

# Optimized Asymmetric Synthesis of Umuravumbolide

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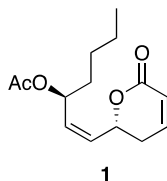
Supporting Information

**ABSTRACT:** Herein, the asymmetric synthesis of umuravumbolide (**1**) is described. The new approach features highly stereoselective transformations ( $dr \geq 95:5$ ) to install both stereocenters and the *Z* olefin, which involve a new radical alkylation, an Ando olefination, and a Krische allylation on a *Z* allylic alcohol, not reported before. The application of such successful reactions, together with the limited use of protecting groups and concession steps, makes it possible to complete the synthesis in 10 steps, resulting in a 39% overall yield from chiral *N*-acyl oxazolidinone **2**.



## 1. INTRODUCTION

The remarkable biological activity of abundant natural products containing 5,6-dihydropyran-2-one structural motifs is usually attributed to the Michael acceptor character of the  $\alpha,\beta$ -unsaturated lactone.<sup>1</sup> Thus, it should come as no surprise that the construction of such cyclic structures has been largely explored, and a handful of useful approaches have already been reported.<sup>2</sup> Instead, the asymmetric synthesis of the groups decorating the pyrone ring is still challenging and therefore a suitable arena to trial the efficiency of new synthetic methodologies. In this context, our interest in developing new stereoselective carbon–carbon bond-forming reactions led us to pay attention to the forge of the diallylic oxygenated motif embedded in the umuravumbolide (**1** in [Figure 1](#)).



**Figure 1.** Umuravumbolide **1**.

Umuravumbolide was first isolated by Van Puyvelde from *Tetradenia Riparia*, a plant of the Lamiaceae family from Central and Southern Africa.<sup>3</sup> Its structure was initially unclear, and it was not until 1995 that Davies-Coleman and Rivett established the *Z* geometry of the olefin and the configuration of both stereocenters,<sup>4</sup> which were later confirmed by the first total synthesis by Ramachandran.<sup>5</sup> Since then, other syntheses based on canonical methodologies have been reported.<sup>6</sup>

Looking for new synthetic avenues, we chose umuravumbolide as an appropriate benchmark for testing different carbon–carbon bond-forming reactions ([Scheme 1](#)). Indeed, we envisaged that the stereocenter on the unsaturated chain might be installed through a highly stereoselective alkylation of

titanium(IV) enolates recently disclosed by our group, whereas the second stereocenter would arise from an allylation reaction. In turn, a classical olefination should yield the desired *Z* carbon–carbon double bond ([Scheme 1](#)).

## 2. RESULTS AND DISCUSSION

According to the retrosynthetic analysis outlined in [Scheme 1](#), the synthesis began with the stereoselective alkylation of the chiral  $\alpha$ -OTBS acyl oxazolidinone **2** ([Scheme 2](#)).<sup>7</sup> Importantly, titanium(IV) enolates from *N*-acyl oxazolidinones show an unexpected biradical character, which grants them a unique reacting profile.<sup>8</sup> Indeed, treatment of such chiral enolates with diacyl peroxides gives rise to highly diastereoselective  $C\alpha$  alkylations through a SET process, in which the enolate acts as a reducing agent that triggers the decarboxylation of the peroxide and the ensuing formation of an alkyl radical.<sup>7a</sup> Then, the carbon–carbon bond formation stems from coupling of such an alkyl radical and the resultant  $C\alpha$  radical. In our case, the titanium(IV) enolate from **2** reacted with dipentanoyl peroxide to afford the desired alkylated product **3** as a single diastereomer ( $dr \geq 97:3$ ) with an 87% yield at 6 mmol scale ([Scheme 2](#)).

Having successfully installed the first stereocenter, the next step involved the removal of the chiral auxiliary ([Scheme 3](#)). We first attempted the reduction of **3** to directly produce aldehyde **4**. However, treatment of **3** with DIBALH led to carbinol species **5**, instead.<sup>9</sup> Preliminary studies on further olefination from **5** were promising, but the unclear and poorly reproducible reduction of **3** with DIBALH made this route impracticable. Alternatively, a two-step process was followed.

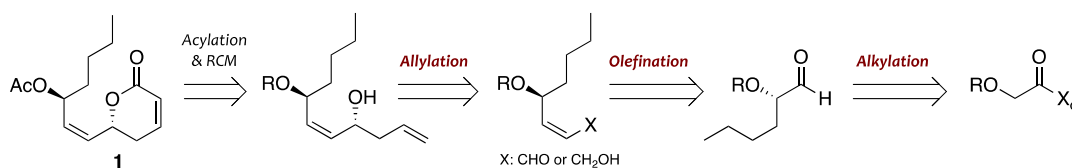
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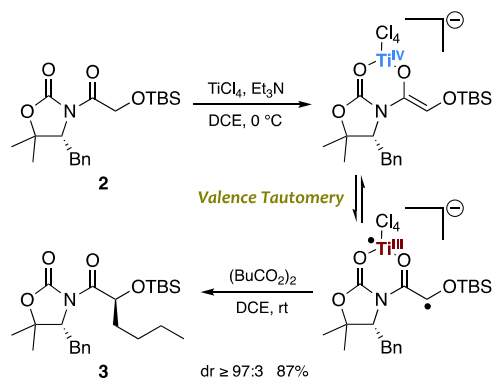
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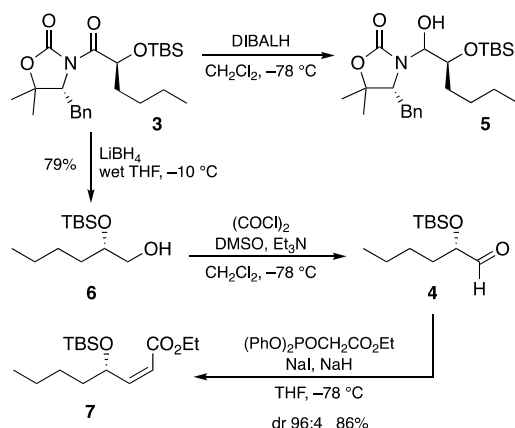
## Scheme 1. Retrosynthetic Analysis of Umuravumbolide 1



## Scheme 2. Diastereoselective Alkylation



## Scheme 3. Removal of the Chiral Auxiliary and Olefination

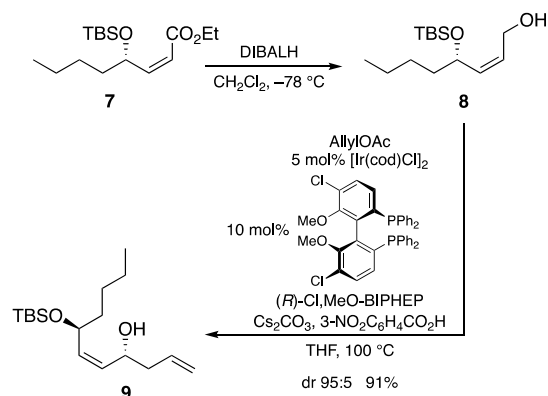


After a short optimization, it was found that the chiral auxiliary could be removed smoothly with LiBH<sub>4</sub> at  $-10\text{ }^{\circ}\text{C}$ , provided that the reaction was performed with freshly opened, commercially available LiBH<sub>4</sub> solution to avoid the undesired migration of the silyl group. Following this basic precaution, pure alcohol **6** was isolated in 79% yield at 4.5 mmol scale. Subsequent Swern oxidation<sup>10</sup> of **6** led quantitatively to aldehyde **4**, which was used in the next step without further chromatographic purification (Scheme 3). The forging of the crucial *Z* olefin was next tested (Scheme 3). Initially, we applied the Still–Gennari olefination<sup>11</sup> conditions using potassium carbonate and 18-crown-6 ether in toluene at  $0\text{ }^{\circ}\text{C}$  to attain a modest control of the geometry of the alkene (dr 70:30) and a 60% of the pure *Z* ester **7**. A slight increase in selectivity was observed when the reaction was performed with KHMDS and 18-crown-6 ether at  $-78\text{ }^{\circ}\text{C}$  (dr 80:20) or NaH at  $-78\text{ }^{\circ}\text{C}$  (dr 87:13). Despite such an improvement, the stereocontrol was still deemed inadequate, and other conditions were further explored. To our delight, Ando olefination<sup>12</sup> proved much more efficient. Indeed, treatment of phenyl phosphonate with NaH in the presence of NaI at  $-78\text{ }^{\circ}\text{C}$  for 2 h afforded the desired  $\alpha,\beta$ -unsaturated ethyl ester

**7** with a *Z/E* 96:4 and 86% yield at 3 mmol scale (Scheme 3).<sup>13</sup>

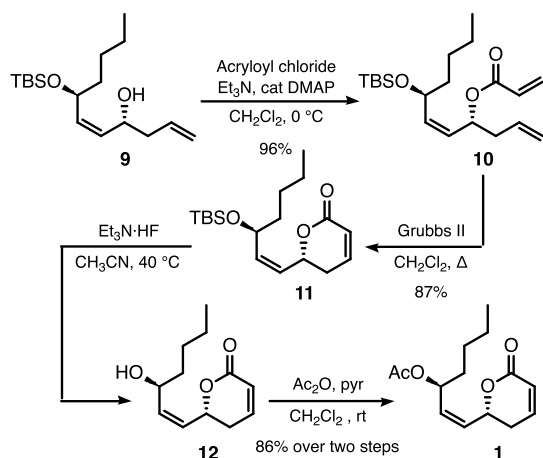
With a practical and efficient sequence toward ester **7** in hand, we faced its conversion into an aldehyde from which we tried to install the second stereocenter through a canonical allylation reaction. Being aware that such a transformation might endanger the stereochemical integrity of the *Z* olefin, we first examined the Leighton method, which is broadly used in asymmetric allylations.<sup>14</sup> Although it has never been tested on *Z*,  $\alpha,\beta$ -unsaturated aldehydes, its mild conditions make it ideal for our purposes. Unfortunately, despite our efforts, we consistently obtained the desired allylic alcohol contaminated by compounds containing *E* olefins.<sup>15</sup> Looking for alternatives, we focused our attention on Krische allylation.<sup>16</sup> To the best of our knowledge, Krische allylation has never been performed on a *Z* allylic alcohol, but its catalytic character and the use of the more stable alcohol partner as a starting material were deemed ideal to overcome the abovementioned limitations. In accordance with such a schedule, ester **7** was quantitatively reduced to alcohol **8** with DIBALH at  $-78\text{ }^{\circ}\text{C}$ . Then, application of the Krische allylation conditions described in the literature (2.5 mol % of the catalyst in THF at  $100\text{ }^{\circ}\text{C}$  for 20 h) gave a clean and highly stereoselective (dr 95:5) allylation but with moderate conversion. The increase of the catalyst loading to 5 mol % improved the yield, and the desired alcohol **9** (dr 95:5) was finally isolated with a remarkable 91% yield when the reaction was performed at a 2.5 mmol scale (Scheme 4).

## Scheme 4. Krische Allylation



Once both stereocenters and the *Z* olefin were installed, we addressed the construction of the pyrone ring.<sup>2</sup> As shown in Scheme 5, treatment of alcohol **9** with acryloyl chloride in the presence of catalytic amounts of DMAP smoothly gave ester **10** in a 96% yield. Then, a ring-closing metathesis was attempted. Initial trials using the Hoveyda–Grubbs catalyst proved unclear. Better results were obtained with Grubbs II, which permitted the isolation of lactone **11** in an 87% yield. Eventually, removal of the TBS-protecting group with Et<sub>3</sub>N·

## Scheme 5. Construction of the Pyrone Ring and Endgame



HF, as well as the final acetylation leading to umuravumbolide **1**, were carried out as reported in the literature with an 86% two-step yield (Scheme 5).<sup>5</sup>

## 3. CONCLUSIONS

In summary, we have reported an optimized synthesis of umuravumbolide **1**. Key steps involve a novel radical-like alkylation of a glycolate titanium(IV) enolate, an Ando olefination to build the *Z* olefin, and a non-reported Krische allylation starting from a sensitive *Z* allylic alcohol to install the second stereocenter in the pyrone ring. The use of such very-stereoselective transformations (*dr*  $\geq$  95:5) without the need for upgrading processes was crucial to accomplishing a straightforward synthesis that minimizes protection/deprotection and concession steps. As a result, the sequence comprises just 10 steps from **2** with a 39% overall yield, which entails the highest yield reported to date by any synthesis of umuravumbolide.

## 4. EXPERIMENTAL SECTION

**4.1. General Information.** Reactions were carried out under a nitrogen atmosphere and with anhydrous solvents, which were dried and purified following standard procedures. The glass material was previously dried in a glassware oven. The commercial reagents were used without purification. Hot plates with aluminum blocks or sand baths were used to carry out reactions that required heating. Analytical thin-layer chromatographies (TLCs) were performed on silica gel 60 F<sub>254</sub> plates. TLCs were analyzed by UV (254 nm) and stained with potassium permanganate or phosphomolybdic acid. The given *R<sub>f</sub>* values are approximate. Purification of the products was conducted by low-pressure column chromatography using SDS silica gel 60 (35–70  $\mu$ m). The measurement of melting points (Mp) was performed with a Stuart Scientific SMP10 apparatus; mp is uncorrected. Specific rotations ( $[\alpha]$ ) were measured on a Perkin-Elmer 241 MC polarimeter at 20 °C using a sodium lamp (D-line,  $\lambda$  589 nm). IR spectra were registered on a Nicolet 6700 FT-IR Thermo Scientific spectrometer (attenuated total reflectance, ATR), just the more indicative frequencies ( $\nu$ ) above 1000  $\text{cm}^{-1}$  are given. NMR spectra (400 and 500 MHz for <sup>1</sup>H NMR and 100.6 and 125.8 MHz for <sup>13</sup>C NMR) were registered on a Bruker 400 Avance III or a Bruker 500 Avance NEO spectrometer. Chemical shifts ( $\delta$ ) were reported in ppm and referenced to

internal TMS for <sup>1</sup>H NMR ( $\delta$  0.00) or CDCl<sub>3</sub> for <sup>13</sup>C NMR ( $\delta$  77.0). Multiplicity is described using the following initials: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and their combinations; the coupling constants are given in Hz. For complex molecules, COSY and/or HSQC were recorded to facilitate the assignment. High-resolution mass spectra (HRMS) were recorded on an Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses de la Universitat de Barcelona (CCiTUB).

**4.2. (*R*)-4-Benzyl-*N*-[(*S*)-2-*tert*-butyldimethylsilyloxyhexanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**3**).** Neat TiCl<sub>4</sub> (720 mL, 6.6 mmol) was added dropwise to a solution of (*R*)-4-benzyl-*N*-*tert*-butyldimethylsilyloxyacetyl-*S*,*S*-dimethyl-1,3-oxazolidin-2-one (**2**, 2.27 g, 6.0 mmol) in DCE (36 mL) at 0 °C. After 5 min, Et<sub>3</sub>N (2.5 mL, 18 mmol) was added dropwise, and the resultant deep purple mixture was stirred at 0 °C for 40 min. A solution of dipentanoyl peroxide (**SI1**, 1.82 g, 9.0 mmol) in DCE (5 mL) was added via *cannula*. The reaction was allowed to warm to rt and stirred for 50 min. Then, it was quenched with sat NH<sub>4</sub>Cl (20 mL). The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  20 mL). The combined organic extracts were dried with MgSO<sub>4</sub>, and the solvent was evaporated. Purification of the residue by flash column chromatography (from 99.5:0.5 to 95:5 hexanes/EtOAc) afforded **3** (2.26 g, 5.2 mmol, 87% yield) as a white solid. mp 66–68 °C; *R<sub>f</sub>* (90:10 hexanes/EtOAc) 0.3;  $[\alpha]_{\text{D}}^{20}$  – 4.6 (*c* 1.0, CHCl<sub>3</sub>); IR (ATR)  $\nu$ : 2953, 2928, 2856, 1770, 1715, 1353, 1248, 1146, 1097  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.37–7.17 (5H, m), 5.34 (1H, dd, *J* = 8.2, 3.3 Hz), 4.58 (1H, dd, *J* = 9.7, 3.9 Hz), 3.09 (1H, dd, *J* = 14.4, 3.9 Hz), 2.87 (1H, dd, *J* = 14.4, 9.7 Hz), 1.73–1.65 (1H, m), 1.59–1.48 (1H, m), 1.47–1.23 (4H, m), 1.38 (3H, s), 1.34 (3H, s), 0.92–0.88 (12H, m), 0.08 (3H, s), 0.06 (3H, s); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  174.7 (C), 152.2 (C), 136.5 (C), 129.1 (CH), 128.6 (CH), 126.8 (CH), 82.7 (C), 71.2 (CH), 63.2 (CH), 35.3 (CH<sub>2</sub>), 35.0 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 27.5 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 22.4 (CH<sub>2</sub>), 22.4 (CH<sub>3</sub>), 18.4 (C), 13.9 (CH<sub>3</sub>), –4.8 (CH<sub>3</sub>), –5.3 (CH<sub>3</sub>); HRMS (+ESI) *m/z*: calcd for C<sub>24</sub>H<sub>40</sub>NO<sub>4</sub>Si [*M* + *H*]<sup>+</sup>, 434.2721; found, 434.2719.

**4.3. (*S*)-2-*tert*-Butyldimethylsilyloxyhexanol (**6**).** A fresh 2.0 M solution of LiBH<sub>4</sub> in THF (14 mL, 28 mmol) was added dropwise to a solution of **3** (2.00 g, 4.6 mmol) in THF (35 mL) and H<sub>2</sub>O (12 mL) at –10 °C. The mixture was stirred for 80 min at –10 °C and quenched with MeOH (20 mL). The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  40 mL). The combined organic extracts were dried with MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by flash column chromatography (from 95:5 to 50:50 hexanes/EtOAc) to give recovered chiral auxiliary (869 mg, 4.2 mmol, 92% yield) as a white solid and alcohol **6** (844 mg, 3.6 mmol, 79% yield) as a colorless oil. *R<sub>f</sub>* (90:10 hexanes/EtOAc) 0.3;  $[\alpha]_{\text{D}}^{20}$  + 10.2 (*c* 1.0, CHCl<sub>3</sub>); IR (ATR)  $\nu$ : br 3386, 2954, 2928, 2857, 1463, 1253, 1097, 1046  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  3.73 (1H, tdd, *J* = 6.4, 5.4, 3.6 Hz), 3.56 (1H, dd, *J* = 11.0, 3.6 Hz), 3.44 (1H, dd, *J* = 11.0, 5.4 Hz), 1.94 (1H, br s), 1.52–1.45 (2H, m), 1.36–1.21 (4H, m), 0.92–0.88 (12H, m), 0.09 (6H, s); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  72.9 (CH), 66.3 (CH<sub>2</sub>), 33.7 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 22.8 (CH<sub>2</sub>), 18.1 (C), 14.0 (CH<sub>3</sub>), –4.5 (CH<sub>3</sub>), –4.6 (CH<sub>3</sub>); HRMS (+ESI) *m/z*: calcd for C<sub>12</sub>H<sub>29</sub>O<sub>2</sub>Si [*M* + *H*]<sup>+</sup>, 233.1931; found, 233.1930.



**4.4. (S)-2-tert-Butyldimethylsilyloxyhexanal (4).** DMSO (656  $\mu$ L, 9.2 mmol) was added dropwise to a solution of (COCl)<sub>2</sub> (423  $\mu$ L, 4.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) at -78 °C. The resultant mixture was stirred for 10 min at -78 °C, and alcohol **6** (716 mg, 3.1 mmol) was added via *cannula* and stirred for 10 min at -60 °C. Then, neat Et<sub>3</sub>N (2.6 mL, 18.5 mmol) was added to the reaction mixture at -78 °C, and the mixture was allowed to warm to rt. The mixture was stirred for 2.5 h, and then, it was quenched with H<sub>2</sub>O (30 mL). The layers were separated, and the aqueous layer was extracted with hexanes (2  $\times$  40 mL). The combined organic extracts were washed with H<sub>2</sub>O (50 mL) and 10% acetic acid aqueous solution (50 mL) and dried with MgSO<sub>4</sub>. The solvent was removed under reduced pressure (H<sub>2</sub>O<sub>2</sub> trap!) to quantitatively afford the crude aldehyde **4** (729 mg) as a yellowish oil, which was used in the next step without further purification. *R*<sub>f</sub> (90:10 hexanes/EtOAc) 0.7; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  9.59 (1H, d, *J* = 1.7 Hz), 3.96 (1H, ddd, *J* = 7.1, 5.7, 1.8 Hz), 1.65–1.59 (2H, m), 1.41–1.18 (4H, m), 0.93–0.88 (12H, m), 0.08 (3H, s), 0.08 (3H, s).

**4.5. Ethyl (S,Z)-4-tert-Butyldimethylsilyloxy-2-octanoate (7).** NaI (465 mg, 3.1 mmol) was added to a solution of ethyl diphenoxyphosphorylacetate (**SI2**) (1.28 g, 4.0 mmol) in THF (30 mL) at 0 °C. After 5 min, NaH 60% dispersion in mineral oil (160 mg, 4.0 mmol) was added (CAUTION: slow addition, release of gas), and the resulting mixture was stirred for 15 min and cooled to -78 °C. Then, a solution of crude aldehyde **4** (729 mg, 3.1 mmol) in THF (8 mL) was added dropwise via *cannula*, and the resultant mixture was stirred for 2 h at -78 °C. The reaction was quenched with sat NH<sub>4</sub>Cl (20 mL) and extracted with Et<sub>2</sub>O (2  $\times$  30 mL). The combined organic extracts were dried with MgSO<sub>4</sub> and concentrated under reduced pressure. Purification of the residue by flash column chromatography (80:20 hexanes/CH<sub>2</sub>Cl<sub>2</sub>) afforded **7** (797 mg, 2.65 mmol, 86% yield from **6**) as a colorless oil. *R*<sub>f</sub> (70:30 hexanes/CH<sub>2</sub>Cl<sub>2</sub>) 0.5; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 7.2 (*c* 1.0, CHCl<sub>3</sub>); IR (ATR)  $\nu$ : 2956, 2929, 2857, 1720, 1252, 1183, 1116, 1080, 1049, 1031 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.14 (1H, dd, *J* = 11.7, 8.2 Hz), 5.68 (1H, dd, *J* = 11.7, 1.3 Hz), 5.33–5.25 (1H, m), 4.17 (2H, q, *J* = 7.1 Hz), 1.62–1.25 (6H, m), 1.29 (3H, t, *J* = 7.1 Hz), 0.93–0.88 (12H, m), 0.05 (3H, s), 0.01 (3H, s); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  165.9 (C), 153.8 (CH), 117.5 (CH), 68.8 (CH), 60.1 (CH<sub>2</sub>), 37.0 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 18.1 (C), 14.2 (CH<sub>3</sub>), 14.0 (CH<sub>3</sub>), -4.6 (CH<sub>3</sub>), -4.9 (CH<sub>3</sub>); HRMS (+ESI) *m/z*: calcd for C<sub>16</sub>H<sub>33</sub>O<sub>3</sub>Si [M + H]<sup>+</sup>, 301.2193; found, 301.2191.

**4.6. (S,Z)-4-tert-Butyldimethylsilyloxy-2-octen-1-ol (8).** A 1.0 M solution of DIBALH in toluene (7.5 mL, 7.5 mmol) was added dropwise to a solution of ester **7** (864 mg, 3.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at -78 °C. The resultant mixture was stirred for 1 h at -78 °C and quenched with sat aqueous solution of Rochelle salt (20 mL). The mixture was stirred for 1 h at rt. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  30 mL). The combined organic extracts were dried with MgSO<sub>4</sub> and concentrated under reduced pressure to quantitatively afford alcohol **8** (776 mg) as a colorless oil, which was used in the next step without further purification. *R*<sub>f</sub> (90:10 hexanes/CH<sub>2</sub>Cl<sub>2</sub>) 0.2; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 6.1 (*c* 1.0, CHCl<sub>3</sub>); IR (ATR)  $\nu$ : br 3309, 2955, 2928, 2857, 1463, 1252, 1073, 1048, 1018 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.63–5.43 (2H, m), 4.37 (1H, q, *J* = 7.0 Hz), 4.27 (1H, dt, *J* = 13.4, 5.2 Hz), 4.17–4.09 (1H, m), 1.66 (1H, br t, *J* = 5.7 Hz),

1.61–1.50 (1H, m), 1.45–1.35 (1H, m), 1.34–1.20 (4H, m), 0.93–0.88 (12H, m), 0.06 (3H, s), 0.04 (3H, s); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  136.0 (CH), 127.6 (CH), 69.1 (CH), 59.1 (CH<sub>2</sub>), 38.2 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 18.2 (C), 14.1 (CH<sub>3</sub>), -4.4 (CH<sub>3</sub>), -4.8 (CH<sub>3</sub>); HRMS (+ESI) *m/z*: calcd for C<sub>14</sub>H<sub>30</sub>NaO<sub>2</sub>Si [M + Na]<sup>+</sup>, 281.1907; found, 281.1904.

**4.7. (4R,7S,Z)-7-tert-Butyldimethylsilyloxy-1,5-undecadien-4-ol (9).** Allyl acetate (2.6 mL, 24.0 mmol) was added to a mixture of **8** (631 mg,  $\approx$ 2.4 mmol), [Ir(cod)Cl]<sub>2</sub> (81 mg, 0.12 mmol, 5 mol %), (R)-Cl<sub>2</sub>MeO-BIPHEP (158 mg, 0.24 mmol, 10 mol %), Cs<sub>2</sub>CO<sub>3</sub> (313 mg, 0.96 mmol), and 3-nitrobenzoic acid (80 mg, 0.48 mmol) in THF (12 mL) in an oven-dried microwave vial (20 mL). The reaction mixture was stirred at 100 °C for 20 h. The resulting mixture was evaporated in vacuo and purified by flash column chromatography (from 97.5:2.5 to 90:10 hexanes/EtOAc) to give allylic alcohol **9** (660 mg, 2.2 mmol, 91% yield from **7**) as a colorless oil. *R*<sub>f</sub> (90:10 hexanes/EtOAc) 0.4; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 13.6 (*c* 1.0, CHCl<sub>3</sub>); IR (ATR)  $\nu$ : 3369 (br), 2955, 2928, 2856, 1463, 1252, 1049, 1005 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.87–5.74 (1H, m), 5.47 (1H, ddd, *J* = 11.4, 8.3, 1.0 Hz), 5.36 (1H, ddd, *J* = 11.4, 8.3, 0.9 Hz), 5.18–5.10 (2H, m), 4.50–4.35 (2H, m), 2.34–2.18 (2H, m), 1.93 (1H, br s), 1.59–1.48 (1H, m), 1.44–1.19 (5H, m), 0.91–0.87 (12H, m), 0.07 (3H, s), 0.05 (3H, s); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  135.6 (CH), 134.1 (CH), 130.5 (CH), 118.2 (CH<sub>2</sub>), 69.0 (CH), 67.1 (CH), 42.2 (CH<sub>2</sub>), 38.2 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 18.2 (C), 14.0 (CH<sub>3</sub>), -4.3 (CH<sub>3</sub>), -4.8 (CH<sub>3</sub>); HRMS (+ESI) *m/z*: calcd for C<sub>17</sub>H<sub>34</sub>NaO<sub>2</sub>Si [M + Na]<sup>+</sup>, 321.2220; found, 321.2217.

**4.8. (4R,7S,Z)-7-tert-Butyldimethylsilyloxy-1,5-undecadien-4-yl Acrylate (10).** DMAP (13 mg, 0.10 mmol), acryloyl chloride (170  $\mu$ L, 2.1 mmol), and Et<sub>3</sub>N (430  $\mu$ L, 3.1 mmol) were added to a solution of **9** (305 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (13 mL) at 0 °C. The solution was allowed to warm to rt, stirred for 2 h, and quenched with sat NH<sub>4</sub>Cl (10 mL) and 2 M HCl (1 mL). The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  15 mL). The combined organic extracts were dried with MgSO<sub>4</sub> and concentrated under reduced pressure. Purification of the residue through a short pad of silica afforded **10** (344 mg, 0.98 mmol, 96% yield) as a colorless oil. *R*<sub>f</sub> (95:5 hexanes/EtOAc) 0.7; [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 9.7 (*c* 1.0, CHCl<sub>3</sub>); IR (ATR)  $\nu$ : 2955, 2929, 2856, 1724, 1404, 1255, 1186, 1045, 1005 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.38 (1H, dd, *J* = 17.3, 1.5 Hz), 6.09 (1H, dd, *J* = 17.3, 10.4 Hz), 5.81 (1H, dd, *J* = 10.4, 1.5 Hz), 5.78–5.62 (2H, m), 5.55 (1H, ddd, *J* = 11.2, 8.5, 0.9 Hz), 5.34 (1H, ddd, *J* = 11.2, 9.6, 1.1 Hz), 5.13–5.05 (2H, m), 4.58–4.48 (1H, m), 2.47–2.30 (2H, m), 1.56–1.45 (1H, m), 1.39–1.24 (5H, m), 0.92–0.87 (3H, m), 0.85 (9H, s), 0.04 (3H, s), -0.01 (3H, s); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  165.1 (C), 138.5 (CH), 132.9 (CH), 130.6 (CH<sub>2</sub>), 128.6 (CH), 125.4 (CH), 118.3 (CH<sub>2</sub>), 69.2 (CH), 68.7 (CH), 39.5 (CH<sub>2</sub>), 38.3 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 18.1 (C), 14.1 (CH<sub>3</sub>), -4.6 (CH<sub>3</sub>), -5.0 (CH<sub>3</sub>); HRMS (+ESI) *m/z*: calcd for C<sub>20</sub>H<sub>36</sub>NaO<sub>3</sub>Si [M + Na]<sup>+</sup>, 375.2326; found, 375.2330.

**4.9. (R)-6-[(S,Z)-3-tert-Butyldimethylsilyloxy-1-hepten-1-yl]-5,6-dihydro-2H-pyran-2-one (11).** A solution of Grubbs II (20 mg, 2.5 mol %) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added dropwise (for 40 min approx) to a refluxing solution of **10** (332 mg, 0.94 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (95 mL). The mixture was stirred for 1 h, and the solvent evaporated. The residue was

purified by flash column chromatography (90:10 hexanes/EtOAc) to afford **11** (267 mg, 0.82 mmol, 87% yield) as a yellowish oil.  $R_f$  (90:10 hexanes/EtOAc) 0.1;  $[\alpha]_D^{20} + 5.1$  (c 1.0, CHCl<sub>3</sub>); IR (ATR)  $\nu$ : 2955, 2929, 2857, 1725, 1380, 1247, 1050, 1023 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.88 (1H, ddd,  $J = 9.8, 5.8, 2.6$  Hz), 6.06 (1H, ddd,  $J = 9.8, 2.6, 1.0$  Hz), 5.62 (1H, ddd,  $J = 11.3, 8.3, 0.7$  Hz), 5.53 (1H, ddd,  $J = 11.3, 8.7, 0.8$  Hz), 5.28–5.21 (1H, m), 4.39–4.34 (1H, m), 2.42 (1H, ddt,  $J = 18.4, 11.2, 2.6$  Hz), 2.28 (1H, dddd,  $J = 18.4, 5.8, 4.2, 1.0$  Hz), 1.60–1.49 (1H, m), 1.42–1.22 (5H, m), 0.91–0.87 (12H, m), 0.06 (3H, s), 0.05 (3H, s); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  163.7 (C), 144.4 (CH), 138.5 (CH), 125.2 (CH), 121.6 (CH), 73.8 (CH), 68.7 (CH), 38.3 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 25.8 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 18.1 (C), 14.0 (CH<sub>3</sub>), -4.3 (CH<sub>3</sub>), -4.9 (CH<sub>3</sub>); HRMS (+ESI)  $m/z$ : calcd for C<sub>18</sub>H<sub>32</sub>NaO<sub>3</sub>Si [M + Na]<sup>+</sup>, 347.2013; found, 347.2011.

**4.10. Deacetylumuravumbolide (12).** Et<sub>3</sub>N·3HF (930  $\mu$ L, 5.7 mmol) was added to a solution of **11** (236 mg, 0.71 mmol) in CH<sub>3</sub>CN (3 mL) at rt and stirred for 16 h. The reaction mixture was partitioned between H<sub>2</sub>O (7 mL) and EtOAc (7 mL), and the aqueous layer was extracted with further EtOAc (2  $\times$  7 mL). The combined organic extracts were dried with MgSO<sub>4</sub>, and the solvent evaporated. The residue was purified by flash column chromatography (from 70:30 to 60:40 hexanes/EtOAc) to afford **12** (128 mg, 0.61 mmol, 86% yield) as a white solid. mp 45–46 °C;  $R_f$  (70:30 hexanes/EtOAc) 0.2;  $[\alpha]_D^{20} - 6.8$  (c 1.0, CHCl<sub>3</sub>) [lit.<sup>4,5</sup>  $[\alpha]_D^{20} - 5.3$  (c 1.3, CHCl<sub>3</sub>)]; IR (ATR)  $\nu$ : 3421 (br), 2958, 2857, 1682, 1417, 1250, 1157, 1052, 1018 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.90 (1H, ddd,  $J = 9.8, 5.6, 2.8$  Hz), 6.08–6.00 (1H, m), 5.75–5.58 (2H, m), 5.34 (1H, ddd,  $J = 11.6, 7.3, 4.6$  Hz), 4.43 (1H, q,  $J = 6.8$  Hz), 2.50–2.32 (2H, m), 2.05 (1H, br s), 1.72–1.55 (1H, m), 1.48–1.39 (1H, m), 1.39–1.13 (4H, m), 0.91 (3H, t,  $J = 6.8$  Hz); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  163.7 (C), 144.7 (CH), 137.8 (CH), 127.5 (CH), 121.5 (CH), 73.7 (CH), 67.8 (CH), 36.8 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>); HRMS (+ESI)  $m/z$ : calcd for C<sub>12</sub>H<sub>22</sub>NO<sub>3</sub> [M + NH<sub>4</sub>]<sup>+</sup>, 228.1594; found, 228.1593.

**4.11. Umuravumbolide (1).** Ac<sub>2</sub>O (110  $\mu$ L, 1.2 mmol) and pyridine (95  $\mu$ L, 1.2 mmol) were added to a solution of **12** (123 mg, 0.58 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.2 mL) at rt. The reaction mixture was stirred at rt for 16 h and evaporated under reduced pressure. The residue was purified by flash column chromatography (80:20 hexanes/EtOAc) to afford **1** (146 mg, 0.58 mmol, quantitative yield) as a colorless oil.  $R_f$  (80:20 hexanes/EtOAc) 0.2;  $[\alpha]_D^{25} + 31.4$  (c 1.0, CHCl<sub>3</sub>) [lit.<sup>4</sup>  $[\alpha]_D^{25} + 30$  (c 2.1, CDCl<sub>3</sub>), lit.<sup>6b</sup>  $[\alpha]_D^{25} + 33.4$  (c 1, CHCl<sub>3</sub>), lit.<sup>6c</sup>  $[\alpha]_D^{25} + 28.6$  (c 0.9, CHCl<sub>3</sub>), lit.<sup>6e</sup>  $[\alpha]_D^{25} + 29$  (c 2.2, CHCl<sub>3</sub>)]; IR (ATR)  $\nu$ : 2956, 2932, 2862, 1717, 1371, 1230, 1149, 1019 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  6.88 (1H, ddd,  $J = 9.8, 6.0, 2.5$  Hz), 6.09–6.03 (1H, m), 5.73 (1H, ddd,  $J = 11.1, 8.2, 0.9$ ), 5.55 (1H, ddd,  $J = 11.1, 9.4, 1.1$  Hz), 5.45–5.39 (2H, m), 2.47 (1H, ddt,  $J = 18.3, 11.7, 2.6$  Hz), 2.29 (1H, dddd,  $J = 18.3, 5.9, 4.1, 1.0$  Hz), 2.04 (3H, s), 1.74–1.66 (1H, m), 1.57–1.48 (1H, m), 1.37–1.20 (4H, m), 0.90 (3H, t,  $J = 7.2$  Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>):  $\delta$  170.1 (C), 163.5 (C), 144.2 (CH), 131.7 (CH), 130.1 (CH), 121.7 (CH), 74.0 (CH), 69.4 (CH), 34.3 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 27.2 (CH<sub>2</sub>), 22.4 (CH<sub>2</sub>), 21.1 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>); HRMS (+ESI)  $m/z$ : calcd for C<sub>14</sub>H<sub>20</sub>NaO<sub>4</sub> [M + Na]<sup>+</sup>, 275.1254; found, 275.1253.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c02304>.

Summary of the synthesis; additional experimental procedures involving the preparation of starting materials; and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of reagents and products (PDF)

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### Notes

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## ■ DEDICATION

Dedicated to Professor Joan Bosch on the occasion of his 75th birthday.

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