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Enantioselective total synthesis of macrolide (+)-neopeltolide†

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The asymmetric total synthesis of the anti-proliferative macrolide (+)-neopeltolide has been completed. The stereochemically defined trisubstituted tetrahydropyran ring was constructed *via* a catalytic hetero-Diels–Alder reaction creating two new chiral centers in a highly diastereoselective manner. The other key features of this synthesis included Brown's asymmetric allylation to install the requisite C-11 and C-13 stereocenters. The synthesis of the oxazole side chain consisted of a hydrozirconation of an alkynyl stannane to establish the *Z* stereochemistry, followed by a palladium catalyzed cross coupling to introduce the desired *Z* olefin in the oxazole side chain.

Introduction

The five oceans and seven seas that surround the earth encompass about 90% of all living organisms.[1] These organisms produce various primary and secondary metabolites that have been found to have complex structural features and biological importance. One of these metabolites, (+)-neopeltolide was isolated in 2007 off the north coast of Jamaica by Wright and co-workers, from a deep water sponge that was approximately half a kilometer below the ocean surface.[2] Subsequently, it was shown that (+)-neopeltolide is a potent *in vitro* anti-proliferative agent against the growth of several cancer cell lines including A549 human lung adenocarcinoma (IC_{50} = 1.2 nM), NCI/ADR-RES ovarian sarcoma (IC_{50} = 5.1 nM) and P388 murine leukemia (IC_{50} = 0.56 nM). In the PANC-1 pancreatic cancer cell line and the DLD-1 colorectal adenocarcinoma cell line, both of which have p53 mutations,[2] (+)-neopeltolide exhibited nanomolar inhibition of cell proliferation that was independent of dose concentration, suggesting that it may act as a cytostatic inhibitor of these cell lines. In addition to anti-proliferatory activity, neopeltolide has also shown anti-fungal activity against *Candida albicans*.[2,3]

Neopeltolide's outstanding biological activity has led to structure–activity relationship (SAR) studies and the identification of its molecular target. In a study led by Kozmin and co-workers it was shown that mitochondrial cytochrome bc_1 is the principal target of (+)-neopeltolide, ultimately inhibiting the production of ATP in the cell.[4] Preliminary SAR and structural studies of (+)-neopeltolide established that the oxazole side chain along with the macrolactone are essential for its biological activity.[4] Of note, leucascandrolide A, which was isolated in 1996, off the east coast of New Caledonia in the Coral Sea from the calcareous sponge *Leucascandra caveolata* by Pietra and co-workers,[5] shares structural similarities with (+)-neopeltolide (Fig. 1). Both neopeltolide and leucascandrolide A contain the same unsaturated oxazole side chain attached to a tetrahydropyran ring and, interestingly, both molecules target mitochondrial cytochrome bc_1. Although these molecules were isolated from opposite sides of the world, Kozmin and co-workers hypothesized that (+)-neopeltolide was a simplified analog of

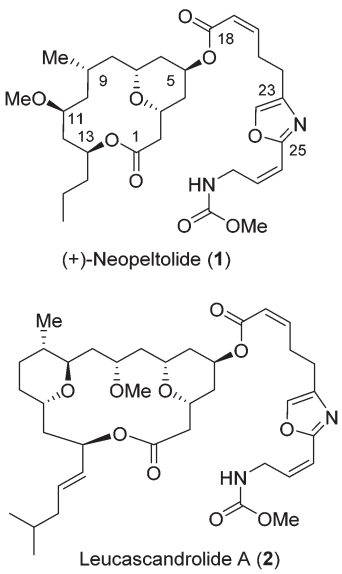

Fig. 1 Structures of (+)-neopeltolide and leucascandrolide A.

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leucascandrolide A. The complex structural features of (+)-neopeltolide, its interesting biological activity, and limited material available from the natural source have led to several total syntheses,[6] and formal syntheses.[7] Herein, we report the enantioselective total synthesis of (+)-neopeltolide.

Results and discussion

Retrosynthetic analysis of neopeltolide revealed some key disconnections, shown in Fig. 2. Disconnection of the alkyl ester oxygen bond of the oxazole side chain would give acid **3**, which can undergo Mitsunobu esterification with the corresponding macrolactone. Yamaguchi macrolactonization of acid **4** would in turn give the desired macrolactone. The tetrahydropyran ring present in acid **4** could be constructed *via* a hetero-Diels–Alder reaction between aldehyde **7** and silyloxy diene ether **8** using Jacobsen's chromium catalyst.[8] Silyloxy diene **8** could be derived from the desymmetrization of glutaric anhydride, followed by a series of Brown's asymmetric allylations to afford the desired stereochemistry at C-11 and C-13. The oxazole side chain **3** would come from a palladium catalyzed cross coupling between oxazole **6** and stannane **5**; followed by a two carbon homologation and Still–Gennari olefination to give the corresponding *Z* olefin. The *Z* geometry in stannane **5** could be established *via* a hydrozirconation reduction of the corresponding alkyne.

The synthesis of the macrolactone ring of (+)-neopeltolide (**1**) commenced with commercially available 3-methylglutaric anhydride **9**, as shown in Scheme 1. This achiral starting material was desymmetrized using PS-30 "Amano" lipase.[9] The resulting acid was obtained in excellent yield and

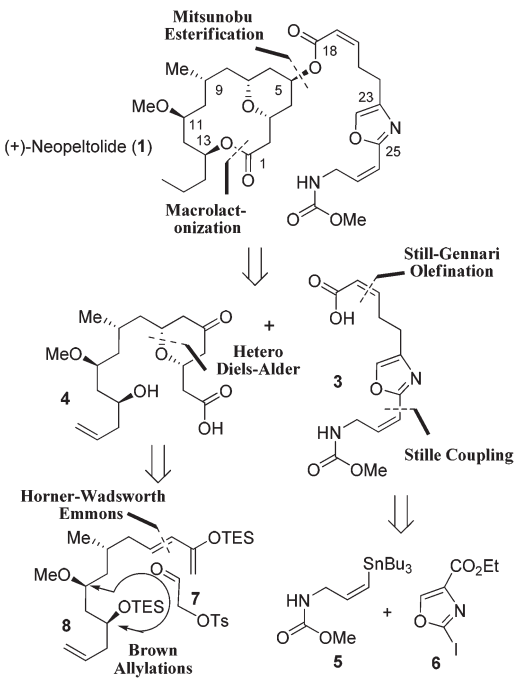
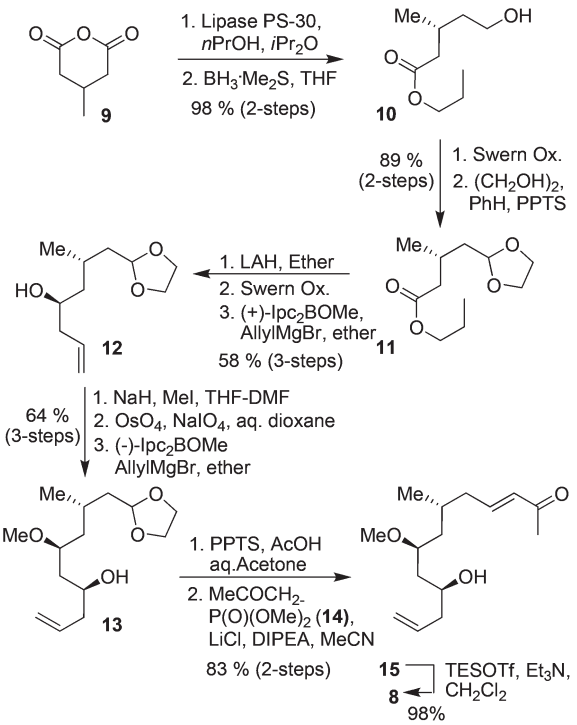


Fig. 2 Retrosynthetic analysis of (+)-neopeltolide.



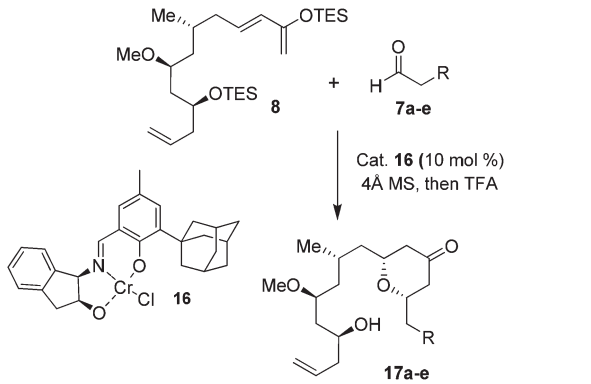
Scheme 1 Diastereoselective synthesis of silyloxy diene **8**.

enantioselectivity (85% ee). Treatment of the corresponding acid with borane–dimethylsulfide complex at 0 °C in tetrahydrofuran selectively reduced the acid in the presence of the propyl ester to furnish alcohol **10** in 98% yield in two steps. Swern oxidation of the alcohol at −78 °C followed by protection of the aldehyde gave acetal **11** in 89% yield in two steps.[10] During our initial efforts, reduction of ester **11** on a large scale (~6 g) with DIBALH (1 M in toluene or dichloromethane) to its aldehyde gave low yields (<20%).

To circumvent this problem we employed a two-step procedure; first, LAH reduction of ester **11** at 0 °C to the corresponding alcohol in 88% yield followed by Swern oxidation gave the desired aldehyde in 76% yield. Treatment of the resulting aldehyde with (+)-Ipc_2BOMe and allyl magnesium bromide at −78 °C gave alcohol **12** in 87% yield which was purified by flash chromatography (99 : 1 dr by ^1H NMR).[11]

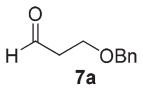
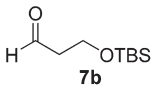
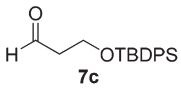
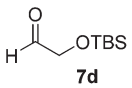
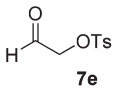
Methylation of alcohol **12** with MeI, followed by Lemieux–Johnson oxidation, afforded the aldehyde in 70% yield in two steps,[12] which was subjected to Brown's allylation protocol to afford alcohol **13** in 91% yield which was purified by flash chromatography (99 : 1 dr by ^1H NMR) (Scheme 1). Deprotection of **13** under acidic conditions revealed the aldehyde which was subjected to Horner–Wadsworth–Emmons olefination giving the α,β-unsaturated ketone **15** in 83% yield in two steps.[13] Treatment of ketone **15** with TESOTf and triethylamine furnished the desired silyloxy diene **8** in 98% yield.

After the synthesis of silyloxy diene **8** was complete, several aldehydes were screened for the hetero-Diels–Alder reaction (Scheme 2). Unfortunately after stirring for seven days aldehydes **7a–7c** gave poor yields (entries 1–3, Table 1). Therefore,



Scheme 2 Hetero-Diels–Alder reaction and synthesis of tetrahydropyranone **17a–e**.

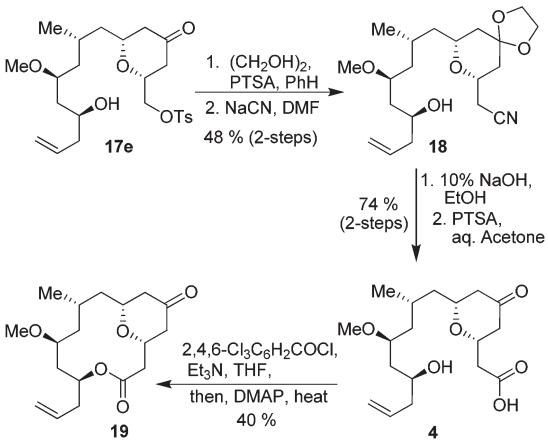
Table 1 Hetero-Diels–Alder reactions with various aldehydes[a]

Entry	Aldehyde	Solvent	Time	Yield[c,d]
1	 **7a**	MTBE[b] or acetone	7 days	Trace
2	 **7b**	MTBE	7 days	31%
3	 **7c**	MTBE	7 days	35%
4	 **7d**	MTBE	40 h	82%
5	 **7e**	Ethyl acetate	36 h	83%

[a] All reactions were carried out at 2.5 M concentration. [b] Methyl *tert*-butyl ether. [c] Isolated yields reported. [d] A mixture of diastereomeric diene **8** was employed for entries 1–4.

we decided to try an aldehyde with a shorter alkyl chain in an effort to increase the reactivity of the carbonyl by placing the oxygen closer, which will create a slight electron withdrawing effect, making the aldehyde more reactive. To our delight, aldehydes **7d** and **7e** gave satisfactory results with 82% and 83% yields, respectively. Hetero-Diels–Alder product **17e** showed excellent diastereoselectivity after purification by flash chromatography (97 : 3 dr by ^{1}H NMR). Although the reaction proceeded well with the TBS protected alcohol, we chose to proceed with the tosyloxyacetaldehyde **7e** because subsequent reactions with the tosyl group were more efficient.[14]

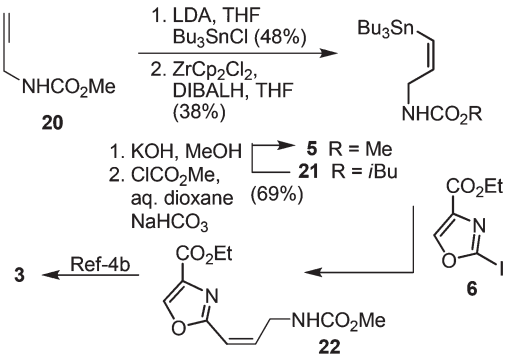
At this point, we tried to displace the tosylate **17e** with NaCN without protecting the ketone, which proved to be unsuccessful due to the acidic nature of the associated ketone α-protons that resulted in decomposition of the starting material. To avoid this problem, ketone **17e** was protected as the corresponding ketal and then treated with NaCN in DMF at 75 °C to give nitrile **18** in 48% yield in two steps (Scheme 3).



Scheme 3 Synthesis of macrolactone **19**.

Treatment of **18** with 10% NaOH gave the desired acid, which was subsequently deprotected under acidic conditions to reveal ketone **4** in 74% yield in two steps. Yamaguchi macrolactonization afforded the desired macrolactone **19** in 40% yield.[15]

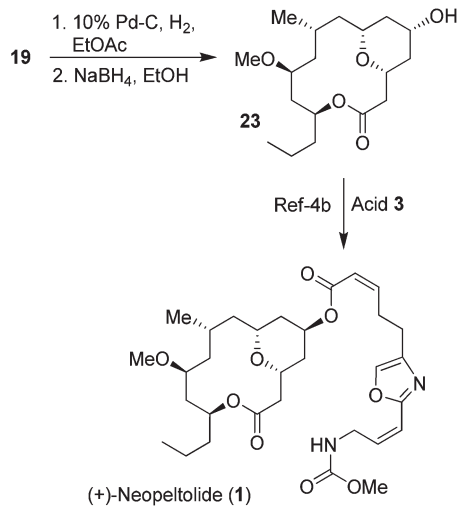
With macrolactone **19** in hand, we turned our attention to the synthesis of the unsaturated oxazole side chain. Treatment of known alkyne **20** with LDA at −78 °C followed by the addition of Bu_3SnCl afforded the desired alkynyl stannane in 48% yield (Scheme 4).[16] Hydrozirconation of the corresponding alkynyl stannane gave a mixture of carbamates **5** and **21** in 38% and 18% yield, respectively.[17] To our delight, treatment of isobutyl carbamate **21** with KOH in methanol followed by methylchloroformate returned the desired methyl carbamate **5** in 69% yield in two steps.



Entry	Pd Catalyst	Mol% Pd Cat.[a]	Temp (°C)	Solvent[b]	Yield[c]
1	$Pd(PPh_3)_2Cl_2$	6	90	Dioxane	–
2	$Pd(PhCN)_2Cl_2$	20	23	DMF	35%
3	$Pd(MeCN)_2Cl_2$	20	23	DMF	51%

[a] Mole% palladium catalyst used; [b] All Reactions were carried out at 0.2 M concentration; [c] Isolated yields after chromatography.

Scheme 4 Stille cross coupling of oxazole **6** and vinyl stannane **5**.



Scheme 5 Synthesis of (+)-neopeltolide.

Iodo oxazole **6** was synthesized according to a literature procedure in 25% yield from ethyl 2-aminooxazole-4-carboxylate using Sandmeyer's modified reaction conditions.[18] With the desired coupling partners in hand, we attempted several Pd coupling conditions, shown in Scheme 4. When $Pd(PPh_3)_2Cl_2$ in dioxane at 90 °C was used, this resulted in decomposition of the vinyl stannane **5**. We turned our attention to other Pd sources that had been previously used in similar coupling strategies.[19] $Pd(MeCN)_2Cl_2$ formed **22** in 51% yield, while $Pd(PhCN)_2Cl_2$ gave the same product in 35% yield. Comparatively, we believe that the decreased yield can be attributed to the steric bulk of phenyl *versus* methyl substituents on the cyano ligands. Oxazole **22** was converted to side chain **3** following a previously reported procedure.[4b]

The synthesis of (+)-neopeltolide is shown in Scheme 5. The terminal olefin of macrolactone **19** was hydrogenated in the presence of 10% Pd/C in ethyl acetate to provide the corresponding saturated side chain in 95% yield. Reduction of the resulting ketone with $NaBH_4$ in ethanol at −10 °C afforded alcohol **23** as a mixture of diastereomers (9 : 1 dr by ^{1}H NMR) in 75% yield. Mitsunobu esterification of **23** with acid **3** furnished (+)-neopeltolide {**1**, $[\alpha]_D^{23}$ +22.7 (*c* 0.41, MeOH); lit.[2] ($[\alpha]_D^{20}$ +24.0 (*c* 0.24, MeOH)} in 78% yield. The ^{1}H and ^{13}C NMR spectra of our synthetic (+)-neopeltolide are identical to the reported spectra for natural (+)-neopeltolide, thus confirming the absolute configuration of our synthetic material.[2]

Conclusions

In summary, we have accomplished an enantioselective synthesis of the anti-proliferatory agent (+)-neopeltolide (2.1% overall yield in 21 steps by the longest linear sequence). The synthetic route was convergent and scalable, and utilized commercially available starting materials. The key features of this synthesis were desymmetrization of methylglutaric anhydride, Brown's asymmetric allylation to form the C-13 and C-11 chiral centers, and an asymmetric hetero-Diels–Alder reaction using Jacobsen's catalyst to form the core tetrahydropyran ring. The synthesis of the oxazole side chain consisted of a hydrozirconation of an alkynyl stannane followed by Stille coupling to install the *Z* olefin at the C-26 position. The synthesis of the side chain involved a Stille coupling as the key step. The synthesis will provide convenient access to a variety of derivatives.

Experimental section

General experimental methods

All moisture sensitive reactions were carried out in a flame dried flask under a nitrogen or argon atmosphere. Anhydrous solvents were obtained as follows: THF and diethyl ether by distillation from sodium and benzophenone; dichloromethane and toluene from CaH_2. All other solvents were of HPLC grade. Column chromatography was performed with 240–400 mesh silica gel under a low pressure of 5–10 psi. TLC was carried out with silica gel 60-F-254 plates visualized under UV light and stained with either phosphomolybdic acid or acidic *p*-anisaldehyde. ^{1}H NMR spectra were recorded at 300, 400 or 500 MHz with chemical shifts reported in ppm (δ). ^{13}C NMR spectra were recorded at 75, 100 or 125 MHz with chemical shifts reported in ppm (δ). Infrared spectra were recorded as thin films on NaCl plates using a Fourier transform spectrometer. Optical rotations were measured using a sodium (589, D line) lamp polarimeter. Mass spectra were recorded at the Mass Spectrometry Center facility. HPLC data were collected using a system composed of a degasser, a quaternary pump, a thermostable column compartment, and a variable wavelength detector.

(*R*)-Propyl 5-hydroxy-3-methylpentanoate (10).[9] To a solution of 3-methylglutaric anhydride (23 g, 180 mmol) in diisopropyl ether (1.8 L) was added immobilized PS-30 "Amano" Lipase (50 g) and *n*-PrOH (29.2 mL, 361 mmol) at 23 °C. The solution was continued to stir at 23 °C for 30 h and then filtered on celite and concentrated. The residue was taken up in saturated $NaHCO_3$ and washed with Et_2O. The water layer was made acidic with 6 M HCl and extracted with Et_2O. The organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to yield a colorless oil (85% ee, reported lit. 92% ee),[9] which was used directly for the next step. Benzyl ester of the corresponding acid was measured by a chiral column AY-3 250 mmL × 4.6 mm, 3 microns; 1 mL min^{-1}; isocratic 9 : 1, hexanes–iPrOH; UV 256 nm; retention time, 3.37 min (minor); retention time, 6.74 min (major).

To a solution of the corresponding acid in dry THF (450 mL) under an argon atmosphere was added BH_3–Me_2S (19.5 mL, 206 mmol) dropwise at 0 °C. The solution was stirred at 0 °C for 1.5 h and then warmed to 23 °C and stirred for a further 5 h until TLC indicated that the reaction was complete. After cooling the reaction mixture to 0 °C, water was carefully added and the solution was warmed to 23 °C. The resulting alcohol was extracted from the water layer with ethyl acetate (×4). The organic extracts were washed with brine,

dried with Na_2SO_4 and concentrated. The resulting thick oil was passed through a short column of silica, eluting with 1 : 1 ethyl acetate–hexanes to give alcohol **10** as a clear thick oil (30.7 g) in 98% yield in two steps. $[\alpha]_D^{20}$ +7.71 (*c* 3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (t, *J* = 6.7 Hz, 2H), 3.54–3.42 (m, 2H), 3.28 (s, 1H), 2.24–2.13 (m, 1H), 2.06–1.90 (m, 2H), 1.56–1.44 (m, 2H), 1.44–1.36 (m, 1H), 1.32 (dt, *J* = 13.6, 6.8 Hz, 1H), 0.86–0.74 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 65.6, 59.8, 41.3, 39.0, 26.8, 21.61, 19.5, 10.0; IR (NaCl) 3225, 2962, 1737, 1235, 1175, 1055 cm^{-1}; ESI-HRMS (*m*/*z*): calcd for $C_9H_{18}O_3$: ($[M + H - CH_3CH_2CH_2OH]^+$), 115.0754; Found, 115.0753.

(*R*)-Propyl 4-(1,3-dioxolan-2-yl)-3-methylbutanoate (11). To a stirred solution of oxalyl chloride (19 mL, 172 mmol) in CH_2Cl_2 (280 mL) at −78 °C was added DMSO (27 mL, 344 mmol) dropwise. After stirring at −78 °C for 45 min, the above alcohol **10** (15 g, 86 mmol) in 80 mL of dichloromethane was added *via* cannula over 15 min. The reaction was stirred at −78 °C for 5 h and then Et_3N (72 mL, 516 mmol) was added, and the solution was warmed to 23 °C overnight. Water was added and the mixture was stirred for 30 min at 23 °C, after which the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated. The concentrate was filtered through a thin pad of silica, eluting with 1 : 2 ethyl acetate–hexanes to remove salts, and concentrated to give the corresponding aldehyde (13.90 g) as a thick clear oil in 94% yield which was used without further purification.

The above aldehyde (6.5 g, 38 mmol) was taken up in benzene (280 mL), and then ethylene glycol (10.5 mL, 190 mmol) and PPTS (2.8 g, 11 mmol) were added. The solution was heated to reflux for 6 h during which water was removed using a Dean–Stark trap. Crude NMR analysis showed that no aldehyde remained. The solution was cooled to 23 °C and concentrated. Cold saturated $NaHCO_3$ was added and the aqueous solution was extracted with Et_2O (3 × 150 mL). The organic layers were washed with a saturated $CuSO_4$ solution and brine, dried with Na_2SO_4 and concentrated. Silica gel column chromatography (1 : 5, ethyl acetate–hexanes) gave **11** as a clear oil (8.14 g) in 95% yield. $[\alpha]_D^{20}$ −1.4 (*c* 1.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (t, *J* = 5.0 Hz, 1H), 4.01 (t, *J* = 6.7 Hz, 2H), 3.96 (t, *J* = 8.0 Hz, 2H), 3.81 (t, *J* = 8.0 Hz, 2H), 2.48–2.29 (m, 1H), 2.26–2.08 (m, 2H), 1.73–1.50 (m, 4H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 103.2, 65.6, 64.5, 41.6, 40.2, 26.6, 21.8, 20.0, 10.3. IR (NaCl) 2966, 2945, 1731, 1171, 1138, 1036 cm^{-1}; CI-HRMS (*m*/*z*): calcd for $C_{11}H_{20}O_4$: ($[M + H]^+$), 217.1440; Found, 217.1429.

(4*R*,6*S*)-7-(1,3-Dioxolan-2-yl)-6-methylhept-1-en-4-ol (12). To a 250 mL round bottom flask was added **11** (7.30 g, 33 mmol) and 100 mL ether, which was cooled to 0 °C. Then lithium aluminum hydride (1.54 g, 41 mmol) was added in five (300 mg) portions. The reaction mixture was stirred for 1 h at 0 °C and then the reaction was quenched at 0 °C with 10 mL MeOH and 100 mL sodium potassium tartrate. The reaction mixture was allowed to warm to 23 °C and stirred for 1 h until the organic and aqueous phases separated. The aqueous layer was extracted with 3× EtOAc, the organic layer was then washed with 1× H_2O and 1× brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography (4 : 6, ethyl acetate–hexanes) gave the corresponding alcohol as a clear oil (4.69 g) in 88% yield which was directly used in the next step.

To a stirred solution of oxalyl chloride (6.5 mL, 58 mmol) in dichloromethane (280 mL) at −78 °C was added DMSO (8.3 mL, 120 mmol) dropwise. After stirring at −78 °C for 45 min, the above alcohol (4.69 g, 29 mmol) in 20 mL of dichloromethane was added *via* cannula over 5 min. The reaction was stirred at −78 °C for 1 h and then Et_3N (24.0 mL, 174 mmol) was added, and the solution was warmed to 23 °C overnight. Water was added and the mixture was stirred for 30 min at 23 °C, after which the organic layer was separated and the aqueous layer was extracted with 3× dichloromethane. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated. The concentrate was filtered through a thin pad of silica eluting with 1 : 4 ethyl acetate–hexanes to give the corresponding aldehyde (3.50 g) as a thick clear oil in 76% yield.

(+)-Ipc_2BOMe (2.05 g, 6.5 mmol) was carefully weighed out in a glove bag and placed in a 50 mL round-bottomed flask under an argon atmosphere. Dry Et_2O (15 mL) was added and the solution was cooled to 0 °C, followed by dropwise addition of allylmagnesium bromide (6 mL, 6.0 mmol, 1 M in Et_2O). After addition, the grey heterogeneous solution was warmed to 23 °C and stirred for 2 h. The mixture was then cooled to −78 °C and the above aldehyde (788 mg, 5.0 mmol) in Et_2O (10 mL) was added *via* cannula, and the resulting solution was stirred for 8 h at −78 °C. Ethanol (1.5 mL) was added, followed by a 3 M NaOH solution (4 mL) and H_2O_2 (8 mL, 30% in H_2O). The solution was warmed to 23 °C and stirred for 12 h and then extracted with Et_2O. The combined organic extracts were dried with Na_2SO_4 and concentrated. Flash chromatography (1 : 5, ethyl acetate–hexanes) gave alcohol **12** as a clear oil (1.1 g) in 87% yield and 99 : 1 dr. $[\alpha]_D^{20}$ +0.7 (*c* 1.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.85–5.68 (m, 1H), 5.12–4.97 (m, 2H), 4.85 (t, *J* = 5.1 Hz, 1H), 3.94–3.86 (m, 2H), 3.79–3.73 (m, 2H), 3.72–3.63 (m, 1H), 2.14 (ddq, *J* = 21.1, 13.9, 7.1 Hz, 2H), 1.92–1.79 (m, 1H), 1.64–1.40 (m, 3H), 1.19 (ddd, *J* = 14.1, 9.4, 3.3 Hz, 1H), 0.91 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 117.6, 103.4, 68.4, 64.5, 64.4, 44.0, 42.5, 41.2, 25.8, 19.7; IR (NaCl) 3362, 2972, 2929, 2862, 1378, 1149, 1053 cm^{-1}; CI-HRMS (*m*/*z*): calcd for $C_{11}H_{20}O_3$: ($[M + H]^+$), 201.1490; Found, 201.1480.

(4*S*,6*S*,8*S*)-9-(1,3-Dioxolan-2-yl)-6-methoxy-8-methylnon-1-en-4-ol (13). To a solution of alcohol **12** (5.76 g, 29 mmol) in THF and DMF (100 mL, 5 : 1) at 0 °C was added NaH (2.3 g, 58 mmol, 60% in mineral oil) portion-wise. The solution was stirred at 0 °C for 15 min and then warmed to 23 °C and stirred for 2 h. The solution was then cooled back to 0 °C and MeI (5.4 mL, 86 mmol) was added dropwise. The solution was warmed to 23 °C and stirred for 18 h and then cooled to 0 °C. Saturated NH_4Cl solution was added followed by ethyl acetate. After separation, the aqueous layer was extracted with ethyl

acetate (3×) and the combined organic layers were washed with water and brine and then dried with Na_2SO_4 and concentrated. Column chromatography (1 : 10, ethyl acetate–hexanes) gave the corresponding methyl ether (6.09 g) as a clear oil in 99% yield, which was directly used in the next step.

To the above acetal (3.60 g) in dioxane and water (100 mL, 3 : 1) was added 2,6-lutidine (3.8 mL, 33 mmol), OsO_4 (2.1 mL, 0.17 mmol, 2.5% solution in *t*-BuOH), and $NaIO_4$ (14.3 g, 67 mmol) at 0 °C. The mixture was warmed to 23 °C and stirred for 3 h, at which time water was added and the aldehyde was extracted with 3× dichloromethane. The combined organic extracts were concentrated and taken up in dichloromethane, washed with $CuSO_4$ saturated solution and brine, dried with Na_2SO_4, and concentrated. Column chromatography (1 : 4 to 1 : 2, ethyl acetate–hexanes) gave the corresponding aldehyde as a colorless oil (2.57 g) in 71% yield, which was directly used in the next step.

A 250 mL round-bottomed flask was charged with (−)-Ipc_2BOMe (6.04 g, 19 mmol) and Et_2O (53 mL), and cooled to 0 °C. Next, allylmagnesium bromide (17.5 mL, 17.5 mmol, 1 M in Et_2O) was added dropwise and the solution was warmed to 23 °C and stirred for 2 h. The mixture was then cooled to −78 °C and then the above aldehyde (3.44 g, 16 mmol) in Et_2O (40 mL) was added *via* cannula. The resulting solution was stirred for 7.5 h at −78 °C. Ethanol (3 mL) was added followed by 3 M NaOH solution (8 mL) and H_2O_2 (16 mL, 30% in H_2O). The solution was warmed to 23 °C and stirred for 12 h and extracted with Et_2O. The combined organic extracts were dried with Na_2SO_4 and concentrated. Flash chromatography (1 : 4, ethyl acetate–hexanes) gave alcohol **13** as colorless oil (3.74 g) in 91% yield and 99 : 1 dr. $[\alpha]_D^{20}$ +1.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.72 (m, 1H), 5.13–5.01 (m, 2H), 4.86 (t, *J* = 5.0 Hz, 1H), 3.99–3.84 (m, 3H), 3.83–3.73 (m, 2H), 3.59–3.48 (m, 1H), 3.33 (s, 3H), 2.96 (br.s, 1H), 2.27–2.10 (m, 2H), 1.85–1.56 (m, 4H), 1.55–1.42 (m, 2H), 1.24–1.13 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 117.4, 103.4, 77.1, 67.9, 64.6, 64.5, 56.7, 42.2, 41.2, 41.0, 39.1, 26.1, 20.3. IR (NaCl) 3340, 2915, 2823, 1442, 1163, 1086 cm^{-1}; ESI-HRMS (*m*/*z*): calcd for $C_{14}H_{26}O_4$: ($[M + Na]^+$), 281.1729; Found, 281.1719.

(6*R*,8*S*,10*S*,*E*)-10-Hydroxy-8-methoxy-6-methyltrideca-3,12-dien-2-one (15). To a solution of alcohol **13** (3.23 g, 12.5 mmol) in acetone (125 mL) was added 5 mL of water, 1 mL of AcOH, and PPTS (2.5 g, 10 mmol). The solution was warmed to 70 °C and stirred for 4 h. Crude NMR showed that the starting material had been partially converted to the desired aldehyde (~50% conversion). Another gram of PPTS and 1 mL of AcOH were added and the solution was heated to reflux for another 12 h. The acetone was removed under vacuum and the resulting residue was quenched with saturated $NaHCO_3$ solution, and extracted with 3× dichloromethane. The combined organic layers were washed with $CuSO_4$ saturated solution and brine, and then dried with Na_2SO_4 and concentrated to give the corresponding aldehyde as a yellowish oil that was used without further purification in the next step.

To LiCl (636 mg, 15 mmol) in MeCN (85 mL) at 23 °C was added dimethyl(2-oxopropyl)phosphonate (2.07 mL, 15 mmol). The resulting solution was stirred for 10 min and DIPEA (2.35 mL, 13.5 mmol) was added. After stirring for an additional 15 min at 23 °C, the above aldehyde (~12.5 mmol) in 20 mL of MeCN was added by a syringe over 5 min. The solution was stirred at 23 °C for 18 h and then diluted with water and extracted with 3× Et_2O. The organic layers were dried with Na_2SO_4, filtered, and concentrated. Column chromatography (1 : 3, ethyl acetate–hexanes) gave 2.65 g (83% yield, in two steps) of the unsaturated ketone **15** as a colorless oil. $[\alpha]_D^{20}$ +10.3 (*c* 2.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81–6.66 (m, 1H), 6.07–5.99 (m, 1H), 5.87–5.70 (m, 1H), 5.12–5.01 (m, 2H), 3.96–3.82 (m, 1H), 3.60–3.49 (m, 1H), 3.33 (s, 3H), 2.91 (br.s, 1H), 2.29–2.12 (m, 6H), 2.12–1.99 (m, 1H), 1.87–1.72 (m, 1H), 1.71–1.57 (m, 2H), 1.55–1.44 (m, 1H), 1.18 (ddd, *J* = 13.7, 8.5, 4.6 Hz, 1H), 0.91 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 146.6, 134.7, 132.6, 117.6, 67.6, 56.9, 42.3, 42.2, 40.9, 40.1, 39.4, 29.2, 26.8, 19.7; IR (NaCl) 3437, 2930, 1672, 1365, 1245, 1088 cm^{-1}; ESI-HRMS (*m*/*z*): calcd for $C_{15}H_{26}O_3$: ($[M + Na]^+$), 277.1780; Found, 277.1768.

(9*R*,11*S*,13*S*,*E*)-13-Allyl-3,3,15,15-tetraethyl-11-methoxy-9-methyl-5-methylene-4,14-dioxa-3,15-disilaheptadec-6-ene (8). Unsaturated ketone **15** (1.85 g, 7.3 mmol) in 35 mL of dichloromethane was cooled to −78 °C. To this solution was added triethylamine (5.06 mL, 36 mmol) and dropwise triethylsilyl trifluoromethane sulfonate (4.11 mL, 18 mmol) at −78 °C. The solution was warmed to 0 °C and stirred for 1.5 h before an ice-cold saturated $NaHCO_3$ solution was added. The layers were separated and the aqueous layer was extracted with 3× dichloromethane. The combined organic layers were washed with 1× brine, dried with Na_2SO_4 and concentrated. The resulting yellow oil was passed through a short silica column (1 : 20 : 0.2, ethyl acetate–hexanes–Et_3N) and concentrated to give **8** as a yellowish oil (3.51 g) in 98% yield, which was directly used in the next step.

2-Oxoethyl 4-methylbenzenesulfonate (7e).[14b] To a stirring solution of (DL)-1,2-isopropylideneglycerol (10 g, 76 mmol) in pyridine (60 mL) at 0 °C was added tosyl chloride (22 g, 113 mmol) followed by DMAP (500 mg, 4.1 mmol). The solution was stirred at 23 °C for 24 h before ice cold H_2O was added followed by extraction with 3× EtOAc. The organic extracts were washed with a saturated $CuSO_4$ solution and brine and then dried with Na_2SO_4 and concentrated. The thick oil was used in the next step without further purification.

The tosyl compound from the above was dissolved in THF (60 mL) and then 2 M HCl (20 mL) was added. The solution was stirred overnight at 23 °C and then cooled to 0 °C and quenched slowly with saturated $NaHCO_3$. Ethyl acetate was added and the layers were separated. The aqueous layer was further extracted with 3× EtOAc and the combined organic layers were dried with Na_2SO_4 and concentrated to yield a clear thick oil, which was used in the next step without further purification.

To the above diol was added a mixture of H_2O–dichloromethane (2 : 1, 210 mL/105 mL) followed by $NaIO_4$. The

solution was stirred at 23 °C for 24 h and then separated, and the water layer was extracted with dichloromethane. The organic layers were dried and concentrated. The resulting oil was taken up in dichloromethane (150 mL), and 4 Å MS (25 g) was added. The mixture was heated to reflux for 3 h and filtered. The filtrate was concentrated to give aldehyde **7e** (10.24 g), in 63% yield, in 3 steps which was stored at −20 °C until used. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2, 2H), 4.50 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 145.7, 131.9, 130.1, 128.1, 71.9, 21.6.

((2*R*,6*R*)-6-((2*S*,4*S*,6*S*)-6-Hydroxy-4-methoxy-2-methylnon-8-en-1-yl)-4-oxotetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (17e). To a flame dried 25 mL round-bottomed flask charged with activated 4 Å MS (1.5 g), diene **8** (2.39 g, 4.9 mmol), and tosyl aldehyde **7e** (1.59 g, 7.4 mmol) in ethyl acetate (2 mL) were added. The solution was cooled to 0 °C and Diels–Alder catalyst (**16**, 241 mg, 0.5 mmol) was added in one portion. The brown mixture was capped and sealed with parafilm and stirred at 23 °C for 36 h. The mixture was filtered through a 1-inch pad of celite (eluting with dichloromethane) and concentrated. The crude mixture was taken up in dichloromethane (15 mL) and TFA (2.0 mL) was added. The mixture was stirred at 23 °C for 1 h, cooled to 0 °C and quenched with a saturated $NaHCO_3$ solution. After separation of the organic layer, the aqueous layer was extracted with 3× dichloromethane, and the organic layer was washed with 1× brine and dried over Na_2SO_4 and concentrated. Column chromatography (6 : 4, 1 : 1, 4 : 6; hexanes–ethyl acetate) gave **17e** as a yellow colored oil (2.0 g) in 83% yield and 97 : 3 dr. $[\alpha]_D^{20}$+5.2 (*c* 7.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 5.90–5.56 (m, 1H), 5.20–5.05 (m, 2H), 4.10–4.02 (m, 2H), 3.97–3.91 (m, 1H), 3.85–3.82 (m, 1H), 3.72–3.59 (m, 1H), 3.59–3.50 (m, 1H), 3.36 (s, 3H), 2.44 (s, 3H), 2.38–2.26 (m, 2H), 2.26–2.15 (m, 2H), 1.82–1.89 (m, 1H), 1.77–1.43 (m, 4H), 1.34–1.14 (m, 4H), 0.90 (d, J = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 144.98, 134.8, 132.5 129.8, 127.8, 117.4, 77.2, 74.9, 73.8, 70.9, 67.8, 56.8, 47.9, 43.5, 43.1, 42.2, 41.2, 39.1, 25.8, 21.5, 19.7; IR (NaCl) 3352, 2978, 2927, 1722, 1360, 1177, 1096 cm^{-1}; ESI-HRMS (*m*/*z*): calcd for $C_{24}H_{36}O_7S$: ($[M + Na]^+$), 491.2079; Found, 491.2056.

2-((7*S*,9*R*)-9-((2*S*,4*S*,6*S*)-6-Hydroxy-4-methoxy-2-methylnon-8-en-1-yl)-1,4,8-trioxaspiro[4.5]decan-7-yl)acetonitrile (18). To a solution of **17e** (520 mg, 1.1 mmol) in benzene (20 mL) was added ethylene glycol (0.65 mL, 11.1 mmol) and PTSA (84 mg, 0.33 mmol). The solution was heated to reflux for 10 h with a Dean–Stark trap attached. After 10 h the solution was cooled to 23 °C, filtered through celite, and then concentrated. The residue was treated with a $NaHCO_3$ solution and extracted with 3× EtOAc. The extracts were dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (1 : 2, ethyl acetate–hexanes) to give the desired acetal as a thick clear oil (342 mg) in 60% yield, which was directly used in the next step.

To a 25 mL round bottom flask was added the above acetal (340 mg, 0.66 mmol) which was dissolved in DMF (5 mL) and then NaCN (195 mg, 4.0 mmol) was added. The solution was heated to 75 °C for 36 h and then cooled to 23 °C. After saturated aqueous $NaHCO_3$ was added the mixture was extracted with 3× EtOAc. The combined extracts were washed with 1× water and 1× brine, dried with Na_2SO_4, and concentrated. The resulting residue was purified by flash chromatography (1 : 2, ethyl acetate–hexanes) to give **18** as a colorless oil (195.5 mg) in 80% yield. $[\alpha]_D^{20}$ +12.1 (*c* 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.80 (m, 1H), 5.16–5.05 (m, 2H), 3.98–3.91 (m, 5H), 3.87–3.74 (m, 1H), 3.72–3.61 (m, 1H), 3.61–3.50 (m, 1H), 3.36 (s, 3H), 2.99 (br.s, 1H) 2.53 (dd, J = 8.0, 4.0 Hz, 2H), 2.23 (dddd, J = 8.5, 5.9, 2.9, 1.4 Hz, 2H), 1.91–1.81 (m, 1H), 1.81–1.74 (m, 2H), 1.75–1.38 (m, 6H), 1.23–1.09 (m, 2H), 0.93 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 117.3, 116.9, 106.6, 77.4, 73.2, 70.3, 67.9, 64.4, 64.2, 56.7, 43.1, 42.2, 41.2, 41.2, 40.2, 38.9, 25.9, 24.4, 19.9; IR (NaCl) 3467, 3071, 2924, 2247, 1377, 1147, 1068 cm^{-1}; ESI-HRMS (*m*/*z*): calcd for $C_{20}H_{33}NO_5$: ($[M + Na]^+$), 390.2256; Found, 390.2245.

2-((2*R*,6*R*)-6-((2*S*,4*S*,6*S*)-6-Hydroxy-4-methoxy-2-methylnon-8-en-1-yl)-4-oxotetrahydro-2*H*-pyran-2-yl)acetic acid (4). 18 (185 mg, 0.50 mmol) was taken up in EtOH (2.0 mL) and 640 μL of a 10% NaOH solution was added. The mixture was stirred at 75 °C for 24 h, and then cooled to 0 °C. The solution was then acidified to pH = 3 with 1 M HCl. The mixture was extracted with 4× ethyl acetate. The organic layers were washed with 1× brine, dried with Na_2SO_4 and then concentrated give the acid as a clear oil, which was used in the next step without further purification.

The above acid was dissolved in 3 mL of acetone and 0.5 mL of H_2O. PTSA (150 mg, 0.79 mmol) was added and the solution was heated to 65 °C for 12 h. The solution was concentrated and H_2O was added along with EtOAc. The layers were separated and the aqueous layer was further extracted with 3× EtOAc. The organic layers were combined, and washed with 1× brine, dried with Na_2SO_4, and concentrated. Column chromatography (2 : 1, ethyl acetate–hexanes) gave acid **4** as a colorless oil (127 mg) in 74% yield in 2 steps. $[\alpha]_D^{20}$ +23.1 (*c* 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89–5.74 (m, 1H), 5.17–5.03 (m, 2H), 4.07–3.95 (m, 2H), 3.77–3.63 (m, 1H), 3.60–3.46 (m, 1H), 3.35 (s, 3H), 2.66–2.48 (m, 2H), 2.44 (dt, J = 14.4, 2.3 Hz, 1H), 2.38–2.27 (m, 2H), 2.26–2.19 (m, 2H), 1.89–1.72 (m, 2H), 1.70–1.55 (m, 3H), 1.56–1.46 (m, 2H), 0.93 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 170.1, 134.8, 117.4, 77.1, 74.5, 73.2, 67.9, 60.6, 56.7, 48.0, 46.9, 43.5, 42.2, 41.3, 39.2, 25.8, 19.5; IR (NaCl) 3415, 3071, 2928, 1720, 1369, 1255, 1074 cm^{-1}; ESI-HRMS (*m*/*z*): calcd for $C_{18}H_{30}O_6$: ($[M + Na]^+$), 365.1940; Found, 365.1954.

(1*R*,5*S*,7*S*,9*S*,11*R*)-5-Allyl-7-methoxy-9-methyl-4,15-dioxabicyclo-[9.3.1]pentadecane-3,13-dione (19). Acid **4** (44 mg, 0.13 mmol) and Et_3N (53 μL, 0.38 mmol) were dissolved in THF (5 mL) and cooled to 0 °C and then 2,4,6-trichlorobenzoyl chloride (30 μL, 0.19 mmol) was added dropwise. The reaction mixture was allowed to warm to 23 °C and stirred for 1.5 h. Then 15 mL of toluene was added and the reaction mixture, which was taken up in a 50 mL syringe, was added dropwise over an 8 h period to a solution of toluene (200 mL) and DMAP

(305 mg, 2.50 mmol) at 80 °C. After the addition was complete the reaction mixture was stirred for an additional 2 h at 80 °C and then cooled to 23 °C. Then the reaction mixture was filtered through a short pad of silica with hexanes–ethyl acetate (1 : 1) and concentrated. The residue was chromatographed on silica gel (85 : 15, 8 : 2, 75 : 25, 7 : 3; hexanes–ethyl acetate) to give lactone **19** in 40% yield. $[\alpha]_D^{20}$ +38.2 (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.80–5.72 (m, 1H), 5.33–5.16 (m, 1H), 5.17–4.99 (m, 2H), 4.04 (dddd, *J* = 11.4, 10.5, 4.2, 2.8 Hz, 1H), 3.60–3.55 (m, 1H), 3.52–3.48 (m, 1H), 3.33 (s, 3H), 2.70 (dd, *J* = 14.7, 4.1 Hz, 1H), 2.58–2.49 (m, 1H), 2.50–2.40 (m, 2H), 2.40–2.21 (m, 4H), 1.88 (ddd, *J* = 14.9, 10.9, 1.8 Hz, 1H), 1.75–1.53 (m, 3H), 1.54–1.39 (m, 1H), 1.37–1.28 (m, 1H), 1.23–1.18 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 169.7, 133.7, 117.6, 79.5, 75.6, 73.2, 72.6, 56.2, 48.6, 46.9, 44.1, 42.4, 41.6, 39.1, 39.09, 29.6, 30.0, 25.2; IR (NaCl) 2950, 2923, 2846, 1727, 1462, 1366, 1248, 1089 cm^{-1}; ESI-HRMS (*m*/*z*): calcd for $C_{18}H_{28}O_5$: ($[M + Na]^+$), 347.1834; Found, 347.1818.

(1*R*,5*S*,7*S*,9*S*,11*R*,13*S*)-13-Hydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (23). Lactone **19** (16 mg, 0.05 mmol) was dissolved in EtOAc (3 mL) and then 10% Pd/C (5 mg) was added. The reaction was flushed with argon followed by H_2 and then placed under 1 atm. of H_2 for 1 h at 23 °C. Then the reaction mixture was filtered through a short pad of celite with EtOAc and concentrated to give 15.5 mg of the corresponding lactone in 95% yield which was used in the next step without further purification.

To a solution of the above lactone (15.5 mg, 0.05 mmol) in EtOH (0.6 mL) at −10 °C was added $NaBH_4$ (4 mg, 0.10 mmol). The resulting solution was stirred at −10 °C for 30 min before the solution was treated with 2–3 drops of AcOH. The mixture was concentrated and purified by column chromatography (7 : 3, 6 : 4, 55 : 45, 1 : 1, 4 : 6; hexanes–ethyl acetate) to give lactone **23** as a clear oil (12.8 mg) in 75% yield and 9 : 1 dr. $[\alpha]_D^{20}$ +21.5 (*c* 0.41, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (td, *J* = 9.9, 4.8 Hz, 1H), 3.91–3.75 (m, 1H), 3.72 (m, 1H), 3.62–3.51 (m, 1H), 3.31 (s, 3H), 3.17 (t, *J* = 10.4 Hz, 1H), 2.62 (dd, *J* = 14.5, 4.3 Hz, 1H), 2.43 (dd, *J* = 14.5, 10.7 Hz, 1H), 2.06–1.90 (m, 1H), 1.92–1.76 (m, 2H), 1.77–1.63 (m, 1H), 1.57–1.39 (m, 3H), 1.40–1.28 (m, 3H), 1.24–1.05 (m, 4H), 1.06–0.93 (m, 3H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 78.5, 75.4, 73.1, 72.2, 67.9, 56.1, 43.9, 42.1, 41.8, 40.6, 39.9, 36.8, 31.1, 25.4, 18.8, 13.8; IR (NaCl) 3429, 2961, 2920, 2871, 1731, 1457, 1372, 1272, 1090 cm^{-1}.

Methyl (*Z*)-(3-(tributylstannyl)allyl)carbamate (5). To a stirred solution of THF (50 mL) and diisopropylamine (8.90 mL, 61 mmol) at 0 °C under argon was added *n*-BuLi (24.3 mL, 2.5 M solution in hexanes, 63 mmol) dropwise, and the mixture was stirred for 15 min and then cooled to −78 °C. Then alkyne **20** (3.27 g, 29 mmol) was dissolved in 20 mL THF added dropwise over a 10 min period. The reaction mixture was stirred for an additional 0.5 h at −78 °C. Tributyltin chloride (8.70 mL, 32 mmol) was added dropwise and the reaction mixture was stirred for 3 h at −78 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ and warmed to 23 °C, the aqueous layer was extracted with 3× EtOAc and the combined organic layers were washed with 1× water and 1× brine and dried over anhydrous Na_2SO_4. The residue was chromatographed on silica gel (98 : 2 to 9 : 1; hexanes–EtOAc; note all solutions contained 1% Et_3N) to give the corresponding alkyne as a pale yellow oil (5.60 g) in 48% yield.

To a 250 mL round bottom flask under argon was added $ZrCp_2Cl_2$ (freshly recrystallized from toluene, 2.60 g, 8.86 mmol) and dissolved in 30 mL THF and cooled to 0 °C. Then DIBALH (8.90 mL, 1 M in dichloromethane, 8.86 mmol) was added dropwise, the resulting solution was stirred for 30 min and a white suspension was formed. Then in a separate round bottom flask the above alkyne (1.98 g, 4.92 mmol) was dissolved in THF (15 mL) and then DIBALH (4.92 mL, 1 M in dichloromethane, 4.92 mmol) was added dropwise at 0 °C and stirred for 20 min. Then *via* cannula the solution of DIBALH and alkynyl stannane at 0 °C was added to the suspension of DIBALH and $ZrCp_2Cl_2$ at 0 °C. After the addition was complete the reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to 23 °C and stirred for an additional 7 h. The reaction was quenched with MeOH (10 mL) and sodium potassium tartrate (~50 mL) and stirred for 1 h. Once the organic and aqueous phases were separated the aqueous phase was extracted with 3× EtOAc. The combined organic layers were washed with 1× H_2O and 1× brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was chromatographed on silica gel (98 : 2, 95 : 5, 94 : 6, 92 : 8, 9 : 1; hexanes–EtOAc; note all solutions contained 1% Et_3N) to give alkene **5** (755 mg) in 38% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (dt, *J* = 12.5, 6.5 Hz, 1H), 6.02 (d, *J* = 12.5 Hz, 1H), 4.63 (br.s, 1H), 3.73 (d, *J* = 5.5 Hz, 2H), 3.67 (s, 3H), 1.44–1.49 (m, 9H), 1.27–1.32 (m, 9H), 0.87 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 143.7, 132.7, 52.0, 46.2, 29.0, 27.1, 13.6, 10.2; IR (NaCl) 3336, 2956, 2925, 2853, 1711, 1600, 1530, 1463, 1251, 1044 cm^{-1}; CI-HRMS (*m*/*z*): calcd for $C_{17}H_{35}NO_2Sn$: ($[M + H - C_4H_{10}]^+$), 348.0985; Found, 348.0994.

Isobutyl (*Z*)-(3-(tributylstannyl)allyl)carbamate (21). 18% yield, 397 mg, ^1H NMR (400 MHz, $CDCl_3$) δ 6.52–6.45 (m, 1H), 6.02 (d, *J* = 12.5 Hz, 1H), 4.64 (br.s, 1H) 3.83 (d, *J* = 6.7 Hz, 2H), 3.75–3.72 (m, 2H), 2.02–1.73 (m, 1H), 1.65–1.34 (m, 6H), 1.34–1.24 (m, 6H), 1.12–0.68 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 143.8, 132.5, 70.9, 46.1, 29.0, 27.9, 27.1, 18.9, 13.5, 10.2; IR (NaCl) 3332, 2953, 2919, 2830, 1718, 1596, 1528, 1467, 1245, 1044 cm^{-1}. ESI-HRMS (*m*/*z*): calcd for $C_{20}H_{41}NO_2Sn$: ($[M + Na]^+$), 470.2061; Found, 470.2063.

Conversion of isobutyl (*Z*)-(3-(tributylstannyl)allyl)carbamate (21) to methyl (*Z*)-(3-(tributylstannyl)allyl)carbamate (5). To a stirred solution of **21** (406 mg, 0.9 mmol) in methanol (20 mL) and water (1 mL) was added KOH (510 mg, 9.1 mmol). The resulting mixture was stirred at 80 °C for 24 h. The mixture was evaporated and the aqueous layer was extracted with 3× EtOAc, and the organic solvent was evaporated to give the crude amine. To this crude amine, dioxane and saturated aqueous $NaHCO_3$ (1 : 1 mixture) were added followed by methylchloroformate (100 mL). The reaction was stirred at 23 °C for 12 h. After this period, the reaction mixture was

concentrated and the residue was extracted with 3× EtOAc. Evaporation of the solvent gave an oil which was purified by column chromatography (98 : 2, 95 : 5, 94 : 6, 92 : 8, 9 : 1; hexanes–EtOAc; note that all solutions contained 1% Et_3N) to give methyl carbamate **5** in two steps (255 mg, 69% yield).

Ethyl (*Z*)-2-(3-((methoxycarbonyl)amino)prop-1-en-1-yl)-oxazole-4-carboxylate (22). Oxazole **6** (445 mg, 1.67 mmol) and stannane **5** (741 mg, 1.83 mmol) under argon were dissolved in 10 mL DMF and then in one portion $Pd(MeCN)_2Cl_2$ (87 mg, 0.33 mmol) was added. The reaction mixture was then stirred for 12 h at 23 °C and then diluted with H_2O (15 mL) and extracted with 4× EtOAc; the combined organic layers were washed with 1× H_2O and 1× brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was chromatographed on silica gel (65 : 35, 60 : 40, 55 : 45, 1 : 1, 4 : 6; hexanes–EtOAc) to give oxazole **22** as a white solid (239 mg) in 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 6.36 (dt, J = 12.1, 1.8 Hz, 1H), 6.21 (dt, J = 12.2, 6.4 Hz, 1H), 5.33 (s, 1H), 4.46–4.31 (m, 4H), 3.68 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.6, 157.0, 143.1, 139.1, 134.3, 115.3, 61.2, 52.1, 39.5, 14.1; IR (NaCl) 3348, 3155, 2983, 2945, 1721, 1526, 1465, 1371, 1273, 1191, 1021 cm^{-1}.

Neopeltolide (1). To a solution of acid **3** (4 mg, 0.014 mmol), alcohol **23** (3 mg, 0.01 mmol) and PPh_3 (4 mg, 0.016 mmol) in 0.5 mL benzene was added diisopropyl azodicarboxylate (31 μL, 0.5 M solution in benzene, 0.016 mmol) at 23 °C. After stirring for 1 h at 23 °C an additional amount of PPh_3 (4 mg, 0.016) and diisopropyl azodicarboxylate (31 μL, 0.5 M solution in benzene, 0.016 mmol) was added at 23 °C. The reaction was stirred for an additional 1 h at 23 °C, and then concentrated under vacuum. The residue was chromatographed on silica gel (8 : 2, 7 : 3, 6 : 4, 1 : 1, 4 : 6; pet ether (b.p. fraction 30 °C–60 °C)–ethyl acetate) to afford neopeltolide **1** (4.1 mg) as a clear oil in 78% yield. $[\alpha]_D^{23}$ +22.7 (*c* 0.41, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.67 (s, 1H), 6.37 (dt, J = 11.5, 7.4 Hz, 1H), 6.28 (dt, J = 11.9, 2.5 Hz, 1H), 6.06–6.01 (m, 1H), 5.89 (dt, J = 11.6, 1.6 Hz, 1H), 5.22–5.15 (m, 2H), 4.31–4.30 (m, 2H), 4.10–4.04 (m, 1H), 3.69–3.63 (m, 4H), 3.61–3.54 (m, 1H), 3.28 (s, 3H), 3.04–2.97 (m, 2H), 2.76–2.68 (m, 3H), 2.31 (dd, J = 14.8, 10.4 Hz, 1H), 1.90–1.76 (m, 2H), 1.77–1.62 (m, 2H), 1.62–1.43 (m, 4H), 1.43–1.18 (m, 6H), 1.17–1.08 (m, 1H), 0.97 (d, J = 6.7 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.0, 166.8, 161.9, 159.6, 150.0, 142.3, 139.2, 135.9, 121.7, 115.9, 77.1, 77.0, 73.9, 71.3, 69.2, 56.4, 52.6, 45.2, 43.5, 43.2, 41.0, 37.9, 37.4, 36.2, 32.6, 29.0, 26.4, 26.0, 20.0, 14.2; IR (NaCl) 3336, 2925, 2854, 1725, 1513, 1461, 1250, 1183, 1082 cm^{-1}.

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