80%) as a colorless oil.

$[\alpha]_D^{27}$ −19.1 (*c* 2.55, $CHCl_3$); IR (film): 3446, 3065, 2936, 2887, 1464, 1430, 1379, 1105, 1040, 954, 822, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.67 (m, 4H), 7.43–7.35 (m, 6H), 4.59 (s, 2H), 3.87–3.83 (m, 1H), 3.69–3.63 (m, 1H), 3.57–3.51 (m, 1H), 3.46–3.42 (m, 1H), 3.35 (s, 3H), 1.86–1.76 (m, 2H), 1.59–1.33 (m, 5H), 1.07 (s, 9H), 0.98 (d, *J*=6.3 Hz, 3H), 0.95 (d, *J*=6.8 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.9, 134.9, 134.4, 129.6, 129.5, 127.6, 127.4, 96.0, 81.1, 72.6, 60.5, 55.7, 37.2, 34.3, 33.1, 32.6, 27.1, 19.7, 19.4, 15.5, 15.4; MS (ESI): *m*/*z* 495.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{28}H_{44}O_4SiNa^+$ $[M+Na]^+$: 495.2901, found: 495.2888.

4.6. Sulfone 16

Triphenylphosphine (272 mg, 1.04 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, 185 mg, 1.04 mmol) and **15** (245 mg, 0.518 mmol) were dissolved in 6 mL of THF, to which was added DIAD (0.20 mL, 1.04 mmol) at 0 °C. After stirring at room temperature for 19 h, the reaction was diluted by the addition of brine and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification on silica gel (Et_2O/hexanes 1:10) provided sulfide (316 mg, 96%) as a colorless oil.

$[\alpha]_D^{29}$ −29.6 (*c* 2.15, $CHCl_3$); IR (film): 3070, 2962, 2931, 2857, 1597, 1500, 1462, 1427, 1385, 1108, 1038, 955, 822, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.65 (m, 4H), 7.57–7.53 (m, 5H),

7.42–7.31 (m, 6H), 4.54 (s, 2H), 3.84–3.79 (m, 1H), 3.55–3.48 (m, 1H), 3.41–3.37 (m, 1H), 3.28 (s, 3H), 3.27–3.23 (m, 1H), 1.85–1.78 (m, 2H), 1.73–1.67 (m, 1H), 1.64–1.56 (m, 3H), 1.02 (s, 9H), 0.99 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.3 Hz, 3H), 0.90 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 136.0, 135.9, 134.9, 134.3, 133.8, 130.0, 129.8, 129.6, 129.5, 127.6, 127.4, 123.9, 96.1, 80.9, 72.4, 55.7, 37.3, 35.5, 33.1, 31.8, 31.1, 27.1, 19.8, 19.4, 15.4, 15.0; MS (ESI): m/z 655.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{35}H_{48}O_3N_4SSiNa^+$ $[M+Na]^+$: 655.3109, found: 655.3109.

To a solution of the above sulfide (520 mg, 0.822 mmol) in EtOH (15 mL) was added mixed 30% aq H_2O_2 (0.93 mL, 8.22 mmol) and ammonium molybdate (206 mg, 0.164 mmol) at room temperature. The mixture was stirred for 24 h and diluted by the addition of brine. The combined organic layers were extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated. Purification on silica gel (EtOAc/hexanes 1:10) provided sulfone **16** (500 mg, 92%) as a colorless oil.

$[\alpha]_D^{27}$ −25.3 (c 2.10, $CHCl_3$); IR (film): 3071, 2960, 2931, 2858, 1594, 1498, 1463, 1428, 1342, 1107, 1037, 956, 822, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.59 (m, 9H), 7.43–7.34 (m, 6H), 4.49 (dd, J=16.1, 6.8 Hz, 2H), 3.90–3.80 (m, 2H), 3.68–3.60 (m, 1H), 3.39–3.35 (m, 1H), 3.31 (s, 3H), 2.05–1.98 (m, 1H), 1.86–1.79 (m, 2H), 1.71–1.65 (m, 1H), 1.57–1.53 (m, 1H), 1.38–1.32 (m, 1H), 1.03 (s, 9H), 0.99 (d, J=7.3 Hz, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.91 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 136.0, 135.9, 134.9, 134.2, 133.2, 131.4, 129.7, 129.7, 129.5, 127.6, 127.4, 125.1, 96.2, 80.7, 72.4, 55.8, 54.5, 37.1, 35.2, 33.9, 27.1, 23.8, 20.0, 19.3, 15.6, 15.2; MS (ESI): m/z 687.3, $[M+Na]^+$; HRMS (MALDI) calcd for $C_{35}H_{48}N_4O_5SSiNa^+$ $[M+Na]^+$: 687.3007, found: 687.3000.

4.7. Olefin 18

To a stirred solution of sulfone **16** (490 mg, 0.737 mmol) in 3 mL of DMF/HMPA (3:1 v/v) was added LiHMDS (1.0 M in THF, 1.11 mL, 1.11 mmol) at −40 °C. This was stirred for 10 min and followed by the addition of aldehyde **17** (316 mg, 0.952 mmol) in 1.0 mL of DMF/HMPA (3:1 v/v) via cannula. The reaction was allowed to warm slowly to room temperature and stirred for 24 h before it was quenched by the addition of satd NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification on silica gel (hexanes) provided **18** (520 mg, 91%) as a colorless oil.

$[\alpha]_D^{29}$ −1.2 (c 2.15, $CHCl_3$); IR (film): 3073, 2956, 2927, 2857, 1462, 1378, 1254, 1108, 1039, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.68 (m, 4H), 7.45–7.36 (m, 6H), 5.59–5.52 (m, 1H), 5.45 (d, J=15.5 Hz, 1H), 4.58 (s, 2H), 3.86–3.81 (m, 1H), 3.42–3.40 (m, 1H), 3.37 (m, 2H), 3.35 (s, 3H), 2.13–2.09 (m, 1H), 1.79–1.73 (m, 3H), 1.62–1.60 (m, 1H), 1.31–1.28 (m, 3H), 1.07 (s, 9H), 0.97 (d, J=6.3 Hz, 3H), 0.93 (d, J=6.8 Hz, 3H), 0.89 (m, 21H), 0.09 (s, 6H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 136.0, 135.9, 135.1, 134.3, 129.6, 129.4, 127.9, 127.6, 127.4, 95.9, 81.2, 75.7, 72.5, 71.6, 55.6, 37.4, 36.5, 35.0, 33.1, 27.1, 25.9, 24.5, 19.9, 19.4, 18.3, 18.2, 15.5, 14.9, −2.1, −5.4; MS (ESI): m/z 793.5, $[M+Na]^+$; HRMS (ESI) calcd for $C_{44}H_{79}O_5Si_3^+$ $[M+H]^+$: 771.5230, found: 771.5256.

4.8. Aldehyde 4

To a stirred solution of compound **18** (520 mg, 0.674 mmol) in THF (15 mL) was added pyridine (1.35 mL, 13.5 mmol) and HF·Py (0.334 mL, 13.5 mmol). The mixture was stirred at room temperature for 3 days before it was quenched with satd $NaHCO_3$. The reaction mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 1:20) to afford alcohol (354 mg, 80%) as a colorless oil.

$[\alpha]_D^{25}$ −2.64 (c 1.35, $CHCl_3$); IR (film): 3489, 3074, 2956, 2931, 2857, 1472, 1379, 1253, 1105, 1038, 836, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.43–7.33 (m, 6H), 5.60–5.53 (m, 1H), 5.45 (d, J=15.8 Hz, 1H), 4.56 (s, 2H), 3.84–3.79 (m, 1H), 3.43–3.39 (m, 1H), 3.33 (s, 3H), 3.29–3.25 (m, 1H), 2.13–2.09 (m, 1H), 2.03–2.00 (m, 1H), 1.83–1.72 (m, 3H), 1.60–1.57 (m, 1H), 1.30–1.26 (m, 1H), 1.28 (s, 3H), 1.05 (s, 9H), 0.95 (d, J=6.3 Hz, 3H), 0.93–0.89 (m, 15H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.9, 135.5, 135.0, 134.3, 129.6, 129.6, 129.5, 127.6, 127.4, 95.9, 81.0, 75.8, 72.6, 71.4, 65.9, 55.7, 37.3, 36.3, 34.8, 33.0, 27.1, 25.9, 23.8, 19.7, 19.4, 18.2, 15.5, 15.3, −2.2; MS (ESI): m/z 679.5, $[M+Na]^+$; HRMS (ESI) calcd for $C_{38}H_{64}O_5Si_2Na^+$ $[M+Na]^+$: 679.4185, found: 679.4172.

To a solution of the above alcohol (250 mg, 0.380 mmol) in CH_2Cl_2 (10 mL) was added DMP (323 mg, 0.761 mmol) and $NaHCO_3$ (128 mg, 1.52 mmol). The reaction was stirred at room temperature for 1 h before it was quenched with satd $NaHCO_3$ and satd $Na_2S_2O_3$. The mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:20–1:10) to afford aldehyde (225 mg, 90%) as a colorless oil.

$[\alpha]_D^{25}$ −16.2 (c 1.20, $CHCl_3$); IR (film): 3074, 2958, 2931, 2857, 1676, 1472, 1379, 1254, 1105, 1037, 837, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.68–7.65 (m, 4H), 7.44–7.34 (m, 6H), 5.77–5.70 (m, 1H), 5.24 (d, J=15.3 Hz, 1H), 4.56 (s, 2H), 3.83–3.78 (m, 1H), 3.41–3.37 (m, 1H), 3.33 (s, 3H), 2.14–2.10 (m, 1H), 1.83–1.70 (m, 3H), 1.58–1.54 (m, 1H), 1.38 (s, 3H), 1.32–1.26 (m, 1H), 1.05 (s, 9H), 0.95 (d, J=6.3 Hz, 3H), 0.93 (s, 9H), 0.90 (d, J=7.0 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 136.0, 135.9, 135.0, 134.3, 132.7, 131.1, 129.6, 129.5, 127.6, 127.4, 96.0, 80.9, 80.4, 72.5, 55.7, 37.3, 36.2, 34.8, 33.1, 27.1, 25.8, 22.9, 19.7, 19.4, 18.3, 15.4, 15.1, −2.2, −2.3; MS (ESI): m/z 677.4, $[M+Na]^+$; HRMS (ESI) calcd for $C_{38}H_{62}O_5Si_2Na^+$ $[M+Na]^+$: 677.4028, found: 677.4042.

To a stirred solution of the above aldehyde (196 mg, 0.299 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 0.36 mL, 0.36 mmol). The reaction was stirred at room temperature for 20 min before it was diluted with brine. The mixture was extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 1:10–1:5) to afford **4** (136 mg, 84%) as a colorless oil.

$[\alpha]_D^{26}$ −59.8 (c 1.85, $CHCl_3$); IR (film): 3445, 3065, 2932, 1733, 1462, 1377, 1104, 1039, 821, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.69–7.66 (m, 4H), 7.44–7.35 (m, 6H), 5.78–5.70 (m, 1H), 5.35 (d, J=15.6 Hz, 1H), 4.56 (s, 2H), 3.87–3.80 (m, 1H), 3.42–3.38 (m, 1H), 3.33 (s, 3H), 3.31–3.27 (m, 1H), 2.18–2.15 (m, 1H), 1.86–1.71 (m, 3H), 1.58 (m, 1H), 1.38 (s, 3H), 1.41–1.33 (m, 1H), 1.06 (s, 9H), 0.96 (d, J=6.3 Hz, 3H), 0.93 (s, 9H), 0.90 (d, J=7.1 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 136.0, 135.9, 134.9, 134.3, 133.3, 129.6, 129.6, 129.5, 127.6, 127.4, 96.0, 80.9, 78.1, 72.6, 55.7, 37.3, 36.0, 34.7, 32.9, 27.1, 22.6, 19.6, 19.4, 15.5, 15.2; MS (ESI): m/z 563.4, $[M+Na]^+$; HRMS (ESI) calcd for $C_{32}H_{48}O_5SiNa^+$ $[M+Na]^+$: 563.3163, found: 563.3144.

4.9. (*R*)-1-(2-((*tert*-Butyldimethylsilyl)oxy)-3-chloropropyl) cyclopropyl 4-methyl benzenesulfonate (20)

To a solution of compound **13** (1.28 g, 7.68 mmol) in CH_2Cl_2 (20 mL) was added imidazole (784 mg, 11.52 mmol) and TBSCl (1.51 g, 9.99 mmol) at 0 °C. The reaction was stirred at room temperature for 15 h before it was quenched with aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:40) to afford TBS ether (2.0 g, 83%) as a colorless oil.

$[\alpha]_D^{26}$ +21.6 (*c* 1.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.34–4.26 (m, 1H), 4.18–4.09 (m, 2H), 3.56–3.49 (m, 2H), 2.65 (dd, *J*=15.5, 5.0 Hz, 1H), 2.47 (dd, *J*=15.2, 7.3 Hz, 1H), 1.24 (t, *J*=7.0 Hz, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H).

To a solution of TBS ether (2.10 g, 7.48 mmol) in Et_2O (30 mL) was added Ti(O*i*-Pr)$_4$ (1.11 mL, 3.74 mmol) and cooled to 0 °C. A solution of EtMgBr (3.0 M in Et_2O, 7.48 mL, 22.43 mmol) was then added dropwise over 1 h to the stirred solution. After 1 h at 0 °C, the reaction mixture was quenched with aq NH_4Cl. The organic layer was extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:10) to afford cyclopropanol (1.86 g, 94%) as a colorless oil.

$[\alpha]_D^{26}$ +7.3 (*c* 1.37, $CHCl_3$); IR (film): 3439, 3086, 2956, 2930, 1472, 1257, 1098, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25–4.19 (m, 1H), 3.65 (dd, *J*=11.0, 7.0 Hz, 1H), 3.56 (dd, *J*=11.0, 5.0 Hz, 1H), 3.27 (br, 1H), 2.02 (dd, *J*=14.8, 4.5 Hz, 1H), 1.79 (dd, *J*=14.8, 5.1 Hz, 1H), 0.92 (s, 9H), 0.84–0.78 (m, 1H), 0.74–0.68 (m, 1H), 0.59–0.54 (m, 1H), 0.44–0.39 (m, 1H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.9, 53.8, 47.4, 40.7, 25.7, 17.9, 13.7, 11.9, −4.6, −4.8; MS (ESI): *m*/*z* 287.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{25}ClO_2SiNa^+$ $[M+Na]^+$: 287.1205, found: 287.1213.

To a solution of the above cyclopropanol (1.38 g, 5.21 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (1.45 mL, 10.42 mmol), DMAP (127 mg, 0.104 mmol) and TsCl (1.49 g, 7.82 mmol) at 0 °C. The reaction was stirred at room temperature for 2 h and then warmed to 40 °C for additional 28 h before it was quenched with aq $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:10) to afford **20** (2.08 g, 95%) as a colorless oil.

$[\alpha]_D^{27}$ +1.7 (*c* 1.82, $CHCl_3$); IR (film): 3015, 2956, 2930, 2857, 1599, 1496, 1472, 1254, 1096, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.3 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 4.27–4.22 (m, 1H), 3.59–3.50 (m, 2H), 2.44 (s, 3H), 2.23 (dd, *J*=15.0, 5.5 Hz, 1H), 1.84 (dd, *J*=15.0, 7.5 Hz, 1H), 1.13–1.01 (m, 2H), 0.88 (s, 9H), 0.75–0.65 (m, 2H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 135.2, 129.8, 127.6, 68.9, 65.9, 64.0, 49.3, 41.2, 25.8, 21.7, 18.0, 15.3, 12.1, 11.1, −4.6, −4.7; MS (ESI): *m*/*z* 441.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{31}ClO_4SSiNa^+$ $[M+Na]^+$: 441.1293, found: 441.1303.

4.10. (*S*)-1-(2-((*tert*-Butyldimethylsilyl)oxy)-3-cyanopropyl) cyclopropyl 4-methyl benzenesulfonate (21)

To a stirred solution of **20** (930 mg, 2.22 mmol) in THF (15 mL) was added TBAF (1.0 M in THF, 4.44 mL, 4.44 mmol). The reaction was stirred at room temperature for 14 h before it was quenched with brine. The mixture was extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 1:5) to afford epoxide (479 mg, 80%) as a colorless oil.

$[\alpha]_D^{25}$ +5.4 (*c* 1.70, $CHCl_3$); IR (film): 3050, 2955, 2925, 2854, 1598, 1460, 1376, 1171, 1095, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=2.1 Hz, 2H), 7.31 (d, *J*=2.0 Hz, 2H), 3.12–3.08 (m, 1H), 2.77–2.75 (m, 1H), 2.49–2.47 (m, 1H), 2.47 (s, 3H), 2.32–2.27 (m, 1H), 1.85–1.80 (m, 1H), 1.19–1.15 (m, 2H), 0.79–0.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 135.3, 129.8, 127.6, 64.4, 49.3, 46.5, 39.1, 21.6, 11.3, 11.1; MS (ESI): *m*/*z* 291.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_{16}O_4SNa^+$ $[M+Na]^+$: 291.0662, found: 291.0667.

To a solution of the above epoxide (622 mg, 2.32 mmol) in CH_3CN (15 mL) was added NaCN (568 mg, 11.59 mmol) and $LiClO_4$ (1.86 g, 11.59 mmol). The reaction was stirred at 70 °C for 7 h before it was quenched with brine. The mixture was extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 1:2) to afford alcohol (639 mg, 93%) as a colorless oil.

$[\alpha]_D^{23}$ −1.6 (*c* 2.40, $CHCl_3$); IR (film): 3527, 3065, 3017, 2927, 2251, 1598, 1496, 1366, 1158, 1094, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 4.35 (m, 1H), 3.02 (m, 1H), 2.60 (dd, *J*=16.8, 4.8 Hz, 1H), 2.51 (dd, *J*=16.8, 6.0 Hz, 1H), 2.44 (s, 3H), 2.19 (dd, *J*=16.1, 5.3 Hz, 1H), 1.84 (dd, *J*=15.1, 8.8 Hz, 1H), 1.22–1.15 (m, 1H), 1.10–1.05 (m, 1H), 0.87–0.81 (m, 1H), 0.68–0.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 134.6, 130.0, 127.6, 117.5, 65.1, 64.0, 42.7, 25.8, 21.7, 12.0, 11.1; MS (ESI): *m*/*z* 318.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{14}H_{17}NO_4SNa^+$ $[M+Na]^+$: 318.0771, found: 318.0781.

To a solution of the above alcohol (720 mg, 2.44 mmol) in CH_2Cl_2 (15 mL) was added imidazole (332 mg, 4.88 mmol), DMAP (60 mg, 0.488 mmol) and TBSCl (552 mg, 3.66 mmol) at 0 °C. The reaction was stirred at room temperature for 1 h and then warmed to 40 °C overnight before it was quenched with aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 1:4) to obtain **21** (889 mg, 89%) as a colorless oil.

$[\alpha]_D^{24}$ +5.6 (*c* 2.40, $CHCl_3$); IR (film): 3016, 2956, 2930, 2858, 2250, 1598, 1496, 1366, 1155, 1096, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=8.3 Hz, 2H), 4.36–4.30 (m, 1H), 2.61 (dd, *J*=16.8, 4.5 Hz, 1H), 2.51 (dd, *J*=16.8, 4.5 Hz, 1H), 2.45 (s, 3H), 2.15–2.04 (m, 2H), 1.08–1.01 (m, 2H), 0.90 (s, 9H), 0.74–0.66 (m, 2H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 134.9, 129.9, 127.6, 117.4, 65.4, 63.6, 43.0, 26.4, 25.7, 21.7, 17.8, 11.8, 11.4, −4.6, −4.9; MS (ESI): *m*/*z* 432.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{31}NO_4SSiNa^+$ $[M+Na]^+$: 432.1635, found: 432.1648.

4.11. (*S*)-1-(2-((*tert*-Butyldimethylsilyl)oxy)pent-4-en-1-yl) cyclopropyl 4-methyl benzenesulfonate (22)

To a stirred solution of **21** (794 mg, 1.94 mmol) in CH_2Cl_2 (20 mL) was DIBAL-H (1.0 M in toluene, 2.91 mL, 2.91 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before it was quenched by aqueous Rochelle salt solution and stirred at room temperature for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification on silica gel (EtOAc/hexanes 3:20) provided aldehyde (590 mg, 74%) as a white solid.

Mp=68–70 °C; $[\alpha]_D^{24}$ +1.8 (*c* 0.55, $CHCl_3$); IR (film): 3544, 2955, 2926, 2855, 1732, 1693, 1598, 1456, 1362, 1176, 1095, 932, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J*=1.7 Hz, 1H), 7.75 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 4.60–4.54 (m, 1H), 2.73 (dd, *J*=5.3, 2.0 Hz, 1H), 2.71–2.47 (m, 1H), 2.45 (s, 3H), 2.12 (dd, *J*=14.5, 6.5 Hz, 1H), 1.94 (dd, *J*=14.9, 6.8 Hz, 1H), 1.10–1.01 (m, 2H), 0.86 (s, 9H), 0.70–0.62 (m, 2H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 144.9, 135.1, 129.9, 127.6, 65.9, 63.9, 50.6, 43.8, 25.7, 21.7, 17.8, 11.9, 11.7, −4.4, −4.8; MS (ESI): *m*/*z* 435.1, $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{32}O_5SSiNa^+$ $[M+Na]^+$: 435.1598, found: 435.1620.

To a stirred suspension of $Ph_3P^+CH_3Br^-$ (961 mg, 2.69 mmol) in THF (8 mL) was added NaHMDS (2.0 M in THF, 1.26 mL, 2.51 mmol) at 0 °C for 30 min. A solution of the above aldehyde (370 mg, 0.897 mmol) in THF (4 mL) was then added to the stirred solution. After 30 min at 0 °C, the reaction mixture was quenched with aq NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:10) to afford olefin **22** (360 mg, 98%) as a white solid.

Mp=78–80 °C; $[\alpha]_D^{24}$ +6.7 (*c* 1.10, $CHCl_3$); IR (film): 3075, 3015, 2955, 2929, 2857, 1641, 1599, 1472, 1364, 1178, 1096, 931, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 5.81–5.71 (m, 1H), 5.04–5.00 (m, 2H), 4.11–4.05 (m, 1H), 2.44 (s, 3H), 2.34–2.27 (m, 1H), 2.21–2.12 (m, 2H), 1.58–1.54 (m, 1H), 1.12–1.06 (m, 1H), 1.02–0.96 (m, 1H), 0.87 (s, 9H), 0.74–0.70 (m,

1H), 0.69–0.55 (m, 1H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 135.6, 134.5, 129.7, 127.6, 117.2, 68.5, 64.7, 42.8, 42.1, 25.9, 21.6, 17.9, 12.2, 11.0, −4.5, −4.5; MS (ESI): *m*/*z* 433.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{21}H_{34}O_4SSiNa^+$ $[M+Na]^+$: 433.1839, found: 433.1844.

4.12. (*S*)-((2-(Bromomethyl)hepta-1,6-dien-4-yl)oxy)(*tert*-butyl)dimethylsilane (23)

To a solution of **22** (400 mg, 0.974 mmol) in CH_2Cl_2 (10 mL) was added $MgBr_2\cdot Et_2O$ (754 mg, 2.92 mmol) at room temperature. The reaction was refluxed at argon for 1 h and then cooled to room temperature. The mixture was quenched with brine, extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by flash chromatography (hexanes) to afford allyl bromide **23** (274 mg, 88%) as a colorless oil.

$[\alpha]_D^{24}$ +2.7 (*c* 1.20, $CHCl_3$); IR (film): 3079, 2955, 2929, 2857, 1640, 1471, 1362, 1210, 1089, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.77 (m, 1H), 5.25 (s, 1H), 5.08–5.03 (m, 2H), 5.00 (s, 1H), 4.04 (d, *J*=10.0 Hz, 1H), 3.98 (d, *J*=10.0 Hz, 1H), 3.91–3.86 (m, 1H), 2.40 (dd, *J*=14.3, 5.5 Hz, 1H), 2.29 (dd, *J*=14.0, 6.5 Hz, 1H), 2.27–2.18 (m, 2H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 134.9, 118.1, 117.3, 70.9, 41.6, 40.6, 37.4, 25.9, 18.1, −4.5; HRMS (+TOF EI): *m*/*z* [M^+−allyl] calcd for $C_{11}H_{22}OSi^{81}Br$: 279.0603; found: 279.0587. HRMS (+TOF EI): *m*/*z* [M^+−allyl] calcd for $C_{11}H_{22}OSi^{79}Br$: 277.0623; found: 277.0605.

4.13. (*S*)-*tert*-Butyldimethyl((2-((tributylstannyl)methyl) hepta-1,6-dien-4-yl)oxy) silane (5)

To a solution of **23** (274 mg, 0.858 mmol) in acetone (10 mL) was added NaI (1.29 g, 8.58 mmol) at room temperature. The reaction mixture was stirred for 1 day and diluted with brine. The mixture was extracted with EtOAc, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (hexanes) to afford allyl iodide (282 mg, 90%) as a colorless oil.

The corresponding allyl iodide (282 mg, 0.770 mmol) was dissolved in THF (8 mL) and treated with bis(tributyltin) (0.58 mL, 1.16 mmol) followed by $Pd_2dba_3\cdot CHCl_3$ (35 mg, 0.0385 mmol). Argon was bubbled through the solution for 25 min and it was then heated to 55 °C for 3 h. Brine was added and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to provide allyl stannane **5** without flash column chromatography in 100% conversion.

4.14. (5*R*,6*S*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-one (26)

To a solution of aldehyde **24** (1.25 g, 4.00 mmol) in toluene (30 mL) was added powdered activated 4 Å MS (600 mg) and cooled to −78 °C. Crotylboronate (*S*,*S*)-**25** (0.80 M stock solution in toluene, 7.5 mL, 6.00 mmol) was then added to the stirred solution at −78 °C. After 2 h at −78 °C, the reaction mixture was quenched by satd K_2CO_3 solution and stirred at room temperature for additional 2 h. The layers were separated and the aqueous phase was extracted with EtOAc and washed with brine. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:20) to afford alcohol (1.34 g, 91%) as a colorless oil.

$[\alpha]_D^{26}$ +2.7 (*c* 1.60, $CHCl_3$); IR (film): 3517, 3071, 2929, 2857, 1729, 1640, 1471, 1390, 1111, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.66 (m, 4H), 7.47–7.39 (m, 6H), 5.89–5.80 (m, 1H), 5.10–5.06 (m, 2H), 3.93–3.82 (m, 2H), 3.79–3.75 (m, 1H), 3.01 (d, *J*=2.2 Hz, 1H), 2.30–2.23 (m, 1H), 1.74–1.64 (m, 2H), 1.07 (s, 9H), 1.05 (d, *J*=1.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 135.6, 134.9, 133.3, 133.2, 129.8, 127.8, 115.3, 63.4, 44.0, 35.7, 26.9, 19.1, 15.8; MS (ESI): *m*/*z* 391.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{32}O_2SiNa^+$ $[M+Na]^+$: 391.2064, found: 391.2073.

To a solution of the above alcohol (720 mg, 1.95 mmol) was added DIPEA (1.0 mL, 5.86 mmol) and DMAP (24 mg, 0.195 mmol). Then acryloyl chloride (0.24 mL, 2.93 mmol) was added dropwise at 0 °C. The reaction was stirred at room temperature for 18 h before it was quenched with satd $NaHCO_3$. The mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:40) to obtain diene (784 mg, 95%) as a colorless oil.

$[\alpha]_D^{26}$ −7.1 (*c* 2.00, $CHCl_3$); IR (film): 3072, 3050, 2931, 2858, 1725, 1472, 1295, 1110, 823, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.43–7.35 (m, 6H), 6.33 (dd, *J*=17.3, 1.5 Hz, 1H), 6.04 (dd, *J*=17.4, 10.8 Hz, 1H), 5.80–5.71 (m, 2H), 5.19–5.16 (m, 1H), 5.15–5.01 (m, 2H), 3.66 (t, *J*=6.0 Hz, 2H), 2.53–2.46 (m, 1H), 1.87–1.77 (m, 2H), 1.05 (s, 9H), 1.00 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 139.4, 135.6, 135.6, 133.8, 133.7, 130.3, 129.6, 128.9, 127.7, 115.6, 74.1, 60.4, 41.4, 34.0, 26.8, 19.2, 15.6; MS (ESI): *m*/*z* 445.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{34}O_3SiNa^+$ $[M+Na]^+$: 445.2169, found: 445.2175.

To a stirred solution of diene (710 mg, 1.68 mmol) in CH_2Cl_2 (50 mL) was added second generation Grubbs catalyst (71 mg, 0.084 mmol) at room temperature. The resulting solution was refluxed under argon for 12 h. The solvent was evaporated and the residue was purified by flash chromatography (EtOAc/hexanes 1:10) to afford lactone **26** (604 mg, 91%) as a colorless oil.

$[\alpha]_D^{25}$ −14.4 (*c* 1.10, $CHCl_3$); IR (film): 3071, 3049, 2930, 2857, 1729, 1471, 1247, 1111, 822, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.37 (m, 6H), 6.33 (dd, *J*=9.7, 2.5 Hz, 1H), 5.94 (dd, *J*=9.8, 2.5 Hz, 1H), 3.97 (dt, *J*=9.5, 3.0 Hz, 1H), 3.97–3.92 (m, 1H), 3.88–3.83 (m, 1H), 2.58–2.49 (m, 1H), 2.01–1.93 (m, 1H), 1.91–1.83 (m, 1H), 1.13 (d, *J*=7.2 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 151.4, 135.6, 135.5, 133.7, 133.5, 129.7, 127.8, 127.8, 120.2, 80.5, 59.4, 35.8, 33.3, 26.9, 19.2, 16.5; MS (ESI): *m*/*z* 417.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{30}O_3SiNa^+$ $[M+Na]^+$: 417.1856, found: 417.2047.

4.15. (5*R*,6*S*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4,5-dimethyl-5,6-dihydro-2*H*-pyran-2-one (27)

A solution of methyllithium (3.0 M in ether, 4.24 mL, 12.72 mmol) was added to a suspension of CuI (1.21 g, 6.36 mmol) in Et_2O (15 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 20 min to form a clear solution. A solution of lactone **26** (837 mg, 2.12 mmol) in Et_2O (5 mL) was added, and the mixture was stirred at 0 °C for 5 h. The reaction was quenched with satd NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 1:10) to obtain mixtures (738 mg, 85%).

To a stirred solution of *i*-Pr_2NH (0.136 mL, 0.968 mmol) in THF (6 mL) was added *n*-BuLi (1.6 M in hexanes, 0.61 mL, 0.968 mmol) at −78 °C. After stirred at 0 °C for 30 min, a solution of the above mixtures (265 mg, 0.649 mmol) was added to the stirred solution at −78 °C. After 30 min, TMSCl (0.41 mL, 3.23 mmol) was added. After additional 30 min, PhSeCl (371 mg, 1.94 mmol) was added to the reaction system. The reaction mixture was stirred at −78 °C for 3 h before it was quenched with satd NH_4Cl. Then it was extracted with EtOAc, washed with brine and dried over Na_2SO_4. The combined organic extracts were concentrated under reduced pressure and dissolved in THF/EtOAc (2 mL/4 mL). $NaHCO_3$ (545 mg, 6.49 mmol) and 30% H_2O_2 (0.27 mL, 6.49 mmol) were added to the above solution at 0 °C. After 40 min, the reaction mixture was warmed to room temperature and stirred overnight. It was quenched with satd NH_4Cl, extracted with EtOAc, washed with brine, dried over Na_2SO_4,

concentrated and purified by flash chromatography (EtOAc/hexanes 1:10) to afford lactone **27** (225 mg, 85%) as a colorless oil.

4.16. (3*S*,4*R*,*Z*)-4,5-Dimethyl-7-(trityloxy)hept-5-ene-1,3-diol (28)

To a solution of lactone **27** (97 mg, 0.237 mmol) in MeOH (5 mL) was added $CeCl_3\cdot 7H_2O$ (265 mg, 0.712 mmol) and $NaBH_4$ (27 mg, 0.721 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C before it was diluted with brine. The mixture was extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 1:10) to give diol (53 mg, 54%, 81% br s, m) as a colorless oil with recovered starting material **27** (32 mg).

$[\alpha]_D^{26}$ −1.5 (*c* 2.90, $CHCl_3$); IR (film): 3409, 3049, 2959, 2929, 2857, 1740, 1471, 1240, 1109, 822, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.67 (m, 4H), 7.47–7.37 (m, 6H), 5.74 (t, *J*=7.3 Hz, 1H), 4.21 (dd, *J*=11.5, 8.3 Hz, 1H), 3.97–3.84 (m, 3H), 3.69 (t, *J*=10.8 Hz, 1H), 2.81–2.74 (m, 1H), 1.83–1.80 (m, 1H), 1.73 (s, 3H), 1.69–1.62 (m, 1H), 1.05 (s, 9H), 0.93 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 135.6, 135.6, 133.0, 132.8, 130.0, 129.9, 127.9, 127.8, 126.2, 72.8, 63.8, 57.2, 40.4, 35.9, 26.8, 19.0, 18.4, 15.3; MS (ESI): *m*/*z* 435.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{25}H_{36}O_3SiNa^+$ $[M+Na]^+$: 435.2326, found: 435.2339.

To a solution of the above diol (273 mg, 0.662 mmol) in CH_2Cl_2 (8 mL) was added Et_3N (0.19 mL, 1.32 mmol), DMAP (8 mg, 0.066 mmol) and TrCl (277 mg, 0.992 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight and quenched with satd $NaHCO_3$. It was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 1:20) to obtain Tr ether (390 mg, 90%) as a colorless oil.

$[\alpha]_D^{27}$ −8.9 (*c* 2.30, $CHCl_3$); IR (film): 3515, 3057, 3023, 2928, 2855, 1490, 1427, 1109, 822, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.65 (m, 4H), 7.45–7.43 (m, 6H), 7.41–7.34 (m, 6H), 7.28–7.21 (m, 6H), 7.19–7.17 (m, 3H), 5.57 (t, *J*=6.5 Hz, 1H), 3.87–3.78 (m, 2H), 3.64–3.54 (m, 3H), 2.65 (s, 1H), 2.33–2.26 (m, 1H), 1.74 (s, 3H), 1.70–1.66 (m, 1H), 1.48–1.43 (m, 1H), 1.03 (s, 9H), 0.86 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 141.7, 135.6, 135.6, 133.6, 133.5, 129.7, 128.8, 128.0, 127.8, 127.7, 126.9, 124.3, 86.9, 71.9, 62.6, 60.0, 41.0, 36.8, 26.9, 19.1, 19.0, 15.5; MS (ESI): *m*/*z* 677.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{44}H_{50}O_3SiNa^+$ $[M+Na]^+$: 677.3421, found: 677.3419.

To a stirred solution of Tr ether (336 mg, 0.513 mmol) in THF (10 mL) was added TBAF (1.0 M in THF, 1.03 mL, 1.03 mmol) at room temperature. The reaction mixture was stirred for 2 h and diluted with brine. It extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 1:4) to give diol **28** (213 mg, 100%) as a colorless oil.

$[\alpha]_D^{23}$ +11.9 (*c* 0.70, $CHCl_3$); IR (film): 3463, 3060, 3024, 2925, 2854, 1712, 1491, 1446, 1157, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 6H), 7.37–7.33 (m, 6H), 7.30–7.26 (m, 3H), 5.71 (t, *J*=7.0 Hz, 1H), 3.80 (t, *J*=5.8 Hz, 2H), 3.68–3.54 (m, 3H), 2.88 (br, 2H), 2.42–2.34 (m, 1H), 1.82–1.78 (m, 1H), 1.76 (s, 3H), 1.71–1.56 (m, 1H), 0.90 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 142.5, 128.7, 127.9, 127.1, 124.5, 87.3, 73.5, 61.8, 59.3, 41.4, 36.2, 18.5, 15.0; MS (ESI): *m*/*z* 439.3, $[M+Na]^+$; HRMS (MALDI) calcd for $C_{28}H_{32}O_3Na^+$ $[M+Na]^+$: 439.2244, found: 439.2257.

4.17. (3*S*,4*R*,*Z*)-3-((*tert*-Butyldimethylsilyl)oxy)-4,5-dimethyl-7-(trityloxy)hept-5-en-1-yl 4-methyl benzenesulfonate (29)

To a solution of diol (213 mg, 0.511 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.14 mL, 1.02 mmol), DMAP (6 mg, 0.051 mmol) and TsCl (146 mg, 0.767 mmol) at 0 °C. The reaction was stirred at room temperature overnight. The mixture was quenched with satd $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/hexanes 3:20) to provide tosylate (290 mg, 99%) as a colorless oil.

$[\alpha]_D^{27}$ −9.9 (*c* 1.20, $CHCl_3$); IR (film): 3504, 3058, 3032, 2960, 2925, 2854, 1597, 1459, 1260, 1094, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J*=8.2 Hz, 2H), 7.49–7.47 (m, 6H), 7.39–7.32 (m, 9H), 7.28 (d, *J*=7.3 Hz, 2H), 5.67 (t, *J*=6.8 Hz, 1H), 4.26–4.17 (m, 2H), 3.62 (dd, *J*=10.7, 7.2 Hz, 1H), 3.45 (dd, *J*=10.3, 7.2 Hz, 1H), 3.40 (t, *J*=9.5 Hz, 1H), 2.49 (s, 3H), 2.30–2.24 (m, 1H), 2.18 (d, *J*=3.3 Hz, 1H), 2.01–1.93 (m, 1H), 1.72 (s, 3H), 1.67 (m, 1H), 0.89 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 144.0, 141.7, 133.3, 129.8, 128.7, 127.9, 127.8, 127.0, 124.9, 87.1, 68.7, 68.3, 59.4, 41.2, 34.3, 21.6, 18.6, 15.0; MS (ESI): *m*/*z* 593.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{35}H_{38}O_5SNa^+$ $[M+Na]^+$: 593.2332, found: 593.2324.

To a stirred solution of tosylate (273 mg, 0.478 mol) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.22 mL, 1.91 mmol) and TBSOTf (0.21 mL, 0.957 mmol) at 0 °C. After stirred at 0 °C for 1 h, the reaction mixture was quenched with satd $NaCHO_3$. It was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:40) to afford TBS ether **29** (311 mg, 95%) as a colorless oil.

$[\alpha]_D^{29}$ −12.9 (*c* 2.20, $CHCl_3$); IR (film): 3058, 3032, 2956, 2856, 1598, 1491, 1364, 1177, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.3 Hz, 2H), 7.51–7.49 (m, 6H), 7.36–7.32 (m, 9H), 7.28 (d, *J*=7.0 Hz, 2H), 5.53 (t, *J*=6.1 Hz, 1H), 3.98 (t, *J*=7.2 Hz, 2H), 3.65 (dd, *J*=11.3, 7.8 Hz, 1H), 3.56–3.48 (m, 2H), 2.49 (s, 3H), 2.41–2.35 (m, 1H), 1.77–1.69 (m, 2H), 1.74 (s, 3H), 0.92 (d, *J*=7.0 Hz, 3H), 0.78 (s, 9H), −0.09 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 144.3, 139.5, 129.8, 128.7, 128.0, 127.9, 127.9, 127.8, 127.3, 127.0, 124.7, 86.8, 71.3, 67.7, 60.6, 39.5, 33.5, 25.8, 21.6, 20.5, 17.9, 14.3, −4.4, −4.8; MS (ESI): *m*/*z* 707.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{41}H_{52}O_5SSiNa^+$ $[M+Na]^+$: 707.3197, found: 707.3208.

4.18. *tert*-Butyl(((3*S*,4*R*,*Z*)-4,5-dimethyl-7-(trityloxy)hepta-1,5-dien-3-yl)oxy) dimethylsilane (30)

To a solution of TBS ether **29** (313 mg, 0.457 mmol) in acetone (8 mL) was added NaI (1.30 g, 9.14 mmol) at room temperature. The reaction mixture was stirred for 2 days and diluted with brine. It was extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:40) to afford iodide (284 mg, 97%) as a colorless oil.

$[\alpha]_D^{27}$ −17.8 (*c* 1.40, $CHCl_3$); IR (film): 3059, 3025, 2956, 2927, 2855, 1458, 1258, 1047, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 6H), 7.36–7.33 (m, 6H), 7.30–7.28 (m, 3H), 5.58 (t, *J*=6.3 Hz, 1H), 3.67 (dd, *J*=11.3, 7.5 Hz, 1H), 3.57–3.49 (m, 2H), 2.97 (t, *J*=6.3 Hz, 2H), 2.50–2.43 (m, 1H), 2.10–1.85 (m, 3H), 1.76 (s, 3H), 0.97 (d, *J*=7.0 Hz, 3H), 0.85 (s, 9H), 0.13 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 140.0, 128.7, 127.8, 126.9, 124.4, 86.7, 75.0, 60.5, 38.6, 38.6, 25.8, 20.6, 18.0, 14.7, 2.3, −4.4, −4.5; MS (ESI): *m*/*z* 633.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{34}H_{45}IO_2SiNa^+$ $[M+Na]^+$: 663.2126, found: 663.2154.

To a solution of iodide (284 mg, 0.443 mmol) in THF (8 mL) was added *t*-BuOK (145 mg, 1.33 mmol) at 0 °C. The reaction was stirred for 5 h before it was quenched with satd NH_4Cl. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:40) to afford olefin **30** (220 mg, 97%) as a colorless oil.

$[\alpha]_D^{27}$ −19.9 (*c* 1.75, $CHCl_3$); IR (film): 3060, 3023, 2956, 2927, 2856, 1491, 1253, 1067, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.52 (m, 6H), 7.37–7.32 (m, 6H), 7.30–7.28 (m, 3H), 5.68–5.55 (m, 2H), 5.09–5.02 (m, 2H), 3.85 (t, *J*=7.3 Hz, 1H), 3.68 (dd, *J*=11.0, 8.0 Hz, 1H), 3.61–3.57 (m, 1H), 2.48–2.41 (m, 1H), 1.76 (s, 3H), 0.97 (d, *J*=6.8 Hz, 3H), 0.84 (s, 9H), −0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 140.7, 140.1, 128.8, 127.7, 126.8, 123.9, 115.1, 86.6, 77.1, 60.7, 41.0, 25.8, 19.8, 18.1, 14.9,−4.1,

−5.1; MS (ESI): *m/z* 535.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{34}H_{44}O_2SiNa^+$ $[M+Na]^+$: 535.3003, found: 535.3012.

4.19. Acid 6

To a stirred solution of olefin **30** (192 mg, 0.374 mmol) in $CHCl_3$ (10 mL) was added aq HCl (1.0 M in H_2O saturated with NaCl, 0.75 mL, 0.749 mmol) at 0 °C. The reaction was stirred at room temperature for 2 days and quenched with satd $NaHCO_3$. The mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:40–1:20) to afford alcohol (87 mg, 86%) as a colorless oil.

$[\alpha]_D^{30}$ −4.2 (*c* 1.45, $CHCl_3$); IR (film): 3401, 2958, 2929, 2857, 1253, 1034, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77–5.64 (m, 2H), 5.15–5.11 (m, 2H), 4.14 (dd, *J*=11.8, 7.0 Hz, 1H), 3.93–3.86 (m, 2H), 2.79–2.72 (m, 1H), 2.30 (br, 1H), 1.67 (s, 3H), 0.90 (d, *J*=6.8 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 140.6, 126.4, 116.3, 77.2, 57.7, 40.6, 25.8, 18.6, 18.2, 15.2, −4.2, −4.7; MS (ESI): *m/z* 293.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{30}O_2SiNa^+$ $[M+Na]^+$: 293.1907, found: 293.1915.

To a solution of the above alcohol (87 mg, 0.322 mmol) in CH_2Cl_2 (5 mL) was added DMP (273 mg, 0.643 mmol) and $NaHCO_3$ (108 mg 1.29 mmol). The reaction mixture was stirred at room temperature for 30 min before it was quenched satd $NaHCO_3$ and satd $Na_2S_2O_3$. The mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/hexanes 1:20) to afford aldehyde (80 mg, 93%) as a colorless oil.

$[\alpha]_D^{25}$ −32.4 (*c* 1.30, $CHCl_3$); IR (film): 3075, 2958, 2929, 2857, 1735, 1691, 1638, 1258, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (d, *J*=8.1 Hz, 1H), 5.90 (d, *J*=8.1 Hz, 1H), 5.76–5.68 (m, 1H), 5.20–5.16 (m, 2H), 4.00 (t, *J*=7.5 Hz, 1H), 3.47–3.39 (m, 1H), 1.92 (s, 3H), 1.06 (d, *J*=7.1 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 164.7, 140.0, 130.6, 116.7, 77.0, 41.4, 25.7, 20.8, 18.1, 15.4, −4.0, −5.1; MS (ESI): *m/z* 291.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{28}O_2SiNa^+$ $[M+Na]^+$: 291.1751, found: 291.1751.

To a solution of the above aldehyde (80 mg, 0.298 mmol) and 2-methyl-2-butene (1 mL) in *tert*-butanol (4 mL) was added dropwise a solution of $NaClO_2$ (81 mg, 0.894 mmol) and NaH_2PO_4 (107 mg, 0.894 mmol) in H_2O (1 mL) 0 °C. Then the reaction mixture was stirred at 0 °C for 40 min, quenched with satd NH_4Cl, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (Et_2O/hexanes 1:20) to give acid **6** (78 mg, 92%) as a colorless oil.

$[\alpha]_D^{27}$ −34.3 (*c* 1.55, $CHCl_3$); IR (film): 3088, 2966, 2929, 2856, 1693, 1634, 1254, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79–5.70 (m, 2H), 5.20–5.15 (m, 2H), 4.02 (t, *J*=7.2 Hz, 1H), 3.71–3.64 (m, 1H), 1.85 (d, *J*=1.0 Hz, 3H), 0.97 (d, *J*=7.1 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 161.0, 139.6, 118.7, 116.2, 77.2, 41.0, 25.8, 20.7, 18.2, 14.7, −4.1, −5.0; MS (ESI): *m/z* 307.2, $[M+Na]^+$; HRMS (ESI) calcd for $C_{15}H_{28}O_3SiNa^+$ $[M+Na]^+$: 307.1700, found: 307.1708.

4.20. Alcohol 32

To a solution of aldehyde **4** (88 mg, 0.163 mmol) and allyl stannane **5** (172 mg, 0.325 mmol) in THF (6 mL) was added $Yb(OTf)_3$ (20 mg, 0.0325 mmol) and *p*-NO_2PhCO_2H (54 mg, 0.325 mmol). The reaction mixture was stirred at room temperature for 24 h. The mixture was quenched with satd $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/hexanes 1:20–1:10) to give alcohol **31** (116 mg, 91%) as a colorless oil.

IR (film): 3444, 3070, 2927, 2859, 1461, 1375, 1098, 1040, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.43–7.34 (m, 6H), 5.86–5.78 (m, 1H), 5.69–5.63 (m, 1H), 5.50–5.44 (m, 1H), 5.06–5.02 (m, 2H), 4.93 (s, 2H), 4.56 (s, 2H), 3.86–3.80 (m, 2H), 3.53–3.50 (m, 1H), 3.42 (m, 1H), 3.33 (s, 3H), 2.35–2.21 (m, 6H), 2.15–1.98 (m, 1H), 1.85–1.74 (m, 3H), 1.61 (m, 1H), 1.30–1.23 (m, 6H), 0.97 (s, 9H), 0.95 (d, *J*=6.0 Hz, 3H), 0.90 (d, *J*=6.7 Hz, 3H), 0.88 (s, 9H), 0.05–0.03 (m, 6H); MS (ESI): *m/z* 803.6, $[M+Na]^+$; HRMS (ESI) calcd for $C_{46}H_{76}O_6Si_2Na^+$ $[M+Na]^+$: 803.5073, found: 803.5087.

To a solution of the above alcohol **31** (124 mg, 0.159 mmol) in DMSO (2 mL) was added IBX (178 mg, 0.635 mmol). The reaction mixture was stirred at room temperature for 10 h. The mixture was diluted with brine, extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/hexanes 1:20) to give ketone (111 mg, 90%) as a colorless oil.

$[\alpha]_D^{25}$ −32.9 (*c* 1.10, $CHCl_3$); IR (film): 3445, 3073, 2928, 2856, 1691, 1582, 1466, 1296, 1105, 1039, 835, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.45–7.35 (m, 6H), 5.86–5.75 (m, 1H), 5.46 (d, *J*=15.6 Hz, 1H), 5.06–5.02 (m, 2H), 5.00 (s, 1H), 4.88 (s, 1H), 4.57 (s, 2H), 3.84–3.81 (m, 1H), 3.41 (m, 1H), 3.34 (s, 3H), 2.28–2.16 (m, 5H), 1.84–1.69 (m, 3H), 1.58–1.55 (m, 1H), 1.45 (s, 3H), 1.34–1.29 (m, 3H), 1.06 (s, 9H), 0.95 (d, *J*=6.3 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H), 0.88 (s, 9H), 0.85 (d, *J*=6.8 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 139.7, 136.0, 135.9, 134.9, 134.3, 133.3, 131.9, 131.9, 129.6, 129.5, 127.6, 127.4, 117.2, 117.1, 96.0, 81.0, 79.1, 72.6, 71.2, 55.7, 43.8, 43.3, 41.7, 37.3, 36.1, 34.5, 33.1, 27.1, 25.9, 24.9, 19.7, 19.4, 18.1, 15.5, 15.3, −4.4, −4.4; MS (ESI): *m/z* 801.5, $[M+Na]^+$; HRMS (MALDI) calcd for $C_{46}H_{74}O_6Si_2Na^+$ $[M+Na]^+$: 801.4916, found: 801.4906.

To a stirred solution of the above ketone (65 mg, 0.0834 mmol) in CH_2Cl_2 (5 mL) was added a solution of *B*-Bromocatecholborane (33 mg, 0.167 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 10 min. The mixture was quenched with satd $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/hexanes 1:20–1:10) to give alcohol **32** (111 mg, 90%) as a colorless oil.

$[\alpha]_D^{25}$ −8.0 (*c* 1.10, $CHCl_3$); IR (film): 3455, 3072, 2929, 2857, 1680, 1614, 1463, 1251, 1108, 822, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (m, 4H), 7.45–7.37 (m, 6H), 5.89–5.75 (m, 1H), 5.51 (d, *J*=15.6 Hz, 1H), 5.06–5.02 (m, 2H), 5.00 (s, 1H), 4.89 (s, 1H), 3.91 (m, 1H), 3.86–3.78 (m, 2H), 3.58–3.53 (m, 1H), 3.33 (AB d, *J*=16.6 Hz, 1H), 3.27 (AB d, *J*=16.3 Hz, 1H), 2.45–2.37 (m, 1H), 2.27–2.16 (m, 4H), 1.96–1.84 (m, 2H), 1.73–1.71 (m, 1H), 1.45 (s, 3H), 1.33–1.21 (m, 4H), 1.07 (s, 9H), 0.91 (d, *J*=6.3 Hz, 3H), 0.88 (s, 9H), 0.85 (d, *J*=2.2 Hz, 3H), 0.83 (d, *J*=2.0 Hz, 3H), 0.07–0.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 139.7, 136.0, 135.8, 134.9, 134.4, 133.8, 132.1, 131.9, 129.7, 129.7, 127.7, 127.5, 117.2, 117.1, 79.1, 73.9, 73.3, 71.2, 43.7, 43.3, 41.7, 39.1, 36.6, 36.4, 35.0, 31.9, 31.5, 30.2, 27.1, 25.9, 24.8, 22.7, 19.2, 18.1, 17.6, 15.8, 14.1, −4.4, −4.5; MS (ESI): *m/z* 757.5, $[M+Na]^+$; HRMS (MALDI) calcd for $C_{44}H_{70}O_5Si_2Na^+$ $[M+Na]^+$: 757.4654, found: 757.4667.

4.21. Macrolactone 2

To a stirred solution of acid **6** (36 mg, 0.128 mmol) in toluene (2.5 mL) was added Et_3N (0.071 mL, 0.511 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.040 mL, 0.256 mmol) at 0 °C. The reaction mixture was stirred for 2 h and cooled to 0 °C. A solution of alcohol **32** (47 mg, 0.064 mmol) and DMAP (31 mg, 0.256 mmol) in toluene (1.5 mL) was then added to the above solution at 0 °C. The resulting mixture was stirred at room temperature for 23 h and quenched with satd $NaHCO_3$. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (Et_2O/hexanes 1:20) to give **33** (58 mg, 90%) as a colorless oil.

IR (film): 3453, 3072, 2961, 2926, 2855, 1732, 1615, 1463, 1255, 836, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (m, 4H), 7.41–7.34 (m, 6H), 6.22 (s, 1H), 5.93–5.75 (m, 3H), 5.64 (s, 1H), 5.47 (d, J=15.3 Hz, 1H), 5.15–5.03 (m, 4H), 4.83 (m, 1H), 4.40–4.37 (m, 1H), 4.08–4.05 (m, 1H), 3.95–3.92 (m, 1H), 3.83 (m, 1H), 2.37–2.21 (m, 6H), 2.21 (m, 1H), 1.84 (s, 3H), 1.80–1.77 (m, 1H), 1.65–1.51 (m, 4H), 1.41 (s, 3H), 1.37–1.21 (m, 3H), 1.05 (s, 9H), 0.99–0.80 (m, 30H), 0.05–0.00 (m, 12H); MS (ESI): m/z 1023.6, $[M+Na]^+$; HRMS (ESI) calcd for $C_{59}H_{96}O_7Si_3Na^+$ $[M+Na]^+$: 1023.6356, found: 1023.6384.

To a stirred solution of **33** (38 mg, 0.0379 mmol) in THF (4 mL) was added HF·Py (95 μL, 3.79 mmol) at room temperature. The reaction was stirred for 3 days and the additional HF·Py (95 μL, 3.79 mmol) was then added. The reaction was stirred for additional 3 days. The mixture was quenched with satd $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/hexanes 1:5–1:2) to give **34** (14 mg, 70%) as colorless oil.

$[\alpha]_D^{24}$ −54.0 (c 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 5.91–5.76 (m, 4H), 5.54 (d, J=15.6 Hz, 1H), 5.30–5.26 (m, 1H), 5.21–5.19 (m, 1H), 5.16–5.12 (m, 2H), 4.98–4.94 (m, 1H), 4.42 (m, 1H), 3.91–3.87 (m, 2H), 3.81–3.78 (m, 1H), 3.74–3.68 (m, 1H), 2.40–2.25 (m, 3H), 2.22 (d, J=0.8 Hz, 3H), 2.16–2.11 (m, 1H), 2.04–1.96 (m, 1H), 1.90 (s, 3H), 1.87–1.84 (m, 2H), 1.78–1.72 (m, 2H), 1.52–1.50 (m, 1H), 1.43 (s, 3H), 1.35–1.28 (m, 2H), 1.08 (d, J=6.6 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H), 0.87 (d, J=6.0 Hz, 3H), 0.85 (d, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 167.5, 160.8, 159.6, 139.7, 134.2, 133.5, 130.1, 120.2, 119.1, 118.4, 116.7, 77.9, 75.9, 75.6, 69.5, 68.5, 48.9, 42.1, 41.0, 36.6, 35.9, 35.3, 32.9, 24.8, 20.1, 19.8, 19.8, 15.4, 15.3, 15.2; MS (ESI): m/z 557.3, $[M+Na]^+$; HRMS (ESI) calcd for $C_{31}H_{50}O_7Na^+$ $[M+Na]^+$: 557.3449, found: 557.3467.

To a stirred solution of **34** (15 mg, 0.0281 mmol) in anhydrous CH_2Cl_2 (28 mL) was added second generation Grubbs catalyst (4.8 mg, 0.00561 mmol) at room temperature. The resulting solution was stirred under argon at room temperature for 12 h. The solvent was filtered and evaporated. The crude product was purified by flash chromatography (EtOAc/hexanes 1:5–1:2–1:1) to afford macrolactone **2** (13 mg, 90%) as a colorless oil.

$[\alpha]_D^{25}$ −76.3 (c 0.14, $CHCl_3$); IR (film): 3433, 2961, 2924, 2853, 1686, 1612, 1460, 1378, 1264, 1158, 971, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 5.85–5.78 (m, 1H), 5.82 (s, 1H), 5.75–5.67 (m, 2H), 5.52 (d, J=15.8 Hz, 1H), 4.97 (m, 1H), 4.53 (s, 1H), 4.16–4.11 (m, 1H), 3.92–3.85 (m, 1H), 3.83–3.80 (m, 1H), 3.78–3.74 (m, 1H), 2.30–2.19 (m, 4H), 2.26 (s, 3H), 2.12–2.08 (m, 2H), 1.98 (s, 3H), 1.98–1.90 (m, 2H), 1.69–1.63 (m, 1H), 1.49 (s, 3H), 1.42–1.35 (m, 1H), 1.19 (d, J=7.1 Hz, 3H), 1.11 (d, J=6.5 Hz, 3H), 0.94 (d, J=6.3 Hz, 3H), 0.88 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 167.3, 160.4, 159.3, 136.1, 133.2, 129.9, 126.7, 120.7, 118.7, 77.7, 75.6, 75.6, 69.5, 68.4, 48.4, 41.0, 40.5, 36.4, 35.8, 31.2, 29.7, 24.0, 21.6, 20.4, 20.2, 15.7, 15.0, 13.9; MS (ESI): m/z 529.3, $[M+Na]^+$; HRMS (MALDI) calcd for $C_{29}H_{46}O_7Na^+$ $[M+Na]^+$: 529.3136, found: 529.3112.

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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.2011.06.025.

References and notes

1. (a) Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Kobayashi, J.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A.; Kitaya, Y.; Omasa, K. *J. Org. Chem.* **2007**, *72*, 4469; (b) Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A. *J. Nat. Prod.* **2007**, *70*, 1661.
2. For synthesis of fragments of iriomoteolide-1a, see: (a) Fang, L.; Xue, H.; Yang, J. *Org. Lett.* **2008**, *10*, 4645; (b) Ghosh, A. K.; Yuan, H. *Tetrahedron Lett.* **2009**, *50*, 1416; (c) Xie, J.; Horne, D. A. *Tetrahedron Lett.* **2009**, *50*, 4485; (d) Xie, J.; Ma, Y.; Horne, D. A. *Org. Lett.* **2009**, *11*, 5082; (e) Chin, Y.-J.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 3674; (f) Wang, S.-Y.; Chin, Y.-J.; Loh, T.-P. *Synthesis* **2009**, 3557; (g) Paterson, I.; Rubenbauer, P. *Synlett* **2010**, 571; (h) Liu, Y.; Wang, J.; Li, H.; Wu, J.; Feng, G.; Dai, W.-M. *Synlett* **2010**, 2184.
3. For synthetic studies toward the total synthesis of the proposed structures of iriomoteolide-1a and -1b, see: (a) Xie, J.; Ma, Y.; Horne, D. A. *Chem. Commun.* **2010**, 4770; (b) Li, S.; Chen, Z.; Xu, Z.; Ye, T. *Chem. Commun.* **2010**, *46*, 4773; (c) Ghosh, A. K.; Yuan, H. *Org. Lett.* **2010**, *12*, 3120.
4. For synthetic studies toward the total synthesis of diastereomers of iriomoteolide-1a, see: Fang, L.; Yang, J.; Yang, F. *Org. Lett.* **2010**, *12*, 3124.
5. Ye, Z.; Deng, L.; Qian, S.; Zhao, G. *Synlett* **2009**, 2469.
6. (a) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32; (b) Yang, J. W.; Fonseca, M. T. H.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108; (c) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193.
7. Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.
8. Mitsunobu, O. *Synthesis* **1981**, 1.
9. (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26; (b) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772; (c) Hayes, P. Y.; Kitching, W. *J. Am. Chem. Soc.* **2002**, *124*, 9718; (d) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.
10. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
11. (a) Kulinkovich, O. G.; Meijere, A. *Chem. Rev.* **2000**, *100*, 2789; (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597.
12. (a) These copper regents include CuI, Li_2CuCl_4, $CuBr{\cdot}SMe_2$, CuCN in addition with non copper regent $BF_3{\cdot}SMe_2$. (b) Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1991**, *32*, 4775.
13. Kulinkovich, O. G.; Kozyrkov, Y. Y.; Bekish, A. V.; Matiushenkov, E. A.; Lysenko, I. L. *Synthesis* **2005**, 1713.
14. Burns, N. Z.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 205.
15. Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
16. Barrero, A. F.; Arseniyadis, S.; Moral, J. F. Q.; Herrador, M. M.; Valdivia, M.; Jiménez, J. *J. Org. Chem.* **2002**, *67*, 2501.
17. (a) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454; (b) Hollenstein, M.; Leumann, C. J. *J. Org. Chem.* **2005**, *70*, 3205.
18. Whitehead, A.; Waetzig, J. D.; Thomas, C. D.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 1421.
19. Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513.
20. (a) Aspinall, H. C.; Greeves, N.; McIver, E. G. *Tetrahedron Lett.* **1998**, *39*, 9283; (b) Li, G.; Zhao, G. *J. Org. Chem.* **2005**, *70*, 4272.
21. (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; (b) Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 911.
22. (a) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49; (b) Coery, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.
23. (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953; (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.
24. Our synthetic spectra data of **2** was in agreement with that of Ghosh's group.