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Supported Synthesis of Oxoapratoxin A

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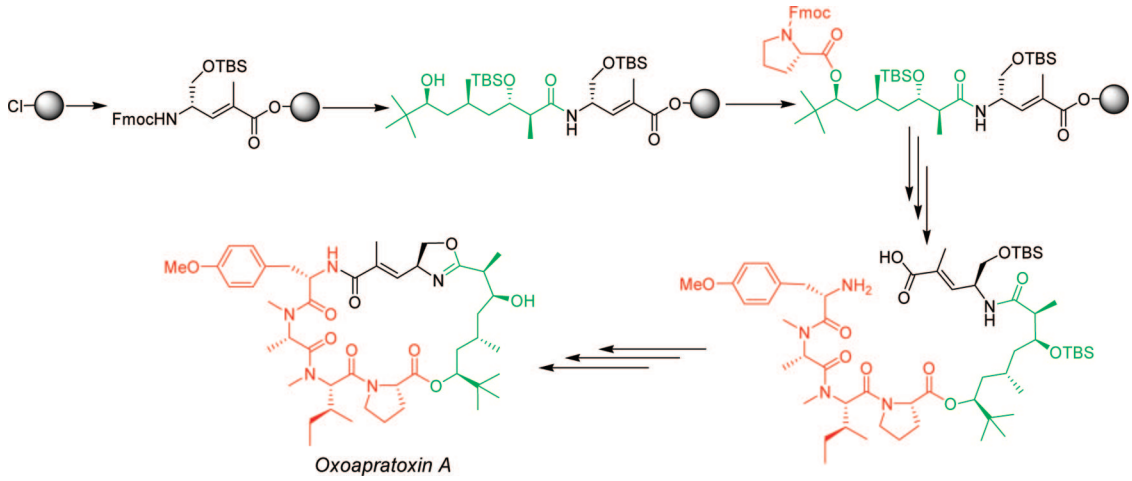

A new synthesis of an oxazoline analogue of apratoxin A has been performed using a solid support. The efficient synthesis of the polyketide part on gram scale and the serine vinylogue is described. The use of chlorotrityl resin allowed the construction of two linear precursors corresponding to two different cyclization sites. This study describes a facile synthesis of analogues for future SAR studies of this potent antitumor compound.

Introduction

Apratoxins A, B, C[1,2] and the more recently discovered E and D[3,4] forms are cyclodepsipeptides of marine origin that present antitumoral activity. These molecules possess a common structure, including a tetrapeptide and a polyketide part, bridged by a thiazoline ring on one side and by an ester bond on the other side (Figure 1).

The mode of action of the highly cytotoxic apratoxin A still remains to be fully elucidated.[5] However, it has attracted much attention, and as such the total synthesis of apratoxin A became a competitive challenge. The more accessible oxazoline analogue of apratoxin A exhibits excellent antitumor activity[9] and thus became our synthetic target. Three total syntheses of apratoxin A,[6−8] one total synthesis of its oxazoline analogue,[9] and one synthesis of its polyketide part[10] have been achieved to date,

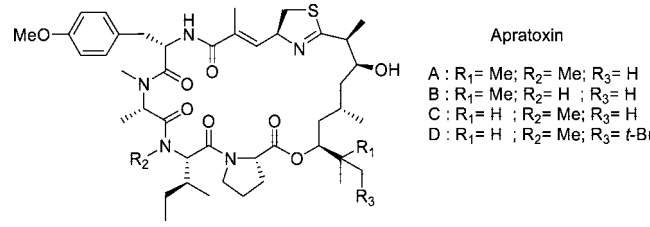

FIGURE 1. Apratoxins.

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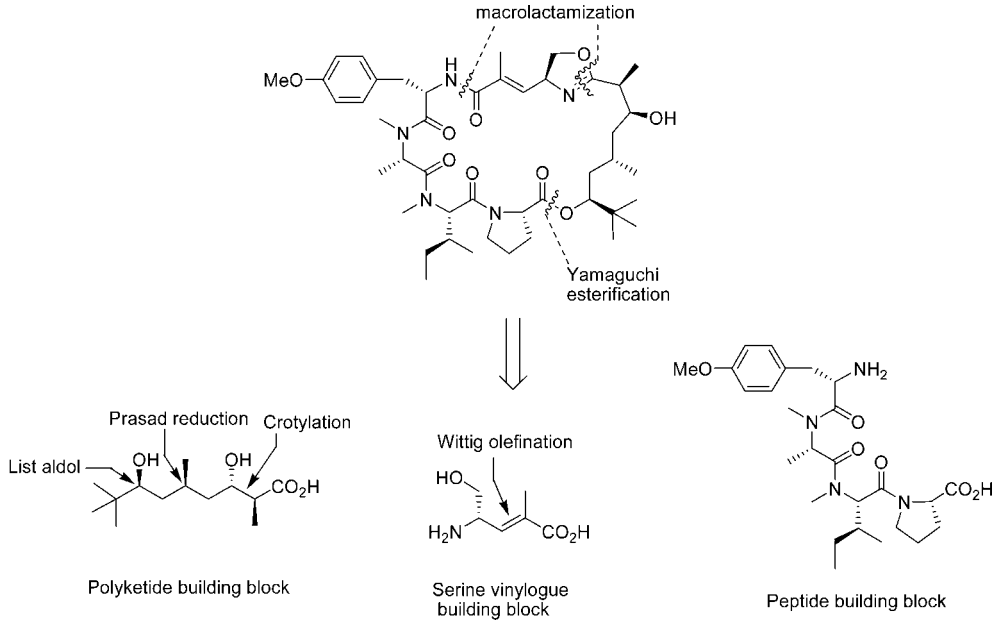
SCHEME 1. Retrosynthesis



all involving formation of the heterocycle before macrocyclization and the same macrocyclization site, between N-Me-Ile and Pro, with a high risk of epimerization at the N-Me-Ile residue. Although it is well-known that such coupling reaction generates epimerization at the C_α center of the C-terminal amino acid, especially when *N*-methylated amino acid residues are involved,[11] the risk of epimerization during macrocyclization was not mentioned in the described syntheses. Herein, we report a more versatile total synthesis of the oxazoline analogue of apratoxin A involving the efficient use of chemistry on solid support,[12] providing a simpler method for further structure−activity relationship studies. This strategy allowed us to investigate three different cyclization sites where no epimerization could occur. As outlined in the retrosynthetic scheme (Scheme 1), the 25-membered macrocycle was closed by lactamization at two different sites or by lactonization. We saw here the opportunity to use supported peptide synthesis methodology to supply a convergent and more convenient synthesis of apratoxin A. Thus, the linear precursors were obtained from three building blocks further coupled together.

Results and Discussion

The first challenge in this synthesis was the preparation of the polyketide moiety, requiring introduction of four stereochemical centers, two alcohol functions, and one carboxylic acid function.

The synthesis was achieved in 12 steps starting from commercially available pivalaldehyde, as outlined in Scheme 2. List's aldolization between pivalaldehyde and acetone using proline as chiral organocatalyst gave the corresponding hydroxyketone **1**,[13] which was reduced by $NaBH_4$ under Prasad reaction conditions (Et_3BOMe, MeOH, THF, −78 °C).[14] The pure *syn* 1,3-diol **2** was isolated after separation of the two diastereoisomers (dr = 95:5)[15,16] in 69% yield. Reaction of the diol **2** with thionyl chloride in pyridine at 0 °C afforded a diastereoisomeric mixture of the cyclic sulfite **3** in quantitative yield. Then the sulfite was oxidized into its corresponding sulfate **4** using $RuCl_3$ as oxidative agent and $NaIO_4$ as co-oxidant in a heterogeneous solvent mixture (CCl_4, ACN, H_2O).[17] The sulfate **4** was then subjected to regioselective substitution, which was the first key step in the synthesis. The less sterically hindered position was preferred for substitution by the allyl group using the corresponding Grignard reagent, with complete inversion of configuration. After sulfate hydrolysis and purification, the desired allylic compound **5** was obtained in 90% yield. Silylation of the resulting secondary alcohol with TESCl and Et_3N proceeded smoothly to give **6**, followed by oxidative cleavage of the terminal double bond with ozone to yield the corresponding aldehyde **7**. The second crucial step was the formation of the last two stereogenic centers. Unfortunately, various attempts to obtain the condensation product from the aldehyde using an *anti*-Evans aldol type of reaction[18] were unsuccessful and led to the complete degradation of the substrate. A different strategy using Brown's crotylation reaction with diisopinocampheylborane yielded the homoallylic alcohol **8** in 93% yield as two separable diastereoisomers (dr = 9:1).[19] After protection of **6** as a silyl ether using TBDMS triflate and imidazole in DCM to give **9**, ozonolysis of the allylic function afforded the aldehyde **10** in 88% yield, which was oxidized with $NaClO_2$ quantitatively to give the corresponding acid **11**.[20] Selective deprotection of the TES-protected alcohol under mild acidic conditions (AcOH, DCM, MeOH, H_2O) led to the desired polyketide **12** in 88% yield. The polyketide moiety was obtained from the pivalalde-

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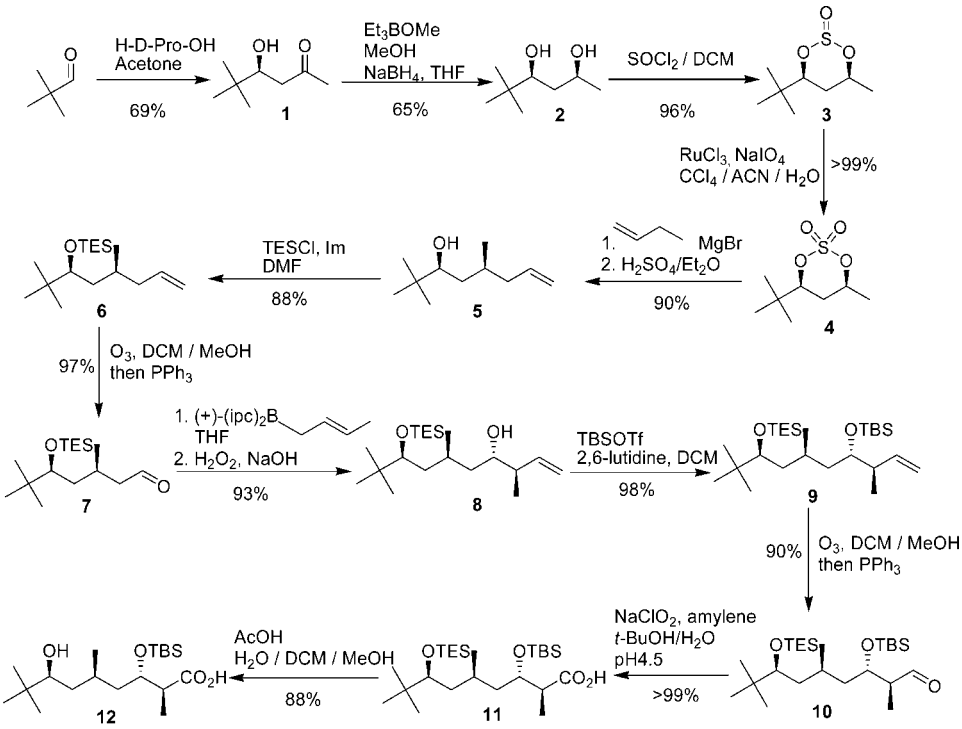
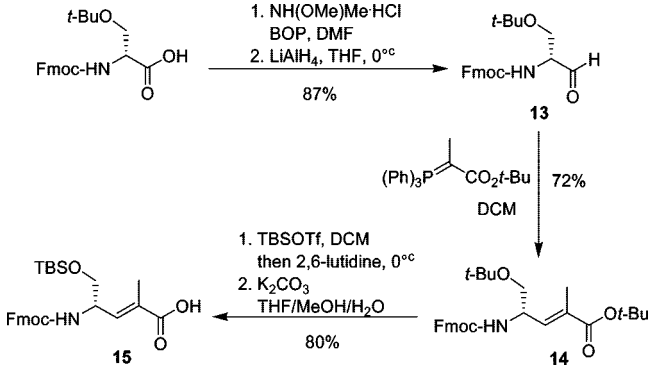
SCHEME 2. Polyketide Synthesis



SCHEME 3. Vinylic Homologation of Serine



hyde in 19% overall yield in 12 steps. This synthesis has been carried out on gram scale.

The synthesis of the vinylic anologue of serine **16** started from the corresponding commercially available protected serine (Scheme 3). Conversion of the N-Fmoc-protected serine into its Weinreb amide proceeded efficiently using BOP as the coupling reagent, followed by treatment with $LiAlH_4$ to yield the corresponding aldehyde **13**, which was used without further purification to avoid epimerization at its C_α chiral center.[21] Wittig condensation of the aldehyde **13** with the preformed phosphorane in DCM furnished the (*E*)-vinylic analogue (or vinylogue) of protected serine **14** with 67% yield in two steps.[22] The last step of this building block synthesis was deprotection of the carboxylic acid. To be consistent with our protection strategy, the *t*-Bu ether of the serine vinylogue was also replaced by its corresponding silylated alcohol. Displacement of the two *t*-Bu groups with TBSOTf under basic conditions gave the persilylated intermediate.[23] Selective hydrolysis of the silylated ester with potassium carbonate completed the synthesis of **15**, which was obtained in 80% yield.

With those two building blocks and the four amino acid derivatives in hand, it was then possible to perform the precursor elongation using the appropriate resin support, i.e., the chlorinated chlorotrityl resin. This method allowed us to direct the synthesis toward different linear precursors. The cyclization site depends on which carboxylic acid was first anchored to the polymeric support.

When the peptide was first synthesized on the resin, followed by the vinylogue moiety and then the polyketide part, the macrocycle should close via the ester bond, but the lactonization reaction between polyketide and peptide moieties, carried under various conditions, failed to yield the expected compound, as already reported by Forsyth.[24] Thus, we decided to focus our efforts on the two lactamization ring closures involving precursors **21** and **24**.

For the linear precursor **21** (Scheme 4), the vinylic analogue of serine was anchored first on the support, followed by removal of the Fmoc protecting group and coupling of the polyketide **12** in the presence of HATU or BOP as coupling reagent, leading to **16**.[25] In the case of precursor **24** (Scheme 5), the polyketide moiety was attached first.

For both supported elongations, esterification of the supported fragment was performed under Yamaguchi conditions,[26] using 5 equiv of proline mixed anhydride (obtained from proline and 2,4,6-trichloro-benzoyl chloride) and DMAP to give **17** and **23**. All successive coupling reactions on both linear intermediates

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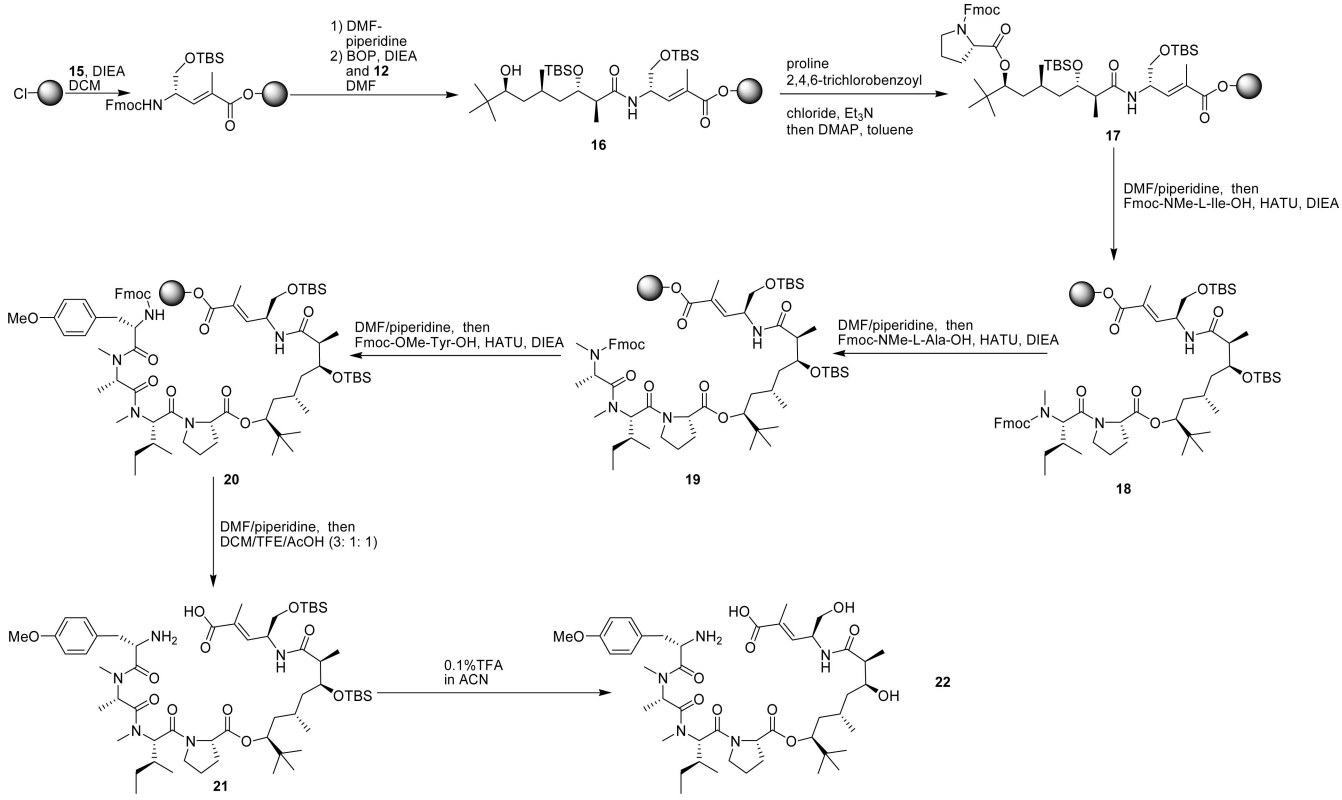
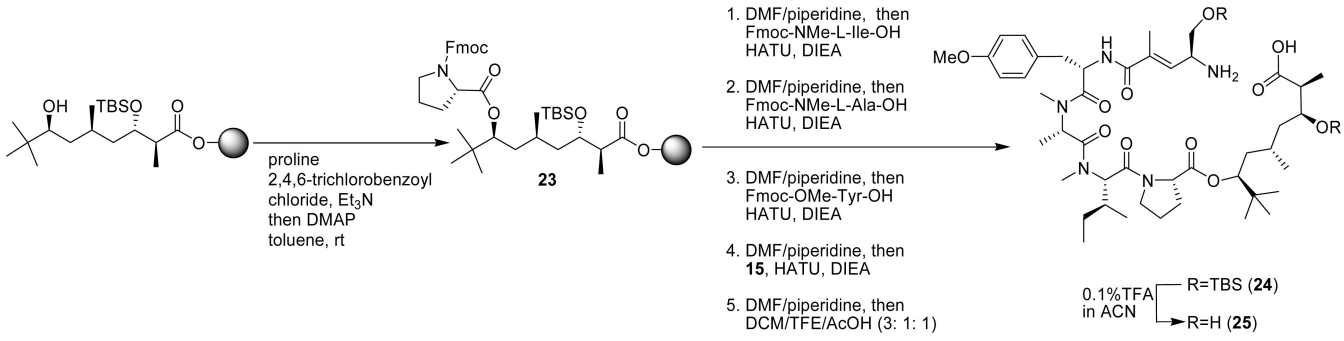
SCHEME 4. First Linear Precursor Elongation



SCHEME 5. Second Linear Precursor Elongation



with *N*-methyl amino acids required the use of HATU, since the use of BOP gave deletion peptides resulting from the lower reactivity of *N*-methylated amino acids.[11] After proline amino group deprotection, the linear precursors elongation was achieved by three coupling−deprotection sequences using *N*-Fmoc-*N*-Me-Ile (intermediate **18**), *N*-Fmoc-*N*-Me-Ala (intermediate **19**), and *N*-Fmoc-Tyr(O-Me) (intermediate **20**) for the linear precursor **21** and with one more coupling followed by Fmoc deprotection of the serine analogue **15** for the linear precursor **24** (supported intermediates are not represented here). The two linear precursors were then obtained after cleavage from the solid support under mild acidic conditions (acetic acid in DCM with TFE). Macrocyclization was attempted from these two linear precursors. Unexpectedly, it appeared that the TBS protecting group of the secondary alcohol had to be removed prior to macrolactamization, otherwise the reaction did not occur. This deprotection reaction was carried out by simply dissolving the linear precursor in a 0.1% TFA in acetonitrile solution followed by evaporation under reduce pressure. This operation was repeated until complete alcohol deprotection. Under these conditions, both primary and secondary TBDMS protected alcohols were released.

The deprotected linear precursors **22** and **25** were then subjected to macrolactamization using HATU as the coupling reagent to yield the macrocyclic compound **26** in 40% to 45% yield after purification by preparative HPLC (the use of BOP or DPPA also led to the desired macrocycle).[24] DAST was used successfully as the cyclodehydrating agent for conversion of the serine moiety into its corresponding oxazoline to yield oxoapratoxin in quantitative yield.[27] Formation of the oxazoline prior to macrocyclization also led to the oxoapratoxin without any noticeable improvement.

In conclusion, we described here an efficient synthesis on solid support of the oxazoline analogue of apratoxin A, including the synthesis on gram scale of the polyketide moiety. We performed the macrolactamization from two different linear precursors without epimerization, using different types of

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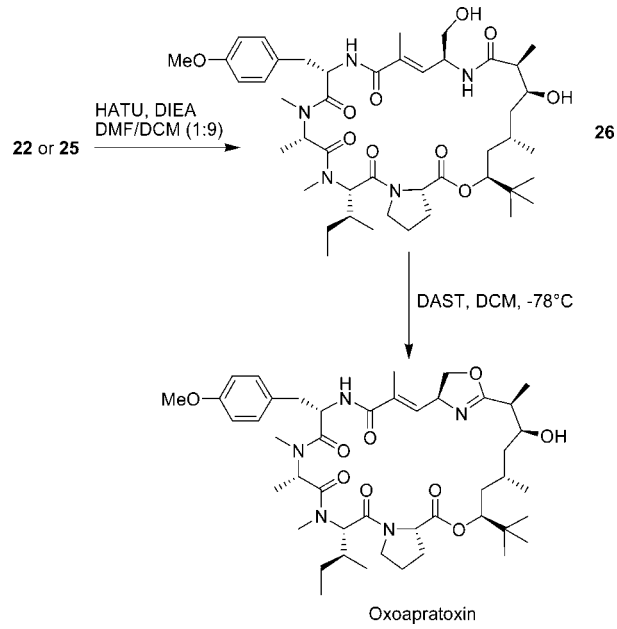
SCHEME 6. Lactamization and Oxazoline Formation



coupling reagents. This versatile construction of oxoapratoxin could allow the facile synthesis of analogues for further SAR studies, incorporating new amino acids and a modified or simplified polyketide part.

Experimental Section

(*S*)-4-Hydroxy-5,5-dimethylhexan-2-one (1). Pivalaldehyde (2.5 g, 29.0 mmol) and D-proline (1.34 g, 11.6 mmol) were dissolved in a solution of DMSO/acetone 4:1 (125 mL). After 4 days, half-saturated ammonium chloride solution was added and the mixture was extracted 3 times with ethyl acetate. The combined organic layers were washed 2 times with water and 1 time with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt 7:3, $R_f = 0.25$) to give the hydroxyketone (2.72 g, 69%) as a pale yellow oil. $[\alpha]^{20}_D = -71.8$ (*c* 0.85, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.89 (s, 9H), 2.18 (s, 3H), 2.47 (dd, $J = 17.3$ Hz, 10.2 Hz, 1H), 2.61 (dd, $J = 17.3$ Hz, 2.1 Hz, 1H), 2.89 (m, 1H), 3.70 (ddd, $J = 10.2$ Hz, 3.4 Hz, 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 25.6 (CH_3), 30.8 (CH_3), 34.1 (C), 45.0 (CH_2), 74.8 (CH), 210.4 (C).

(2*S*,4*S*)-5,5-Dimethylhexan-2,4-diol (2). To a solution of 5,5-dimethyl-4-hydroxyhexan-2-one **1** (2.37 g, 16.2 mmol) in an anhydrous mixture of THF/MeOH 4:1 at −78 °C was added $MeOBEt_2$ (18 mL, 1 M/THF, 18 mmol). After 20 min under stirring, $NaBH_4$ (684 mg, 18.0 mmol) was added in small portions. The reaction mixture was stirred for 4 h at −78° and was quenched by addition of a 30% H_2O_2 solution (7.5 mL). The reaction mixture was then stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed 3 times with water, dried over Na_2SO_4 and concentrated under reduce pressure. The residue was azeotroped 3 times with methanol and purified by column chromatography on silica gel (hexane/AcOEt 1:1, $R_f = 0.28$). The (2*S*,4*S*)-5,5-dimethylhexan-2,4-diol *syn* isomer was isolated as a white solid in 65% yield (1.56 g). The *anti* isomer was also isolated (94 mg) (hexane/AcOEt 1:1, $R_f = 0.37$) (*syn*/*anti* 95:5). *syn* isomer: $[\alpha]^{20}_D = -5.1$ (*c* 0.99, $CHCl_3$). Mp: 43 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.86 (s, 9H), 1.18 (d, $J = 6.2$ Hz, 3H), 1.38 (dt, $J = 14.3$ Hz, 10.2 Hz, 1H), 1.58 (d broad, $J = 14.3$ Hz, 1H), 3.20 (m, 2H), 3.47 (dd, $J = 10.2$ Hz, 1.0 Hz, 1H), 3.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 24.1 (CH_3), 25.5 (CH_3), 34.8 (C), 38.7 (CH_2), 69.3 (CH), 81.0 (CH). *anti* isomer: $[\alpha]^{20}_D = -38.2$ (*c* 1.57, $CHCl_3$). Mp: 86 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.93 (s, 9H), 1.31 (d, $J = 6.4$ Hz, 3H), 1.55−1.65 (m, 2H), 2.0−2.1 (broad m, 2H), 3.60 (m, 1H), 4.19 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 23.2 (CH_3), 25.7 (CH_3), 34.6 (C), 38.9 (CH_2), 65.5 (CH), 75.7 (CH). $[\alpha]^{20}_D$ and NMR values are consistent with those given in the literature.[28,29]

(4*S*,6*S*)-4-*tert*-Butyl-6-methyl-2-oxo-1,3,2-dioxathiane (3). To a solution of diol **2** (995 mg, 6.8 mmol) in pyridine (30 mL) at 0 °C was added dropwise thionyl chloride (2.5 mL, 34 mmol). After being stirred for 30 min at 0 °C, the mixture was diluted with water, and the aqueous layer extracted 3 times with DCM. The organic layer was washed 2 times with $KHSO_4$ (1 M), water, and saturated $NaHCO_3$ and dried over Na_2SO_4. After evaporation, the pure (4*S*,6*S*)-4-*tert*-butyl-6-methyl-2-oxo-1,3,2-dioxathiane (cyclic sulfite) was obtained as white crystals in 96% yield (1.26 g). The two diastereoisomers were isolated by silica gel chromatography for characterization. R_f (hexane/AcOEt 8:2) 0.23 and 0.37. First diastereoisomer (slow elution) (R_f 0.23): $[\alpha]^{20}_D = -27$ (*c* 1, $CHCl_3$). Mp: 70.5 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.88 (s, 9H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.60−1.85 (m, 2H), 4.57 (dd, $J = 11.6$ Hz, 2.4 Hz, 1H), 4.94−5.07 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 22.8 (CH_3), 26.6 (CH_3), 35.1 (CH_2), 35.2 (C), 66.7 (CH), 76.3 (CH). Second diastereoisomer (fast elution) (R_f 0.37): $[\alpha]^{20}_D = -21.2$ (*c* 0.99, $CHCl_3$). Mp: 71 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.84 (s, 9H), 1.27 (d, $J = 6.3$ Hz, 3H), 1.41−1.60 (m, 2H), 3.97 (dd, $J = 11.1$ Hz, 2.7 Hz, 1H), 4.38−4.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.4 (CH_3), 25.3 (CH_3), 31.8 (CH_2), 34.3 (C), 74.0 (CH), 84.6 (CH).

(4*S*,6*S*)-4-*tert*-Butyl-6-methyl-2-dioxo-1,3,2-dioxathiane (4). To a solution of the cyclic sulfite **3** (1.485 g, 7.72 mmol) in a 150 mL H_2O/ACN/CCl_4 mixture (2:1:1 respectively) was added at room temperature $RuCl_3$ (80 mg, 0.39 mmol) followed by $NaIO_4$ (2.5 g, 11.58 mmol). After being stirred for 2 h, the mixture was diluted in diethylether (250 mL), washed with distilled water (twice), saturated $NaHCO_3$, and brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The pure (4*S*,6*S*)-4-*tert*-butyl-6-methyl-2-dioxo-1,3,2-dioxathiane **4** was obtained in quantitative yield (1.61 g) as white crystals. $R_f = 0.15$ (hexane/AcOEt 8:2). $[\alpha]^{20}_D = -4.0$ (*c* 1.01, $CHCl_3$). Mp: 112 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.00 (s, 9H), 1.47 (d, $J = 6.3$ Hz, 3H), 1.85 (t, $J = 8.6$ Hz, 1H), 1.85 (t, $J = 5.5$ Hz, 1H), 4.52 (dd, $J = 8.6$ Hz, 5.5 Hz, 1H), 4.92 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 20.8 (CH_3), 25.2 (CH_3), 31.6 (CH_2), 34.3 (C), 81.1 (CH), 91.8 (CH).

(3*S*,5*S*)-2,2,5-Trimethyloct-7-en-3-ol (5). To a solution of (4*S*,6*S*)-4-*tert*-butyl-6-methyl-2-dioxo-1,3,2-dioxathiane **4** (1.64 g, 7.87 mmol) and CuI (1.8 g, 9.45 mmol) in anhydrous THF (20 mL) at −25 °C under argon was added dropwise allylmagnesium chloride (15.8 mL, 2M/THF). The reaction mixture was stirred for 5 h at −25 °C and allowed to warm to room temperature, and THF was removed under vacuum. To a solution of the residue in diethylether (75 mL) was added a 20% H_2SO_4 solution (30 mL) at room temperature. After being stirred overnight, the layers were separated, and the aqueous layer was extracted twice by diethylether. The combined organic layers were dried over K_2CO_3 and Na_2SO_4, filtered and concentrated under reduced pressure. Purification on silica gel afforded the unsaturated alcohol **5** as a colorless oil (1.21 g, 90%). $R_f = 0.24$ (hexane/AcOEt 9:1). $[\alpha]^{20}_D = -42.9$ (*c* 1.61, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.88 (s, 9H), 0.94 (d, $J = 6.6$ Hz, 3H), 1.19 (ddd, $J = 14.3$ Hz, 10.2 Hz, 4.0 Hz, 1H), 1.41 (ddd, $J = 14.3$ Hz, 9.2 Hz, 1.8 Hz, 1H), 1.79 (m, 1H), 1.85 (m, 1H), 2.20 (m, 1H), 3.30 (dd, $J = 10.2$ Hz, 1.8 Hz, 1H), 4.96−5.05 (m, 2H), 5.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ

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(29) Chopade, P. R.; Davis, T. A.; Prasad, E.; Flowers, R. A. *Org. Lett.* **2004**, *6*, 2685–2688.

(ppm): 20.9 (CH_3), 25.6 (CH_3), 29.8 (CH), 35.0 (C), 38.4 (CH_2), 39.8 (CH_2), 77.5 (CH), 116.0 (CH_2), 137.1 (CH).

((3*S*,5*S*)-2,2,5-trimethyloct-7-en-3-yloxy)triethylsilane (6). To a solution of (3*S*,5*S*)-2,2,5-trimethyloct-7-en-3-ol **4** (300 mg, 1.77 mmol) and 1-*H*-imidazole (241 mg, 3.54 mmol) in anhydrous DMF (6 mL) at room temperature under argon was added TESCl dropwise (445 μL, 2.66 mmol). The solution was stirred overnight, diluted with AcOEt, and washed 3 times with distilled water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (hexane, R_f = 0.52) to yield 442 mg (88%) of pure ((3*S*,5*S*)-2,2,5-trimethyloct-7-en-3-yloxy)triethylsilane **6** as a colorless oil. $[\alpha]^{20}_D = -27.1$ (*c* 1.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.62 (q, J = 7.9 Hz, 6H), 0.84 (s, 9H), 0.90 (d, J = 6.5 Hz, 3H), 0.97 (t, J = 7.9 Hz, 9H), 1.21 (ddd, J = 14.1 Hz, 8.5 Hz, 3.6 Hz, 1H), 1.38 (ddd, J = 14.1 Hz, 9.5 Hz, 2.1 Hz, 1H), 1.60−1.80 (m, 2H), 2.19 (m, 1H), 3.36 (dd, J = 8.5 Hz, 2.1 Hz), 4.98−5.05 (m, 2H), 5.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 5.8 (CH_2), 7.2 (CH_3), 20.9 (CH_3), 29.6 (CH_3), 35.6 (C), 40.1 (CH_2), 40.4 (CH_2), 78.7 (CH), 115.9 (CH_2), 137.1 (CH).

(3*R*,5*S*)-3,6,6-Trimethyl-5-(triethylsilyloxy)heptanal (7). ((3*S*,5*S*)-2,2,5-Trimethyloct-7-en-3-yloxy)triethylsilane **6** (1.307 g, 4.56 mmol) was dissolved in 60 mL of DCM/MeOH 5:1 mixture under argon and cooled to −76 °C. Ozone was then bubbled into the mixture until the appearance of a persistant azure blue color. Excess of ozone was then removed by bubbling nitrogen, and the intermediate ozonide was neutralized by addition of PPh_3 (3 g, 11.4 mmol). After 20 min at −76 °C, the mixture was allowed to reach room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/DCM 8:2, R_f = 0.2) to afford 1.278 g (97%) of the pure aldehyde **7** as a colorless oil. $[\alpha]^{20}_D = -14.4$ (*c* 1.11, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.60 (q, J = 7.8, 6H), 0.83 (s, 9H), 0.95 (t, J = 7.8 Hz, 9H), 0.98 (d, J = 8.4 Hz, 3H), 1.38 (ddd, J = 14.2 Hz, 8.2 Hz, 3.6 Hz, 1H), 1.40 (ddd, J = 14.2 Hz, 9.5 Hz, 2.5 Hz, 1H), 2.03−2.18 (m, 2H), 2.47 (broad d, J = 13.7 Hz, 1H), 3.28 (dd, J = 8.2 Hz, 2.5 Hz, 1H), 9.76 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 5.5 (CH_2), 7.1 (CH_3), 21.5 (CH_3), 25.6 (CH), 26.1 (CH_3), 35.6 (C), 40.7 (CH_2), 50.1 (CH_2), 78.6 (CH), 202.6 (CH).

(3*S*,4*R*,6*S*,8*S*)-3,6,9,9-Tetramethyl-8-(triethylsilyloxy)dec-1-en-4-ol (8). To an excess of *t*-butene was added potassium *tert*-butylate (8.38 mmol, 1 M/THF) at −78 °C. After 10 min of stirring at −78 °C, *n*-BuLi (8.38 mmol, 1.6 M/hexane) was added dropwise. The temperature was then allowed to raise to −45 °C, and the mixture was stirred for 30 min. The mixture was then cooled to −78 °C, and a solution of diisopinocamphenylborane (2.65 g, 8.38 mmol) in a minimum of THF was added dropwise. After stirring for 45 min at −78 °C, $BF_3 \cdot Et_2O$ (1.38 mL, 10.89 mmol) was quickly added, immediately followed by a solution of aldehyde **7** (1.2 g, 4.19 mmol, 1 equiv) in THF (5 mL). The mixture was stirred at −78 °C for 5 h and quenched by addition of 3 N NaOH (25 mL) and 30% H_2O_2 (25 mL). After 1 h of stirring at room temperature, the mixture was diluted with AcOEt and brine. The aqueous layer was extracted 3 times with AcOEt, and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography (hexane/AcOEt 93:7, R_f = 0.38) afforded 1.34 g (93%) of the homoallylic alcohol **8** as a colorless oil (9:1 dr, *anti* as the major product, isolated from the *syn* isomer). $[\alpha]^{20}_D = -18.4$ (*c* 1.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.62 (q, J = 7.0 Hz, 6H), 0.84 (s, 9H), 0.93 (d, J = 6.6 Hz, 3H), 0.96 (t, J = 7.7 Hz, 9H), 1.03 (d, J = 6.8 Hz, 3H), 1.00−1.50 (m, 5H), 1.81 (m, 1H), 2.15 (hex, broad, J = 7.0 Hz, 1H), 3.32 (dd, J = 7.5 Hz, 2.5 Hz, 1H), 3.49 (ddd, J = 10.4 Hz, 8.1 Hz, 2.1 Hz, 1H), 5.08−5.14 (m, 2H), 5.75 (ddd, J = 17.9 Hz, 11.9 Hz, 8.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 5.7 (CH_2), 7.2 (CH_3), 16.3 (CH_3), 20.8 (CH_3), 26.2 (CH_3), 26.6 (CH), 35.7 (C), 41.1 (CH_2), 42.2 (CH_2), 45.1 (CH), 72.0 (CH), 78.6 (CH), 116.3 CH_2), 140.5 (CH).

(3*R*,4*S*,6*S*,8*S*)-4-*tert*-Butyldimethylsilyloxy-3,6,9,9-tetramethyl-8-triethylsilyloxy Dec-1-ene (9). To a solution of alcohol **6** (980 mg, 2.86 mmol) in 40 mL of anhydrous DCM was added, at −25 °C, 2,6-lutidine (1 mL, 8.58 mmol) followed by TBDMSOTf (1.31 mL, 5.70 mmol). After being stirred for 2 h at this temperature, the reaction was quenched by addition of a saturated ammonium chloride solution. The aqueous layer was extracted 3 times with DCM, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/AcOEt 98:2, R_f = 0.59) to afford the protected homoallylic alcohol as a colorless oil (1.28 g, 98%). $[\alpha]^{20}_D = -22$ (*c* 1.09, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.06 (s, 3H), 0.08 (s, 3H), 0.62 (q, J = 7.9 Hz, 6H), 0.75 (s, 9H), 0.81 (s, 9H), 0.88 (t, J = 7.7 Hz, 9H), 0.93 (d, J = 8.9 Hz, 3H), 0.97 (d, J = 7.9, 3H), 1.13−1.30 (m, 2H), 1.42 (ddd, J = 14.1 Hz, 8.2 Hz, 4.5 Hz, 1H), 1.51 (ddd, J = 14.1 Hz, 9.7 Hz, 5.2 Hz, 1H), 1.66 (m, 1H), 2.36 (m, 1H), 3.32 (dd, J = 6.1 Hz, 3.5 Hz, 1H), 3.75 (dt, J = 6.1 Hz, 3.4 Hz, 1H), 4.95−5.04 (m, 2H), 5.73 (ddd, J = 17.8 Hz, 9.8 Hz, 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −3.8 (CH_3), −3.3 (CH_3), 6.4 (CH_2), 7.9 (CH_3), 14.0 (CH_3), 18.9 (C), 21.3 (CH), 26.4 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 36.7 (C), 39.7 (CH), 44.0 (CH_2), 44.6 (CH), 73.7 (CH), 79.2 (CH), 115.1 (CH_2), 141.8 (CH).

(2*R*,3*R*,5*S*,7*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,5,8,8-tetramethyl-7(triethylsilyloxy)nonanal (10). The protected homoallylic alcohol **9** (1.257 g, 2.75 mmol) was dissolved in a DCM/MeOH 5:1 mixture (60 mL) under argon, and the mixture was cooled to −76 °C. Ozone was then bubbled into the mixture until the appearance of a persistant azure blue color. Excess of ozone was then removed by bubbling nitrogen, and the intermediate ozonide was neutralized by addition of PPh_3 (1.8 g, 6.86 mmol). After 20 min at −76 °C, the mixture was allowed to reach room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/DCM 95:5, R_f = 0.23) to afford 1.14 g (90%) of the pure aldehyde **10** as a colorless oil. $[\alpha]^{20}_D = -16.7$ (*c* 1.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.09 (s, 3H), 0.10 (s, 3H), 0.61 (q, J = 7.9, 6H), 0.83 (s, 9H), 0.89 (s, 9H), 0.94 (d, J = 7.7, 3H), 0.96 (t, J = 7.9 Hz, 9H), 1.14 (d, J = 7.0 Hz, 3H), 1.13−1.30 (m, 3H), 1.42 (ddd, J = 14.4 Hz, 7.8 Hz, 3.6 Hz, 1H), 2.56 (qdd, J = 7.1 Hz, 3.6 Hz, 1.3 Hz, 1H), 3.30 (dd, J = 6.2 Hz, 3.6 Hz, 1H), 4.19 (dt, J = 8.8 Hz, 3.6 Hz, 1H), 9.71 (d, J = 1.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −4.8 (CH_3), −3.8 (CH_3), 5.6 (CH_2), 6.1 (CH_3), 8.8 (CH_3), 17.0 (C), 20.5 (CH), 25.8 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 36.7 (C), 41.0 (CH_2), 43.1 (CH_2), 52.5 (CH), 70.0 (CH), 78.4 (CH), 203.7 (CH).

(2*S*,3*S*,5*S*,7*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,5,8,8-tetramethyl-7-(triethylsilyloxy)nonanoic Acid (11). To a solution of aldehyde **10** (900 mg, 1.96 mmol) in *tert*-butanol (6.5 mL), water (3.5 mL) and 2-methyl-2-butene (720 μL, 6.77 mmol) at 0 °C was added a solution of $NaClO_2$ (540 mg, 5.97 mmol) in a phosphate buffer (pH = 4.5) (6.3 mL). After being stirred for 5 min at 0 °C the solution was allowed to reach room temperature and was stirred for another 30 min, then the reaction was diluted with brine. The aqueous layer was extracted 3 times with AcOEt, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the pure carboxylic acid **11** as a colorless thick oil (930 mg, quantitative). $[\alpha]^{20}_D = -46.1$ (*c* 11.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.10 (s, 3H), 0.11 (s, 3H), 0.61 (q, J = 7.9 Hz, 6H), 0.84 (s, 9H), 0.90 (s, 9H), 0.93 (d, J = 6.1, 3H), 0.96 (t, J = 7.9 Hz, 9H), 1.17 (d, J = 7.1 Hz, 3H), 1.12−1.30 (m, 1H), 1.43 (ddd, J = 14.4 Hz, 7.8 Hz, 3.5 Hz, 1H), 1.65 (m, 2H), 2.72 (qd, J = 7.1 Hz, 4.1 Hz, 1H), 3.31 (dd, J = 6.1 Hz, 3.5 Hz, 1H), 4.16 (m, 1H), 10.9 (s, broad, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −5.0 (CH_3), −4.1 (CH_3), 5.7 (CH_2), 7.1 (CH_3), 10.6 (CH_3), 18.0 (C), 20.5 (CH), 25.8 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 35.9 (C), 40.0 (CH_2), 43.1 (CH_2), 45.8 (CH), 70.8 (CH), 78.5 (CH), 179.5 (C).

(2*R*,3*S*,5*R*,7*S*)-3-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-2,5,8,8-tetramethylnonanoic Acid (12). The acid **11** (1.5 g, 3.16 mmol)

was dissolved in 125 mL of a mixture of acetic acid, DCM, water and methanol in a 3:1:2:1 ratio, respectively, and stirred for 3 h. Then, the reaction was diluted with AcOEt and water, and the aqueous layer extracted 3 times with AcOEt. The combined organic layers were washed 2 times with brine, dried over $MgSO_4$ and finally concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane/AcOEt 3:1, R_f = 0.25) to afford the pure carboxylic acid **12** (1 g, 88%) as white crystals. $[\alpha]^{20}_D = -39.3$ (*c* 1.12, $CHCl_3$). Mp: 70.5 °C. HRMS (ESI): 361.2769 (calcd for $C_{19}H_{40}O_4Si+H^+$: 361.2774). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.09 (s, 3H), 0.11 (s, 3H), 0.61 (q, *J* = 7.9 Hz, 6H), 0.87(s, 9H), 0.89 (s, 9H), 0.95 (d, *J* = 6.6, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.25−1.33 (m, 1H), 1.66 (ddd, *J* = 12.0 Hz, 8.7 Hz, 3.0 Hz, 1H), 1.79 (m, 1H), 2.72 (qd, *J* = 7.2 Hz, 4.5 Hz, 1H), 3.26 (dd, *J* = 9.3 Hz, 2.7 Hz, 1H), 4.11 (ddd, *J* = 7.5 Hz, 4.2 Hz, 3.0 Hz, 1H), 11.0 (broad s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −4.4 (CH_3), −4.7 (CH_3), 11.2 (CH_3), 18.0 (C), 21.1 (CH), 25.6 (CH_3), 25.8 (CH_3), 26.3 (CH_3), 34.9 (C), 39.6 (CH_2), 39.7 (CH_2), 45.9 (CH), 71.4 (CH), 77.3 (CH), 179.2 (C).

Macrolactamization of Linear Precursors 22 and 25 (26). To a solution of the linear precursor **22** or **25** in DCM/DMF (9:1) at a concentration of 8×10^{-4} M was added DIEA (5 equiv) followed by HATU (2 equiv). The mixture was stirred overnight, and the solvent was removed under reduce pressure. The residue was then taken up in AcOEt and washed successively with a saturated solution of citric acid, saturated solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the macrocyclic compound **26** as a white foam with a 70% yield (HPLC evaluation) and 45% yield after preparative HPLC purification (isolated compound). t_R: 12.03 min. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.86 (s, 9H), 0.95−1.06 (m, 10H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.13 (m, 1H), 1.18 (d, *J* = 10.1 Hz, 3H), 1.20−1.37 (m, 3H), 1.70−2.15 (m, 8H), 2.20−2.35 (m, 2H), 2.59 (s, 3H), 2.65 (s, 3H), 2.75 (m, 1H), 3.06−3.18 (m, 2H), 3.27 (m, 1H), 3.56−3.72 (m, 3H), 3.78 (s, 3H), 4.08 (m, 1H), 4.15 (m, 1H), 4.32 (m, 1H), 4.40 (m, 1H), 4.71 (m, 1H), 4.73−4.89 (dd, *J* = 12.3 Hz, 3.0 Hz, 1H), 4.96 (d, *J* = 12.9 Hz, 1H), 5.02−5.18 (m, 1H), 5.25 (d, *J* = 11.1 Hz, 1H), 6.19 (dd, *J* = 9.0 Hz, 0.9 Hz, 1H), 6.41 (m, 1H), 6.53 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H). HRMS FAB+: 842.5278 (calcd 842.5201).

Oxazoline Analogue of Apratoxin A (Oxoapratoxin A). To a solution of macrocycle **26** (100 mg, 0.12 mmol) in 2 mL of DCM at −80 °C was added DAST (15.2 μL, 1 equiv). After 1 h, an additional 1 equiv of DAST was added, and the mixture was stirred for 1 h. The reaction was quenched at −80 °C by addition of a 4 M solution of NH_4OH, diluted with chloroform and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give oxoapratoxin in 58% yield (HPLC evaluation) and 35% yield after preparative HPLC purification (35 mg of isolated compound). t_R: 11.20 min. $[\alpha]^{20}_D = -116.7$ (*c* 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.87 (s, 9H), 0.90−1.01 (m, 10H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.11 (m, 1H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.25 (m, 1H), 1.29 (m, 1H), 1.43 (m, 1H), 1.74−1.86 (m, 3H), 1.91 (d, *J* = 0.9 Hz, 3H), 2.05 (m, 1H), 2.13 (m, 1H), 2.25 (m, 1H), 2.33 (m, 1H), 2.42 (m, 1H), 2.74 (s, 3H), 2.81 (s, 3H), 2.86 (m, 1H), 3.00−3.25 (m, 2H), 3.30 (q, *J* = 6.6 Hz, 1H), 3.56−3.72 (m, 3H), 3.78 (s, 3H), 4.19 (broad m, 2H), 4.40 (m, 1H), 4.71 (m, 1H), 4.73−4.81 (m, 1H), 4.96 (dd, *J* = 12.4 Hz, 1.77 Hz, 1H), 5.05 (td, *J* = 10.8 Hz, 4.8 Hz, 1H), 5.24 (d, *J* = 11.5 Hz, 1H), 5.98 (d, *J* = 9.5 Hz, 1H), 6.18 (dd, *J* = 9.0 Hz, 0.9 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H). HRMS (FAB+): 824.5148 (calcd 824.5174).

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Supporting Information Available: Experimental procedures for all other compounds, ^{1}H and ^{13}C NMR spectra and optical rotation for compounds **13**−**15**, HPLC and MS spectra for supported intermediates and linear precursors. This material is available free of charge via the Internet at http://pubs.acs.org.

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