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Asymmetric Total Synthesis of Epolactaene. Part 2: Introduction of the Side Chain and Synthesis of (+)-Epolactaene and Its Enantiomer.†

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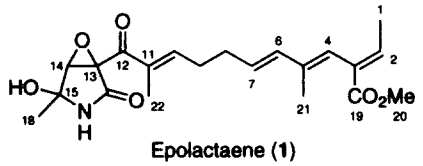
Abstract

A total synthesis of the novel neuritogenic agent (+)-epolactaene ((+)-**1**) has been achieved *via* a convergent route that utilized epoxyamide **8**, C7–C11 fragment **7**, and C1–C6 Wittig reagent derived from phosphonium salt **19** followed by cyclization to form the lactam. The absolute configuration of natural epolactaene is definitively established as (13*R*,14*R*). Synthesis of (–)-**1**, the enantiomer of this natural epolactaene, is also described.

Introduction

In the preceding paper,[1] we discussed the enantioselective synthesis of the epoxy-γ-lactam structure of epolactaene (**1**, Figure 1) with several key reactions. In this paper, we give full details of the completion of the total synthesis of epolactaene[2] including stereoselective synthesis of the side chain.



Epolactaene (**1**)

Figure 1

Results and Discussion

On the basis of our results of the model compound of epolactaene,[1] we planned to complete total synthesis *via* the convergent approach shown in Scheme 1. First we planned to obtain the epolactaene (**1**) by oxidation

† With regard to this investigation, a patent application was filed before Japanese Patent Office on October 30, 1997 as a patent filing number of H09-297983.

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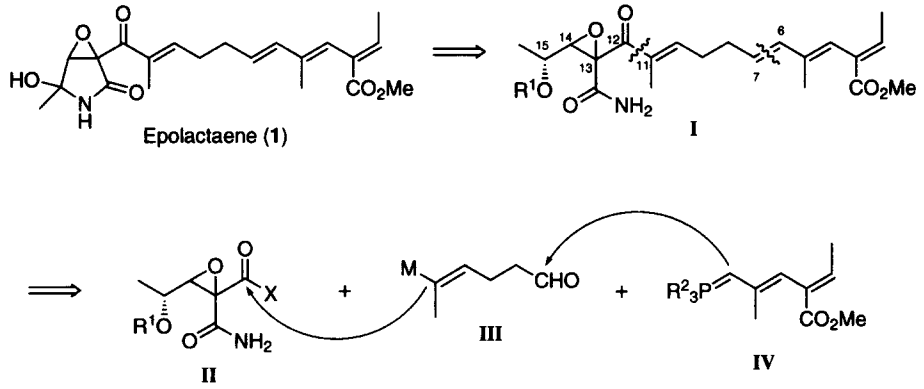
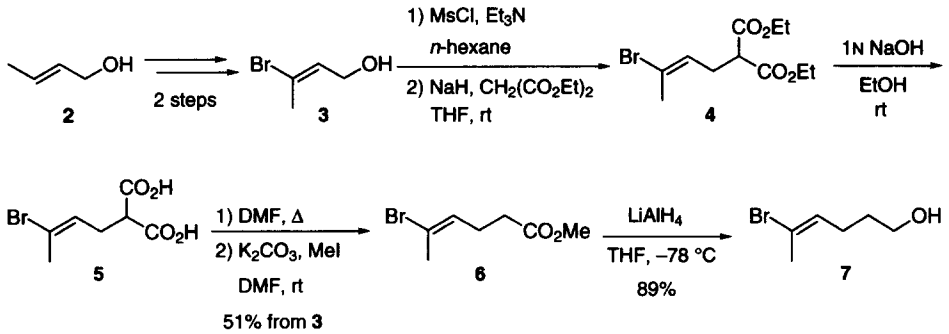
of the alcohol **I**, as with the model compound. Next, we planned to divide the key intermediate **I** into the three component disconnection of the C11–C12 bond and C6–C7 bond: optically active epoxy-γ-lactam precursor **II**, both enantiomers of which had been synthesized in the preceding paper; C7–C11 unit **III**; and Wittig reagent **IV**.



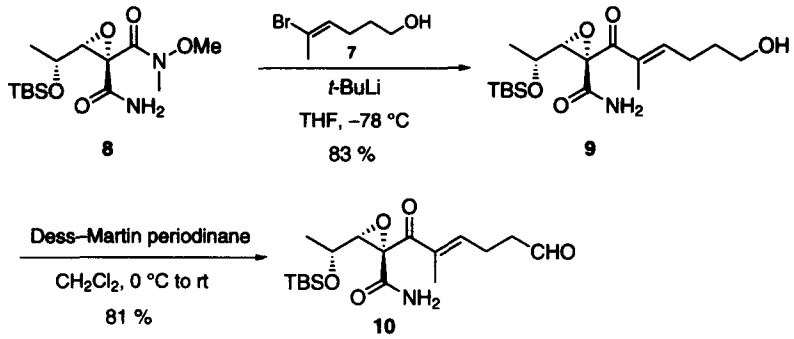
Scheme 1

Following this strategy, we initially synthesized vinylbromide **7**, corresponding to the C7–C11 unit **III** using the method described in Scheme 2. (*E*)-3-Bromobut-2-en-1-ol (**3**),[3] which was obtained from (*E*)-crotyl alcohol (**2**) using Corey's protocol, was increased by two carbon units by mesylation with methanesulfonyl chloride and triethylamine in hexane followed by treatment with sodium hydride and diethyl malonate. Hydrolysis of **4** under basic conditions and decarboxylation of the resulting dicarboxylic acid in *N,N*-dimethylformamide (DMF) at 100 °C provided the corresponding carboxylic acid, and subsequent esterification to give **6** in 51% yield from **3**. Reduction of **6** using lithium aluminum hydride in THF at –78 °C provided the desired C7–C11 unit **7** in 89% yield.

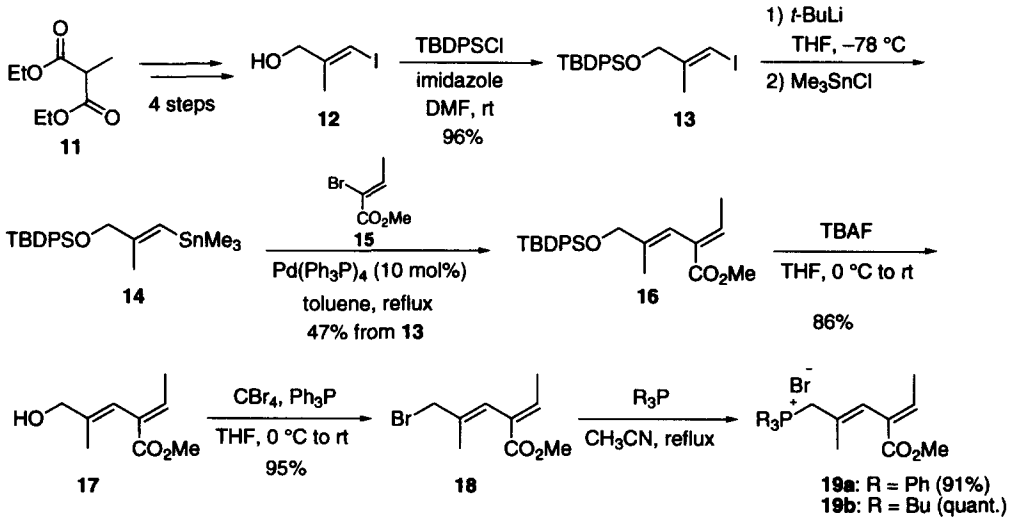


Scheme 2

The epoxy-γ-lactam precursor and the resulting C7–C11 unit **7** were coupled by the method shown in Scheme 3. Vinyllithium, generated from **7** and 2.9 eq. of *tert*-butyllithium in THF at –78 °C, was treated with *syn* Weinreb amide **8**[1] to provide α,β-unsaturated ketone **9** in 83% yield. To introduce the C1–C6 unit by Wittig reaction (*vide infra*), the primary alcohol of **9** was converted to aldehyde **10** in 81% yield by Dess–Martin oxidation.[4]



Scheme 3



Scheme 4

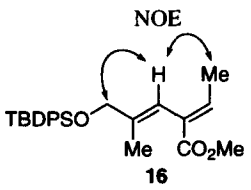
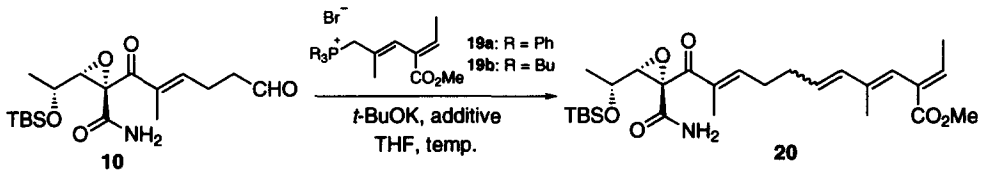


Figure 2

We then attempted to synthesize the phosphonium salts **19a** and **19b** corresponding to the C1–C6 unit (Scheme 4). (*E*)-3-Iodo-2-methylprop-2-en-1-ol (**12**),[5] synthesized in 4 steps from diethyl methylmalonate following Baker's procedure, was silylated with the *tert*-butyldiphenylsilyl (TBDPS) group to provide **13** in 96% yield. The vinyliodide **13** was converted to vinyllithium by halogen–lithium exchange with *tert*-

butyllithium in THF at –78 °C followed by treatment with trimethyltin chloride. The resulting vinylstannane **14** was subjected to Stille coupling[6] with methyl (*Z*)-2-bromobut-2-enoate (**15**),[7] derived from methyl (*E*)-crotonate in 2 steps, in the presence of the catalytic amount of tetrakis(triphenylphosphine)palladium in toluene at reflux to provide diene **16** in 47% yield from **13** stereoselectively. The (*E,E*)-stereochemistry of **16** was determined from NOE experiments of the ^{1}H NMR spectrum of the diene **16** (Figure 2). Conversion from diene **16** to the desired phosphonium salt **19** was accomplished by the following 3 steps: deprotection of the silyl group with tetrabutylammonium fluoride (TBAF) in THF to give primary alcohol **17** in 86% yield, transformation of **17** to bromide **18** using carbon tetrabromide and triphenylphosphine in 95% yield, and exposure of triphenylphosphine or tributylphosphine to **18** to provide phosphonium salt **19a** (R=Ph) or **19b** (R=Bu).

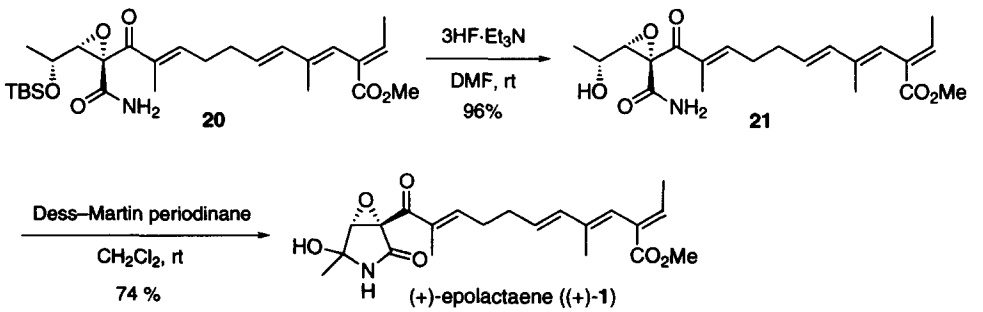
Table 1



entry	R	**19** (eq.)	additive	temp.	*E* : *Z*[a]	yield(%)
1	Ph	2.4	None	–78 °C	------	trace
2	Ph	2.4	18-crown-6/CH_3CN	–46 °C	1 : 1	27
3	Ph	5.0	18-crown-6/CH_3CN	–46 °C	1 : 1	68
4	Bu	5.0	18-crown-6/CH_3CN	–46 °C	10 : 1	69

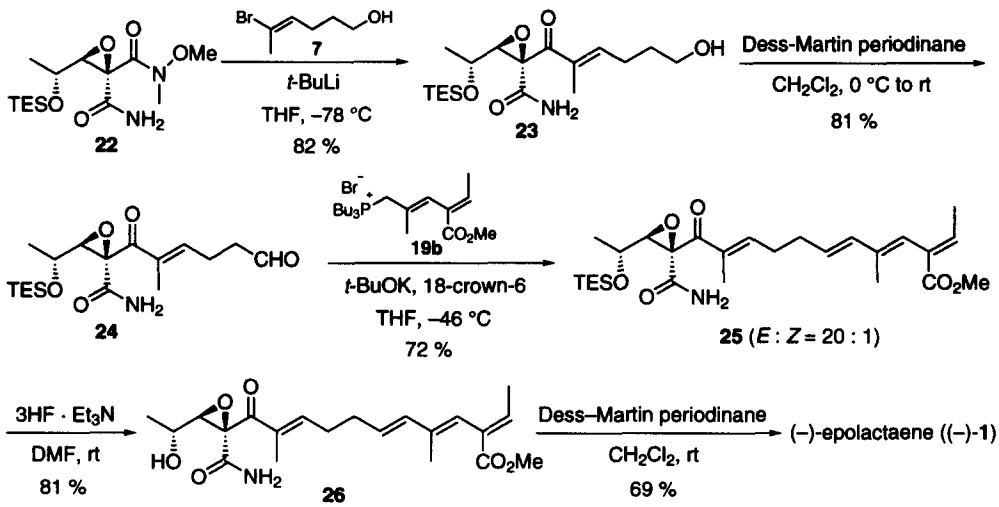
[a] Ratios were determined by ^{1}H NMR of the crude mixture.

In the next step, we examined the Wittig reaction using aldehyde **10** and phosphonium salt **19** (summarized in Table 1). An initial generation of ylide from triphenylphosphonium salt **19a** using potassium *tert*-butoxide in THF at –78 °C followed by the addition of aldehyde **10** unfortunately yielded poor result (entry 1). Facilitating the formation of ylide by the addition of 18-crown-6/CH_3CN at –46 °C resulted in a 27% yield of triene **20** as a 1:1 mixture of *E* and *Z* isomer (entry 2). Treatment of aldehyde **10** with 5 eq. of **19a** to prevent lack of the ylide by decomposition in this condition increased the yield to 68% (entry 3). The *E*-selectivity was improved using tributylphosphonium salt[8] **19b** to provide the desired triene **20** in 69% yield with 10:1 stereoselectivity (entry 4), and the **20** was separated from the minor *Z* isomer by silica gel flash column chromatography to give pure *E* isomer. The stereochemistry of the major product was confirmed by the large coupling constant ($J_{6,7}$ = 15 Hz) observed in the ^{1}H NMR spectrum.



Scheme 5

The stage was now set for the construction of the epoxy-γ-lactam ring and completion of this total synthesis outlined in Scheme 5. Removal of TBS group from **20** with triethylamine trihydrofluoride in DMF liberated the secondary alcohol **21** (96%). Finally, Dess–Martin oxidation of **21** in dichloromethane (CH_2Cl_2) gave the corresponding methyl ketone, and this was spontaneously cyclized to epoxy-γ-lactam to provide (13*R*,14*R*)-epolactaene (**1**) in 74% yield as an approximately 5:1 diastereomeric mixture at C15, as with the natural product. Synthetic epolactaene exhibited physical and spectroscopic data identical with those of the natural product (^{1}H NMR, ^{13}C NMR, and HRMS), including optical rotation ($[\alpha]^{22}_D$ +37 (*c* 0.2, MeOH), lit.[9] $[\alpha]^{22}_D$ +32 (*c* 0.1, MeOH)). According to these results, the absolute configuration of natural (+)-epolactaene was definitively established as (13*R*,14*R*), as we expected.[1]



Scheme 6

Since we were interested in the biological activity,[10] a sequence of reactions similar to the above was applied to the enantiomer of natural epolactaene starting from *anti* epoxide **22**, which had been synthesized in the preceding paper.[1] Addition of the vinyllithium to Weinreb amide **22** gave α,β-unsaturated ketone **23** in 82% yield (Scheme 6). After Dess–Martin oxidation of **23** (81%), the resulting aldehyde **24** was subjected to *E*-selective Wittig reaction with tributylphosphonium salt **19b** under the same condition as above to furnish triene **25** in 72% yield. In this case, the stereoselectivity was slightly increased to 20:1. The resulting triene **25** was subjected to silica gel flash column chromatography to provide the pure *E* isomer. Finally, deprotection of the silyl group with triethylamine trihydrofluoride in DMF (81%) followed by Dess–Martin oxidation provided (–)-epolactaene ((–)-**1**) in 69% yield. The physical and spectroscopic data on the synthetic (–)-epolactaene were of course, identical with those of the natural product and synthetic (+)-epolactaene ((+)-**1**) (^{1}H NMR, ^{13}C NMR and HRMS), with the exception of the sign of the optical rotation ($[\alpha]^{22}_D$ –30 (*c* 0.1, MeOH)).

Conclusion

Total synthesis of neuritogenic compound, epolactaene, has been completed *via* a convergent route involving an *E*-selective Wittig reaction as a key step. The entire synthesis proceeds in 14 steps from known aldehyde. In addition, both (+)- and (–)-epolactaenes have been synthesized and the absolute configuration of the natural product has been confirmed to be (13*R*,14*R*).

Experimental Section

General

Unless otherwise noted, all reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. All other dry solvents were purchased from Aldrich in SureSeal™ containers. All other commercially obtained reagents were used as received. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-EX-270 spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. In NMR spectral lists, chemical shifts which are assigned to minor isomer, are marked with an asterisk. Infrared spectra were recorded on a JASCO FT-IR-8900 spectrometer. Optical rotations were measured on a JASCO P-1030 or DIP-370 polarimeter. Mass spectra were obtained on a JEOL HX-100, an SX-102A or a JMS-AX-505H mass spectrometer. Analytical TLC was performed on 0.25 mm pre-coated Merck silica gel 60 F_{254} plates. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh).

Diethyl (*E*)-2-(3-bromobut-2-enyl)malonate (4):

Methanesulfonyl chloride (2.8 mL, 36 mmol) was added to a solution of (*E*)-3-bromobut-2-en-1-ol (**3**) (4.53 g, 30 mmol) and triethylamine (5.4 mL, 39 mmol) in THF (100 mL) at 0 ℃. The reaction mixture was stirred for 30 min at this temperature and then directly filtered. The filtrate was added dropwise at 0 ℃ to a solution of diethyl malonate (9.7 mL, 60 mmol) in THF (150 mL), pretreated with sodium hydride (55% in mineral oil, 2.62 g, 60 mmol) at 0 ℃, and the stirring was continued for another 2 hours at this temperature. A saturated aqueous NH_4Cl solution was added to the mixture, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting residue was purified by flash chromatography (SiO_2, 5–10% ethyl acetate in hexane) to yield malonate ester **4** as a colorless oil: ^1H NMR (270 MHz, $CDCl_3$) δ 1.23-1.31 (m, 6H), 2.25 (s, 3H), 2.61 (dd, J = 7.6 Hz, 7.2 Hz, 2 H), 3.37 (t, J = 7.6 Hz, 1 H), 4.21 (q, J = 7.2 Hz , 4 H), 5.81 (t, J = 8.3 Hz, 1 H).

(*E*)-2-(3-Bromobut-2-enyl)malonic acid (5):

A 1N aqueous solution of NaOH (80 mL) was added to the resulting solution of malonic ester **4** in ethanol (80 mL) at room temperature. After stirring for 10 hours, the reaction mixture was neutralized with a 1N aqueous solution of HCl and EtOH was removed *in vacuo*. Ethyl acetate was added, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting dicarboxylic acid **5** was used in the next step without further purification: ^1H NMR (270 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.67 (dd, J = 7.8 Hz, 7.0 Hz, 2 H), 3.51 (t, J = 7.8 Hz, 1 H), 5.85 (t, J = 7.0 Hz, 1 H), 6.46 (br. s, 2H).

Methyl (*E*)-5-Bromohex-4-enoate (6):

A solution of the resulting crude dicarboxylic acid **5** in DMF (100 mL) was heated at 100 ℃ for 2 hours, and then cooled to room temperature. Potassium carbonate (6.22 g, 45 mmol) and iodomethane (2.4 mL, 39 mmol) were added to the reaction mixture and the stirring was continued for 1 hour at room temperature. Water was added, and the organic material was extracted with ether, the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 5–10% ethyl acetate in hexane) provided 3.14 g (51% from **3**) of methyl ester **6** as a colorless oil: IR (film) υ_{max} 2953, 2922, 1740, 1653, 1437, 1366, 1202, 1170, 1098, 852, 633 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.29-2.43 (m, 4 H), 3.69 (s, 3 H), 5.82 (t, J = 6.3 Hz, 1 H).

(*E*)-5-Bromohex-4-en-1-ol (7):

Lithium aluminum hydride ($LiAlH_4$) (1.14 g, 30 mmol) was added to a solution of the methyl ester **6** (3.13 g, 15 mmol) in THF (50 mL) at –78 ℃ and the reaction mixture was stirred for 30 min at this temperature. Water (1.1 mL), a 4N aqueous solution of NaOH (1.1 mL), and water (3.4 mL) were added successively and the reac-

tion mixture was allowed to warm to room temperature. After stirring for 30 min, the mixture was filtered using hyflo super-cell® and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2, 10–25 % ethyl acetate in hexane) to yield 2.40 g (89%) of alcohol **7** as a colorless oil: IR (film) υ_{max} 3332, 2938, 2870, 1651, 1430, 1379, 1104, 1054, 636 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.65 (quin, J = 6.8 Hz, 2 H), 2.13 (q, J = 7.5 Hz, 2 H), 2.23 (s, 3H), 3.66 (t, J = 6.3 Hz, 2 H), 5.85 (td, J = 7.8 Hz, 1.2 Hz 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 23.1, 25.9, 31.8, 61.9, 119.8, 130.4; Anal. Calcd for $C_6H_{11}OBr$: C, 40.25; H, 6.19. Found: C, 40.05; H, 6.27.

(2*R*,3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(*E*)-6-hydroxy-2-methylhex-2-enoyl)]oxirane-2-carboxamide (9):

tert-Butyllithium (1.64 M in THF, 2.5 mL, 4.2 mmol) was added dropwise to a solution of **7** (269 mg, 1.5 mmol) in THF (5 mL) at –78 °C, and the reaction mixture was stirred for 20 min at this temperature. A solution of TBS ether **8** (99 mg, 0.3 mmol) in THF (3 mL) was added to the mixture dropwise at –78 °C and the stirring was continued for another 1 hour at this temperature. A saturated aqueous NH_4Cl solution was added, and the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 40–70% ethyl acetate in hexane) provided 91.5 mg (83%) of alcohol **9** as a colorless foam: IR (KBr) υ_{max} 3414, 3170, 2955, 2931, 2860, 1681, 1640, 1603, 1394, 1313, 1259, 1111, 1007, 926, 839, 778 cm^{-1}; $[\alpha]^{22}_D$ –56.7 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.11 (s, 3 H), 0.90 (s, 9 H), 1.29 (d, J = 6.5 Hz, 3 H), 1.73-1.84 (m, 2 H), 1.82 (s, 3 H), 2.43 (q, J = 7.4 Hz, 2 H), 3.27 (d, J = 8.0 Hz, 1 H), 3.66-3.73 (m, 3 H), 5.84 (br s, 1 H), 6.47 (br s, 1 H), 7.00 (td, J = 7.3 Hz, 1.1 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ –4.7, –4.5, 11.2, 18.0, 20.4, 25.7 (x 3), 26.0, 31.2, 62.1, 65.2, 66.9, 67.6, 135.3, 149.4, 167.1, 192.7; HRMS, calcd for $C_{18}H_{34}NO_5Si$ $(M+H)^+$ 372.2206, found 372.2205.

(2*R*,3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(*E*)-2-methyl-6-oxohex-2-enoyl]oxirane-2-carboxamide (10):

Dess–Martin periodinane (178 mg, 0.42 mmol) was added to a solution of alcohol **9** (51.1 mg, 0.14 mmol) in CH_2Cl_2 (1.5 mL) at room temperature and the reaction mixture was stirred for 20 min at this temperature. A 1 M solution of $Na_2S_2O_3$ and a saturated aqueous $NaHCO_3$ solution were added, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 30–50% ethyl acetate in hexane) gave 41.0 mg (81%) of aldehyde **10** as a colorless foam: IR (KBr) υ_{max} 3418, 3336, 3225, 2956, 2931, 2859, 1683, 1589, 1391, 1259, 1006, 924, 837, 779 cm^{-1}; $[\alpha]^{22}_D$ –69.2 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 1.27 (d, J = 6.2 Hz, 3 H), 1.83 (s, 3 H), 2.59-2.73 (m, 4 H), 3.25 (d, J = 8.0 Hz, 1 H), 3.67 (dq, J = 8.0 Hz, 6.2 Hz, 1 H), 6.16 (br s, 1 H), 6.49 (br s, 1 H), 6.91 (t, J = 6.8 Hz, 1 H), 9.82 (s, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ –4.8, –4.5, 11.3, 18.0, 20.3, 21.8, 25.7 (x 3), 42.2, 65.1, 66.7, 67.5, 135.7, 146.8, 167.1, 192.6, 200.3; HRMS, calcd for $C_{18}H_{32}NO_5Si$ $(M+H)^+$ 370.2050, found 370.2068.

(*E*)-3-(*tert*-Butyldiphenylsilyl)oxy-1-iodo-2-methylpropene (13):

TBDPSCl (10 mL, 39 mmol) was added to a solution of (*E*)-3-iodo-2-methylprop-2-en-1-ol (**12**) (7.00 g, 36 mmol) and imidazole (7.28 g, 107 mmol) in DMF (100 mL) at room temperature and the reaction mixture was stirred for 1 hour at this temperature. A saturated aqueous $NaHCO_3$ solution was added, the organic material was extracted with ether, and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 3 % ethyl acetate in hexane) furnished 14.9 g (96%) of TBDPS ether **13** as a colorless oil: IR (film) υ_{max} 3071, 3050, 2959, 2931, 2857, 1471, 1428, 1368, 1281, 1112, 826, 740, 702, 614, 505 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.06 (s, 9 H),

1.75 (s, 3 H), 4.11 (s, 2 H), 6.29 (s, 1 H), 7.35-7.44 (m, 6 H), 7.63-7.66 (m, 4 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.3, 21.2, 26.8 (x 3), 67.6, 76.0, 127.8 (x 4), 129.8 (x 2), 133.1 (x 2), 135.5 (x 4), 146.4; HRMS, calcd for $C_{20}H_{24}OISi$ $(M - H)^+$ 435.0641, found 435.0651. Anal. Calcd for $C_{20}H_{25}OISi$: C, 55.05; H, 5.77. Found: C, 54.97; H, 5.82.

Methyl (*E*)-5-[(*tert*-butyldiphenylsilyl)oxy]-2-[(*E*)-ethylidene]-4-methylpent-3-enoate (16):

tert-Butyllithium (1.64 M in THF, 7.6 mL, 12.5 mmol) was added dropwise to a solution of TBDPS ether **13** (2.18 g, 5.0 mmol) in THF (50 mL) at –78 °C and the reaction mixture was stirred for 10 min at this temperature. A solution of trimethyltin chloride (1.0 M in THF, 10 mL, 10 mmol) was added dropwise at –78 °C and the stirring was continued for another 20 min at this temperature. A saturated aqueous NH_4Cl solution was added and the organic material was extracted with ethyl acetate, the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration to yield vinylstannane **14**. Methyl (*Z*)-2-bromobut-2-enoate (**15**) (895 mg, 5.0 mmol) and $Pd(PPh_3)_4$ (578 mg, 0.50 mmol) were added to a solution of the crude **14** in toluene (50 mL) and the reaction mixture was heated under reflux for 12 hours. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (SiO_2, 3–5% ethyl acetate in hexane) to give 961 mg (47%) of diene **16** as a colorless oil: IR (film) υ_{max} 2952, 2933, 2858, 1720, 1429, 1250, 1194, 1112, 825, 741, 703, 615, 505 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.08 (s, 9 H), 1.48 (s, 3 H), 1.73 (d, J = 7.2 Hz, 3 H), 3.74 (s, 3 H), 4.19 (s, 2 H), 6.17 (br s, 1 H), 6.93 (q, J = 7.2 Hz, 1 H), 7.34-7.46 (m, 6 H), 7.69-7.74 (m, 4 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.2, 15.5, 19.3, 26.8 (x 3), 51.7, 68.1, 117.0, 127.6 (x 4), 129.6 (x 2), 130.4, 133.7 (x 2), 135.5 (x 4), 139.0, 139.5, 168.1; HRMS, calcd for $C_{25}H_{33}O_3Si$ $(M + H)^+$ 409.2199, found 409.2175. Anal. Calcd for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.66; H, 7.82.

Methyl (*E*)-2-[(*E*)-ethylidene]-5-hydroxy-4-methylpent-3-enoate (17):

TBAF (1.0 M in THF, 3.6 mL, 3.6 mmol) was added to a solution of diene **16** (1.33g, 3.2 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature and stirred for 3 hours. Water was added, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 15–30% ethyl acetate in hexane) afforded 473 mg (86%) of alcohol **17** as a colorless oil: IR (film) υ_{max} 3430, 2951, 2915, 2857, 1718, 1634, 1436, 1265, 1197, 1136, 1043, 1020, 759, 732 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.56 (s, 3 H), 1.63 (br s, 1 H), 1.74 (d, J = 7.3 Hz, 3 H), 3.74 (s, 3 H), 4.16 (s, 2 H), 6.04 (s, 1 H), 6.95 (q, J = 7.3 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.3, 15.6, 51.8, 67.8, 117.9, 130.0, 139.6, 140.5, 167.9; HRMS, calcd for $C_9H_{14}O_3$ M^+ 170.0943, found 170.0941. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.18; H, 8.00.

Methyl (*E*)-5-bromo-2-[(*E*)-ethylidene]-4-methylpent-3-enoate (18):

Carbon tetrabromide (1.03 g, 3.1 mmol) was added to a solution of the alcohol **17** (264 mg, 1.6 mmol) and triphenylphosphine (813 mg, 3.1 mmol) in THF (10 mL) at 0 °C and the reaction mixture was stirred for 30 min at this temperature. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (SiO_2, 0–3% ethyl acetate in hexane) to give 343 mg (95%) of bromide **18** as a colorless oil: IR (film) υ_{max} 2950, 1720, 1635, 1435, 1255, 1218, 1195, 1127, 1059, 1026, 1000, 760, 731, 615 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.69 (d, J = 1.2 Hz, 3 H), 1.75 (dd, J = 7.3 Hz, 1.3 Hz, 3 H), 3.74 (s, 3 H), 4.07 (s, 2 H), 6.17 (br s, 1 H), 6.99 (q, J = 7.3 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.5, 16.6, 39.8, 51.9, 123.4, 129.6, 137.2, 140.8, 167.3; HRMS, calcd for $C_9H_{13}O_2Br$ M^+ 232.0099, found 232.0093.

Triphenyl-[(2*E*, 4*E*)-4-methoxycarbonyl-2-methylhexa-2,4-dienyl]phosphonium bromide (19a):

Triphenylphosphine (21.0 mg, 0.08 mmol) was added to a solution of the bromide **18** (16.3 mg, 0.07 mmol) in acetonitrile (3 mL) and the reaction mixture was heated under reflux for 3 hours. The solvent was removed *in vacuo* and the resulting residue was recrystalized with acetonitrile and ethyl acetate to afford 31.6 mg (91%) of

phosphonium salt **19a** as colorless prisms: mp 199-201 °C; IR (KBr) υ_{max} 3407, 3054, 3005, 2844, 2775, 1711, 1588, 1485, 1437, 1265, 1112, 1025, 996, 751, 719, 692, 506, 497 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.40 (d, J = 1.7 Hz, 3 H), 1.68 (d, J = 7.2 Hz, 3 H), 3.65 (s, 3 H), 4.88 (d, J = 15.3 Hz, 2 H), 5.98 (br s, 1 H), 6.89 (q, J = 7.2 Hz, 1 H), 7.65-7.73 (m, 6 H), 7.77-7.85 (m, 3 H), 7.90-7.98 (m, 6 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.8, 20.6, 33.8 (d, J = 47.1 Hz), 51.7, 118.4 (d, J = 85.2 Hz) (x 3), 128.3, 128.4, 128.6, 130.1 (x 6), 134.2 (x 6), 134.9 (x 3), 141.7, 166.7; HRMS, calcd for $C_{27}H_{28}O_2P$ $(M-Br)^+$ 415.1827, found 415.1836. Anal. Calcd for $C_{27}H_{28}O_2BrP$: C, 65.46; H, 5.70; P, 6.25. Found: C, 65.43; H, 5.73; P, 6.23.

Tributyl-[(2*E*, 4*E*)-4-methoxycarbonyl-2-methylhexa-2,4-dienyl]phosphonium bromide (19b):

Tributylphosphine (0.18 mL, 0.74 mmol) was added to a solution of the bromide **18** (132 mg, 0.57 mmol) in acetonitrile (4 mL) and the reaction mixture was heated under reflux for 20 min. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (SiO_2, 0–2% methanol in chloroform) to yield 249 mg (quantitative) of phosphonium salt **21b** as a colorless oil: IR (film) υ_{max} 3401, 2960, 2934, 2874, 1714, 1464, 1436, 1252 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (t, J = 7.0 Hz, 9 H), 1.50-1.68 (m, 12 H), 1.71-1.78 (m, 3 H), 1.76 (s, 3 H), 2.45-2.56 (m, 6 H), 3.69 (d, J = 15.8 Hz, 2 H), 3.74 (s, 3 H), 6.06 (br d, J = 5.0 Hz, 1 H), 7.10 (q, J = 7.1 Hz, 1 H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.4 (x 3), 15.8, 19.2 (d, J = 46.2 Hz) (x 3), 20.4, 23.9 (x 3), 24.1 (x 3), 29.3 (d, J = 44.6 Hz), 51.9, 126.8, 127.0, 129.0, 141.3, 166.7; HRMS calcd for $C_{21}H_{40}O_2P$ $(M-Br)^+$ 355.2766, found 355.2776.

Methyl (3*E*, 5*E*, 9*E*)-11-[(2*R*, 3*S*)-3-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-(carbamoyl)oxiranyl]-4,10-dimethyl-2-[(*E*)-ethylidene]-11-oxoundeca-3,5,9-trienoate (20):

Potassium *tert*-butoxide (1.0 M in THF, 0.33 mL, 0.33 mmol) was added to a solution of the phosphonium salt **19b** (179 mg, 0.41 mmol) and 18-crown-6/CH_3CN (125 mg, 0.41 mmol) in THF (1 mL) at –78 °C. The reaction mixture was allowed to warm to –46 °C and stirred for 15 min. A solution of aldehyde **10** (30.1 mg, 0.081 mmol) in THF (1 mL) was added to the reaction mixture at –46 °C and the stirring was continued for another 10 min at this temperature. A saturated aqueous $NaHCO_3$ solution was added, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 10–25% ethyl acetate in hexane) afforded 28.6 mg (69%) of triene (*E*:*Z*=10:1). This mixture was then separated by flash chromatography (SiO_2, 8% ethyl acetate in benzene) to obtain 16.8 mg of *E* isomer **20** as a colorless oil: IR (film) υ_{max} 3476, 3334 2953, 2931, 2858, 1714, 1695, 1436, 1259, 1111, 1006, 836, 779 cm^{-1}; $[\alpha]^{22}_D$ –58.4 (*c* 0.50, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.89 (s, 9 H), 1.27 (d, J = 6.3 Hz, 3 H), 1.63 (s, 3 H), 1.73 (dd, J = 7.2 Hz, 1.2 Hz, 3 H), 1.81 (s, 3 H), 2.34-2.50 (m, 4 H), 3.29 (d, J = 8.2 Hz, 1 H), 3.68-3.77 (m, 1 H), 3.73 (s, 3 H), 5.72 (dt, J = 15.4 Hz, 6.8 Hz, 1 H), 5.90 (br s, 1 H), 5.96 (br s, 1 H), 6.25 (d, J = 15.4 Hz, 1 H), 6.28 (br s, 1 H), 6.91-6.99 (m, 2 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ –4.7, –4.5, 11.3, 14.3, 15.8, 18.0, 20.4, 25.7 (x 3), 28.8, 31.4, 51.9, 65.1, 66.8, 67.5, 122.9, 128.4, 130.4, 135.2, 135.5, 138.1, 139.8, 148.3, 167.0, 167.8, 192.6; HRMS, calcd for $C_{27}H_{43}NO_6SiNa$ $(M+Na)^+$ 528.2757, found 528.2754.

Methyl (3*E*, 5*E*, 9*E*)-11-[(2*R*, 3*S*)-2-carbamoyl-3-[(*R*)-1-hydroxyethyl]oxiranyl]-4,10-dimethyl-2-[(*E*)-ethylidene]-11-oxoundeca-3,5,9-trienoate (21):

Triethylamine trihydrofluoride (50 μL) was added to a solution of triene **20** (3.6 mg, 0.007 mmol) in DMF (0.5 mL) at room temperature and the reaction mixture was stirred for 1 day. The solvent was concentrated, and the resulting residue was purified by flash chromatography (SiO_2, 50–80% ethyl acetate in hexane) to give 2.7 mg (96%) of alcohol **21** as a colorless oil: IR ($CHCl_3$) υ_{max} 3693, 3606, 3510, 3494, 2984, 2953, 1702, 1602, 1438, 1275, 1138, 1056, 966 cm^{-1}; $[\alpha]^{22}_D$ –64.3 (*c* 0.30, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.34 (d, J = 6.4 Hz, 3 H), 1.63 (s, 3 H), 1.75 (d, J = 7.2 Hz, 3 H), 1.81 (s, 3 H), 2.33-2.50 (m, 4 H), 3.29 (d, J = 8.0 Hz, 1 H), 3.74 (s, 3 H), 3.77-3.84 (m, 1 H), 5.70 (dt, J = 15.3 Hz, 6.8 Hz, 1 H), 5.93 (br s, 1 H), 5.97 (s, 1 H),

6.25 (d, J = 15.3 Hz, 1 H), 6.45 (br s, 1 H), 6.91-6.99 (m, 2 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.3, 14.3, 15.8, 19.3, 28.5, 31.3, 52.0, 65.6, 65.8, 66.2, 123.0, 128.2, 130.3, 135.0, 135.8, 138.2, 140.0, 148.5, 166.9, 168.0, 192.7; HRMS, calcd for $C_{21}H_{29}NO_6Na$ $(M + Na)^+$ 414.1893, found 414.1887.

Methyl (3*E*, 5*E*, 9*E*)-4,10-dimethyl-2-[(*E*)-ethylidene]-11-[(1*R*, 5*R*)-4-hydroxy-4-methyl-2-oxo-6-oxa-3-azabicyclo[3.1.0]hex-1-yl]-11-oxo-3,5,9-undecatrienoate ((+)-epolactaene, (+)-1):

Dess–Martin periodinane (66 mg, 0.078 mmol) was added to a solution of alcohol **21** (6.1 mg, 0.016 mmol) in CH_2Cl_2 (0.5 mL) at room temperature and the reaction mixture was stirred for 1 hour at this temperature. A 1 M solution of $Na_2S_2O_3$ and a saturated aqueous $NaHCO_3$ solution were added, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 40–60% ethyl acetate in hexane) furnished 4.5 mg (74%) of (+)-epolactaene ((+)-**1**) as a colorless oil: IR ($CHCl_3$) υ_{max} 3693, 3423, 2954, 1731, 1689, 1603, 1438, 1280, 1140, 1064, 967, 952 cm^{-1}; $[\alpha]^{22}_D$ +37.0 (*c* 0.20, MeOH); ^{1}H NMR (270 MHz, CD_3OD) δ 1.52 and 1.56* (each s, 3 H), 1.62 (d, J = 0.9 Hz, 3 H), 1.72 (dd, J = 7.1 Hz, 1.3 Hz, 3 H), 1.83 (s, 3 H), 2.33-2.38 (m, 2 H), 2.43-2.52 (m, 2 H), 3.72 (s, 3 H), 3.98 and 4.06* (each s, 1 H), 5.78 (dt, J = 15.5 Hz, 7.1 Hz, 1 H), 5.94 (br s, 1 H), 6.28 and 6.26* (each d, J = 15.5 Hz, J *= 15.7 Hz, 1 H), 6.93 (qd, J = 7.2 Hz, 0.9 Hz, 1 H), 7.02 and 6.74* (td and br t* J = 6.9 Hz, 1.2 Hz, J *= 7.0 Hz, 1 H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 11.2, 14.6, 16.0, 22.2, 30.2, 32.5, 52.4, 64.0, 66.1, 84.8, 123.6, 129.7, 131.9, 136.6, 137.3, 139.6, 140.9, 150.1, 169.5, 172.2, 192.1; HRMS, calcd for $C_{21}H_{27}NO_6Na$ $(M + Na)^+$ 412.1736, found 412.1753.

(2*S*, 3*R*)-2-[(*E*)-6-Hydroxy-2-methylhex-2-enoyl]-3-[(*R*)-1-[(triethylsilyl)oxy]-ethyl]oxirane-2-carboxamide (23):

tert-Butyllithium (1.64 M in THF, 3.9 mL, 6.4 mmol) was added dropwise to a solution of vinylbromide **7** (405 mg, 2.3 mmol) in THF (5 mL) at –78 °C, and the reaction mixture was stirred for 20 min at this temperature. A solution of TES ether **22** (150 mg, 0.45 mmol) in THF (5 mL) was added dropwise at –78 °C, the stirring was continued for another 2 hours at this temperature. A saturated aqueous NH_4Cl solution was added and the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 50–70% ethyl acetate in hexane) provided 137 mg (82%) of alcohol **23** as a colorless foam: IR (KBr) υ_{max} 3405, 3194, 2956, 2878, 1692, 1660, 1633, 1413, 1396, 1323, 1275, 1240, 1164, 1111, 1003, 774, 745, 730 cm^{-1}; $[\alpha]^{22}_D$ +55.1 (*c* 0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.61 (q, J = 7.9 Hz, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.35 (d, J = 6.2 Hz, 3 H), 1.74-1.82 (m, 2 H), 1.83 (s, 3 H), 2.38-2.48 (m, 2 H), 3.18 (d, J = 7.4 Hz, 1 H), 3.70 (t, J = 6.1 Hz, 2 H), 3.76-3.86 (m, 1 H), 5.63 (br s, 1 H), 6.47 (br s, 1 H), 7.12 (t, J = 7.7 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 4.9 (x 3), 6.7 (x 3), 11.2, 21.7, 26.2, 31.2, 62.2, 65.4, 66.0, 66.1, 135.2, 150.0, 166.6, 193.4; HRMS, calcd for $C_{18}H_{34}NO_5Si$ $(M + H)^+$ 372.2206, found 372.2213. Anal. Calcd for $C_{18}H_{33}NO_5Si$: C, 58.19; H, 8.95; N, 3.77. Found: C, 58.04; H, 8.72; N, 3.67.

(2*S*, 3*R*)-2-[(*E*)-2-Methyl-6-oxohex-2-enoyl]-3-[(*R*)-1-[(triethylsilyl)oxy]ethyl]-oxirane-2-carboxamide (24):

Dess–Martin periodinane (206 mg, 0.48 mmol) was added to a solution of alcohol **23** (60.0 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) at room temperature and the reaction mixture was stirred for 2 hours at this temperature. A 1 M solution of $Na_2S_2O_3$ and a saturated aqueous $NaHCO_3$ solution were added, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 30–40% ethyl acetate in hexane) gave 48.1 mg (81%) of aldehyde **24** as a colorless foam: IR (KBr) υ_{max} 3402, 3183, 2956, 2878, 1728, 1692, 1661, 1637, 1414, 1323, 1241, 1164, 1111, 1005, 775, 746, 729, 622 cm^{-1}; $[\alpha]^{22}_D$ +61.0 (*c* 0.50, $CHCl_3$); ^{1}H NMR (270

MHz, $CDCl_3$) δ 0.60 (q, *J* = 7.9 Hz, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.34 (d, *J* = 6.4 Hz, 3 H), 1.84 (s, 3 H), 2.55-2.72 (m, 4 H), 3.16 (d, *J* = 7.3 Hz, 1 H), 3.75-3.86 (m, 1 H), 5.58 (br s, 1 H), 6.46 (br s, 1 H), 7.00 (t, *J* = 7.1 Hz, 1 H), 9.81 (s, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 4.9 (x 3), 6.7 (x 3), 11.3, 21.7, 21.9, 42.2, 65.3, 65.9, 66.0, 135.7, 147.2, 166.3, 193.5, 200.3; HRMS, calcd for $C_{18}H_{32}NO_5Si$ $(M + H)^+$ 370.2050, found 370.2029.

Methyl (3*E*, 5*E*, 9*E*)-11-[(2*S*, 3*R*)-2-carbamoyl-3-[(*R*)-1-[(triethylsilyl)oxy]-ethyl]oxiranyl]-4,10-dimethyl-2-[(*E*)-ethylidene]-11-oxoundeca-3,5,9-trienoate (25):

Potassium *tert*-butoxide (1.0 M in THF, 50 μL, 0.05 mmol) was added to a solution of the phosphonium salt **19b** (30.5 mg, 0.07 mmol) and 18-crown-6/CH_3CN (21.4 mg, 0.07 mmol) in THF (1 mL) at –78 °C. The reaction mixture was allowed to warm to –46 °C and stirred for 20 min, a solution of aldehyde **24** (5.0 mg, 0.014 mmol) in THF (1 mL) was added at –46 °C, and the stirring was continued for another 20 min at this temperature. A saturated aqueous $NaHCO_3$ solution was added, the organic material was extracted with ethyl acetate, and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 20–30% ethyl acetate in hexane) afforded 4.9 mg (72%) of triene (*E*:*Z*=20:1). This mixture was separated by flash chromatography (SiO_2, 8% ethyl acetate in benzene) to obtain 4.2 mg of *E* isomer **25** as a colorless oil: IR (film) υ_{max} 3467, 3336, 3193, 2955, 2878, 1695, 1639, 1590, 1436, 1378, 1254, 1113, 1005, 748 cm^{-1}; $[\alpha]^{22}_D$ +44.5 (*c* 0.50, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.62 (q, *J* = 7.8 Hz, 6 H), 0.97 (t, *J* = 7.8 Hz, 9 H), 1.35 (d, *J* = 6.1 Hz, 3 H), 1.63 (s, 3 H), 1.74 (dd, *J* = 7.1 Hz, 1.1 Hz, 3 H), 1.82 (s, 3 H), 2.34-2.50 (m, 4 H), 3.22 (d, *J* = 7.7 Hz, 1 H), 3.74 (s, 3 H), 3.75-3.88 (m, 1 H), 5.72 (dt, *J* = 15.6 Hz, 6.8 Hz, 1 H), 5.92 (br s, 1 H), 5.97 (s, 1 H), 6.26 (d, *J* = 15.6 Hz, 1 H), 6.35 (br s, 1 H), 6.96 (q, *J* = 7.1 Hz, 1 H), 7.04 (t, *J* = 7.3 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 4.8 (x 3), 6.7 (x 3), 11.3, 14.3, 15.8, 21.7, 29.0 31.5, 51.8, 65.1, 65.9, 66.0, 122.8, 128.4, 130.4, 135.1, 135.3, 138.1, 139.8, 148.8, 166.6, 167.8, 193.4; HRMS, calcd for $C_{27}H_{44}NO_6Si$ $(M + H)^+$ 506.2938, found 506.2939.

Methyl (3*E*, 5*E*, 9*E*)-11-[(2*S*, 3*R*)-2-carbamoyl-3-[(*R*)-1-hydroxyethyl]oxiranyl]-4,10-dimethyl-2-[(*E*)-ethylidene]-11-oxoundeca-3,5,9-trienoate (26):

Triethylamine trihydrofluoride (20 μL) was added to a solution of triene **25** (9.3 mg, 0.018 mmol) in DMF (0.5 mL) at room temperature and the reaction mixture was stirred for 1 hour. The solvent was concentrated, and the resulting residue was purified by flash chromatography (SiO_2, 50–80% ethyl acetate in hexane) to give 5.8 mg (81%) of alcohol **26** as a colorless oil: IR (film) υ_{max} 3435, 3337, 2979, 2950, 1689, 1637, 1595, 1436, 1265, 1213, 1136, 1060, 1024, 966, 760, 616 cm^{-1}; $[\alpha]^{22}_D$ +18.3 (*c* 0.20, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.39 (d, *J* = 6.3 Hz, 3 H), 1.62 (s, 3 H), 1.73 (dd, *J* = 7.3 Hz, 1.2 Hz, 3 H), 1.81 (s, 3 H), 2.33-2.51 (m, 4 H), 2.82 (d, *J* = 3.2 Hz, 1 H), 3.17 (d, *J* = 7.9 Hz, 1 H), 3.70-3.77 (m, 1 H), 3.73 (s, 3 H), 5.70 (dt, *J* = 15.6 Hz, 6.8 Hz, 1 H), 5.95 (s, 1 H), 6.08 (br s, 1 H), 6.26 (d, *J* = 15.6 Hz, 1 H), 6.35 (br s, 1 H), 6.94 (q, *J* = 7.3 Hz, 1 H), 7.10 (t, *J* = 6.8 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.3, 14.3, 15.8, 20.3, 28.9, 31.4, 51.9, 65.4, 65.7, 66.1, 122.9, 128.3, 130.4, 135.1, 135.6, 138.2, 139.9, 149.7, 167.1, 167.9, 192.8; HRMS, calcd for $C_{21}H_{30}NO_6$ $(M + H)^+$ 392.2073, found 392.2093.

Methyl (3*E*, 5*E*, 9*E*)-4,10-dimethyl-2-[(*E*)-ethylidene]-11-[(1*S*, 5*S*)-4-hydroxy-4-methyl-2-oxo-6-oxa-3-azabicyclo[3.1.0]hex-1-yl]-11-oxoundeca-3,5,9-trienoate ((–)-Epolactaene, (–)-1):

Dess–Martin periodinane (23.8 mg, 0.056 mmol) was added to a solution of alcohol **26** (2.2 mg, 0.006 mmol) in CH_2Cl_2 (0.5 mL) at room temperature and the reaction mixture was stirred for 30 min at this temperature A 1 M solution of $Na_2S_2O_3$ and a saturated aqueous $NaHCO_3$ solution were added, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 40–60% ethyl acetate in hexane) furnished 1.5 mg (69%) of (–)-epolactaene ((–)-**1**) as a colorless oil: $[\alpha]^{22}_D$ –30.0 (*c* 0.10, MeOH);

HRMS, calcd for $C_{21}H_{28}NO_6$ $(M+H)^+$ 390.1917, found 390.1936.

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