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► **To cite this version:**

Yangguang Gao, Zhou Cao, Qiang Zhang, Rui Guo, Fei Ding, et al.. Total Synthesis of the Proposed Structure of Penasulfate A:L-Arabinose as a Source of Chirality. *Journal of Natural Products*, 2019, 82 (7), pp.1908–1916. 10.1021/acs.jnatprod.9b00245 . hal-02889336

**HAL Id: hal-02889336**

**<https://hal.science/hal-02889336>**

Submitted on 15 Oct 2020

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## **Total Synthesis of the Proposed Structure of Penasulfate A. L-Arabinose as a Source of Chirality**

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**ABSTRACT:** The total synthesis of putative penasulfate A was effectively achieved by a convergent strategy with a longest linear sequence of 14 steps and overall yield of 8.6%. The highlights of our strategy involved an *E*-selective olefin cross-metathesis (OCM), Suzuki cross-coupling, and a copper(I)-catalyzed coupling reaction.

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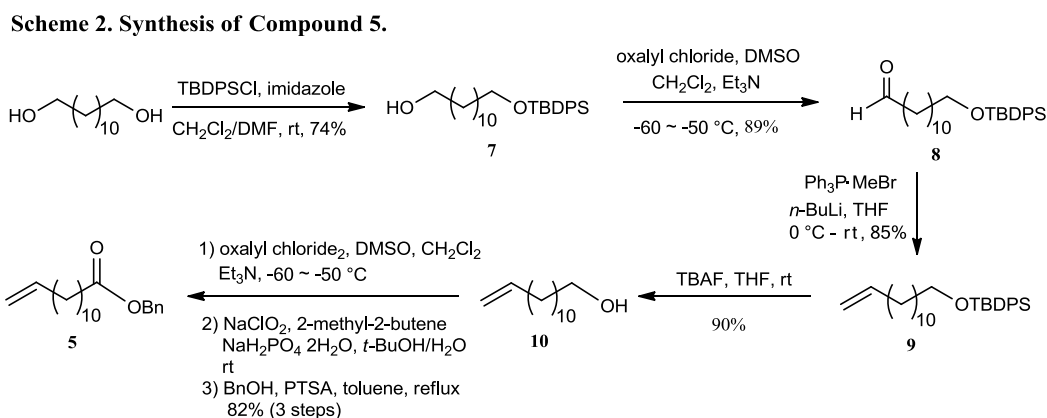
$\alpha$ -Glucosidases are enzymes that are capable of catalyzing the hydrolysis of glycosidic bonds by liberating  $\alpha$ -linked glucose from oligosaccharides or glycoconjugates.  $\alpha$ -Glucosidases participate not only in the degradation of oligosaccharides but also in glycoprotein processing involved in protein folding within the endoplasmic reticulum and in stabilization of glycoproteins on the cell surface.<sup>1,2</sup> Therefore,  $\alpha$ -glucosidase inhibitors hold promise to treat several diseases, such as diabetes, viral infections, cancers, and obesity.<sup>3-6</sup> Acarbose and miglitol, which display potent inhibitory activity against  $\alpha$ -glucosidase, have already been employed as therapeutic drugs to treat type II diabetes in the clinic.<sup>7</sup> Another example of an  $\alpha$ -glucosidase inhibitor utilized as a drug is *N*-butyl-1-deoxynojirimycin (Zavesca), which is applied to control a lysosomal storage disorder called Gaucher's disease.<sup>8</sup>

Penasulfate A, which was isolated from a *Penares sp.* marine sponge by Fusetani and co-workers, features a methyl pipercolate acylated with a disulfated fatty acid and has an IC<sub>50</sub> value of 4.4  $\mu$ M against  $\alpha$ -glucosidase,<sup>9</sup> displaying good inhibitory activity in the low microgram/mL range along with its congeners, penarolide sulfate A<sub>1</sub> and A<sub>2</sub>.<sup>10</sup> As a part of our ongoing research on the total synthesis of penarolide sulfate A<sub>2</sub>, aimed to enable the synthesis of analogs as potential anti-diabetes drugs,<sup>11</sup> herein, we report the first synthesis of penasulfate A using stereogenic centers derived from natural L-arabinose.

Penasulfate A (**1**) consists of a methyl pipercolate acylated with a saturated fatty acid that contains one methyl-bearing stereocenter and two sulfate groups. The retrosynthetic strategy to **1** is delineated in Scheme 1. Penasulfate A (**1**) can be obtained from disulfation of the diol **2**, which was obtained from Suzuki cross-coupling between vinyl iodide **3** and pinacol alkenyl boronate **4**, followed by amidation with (*R*)-piperidine-2-carboxylic acid methyl ester. Compound **3** was assembled from olefin cross-metathesis between carboxylic acid **5** and the known compound **6**.<sup>12</sup> Notably, the two adjacent hydroxy groups in penasulfate A (**1**) were envisioned to be installed using a chiral template derived from natural

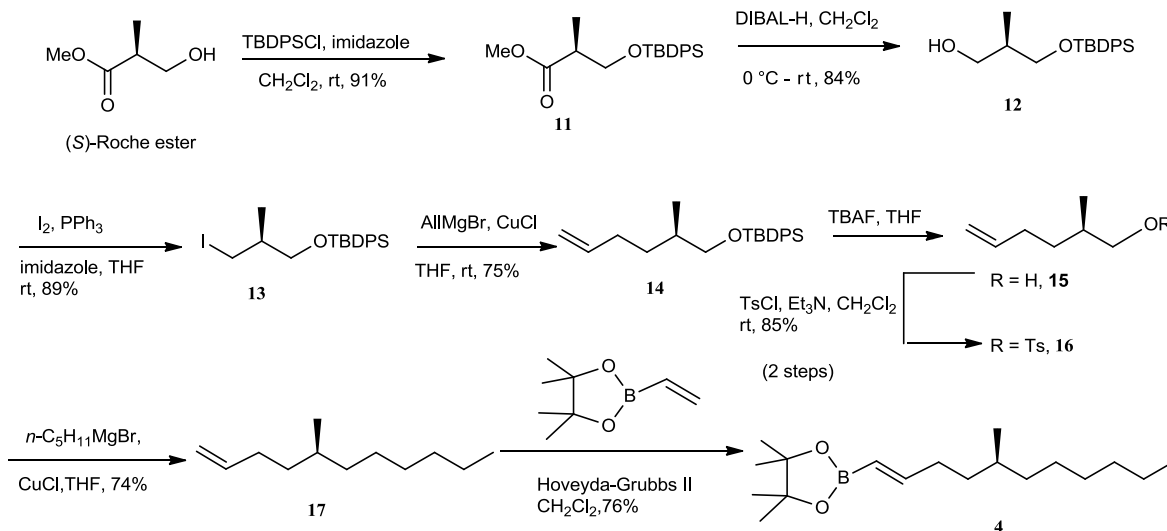


benzyl ester **5** in 82% yield over three steps through a sequence of Swern oxidation, Pinnick oxidation,<sup>17</sup> and esterification with benzyl alcohol using a catalytic amount of *p*-toluenesulfonic acid (PTSA).



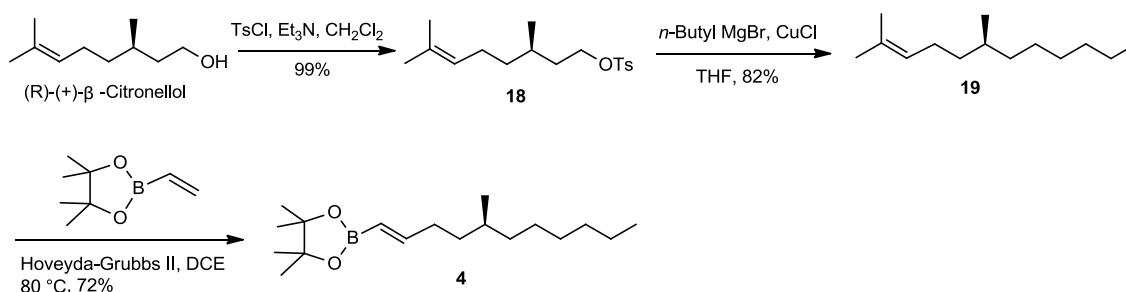
The construction of the eastern building block **4** is summarized in Scheme 3. Silylation of (*S*)-Roche ester was achieved by treatment with TBDPSCl and imidazole in CH<sub>2</sub>Cl<sub>2</sub> to produce compound **11** in 91% yield.<sup>18</sup> Reduction of compound **11** by an excess amount of DIBAL-H in CH<sub>2</sub>Cl<sub>2</sub> afforded an 84% yield of primary alcohol **12**,<sup>19</sup> which was treated with iodine, PPh<sub>3</sub>, and imidazole in THF at room temperature to yield the iodo product **13** in 89% yield.<sup>20</sup> Coupling of compound **13** with allylmagnesium bromide in THF in the presence of CuCl<sup>21</sup> proceeded smoothly to give a 75% yield of the known compound **14**.<sup>22</sup> Subsequent deprotection of compound **14** by TBAF in THF generated compound **15**. It should be noted that compound **15** had a low boiling point, necessitating care when concentrating under reduced pressure. Therefore, after purification, compound **15**, containing a minimal amount of petroleum ether and EtOAc, was directly subjected to the following step. Tosylation of compound **15** by treatment with TsCl and Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> gave an 85% yield of compound **16**,<sup>23</sup> which coupled with *n*-pentylmagnesium bromide and catalytic CuCl to yield compound **17** in 74% yield. Initially, olefin cross-metathesis between compound **17** and pinacol vinyl boronate under the catalysis of Grubbs II catalyst<sup>24</sup> in CH<sub>2</sub>Cl<sub>2</sub> only returned starting material. However, the reaction was successfully carried out in the presence of Hoveyda-Grubbs II catalyst<sup>25</sup> to provide compound **4** in 76% yield.

### Scheme 3. Synthesis of Compound 4



The second-generation synthesis of pinacol alkenyl boronate **4** began with commercially available (*R*)-(+)- $\beta$ -citronellol as depicted in Scheme 4. (*R*)-(+)- $\beta$ -citronellol was converted to its tosylate by treatment with TsCl and Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> to afford compound **18** in almost quantitative yield (99%), which coupled with freshly prepared *n*-butylmagnesium bromide in dry THF and catalytic CuCl to provide an 82% yield of compound **19**.<sup>26</sup> Olefin cross-metathesis between compound **19** and pinacol vinyl boronate was promoted by Hoveyda-Grubbs II catalyst in 1,2-dichloroethane (DCE) to furnish compound **4** in 72% yield.

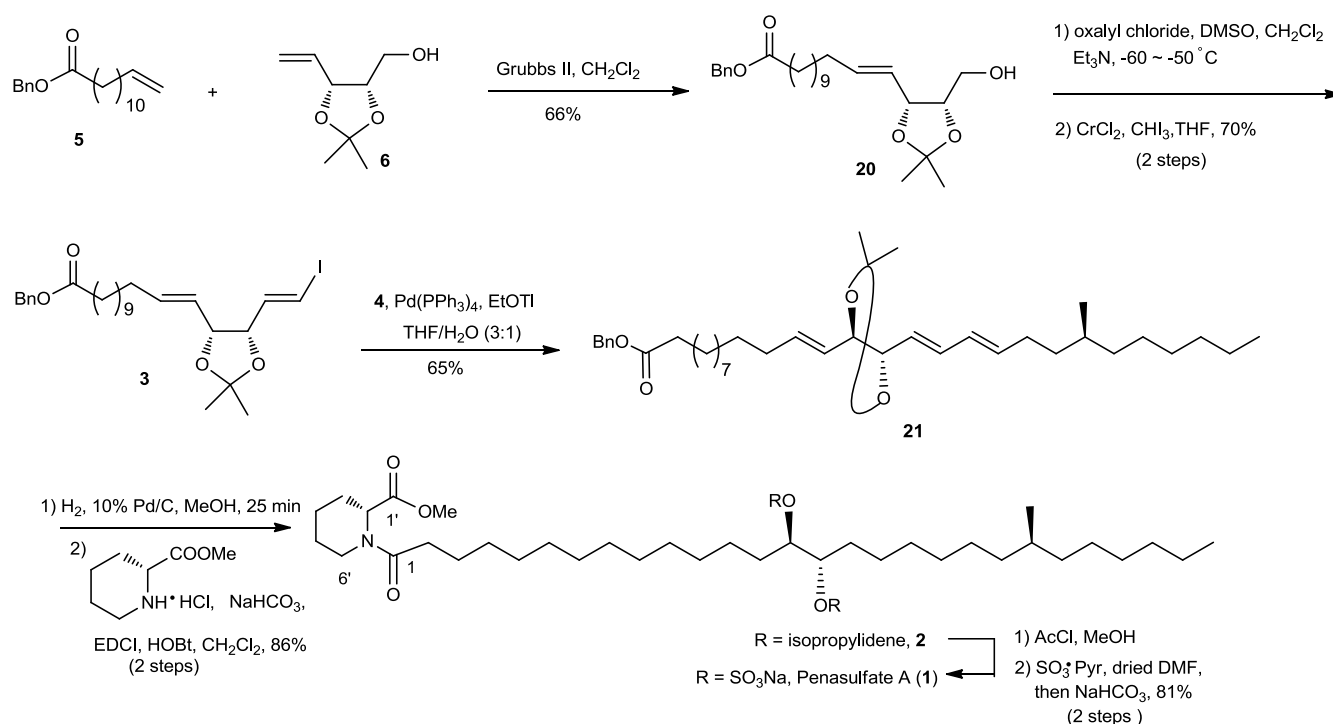
### Scheme 4. An Optimized Synthesis of Compound 4



With all of the required building blocks **4–6** in hand, our attention then shifted to the completion of the total synthesis of penasulfate A (**1**) as described in Scheme 5. Olefin cross-metathesis of compound **5** with the known compound **6**<sup>12</sup> was promoted by a catalytic amount of the Grubbs II catalyst to afford a 66% yield of compound **20**, exclusively in the *E* form. Swern oxidation of compound **20** followed by selective Takai olefination<sup>27</sup> gave a 70% yield of the substituted vinyl iodide **3** over two steps. The sub-

sequent Suzuki cross-coupling between compound **3** and compound **4** was carried out successfully using Pd(PPh<sub>3</sub>)<sub>4</sub>, EtOTf, THF/H<sub>2</sub>O (3:1) conditions to give the coupling product **21** in 65% yield.<sup>28</sup> Based on <sup>1</sup>H NMR and COSY spectra, the fact that the newly formed conjugated diene has a *J* value of 14.8 Hz at 6.19 ppm and 15.2 Hz at 6.02 ppm, respectively, indicated that compound **21** possessed a (16*E*, 18*E*)-diene segment. The <sup>13</sup>C NMR and DEPT 135 spectra presented six peaks at 136.5, 136.0, 134.2, 129.2, 126.4 and 126.0 ppm, respectively. These were attributed to the characteristic signals of the triene in compound **21**. Hydrogenation of compound **21** in MeOH in the presence of 10% Pd/C reduced the double bonds and removed the benzyl group to provide the carboxylic acid, which was subjected to amidation using EDCI/HOBt to provide compound **2** in 86% yield over two steps.<sup>29</sup> Hydrogenation lasting for more than 0.5 h led to the removal of the acetonide group due to the liberated

Scheme 5. Synthesis of Penasulfate A (**1**)



carboxylic acid. At the last step, acetonide removal from compound **2** proceeded smoothly under acidic conditions to give the crude diol, which was treated with SO<sub>3</sub>·Pyr in dry DMF at room temperature and washed with saturated NaHCO<sub>3</sub> to afford an 81% yield of the target compound **1** as a bis-sodium salt.<sup>30</sup>

Of note, some minor peaks were present in both the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of synthetic

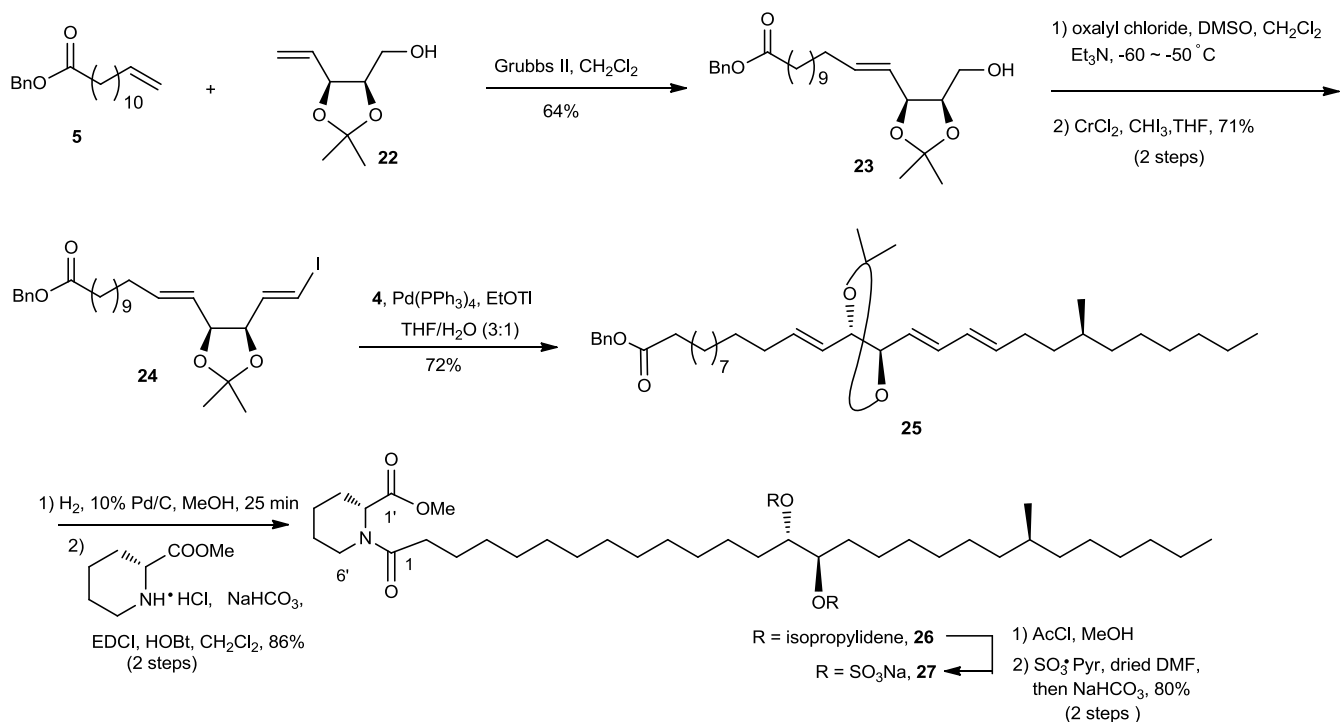


penasulfate A (**1**). As the original paper reported penasulfate A as a mixture (with a 4:1 ratio based on D- and L-pipecolic acid), it is possible that the minor doubling of some peaks in the pipecolic acid portion of the structure were due to the presence of the minor stereoisomer, but our synthetic product was derived from the methyl-D-pipecolate which was optically pure and did not have the minor L-pipecolate isomer present, thus these minor signals were caused by a rotameric conformer of the secondary amide rather than by epimerization. A similar phenomenon has been reported in the literature.<sup>9,12,31</sup> The spectroscopic and analytical data (<sup>1</sup>H, <sup>13</sup>C NMR, HRMS, and specific rotation) of synthetic compound **1** were in agreement with that of the natural product reported by Fusetani et al,<sup>9</sup> except for slight differences in the <sup>1</sup>H NMR data and <sup>13</sup>C NMR data at C-14 and C-15.

The small but significant differences in the <sup>1</sup>H and <sup>13</sup>C NMR data at C-14 and C-15 led us to be suspicious that the absolute configuration for C-14 and C-15 could be reversed (14S,15R instead of 14R,15S) in the original paper. In the original paper, the diol of penasulfate A was converted to its bis-bromobenzoate derivative, ECD spectroscopy indicated that the diol had an anti configuration. To determine the absolute configurations at C-14/C-15, mono-Mosher's ester derivatives were prepared. However, it would be challenging to correctly assign the positions of the mono-Mosher's esters in penasulfate A due to the numerous methylenes in the chain and the general structural similarities on both sides of the disulfate (the positions of the Mosher's esters were determined by MS fragmentations. It may be that the anti configuration assignment was correct, but the assigned absolute configuration for C-14/C-15 could be mistaken. Thus, synthesis of 14S,15R diastereoisomer of penasulfate A to furnish a sample for comparison is necessary.

In Scheme 6, the synthesis of compound **27** was achieved with eight steps from compound **22** (instead of compound **6**) following the same procedures as described for the preparation of penasulfate A, while compound **22** was a known compound and obtained over three steps from D-arabinose.<sup>32</sup> With compound **27** in hand, it was found that the stereogenic centers reversion at C-14 and C-15 had quite minor effect on both <sup>1</sup>H and <sup>13</sup>C NMR data compared with that of compound **1**, and a bigger difference

**Scheme 6. Synthesis of Compound 27**



from natural product was present at C-14/C-15 (81.84 ppm) in <sup>13</sup>C NMR data of compound **27** than that of compound **1**, furthermore, the specific rotation of compound **27** was +18.8 (c 0.053, MeOH), which had a larger deviation from the rotation of the natural product (+10). Thus, these results demonstrated that the current synthetic compound **1** seemed to be a better fit for the natural product. In consideration of the significant chemical shift deviation from the natural product at C-14 and C-15, it is possible that there is a minor structural difference between the natural product and compound **1**. Therefore, the present synthesis may be contributed to total synthesis of the proposed structure of penasulfate A.

To summarize, the total syntheses of the proposed structure of penasulfate A and its 14*S*,15*R* diastereoisomer were developed. Olefin cross-metathesis and Suzuki cross-coupling were employed for the construction the skeleton of the title compound. L-arabinose and D-arabinose was respectively utilized as a chiral pool source of the two adjacent hydroxy groups of penasulfate A and its 14*S*,15*R* diastereoisomer, while the methyl-bearing stereocenter was derived from either (*S*)-Roche ester or (*R*)-(+)-β-citronellol. Our protocol is effective and convergent, which provides considerable flexibility for the synthesis of related analogues of penasulfate A.

## EXPERIMENTAL SECTION

### General Experimental Procedures

Optical rotations were measured with a AUTOPOL IV automatic polarimeter using a 10 cm cell.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were collected with Bruker Avance III spectrometer at 400 MHz, 100 MHz respectively, relative to  $\text{Me}_4\text{Si}$  ( $\delta = 0$  ppm) as an internal standard. HRMS data were obtained using a ThermoFisher Q-Exactive mass spectrometer. All reagents were purchased from commercial company and used directly without further purification unless otherwise mentioned. Reactions were monitored by silica gel 60 F254 TLC plates, and TLC plates were stained with a mixed solution of sulfuric acid and methanol (1:2) followed by heating. Purification was performed by column chromatography using silica gel (100–200 mesh). Dried THF was distilled from benzophenone and sodium. DMF,  $\text{CH}_2\text{Cl}_2$  were dried with  $\text{CaH}_2$ . All air-sensitive reactions were carried out under a nitrogen atmosphere.

**Benzyl Tetradec-13-enoate (5).** Oxalyl chloride (0.80 mL, 8.80 mmol) was dissolved in 10 mL of dry  $\text{CH}_2\text{Cl}_2$ , to which was added dropwise a solution of DMSO (1.50 mL, 19.41 mmol) in 10 mL of  $\text{CH}_2\text{Cl}_2$  over 5 min at  $-60 \sim -50$  °C under a nitrogen atmosphere. After that, compound **10** (1.00 g, 5.04 mmol) in 10 mL of  $\text{CH}_2\text{Cl}_2$  was added to the above solution. The mixture was allowed to stir for 1 h at the same temperature. Then,  $\text{Et}_3\text{N}$  (2.64 mL, 18.84 mmol) was added to the resulting slurry followed by pouring 15 mL of  $\text{H}_2\text{O}$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL), washed with brine, and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Filtration and concentration gave the crude product, which was directly subjected to the next step without further purification. The obtained crude product was dissolved in 15 mL of *t*-BuOH, to which was added sequentially 2-methyl-2-butene (3.20 mL, 38.10 mmol),  $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$  (2.26 g, 14.49 mmol). Then, a solution of  $\text{NaClO}_2$  (1.60 g, 17.69 mmol) in  $\text{H}_2\text{O}$  (10 mL) was added to the above mixture *via* a dropping funnel. The resulting solution was allowed to stir at rt. After the complete consumption of the starting material, 10 mL of EtOAc was poured into the solution to dilute. The aqueous layer was extracted with EtOAc ( $3 \times 10$  mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , fil-

tered, then evaporated in vacuo. The residue was dissolved in 15 mL of dried toluene, followed by the addition of PTSA (40 mg, 0.23 mmol) and benzyl alcohol (0.75 mL, 7.23 mmol), and stirred at reflux temperature for 5h. Et<sub>3</sub>N (1.5 mL) was added to quench the reaction, concentrated in vacuo. Purification of the resultant residue by silica gel column chromatography (petroleum ether/EtOAc = 50:1) afforded compound **5** (1.25 g, 82%) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35–7.34 (m, 5H), 5.87–5.77 (m, 1H), 5.12 (s, 2H), 4.99 (dd, *J* = 17.2, 2.0 Hz, 1H), 4.93 (dt, *J* = 10.0, 0.8 Hz, 1H), 2.36 (t, *J* = 7.6 Hz, 2H), 2.04 (q, *J* = 6.8 Hz, 2H), 1.65 (t, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 6.8 Hz, 2H), 1.26 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.8, 139.3, 136.2, 128.6, 128.2, 114.2, 66.1, 34.4, 33.9, 29.6, 29.5 (2C), 29.3, 29.2, 29.0, 25.0; HRESIMS: *m/z* 311.1978 [M + Na]<sup>+</sup> (calcd for C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>Na, 311.1982).

**12-((*tert*-Butyldiphenylsilyl)oxy) dodecan-1-ol (7).** To a solution of 1,12-dodecanediol (10.00 g, 49.42 mmol) in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and DMF (140 mL, v/v = 2.5:1) were added imidazole (10.09 g, 148.26 mmol), TBDPSCl (15.62 g, 56.83 mmol) in sequence. The mixture was allowed to stir at rt. H<sub>2</sub>O (100 mL) was poured into the mixture after the completion of the reaction, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, then concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/EtOAc = 10:1) to furnish compound **7** as a colorless liquid (16.12 g, 74%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.69 (d, *J* = 2.0 Hz, 4H), 7.46–7.37 (m, 6H), 3.69 (t, *J* = 6.4 Hz, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 1.60–1.55 (m, 4H), 1.36–1.28 (m, 16H), 1.08 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 135.7, 134.3, 129.6, 127.7, 64.1, 63.1, 32.9, 32.7, 29.7 (2C), 29.6, 29.5, 27.0, 25.9 (2C), 19.3; HRESIMS: *m/z* 463.3001 [M + Na]<sup>+</sup> (calcd for C<sub>28</sub>H<sub>44</sub>O<sub>2</sub>SiNa, 463.3008).

**12-((*tert*-Butyldiphenylsilyl)oxy)dodecanal (8).** To a solution of oxalyl chloride (1.26 mL, 13.86 mmol) in 10 mL of dry CH<sub>2</sub>Cl<sub>2</sub> at –60 ~ –50 °C under a nitrogen atmosphere was added a solution of DMSO (2.35 mL, 30.41 mmol) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> *via* a dropping funnel over 5 min. After that, compound **7** (3.50 g, 7.94 mmol) in 10 mL CH<sub>2</sub>Cl<sub>2</sub> was added to the above solution. The mixture was allowed to stir for 1 h at the same temperature. Then, Et<sub>3</sub>N (3.92 mL, 27.97 mmol) was added to quench

the reaction followed by the addition of 15 mL of H<sub>2</sub>O. The organic layer was separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, then concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc = 20:1) to afford compound **8** as a colorless liquid (3.10 g, 89%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.77 (s, 1H), 7.69 (d, *J* = 7.2 Hz, 4H), 7.43–7.37 (m, 6H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.66–1.54 (m, 4H), 1.35–1.27 (m, 14H), 1.07 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 203.0, 135.6, 134.2, 129.5, 127.6, 64.1, 44.0, 32.6, 29.6 (2C), 29.5, 29.4, 29.2, 26.9, 25.8, 22.1, 19.3; HRESIMS: *m/z* 461.2838 [M + Na]<sup>+</sup> (calcd for C<sub>28</sub>H<sub>42</sub>O<sub>2</sub>SiNa, 461.2852).

***tert*-Butyldiphenyl (tridec-12-en-1-yloxy)silane (9).** To a suspension of methyltriphenylphosphonium bromide (2.20 g, 6.16 mmol) in anhydrous THF (15 mL) was added dropwise *n*-BuLi solution (2.60 mL, 2.5 M in hexane, 6.5 mmol) at 0 °C under a nitrogen atmosphere. The resulting yellow suspension was warmed to rt and stirred for 45 min. Compound **8** (2.24 g, 5.10 mmol) in 10 mL of THF was added to the yellow suspension *via* a dropping funnel at 0 °C. The mixture was allowed to warm to rt gradually and stir at rt until the disappearance of compound **8**. Satd. NH<sub>4</sub>Cl solution (20 mL) was poured into the suspension to quench the reaction. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, then evaporated in vacuo. Column chromatography (pure petroleum ether) of the residue on silica gel column provided compound **9** (1.89 g, 85%) as a colorless liquid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.71 (d, *J* = 6.4 Hz, 4H), 7.45–7.39 (m, 6H), 5.90–5.80 (m, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.97 (d, *J* = 10.0 Hz, 1H), 3.70 (t, *J* = 6.4 Hz, 2H), 2.08 (q, *J* = 6.8 Hz, 2H), 1.63–1.57 (m, 2H), 1.42–1.30 (m, 16H), 1.09 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 139.4, 135.7, 134.4, 129.6, 127.7, 114.3, 64.2, 34.0, 32.8, 29.9, 29.8, 29.7, 29.5, 29.3, 29.1, 27.0, 25.9, 19.4; HRESIMS: *m/z* 437.3236 [M + H]<sup>+</sup> (calcd for C<sub>29</sub>H<sub>45</sub>OSi, 437.3240).

**Tridec-12-en-1-ol (10).** To a solution of compound **9** (2.80 g, 6.42 mmol) in 10 mL of THF was added TBAF·3H<sub>2</sub>O (2.44 g, 7.70 mmol) at rt. The stirring was continued until no starting material remained. Concentration under reduced pressure furnished a crude product, which was further purified by silica

gel column chromatography (petroleum ether/EtOAc = 6:1) to afford compound **10** (1.14 g, 90%) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.84–5.74 (m, 1H), 4.96 (ddd,  $J = 17.2, 3.6, 2.0$  Hz, 1H), 4.90 (dt,  $J = 10.0, 1.2$  Hz, 1H), 3.59 (t,  $J = 6.8$  Hz, 2H), 2.01 (q,  $J = 7.2$  Hz, 2H), 1.98 (d,  $J = 4.8$  Hz, 1H), 1.57–1.50 (m, 2H), 1.35–1.25 (m, 16H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  139.3, 114.2, 63.0, 33.9, 32.9, 29.7 (2C), 29.6 (2C), 29.24, 29.0, 25.9; HRESIMS:  $m/z$  199.2055 [ $\text{M} + \text{H}$ ] $^+$  (calcd for  $\text{C}_{13}\text{H}_{27}\text{O}$ , 199.2062).

**(S)-Methyl 3-((tert-Butyldiphenylsilyl)oxy)-2-methylpropanoate (11).** To a solution of (*S*)-Roche ester (4.00 g, 33.86 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (80 mL) was added imidazole (6.92 g, 101.64 mmol), TBDPSCl (11.20 g, 40.75 mmol) in sequence at rt.  $\text{H}_2\text{O}$  (100 mL) was poured into the above mixture after the completion of the reaction. The organic layer was separated, extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 100$  mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, then concentrated. Purification of the obtained residue by column chromatography (petroleum ether/EtOAc = 50:1) gave compound **11** (10.98 g, 91%) as a colorless liquid.  $[\alpha]_{\text{D}}^{25} +10.6$  ( $c$  1.39,  $\text{CHCl}_3$ ) {lit.  $[\alpha]_{\text{D}}^{22} +12.9$  ( $c$  1.0,  $\text{CHCl}_3$ )} $^{18\text{c}}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 6.4$  Hz, 4H), 7.45–7.37 (m, 6H), 3.84 (dd,  $J = 9.6, 6.8$  Hz, 1H), 3.73 (dd,  $J = 10.0, 6.0$  Hz, 1H), 3.69 (s, 3H), 2.77–2.69 (m, 1H), 1.17 (d,  $J = 6.8$  Hz, 3H), 1.04 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.5, 135.7, 133.7, 133.6, 129.8, 127.8, 66.0, 51.7, 42.5, 26.8, 19.4, 13.6; HRESIMS:  $m/z$  379.1694 [ $\text{M} + \text{Na}$ ] $^+$  (calcd for  $\text{C}_{21}\text{H}_{28}\text{O}_3\text{SiNa}$ , 379.1705).

**(R)-3-((tert-Butyldiphenylsilyl)oxy)-2-methylpropan-1-ol (12).** To a solution of compound **11** (1.12 g, 3.14 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) was added dropwise a solution of DIBAL-H (4.8 mL, 1.5 M in toluene, 7.2 mmol) in 10 mL of dry THF on an ice bath under a nitrogen atmosphere. The mixture was allowed to warm to rt and stir for 3 h. After cooling in an ice bath, a satd. solution of K/Na tartrate (10 mL) was added to the mixture cautiously. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL), and the combined organic layer was evaporated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 20:1) to afford compound **12** (0.87 g, 84%) as a colorless liquid.  $[\alpha]_{\text{D}}^{25} +3.7$  ( $c$  2.65,  $\text{CHCl}_3$ ) {lit.  $[\alpha]_{\text{D}}^{25} +5.2$  ( $c$  1.0,  $\text{CHCl}_3$ )} $^{12\text{c}}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$

7.71–7.69 (m, 4H), 7.48–7.39 (m, 6H), 3.75 (dd,  $J = 10.4, 4.8$  Hz, 1H), 3.69 (d,  $J = 6.8$  Hz, 2H), 3.62 (dd,  $J = 10.0, 7.6$  Hz, 1H), 2.67 (br, 1H), 2.05–1.97 (m, 1H), 1.09 (s, 9H), 0.85 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  135.7 (2C), 133.3 (2C), 129.9, 127.9, 68.7, 67.6, 37.4, 27.0, 19.3, 13.3; HRESIMS:  $m/z$  329.1928  $[\text{M} + \text{H}]^+$  (calcd for  $\text{C}_{20}\text{H}_{29}\text{O}_2\text{Si}$ , 329.1937).

**(S)-tert-Butyl(3-iodo-2-methylpropoxy)diphenylsilane (13).** To a solution of compound **12** (0.82 g, 2.49 mmol) in 10 mL of THF were added  $\text{I}_2$  (0.82 g, 3.23 mmol),  $\text{PPh}_3$  (0.98 g, 3.73 mmol), imidazole (0.51 g, 7.46 mmol) successively. A solution of satd.  $\text{Na}_2\text{S}_2\text{O}_3$  (10 mL) was poured into the above solution after the complete consumption of the starting material (monitoring by TLC). The aqueous layer was extracted with EtOAc ( $3 \times 20$  mL), and the combined organic layer was evaporated in vacuo. Column chromatography (pure petroleum ether) of the residue on silica gel provided compound **13** (0.97 g, 89%) as a colorless liquid.  $[\alpha]_{\text{D}}^{25} +3.0$  ( $c$  1.18,  $\text{CHCl}_3$ ) {lit.  $[\alpha]_{\text{D}}^{23} +5.58$  ( $c$  2.06,  $\text{CHCl}_3$ )}<sup>20a</sup>;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70–7.67 (m, 4H), 7.45–7.38 (m, 6H), 3.60 (dd,  $J = 10.0, 4.8$  Hz, 1H), 3.48 (dd,  $J = 10.4, 7.2$  Hz, 1H), 3.41 (dd,  $J = 9.6, 5.2$  Hz, 1H), 3.34 (dd,  $J = 9.6, 6.0$  Hz, 1H), 1.78–1.70 (m, 1H), 1.07 (s, 9H), 0.97 (d,  $J = 6.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  135.8, 135.7, 133.7, 133.6, 129.8, 127.8, 67.5, 37.7, 27.0, 19.4, 17.5, 13.7; HRESIMS:  $m/z$  439.0947  $[\text{M} + \text{H}]^+$  (calcd for  $\text{C}_{20}\text{H}_{28}\text{IOSi}$ , 439.0954).

**(R)-tert-Butyl((2-methylhex-5-en-1-yl)oxy)diphenylsilane (14).** To a solution of compound **13** (1.70 g, 3.88 mmol) in dry THF (20 mL) was added  $\text{CuCl}$  (38.0 mg, 0.39 mmol) under a nitrogen atmosphere. A solution of allylmagnesium bromide (11.8 mL, 1.0 M in  $\text{Et}_2\text{O}$ , 11.8 mmol) was added to the above mixture *via* a dropping funnel. The solution was allowed to stir at rt until the completion of the reaction. A solution of satd.  $\text{NH}_4\text{Cl}$  was poured into the reaction mixture, extracted with EtOAc ( $3 \times 20$  mL), and the combined organic layer was evaporated in vacuo. The residue was purified by silica gel column chromatography (pure petroleum ether) to yield compound **14** (1.02 g, 75%) as a colorless liquid.  $[\alpha]_{\text{D}}^{25} -0.50$  ( $c$  0.2,  $\text{CHCl}_3$ ) {lit.  $[\alpha]_{\text{D}}^{20} -0.43$  ( $c$  3.5,  $\text{CHCl}_3$ )}<sup>22</sup>;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67–7.65 (m, 4H), 7.40–7.37 (m, 6H), 5.84–5.74 (m, 1H), 4.97 (dd,  $J = 17.2, 1.6$  Hz, 1H), 4.93 (d,  $J = 10.4$  Hz),

3.53–3.41 (m, 2H), 2.10–1.96 (m, 2H), 1.71–1.64 (m, 1H), 1.05 (s, 9H), 0.92 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  139.3, 135.7, 134.2, 129.6, 127.7, 114.2, 68.8, 35.3, 32.4, 31.3, 27.0, 19.4, 16.8; HRESIMS:  $m/z$  253.2293  $[\text{M} + \text{H}]^+$  (calcd for  $\text{C}_{23}\text{H}_{33}\text{OSi}$ , 253.2301).

**(R)-2-Methylhex-5-en-1-yl 4-methylbenzenesulfonate (16).** Compound **14** (1.33 g, 3.76 mmol) was dissolved in 20 mL of THF, to which was added TBAF·3H<sub>2</sub>O (1.43 g, 4.52 mmol). The solution was stirred at rt until the completion of the reaction. The solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography (petroleum ether/EtOAc = 10:1) to afford the deprotected product **15**. Compound **15** (containing a minimal amount of petroleum ether and EtOAc) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (15 mL) followed by adding 1 mL Et<sub>3</sub>N and TsCl (2.38 g, 12.48 mmol) in sequence. H<sub>2</sub>O (15 mL) was poured into the mixture after the thorough consumption of the starting material, extracted with  $\text{CH}_2\text{Cl}_2$  (3 × 20 mL), and the combined organic layer was evaporated in vacuo. Column chromatography (petroleum ether/EtOAc = 20:1) of the residue yielded compound **16** (0.86 g, 85%) as a colorless oil.  $[\alpha]_{\text{D}}^{25} -4.6$  ( $c$  0.33,  $\text{CHCl}_3$ ) {lit.  $[\alpha]_{\text{D}}^{20} -5.098$  ( $c$  1.04,  $\text{CHCl}_3$ )}<sup>23</sup>;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (d,  $J = 6.8$  Hz, 2H), 7.34 (d,  $J = 8.0$  Hz, 2H), 5.75–5.68 (m, 1H), 4.97–4.91 (m, 2H), 3.90–3.80 (m, 2H), 2.45 (s, 3H), 2.02–1.95 (m, 2H), 1.81–1.79 (m, 1H), 1.43–1.41 (m, 1H), 1.22–1.18 (m, 1H), 0.89 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  144.7, 138.1, 133.1, 129.8, 127.9, 114.8, 74.9, 32.2, 31.8, 30.7, 21.6, 16.3; HRESIMS:  $m/z$  291.1019  $[\text{M} + \text{Na}]^+$  (calcd for  $\text{C}_{14}\text{H}_{20}\text{O}_3\text{S}$ , 291.1031).

**(S)-5-Methylundec-1-ene (17).** To a solution of **16** (1.70 g, 6.33 mmol) in dry THF (20 mL) was added CuCl (62.0 mg, 0.63 mmol) under a nitrogen atmosphere. A solution of *n*-pentylmagnesium bromide (19 mL, 1 M in THF, 19.02 mmol) was added dropwise to the above mixture. The stirring was continued at rt until the completion of the reaction. A solution of satd.  $\text{NH}_4\text{Cl}$  was poured into the reaction mixture, extracted with EtOAc (3 × 20 mL), and the combined organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (pure petroleum ether) to furnish compound **17** (0.79 g, 74%) as a colorless oil.  $[\alpha]_{\text{D}}^{25} -5.0$  ( $c$  0.08,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$\delta$  5.87–5.77 (m, 1H), 5.00 (d,  $J = 12.8$  Hz, 1H), 4.92 (d,  $J = 10.0$  Hz, 1H), 2.12–1.99 (m, 2H), 1.44–1.39 (m, 3H), 1.22 (m, 10H), 0.89 (t,  $J = 6.4$  Hz, 3H), 0.86 (d,  $J = 6.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  139.6, 114.1, 37.1, 36.4, 32.5, 32.1, 31.6, 29.8, 27.2, 22.9, 19.7, 14.3; HRESIMS:  $m/z$  206.1463  $[\text{M} - \text{H} + \text{K}]^+$  (calcd for  $\text{C}_{12}\text{H}_{23}\text{K}$ , 206.1437).

**(R)-3,7-Dimethyloct-6-en-1-yl-4-methylbenzenesulfonate (18).** (*R*)-(+)-  $\beta$ -citronellol (1.00 g, 6.40 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL), to which were added  $\text{Et}_3\text{N}$  (1 mL) and  $\text{TsCl}$  (1.83 g, 9.60 mmol). The mixture was continued to stir at rt until the starting material was consumed.  $\text{H}_2\text{O}$  (10 mL) was poured into the above mixture, extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10$  mL), combined the organic layer and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/ $\text{CH}_2\text{Cl}_2 = 3:1$ ) on silica gel to get compound **18** (1.97 g, 99%) as a colorless oil.  $[\alpha]_{\text{D}}^{25} -11.34$  ( $c$  1.98,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (d,  $J = 8.4$  Hz, 2H), 7.34 (d,  $J = 8.4$  Hz, 2H), 5.02 (t,  $J = 7.2$  Hz, 1H), 4.08–4.04 (m, 2H), 2.45 (s, 3H), 2.00–1.86 (m, 2H), 1.72–1.64 (m, 1H), 1.67 (s, 3H), 1.57 (s, 3H), 1.55–1.48 (m, 1H), 1.47–1.38 (m, 1H), 1.14–1.06 (m, 1H), 0.81 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  144.6, 133.2, 131.5, 129.8, 127.9, 124.3, 69.1, 36.7, 35.7, 28.9, 25.7, 25.3, 21.6, 19.0, 17.6; HRESIMS:  $m/z$  311.1670  $[\text{M} + \text{H}]^+$  (calcd for  $\text{C}_{17}\text{H}_{27}\text{O}_3\text{S}$ , 311.1681).

**(S)-2,6-Dimethyldodec-2-ene (19).** Under a nitrogen atmosphere, magnesium ribbon (0.60 g) was polished to turn silvery-white and cut into pieces. Then, the magnesium pieces (0.50 g, 20.83 mmol) were placed in a three-necked flask, to which was added 10 mL of dried THF followed by the addition of two iodine crystals and a solution of *n*-butyl bromide (3.40 g, 24.81 mmol) in THF (10 mL). The mixture was stirred for 1 h at rt. To a solution of compound **18** (1.00 g, 3.22 mmol) in 5 mL of THF were added  $\text{CuCl}$  (31.5 mg, 0.32 mmol) and the above Grignard reagent in sequence. The resulting solution was stirred at rt until compound **18** disappeared. Satd.  $\text{NH}_4\text{Cl}$  solution (20 mL) was poured into the reaction mixture, which was then extracted with  $\text{EtOAc}$  ( $3 \times 20$  mL), the combined organic layers were concentrated in vacuo. The residue was purified by column chromatography (pure petroleum ether) on silica gel to get compound **19** (0.52 g, 82 %) as a colorless oil.  $[\alpha]_{\text{D}}^{25} -1.33$  ( $c$  0.375,  $\text{CHCl}_3$ ) {lit.  $[\alpha]_{\text{D}}^{20}$

-1.0 (c 5.42, CHCl<sub>3</sub>)<sup>26c</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.11 (tt, *J* = 7.2, 1.2 Hz, 1H), 2.03–1.90 (m, 2H), 1.68 (d, *J* = 0.8 Hz, 3H), 1.61 (s, 3H), 1.39–1.26 (m, 11H), 1.17–1.09 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 130.9, 125.1, 37.2, 37.0, 32.4, 32.0, 29.7, 27.0, 25.7, 25.6, 22.7, 19.6, 17.6, 14.1; HRESIMS: *m/z* 219.2147 [M + Na]<sup>+</sup> (calcd for C<sub>14</sub>H<sub>28</sub>Na, 219.2089).

**Pinacol Vinyl Boronate 4. Method A:** To a mixture of compound **17** (0.95 g, 5.65 mmol) and pinacol vinylboronate (3.00 g, 19.5 mmol) in 15 mL of CH<sub>2</sub>Cl<sub>2</sub> was added Hoveyda-Grubbs II catalyst (0.35 g, 0.56 mmol). The solution was stirred at reflux temperature until the completion of the reaction. The solvent was evaporated in vacuo to give the crude product, which was purified by silica gel column chromatography (petroleum ether/EtOAc = 50:1) to provide compound **4** (1.26 g, 76%) as a yellow oil. [ $\alpha$ ]<sub>D</sub><sup>25</sup> -0.12 (c 4.10, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.61 (dt, *J* = 18.0, 6.4 Hz, 1H), 5.40 (d, *J* = 18.0 Hz, 1H), 2.20–2.06 (m, 2H), 1.44–1.36 (m, 3H), 1.25 (m, 20H), 1.09–1.07 (m, 2H), 0.86 (t, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 155.3, 83.1, 37.0, 35.5, 33.5, 32.4, 32.0, 29.8, 29.7, 27.0, 24.9 (2C), 22.8, 19.6, 14.2; HRESIMS: *m/z* 317.2624 [M + Na]<sup>+</sup> (calcd for C<sub>18</sub>H<sub>35</sub>BO<sub>2</sub>Na, 317.2622). **Method B:** Except for replacing compound **17** by compound **19** and adopting 1,2-dichloro ethane as solvent, a similar procedure as Method A was applied to synthesize compound **4** (1.20 g, 72%).

**Cross-Metathesis Product 20.** To a mixture of compound **5** (1.67 g, 5.52 mmol) and compound **6** (1.00 g, 6.32 mmol) in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> was added Grubbs II catalyst (268.7 mg, 0.32 mmol). The solution was allowed to stir at reflux temperature until the completion of the reaction. Concentration of the solvent gave the crude product, which was purified by silica gel column chromatography (petroleum ether/EtOAc = 2:1) to provide compound **20** (1.57 g, 66%) as a colorless oil. [ $\alpha$ ]<sub>D</sub><sup>25</sup> -5.9 (c 0.625, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.34–7.31 (m, 5H), 5.82 (dt, *J* = 15.2, 14.8 Hz, 1H), 5.47 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.11 (s, 2H), 4.62 (t, *J* = 7.6 Hz, 1H), 4.21 (q, *J* = 5.6 Hz, 1H), 3.58 (t, *J* = 5.6 Hz, 2H), 2.35 (t, *J* = 8.0 Hz, 2H), 2.05 (q, *J* = 7.2 Hz, 2H), 1.86 (t, *J* = 6.4 Hz, 1H), 1.65–1.62 (m, 2H), 1.50

(s, 3H), 1.38 (s, 3H), 1.37 (m, 2H), 1.28–1.25 (m, 12H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.8, 137.1, 136.2, 128.6, 128.2, 124.2, 108.6, 78.4, 78.3, 66.2, 62.3, 34.4, 32.4, 29.5 (2C), 29.3, 29.2 (2C), 29.0, 27.9, 25.3, 25.0; HRESIMS:  $m/z$  441.2611 [ $\text{M} + \text{Na}$ ] $^+$  (calcd for  $\text{C}_{25}\text{H}_{38}\text{O}_5\text{Na}$ , 441.2611).

**Vinyl Iodide 3.** To a solution of oxalyl chloride (0.34 mL, 3.74 mmol) in 8 mL of dry  $\text{CH}_2\text{Cl}_2$  was added dropwise a solution of DMSO (0.63 mL, 8.15 mmol) in 5 mL of  $\text{CH}_2\text{Cl}_2$  over 5 min at  $-60 \sim -50$  °C under a nitrogen atmosphere. After that, compound **20** (0.86 g, 1.99 mmol) in 10 mL of  $\text{CH}_2\text{Cl}_2$  was added to the above solution. The mixture was allowed to stir for 1 h at the same temperature. Then,  $\text{Et}_3\text{N}$  (1.12 mL, 7.99 mmol) was added to the resulting slurry followed by pouring 15 mL of  $\text{H}_2\text{O}$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL). The combined organic layers were washed with brine, and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Filtration and concentration gave the crude aldehyde, which was directly subjected to the next step without further purification. To a suspension of anhydrous  $\text{CrCl}_2$  (1.94 g, 15.92 mmol) in 20 mL of dry THF under a nitrogen atmosphere was added a mixed solution of the above aldehyde and  $\text{CHI}_3$  (2.35 g, 5.97 mmol) in 20 mL of dry THF *via* a dropping funnel. A pre-cooled satd. NaCl solution (15 mL) was poured into the reddish brown suspension after TLC indicated the starting material had disappeared. The aqueous layer was extracted with EtOAc ( $3 \times 20$  mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , evaporated in vacuo. The residue was subjected to column chromatography (petroleum ether/EtOAc = 20:1) to give compound **3** (0.77 g, 70%) as a yellow oil.  $[\alpha]_{\text{D}}^{25} -37.2$  ( $c$  0.423,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.33 (m, 5H), 6.46 (dd,  $J = 14.4, 6.8$  Hz, 1H), 6.37 (d,  $J = 14.4$  Hz, 1H), 5.76 (dt,  $J = 15.6, 14.0$  Hz, 1H), 5.34 (dd,  $J = 15.2, 8.0$  Hz, 1H), 5.11 (s, 2H), 4.58 (t,  $J = 8.0$  Hz, 1H), 4.51 (t,  $J = 6.4$  Hz, 1H), 2.35 (t,  $J = 7.6$  Hz, 2H), 2.06 (q,  $J = 7.2$  Hz, 2H), 1.68–1.60 (m, 2H), 1.51 (s, 3H), 1.37 (s, 3H), 1.37 (m, 2H), 1.26 (m, 12H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.8, 142.8, 136.9, 136.2, 128.6, 128.2, 124.9, 109.0, 80.9, 79.4, 79.1, 66.1, 34.4, 32.3, 29.6, 29.5, 29.3, 29.2 (2C), 29.0, 28.0, 25.5, 25.0; HRESIMS:  $m/z$  563.1635 [ $\text{M} + \text{Na}$ ] $^+$  (calcd for  $\text{C}_{26}\text{H}_{37}\text{IO}_4\text{Na}$ , 563.1629).

**Suzuki Coupling Product 21.** Compound **3** (0.24 g, 0.433 mmol) and compound **4** (0.15 g, 0.51 mmol) were dissolved in a mixed solvent of THF and  $\text{H}_2\text{O}$  (10 mL, v/v = 3:1) under a nitrogen atmos-

phere, sonicated and degassed for 20 min. To the solution was added Pd(PPh<sub>3</sub>)<sub>4</sub> (46.2 mg, 0.04 mmol) at rt. The resultant solution was allowed to stir for 5 min. Then, EtOTf (48 μL, 0.68 mmol) was added *via* a syringe. The reaction mixture was stirred for another 1 h before adding satd. NaHCO<sub>3</sub> solution to basify the solution to pH 7.0. After filtration and extraction with EtOAc (3×20 mL), the organic layers were concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/ EtOAc = 20:1) to give compound **21** (0.17 g, 65 %) as a colorless oil.  $[\alpha]_D^{25} -13.3$  (*c* 0.075, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35–7.34 (m, 5H), 6.19 (dd, *J* = 14.8, 10.4 Hz, 1H), 6.03 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.74–5.66 (m, 2H), 5.46 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.38 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.11 (s, 2H), 4.58–4.52 (m, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.10–2.00 (m, 4H), 1.64 (t, *J* = 7.6 Hz, 2H), 1.51 (s, 3H), 1.38 (s, 3H), 1.36 (m, 3H), 1.25 (m, 22H), 1.10–1.09 (m, 2H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.8, 136.5, 136.2, 136.0, 134.2, 129.2, 128.6, 128.2, 126.4, 126.0, 108.4, 80.1, 79.8, 66.1, 37.0, 36.5, 34.4, 32.4, 32.0, 30.3, 29.7, 29.6, 29.5, 29.3, 29.2 (2C), 29.0, 28.2, 27.0, 25.7, 25.0, 22.8, 19.5, 14.2; HRESIMS: *m/z* 617.4543 [M + Na]<sup>+</sup> (calcd for C<sub>39</sub>H<sub>62</sub>O<sub>4</sub>Na, 617.4546).

**Amide 2.** To a solution of compound **21** (100.0 mg, 0.168 mmol) in MeOH (10 mL) was added 10% Pd/C (20.0 mg). The suspension was allowed to stir for 25 min at rt under a hydrogen atmosphere, filtered, then the filtrate was evaporated in vacuo to provide a crude carboxylic acid. To a solution of (*R*)-piperidine-2-carboxylic acid methyl ester hydrochloride (36.0 mg, 0.20 mmol) in 5 mL of dry CH<sub>2</sub>Cl<sub>2</sub> was added NaHCO<sub>3</sub> (50.0 mg, 0.60 mmol). The mixture was stirred for 0.5 h before the sequential addition of the above carboxylic acid, EDCI (77.0 mg, 0.40 mmol) and HOBt (1.15 g, 0.50 mmol). The solution was allowed to stir at rt until the completion of the reaction. H<sub>2</sub>O (10 mL) was poured into the solution, which was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×10 mL). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 2:1) to provide compound **2** (92.0 mg, 86%) as a colorless oil.  $[\alpha]_D^{25} -36.3$  (*c* 0.08, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.39 (d, *J* = 5.2 Hz, 1H), 4.59–4.56 (con-

former), 4.02–4.00 (m, 2H), 3.78 (m, 1H), 3.76 (conformer), 3.72 (s, 3H), 3.22 (dt,  $J = 13.2, 2.8$  Hz, 1H), 2.36 (t,  $J = 7.6$  Hz, 2H), 2.24 (m, 1H), 1.73–1.54 (m, 9H), 1.48–1.43 (m, 5H), 1.41 (s, 3H), 1.33 (s, 3H), 1.25 (m, 32H), 1.08–1.06 (m, 2H), 0.88 (t,  $J = 6.8$  Hz, 3H), 0.83 (d,  $J = 6.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.4, 172.1, 107.3, 78.2, 52.2, 51.8, 43.5, 37.2, 33.6, 32.8, 32.0, 30.0, 29.8 (2C), 29.7 (4C), 29.6, 29.5, 28.7, 27.1 (2C), 26.7, 26.3, 26.1, 25.5, 25.2, 22.8, 21.1, 19.8, 14.2; HRESIMS:  $m/z$  658.5394  $[\text{M} + \text{Na}]^+$  (calcd for  $\text{C}_{39}\text{H}_{73}\text{NO}_5\text{Na}$ , 658.5386).

**Penasulfate A (1).** Compound **2** (20.0 mg, 0.03 mmol) was dissolved in a methanolic 1% AcCl solution (1  $\mu\text{L}$  AcCl in 1 mL MeOH). The mixture was allowed to stir at rt until the completion of the reaction, then concentrated in vacuo. The residue was dissolved in 1 mL of dried DMF, to which was added  $\text{SO}_3\cdot\text{Pyr}$  (99.0 mg, 0.62 mmol). The mixture was stirred for 5 h at rt, followed by basification to pH 9.0 with satd.  $\text{NaHCO}_3$  solution, filtration and concentration in vacuo. The residue was purified by silica gel column chromatography (EtOAc/MeOH = 8:1) to provide disodium penasulfate **A (1)** (20.4 mg, 81%) as a white powder.  $[\alpha]_{\text{D}}^{25} +11.8$  ( $c$  0.144, MeOH) {lit.  $[\alpha]_{\text{D}}^{29} +10$  ( $c$  0.03, MeOH)}<sup>9</sup>;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  5.26 (d,  $J = 5.2$  Hz, 1H), 4.65–4.63 (m, 2H), 4.45 (conformer), 3.87 (d,  $J = 14.0$  Hz, 1H), 3.75 (conformer), 3.72 (s, 3H), 3.21 (dt,  $J = 13.2, 2.8$  Hz, 1H), 2.60 (conformer), 2.43 (t,  $J = 7.2$  Hz, 2H), 2.31–2.23 (m, 1H), 1.80–1.50 (m, 14H), 1.31–1.29 (m, 32H), 1.11 (m, 2H), 0.90 (t,  $J = 7.2$  Hz, 3H), 0.85 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  175.9, 175.7 (conformer), 173.0, 172.7 (conformer), 81.8, 80.5 (conformer), 57.6 (conformer), 53.4, 53.0 (conformer), 52.7, 44.8, 40.6 (conformer), 38.2, 38.1 (conformer), 34.2, 33.9, 33.1, 30.9, 30.8, 30.7 (2C), 30.6 (2C), 30.5 (3C), 30.4, 30.3, 28.2 (conformer), 28.1 (2C), 27.6, 26.5, 26.4 (2C), 26.3, 25.7 (conformer), 23.7, 21.9 (conformer), 21.8, 20.1, 14.4; HRESIMS:  $m/z$  776.4065  $[\text{M} - \text{Na}]^-$  (calcd for  $\text{C}_{36}\text{H}_{67}\text{NO}_{11}\text{S}_2\text{Na}$ , 776.4053).

**Disulfate 27.** All of the prior steps (prior to the final step) were performed as for the synthesis of **1**, except for replacement of compound **6** by compound **22** derived from D-arabinose over 3 steps, then compound **27** was obtained (25.0 mg, 80%) as a white powder.  $[\alpha]_{\text{D}}^{25} +18.8$  ( $c$  0.053, MeOH);  $^1\text{H}$

NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  5.25 (d,  $J$  = 5.2 Hz, 1H), 4.64–4.62 (m, 2H), 4.45 (conformer), 3.87 (d,  $J$  = 14.4 Hz, 1H), 3.76 (conformer), 3.72 (s, 3H), 3.21 (dt,  $J$  = 12.8, 2.8 Hz, 1H), 2.42 (t,  $J$  = 7.6 Hz, 2H), 2.32–2.16 (m, 1H), 1.77–1.50 (m, 14H), 1.30 (m, 32H), 1.11 (m, 2H), 0.89 (t,  $J$  = 7.2 Hz, 3H), 0.85 (d,  $J$  = 6.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD)  $\delta$  175.9, 173.0, 81.8, 57.7 (conformer), 53.4, 53.0 (conformer), 52.7, 44.9, 40.6 (conformer), 38.3, 34.3, 34.0, 33.1, 30.9, 30.8, 30.7 (3C), 30.6, 30.5 (3C), 30.4, 30.3, 28.2, 28.1, 27.6, 26.6, 26.4, 26.3, 23.7, 21.9, 21.8, 20.1, 14.4; HRESIMS:  $m/z$  776.4055 [M – Na]<sup>–</sup> (calcd for C<sub>36</sub>H<sub>67</sub>NO<sub>11</sub>S<sub>2</sub>Na, 776.4053).

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of NMR spectra of compound **1–5**, **7–14** and **16–21**, **27**, DEPT 135, COSY and HSQC spectra of compound **1**, DEPT 135 and COSY spectra of compound **21** (PDF)

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## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENT

The authors thank NSF of China (21602082, 21602081, 21702051) for financial support. The authors also thank Open Research Fund of State Key Laboratory of Environmental Chemistry and Ecotoxicology (KF2016-01) for support in part.

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## Graphic Abstract

