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# Total Synthesis and Absolute Configuration of Curvularides A-E

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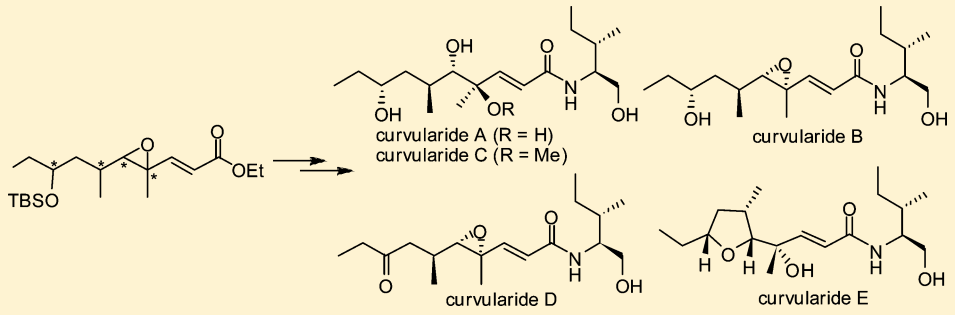
Supporting Information




**ABSTRACT:** The first total synthesis of curvularides A−E, isolated from a culture broth of the endophytic fungus *Curvularia geniculata*, is described. The divergent total synthesis reported herein confirmed the absolute configurations of curvularides A−E and supported that these natural products might be obtained from a common biosynthetic pathway. The key steps involved in the synthesis were the diastereoselective hydrogenation of *exo*-methylene-γ-butyrolactone to α-methyl-γ-butyrolactone, Sharpless kinetic resolution, Sharpless asymmetric epoxidations, and intramolecular and intermolecular epoxide openings.

## INTRODUCTION

Curvularides A−E (**1**−**5**) (Figure 1A), antifungal hybrid peptide−polyketides, were isolated from a culture broth of the endophytic fungus *Curvularia geniculata* CTOM11.[1] Structure elucidation was based on spectroscopic analysis, while the relative configurations of curvularides A and E were determined by X-ray crystallography. The absolute configuration of curvularide B at C8 position was determined as *R* by the Mosher method. However, the configuration of the epoxide group could not be unambiguously established. As curvularides A−E are closely related, they are expected to share the same biosynthetic pathway and stereochemistry.[1] Curvularide B is an epoxide derivative of curvularide A, while curvularide C is an *O*-methyl analogue. Curvularide D is a keto derivative of curvularide B. The tetrahydrofuran ring containing curvularide E is a derivative of curvularides A−D. They share structural similarities with coronatine and jasmonoyl-L-isoleucine, which are important phytohormones and signaling metabolites in plants[2,3] and contain 12-carbon polyketide conjugated with L-isoleucine or other amino acids. Curvularides are expected to play an ecological role by preventing phytopathogenic fungi from growing in plant hosts. Curvularide B exhibited antifungal activity against *Candida albicans* and showed synergistic activity along with fluconazole.[1]

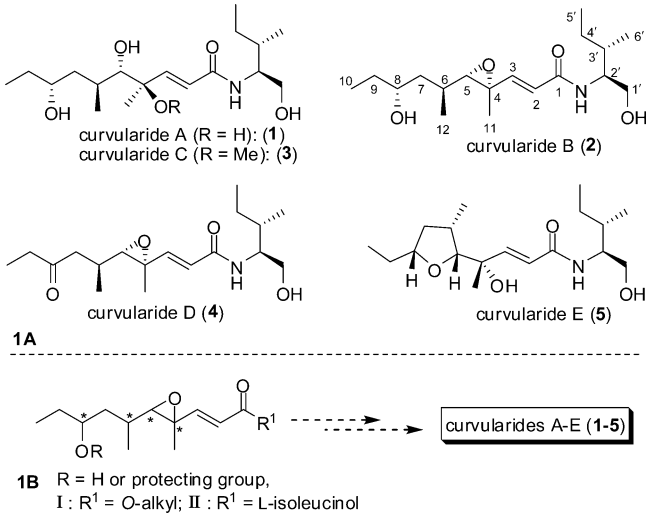



**Figure 1.** (A) Curvularides A−E (**1**−**5**). (B) Synthetic plan for curvularides.

We became interested in the total synthesis of curvularides because of their biological activities, structural complexity, and incompletely assigned epoxide stereochemistry of curvularides B (**2**) and D (**4**). From a biogenesis point of view, we hypothesized that curvularides A−E (**1**−**5**) could be obtained in a divergent manner if we were able to synthesize frameworks like the epoxy α,β-unsaturated ester **I** or the peptide−polyketide **II** (Figure 1B). The peptide−polyketide **II**, which is a planar structure of curvularide B, is expected to be formed by a peptide coupling reaction between the acid derived from **I** and L-isoleucinol. Curvularide B/**II** can be converted to other curvularides by appropriate transformations such as oxidation of secondary hydroxyl to provide D (**4**), intermolecular epoxide

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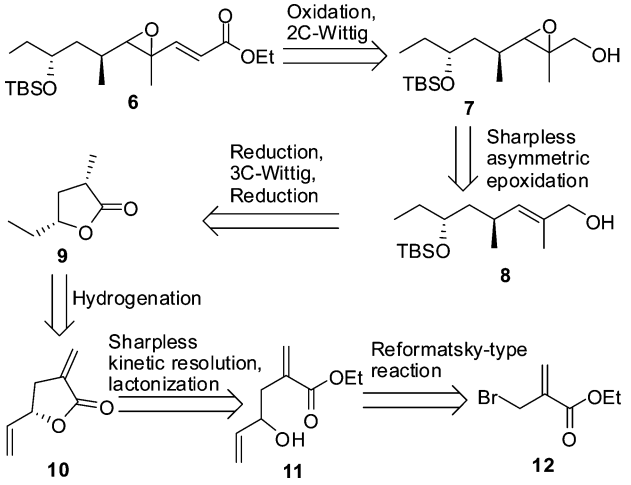
opening to provide A (**1**) and C (**3**), and intramolecular epoxide opening to provide E (**5**). Alternatively, these natural products can also be obtained from operating the above-mentioned transformations in **I**, followed by the late-stage peptide coupling with L-isoleucinol. Herein, we describe the first total synthesis and confirmation of the absolute configurations of curvularides A–E (Figure 1A) through a divergent synthetic approach.

## RESULTS AND DISCUSSION

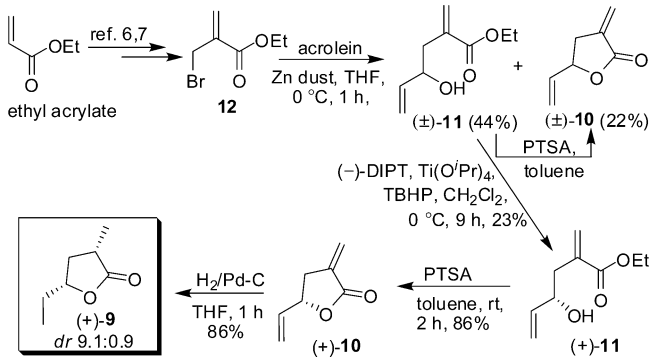
Based on the proposed relative and absolute configurations,[1] we envisioned that $\alpha,\beta$-unsaturated epoxy ester **6** (Scheme 1), in which the required epoxide can be installed, could be the suitable framework to deliver curvularides A–E with the necessary stereochemistry. As outlined in Scheme 1, **6** could be obtained from the epoxy alcohol **7** via oxidation of the primary hydroxyl and subsequent 2C-Wittig reaction. Depending upon the requisite epoxide stereochemistry, **7** should be easily accessed from allylic alcohol **8** by using Sharpless asymmetric epoxidation. The key intermediate **8** could be realized from $\gamma$-butyrolactone **9** by reduction, followed by 3C-Wittig reaction, protection, and further reduction. The lactone **9** was expected to be accessed diastereoselectively from hydrogenation of **10**, which, in turn, was planned from **11** by using Sharpless kinetic resolution followed by lactonization. Allylic alcohol **11** could be derived by reacting **12** with acrolein in Reformatsky-type reaction conditions.

**Scheme 1. Retrosynthetic Plan for 6**




The synthetic approach we planned for $\gamma$-butyrolactone **9** was based on the literature-reported[4,5] diastereoselective hydrogenation of the *exo*-methylene-$\gamma$-butyrolactone to $\alpha$-methyl-$\gamma$-butyrolactone. The synthesis of enantiomerically pure *exo*-methylene butyrolactone (+)-**10** was commenced from the MBH reaction between ethyl acrylate and formaldehyde.[6] Bromination of the resultant allylic alcohol afforded ethyl $\alpha$-bromomethylacrylate[7] (**12**) (Scheme 2), which under Reformatsky-type reaction conditions[8] with acrolein yielded allylic alcohol (±)-**11** and lactone (±)-**10** in a 2:1 ratio with a combined yield of 66%. It is interesting to note that the formation of allylic alcohol (±)-**11** was largely predominant (>95% by TLC) in the reaction mixture, but during the chromatographic purification, lactone (±)-**10** was developed in considerable amount. After column chromatographic separation, (±)-**11** was subjected to a Sharpless kinetic resolution to afford the enantiomerically pure (+)-**11** in 23% yield and 99% ee.[9] Treatment of (+)-**11** with PTSA in toluene resulted in (+)-**10** in 86% yield, whereas under the same reaction conditions, racemic (±)-**11** yielded (±)-**10**. Hydrogenation of the *exo*-methylene-$\gamma$-butyrolactone **10** in THF reduced the *exo*-methylene group as well as the terminal olefinic bonds, diastereoselectively furnishing $\alpha$-methyl-$\gamma$-butyrolactone **9** in 86% yield (dr 9.1:0.9, $^1$H NMR). Employing other solvents such as EtOH,[4,5] EtOAc, MeOH, and hexane ended up affording the desired product in lower yields due to the allylic C–O bond cleavage.

**Scheme 2. Synthesis of Lactone (+)-9**




The key fragment **6** can be accessed in an enantiomerically pure form from (+)-**9**, but due to the moderate yield at kinetic resolution step ((+)-**11**, 23%), we decided to proceed with the racemic lactone (±)-**9** and hoped to separate undesired isomer after the formation of diastereomers at the Sharpless asymmetric epoxidation step. To this end, lactone (±)-**9**, which was easily obtained diastereoselectively from (±)-**10** by hydrogenation, was reduced to its corresponding lactol and subsequently subjected to a 3C-Wittig reaction to afford $\alpha,\beta$-unsaturated ester[10] (±)-**13** (Scheme 3). After silyl ether protection, it was reduced to allylic alcohol (±)-**8**. Subsequent Sharpless asymmetric epoxidation furnished an inseparable diastereomeric mixture **7a** and **7b** (dr 1:1). Oxidation of the primary hydroxyl group of this diastereomeric mixture followed by 2C-Wittig reaction provided epoxy esters **6a** and **6b** (dr 1:1), which were subjected to silyl deprotection using[11−13] TBAF for 36 h, resulting in the chromatographically separable five-membered **14** and six-membered **15** along with the epoxy alcohol **16a** in the ratio of (4.1:1:5.2) and in 93% combined yield. Interestingly, the treatment of **6a** and **6b** (dr 1:1) with HF–pyridine in THF at 0 °C to rt gave the same results,[14] except that the **14** to **15** ratios (1:5.1) were reversed. Successful acetylation only on **15** to give **15a** indicated, after spectroscopic analysis, that **14** was tetrahydrofuran derivative and **15** was a tetrahydropyran derivative. At this stage, the isolation of an enantiomerically pure epoxy alcohol **16a** in 47% yield from 1:1 diastereomeric mixture of **6a** and **6b** suggested that only one of the diastereomers was preferentially involved in the formation of five-membered **14** and six-membered **15** in 46% combined yield. We considered that ester hydrolysis of **14** and subsequent coupling with L-isoleucinol would provide the peptide–polyketide framework, whose spectral data can be compared with the data of curvularide E (**5**). This comparison is expected to disclose the stereochemistry of epoxy alcohol from which five-membered and six-membered products resulted. Thus, **14** was subjected to an ester hydrolysis to furnish **17**, which was subsequently coupled with L-isoleucinol in the presence of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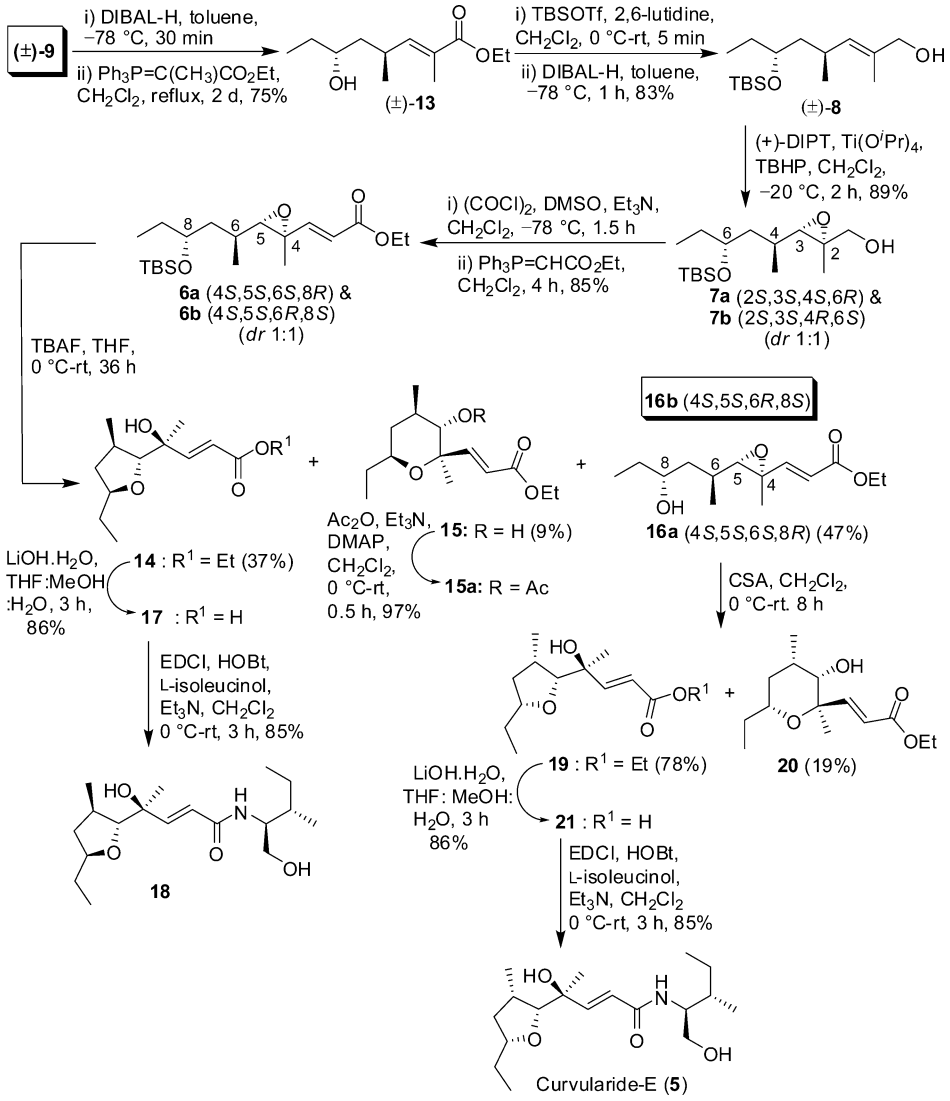
**Scheme 3. Synthesis of Compound 18 and Curvularide E (5)**




peptide coupling reagents to produce peptide−polyketide **18** in 73% yield in two steps. Divergence of $^{1}$H and $^{13}$C NMR data of **18** from curvularide E (**5**) revealed that **14** and **15** might have been obtained from the epoxy alcohol **16b**, which was not isolable in our hands. Thus, we expected that the stable epoxy alcohol **16a** should be with the required stereochemistry to deliver the curvularide E (**5**). Accordingly, **16a** was treated[11,12] with 0.2 equiv of CSA in $CH_2Cl_2$ at 0 °C to rt for 8 h to furnish chromatographically separable five-membered **19** and six-membered **20** in favor of the required one (4.1:0.9) in 97% combined yield. Finally, ester hydrolysis of **19** and subsequent coupling with L-isoleucinol gave the desired curvularide E (**5**) in 85% yield. The spectral data of the synthetic sample and optical rotation [$[\alpha]^{26}_{D}$ = −7.2 (*c* 0.48, $CHCl_3$); lit.[1] $[\alpha]^{28}_{D}$ = −7.8 (*c* 0.33, $CHCl_3$)] is identical with the data reported for the natural product.

As epoxide orientation in curvularide B and D was not conclusively defined,[1] we planned the synthesis of both enantiomerically pure epoxy esters **6a** and **6b**′ (Scheme 4) from allylic alcohol (−)-**8**, which was synthesized from lactone (+)-**9** via (+)-**13**. Accordingly, epoxy alcohols **7a** and **7b**′ were synthesized separately from (−)-**8** by using appropriate Sharpless asymmetric epoxidation conditions. Oxidation of the epoxy alcohols **7a** and **7b**′ resulted in the corresponding aldehydes, which were treated with the 2C-Wittig reagent to give *α*,*β*-unsaturated esters **6a** and **6b**′, respectively. Here, **6a** was treated with TBAF to achieve a silyl deprotected epoxy alcohol, which is identical in all respects with **16a**, obtained according to Scheme 3. This further confirmed the stereochemistry of epoxy alcohols **6a**, **16a** (4*S*,5*S*,6*S*,8*R*), and **16b** (4*S*,5*S*,6*R*,8*S*).

Ester hydrolysis of **6a** and **6b**′ gave the corresponding acids **22** and **23**, respectively. Coupling of L-isoleucinol with **22** and **23** gave corresponding peptide−polyketides **24** and **25**, respectively. Silyl deprotection of **24** provided the desired curvularide B (**2**) in 86% yield, matched $^{1}$H and $^{13}$C spectra and optical rotation [$[\alpha]^{26}_{D}$ = +11.3 (*c* 0.26, $CHCl_3$); lit.[1] $[\alpha]^{28}_{D}$ = +10.2 (*c* 0.43, $CHCl_3$)] with the natural product. The deprotection of **25**[15] yielded a mixture of five-membered **26** and six-membered **27** in 1:0.3 ratio with a combined yield of 79%.

For the synthesis of curvularide D (**4**), primary hydroxyl in **24** was acetylated to give **28**, which upon treatment with TBAF gave the epoxy alcohol **29** in 82% yield over two steps. The secondary hydroxyl of **29** was oxidized by using DMP[16,17] to produce acetyl derivative of curvularide D, finally acetyl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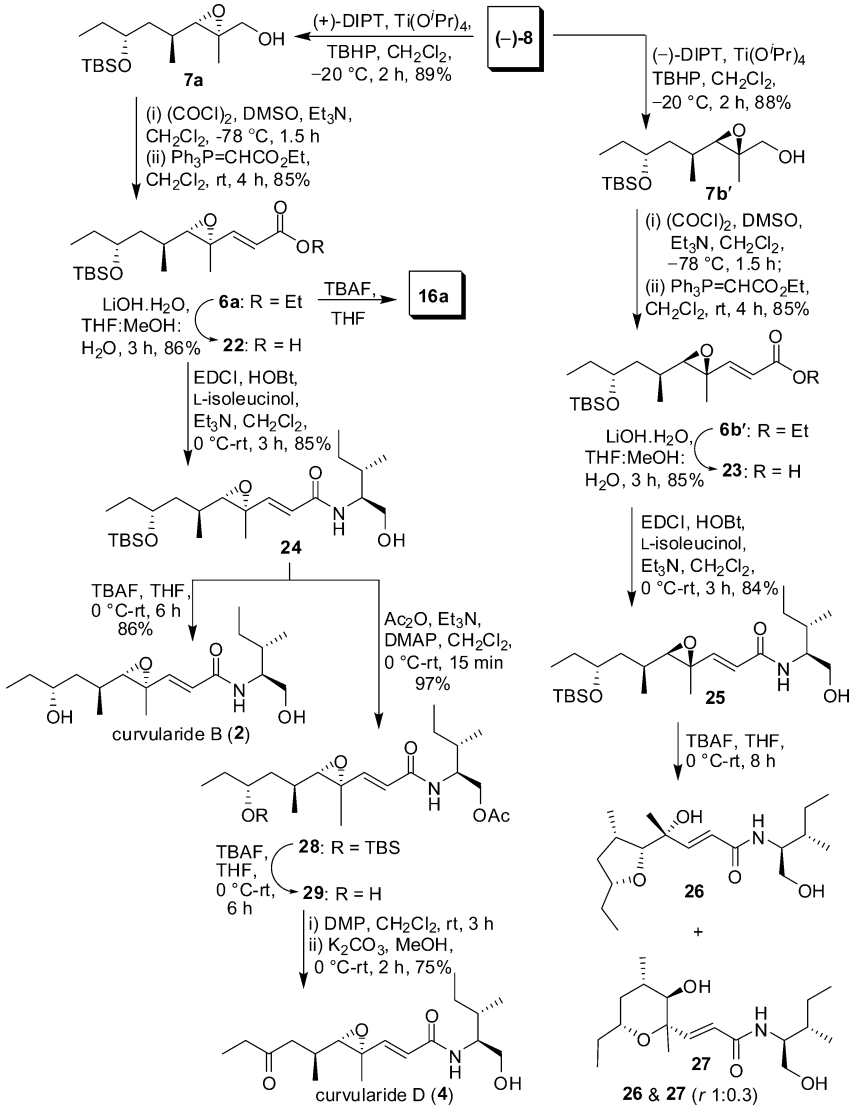
**Scheme 4. Synthesis of Curvularides B (2) and D (4)**




deprotection with $K_2CO_3$ in MeOH achieved the anticipated curvularide D (**4**) in 75% yield over two steps. The spectral data of synthetic curvularides D agree well with the natural product data.[18]

According to our strategy, the synthesis of curvularides A−E from a common intermediate, the next target became the synthesis of curvularides A and C from epoxy alcohol **16a**.[19] The secondary hydroxyl group in **16a** was protected as acetate **30** in excellent yield. After various attempts, **30** was treated with 0.2 equiv of TFA in a THF/$H_2O$ system (1:1)[20] to afford the desired diol **31** as major along with its inseparable diastereomer (dr 9.2:0.8, $^1$H NMR) in 77% yield. Subsequent ester hydrolysis followed by coupling with L-isoleucinol afforded curvularide A (**1**) in 69% yield in two steps (Scheme 5).

To get a curvularide C (**3**), intermolecular epoxide opening of **30** in MeOH in the presence of $BF_3$·$OEt_2$ afforded[21,22] the desired *O*-methylated tertiary hydroxyl derivative **33** as the major product along with its inseparable diastereomer (dr 9.3:0.7, $^1$H NMR) in 84% yield. Under basic hydrolysis conditions, **33** gave the corresponding secondary hydroxyl $\alpha,\beta$-unsaturated carboxylic acid **34** in 85% yield. Finally, coupling it with L-isoleucinol completed the total synthesis of curvularide C (**3**) in 84% yield. The data of synthesized curvularides A [$[\alpha]^{27}_D$ = −9.9 (*c* 0.15, $CHCl_3$); lit.[1] $[\alpha]^{27}_D$ = −9.3 (*c* 0.26, $CHCl_3$)] and C agree well with the data reported for natural products, except the difference in optical rotation of curvularide C [($[\alpha]^{27}_D$ = −42.9 (*c* 0.19, $CHCl_3$); lit.[1] $[\alpha]^{28}_D$ = −14.2 (*c* 0.32, $CHCl_3$)].

## ■ CONCLUSION

In conclusion, the first total synthesis of curvularides A−E was achieved through a divergent synthetic strategy, which supported a common biosynthetic pathway as well as confirmed the absolute configurations. The synthesis and biological activity of curvularide analogues are in progress in our laboratory and will be reported in due course.

## ■ EXPERIMENTAL SECTION

**Ethyl α-Bromomethylacrylate (12):.**[6,7] The formaldehyde (11.4 mL, 152.46 mmol) and ethyl acrylate (46.2 g, 462.0 mmol) were mixed with a 1:1 (v/v) mixture of 1,4-dioxane−water. To this was added 1,4-diazabicyclo[2.2.2]octane (17.1 g, 152.46 mmol), and the mixture was stirred for 36 h at rt. The mixture was diluted with ether (2 × 250 mL) and washed with $H_2O$ (150 mL). The organic phase was dried with $Na_2SO_4$, filtered, and concentrated under reduced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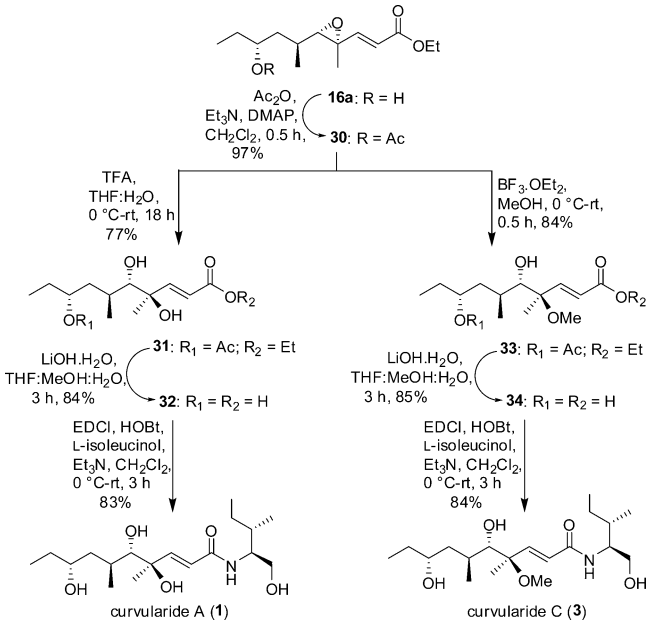
**Scheme 5. Synthesis of Curvularides A (1) and C (3)**




pressure. The residue was purified by silica gel column chromatography (12% EtOAc/hexane) to furnish ethyl 2-(hydroxymethyl)-acrylate as an oily liquid (45.79 g, 75%) ($R_f$ = 0.4, 20% EtOAc/hexanes).

To a stirred solution of ethyl $\alpha$-hydroxymethylacrylate (40 g, 307.69 mmol) in dry ether (650 mL) at −10 °C was added phosphorus(III) bromide (33.31 g, 123.08 mmol). The temperature was allowed to rise to 20 °C, and stirring was continued for 3 h. Water (150 mL) was added at −10 °C, and the reaction mixture was extracted with hexane (3 × 500 mL). The organic phase was washed with saturated NaCl solution, dried with $Na_2SO_4$, and filtered. The solvents were evaporated, and the residue was purified by column chromatography (2% EtOAc/hexanes) to furnish ethyl $\alpha$-bromomethylacrylate (**12**) (51.5 g, 87%) as a yellow oil: $R_f$ = 0.5, 5% EtOAc/hexanes; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.30 (s, 1H), 5.92 (s, 1H), 4.25 (q, $J$ = 7.1 Hz, 2H), 4.16 (s, 2H), 1.30 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.5, 137.3, 128.6, 61.0, 29.2, 13.9; IR (neat) $\nu_{max}$ 3566, 2921, 2852, 1741, 1693, 1647, 1531,1463, 1396, 772 cm$^{-1}$.

**Ethyl 4-Hydroxy-2-methylenehex-5-enoate ((±)-11).** To ice-cooled activated zinc (20.31 g, 312.5 mmol) was added a few drops of $\alpha$-bromomethylacrylate (**12**) under nitrogen. The suspension was stirred, and the rest of the ester **12** (30.0 g, 156.25 mmol), dissolved in THF (500 mL), was added slowly. After the mixture was stirred for 1 h, acrolein (31.28 mL, 468.75 mmol), dissolved in THF (435 mL), was added slowly, and the mixture was allowed to stir for 5 min at 0 °C. The mixture was diluted with a saturated $NH_4Cl$ solution, filtered, and extracted with EtOAc (2 × 1 L). The combined organic layers were washed with $H_2O$ and brine, dried with $Na_2SO_4$, filtered, and concentrated. Purification of residue by flash column chromatography over silica gel (10% EtOAc/hexanes) afforded allylic alcohol (±)-**11** (11.69 g, 44%) as a slightly yellow oil ($R_f$ = 0.4, 20% EtOAc/hexanes) and lactone (±)-**10** (4.3 g, 22%) as a light yellow oil ($R_f$ = 0.5, 20% EtOAc/hexanes).

***(S)*-Ethyl 4-Hydroxy-2-methylenehex-5-enoate ((+)-11).** To a suspension of activated powdered 4 Å molecular sieves (300 mg) in $CH_2Cl_2$ (10 mL) were added $Ti(O^iPr)_4$ (1.75 mL, 5.882 mmol) and (−)-DIPT (1.48 mL, 7.058 mmol) sequentially at 0 °C. After being stirred for 30 min, TBHP (3.5 mL, 3.7 M in toluene) was added and stirring continued for another 0.5 h at the same temperature. To the above solution was added compound (±)-**11** (1.0 g, 5.882 mmol) in $CH_2Cl_2$ (8 mL) and the mixture stirred for 9 h at 0 °C. The reaction mixture was quenched with $H_2O$, stirred for 2 h at rt, and filtered. The solvent was removed under reduced pressure; the compound was extracted with EtOAc (2 × 50 mL), washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (12% EtOAc/hexanes) to afford (+)-**11** (230 mg, 23%) as a light yellow oil: $R_f$ = 0.4, 20% EtOAc/hexanes; $[\alpha]^{25}_D$ = +25.1 ($c$ 0.37, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.21 (s, 1H), 5.83 (m, 1H), 5.63 (s, 1H), 5.22 (d, $J$ = 17.0 Hz, 1H), 5.02 (d, $J$ = 10.4 Hz, 1H), 4.24 (m, 1H), 4.20 (q, $J$ = 7.1 Hz, 2H), 2.58 (dd, $J$ = 13.8, 4.5 Hz, 1H), 2.44 (dd, $J$ = 13.8, 8.1 Hz), 2.41 (m, 1H), 1.30 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 167.1, 139.9, 136.6, 127.5, 114.2, 71.1, 60.5, 39.6, 13.7; IR (neat) $\nu_{max}$ 3476, 2982, 1712, 1299, 1152, 1027, 946, 815 cm$^{-1}$; HRMS (ESI) calcd for $C_9H_{14}O_3Na$ [M + Na]$^+$ 193.0835, found 193.0834.

***(S)*-3-Methylene-5-vinyldihydrofuran-2(3*H*)-one ((+)-10).** To a stirred solution of alcohol (+)-**11** (230 mg, 1.352 mmol) in toluene (4 mL) at rt was added $p$-toluenesulfonic acid (23.25 mg, 0.135 mmol) and the reaction mixture allowed to stir at rt for 2 h. The reaction mixture was quenched by the addition of $H_2O$ and extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/hexane) to furnish (+)-**10** (144 mg, 86%) as a light yellow oil: $R_f$ = 0.5, 20% EtOAc/hexanes; $[\alpha]^{25}_D$ = +47.6 ($c$ 0.52, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.16 (t, $J$ = 2.4 Hz, 1H), 5.83 (m, 1H), 5.59 (t, $J$ = 2.4 Hz, 1H), 5.33 (d, $J$ = 17.1 Hz, 1H), 5.21 (d, $J$ = 10.4 Hz, 1H), 4.89 (q, $J$ = 6.6 Hz, 1H), 3.11 (ddt, $J$ = 17.0, 8.1, 2.4 Hz, 1H), 2.65 (dm, $J$ = 17.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 169.6, 135.5, 133.6, 121.8, 117.2, 76.9, 33.3; IR (neat) $\nu_{max}$ 2921, 2854, 1758, 1661, 1424, 1320, 1263, 985, 938, 753 cm$^{-1}$; HRMS (ESI) calcd for $C_7H_9O_2$ [M + H]$^+$ 125.0597, found 125.0597.

***(3S,5R)*-5-Ethyl-3-methyldihydrofuran-2(3*H*)-one ((+)-9).** A solution of lactone (+)-**10** (144 mg, 1.161 mmol) in THF (12 mL) was hydrogenated at 1 atmospheric balloon pressure in the presence of a catalytic amount of 10% Pd/C (14.4 mg) for 1 h. The mixture was then filtered through a pad of Celite, washed with EtOAc (50 mL), evaporated, and purified by column chromatography (8% EtOAc/hexane) to give a saturated *syn* product (+)-**9** (128 mg (dr 9.1:0.9), 86%) as an oily liquid: $R_f$ = 0.6, 20% EtOAc/hexanes; $[\alpha]^{25}_D$ = +10.0 ($c$ 0.26, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.21 (m, 1H), 2.58 (m, 1H), 2.43 (ddd, $J$ = 12.0, 8.3, 5.2 Hz, 1H), 1.72 (m, 1H), 1.61 (m, 1H), 1.44 (m, 1H), 1.22 (d, $J$ = 6.8 Hz, 3H), 0.98 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 179.5, 79.7, 36.7, 35.8, 28.3, 15.0, 9.3; IR (neat) $\nu_{max}$ 2920, 2852, 1741, 1462 cm$^{-1}$; HRMS (ESI) calcd for $C_7H_{13}O_2$ [M + H]$^+$ 129.0910, found 129.0912.

***(E)*-Ethyl-6-hydroxy-2,4-dimethyloct-2-enoate ((±)-13).** To a solution of saturated lactone (±)-**9** (1.1 g, 8.59 mmol) in toluene (42 mL) at −78 °C was added DIBAL-H (9.45 mL, 9.45 mmol). The reaction mixture was stirred for 1 h at that temperature and was quenched by the addition of methanol (1.73 mL). The reaction mixture was then allowed to rt and diluted with EtOAc (20 mL), a saturated solution of sodium potassium tartarate (24 mL) was added, and the mixture was stirred for 1 h. The compound was filtered, extracted with EtOAc (150 mL), washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Column chromatography purification (10% EtOAc/hexanes) afforded lactol (0.945 g) as a colorless oil ($R_f$ = 0.5, 20% EtOAc/hexanes), which was used in the next step without any characterization.

To a solution of lactol (0.945 g, 7.27 mmol) in $CH_2Cl_2$ (36 mL) was added (carbethoxyethylidene)triphenylphosphorane (13.19 g, 36.35 mmol). The reaction mixture was then allowed to reflux for 2 days. The reaction mixture was cooled to rt, filtered, and concentrated in vacuo. The residue was purified by column chromatography (8% EtOAc/hexane) to furnish (±)-**13** (1.38 g, 75%) as a colorless oil ($R_f$ = 0.6, 20% EtOAc/hexanes).

**General Procedure for TBS Protection.** To a stirred solution of secondary alcohol **13** (1.36 g, 6.36 mmol) in dry $CH_2Cl_2$ (30 mL) at 0 °C was added 2,6-lutidine (2.22 mL, 19.08 mmol) and the mixture allowed to stir for 5 min. Then TBSOTf (2.48 mL, 10.81 mmol) was added dropwise at the same temperature. After the starting material disappeared on TLC, the reaction mixture was quenched with $H_2O$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and extracted with EtOAc (100 mL). The organic layer was washed with brine, dried over $Na_2SO_4$, filtered, concentrated in vacuo, and purified by column chromatography (4% EtOAc/hexanes) to yield TBS ether of **13** (2.01 g, 96%) as a colorless oil: $R_f$ = 0.6, 10% EtOAc/hexanes.

**General Procedure for the Reduction of Ester to Alcohol.** To a solution of TBS ether of **13** (2.0 g, 6.1 mmol) in toluene (30 mL) at −78 °C was added DIBAL-H (12.2 mL, 12.20 mmol). The reaction mixture was stirred for 1 h at that temperature and quenched by the addition of methanol (1.2 mL). The reaction mixture was then allowed to rt and diluted with EtOAc (50 mL), a saturated solution of sodium potassium tartarate was added (17 mL), and the mixture was stirred for 1 h and filtered. The compound was extracted with EtOAc (150 mL), washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (14% EtOAc/hexanes) to afford allylic alcohol **8** (1.52 g, 87%) as a colorless oil: $R_f$ = 0.3, 20% EtOAc/hexanes.

**General Procedure for Sharpless Asymmetric Epoxidation To Give 7.** To a suspension of activated powdered 4 Å molecular sieves (0.5 g) in $CH_2Cl_2$ (12 mL) were added sequentially $Ti(O^iPr)_4$ (1.56 mL, 5.24 mmol) and (+)-DIPT or (−)-DIPT (1.22 mL, 6.28 mmol) at −20 °C. After the mixture was stirred for 30 min, TBHP (3.12 mL, 11.53 mmol, 3.7 M in toluene) was added and stirring continued for another 0.5 h at the same temperature. To the above solution was added allylic alcohol **8** (1.5 g, 5.24 mmol) in $CH_2Cl_2$ (15 mL) and the mixture stirred for 1 h at −20 °C. The reaction mixture was quenched with $H_2O$, allowed to warm to rt, and stirred for 1 h. After the mixture was recooled to 0 °C, a solution of NaOH (30% w/v) in saturated NaCl was added and the mixture stirred at 0 °C for 1 h. After filtration, solvent was removed under reduced pressure, extracted with EtOAc (2 × 100 mL), washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (16% EtOAc/hexanes) to afford **7** (1.41 g, 89%) as a colorless oil ($R_f$ = 0.3, 25% EtOAc/hexanes).

**General Procedure for Swern Oxidation and 2C-Wittig Reaction To Give 6.** Oxalyl chloride (0.81 mL, 9.28 mmol) in dry $CH_2Cl_2$ (20 mL) was cooled to −78 °C under nitrogen atmosphere. Dimethyl sulfoxide (1.31 mL, 18.56 mmol) was added dropwise. After 15 min, epoxy alcohol **7** (1.4 g, 4.64 mmol) in dry $CH_2Cl_2$ (20 mL) was added to the reaction mixture via cannula and stirred for 30 min at −78 °C. Then $Et_3N$ (3.23 mL, 23.2 mmol) was added and the mixture stirred for 15 min. Further reaction was carried out at 0 °C. The solvent was concentrated, extracted with EtOAc (2 × 100 mL), and washed with $H_2O$ and brine, and the organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (4% EtOAc/hexanes) to afford aldehyde (1.24 g, 89%) as a colorless oil: $R_f$ = 0.6, 10% EtOAc/hexanes.

To a solution of aldehyde (1.23 g, 4.1 mmol) in $CH_2Cl_2$ (20 mL) was added (carbethoxymethylene)triphenylphosphorane (2.86 g, 8.2 mmol). The reaction mixture was stirred for 4 h at rt. After completion of the reaction, the solvent was evaporated under reduced pressure. The residue was filtered and purified by column chromatography (5% EtOAc/hexane) to furnish **6** (1.45 g, 95%) as a colorless oil ($R_f$ = 0.6, 10% EtOAc/hexanes).

**General Procedure for TBS Deprotection.** A solution of $Bu_4NF$ (0.36 mL, 0.362 mmol, 1 M solution in THF) was added dropwise to a solution of TBS ether compound (80 mg, 0.181 mmol) in THF (1 mL) at rt, and the reaction mixture was stirred at this temperature until completion of the starting material. Then $H_2O$ was added, the mixture was stirred for 20 min, and THF was removed under reduced pressure. The remaining aqueous phase was extracted with EtOAc (25 mL) and washed with brine, and the organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexanes) to afford TBS-deprotected compound (51 mg, 86%).

**Synthesis of Compounds 14, 15, and 16a.** By following the general procedure described for TBS deprotection, compound **14** (103 mg, 37%) as a light yellow oil, **15** (26 mg, 9%) as a light yellow oil, and **16a** (131 mg, 47%) as a colorless oil were prepared from **6a** and **6b** (400 mg, 1.081 mmol).

*(S,E)-Ethyl 4-((2R,3R,5S)-5-Ethyl-3-methyltetrahydrofuran-2-yl)-4-hydroxypent-2-enoate (**14**).* $R_f$ = 0.6, 20% EtOAc/hexanes. $[\alpha]^{25}_D$ = +26.5 (*c* 1.05, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.86 (d, *J* = 15.6 Hz, 1H), 6.08 (d, *J* = 15.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.79 (m, 1H), 3.41 (d, *J* = 7.7 Hz, 1H), 2.33 (br s, 1H), 2.17 (m, 1H), 1.60 (m, 1H), 1.44 (m, 1H), 1.33 (s, 3H), 1.33−1.17 (m, 2H), 1.02 (d, *J* = 6.0 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.6, 149.9, 119.7, 90.1, 81.2, 74.5, 60.2, 41.8, 34.5, 28.7, 25.4, 19.0, 14.2, 10.1. IR (neat): $\nu_{max}$ 3380, 2972, 2661, 1712, 1623, 1459, 1371, 1303, 1103, 1035 cm$^{-1}$. HRMS (ESI): calcd for $C_{14}H_{24}O_4Na$ $[M + Na]^+$ 279.1566, found 279.1566.

*(E)-Ethyl-3-((2R,3S,4R,6S)-6-Ethyl-3-hydroxy-2,4-dimethyltetrahydro-2H-pyran-2-yl)acrylate (**15**).* $R_f$ = 0.5, 10% EtOAc/hexanes. $[\alpha]^{25}_D$ = −45.8 (*c* 0.48, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.11 (d, *J* = 15.8 Hz, 1H), 6.02 (d, *J* = 15.8 Hz, 1H), 4.18 (q, *J* = 7.5 Hz, 2H), 3.51 (m, 1H), 3.01 (d, *J* = 9.8 Hz, 1H), 2.03 (br s, 1H), 1.77 (m, 1H), 1.66 (m, 1H), 1.55−1.36 (m, 2H), 1.30 (m, 1H), 1.28 (s, 3H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 167.2, 152.8, 118.9, 78.0, 76.2, 70.8, 60.3, 39.2, 32.3, 28.8, 18.4, 15.5, 14.2, 9.9. IR (neat): $\nu_{max}$ 3375, 1623, 1460, 1372, 1303, 1059, 988 cm$^{-1}$. HRMS (ESI): calcd for $C_{14}H_{24}O_4Na$ $[M + Na]^+$ 279.1566, found 279.1562.

*(E)-Ethyl-3-((2S,3S)-3-((2S,4R)-4-hydroxyhexan-2-yl)-2-methyloxiran-2-yl)acrylate (**16a**).* $R_f$ = 0.4, 20% EtOAc/hexanes. $[\alpha]^{25}_D$ = +36.2 (*c* 0.56, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.76 (d, *J* = 16.0 Hz, 1H), 6.01 (d, *J* = 16.0 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.65 (m, 1H), 2.64 (d, *J* = 9.0 Hz, 1H), 1.94 (brs, 1H), 1.72−1.62 (m, 2H), 1.55−1.44 (m, 3H), 1.48 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 6.0 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.0, 149.4, 121.4, 71.0, 70.7, 60.4, 59.5, 42.4, 30.8, 30.7, 16.5, 15.1, 14.1, 9.85. IR (neat): $\nu_{max}$ 3387, 2963, 2930, 1716, 1651, 1457, 1367, 1035, 978 cm$^{-1}$. HRMS (ESI): calcd for $C_{14}H_{24}O_4Na$ $[M + Na]^+$ 279.1566, found 279.1564.

**General Procedure for Acetylation.** To a solution of primary or secondary hydroxyl compound (80 mg, 0.312 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C were added $Ac_2O$ (0.029 mL, 0.312 mmol), $Et_3N$ (0.087 mL, 0.624 mmol), and DMAP (cat amount), and the mixture was stirred for 30 min. After completion of the reaction, $H_2O$ was added and the mixture stirred for 10 min. The residue was extracted with EtOAc (50 mL) and washed with water and brine, and the organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane) to furnish acetylated product (90.5 mg, 97%).

*(E)-Ethyl 3-((2R,3S,4R,6S)-3-Acetoxy-6-ethyl-2,4-dimethyltetrahydro-2H-pyran-2-yl)acrylate (**15a**).* By following the general procedure described for acetylation, acetate **15a** (17 mg, 97%) as a colorless oil was prepared from compound **15** (15 mg, 0.058 mmol). $R_f$ = 0.4, 10% EtOAc/hexanes). $[\alpha]^{25}_D$ = −34.9 (*c* 0.81, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.74 (d, *J* = 15.8 Hz, 1H), 5.98 (d, *J* = 15.8 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.54 (m, 1H), 2.09 (s, 3H), 1.92 (m, 1H), 1.72 (ddd, *J* = 12.8, 4.5, 2.2 Hz, 1H), 1.57−1.38 (m, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H). IR (neat): $\nu_{max}$ 3620, 2967, 2933, 1741, 1721, 1516, 1462, 1371, 1274, 1036, 987, 724 cm$^{-1}$. HRMS (ESI): calcd for $C_{16}H_{26}O_5Na$ $[M + Na]^+$ 321.1672, found 321.1670.

**General Procedure for Ester Hydrolysis.** To the ester compound (300 mg, 1.171 mmol) in THF/MeOH/$H_2O$ (3:1:1, 5 mL) at 0 °C was added $LiOH·H_2O$ (196.5 mg, 4.684 mmol), and the reaction was allowed to stir for 3 h. The reaction mixture was acidified to pH 2 with 1 N HCl, the residue was extracted with EtOAc (50 mL) and washed with $H_2O$ and brine, and the organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane) to furnish the acid (230 mg, 86%).

*(S,E)-4-((2R,3R,5S)-5-Ethyl-3-methyltetrahydrofuran-2-yl)-4-hydroxypent-2-enoic Acid (**17**).* By following the general procedure described for ester hydrolysis, acid **17** (230 mg, 86%) as a white amorphous solid was prepared from ester **14** (300 mg, 1.171 mmol).


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$R_f$ = 0.4 (40% EtOAc/hexanes). Mp: 84−86 °C. $[\alpha]^{24}_D$ = +21.5 (*c* 0.72, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.99 (d, *J* = 15.8 Hz, 1H), 6.12 (d, *J* = 15.8 Hz, 1H), 3.82 (m, 1H), 3.44 (d, *J* = 7.9 Hz, 1H), 2.25−2.13 (m, 2H), 1.62 (m, 1H), 1.46 (m, 1H), 1.35 (s, 3H), 1.23 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.5, 152.3, 119.1, 90.0, 81.4, 74.6, 41.7, 34.6, 28.6, 25.3, 18.9, 10.1. IR (neat): $\nu_{max}$ 3379, 2970, 1624, 1459, 1415, 1382, 1302, 1103, 1036 $cm^{-1}$. HRMS (ESI): calcd for $C_{12}H_{20}O_4Na$ $[M + Na]^+$ 251.1253, found 251.1250.

**General Procedure for Peptide Coupling.** To a stirred solution of the acid (50 mg, 0.219 mmol) in $CH_2Cl_2$ (1 mL) were added EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) (83.9 mg, 0.438 mmol) and HOBt (hydroxybenzotriazole) (59.18 mg, 0.438 mmol) at 0 °C, and the mixture was stirred for 10 min. To this reaction mixture was added L-isolucinol (30.8 mg, 0.263 mmol) followed by $Et_3N$ (0.183 mL, 1.314 mmol). Then the reaction mixture was allowed to stir for 3 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with 1 N HCl, aq saturated $NaHCO_3$, and brine. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexanes) to afford peptide−polyketide (61 mg, 85%).

*(S,E)-4-((2R,3R,5S)-5-Ethyl-3-methyltetrahydrofuran-2-yl)-4-hydroxy-N-((2S,3S)-1-hydroxy-3-methylpentan-2-yl)pent-2-enamide (**18**).* By following the general procedure described for peptide coupling, compound **18** (61 mg, 85%) as a white amorphous solid was prepared from acid **17** (50 mg, 0.219 mmol). $R_f$ = 0.3, 50% EtOAc/hexanes). Mp: 121−123 °C. $[\alpha]^{24}_D$ = −23.7 (*c* 0.24, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.87 (d, *J* = 15.0 Hz, 1H), 6.14 (d, *J* = 15.0 Hz, 1H), 6.06 (d, *J* = 7.0 Hz, 1H), 3.87 (m, 1H), 3.80 (m, 1H), 3.74 (dd, *J* = 11.0 Hz, 3.0 Hz, 1H), 3.68 (dd, *J* = 11.0 Hz, 6.0 Hz, 1H), 3.46 (d, *J* = 7.0 Hz, 1H), 2.80 (brs, 1H), 2.23−2.09 (m, 2H), 1.66 (m, 1H), 1.61 (m, 1H), 1.50 (m, 1H), 1.44 (m, 1H), 1.32 (s, 3H), 1.27−1.10 (m, 2H), 1.02 (d, *J* = 6.0 Hz, 3H), 0.93 (d, *J* = 6.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 166.5, 146.3, 121.7, 90.2, 81.2, 74.8, 63.5, 56.1, 41.7, 35.8, 34.6, 28.7, 25.6, 25.5, 19.1, 15.4, 11.3, 10.1. IR (neat): $\nu_{max}$ 3371, 3060, 2930, 1624, 1578, 1450, 1382, 1283, 1039 $cm^{-1}$. HRMS (ESI): calcd for $C_{18}H_{33}O_4NNa$ $[M + Na]^+$ 350.2301, found 350.2296.

*(S,E)-Ethyl 4-((2R,3S,5R)-5Ethyl-3-methyltetrahydrofuran-2-yl)-4-hydroxypent-2-enoate (**19**).* To a stirred solution of compound **16a** (100 mg, 0.390 mmol) in $CH_2Cl_2$ (2 mL) was added 10-camphorsulfonic acid (18.11 mg, 0.078 mmol) at 0 °C, and the resulting solution was stirred at rt for 8 h. Then the reaction mixture was quenched with aq $Na_2CO_3$, extracted with EtOAc (50 mL), washed with brine, dried over $Na_2SO_4$, filtered, evaporated, and purified by using silica gel column chromatography (8% EtOAc/hexanes) to furnish **19** (78 mg, 78%) as a colorless oil ($R_f$ = 0.6, 20% EtOAc/hexanes) and compound **20** (19 mg, 19%) as a colorless oil ($R_f$ = 0.4, 20% EtOAc/hexanes). Data for **19**. $[\alpha]^{24}_D$ = +12.3 (*c* 0.98, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.94 (d, *J* = 15.8 Hz, 1H), 6.07 (d, *J* = 15.8 Hz, 1H), 4.18 (q, *J* = 6.9 Hz, 2H), 3.74 (m, 1H), 3.67 (d, *J* = 6.9 Hz, 1H), 2.38−2.28 (m, 2H), 2.11 (m, 1H), 1.65 (m, 1H), 1.51 (m, 1H), 1.35 (s, 3H), 1.31 (t, *J* = 6.9 Hz, 3H), 1.24 (m, 1H), 1.04 (d, *J* = 7.9 Hz, 3H), 0.95 (t, *J* = 6.9 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 166.7, 150.7, 119.5, 85.3, 79.4, 74.2, 60.2, 40.0, 35.7, 29.0, 27.4, 16.6, 14.1, 10.5. IR (neat): $\nu_{max}$ 3380, 2977, 2934, 1712, 1623, 1460, 1373, 1300, 1278, 1182, 1033, 870 $cm^{-1}$. HRMS (ESI): calcd for $C_{14}H_{24}O_4Na$ $[M + Na]^+$ 279.1566, found 279.1562.

*(E)-Ethyl 3-((2R,3S,4S,6R)-6-Ethyl-3-hydroxy-2,4-dimethyltetrahydro-2H-pyran-2-yl)acrylate (**20**).* $[\alpha]^{24}_D$ = +12.5 (*c* 0.87, $CHCl_3$). NMR (300 MHz, $CDCl_3$): $\delta$ 6.88 (d, *J* = 15.8 Hz, 1H), 5.86 (d, *J* = 15.8 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.35 (brs, 1H), 1.79 (m, 1H), 1.60−1.39 (m, 2H), 1.33 (t, *J* = 6.7 Hz, 3H), 1.31 (s, 3H), 1.15 (m, 1H), 0.99 (d, *J* = 6.0 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 166.3, 150.9, 121.0, 78.2, 73.4, 73.0, 60.6, 32.3, 31.2, 29.0, 26.2, 18.2, 14.2, 9.8. IR (neat): $\nu_{max}$ 3609, 2963, 2929, 2874, 1709, 1648, 1531, 1461, 1394, 1284, 1031, 989, 865, 658 $cm^{-1}$. HRMS (ESI): calcd for $C_{14}H_{24}O_4Na$ $[M + Na]^+$ 279.1566, found 279.1561.

*(S,E)-4-((2R,3S,5R)-5-Ethyl-3-methyltetrahydrofuran-2-yl)-4-hydroxypent-2-enoic Acid (**21**).* By following the general procedure described for ester hydrolysis, acid **21** (92 mg, 86%) as a white amorphous solid was prepared from ester **19** (120 mg, 0.468 mmol). $R_f$ = 0.4, 40% EtOAc/hexanes. Mp = 80 °C. $[\alpha]^{24}_D$ = −1.1 (*c* 0.27, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.07 (d, *J* = 15.8 Hz, 1H), 6.11 (d, *J* = 15.8 Hz, 1H), 3.76 (m, 1H), 3.71 (d, *J* = 6.9 Hz, 1H), 2.34 (m, 1H), 2.12 (td, *J* = 12.8, 6.9 Hz, 1H), 1.67 (m, 1H), 1.52 (m, 1H), 1.37 (s, 3H), 1.26 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.7, 153.3, 119.0, 85.4, 79.6, 74.4, 40.0, 35.8, 29.0, 27.3, 16.6, 10.5. IR (neat): $\nu_{max}$ 3443, 2930, 2871, 1699, 1379, 1287, 1173, 1029, 991, 858, 774 $cm^{-1}$. HRMS (ESI) calcd for $C_{12}H_{20}O_4Na$ $[M + Na]^+$ 251.1253, found 251.1250.

*Curvularide E (**5**).* By following the general procedure described for peptide coupling, curvularide E (**5**) (76 mg, 85%) as a white solid was prepared from acid **21** (62 mg, 0.271 mmol). $R_f$ = 0.3, 50% EtOAc/hexanes). Mp: 118−120 °C. $[\alpha]^{26}_D$ = −7.2 (*c* 0.48, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.92 (d, *J* = 15.0 Hz, 1H), 6.26 (d, *J* = 9.0 Hz, 1H), 6.18 (d, *J* = 15.0 Hz, 1H), 3.89 (m, 1H), 3.76 (m, 1H), 3.82−3.68 (m, 3H), 3.72 (d, *J* = 7.0 Hz, 1H), 2.87 (brs, 1H), 2.38 (m, 1H), 2.18 (td, *J* = 12.0. 7.0 Hz, 1H), 1.76−1.66 (m, 2H), 1.61−1.51 (m, 2H), 1.40 (s, 3H), 1.28 (m, 1H), 1.22 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 1.0 (t, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.0 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 166.7, 146.8, 121.7, 85.4, 79.5, 74.5, 63.2, 56.0, 40.0, 35.7, 35.6, 29.2, 27.6, 25.6, 16.9, 15.5, 11.4, 10.6. IR (neat): $\nu_{max}$ 3339, 3238, 3065, 2960, 2930, 2873, 1669, 1625, 1575, 1457, 1381, 1279, 1074, 1022, 985, 703 $cm^{-1}$. HRMS (ESI): calcd for $C_{18}H_{33}O_4NNa$ $[M + Na]^+$ 350.2301, found 350.2296.

*(4S,6R,E)-Ethyl 6-Hydroxy-2,4-dimethyloct-2-enoate ((+)-**13**).* Compound (+)- **13** (628 mg, 75%) as a colorless oil was prepared from saturated lactone (+)-**9** (500 mg, 3.906 mmol). $R_f$ = 0.6, 20% EtOAc/hexanes. $[\alpha]^{26}_D$ = +3.8 (*c* 0.18, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.59 (d, *J* = 9.0 Hz, 1H), 4.17 (q, *J* = 6.7 Hz, 2H), 3.54 (m, 1H), 2.70 (m, 1H), 1.84 (s, 3H), 1.56 - 1.34 (m, 4H), 1.28 (t, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 168.3, 147.5, 126.0, 71.0, 60.4, 43.6, 30.3, 30.0, 19.4, 14.1, 12.2, 9.7. IR (neat): $\nu_{max}$ 3620, 2962, 2925, 2855, 1741, 1707, 1516, 1462, 1267, 1095, 750 $cm^{-1}$. HRMS (ESI): calcd for $C_{12}H_{22}O_3Na$ $[M + Na]^+$ 237.1461, found 237.1457.

*TBS Ether of (+)-**13**.* By following the general procedure described for TBS protection, TBS ether of (+)-**13** (884 mg, 96%) as a colorless oil was prepared from compound (+)-**13** (600 mg, 2.803 mmol). $R_f$ = 0.6, 10% EtOAc/hexanes. $[\alpha]^{26}_D$ = +1.2 (*c* 0.40, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.52 (dq, *J* = 10.1, 1.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.56 (p, *J* = 5.8 Hz, 1H), 2.61 (m, 1H), 1.82 (d, *J* = 1.5 Hz, 3H), 1.53−1.37 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.0 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.86 (t, *J* = 7.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 168.4, 147.9, 125.9, 71.0, 60.3, 43.4, 29.8, 29.5, 25.8, 19.6, 18.0, 14.2, 12.3, 9.3, −4.3, −4.6. IR (neat): $\nu_{max}$ 2928, 2857, 1712, 1462, 1368, 1255, 1052, 834, 774 $cm^{-1}$. HRMS (ESI): calcd for $C_{18}H_{36}O_3SiNa$ $[M + Na]^+$ 351.2325, found 351.2321.

*(4S,6R,E)-6-(tert-Butyldimethylsilyloxy)-2,4-dimethyloct-2-en-1-ol ((−)-**8**).* By following the general procedure described for a reduction of ester to alcohol, allylic alcohol (−)-**8** (608 mg, 87%) as a colorless oil was prepared from the TBS ether of (+)-**13** (800 mg, 2.439 mmol). $R_f$ = 0.3, 20% EtOAc/hexanes. $[\alpha]^{26}_D$ = −26.0 (*c* 0.20, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.21 (d, *J* = 9.4 Hz, 1H), 3.99 (s, 2H), 3.56 (m, 1H), 2.50 (m,1H), 1.66 (s, 3H), 1.48 (m, 1H), 1.42−1.32 (m, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.04 (d, *J* = 4.6 Hz, 6H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 132.9, 71.2, 69.0, 44.3, 29.9, 28.3, 25.8, 20.6, 18.1, 13.7, 9.3, −4.2, −4.4. IR (neat): $\nu_{max}$ 3566, 2926, 2857, 2623, 1741, 1706, 1693, 1647, 1516, 1463, 1436, 1053, 1011, 835, 774 $cm^{-1}$. HRMS (ESI) calcd for $C_{16}H_{34}O_2SiNa$ $[M + Na]^+$ 309.2220, found 309.2223.

*((2S,3S)-3-((2S,4R)-4-(tert-Butyldimethylsilyloxy)hexan-2-yl)-2-methyloxiran-2-yl) methanol (**7a**).* By following the general procedure described for Sharpless asymmetric epoxidation, epoxy alcohol **7a** (470 mg, 89%) as a colorless oil was prepared from allylic alcohol (−)-**8** (500 mg, 1.748 mmol). $R_f$ = 0.3, 25% EtOAc/hexanes. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 3.79 (m, 1H), 3.67 (d, *J* = 11.5 Hz, 1H), 3.57 (d, *J* = 11.5 Hz, 1H), 2.74 (d, *J* = 9.8 Hz, 1H), 2.32 (m, 1H), 2.02 (m, 1H), 1.78−1.43 (m, 3H), 1.29 (s, 3H), 0.93 (d, *J* = 6.6 Hz,


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3H), 0.88 (s, 9H), 0.88 (t, $J$ = 7.4 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 70.6, 65.5, 65.0, 60.7, 41.9, 30.0, 28.9, 25.9, 18.1, 16.2, 14.2, 9.2, −4.2, −4.5. IR (neat): $\nu_{max}$ 3444, 2923, 2854, 1462, 1252, 1038, 833 cm$^{-1}$. HRMS (ESI): calcd for $C_{16}H_{34}O_3SiNa$ $[M + Na]^+$ 325.2169, found 325.2176.

*((2R,3R)-3-((2S,4R)-4-(tert-Butyldimethylsilyloxy)hexan-2-yl)-2-methyloxiran-2-yl)methanol (**7b′**).* By following the general procedure described for Sharpless asymmetric epoxidation, epoxy alcohol **7b′** (93 mg, 88%) as a colorless oil was prepared from allylic alcohol (−)-**8** (100 mg, 0.349 mmol). $R_f$ = 0.3, 25% EtOAc/hexanes. $[\alpha]^{25}_D$ = −87.0 ($c$ 0.14, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 3.67 (d, $J$ = 11.5 Hz, 1H), 3.65 (m, 1H), 3.58 (d, $J$ = 11.5 Hz, 1H), 2.76 (d, $J$ = 10.0 Hz, 1H), 2.32 (m, 1H), 2.01 (m, 1H), 1.62 (m, 1H). 1.55 (brs, 1H), 1.48 (m, 1H), 1.30 (s, 3H), 1.08 (d, $J$ = 6.5 Hz, 3H), 0.87 (s, 9H), 0.86 (t, $J$ = 7.8 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 70.2, 65.5, 65.3, 61.6, 40.1, 30.7, 28.7, 25.8, 18.0, 17.2, 14.4, 9.2, −4.2, −4.5. IR (neat): $\nu_{max}$ 3620, 2925, 2855, 1647, 1546, 1516, 1426, 833, 673 cm$^{-1}$. HRMS (ESI): calcd for $C_{16}H_{34}O_3SiNa$ $[M + Na]^+$ 325.2169, found 325.2173.

*(E)-Ethyl 3((2S,3S)-3-((2S,4R)-4-(tert-Butyldimethylsilyloxy)hexan-2-yl)-2-methyloxiran-2-yl)acrylate (**6a**).* By following the general procedure described for Swern oxidation and 2C-Wittig reaction, unsaturated ester **6a** (469 mg, 85%) as a colorless oil was prepared from epoxy alcohol **7a** (450 mg, 1.490 mmol). $R_f$ = 0.6, 10% EtOAc/hexanes). $[\alpha]^{25}_D$ = −2.8 ($c$ 0.35, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.74 (d, $J$ = 15.6 Hz, 1H), 5.99 (d, $J$ = 15.6 Hz, 1H), 4.18 (q, $J$ = 7.1 Hz, 2H), 3.77 (m, 1H), 2.55 (d, $J$ = 9.0 Hz, 1H), 1.79−1.32 (m, 5H), 1.42 (s, 3H), 1.27 (t, $J$ = 7.1 Hz, 3H), 0.92 (d, $J$ = 6.6 Hz, 3H), 0.87 (s, 9H), 0.86 (t, $J$ = 7.5 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.1, 150.0, 121.2, 70.7, 70.4, 60.4, 58.3, 41.6, 30.0, 29.4, 25.8, 18.0, 16.1, 15.1, 14.1, 9.1, −4.2, −4.6. IR (neat): $\nu_{max}$ 2956, 2924, 2854, 1722, 1463, 1304, 1254, 1168, 1067, 1036, 833 cm$^{-1}$. HRMS (ESI): calcd for $C_{20}H_{38}O_4SiNa$ $[M + Na]^+$ 393.2431, found 393.2431.

*(E)-Ethyl 3-((2R,3R)-3-((2S,4R)-4-((tert-Butyldimethylsilyl)oxy)-hexan-2-yl)-2-methyloxiran-2-yl)acrylate (**6b′**).* By following the general procedure described for Swern oxidation and 2C-wittig reaction, unsaturated ester **6b′** (83 mg, 85%) as a colorless oil was prepared from epoxy alcohol **7b′** (80 mg, 0.264 mmol). $R_f$ = 0.6, 10% EtOAc/hexanes. $[\alpha]^{26}_D$ = +12.5 ($c$ 0.12, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.75 (d, $J$ = 15.4 Hz, 1H), 6.01 (d, $J$ = 15.4 Hz, 1H), 4.19 (q, $J$ = 6.6, 7.7 Hz, 2H), 3.65 (m, 1H), 2.57 (d, $J$ = 8.8 Hz, 1H), 1.65 (m,1H), 1.57−1.37 (m, 4H), 1.45 (s, 3H), 1.28 (t, 3H), 1.09 (d, $J$ = 6.6 Hz, 3H), 0.87 (s, 9H), 0.85 (t, $J$ = 7.7 Hz, 3H), 0.04 (d, $J$ = 9.9 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 166.1, 150.0, 121.4, 70.2, 70.0, 60.5, 59.2, 40.0, 30.6, 29.2, 25.8, 18.0, 17.0, 15.3, 14.2, 9.1, −4.2, −4.6. IR (neat): $\nu_{max}$ 2926, 2857, 1824, 1654, 1460, 1374, 1301, 1255, 1168, 1066, 1032, 834, 775 cm$^{-1}$. HRMS (ESI): calcd for $C_{20}H_{38}O_4SiNa$ $[M + Na]^+$ 393.2431, found 393.2438.

*(E)-3-((2S,3S)-3-((2S,4R)-4-(tert-Butyldimethylsilyloxy)hexan-2-yl)-2methyloxiran-2-yl)acrylic Acid (**22**).* By following the general procedure described for ester hydrolysis, acid **22** (359 mg, 86%) as a colorless oil was prepared from ester **6a** (450 mg, 1.216 mmol). $R_f$ = 0.4, 40% EtOAc/hexanes). $[\alpha]^{25}_D$ = −8.7 ($c$ 0.25, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.85 (d, $J$ = 15.8 Hz, 1H), 5.97 (d, $J$ = 15.8 Hz, 1H), 3.77 (dq, $J$ = 7.5, 5.2 Hz, 1H), 2.52 (d, $J$ = 9.0 Hz, 1H), 1.72 (m, 1H), 1.67−1.31 (m, 4H), 1.45 (s, 3H), 0.95 (d, $J$ = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (t, $J$ = 7.5 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 171.4, 152.7, 120.5, 70.9, 70.4, 58.4, 41.6, 30.0, 29.4, 25.8, 18.0, 16.1, 15.0, 9.1, −4.2, −4.6. IR (neat): $\nu_{max}$ 3620, 3376, 2959, 2931, 1696, 1624, 1463, 1308, 1254 cm$^{-1}$. HRMS (ESI): calcd for $C_{18}H_{34}O_4SiNa$ $[M + Na]^+$ 365.2118, found 365.2121.

*(E)-3-((2R,3R)-3-((2S,4R)-4-((tert-Butyldimethylsilyl)oxy)hexan-2-yl)-2-methyloxiran-2-yl)acrylic Acid (**23**).* By following the general procedure described for ester hydrolysis, acid **23** (51 mg, 85%) as a colorless oil was prepared from ester **6b′** (65 mg, 0.149 mmol). $R_f$ = 0.4, 40% EtOAc/hexanes. $[\alpha]^{26}_D$ = +1.9 ($c$ 0.07, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.85 (d, $J$ = 15.4 Hz, 1H), 6.02 (d, $J$ = 15.4 Hz, 1H), 3.66 (m, 1H), 2.58 (d, $J$ = 9.9 Hz, 1H), 2.38 (m, 1H), 1.74−1.44 (m, 2H), 1.46 (s, 3H), 1.09 (d, $J$ = 6.6 Hz, 3H), 0.87 (s, 9H), 0.85 (t, $J$ = 7.7 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 171.9, 152.6, 122.3, 71.4, 70.1, 59.5, 40.0, 30.7, 29.3, 25.8, 18.0, 17.1, 14.1, 9.2, −4.2, −4.6. IR (neat): $\nu_{max}$ 3620, 3376, 2922, 2853, 1704, 1640, 1516, 1462, 833 cm$^{-1}$. HRMS (ESI): calcd for $C_{18}H_{34}O_4SiNa$ $[M + Na]^+$ 365.2118, found 365.2120.

*(E)-3-((2S,3S)-3-((2S,4R)-4-(tert-Butyldimethylsilyloxy)hexan-2-yl)-2-methyloxiran-2-yl)-N-((2S,3S)-1-hydroxy-3-methylpentan-2-yl)-acrylamide (**24**).* By following the general procedure described for peptide coupling, compound **24** (352 mg, 85%) as a colorless oil was prepared from acid **22** (320 mg, 0.935 mmol). $R_f$ = 0.2, 50% EtOAc/hexanes. $[\alpha]^{26}_D$ = −6.2 ($c$ 0.82, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.69 (d, $J$ = 15.0 Hz, 1H), 6.04 (brs, 1H), 5.97 (d, $J$ = 15.0 Hz, 1H), 3.83 (m, 1H), 3.76 (m, 1H), 3.70 (dd, $J$ = 11.0, 3.0 Hz, 1H), 3.63 (dd, $J$ = 11.0, 6.0 Hz, 1H), 2.97 (brs, 1H), 2.49 (d, $J$ = 9.0 Hz, 1H), 1.76−1.56 (m, 3H), 1.55−1.42 (m, 3H), 1.42 (s, 3H), 1.34 (m, 1H), 1.16 (m, 1H), 0.96−0.91 (m, 6H), 0.90−0.86 (m, 6H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.0, 145.7, 123.2, 71.2, 70.3, 63.0, 58.9, 55.8, 41.2, 35.6, 30.1, 29.2, 25.8, 25.5, 18.0, 15.9, 15.4, 11.2, 9.1, −4.2, −4.6. IR (neat): $\nu_{max}$ 3367, 2960, 2930, 1624, 1540, 1462, 1383, 1254, 1073 cm$^{-1}$. HRMS (ESI): calcd for $C_{24}H_{48}NO_4Si$ $[M + H]^+$ 442.3347, found 442.3335.

*(E)-3-((2R,3R)-3-((2S,4R)-4-((tert-Butyldimethylsilyl)oxy)hexan-2-yl)-2-methyloxiran-2-yl)-N-((2S,3S)-1-hydroxy-3-methylpentan-2-yl)acrylamide (**25**).* By following the general procedure described for peptide coupling, compound **25** (38 mg, 84%) as a colorless oil was prepared from acid **23** (35 mg, 0.102 mmol). $R_f$ = 0.2, 50% EtOAc/hexanes). $[\alpha]^{26}_D$ = −56.1 ($c$ 0.23, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.76 (d, $J$ = 15.0 Hz, 1H), 6.0 (d, $J$ = 15.0 Hz, 1H), 5.72 (d, $J$ = 8.0 Hz, 1H), 3.87 (m, 1H), 3.75 (dd, $J$ = 11.0, 3.0 Hz, 1H), 3.69 (dd, $J$ = 11.0, 6.0 Hz, 1H), 3.66 (m, 1H), 2.58 (m, 1H), 2.54 (d, $J$ = 10.0 Hz, 1H), 1.71−1.58 (m, 3H), 1.55−1.36 (m, 3H), 1.44 (s, 3H), 1.25 (m, 1H), 1.16 (m, 1H), 1.08 (d, $J$ = 6.0 Hz, 3H), 0.94 (d, $J$ = 7.0 Hz, 3H), 0.91 (t, $J$ = 7.5 Hz, 3H), 0.87 (s, 9H), 0.85 (t, $J$ = 7.0 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.1, 146.2, 122.8, 71.9, 70.1, 63.8, 59.6, 56.2, 39.9, 35.7, 30.7, 29.2, 25.8, 25.6, 18.0, 17.0, 15.8, 15.5, 11.4, 9.1, −4.2, −4.6. IR (neat): $\nu_{max}$ 3649, 3620, 2959, 2929, 1741, 1693, 1645, 1517, 1463, 1252, 1068, 833, 773 cm$^{-1}$. HRMS (ESI): calcd for $C_{24}H_{48}O_4NSi$ $[M + H]^+$ 442.3347, found 442.3339.

*Curvularide B (**2**).* By following the general procedure described for TBS deprotection, curvularide B (**2**) (53 mg, 86%) as a light brown oil was prepared from compound **24** (83 mg, 0.188 mmol). $R_f$ = 0.2, 80% EtOAc/hexanes). $[\alpha]^{26}_D$ = +11.3 ($c$ 0.26, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.76 (d, $J$ = 15.0 Hz, 1H), 6.31 (brd, $J$ = 7.5 Hz, 1H), 6.04 (d, $J$ = 15.0 Hz, 1H), 3.87 (m, 1H), 3.72 (dd, $J$ = 11.8, 3.2 Hz, 1H), 3.66 (dd, $J$ = 11.8, 6.4 Hz, 1H), 3.63 (m, 1H), 3.27 (br, 1H), 2.59 (d, $J$ = 8.6 Hz, 1H), 2.03 (br s, 1H), 1.71−1.58 (m, 3H), 1.54−1.42 (m, 3H), 1.46 (s, 3H), 1.15 (m, 1H), 0.98 (d, $J$ = 6.5 Hz, 3H), 0.95 (t, $J$ = 7.5 Hz, 3H), 0.93 (d, $J$ = 6.5 Hz, 3H), 0.89 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.0, 145.0, 123.2, 71.6, 71.2, 63.0, 60.2, 55.8, 42.5, 35.6, 30.9, 30.7, 25.5, 16.6, 15.7, 15.4, 11.2, 9.9. IR (neat): $\nu_{max}$ 3289, 2962, 2927, 2876, 1667, 1626, 1545, 1459, 1345, 1069, 974, 753 cm$^{-1}$. HRMS (ESI) calcd for $C_{18}H_{33}O_4NNa$ $[M + Na]^+$ 350.2301, found 350.2297.

**Synthesis of Compound 26 and 27.** By following the general procedure described for TBS deprotection, **26** (15.4 mg, 61%) and **27** (4.6 mg, 18%) as a colorless oil were prepared from compound **25** (34 mg, 0.077 mmol).

*(R,E)-4-((2S,3S,5R)-5-Ethyl-3-methyltetrahydrofuran-2-yl)-4-hydroxy-N-((2S,3S)-1-hydroxy-3-methylpentan-2-yl)pent-2-enamide (**26**).* $R_f$ = 0.2, 80% EtOAc/hexanes. $[\alpha]^{26}_D$ = −15.0 ($c$ 0.15, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.88 (d, $J$ = 15.4 Hz, 1H), 6.13 (d, $J$ = 15.4 Hz, 1H), 5.72 (d, $J$ = 6.6 Hz, 1H), 3.88 (m, 1H), 3.81 (m, 1H), 3.77 (dd, $J$ = 11.0, 3.3 Hz, 1H), 3.70 (dd, $J$ = 11.0, 6.6 Hz,1H), 3.47 (d, $J$ = 7.7 Hz, 1H), 2.33 (m, 1H), 2.22−2.13 (m, 2H), 1.73−1.39 (m, 4H), 1.34 (s, 3H), 1.17 (m, 1H), 1.04 (d, $J$ = 5.5 Hz, 3H), 0.95 (d, $J$ = 6.6 Hz, 3H), 0.92 (t, $J$ = 7.7 Hz, 3H), 0.88 (t, $J$ = 7.7 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 166.6, 146.5, 121.5, 90.2, 81.3, 74.7, 64.1, 56.4, 41.8, 35.9, 34.7, 28.7, 25.8, 25.6, 19.0, 15.5, 11.4, 10.2. IR (neat): $\nu_{max}$ 3348, 3293, 2923, 2860, 1665, 1623, 1543, 1457, 1365, 1060, 768,

668 $cm^{-1}$. HRMS (ESI): calcd for $C_{18}H_{34}O_4N$ $[M + H]^+$ 328.2482, found 328.2479.

*(E)-3-((2S,3R,4S,6R)-6-Ethyl-3-hydroxy-2,4-dimethyltetrahydro-2H-pyran-2-yl)-N-((2S,3S)-1-hydroxy-3-methylpentan-2-yl)-acrylamide (**27**).* $R_f$ = 0.3, 80% EtOAc/hexanes). $[\alpha]^{26}_D$ = −2.4 (*c* 0.28, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.0 (d, *J* = 14.8 Hz, 1H), 6.13 (d, *J* = 9.2 Hz, 1H), 6.04 (d, *J* = 14.8 Hz, 1H), 3.87 (m, 1H), 3.71 (dd, *J* = 11.1, 3.7 Hz,1H), 3.57 (dd, *J* = 11.1, 6.5 Hz, 1H), 3.52 (m, 1H), 2.96 (d, *J* = 10.2 Hz, 1H), 2.30 (m, IH), 2.03 (m, 1H), 1.78 (m, 1H), 1.72−1.60 (m, 2H), 1.55−1.34 (m, 3H), 1.27 (s, 3H), 1.16 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 167.3, 149.5, 120.4, 78.3, 70.9, 64.0, 56.3, 39.3, 35.8, 32.1, 28.9, 25.6, 18.5, 15.7, 15.5, 14.1, 11.4, 10.0. IR (neat): $\nu_{max}$ 3349, 2922, 2856, 1738, 1623, 1458, 1370, 1063 $cm^{-1}$. HRMS (ESI): calcd for $C_{18}H_{34}O_4N$ $[M + H]^+$ 328.2482, found 328.2482.

**(2S,3S)-2-((*E*)-3-((2S,3S)-3-((2S,4R)-4-(*tert*-Butyldimethylsilyloxy)hexan-2-yl)-2-methyloxiran-2-yl)acrylamido)-3-methylpentyl Acetate (28).** By following the general procedure described for acetylation, acetate **28** (234 mg, 97%) as a colorless oil was prepared from compound **24** (220 mg, 0.498 mmol). $R_f$ = 0.5, 30% EtOAc/hexanes). $[\alpha]^{26}_D$ = −16.1 (*c* 0.82, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.71 (d, *J* = 15.1 Hz, 1H), 5.90 (d, *J* = 15.1 Hz, 1H), 5.61 (d, *J* = 8.8 Hz, 1H), 4.24 (dd, *J* = 11.1, 6.2 Hz, 1H), 4.12 (m, 1H), 4.04 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.76 (m, 1H), 2.46 (d, *J* = 9.2 Hz, 1H), 2.04 (s, 3H), 1.76−1.11 (m, 8H), 1.42 (s, 3H), 0.94 (d, *J* = 7.3 Hz, 3H), 0.91−0.84 (m, 6H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.1, 165.0, 146.1, 122.7, 71.3, 70.3, 64.2, 58.7, 52.3, 41.4, 36.1, 30.0, 29.3, 25.8, 25.3, 20.8, 18.0, 16.0, 15.5, 15.2, 11.2, 9.1, −4.2, −4.6. IR (neat): $\nu_{max}$ 3620, 3566, 3278, 2960, 2929, 2857, 1742, 1707, 1645, 1533, 1463, 1367, 1236, 1065, 834, 774 $cm^{-1}$. HRMS (ESI): calcd for $C_{26}H_{50}O_5NSi$ $[M + H]^+$ 484.3452, found 484.3447.

**(2S,3S)-2-((*E*)-3-((2S,3S)-3-((2S,4R)-4-Hydroxyhexan-2-yl)-2-methyloxiran-2-yl)acrylamido)-3-methylpentyl Acetate (29).** By following the general procedure described for TBS deprotection, compound **29** (124 mg, 85%) as a colorless oil was prepared from **28** (190 mg, 0.393 mmol). $R_f$ = 0.4, 50% EtOAc/hexanes). $[\alpha]^{26}_D$ = −26.4 (*c* 0.26, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.74 (d, *J* = 15.1 Hz, 1H), 5.93 (d, *J* = 15.1 Hz, 1H), 5.85 (d, *J* = 9.0 Hz, 1H), 4.22 (dd, *J* = 11.3, 6.0 Hz, 1H), 4.12 (m, 1H), 4.05 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.59 (m, 1H), 2.55 (d, *J* = 9.0 Hz, 1H), 2.04 (s, 3H), 1.68−1.55 (m, 3H), 1.54−1.39 (m, 3H), 1.46 (s, 3H), 1.34−1.08 (m, 2H), 1.01−0.87 (m, 12H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.1, 164.8, 145.4, 123.0, 71.5, 71.3, 64.3, 60.1, 52.3, 42.6, 36.1, 31.0, 30.7, 25.4, 20.8, 16.7, 15.7, 15.2, 11.3, 9.9. IR (neat): $\nu_{max}$ 3620, 3566, 2961, 2924, 2855, 1741, 1707, 1693, 1646, 1546, 1572, 1516, 1426, 675 $cm^{-1}$. HRMS (ESI): calcd for $C_{20}H_{35}O_5NNa$ $[M + Na]^+$ 392.2407, found 392.2410.

**Curvularide D (4).** To a stirred solution of alcohol **29** (88 mg, 0.238 mmol) in $CH_2Cl_2$ (2 mL) was added Dess−Martin periodinane (DMP) (202 mg, 0.476 mmol) at 0 °C, and the resulting solution was stirred at rt for 3 h. Then the reaction mixture was quenched with 1:1 mixture of saturated aq $NaHCO_3$ solution (3 mL) and saturated aq $Na_2S_2O_3$ (3 mL), stirred for 20 min to get clear solution, and then extracted with EtOAc (50 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, evaporated, and purified by using silica gel column chromatography (20% EtOAc/hexanes) to furnish the ketone (76 mg, 87%) as a colorless liquid. $R_f$ = 0.5, 40% EtOAc/hexanes). $[\alpha]^{26}_D$ = −8.3 (*c* 0.15, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.69 (d, *J* = 15.1 Hz, 1H), 5.90 (d, *J* = 15.1 Hz, 1H), 5.69 (brs, 1H), 4.24 (dd, *J* = 11.1, 6.0 Hz, 1H), 4.12 (m, 1H), 4.04 (dd, *J* = 11.1, 3.4 Hz, 1H), 2.66 (dd, *J* = 16.2, 4.5 Hz, 1H), 2.54 (d, *J* = 9.6 Hz, 1H), 2.50−2.30 (m, 3H), 2.04 (s, 3H), 2.0 (m, 1H), 1.67−1.42 (m, 2H), 1.46 (s, 3H), 1.18 (m, 1H), 1.06 (t, *J* = 7.5 Hz, 3H), 1.01−0.88 (m, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 209.9, 171.1, 164.8, 145.5, 123.1, 70.0, 64.3, 59.6, 52.3, 46.6, 36.5, 36.1, 29.5, 25.4, 20.9, 16.4, 15.5, 15.3, 11.3, 7.7. IR (neat): $\nu_{max}$ 3348, 2923, 2855, 1736, 1631, 1542, 1458, 1371, 1235, 977 $cm^{-1}$. HRMS (ESI): calcd for $C_{20}H_{34}O_5N$ $[M + H]^+$ 368.2431, found 368.2436.

To a stirred solution of above obtained ketone (60 mg, 0.163 mmol) in MeOH (0.8 mL) was added $K_2CO_3$ (45 mg, 0.326 mmol) at 0 °C, and the resulting solution was stirred at rt for 2 h. Then the reaction mixture was quenched with aq $NH_4Cl$, extracted with EtOAc (50 mL), washed with brine, dried over $Na_2SO_4$, filtered, evaporated, and purified by using silica gel column chromatography (50% EtOAc/hexanes) to furnish curvularide D (**4**) (46.5 mg, 87%) as a colorless oil. $R_f$ = 0.3, 70% EtOAc/hexanes. $[\alpha]^{26}_D$ = +8.3 (*c* 0.34, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.73 (d, *J* = 15.0 Hz, 1H), 6.24 (brd, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 15.0 Hz, 1H), 3.89 (m, 1H), 3.75 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.69 (dd, *J* = 11.0, 6.0 Hz, 1H), 2.70 (dd, *J* = 16.0, 5.0 Hz, 1H), 2.63 (d, *J* = 10.0 Hz, 1H), 2.55−2.40 (m, 3H), 2.49 (t, *J* = 8.0 Hz, 1H), 2.06 (m, 1H), 1.70 (m, 1H), 1.56 (m, 1H), 1.51 (s, 3H), 1.22 (m, 1H), 1.12 (t, *J* = 7.5 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.0 (d, *J* = 7.0 Hz, 1H), 0.97 (t, *J* = 7.5 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 210.1, 165.9, 145.4, 123.2, 70.0, 63.4, 59.5, 56.0, 46.6, 36.5, 35.6, 29.5, 25.5, 16.3, 15.4, 11.3, 7.7. IR (neat): $\nu_{max}$ 3290, 2964, 2926, 2879, 1708, 1667,1627, 1545, 1460, 1070, 978, 753 $cm^{-1}$. HRMS (ESI): calcd for $C_{18}H_{31}O_4NNa$ $[M + Na]^+$ 348.2145, found 348.2141.

**(*E*)-Ethyl 3-((2S,3S)-3-((2S,4R)-4-Acetoxyhexan-2-yl)-2-methyloxiran-2-yl)acrylate (30).** By following the general procedure described for acetylation, compound **30** (170 mg, 97%) as a gummy liquid was prepared from compound **16a** (150 mg, 0.585 mmol). $R_f$ = 0.5, 15% EtOAc/hexanes). $[\alpha]^{26}_D$ = +23.7 (*c* 0.53, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.73 (d, *J* = 15.8 Hz, 1H), 5.99 (d, *J* = 15.8 Hz, 1H), 4.98 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.58 (d, *J* = 8.5 Hz, 1H), 2.04 (s, 3H), 1.89 (m, 1H), 1.69−1.52 (m, 2H), 1.52−1.40 (m, 2H), 1.42 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 6.3 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.0, 166.1, 149.7, 121.4, 72.7, 70.2, 60.5, 58.5, 38.8, 30.1, 27.6, 21.2, 16.0, 15.1, 14.1, 9.4. IR (neat): $\nu_{max}$ 3372, 1721, 1623, 1461, 1374, 1304, 1243, 1172, 1029 $cm^{-1}$. HRMS (ESI): calcd for $C_{16}H_{26}O_5Na$ $[M + Na]^+$ 321.1672, found 321.1666.

**(4S,5R,6S,8R,*E*)-Ethyl 8-Acetoxy-4,5-dihydroxy-4,6-dimethyldec-2-enoate (31).** To a stirred solution of compound **30** (80 mg, 0.268 mmol) in a THF/$H_2O$ (1.5 mL, 1:1) was added TFA (0.0536 mmol) at 0 °C, and the resulting solution was stirred at rt for 18 h. Then the reaction mixture was quenched with sodium bicarbonate, extracted with EtOAc, washed with brine, dried over $Na_2SO_4$, filtered, evaporated, and purified by using silica gel column chromatography (20% EtOAc/hexanes) to furnish **31** (65.5 mg, 77%) as a liquid. $R_f$ = 0.5, 40% EtOAc/hexanes). $[\alpha]^{25}_D$ = −28.1 (*c* 0.45, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.96 (d, *J* = 15.1 Hz, 1H), 6.13 (d, *J* = 15.1 Hz, 1H), 4.84 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.41 (s, 1H), 2.37 (m, 1H), 2.0 (s, 3H), 1.99 (m, 1H), 1.73−1.49 (m, 4H), 1.37 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.22 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 8.0 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.2, 166.4, 150.2, 119.8, 80.8, 75.9, 73.7, 60.4, 34.4, 31.4, 28.0, 26.7, 21.0, 19.1, 14.2, 9.6. IR (neat): $\nu_{max}$ 3620, 2967, 2925, 2855, 1708, 1648, 1546, 1462, 1372, 1265, 1176, 1030, 987, 729 $cm^{-1}$. HRMS (ESI): calcd for $C_{16}H_{28}O_6Na$ $[M + Na]^+$ 339.1778, found 339.1777.

**(4S,5R,6S,8R,*E*)-4,5,8-Trihydroxy-4,6-dimethyldec-2-enoic Acid (32).** By following the general procedure described for ester hydrolysis, acid compound **32** (16.5 mg, 84%) as a colorless oil was prepared from ester **31** (25 mg, 0.079 mmol). $R_f$ = 0.2, EtOAc. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.12 (d, *J* = 15.9 Hz, 1H), 6.13 (d, *J* = 15.9 Hz, 1H), 3.62 (m, 1H), 3.33 (d, *J* = 4.0 Hz, 1H), 2.31 (m, 1H), 2.02 (m, 1H), 1.62 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.31 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 1H), 0.88 (t, *J* = 7.0 Hz, 1H). $^{13}C$ NMR (125 MHz, $CD_3OD$): $\delta$ 154.6, 120.7, 82.2, 77.1, 72.3, 39.4, 32.8, 32.3, 30.7, 25.2, 20.18, 10.5. HRMS (ESI): calcd for $C_{12}H_{22}O_5Na$ $[M + Na]^+$ 269.1364, found 269.1361.

**Curvularide A (1).** By following the general procedure described for peptide coupling, curvularide A (**1**) (10.5 mg, 83%) as a solid was prepared from acid **32** (9 mg, 0.036 mmol). $R_f$ = 0.5, 10% MeOH/EtOAc. Mp: 123−125 °C. $[\alpha]^{27}_D$ = −9.9 (*c* 0.15, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.82 (d, *J* = 15.0 Hz, 1H), 6.51 (d, *J* = 8.9 Hz, 1H), 6.13 (d, *J* = 15.0 Hz, 1H), 3.86 (m, 1H), 3.75 (m, 1H), 3.66−3.50 (m, 3H), 3.35 (brs, 1H), 2.29 (m, 1H), 2.09 (m, 1H), 2.01 (m, 1H), 1.84 (m, 1H), 1.59 (m, 1H), 1.50−1.40 (m, 3H), 1.29 (s, 3H),

1.23 (m, 2H), 1.12 (m, 1H), 1.03 (d, $J$ = 7.0 Hz, 3H), 0.91 (t, $J$ = 7.0 Hz, 3H), 0.90 (d, $J$ = 7.0 Hz, 3H), 0.87 (t, $J$ = 7.9 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 167.3, 149.8, 122.0, 80.6, 72.9, 62.6, 56.1, 38.9, 36.0, 31.5, 31.4, 25.7, 24.1, 21.7, 15.4, 11.4, 10.1. IR (neat): $\nu_{max}$ 3620, 2962, 2930, 2870, 1693, 1647, 1546, 1463, 1396, 1340, 1060, 978, 771 cm$^{-1}$. HRMS (ESI): calcd for $C_{18}H_{36}O_5N$ [M + H]$^+$ 346.2588, found 346.2588.

**(4*R*,5*S*,6*S*,8*R*,*E*)-Ethyl 8-Acetoxy-5-hydroxy-4-methoxy-4,6-dimethyldec-2-enoate (33).** To a stirred solution of compound **30** (100 mg, 0.335 mmol) in MeOH (1.6 mL) was added $BF_3{\cdot}OEt_3$ (0.067 mmol) at 0 °C, and the resulting solution was stirred at rt for 30 min. Then the reaction mixture was quenched with water, extracted with EtOAc (50 mL), washed with brine, dried over $Na_2SO_4$, filtered, evaporated, and purified by using silica gel column chromatography (20% EtOAc/hexanes) to furnish **33** (93 mg, 84%) as a colorless oil. $R_f$ = 0.3, 30% EtOAc/hexanes. $[\alpha]^{27}_D$ = −22.8 ($c$ 0.35, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.92 (d, $J$ = 16.6 Hz, 1H), 5.93 (d, $J$ = 16.6 Hz, 1H), 4.87 (m, 1H), 4.21 (q, $J$ = 7.1 Hz, 2H), 3.37 (dd, $J$ = 6.0, 2.3 Hz, 0.5H), 3.20 (s, 3H), 3.17 (d, $J$ = 3.8 Hz, 0.5H), 2.54 (d, $J$ = 6.0 Hz, 1H), 2.04 (s, 3H), 1.93 (m, 1H), 1.69−1.46 (m, 3H), 1.33 (s, 3H), 1.30 (t, $J$ = 7.1 Hz, 3H), 1.24 (m, 1H), 1.02 (d, $J$ = 6.8 Hz, 3H), 0.84 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 171.1, 165.8, 148.4, 122.8, 82.0, 80.3, 73.6, 60.5, 50.6, 34.5, 30.6, 28.1, 21.0, 19.3, 18.6, 14.2, 9.5. IR (neat): $\nu_{max}$ 3379, 1716, 1623, 1462, 1374, 1304, 1246, 1178 cm$^{-1}$. HRMS (ESI): calcd for $C_{17}H_{30}O_6Na$ [M + Na]$^+$ 353.1934, found 353.1934.

**(4*R*,5*S*,6*S*,8*R*,*E*)-5,8-Dihydroxy-4-methoxy-4,6-dimethyldec-2-enoic Acid (34).** By following the general procedure described for ester hydrolysis, acid compound **34** (27 mg, 85%) as a light yellow oil was prepared from ester **33** (40 mg, 0.121 mmol). $R_f$ = 0.2, EtOAc. $[\alpha]^{26}_D$ = −74.4 ($c$ 0.21, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.97 (d, $J$ = 16.6 Hz, 1H), 5.95 (d, $J$ = 16.6 Hz, 1H), 5.64−5.17 (br, 2H), 3.53 (m, 1H), 3.35 (d, $J$ = 3.8 Hz, 1H), 3.21 (s, 3H), 1.93 (m, 1H), 1.70 (m, 1H), 1.51−1.39 (m, 2H), 1.36 (s, 3H), 1.24 (m, 1H), 1.0 (d, $J$ = 6.8 Hz, 3H), 0.90 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.6, 150.4, 122.3, 82.0, 80.7, 72.1, 50.7, 39.2, 31.6, 31.0, 20.6, 18.4, 9.9. IR (neat): $\nu_{max}$ 3378, 1624, 1462, 1304, 999 cm$^{-1}$. HRMS (ESI): calcd for $C_{13}H_{24}O_5Na$ [M + Na]$^+$ 283.1516, found 283.1512.

**Curvularide C (3).** By following the general procedure described for peptide coupling, curvularide C (**3**) (21 mg, 84%) as a yellowish oil was prepared from acid **34** (18 mg, 0.069 mmol). $R_f$ = 0.6, 10% MeOH/EtOAc). $[\alpha]^{27}_D$ = −42.9 ($c$ 0.19, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.70 (d, $J$ = 16.0 Hz, 1H), 6.36 (d, $J$ = 8.0 Hz, 1H), 5.97 (d, $J$ = 16.0 Hz, 1H), 3.87 (m, 1H), 3.75 (dd, $J$ = 11.0, 3.0 Hz, 1H), 3.65 (dd, $J$ = 11.0, 7.0 Hz, 1H), 3.44 (m, 1H), 3.37 (brd, $J$ = 3.0 Hz, 1H), 3.22 (s, 3H), 3.04−2.72 (br, 3H), 1.88 (m, 1H), 1.71 (m, 1H), 1.66 (m, 1H), 1.51 (m, 1H), 1.47−1.38 (m, 2H), 1.33 (s, 3H), 1.25−1.11 (m, 2H), 1.03 (d, $J$ = 7.0 Hz, 3H), 0.94 (d, $J$ = 7.0 Hz, 3H), 0.92 (t, $J$ = 7.0 Hz, 3H), 0.90 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.8, 144.0, 125.5, 81.7, 80.5, 72.2, 63.1, 56.0, 50.6, 39.0, 35.6, 31.5, 31.2, 25.6, 21.2, 18.0, 15.3, 11.3, 10.0. IR (neat): $\nu_{max}$ 3620, 2963, 2930, 1693, 1676, 1647, 1546, 1532, 1463, 1426, 1367, 1061, 991 cm$^{-1}$. HRMS (ESI): calcd for $C_{19}H_{37}O_5NNa$ [M + Na]$^+$ 382.2563, found 382.2569.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1$H and $^{13}$C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

This paper is dedicated to Dr. M. Marthanda Murthy on the occasion of his 60th birthday.

## ■ REFERENCES

(1) Chomcheon, P.; Wiyakrutta, S.; Agree, T.; Sriubolmas, N.; Ngamrojanavanich, N.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. *Chem.—Eur. J.* **2010**, *16*, 11178−11185.

(2) Fonseca, S.; Chini, A.; Hamberg, M.; Adie, B.; Porzel, A.; Kramell, R.; Miersch, O.; Wasternack, C.; Solano, R. *Nat. Chem. Biol.* **2009**, *5*, 344−350.

(3) Thines, B.; Katsir, L.; Melotto, M.; Niu, Y.; Mandaokar, A.; Liu, G.; Nomura, K.; He, S. Y.; Howe, G. A.; Browse, J. *Nature* **2007**, *448*, 661−665.

(4) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412−4428.

(5) Dumeunier, R.; Markó, I. E. *Tetrahedron Lett.* **2000**, *41*, 10219−10222.

(6) Yu, Ch.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413−5418.

(7) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924−926.

(8) Richter, F.; Bauer, M.; Perez, C.; Mössmer, C. M.; Maier, M. E. *J. Org. Chem.* **2002**, *67*, 2474−2480.

(9) Determined by chiral HPLC (250 × 4.6) mm; MP *n*-hexane/IPA (90/10, v/v); flow rate 1.0 mL/min; temp 25 °C.

(10) Ghosh, A. K.; Gong, G. *J. Org. Chem.* **2006**, *71*, 1085−1093.

(11) Katagiri, T.; Fujiwara, K.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2008**, *49*, 233−237.

(12) Takemura, A.; Katagiri, Y.; Fujiwara, K.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2011**, *52*, 1222−1224.

(13) Initially, we expected that **6a** or **6b** with CSA in $CH_2Cl_2$ at 0 °C would lead to silyl deprotection followed by in situ formation of five-membered ring. However, this mixture of **6a** and **6b** displayed formation of conjugated *exo*-methylene epoxide opening product with TBS intact as major and without TBS as the minor product along with small amounts of five-membered and six-membered products.

(14) Morimoto, Y.; Nishikawa; Ueba, C.; Tanaka, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 810−812.

(15) We observed that after silyl ether cleavage of **25** the resulting epoxy alcohol immediately underwent cyclization. Compounds **6b** and **7b** in Scheme 3 and **6b′** and **7b′** in Scheme 4, respectively, have an enantiomeric relation. The more reactive epoxy alcohol **16b**, which was obtained from **7b** via **6b** in Scheme 3, and the polyketide portion of the epoxy alcohol of **25**, which was obtained from **7b′** via **6b′** in Scheme 4, have an enantiomeric relation. This stereochemical configuration seems to be very unstable and prone to cyclization, apparently from quick cyclization of **16b** to **14** and **15** and of **25** to **26** and **27**.

(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(17) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(18) The specific rotation of synthesized curvularide D is ($[\alpha]^{26}_D$ = +8.3 ($c$ 0.34, $CHCl_3$)) where the lit.[1] is ($[\alpha]^{28}_D$ = −1.5 ($c$ 0.35, $CHCl_3$)). However, after repurification, the provided natural product sample showed specific rotation ($[\alpha]^{29}_D$ = +8.8 ($c$ 0.13, $CHCl_3$)), which agrees well with the synthetic product.

(19) Our initial attempts at epoxide opening of **6a** in acidic conditions resulted in a mixture of compounds (mainly TBS deprotected compound), and MeOH as a solvent in the presence of

$BF_3OEt_2$ gave a mixture of five-membered **19** (minor) and six-membered **20**, (major) along with small amounts of corresponding tertiary methoxy diol compound.
(20) Hanessian, S.; Margarita, R.; Hall, A.; Johnstone, S.; Tremblay, M.; Parlanti, L. *J. Am. Chem. Soc.* **2002**, *124*, 13342−13343.
(21) BASF Aktiengesellschaft Patent: US5703017 A1, 1997.
(22) BASF Aktiengesellschaft Patent: US5840722 A1, 1998.