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## SECOND-GENERATION SYNTHESIS OF A CHIRAL BUILDING BLOCK FOR OXYGENATED TERPENOIDS VIA A RING-CONTRACTIVE COUPLING WITH A SECONDARY ALCOHOL<sup>†</sup>

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**Abstract** – A much improved second-generation synthesis of a chiral building block, developed for the syntheses of C17-oxygenated steroids/triterpenoids and C9-oxygenated labdane diterpenoids, was accomplished by exploiting a ring-contractive coupling between an  $\alpha$ -bromo- $\delta$ -valerolactone and (*R*)-seudenol, wherein the use of *t*-BuOK as a base allowed clean conversion to the corresponding tetrahydrofuran-2-carboxylate even with a small excess of the alcohol component.

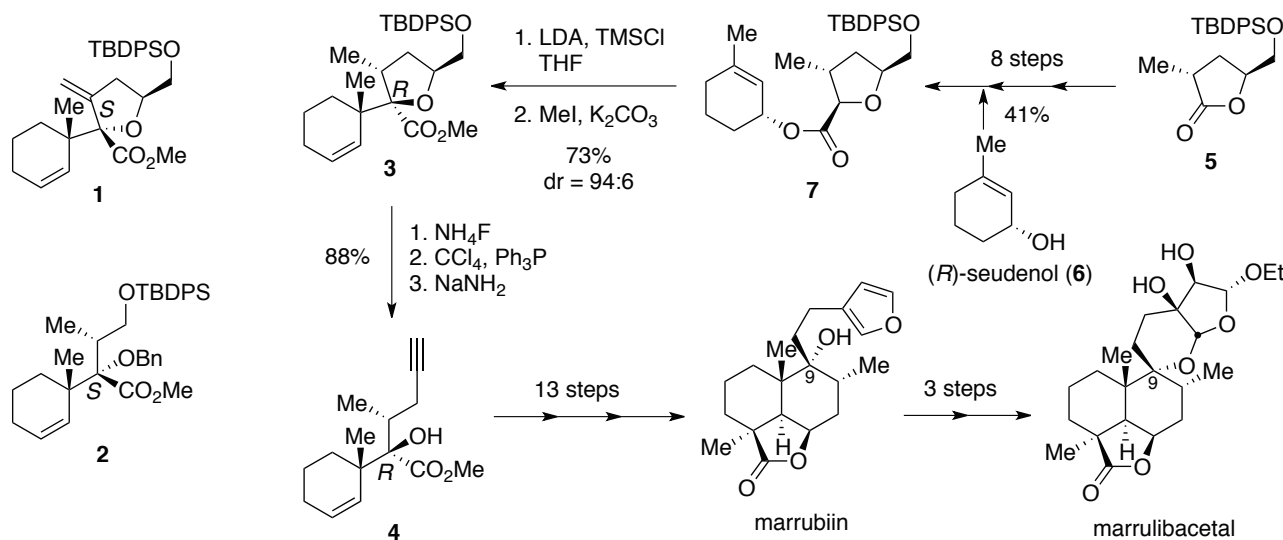
### INTRODUCTION

An oxygen functionality is often incorporated into steroids/triterpenoids and labdane diterpenoids at C17 and C9, respectively, during biosynthesis.<sup>1,2</sup> Due to their important biological activities and structural complexity, much efforts have been devoted to the stereoselective synthesis of these oxygenated natural products.<sup>3</sup> In all cases, polycyclic compounds having an angular methyl group such as Hajos–Parrish ketone have been employed as starting materials and an oxygen-substituted quaternary stereocenter has been created in a stereoselective manner.<sup>4</sup>

To synthesize these classes of natural products, we prepared cyclohexene derivatives **1–4** as chiral building blocks through a stereoselective Ireland–Claisen rearrangement (Scheme 1).<sup>5,6</sup> The synthetic utility of building block **4**, prepared from tetrahydrofuran derivative **3** in 88% yield for a three-step sequence, was demonstrated by total syntheses of the labdane diterpenoids marrubiin and marrulibacetal;<sup>7</sup> however, the lengthy preparation of ester **7** starting from lactone **5** (8 steps) left considerable room for improvement. Therefore, we felt compelled to establish an alternative synthetic route and improve the efficiency to permit large-scale preparations. We herein describe a much more efficient approach to synthesize building

<sup>†</sup> Dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday

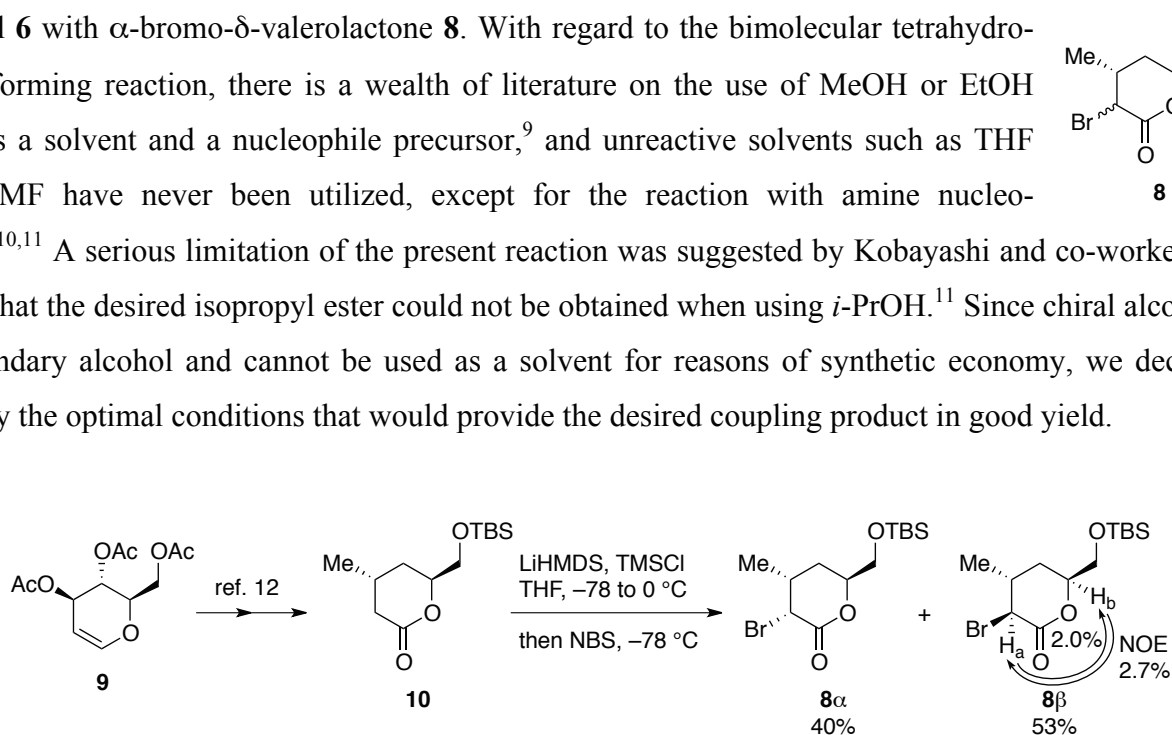
block **4** by employing a secondary alcohol for the first time in the ring-contractive alcoholysis<sup>8</sup> of an  $\alpha$ -bromo- $\delta$ -valerolactone.



**Scheme 1.** Structures of chiral building blocks **1–4**, and total syntheses of marrubiin and marrulibacetal from lactone **5** via tetrahydrofuran derivative **3** and enyne **4**

## RESULTS AND DISCUSSION

The preparation of tetrahydrofuran-2-carboxylate **7** by esterification of the corresponding carboxylic acid with (*R*)-seudenol (**6**) suffered from poor reproducibility, probably because of the self-decomposition of the acid. Hence, we surmised that ester **7** could be obtained by treatment of the alkoxide generated from alcohol **6** with  $\alpha$ -bromo- $\delta$ -valerolactone **8**. With regard to the bimolecular tetrahydrofuran-forming reaction, there is a wealth of literature on the use of MeOH or EtOH both as a solvent and a nucleophile precursor,<sup>9</sup> and unreactive solvents such as THF and DMF have never been utilized, except for the reaction with amine nucleophiles.<sup>10,11</sup> A serious limitation of the present reaction was suggested by Kobayashi and co-workers, who noted that the desired isopropyl ester could not be obtained when using *i*-PrOH.<sup>11</sup> Since chiral alcohol **6** is a secondary alcohol and cannot be used as a solvent for reasons of synthetic economy, we decided to identify the optimal conditions that would provide the desired coupling product in good yield.

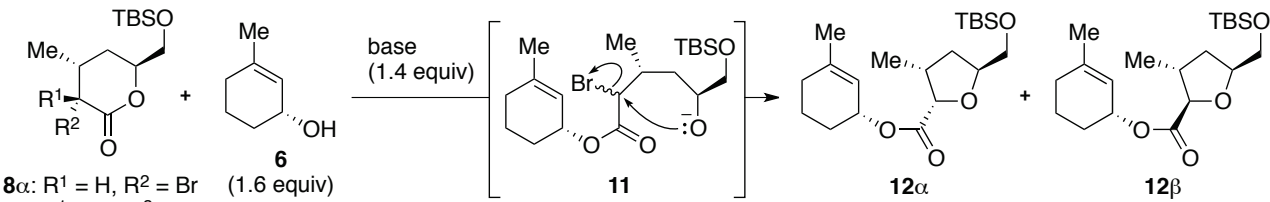


**Scheme 2.** Preparation of  $\alpha$ -bromo- $\delta$ -valerolactone **8**

Compound **8** was prepared by a one-pot procedure (silyl ketene acetal formation, followed by treatment with NBS at  $-78$  °C) from the known lactone **10**,<sup>12</sup> which could be easily obtained from 3,4,6-tri-*O*-acetyl-D-glucal (**9**) on a 10-g scale (Scheme 2).<sup>13,14</sup> To evaluate the effect of stereochemistry on the following ring-contractive coupling, the diastereomers were separated by column chromatography to afford **8 $\alpha$**  and **8 $\beta$**  in 40% and 53% yields, respectively. The stereochemical assignments of the newly formed stereocenter were verified by the diagnostic <sup>1</sup>H NOE correlations between H<sub>a</sub> and H<sub>b</sub> of the major isomer **8 $\beta$** .

The key ring-contractive coupling of secondary alcohol **6** was first explored with major diastereomer **8 $\beta$**  (Table 1). The initial attempt using K<sub>2</sub>CO<sub>3</sub> as a base in DMF met with failure, and lactone **8 $\beta$**  decomposed upon heating to reflux (entry 1). Fortunately, desired coupling products **12 $\alpha$**  and **12 $\beta$**  could be detected in the reaction with Cs<sub>2</sub>CO<sub>3</sub> or NaH, albeit in low yields (entries 2–4), and higher yields (39% and 51%, respectively) were obtained with other sodium bases, *t*-BuONa and NaHMDS (entries 5 and 6).<sup>15</sup> While the reaction with a lithium base (LiHMDS) required a higher temperature (0 °C) and gave a lower yield (35%) than that with NaHMDS (entry 7), the highest yield (82%) was obtained by using KHMDS at  $-40$  °C (entry 8). Switching to the more inexpensive base *t*-BuOK significantly shortened the reaction time (7 h  $\rightarrow$  0.7 h) without affecting the chemical yield (85%) and diastereomer ratio (1.2:1, entry 9). A comparable result (83% yield, dr = 1.2:1) was obtained with the minor isomer **8 $\alpha$** , indicating that the

**Table 1.** Ring-contractive coupling between  $\alpha$ -bromo- $\delta$ -valerolactone **8** and chiral secondary alcohol **6**



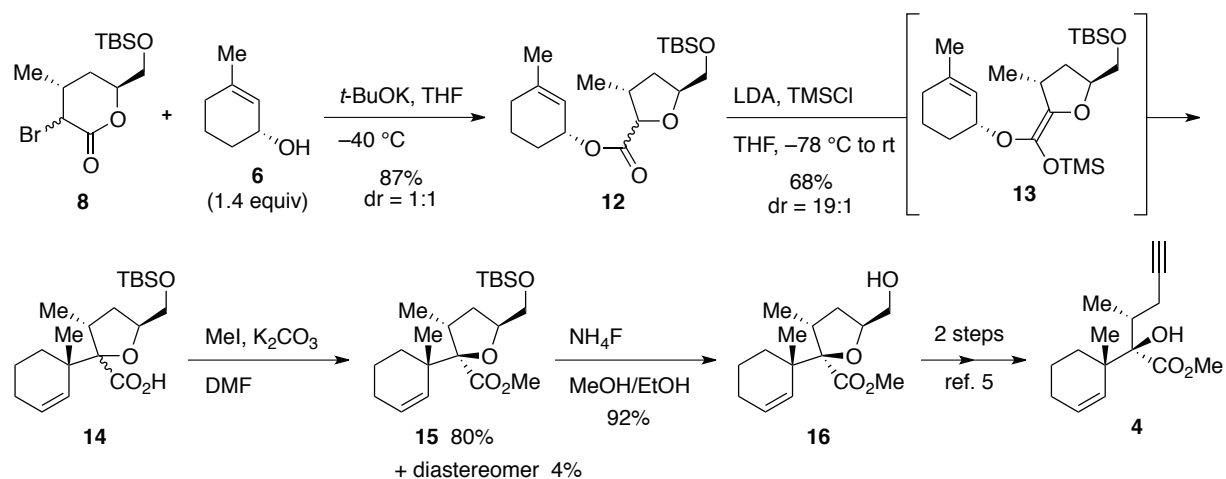
$\mathbf{8\alpha}$ : R<sup>1</sup> = H, R<sup>2</sup> = Br  
 $\mathbf{8\beta}$ : R<sup>1</sup> = Br, R<sup>2</sup> = H

Entry	R <sup>1</sup>	R <sup>2</sup>	Base	Solvent	Temp, °C	Time, h	Yield, %	<b>12<math>\alpha</math></b> : <b>12<math>\beta</math></b> <sup>a</sup>	
1	<b>8<math>\beta</math></b>	Br	H	K <sub>2</sub> CO <sub>3</sub>	DMF	reflux	4.5	decomp	—
2	<b>8<math>\beta</math></b>	Br	H	Cs <sub>2</sub> CO <sub>3</sub>	DMF	rt	21	trace	—
3	<b>8<math>\beta</math></b>	Br	H	NaH	DMF	0	7	9	1.0:1
4	<b>8<math>\beta</math></b>	Br	H	NaH	THF	0	7.5	trace	—
5	<b>8<math>\beta</math></b>	Br	H	<i>t</i> -BuONa	THF	0	5.5	39	3.1:1
6	<b>8<math>\beta</math></b>	Br	H	NaHMDS	THF	$-20$	6	51	2.9:1
7	<b>8<math>\beta</math></b>	Br	H	LiHMDS	THF	0	7	35	1:1.5
8	<b>8<math>\beta</math></b>	Br	H	KHMDS	THF	$-40$	7	82	1.0:1
9	<b>8<math>\beta</math></b>	Br	H	<i>t</i> -BuOK	THF	$-40$	0.7	85	1:1.2
10	<b>8<math>\alpha</math></b>	H	Br	<i>t</i> -BuOK	THF	$-40$	0.7	83	1:1.2

<sup>a</sup> Determined by 500 MHz <sup>1</sup>H NMR.

reactivity of  $\alpha$ -bromo- $\delta$ -valerolactone **8** was not influenced by the stereochemistry at the  $\alpha$ -position and that both isomers **8 $\alpha$**  and **8 $\beta$**  could be employed for the ring-contractive coupling without separation. In fact, treatment of the diastereomer mixture **8** with alcohol **6** under the optimized conditions afforded ester **12** in 87% yield in a ratio of 1:1 (Scheme 3). Since esters **12 $\alpha$**  and **12 $\beta$**  did not epimerize under the coupling conditions, the formation of a mixture of stereoisomers **12 $\alpha$**  and **12 $\beta$**  would be a result of the epimerization of isomers **8 $\alpha$**  and **8 $\beta$** .<sup>16</sup>

It is anticipated that almost identical results would be obtained by the Ireland–Claisen rearrangement of esters **12 $\alpha$**  and **12 $\beta$**  due to the predominant formation of (*Z*)-silyl ketene acetal **13** from either stereoisomer. While diastereomers **12 $\alpha$**  and **12 $\beta$**  were inseparable and could not be employed independently for the rearrangement, the fact that acid **14** was obtained from **12** in 68% yield with comparable selectivity to that observed with ester **7** indirectly supported our speculation. After esterification with MeI in the presence of K<sub>2</sub>CO<sub>3</sub>, the isomers could be separated by column chromatography, giving isomer **15** in 80% yield along with 4% of its diastereomer. Since alcohol **16**, obtained by removal of the TBS group with NH<sub>4</sub>F in MeOH/EtOH (92% yield),<sup>17</sup> was identical to our intermediate, we then proceeded to complete the synthesis following a two-step sequence involving chlorination and base-induced double eliminative ring-opening.<sup>5</sup>



**Scheme 3.** Conversion to building block **4**

In conclusion, we have achieved the second-generation synthesis of a chiral building block for the syntheses of C17-oxygenated steroids/triterpenoids and C9-oxygenated labdane diterpenoids with an overall yield of 41% via a seven-step sequence from known lactone **10**. The use of *t*-BuOK plays a pivotal role in achieving rapid and high-yielding ring-contractive coupling. To the best of our knowledge, this is the first report on the use of a secondary alcohol as a nucleophile in this tandem reaction. Of particular note is that the reaction proceeded to completion with only a small excess of the alcohol component in contrast to prior works that used alcohols as solvent, and our method would allow for the use of expensive and/or

solid alcohols as substrates. Further studies aimed at expanding the synthetic utility of the protocol are currently underway in our laboratory, and the results will be reported in due course.

## EXPERIMENTAL

**(4*R*,6*S*)-3-Bromo-6-[(*tert*-butyldimethylsilyl)oxymethyl]-4-methyltetrahydropyran-2-one (8).** BuLi in hexane (1.45 M, 3.7 mL, 5.37 mmol) was added to a cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of HMDS (1.3 mL, 6.23 mmol) in THF (10 mL). After 30 min of stirring at  $0\text{ }^{\circ}\text{C}$ , the LiHMDS solution was added by cannula to a cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of lactone **10** (1.00 g, 3.89 mmol) in THF (13 mL), and the resulting mixture was stirred for 1 h. TMSCl (0.78 mL, 6.15 mmol) was then added, and the mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 30 min. After recooling to  $-78\text{ }^{\circ}\text{C}$ , a solution of *N*-bromosuccinimide (1.01 g, 6.08 mmol) in THF (12 mL) was added, and the mixture was stirred for 40 min. The reaction was quenched with pH 7 phosphate buffer (80 mL), and the resulting mixture was extracted with AcOEt ( $2 \times 100\text{ mL}$ ). The combined organic extracts were washed with brine ( $2 \times 70\text{ mL}$ ) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Filtration and evaporation in vacuo furnished the crude product (1.82 g, yellow oil), which was purified by column chromatography (silica gel 30 g, 40:1 $\rightarrow$ 20:1 hexane/AcOEt) to give bromide **8 $\alpha$**  (523 mg, 40%) as a pale yellow oil and bromide **8 $\beta$**  (700 mg, 53%) as a colorless oil.

**(3*R*,4*R*,6*S*)-3-Bromo-6-[(*tert*-butyldimethylsilyl)oxymethyl]-4-methyltetrahydropyran-2-one (8 $\alpha$ ).**  $R_f$  0.63 (4:1 hexane/AcOEt);  $[\alpha]_D^{24} +15.2$  ( $c$  2.01, benzene); IR (neat) 2953, 2930, 2857, 1736, 1471, 1375, 1252, 1196, 1123, 1094, 1043, 914, 837  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.07 (s, 3H,  $\text{SiCH}_3$ ), 0.08 (s, 3H,  $\text{SiCH}_3$ ), 0.89 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 1.14 (d,  $J = 6.3\text{ Hz}$ , 3H,  $\text{CHCH}_3$ ), 1.87 (ddd,  $J = 7.3, 10.0, 14.0\text{ Hz}$ , 1H, one of  $\text{MeCHCH}_2$ ), 1.95 (dt,  $J = 14.0, 5.7\text{ Hz}$ , 1H, one of  $\text{MeCHCH}_2$ ), 2.35 (dddq,  $J = 3.4, 5.7, 10.0, 6.3\text{ Hz}$ , 1H,  $\text{CHMe}$ ), 3.71 (dd,  $J = 3.5, 11.0\text{ Hz}$ , 1H, one of  $\text{TBSOCH}_2$ ), 3.81 (dd,  $J = 4.6, 11.0\text{ Hz}$ , 1H, one of  $\text{TBSOCH}_2$ ), 4.42 (d,  $J = 3.4\text{ Hz}$ , 1H,  $\text{BrCHC}=\text{O}$ ), 4.69 (dddd,  $J = 3.5, 4.6, 5.7, 7.3\text{ Hz}$ , 1H,  $\text{OCHCH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$   $-5.4$  ( $\text{CH}_3$ ),  $-5.3$  ( $\text{CH}_3$ ), 18.3 (C), 18.6 ( $\text{CH}_3$ ), 25.9 ( $\text{CH}_3$ ), 27.7 ( $\text{CH}_2$ ), 29.7 (CH), 49.9 (CH), 65.4 ( $\text{CH}_2$ ), 78.2 (CH), 167.4 (C); HRMS (ESI)  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{13}\text{H}_{25}\text{BrO}_3\text{SiNa}$  359.0654; found 359.0666.

**(3*S*,4*R*,6*S*)-3-Bromo-6-[(*tert*-butyldimethylsilyl)oxymethyl]-4-methyltetrahydropyran-2-one (8 $\beta$ ).**  $R_f$  0.50 (4:1 hexane/AcOEt);  $[\alpha]_D^{24} +9.06$  ( $c$  1.98, benzene); IR (neat) 2955, 2930, 2857, 1744, 1462, 1385, 1362, 1250, 1179, 1130, 1098, 837  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.08 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ), 0.90 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 1.24 (d,  $J = 7.0\text{ Hz}$ , 3H,  $\text{CHCH}_3$ ), 1.69 (dt,  $J = 14.4, 5.0\text{ Hz}$ , 1H, one of  $\text{MeCHCH}_2$ ), 2.39 (ddd,  $J = 5.1, 9.6, 14.4\text{ Hz}$ , 1H, one of  $\text{MeCHCH}_2$ ), 2.53 (dddq,  $J = 5.0, 5.1, 6.0, 7.0\text{ Hz}$ , 1H,  $\text{CHMe}$ ), 3.77 (dd,  $J = 4.0, 11.0\text{ Hz}$ , 1H, one of  $\text{TBSOCH}_2$ ), 3.81 (dd,  $J = 4.9, 11.0\text{ Hz}$ , 1H, one of  $\text{TBSOCH}_2$ ), 4.23 (d,  $J = 6.0\text{ Hz}$ , 1H,  $\text{BrCHC}=\text{O}$ ), 4.52 (dddd,  $J = 4.0, 4.9, 5.0, 9.6\text{ Hz}$ , 1H,  $\text{OCHCH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$   $-5.4$  ( $\text{CH}_3$ ),  $-5.3$  ( $\text{CH}_3$ ), 18.4 (C), 19.4 ( $\text{CH}_3$ ), 25.9 ( $\text{CH}_3$ ), 28.6 ( $\text{CH}_2$ ), 34.1 (CH), 47.7 (CH),

65.0 (CH<sub>2</sub>), 77.8 (CH), 167.1 (C); HRMS (ESI)  $m/z$  [M + Na]<sup>+</sup> calcd for C<sub>13</sub>H<sub>25</sub>BrO<sub>3</sub>SiNa 359.0654; found 359.0637.

**(R)-3-Methylcyclohex-2-en-1-yl (3R,5S)-5-[(tert-Butyldimethylsilyl)oxymethyl]-3-methyltetrahydrofuran-2-carboxylate (12).** Potassium *tert*-butoxide (2.45 g, 21.8 mmol) was added to a solution of alcohol **6** (2.56 g, 22.8 mmol) in THF (120 mL), and the mixture was stirred for 5 min. After cooling to -78 °C, a mixture of bromides **8** $\alpha$  and **8** $\beta$  (5.50 g, 16.3 mmol) in THF (40 mL) was added, and the resulting mixture was allowed to warm to -40 °C. After 40 min of stirring, the reaction was quenched with AcOH (3 mL) in Et<sub>2</sub>O (12 mL), and pH 7 phosphate buffer (90 mL) was added. The resulting mixture was extracted with AcOEt (2  $\times$  300 mL), and the combined organic extracts were washed with brine (200 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation in vacuo furnished the crude product (8.89 g, yellow oil), which was purified by column chromatography (silica gel 90 g, 20:1  $\rightarrow$  10:1 hexane/AcOEt) to give a 1:1 mixture of esters **12** $\alpha$  and **12** $\beta$  (5.25 g, 87%) as a colorless oil.  $R_f$  0.67 (4:1 hexane/AcOEt);  $[\alpha]_D^{24}$  +97.2 ( $c$  1.11, CHCl<sub>3</sub>); IR (neat) 2932, 2857, 1742, 1460, 1379, 1253, 1196, 1101, 837 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.046 (s, 1.5H, SiCH<sub>3</sub>), 0.049 (s, 1.5H, SiCH<sub>3</sub>), 0.06 (s, 3H, SiCH<sub>3</sub>), 0.89 (s, 4.5H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.90 (s, 4.5H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.00 (d,  $J$  = 6.9 Hz, 1.5H, CHCH<sub>3</sub>), 1.47 (d,  $J$  = 6.9 Hz, 1.5H, CHCH<sub>3</sub>), 1.62–1.81 (m, 5H, CO<sub>2</sub>CH(CH<sub>2</sub>)<sub>2</sub>, one of MeCHCH<sub>2</sub>), 1.70 (s, 3H, =CCH<sub>3</sub>), 1.89–2.07 (m, 3H, =CCH<sub>2</sub>, one of MeCHCH<sub>2</sub>), 2.39 (m, 0.5H, CHMe), 2.62 (m, 0.5H, CHMe), 3.58 (dd,  $J$  = 6.3, 10.3 Hz, 0.5H, one of TBSOCH<sub>2</sub>), 3.61 (d,  $J$  = 4.6 Hz, 1H, TBSOCH<sub>2</sub>), 3.78 (dd,  $J$  = 5.2, 10.3 Hz, 0.5H, one of TBSOCH<sub>2</sub>), 3.98 (d,  $J$  = 6.3 Hz, 0.5H, OCHC=O), 4.19 (m, 0.5H, OCHCH<sub>2</sub>), 4.41 (m, 0.5H, OCHCH<sub>2</sub>), 4.47 (d,  $J$  = 7.5 Hz, 0.5H, OCHC=O), 5.28 (m, 0.5H, CO<sub>2</sub>CH), 5.33 (m, 0.5H, CO<sub>2</sub>CH), 5.45 (m, 0.5H, =CH), 5.47 (m, 0.5H, =CH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  -5.3 (CH<sub>3</sub>), -5.24 (CH<sub>3</sub>), -5.19 (CH<sub>3</sub>), -5.18 (CH<sub>3</sub>), 15.0 (CH<sub>3</sub>), 18.45 (CH<sub>3</sub>), 18.46 (C), 18.48 (C), 19.1 (CH<sub>2</sub>), 23.9 (CH<sub>3</sub>), 26.0 (CH<sub>3</sub>), 26.1 (CH<sub>3</sub>), 28.0 (CH<sub>2</sub>), 28.2 (CH<sub>2</sub>), 29.97 (CH<sub>2</sub>), 30.00 (CH<sub>2</sub>), 35.0 (CH<sub>2</sub>), 36.3 (CH<sub>2</sub>), 36.6 (CH), 38.2 (CH), 65.7 (CH<sub>2</sub>), 65.9 (CH<sub>2</sub>), 69.2 (CH), 69.4 (CH), 80.0 (CH), 80.5 (CH), 81.2 (CH), 84.2 (CH), 119.9 (CH), 120.0 (CH), 141.3 (C), 141.4 (C), 172.1 (C), 172.7 (C); HRMS (ESI)  $m/z$  [M + Na]<sup>+</sup> calcd for C<sub>20</sub>H<sub>36</sub>O<sub>4</sub>SiNa 391.2281; found 391.2260.

**Methyl (2R,3R,5S)-5-[(tert-Butyldimethylsilyl)oxymethyl]-3-methyl-2-[(S)-1-methylcyclohex-2-en-1-yl]tetrahydrofuran-2-carboxylate (15).** BuLi in hexane (1.48 M, 2.8 mL, 4.14 mmol) was added to a cooled (-78 °C) solution of diisopropylamine (0.70 mL, 4.99 mmol) in THF (10 mL). After 30 min of stirring at 0 °C, the LDA solution was added by cannula to a cooled (-78 °C) mixture of esters **12** $\alpha$  and **12** $\beta$  (1.11 g, 3.01 mmol) in THF (44 mL) before TMSCl (0.50 mL, 3.94 mmol) was added. After 10 min, the reaction mixture was allowed to warm to room temperature and stirred for 36 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (50 mL), and the resulting mixture was extracted with AcOEt (3  $\times$  100 mL). The combined organic extracts were washed with brine (100 mL), and dried over anhydrous

Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation in vacuo furnished the crude product (1.52 g, yellow oil), which was chromatographed (silica gel 25 g, 10:1→7:1→5:1 hexane/AcOEt) to give carboxylic acid **14** (756 mg, 68%) as a yellow oil.

Potassium carbonate (217 mg, 1.57 mmol) was added to an ice-cooled (0 °C) mixture of carboxylic acid **14** (194 mg, 0.53 mmol) and iodomethane (100 μL, 1.61 mmol) in DMF (5.3 mL). After 6 h of stirring, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL), and the resulting mixture was extracted with 2:3 hexane/AcOEt (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation in vacuo furnished the crude product (342 mg, pale yellow oil), which was purified by flash column chromatography (silica gel 30 g, 200:1 hexane/AcOEt) to give methyl ester **15** (161 mg, 80%) and its diastereomer (8.6 mg, 4%) as colorless oils. *R*<sub>f</sub> 0.49 (10:1 hexane/AcOEt); [α]<sub>D</sub><sup>22</sup> +7.93 (*c* 2.07, benzene); IR (neat) 3019, 2930, 2859, 1732, 1460, 1254, 1227, 1098, 837, 777 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.04 (s, 3H, SiCH<sub>3</sub>), 0.05 (s, 3H, SiCH<sub>3</sub>), 0.88 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.02 (d, *J* = 6.9 Hz, 3H, CHCH<sub>3</sub>), 1.08 (s, 3H, =CHCCH<sub>3</sub>), 1.48–1.61 (m, 3H, one of MeCCH<sub>2</sub>CH<sub>2</sub>, one of MeCCH<sub>2</sub>CH<sub>2</sub>, one of MeCHCH<sub>2</sub>), 1.63 (m, 1H, one of MeCCH<sub>2</sub>CH<sub>2</sub>), 1.85 (dt, *J* = 3.7, 13.0 Hz, 1H, one of MeCCH<sub>2</sub>CH<sub>2</sub>), 1.91 (m, 2H, =CHCH<sub>2</sub>), 2.05 (ddd, *J* = 4.8, 8.5, 12.6 Hz, 1H, one of MeCHCH<sub>2</sub>), 2.45 (m, 1H, CHMe), 3.56 (dd, *J* = 5.7, 10.3 Hz, 1H, one of TBSOCH<sub>2</sub>), 3.63 (dd, *J* = 4.0, 10.3 Hz, 1H, one of TBSOCH<sub>2</sub>), 3.71 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.21 (m, 1H, OCHCH<sub>2</sub>), 5.66 (dt, *J* = 10.4, 4.0 Hz, 1H, =CHCH<sub>2</sub>), 5.95 (d, *J* = 10.4 Hz, 1H, MeCCH=); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ -5.3 (CH<sub>3</sub>), -5.2 (CH<sub>3</sub>), 17.8 (CH<sub>3</sub>), 18.4 (C), 19.4 (CH<sub>2</sub>), 23.5 (CH<sub>3</sub>), 25.0 (CH<sub>2</sub>), 26.0 (CH<sub>3</sub>), 30.5 (CH<sub>2</sub>), 36.7 (CH), 37.1 (CH<sub>2</sub>), 42.0 (C), 51.4 (CH<sub>3</sub>), 65.4 (CH<sub>2</sub>), 78.2 (CH), 94.0 (C), 127.1 (CH), 132.9 (CH), 173.8 (C); HRMS (ESI) *m/z* [M + Na]<sup>+</sup> calcd for C<sub>21</sub>H<sub>38</sub>O<sub>4</sub>SiNa 405.2437; found 405.2433.

**Methyl (2*S*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxymethyl]-3-methyl-2-[(*S*)-1-methylcyclohex-2-en-1-yl]tetrahydrofuran-2-carboxylate.** *R*<sub>f</sub> 0.41 (10:1 hexane/AcOEt); [α]<sub>D</sub><sup>20</sup> -11.2 (*c* 1.04, CHCl<sub>3</sub>); IR (neat) 3028, 2929, 2859, 1732, 1462, 1252, 1227, 1101, 837, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.06 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.89 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.05 (d, *J* = 7.2 Hz, 3H, CHCH<sub>3</sub>), 1.09 (s, 3H, =CHCCH<sub>3</sub>), 1.51 (dt, *J* = 12.3, 7.2 Hz, 1H, one of MeCHCH<sub>2</sub>), 1.55–1.74 (m, 3H, MeCCH<sub>2</sub>CH<sub>2</sub>, one of MeCCH<sub>2</sub>CH<sub>2</sub>), 1.84 (dt, *J* = 13.3, 3.7 Hz, 1H, one of MeCCH<sub>2</sub>CH<sub>2</sub>), 1.92 (m, 2H, =CHCH<sub>2</sub>), 2.07 (ddd, *J* = 6.6, 8.9, 12.3 Hz, 1H, one of MeCHCH<sub>2</sub>), 2.45 (m, 1H, CHMe), 3.68 (d, *J* = 4.5 Hz, 2H, TBSOCH<sub>2</sub>), 3.71 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.22 (m, 1H, OCHCH<sub>2</sub>), 5.72 (m, 2H, MeCCH=CH); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ -5.3 (CH<sub>3</sub>), -5.2 (CH<sub>3</sub>), 18.4 (C), 18.6 (CH<sub>3</sub>), 19.3 (CH<sub>2</sub>), 23.5 (CH<sub>3</sub>), 25.0 (CH<sub>2</sub>), 26.0 (CH<sub>3</sub>), 31.4 (CH<sub>2</sub>), 37.2 (CH<sub>2</sub>), 37.4 (CH), 42.6 (C), 51.3 (CH<sub>3</sub>), 64.9 (CH<sub>2</sub>), 78.6 (CH), 94.9 (C), 127.7 (CH), 132.8 (CH), 173.5 (C); HRMS (ESI) *m/z* [M + Na]<sup>+</sup> calcd for C<sub>21</sub>H<sub>38</sub>O<sub>4</sub>SiNa 405.2437; found 405.2438.

**Methyl (2*R*,3*R*,5*S*)-5-(Hydroxymethyl)-3-methyl-2-[(*S*)-1-methylcyclohex-2-en-1-yl]tetrahydrofuran-2-carboxylate (**16**).** NH<sub>4</sub>F (47.7 mg, 1.28 mmol) was added to a solution of TBS ether **15** (125 mg,

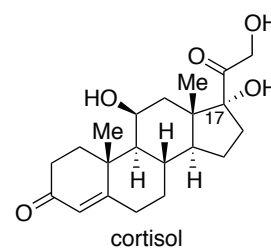
0.326 mmol) in 5:2 MeOH/EtOH (3.5 mL). After 48 h of stirring, the reaction mixture was partitioned between AcOEt (40 mL) and H<sub>2</sub>O (10 mL), and the aqueous layer was extracted with AcOEt (40 mL). The combined organic extracts were washed with brine (2 × 30 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation in vacuo furnished the crude product (127 mg, pale yellow oil), which was purified by column chromatography (silica gel 2 g, 3:1 hexane/AcOEt) to give alcohol **16** (81.3 mg, 92%) as a colorless oil. *R<sub>f</sub>* 0.31 (3:1 hexane/AcOEt); [ $\alpha$ ]<sub>D</sub><sup>23</sup> +22.1 (*c* 1.03, CHCl<sub>3</sub>) [lit.<sup>4</sup> [ $\alpha$ ]<sub>D</sub><sup>22</sup> +19.5 (*c* 1.17, CHCl<sub>3</sub>)]; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.06 (d, *J* = 7.0 Hz, 3H, CHCH<sub>3</sub>), 1.20 (s, 3H, =CHCCH<sub>3</sub>), 1.51–1.71 (m, 4H, MeCCH<sub>2</sub>CH<sub>2</sub>, one of MeCCH<sub>2</sub>CH<sub>2</sub>, one of MeCHCH<sub>2</sub>), 1.81 (dt, *J* = 3.3, 12.8 Hz, 1H, one of MeCCH<sub>2</sub>CH<sub>2</sub>), 1.91–1.95 (m, 2H, =CHCH<sub>2</sub>), 2.04 (ddd, *J* = 5.6, 9.1, 12.5 Hz, 1H, one of MeCHCH<sub>2</sub>), 2.55 (m, 1H, CHMe), 3.46 (dd, *J* = 4.4, 11.5 Hz, 1H, one of CH<sub>2</sub>OH), 3.73 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.74 (m, 1H, one of CH<sub>2</sub>OH), 4.32 (m, 1H, OCHCH<sub>2</sub>), 5.75 (m, 1H, =CHCH<sub>2</sub>), 5.83 (m, 1H, MeCCH=).

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15. The reason for the preferential formation of isomer **12** $\alpha$  under these conditions is unclear at present.
16. Exposure of epimer **8** $\alpha$  to *t*-BuOK (1.4 equiv) in THF at  $-40$  °C led to epimerization to provide a mixture of **8** $\alpha$  and **8** $\beta$  in 72% yield in a ratio of 1:1.5 when quenched after 5 min, whereas a 1:2.3 mixture was obtained from epimer **8** $\beta$  under identical conditions (79% yield).
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