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# Total Synthesis of (-)-5,6-seco-Germacrane Lactone

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## 1. Introduction

5.6-seco-Germacrane lactone (1) was isolated from an extract of Santolina chamaecyparissus L. ssp. squarrosa (DC.) Nyman, naturally grown on the Mediterranean coast of Spain.<sup>1</sup> The flower of this plant is used in folk medicine because of its antispasmodic, anti-inflammatory, antiseptic, antimicrobial, and digestive properties.<sup>2</sup> In addition, this traditional general healing agent also has many positive effects, e.g., to improve headache, stomachache, dizziness, catarrh, and eye problems such as sties and eye fatigue, and its diuretic activity and blood cleansing abilities.<sup>3</sup> The structural feature of **1** is an  $\alpha$ -methylene lactonic acid having three stereogenic centers at the C1, C2, and C7 positions. However, those absolute configurations remain a matter of speculation based on a plausible biogenetic pathway;<sup>1</sup> that is, 1 can be derived from the germacrane 2, which was isolated from the same extract, through oxidative cleavage of the C5-C6 bond to afford the intermediate seco-germacrane dicarboxylic acid, followed by a  $\gamma$ -lactonic ring-closing reaction (Scheme 1). This rational hypothesis is of interest because such a biosynthetic pathway of the linear sesquiterpene lactones has not been reported to our knowledge.<sup>4</sup> For example, research on biosynthetic mechanisms for some analogues such as anthecotuloide<sup>5</sup> and anthepseudolide<sup>6</sup> from Anthemis sp.

ABSTRACT

The first total synthesis of (–)-5,6-*seco*-germacrane lactone has been achieved. The synthetic highlight of our approach includes  $sp^2$ - $sp^3$  Suzuki–Miyaura cross coupling of a vinyl bromide and an alkyl 9-BBN derivative. The vinyl bromide was easily prepared from the chiral lactonic building block using a one-pot regioselective bromination. The asymmetric carbon center of the alkyl boron compound was formed using the zirconium-catalyzed carbomagnesation of 2,5-dihydrofuran.

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suggested that such irregular sesquiterpene lactones in nature could be formed from either the fragmentation of the corresponding germacranolides, which are derived from farnesyl diphosphate, or the condensation of geranyl diphosphate with dimethylallyl diphosphate followed by an oxidation process. Against this background, we initiated a synthetic study of 1 to establish those stereogenic centers and its biogenetic pathway, and to provide a sufficient amount of 1 synthetically for the evaluation of its biological activity. We describe herein the first total synthesis of (–)-1 from the known chiral building block (–)-3.



Scheme 1. Proposed Biogenetic Pathway of 1.

# 2. Results and discussion

We began the total synthesis of (-)-1 from the chiral building block (-)-3, which can be easily prepared from commercially

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available 1,4-pentadien-3-ol in three steps, Cincluding Ethe N Sharpless asymmetric dihydroxylation.<sup>7,8a</sup> The allyl alcohol derivative (–)-3 was successfully converted into vinyl bromide (– )-4 via the dibromo intermediate in excellent yield in a single pot (Scheme 2).<sup>8,9</sup> The chiral HPLC analysis of (–)-4 revealed the enantiomeric purity of (–)-4 to be 95% ee.<sup>10</sup> This two-step reaction was based on one-pot methodology for bromination of allyl alcohol derivatives and the sequential regioselective HBr elimination that was developed recently by our group.<sup>9</sup>



#### Scheme 2. Synthesis of (-)-4.

Next, we synthesized the intermediate (–)-**6** as the Suzuki– Miyaura coupling partner with the vinyl bromide (–)-**4** utilizing the method of zirconocene-catalyzed carbomagnesation described by Hoveyda et al.<sup>11</sup> The reaction of 2,5-dihydrofuran with 5.1 equiv of *n*PrMgCl in the presence of 10 mol % of (*S*)-[EBTHI]ZrCl<sub>2</sub> in THF at 70 °C produced homoallylic alcohol (– )-**5** and the subsequent TBDPS protection afforded (–)-**6** in 32% yield in two steps (Scheme 3).



Scheme 3. Synthesis of (-)-6.



Scheme 3. Total Synthesis of (–)-1.

We next attempted a *B*-alkyl Suzuki–Miyaura cross coupling with (–)-6 and (–)-4. Through trial and error,<sup>12</sup> we found the optimal reaction conditions and procedure, as follows. Hydroboration of the terminal olefin (–)-6 with 9borabicyclo[3.3.1]nonane (9-BBN) dimer in THF was completed. After that, 3 M aqueous  $Cs_2CO_3$  was added with vigorous stirring at room temperature for 50 min. Then, this solution was added to a solution of the vinyl bromide (–)-4 and catalytic amounts of Pd<sub>2</sub>(dba)<sub>3</sub> and XPhos in 1,4-dioxane, and the mixture was stirred at 70 °C for 3.5 h to give the desired product (–)-7 in excellent yield (Scheme 4).<sup>13</sup> Fortunately, no diastereomer was detected at the NMR analysis. This indicated that the coupling partner (–)-6 as well as (–)-4 was almost optically pure. Introduction of an *exo*methylene group on the  $\gamma$ -lactone by the two-step Eschenmoser methylenation procedure,<sup>14</sup> followed by removal of the TBDPS group using tetrabutylammonium fluoride, then provided (–)-9. Swern oxidation and the subsequent Pinnick oxidation gave the corresponding  $\gamma$ -lactonic acid (–)-11 in sufficient yield, without any epimerization in the process. At the final stage, the *p*methoxybenzyl group of (–)-11 was removed with DDQ to afford (–)-1 in moderate yield, which was identical spectroscopically to that reported by Carda et al.<sup>1</sup>

#### 3. Conclusion

In conclusion, the first total synthesis of (-)-1 was achieved from the known chiral building block (-)-3 with diversity in eight steps and an overall yield of 14%. The key step in our synthesis was an sp<sup>2</sup>-sp<sup>3</sup> Suzuki–Miyaura cross coupling between the vinyl bromide (-)-4 and the alkylborane derived from (-)-6. Our synthetic strategy would allow the synthesis of the related analogues and derivatives of 1, including its diastereomers, without any difficulty. In addition, through this synthetic research, the absolute stereochemistries of all stereogenic carbon centers in 1 were determined, and thereby its novel biosynthetic mechanism, as proposed by Carda et al., could be strongly supported. A further investigation related to the synthesis of analogues and their biological assay is in progress.

# 4. Experimental section

#### 4.1. General remarks

Infrared spectra were recorded with a Horiba FT-710 model spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectral data were obtained with a Bruker Avance 600, a JEOL JNM-LA 500 instruments. Chemical shifts are quoted in ppm using tetramethylsilane (TMS,  $\delta = 0$  ppm) as the reference for <sup>1</sup>H NMR spectroscopy, and CDCl<sub>3</sub> ( $\delta = 77.0$  ppm) for <sup>13</sup>C NMR spectroscopy. Mass spectra were measured with a Bruker Daltonics microTOF or a Hitachi double-focusing M-80B spectrometer. Column chromatography was carried out on silica gel (Kanto Chemical Co. or Merck Co. Ltd). All reactions were performed under an argon atmosphere. Compounds **3**, **4**, and **5** are known and their analytical data have been reported.<sup>15</sup>

# 4.2. One-pot synthesis of (R)-5-[(S)-2-bromo-1-(4methoxybenzyloxy)allyl]dihydrofuran-2(3H)-one ((-)-4)

A mixture of the lactone (–)-**3** (0.45 g, 1.7 mmol) and pyridinium bromide perbromide (>85%) (0.72 g, 1.9 mmol) in CH<sub>3</sub>CN (17 mL) was stirred at room temperature for 12 h. DBU (0.79 mL, 5.3 mmol) was added to the reaction mixture at 0 °C and the mixture was then heated at 60 °C for 5 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl at 0 °C, and the reaction mixture was extracted with ethyl acetate (20 mL x 3), washed with brine (20 mL), dried over MgSO<sub>4</sub>, concentrated in vacuo, and purified by silica gel column chromatography (CHCl<sub>3</sub>/CH<sub>3</sub>CN = 20/1) to afford the bromoalkene (–)-**4** (0.55 g, 94%).

# 4.3. (R)-3-[(tert-buthyldiphenylsilyloxy)methyl]-4-methylpent-1ene ((-)-6)

2,5-Dihydrofuran (0.10 mL, 1.4 mmol) was dissolved in anhydrous THF (1.6 mL) in a flamed-dried 30 mL round-bottom flask. After the addition of nPrMgCl (2.0 M in Et<sub>2</sub>O, 3.4 mL, 6.8

mmol), the reaction mixture was allowed to stir for 5 min. Then,  $\bigvee$ (S)-[EBTHI]ZrCl<sub>2</sub> (59 mg, 0.14 mmol) was added and stirred at 70 °C for 6 h. After the solution was cooled to 0 °C, excess Grignard reagent was quenched through the dropwise addition of 1 M HCl aq. (9.0 mL). The mixture was diluted with H<sub>2</sub>O (30 mL) and washed with methyl tert-butyl ether (10 mL  $\times$  3). Combined organic layers were dried over MgSO<sub>4</sub>, concentrated in vacuo, and the residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> (0.40 mL). After the addition of triethylamine (0.19 mL, 1.4 mmol), N,Ndimethyl-4-aminopyridine (5.7 mg, 0.047 mmol), and TBDPSCl (0.14 mL, 0.54 mmol) at 0 °C, the mixture was stirred at room temperature for 12 h. The reaction was quenched with H<sub>2</sub>O (10 mL), and the reaction mixture was extracted with CHCl<sub>3</sub> (10 mL  $\times$  3), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo, and purified by silica gel column chromatography (hexane/ethyl acetate = 50/1) to afford (–)-6 (0.15 g, 32% in 2 steps from 2,5-dihydrofuran) as a pale yellow oil;  $[\alpha]_D^{20}$  –19.8° (*c* 1.00, CHCl<sub>3</sub>); IR (neat) 3070, 2954, 2862, 2792, 1589, 1466, 1427, 1103, 995 cm<sup>-1</sup>; <sup>1</sup>H NMR  $(500 \text{ MHz}, \text{CDCl}_3) \delta = 0.80 \text{ (d, } J = 6.6 \text{ Hz}, 3\text{H}), 0.86 \text{ (d, } J = 6.6 \text{ Hz})$ Hz, 3H), 1.04 (s, 9H), 1.88 (dsep, J = 6.6, 6.6 Hz, 1H), 1.98–2.06 (m, 1H), 3.63 (dd, J = 10.0, 6.2 Hz, 1H), 3.67 (dd, J = 10.0, 6.2 Hz, 1H), 4.97-5.07 (m, 2H), 5.68 (ddd, J = 17.0, 10.0, 9.5 Hz, 1H), 7.33–7.44 (m, 6H), 7.66 (d, J = 6.3 Hz, 4H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta = 18.7$  (CH<sub>3</sub>), 19.3 (C), 20.9 (CH<sub>3</sub>), 26.9 (CH<sub>3</sub> × 3), 27.6 (CH), 52.8 (CH), 65.4 (CH<sub>2</sub>), 116.4 (CH<sub>2</sub>), 127.6 (CH × 4), 129.5 (CH × 2), 134.0 (C × 2), 135.7 (CH × 4), 138.3 (CH); HRMS-ESI: m/z [M+Na]<sup>+</sup> calcd for C<sub>23</sub>H<sub>32</sub>OSiNa: 375.2115, found: 375.2113.

# 4.4. (R)-5-{(1R,5S)-5-[(tert-buthyldiphenylsilyloxy)methyl]-1-(4methoxybenzyloxy)-6-methyl-2-methyleneheptyl}dihydrofuran-2(3H)-one ((-)-7)

A mixture of (-)-6 (0.10 g, 0.29 mmol) and 9-BBN dimer (72 mg, 0.30 mmol) in THF (0.65 mL) was stirred at room temperature for 1 h and then at 50 °C for 3 h. After that, 3 M  $Cs_2CO_3$  aq. (0.23 mL) was added with vigorous stirring at room temperature for 50 min. Then, this solution was added to a solution of the vinyl bromide (-)-4 (46 mg, 0.13 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (12.4 mg, 0.014 mmol), and XPhos (15.6 mg, 0.033 mmol) in 1,4-dioxane (0.65 mL), and the mixture was stirred at 70 °C for 3.5 h. After the addition of H<sub>2</sub>O (10 mL), the reaction mixture was extracted with ethyl acetate (10 mL  $\times$  3), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo, and purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) to afford (-)-7 (73 mg, 89%) as a colorless oil;  $[\alpha]_{D}^{20}$  –30.8° (c 1.00, CHCl<sub>3</sub>); IR (neat) 3070, 2954, 2862, 1782, 1612, 1466, 1250, 1111, 1033 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 0.85$  (d, J = 7.1 Hz, 3H), 0.86 (d, J = 6.1 Hz, 3H), 1.05 (s, 9H), 1.32-1.40 (m, 1H), 1.45-1.56 (m, 2H), 1.79-1.95 (m, 3H), 1.96-2.09 (m, 2H), 2.31-2.41 (m, 1H), 2.45-2.55 (m, 1H), 3.55-3.66 (m, 2H), 3.70 (d, J = 5.8 Hz, 1H), 3.79 (s, 3H), 4.23 (d, J = 11.4 Hz, 1H), 4.49 (ddd, J = 7.4, 6.7, 5.8 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 5.11 (s, 2H), 6.85 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.33–7.44 (m, 6H), 7.65 (d, J = 7.2 Hz, 4H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta = 19.3$  (C), 19.5 (CH<sub>3</sub>), 19.9 (CH<sub>3</sub>), 24.5 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 26.9 (CH<sub>3</sub> × 3), 28.3 (CH), 28.4 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 46.4 (CH), 55.2 (CH<sub>3</sub>), 64.4 (CH<sub>2</sub>), 70.1 (CH<sub>2</sub>), 80.8 (CH), 84.2 (CH), 113.8 (CH × 2), 114.7 (CH<sub>2</sub>), 127.6 (CH × 4), 129.4 (CH × 2), 129.6 (CH × 2), 129.9 (C), 133.9 (C × 2), 135.6 (CH  $\times$  4), 144.9 (C), 159.2 (C), 177.1 (C); HRMS-ESI: m/z $[M+Na]^+$  calcd for C<sub>38</sub>H<sub>50</sub>O<sub>5</sub>SiNa: 637.3320, found: 637.3319.

4.5. (R)-5-{(1R,5S)-5-[(tert-buthyldiphenylsilyloxy)methyl]-1-(4methoxybenzyloxy)-6-methyl-2-methyleneheptyl}-3methylenedihydrofuran-2(3H)-one ((-)-8)

To a mixture of (-)-7 (0.10 g, 0.17 mmol), Eschenmoser's salt (0.16 g, 0.85 mmol), and N,N-diisopropylethylamine (0.15 mL, 0.85 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.7 mL) was added TMSOTf (33 µL, 0.19 mmol) at 0 °C. After being stirred at room temperature for 6 min, the reaction was quenched with the addition of sat. NaHCO<sub>3</sub> aq. (5 mL), extracted with CHCl<sub>3</sub> (10 mL  $\times$  3), washed with brine (10 mL), dried over MgSO<sub>4</sub>, and concentrated in vacuo. The resulting crude mixture was dissolved in CH<sub>2</sub>C<sub>2</sub> (1.7 mL), and then, to the solution was added mCPBA (0.11 mg, 0.68 mmol) at 0 °C. After being stirred at room temperature for 1 h, the reaction was quenched with the addition of sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aq. (10 mL), extracted with  $CHCl_3$  (10 mL  $\times$  3), washed with sat. NaHCO<sub>3</sub> aq. (20 mL) and brine (10 mL), dried over MgSO<sub>4</sub>, concentrated in vacuo, and purified by silica gel column chromatography  $(CHCl_3/CH_3CN = 80/1)$  to afford (-)-8 (66 mg, 61%) as a pale yellow oil; [α]<sub>D</sub><sup>20</sup> -30.6° (c 0.64, CHCl<sub>3</sub>); IR (neat) 3070, 2954, 2862, 1766, 1612, 1466, 1250, 1111, 1034 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 0.85$  (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 1.05 (s, 9H), 1.33-1.41 (m, 1H), 1.46-1.56 (m, 2H), 1.81-1.94 (m, 2H), 1.97-2.08 (m, 1H), 2.57 (dddd, J = 17.1, 6.0, 3.0, 2.5 Hz, 1H), 2.72 (dddd, J = 17.1, 7.6, 2.9, 2.5 Hz, 1H), 3.56-3.66 (m, 2H), 3.69 (d, J = 6.0 Hz, 1H), 3.79 (s, 3H), 4.24(d, J = 11.2 Hz, 1H), 4.44–4.55 (m, 1H), 4.51 (d, J = 11.2 Hz, 1H), 5.10 (br s, 1H), 5.12 (br s, 1H), 5.53 (dd, J = 2.5, 2.5 Hz, 1H), 6.18 (dd, J = 3.0, 2.9 Hz, 1H), 6.85 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.33-7.45 (m, 6H), 7.65 (d, J = 7.4 Hz, 4H);<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 19.3 (C), 19.6 (CH<sub>3</sub>), 19.9 (CH<sub>3</sub>), 26.2 (CH<sub>2</sub>), 26.9 (CH<sub>3</sub>  $\times$  3), 28.3 (CH), 29.4 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 46.4 (CH), 55.3 (CH<sub>3</sub>), 64.4 (CH<sub>2</sub>), 70.2 (CH<sub>2</sub>), 77.4 (CH), 83.9 (CH), 113.8 (CH × 2), 115.1 (CH<sub>2</sub>), 121.3 (CH<sub>2</sub>), 127.6 (CH × 4), 127.7 (C), 129.4 (CH × 2), 129.6 (CH × 2), 129.9 (C), 133.9 (C), 134.4 (C), 135.6 (CH × 4), 144.9 (C), 159.2 (C), 170.1 (C); HRMS-ESI: m/z [M+Na]<sup>+</sup> calcd for C<sub>39</sub>H<sub>50</sub>O<sub>5</sub>SiNa: 649.3320, found: 649.3318.

4.6. (R)-5-[(1R,5S)-5-hydroxymethyl-1-(4-methoxybenzyloxy)-6methyl-2-methyleneheptyl]-3-methylenedihydrofuran-2(3H)-one ((-)-9)

A mixture of (-)-8 (19 mg, 0.031 mmol) and TBAF (1 M in THF, 46 µL, 0.046 mmol) in THF (0.30 mL) was stirred at room temperature for 6 h. After the addition of sat. NH<sub>4</sub>Cl aq. (5.0 mL), the mixture was extracted with ethyl acetate (10 mL  $\times$  3), washed with brine (10 mL), dried over MgSO<sub>4</sub>, concentrated in vacuo, and purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 1/1) to afford (-)-9 (8.5 mg, 72%) as a pale yellow oil;  $[\alpha]_D^{20}$  -49.6° (c 1.00, CHCl<sub>3</sub>); IR (neat) 3502, 2954, 2870, 1766, 1612, 1466, 1033 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 0.92$  (d, J = 6.6 Hz, 6H), 1.29–1.37 (m, 1H), 1.43-1.64 (m, 3H), 1.81 (m, 1H), 1.95-2.17 (m, 2H), 2.68 (dddd, J = 17.5, 5.9, 2.7, 2.4 Hz, 1H), 2.85 (dddd, J = 17.5, 8.5, 2.9, 2.4 Hz, 1H), 3.59 (dd, J = 10.6, 5.8 Hz, 1H), 3.66 (dd, J = 10.6, 5.8 Hz, 1H), 3.76 (d, J = 5.2 Hz, 1H), 3.80 (s, 3H), 4.27 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.61 (ddd, J = 8.5, 5.9, 5.2 Hz, 1H), 5.14 (s, 1H), 5.18 (s, 1H), 5.58 (dd, J = 2.4, 2.4 Hz, 1H), 6.20 (dd, J = 2.9, 2.7 Hz, 1H), 6.87 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 19.6 (CH<sub>3</sub>), 19.8 (CH<sub>3</sub>), 26.3 (CH<sub>2</sub>), 28.2 (CH), 29.3 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 46.4 (CH), 55.3 (CH<sub>3</sub>), 63.4 (CH<sub>2</sub>), 70.2 (CH<sub>2</sub>), 77.8 (CH), 83.5 (CH), 113.8  $(CH \times 2)$ , 115.4  $(CH_2)$ , 121.4  $(CH_2)$ , 129.4  $(CH \times 2)$ , 129.8 (C), 134.3 (C), 145.1 (C), 159.3 (C), 170.2 (C); HRMS-ESI: m/z  $[M+Na]^+$  calcd for C<sub>23</sub>H<sub>32</sub>O<sub>5</sub>Na: 411.2143, found: 411.2139.

# 4.7. (S)-5-{(R)-(4-methoxybenzyloxy)[(R)-4-methylene-5oxotetrahydrofuran-2-yl]methyl}-2-isopropylhex-5-enal((-)-**10**)

To a solution of  $(COCl)_2$  (3.3 µL, 0.039 mmol) in  $CH_2Cl_2$  (0.2 mL) was added DMSO (2.7 µL, 0.038 mmol) at -78 °C. The

mixture was stirred for 5 min, and (-)-9 (7.5 mg, 0.019 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) was added slowly. After being stirred at -78 °C for 1 h, triethylamine (16 µL, 0.12 mmol) was added and stirred for 2 h. After the addition of H<sub>2</sub>O (10 mL) at 0 °C, the mixture was extracted with  $CHCl_3$  (5 mL  $\times$  3), washed with sat. NaHCO<sub>3</sub> aq. (10 mL), sat. NH<sub>4</sub>Cl aq. (10 mL), and brine (10 mL), dried over MgSO<sub>4</sub>, concentrated in vacuo, and purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to afford (–)-10 (7.2 mg, 97%) as a pale yellow oil;  $[\alpha]_{D}^{20}$  –28.8° (*c* 1.00, CHCl<sub>3</sub>); IR (neat) 2954, 2931, 2870, 1766, 1720, 1612, 1458, 1034 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 0.98$  (d, J = 7.0Hz, 3H), 1.00 (d, J = 6.3 Hz, 3H), 1.55–1.69 (m, 2H), 1.81–1.90 (m, 1H), 1.95-2.09 (m, 2H), 2.13-2.19 (m, 1H), 2.65 (dddd, J =17.1, 5.9, 3.1, 2.4 Hz, 1H), 2.85 (dddd, *J* = 17.1, 7.6, 2.7, 2.4 Hz, 1H), 3.74 (d, *J* = 5.4 Hz, 1H), 3.80 (s, 3H), 4.27 (d, *J* = 11.3 Hz, 1H), 4.54 (d, J = 11.3 Hz, 1H), 4.57 (ddd, J = 7.6, 5.9, 5.2 Hz, 1H), 5.17 (s, 1H), 5.17 (s, 1H), 5.58 (dd, J = 2.4, 2.4 Hz, 1H), 6.20 (dd, J = 3.1, 2.7 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 9.66 (d, J = 3.4 Hz, 1H); <sup>13</sup>C NMR (126 MHz,  $CDCl_3$ )  $\delta = 19.6$  (CH<sub>3</sub>), 20.2 (CH<sub>3</sub>), 23.7 (CH<sub>2</sub>), 28.4 (CH), 29.3 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>), 57.8 (CH), 70.3 (CH<sub>2</sub>), 77.4 (CH), 83.5 (CH), 113.8 (CH × 2), 115.5 (CH<sub>2</sub>), 121.4 (CH<sub>2</sub>), 129.4 (CH × 2), 129.7 (C), 134.2 (C), 144.2 (C), 159.3 (C), 170.0 (C), 205.3 (CH); HRMS-ESI: m/z [M+Na]<sup>+</sup> calcd for C<sub>23</sub>H<sub>30</sub>O<sub>5</sub>Na: 409.1985, found: 409.1988.

# 4.8. (S)-5-{(R)-(4-methoxybenzyloxy)[(R)-4-methylene-5oxotetrahydrofuran-2-yl]methyl}-2-isopropylhex-5-enoic acid ((-)-11)

To a mixture of (-)-10 (7.2 mg, 0.019 mmol) in tBuOH/H<sub>2</sub>O (0.30 mL/0.074 mL) was added 2-methyl-2-butene (10 µL, 0.094 mmol) and NaH<sub>2</sub>PO<sub>4</sub> (3.2 mg, 0.021 mmol) at room temperature, then NaClO<sub>2</sub> (7.4 mg, 0.066 mmol) at 0 °C. After being stirred at room temperature for 50 min, H<sub>2</sub>O (2.0 mL) and sat. NH<sub>4</sub>Cl aq. (10 mL) were added at 0 °C. The mixture was extracted with ethyl acetate (10 mL  $\times$  3), dried over MgSO<sub>4</sub>, concentrated in vacuo, and purified by silica gel column chromatography (ethyl acetate) to afford (-)-11 (6.6 mg, 88%) as a pale yellow oil;  $[\alpha]_{D}^{20}$  –49.3° (*c* 0.48, CHCl<sub>3</sub>); IR (neat) 3525, 2962, 2931, 2862, 1766, 1705, 1612, 1466, 1033 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 0.98$  (d, J = 6.9 Hz, 6H), 1.61–1.86 (m, 2H), 1.87–1.98 (m, 1H), 1.98-2.14 (m, 2H), 2.19-2.26 (m, 1H), 2.64 (dddd, J = 17.1, 5.2, 2.5, 2.4 Hz, 1H), 2.85 (dddd, *J* = 17.1, 7.6, 3.1, 2.7 Hz, 1H), 3.74 (d, J = 5.8 Hz, 1H), 3.80 (s, 3H), 4.27 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.58 (ddd, J = 7.6, 5.8, 5.2 Hz, 1H), 5.16 (s, 2H), 5.57 (dd, J = 2.5, 2.4 Hz, 1H), 6.19 (dd, J = 3.1, 2.7 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  = 20.0 (CH<sub>3</sub>), 20.3 (CH<sub>3</sub>), 27.2 (CH), 29.4 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 30.5 (CH<sub>2</sub>), 51.8 (CH), 55.3 (CH<sub>3</sub>), 70.3 (CH<sub>2</sub>), 77.5 (CH), 83.5 (CH), 113.8 (CH × 2), 115.7 (CH<sub>2</sub>), 121.5 (CH<sub>2</sub>), 129.4 (CH × 2), 129.7 (C), 134.3 (C), 144.0 (C), 159.3 (C), 170.1 (C), 179.9 (C); HRMS-ESI: m/z [M+Na]<sup>+</sup> calcd for C<sub>23</sub>H<sub>30</sub>O<sub>6</sub>Na: 425.1935, found: 425.1938.

### 4.9. (-)-5,6-seco-Germacrane Lactone ((-)-1)

A mixture of (–)-**11** (11 mg, 0.027 mmol) and DDQ (6.8 mg, 0.030 mmol) in CH<sub>2</sub>Cl<sub>2</sub>/pH 6.9 phosphate buffer (0.45 mL/0.11 mL) was stirred at room temperature for 12 h. After the addition of sat. NH<sub>4</sub>Cl aq. (5.0 mL) at 0 °C, the mixture was extracted with ethyl acetate (10 mL × 3), dried over MgSO<sub>4</sub>, concentrated in vacuo, and purified by silica gel column chromatography (hexane/ethyl acetate = 1/3) to afford (–)-**1** (3.4 mg, 44%) as a colorless oil;  $[\alpha]_D^{20}$  –24.5° (*c* 0.17, CHCl<sub>3</sub>); IR (neat) 3452, 2962, 2931, 2858, 1759, 1712, 1034 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta = 0.98$  (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.68–1.86 (m, 2H), 1.90–1.97 (m, 1H), 2.03–2.11 (m, 1H), 2.14–2.25 (m,

2H), 2.81 (dddd, J = 17.3, 5.6, 2.9, 2.4 Hz, 1H), 2.95 (dddd, J = 17.3, 8.0, 2.7, 2.4 Hz, 1H), 4.07 (d, J = 5.7 Hz, 1H), 4.61 (ddd, J = 8.0, 5.7, 5.6 Hz, 1H), 5.08 (br s, 1H), 5.17 (br s, 1H), 5.66 (dd, J = 2.4, 2.4 Hz, 1H), 6.25 (dd, J = 2.9, 2.7 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta = 20.0$  (CH<sub>3</sub>), 20.4 (CH<sub>3</sub>), 27.5 (CH<sub>2</sub>), 29.8 (CH), 29.9 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 51.6 (CH), 77.3 (CH), 78.1 (CH), 114.2 (CH<sub>2</sub>), 122.6 (CH<sub>2</sub>), 133.9 (C), 146.0 (C), 170.0 (C), 179.3 (C); HRMS-ESI: m/z [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>22</sub>O<sub>5</sub>Na: 305.1359, found: 305.1354.

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