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Total synthesis of neopeltolide and analogs

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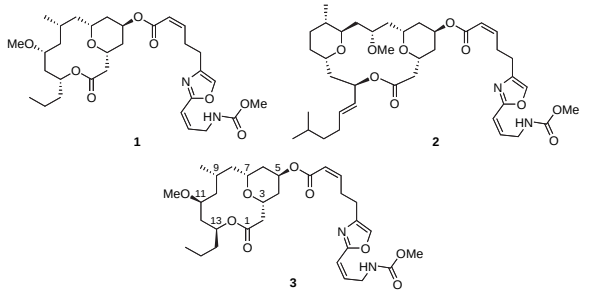
ABSTRACT

Neopeltolide, a potent cytotoxin from a Carribean sponge, was synthesized through a brief sequence that highlights the use of ethers as oxocarbenium ion precursors. Other key steps include an acid-mediated etherification and sequence that features a Sonogashira reaction, an intramolecular alkyne hydrosilylation reaction, and a Tamao oxidation. The alkene that is required for the oxidative cyclization can be hydrogenated to provide access to the natural product or an epimer, or can be epoxidized or dihydroxylated to form polar analogs.

1. Introduction

In 2007 Wright and co-workers reported[1] the isolation of neopeltolide from the sponge *Daedolapelta* of the Neopeltodae family of the Jamaican coast. This compound was initially assigned as structure **1** based on extensive NMR analysis. Neopeltolide exhibits potent cytotoxic and *anti*-fungal activity, with IC_{50} values of <10 nM against a number of cancer cell lines and an MIC of 0.62 μg/mL (1 μM) against *Candida albicans*. Although neopeltolide is structurally less complex than the related macrolide leucascandrolide A (**2**),[2] a well studied synthetic target,[3] its biological activity is comparable or superior. Neopeltolide's interesting biological activity and accessible structure have inspired extensive interest in its total synthesis. Panek[4] and Scheidt[5] independently reported total syntheses of neopeltolide, and through these efforts showed that the correct structure is **3**. Since these reports a number of elegant total and formal syntheses have been disclosed.[6]



Synthesis has allowed for further biological studies of neopeltolide. Kozmin and co-workers identified cytochrome bc_1,[6d] a mitochondrial enzyme that is involved in ATP synthesis, as a viable cellular target for **2** and **3**. Crews and co-workers reported[6h] that neopeltolide exhibits cell line selectivity for its cytotoxic activity. Several groups have prepared neopeltolide analogs and studied their cytotoxicity. These efforts have shown that the oxazole-containing side chain, while showing no activity on its own, is essential for activity and significant changes to this unit are generally not tolerated.[6g,h] Several stereochemical changes in the lactone core are tolerated, though **1** is nearly two orders of magnitude less active than **3**.[6g,h,i] Removing the C9 methyl group or the C11 methoxy group does not dramatically alter activity.[6k] This is significant because these analogs can be prepared more readily than neopeltolide. No efforts toward altering the physical properties of neopeltolide through introducing hydrophilic functional groups have been reported.

Our interest in neopeltolide arose from a desire to apply our recently-developed oxidative cyclization protocol[7] in the context of natural product synthesis. This method proceeds through DDQ-mediated carbon–hydrogen bond cleavage of benzylic or allylic ethers to form oxocarbenium ions. These electrophiles react with appended nucleophiles to form tetrahydropyrans with excellent stereocontrol. The use of oxidative carbon–hydrogen bond cleavage also allows for the formation of macrocyclic oxocarbenium ions through cyclic ether oxidation (Scheme 1).[8] These intermediates, which can be utilized for stereoselective transannular reactions, have been prepared previously through conventional intramolecular condensation reactions between alcohols or silyl ethers and aldehydes.[1,5,6a,9] The generality of this approach, however, has not been established. Rychnovsky and co-workers, for example,

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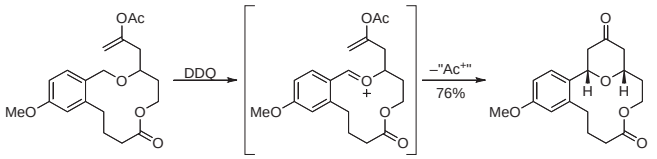
conducted computational studies to show that the efficient formation of the macrocyclic oxocarbenium ion in their kendomycin synthesis arose from conformational preorganization of the hydroxyl and aldehyde groups.[9d] Oxidizing a pre-formed macrocycle represents a potentially more general approach to this type of intermediate.



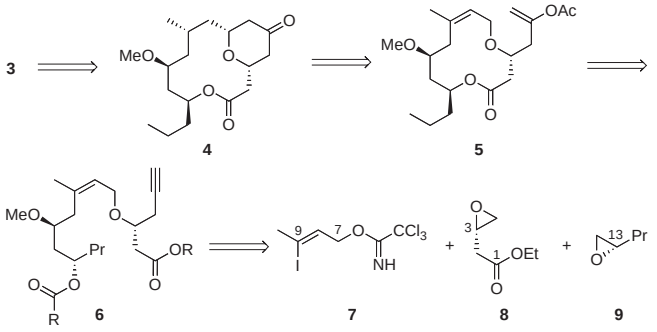
Scheme 1. Oxidative cyclization through a macrocyclic oxocarbenium ion.

The formation of the neopeltolide macrolactone from a macrocyclic allylic ether precursor is advantageous from a strategic perspective since etherification can be used as an early stage fragment coupling reaction. The stable ether linkage obviates the need for protecting groups during the sequence and for the introduction of activating groups for electrophile formation. In this manuscript we report the total synthesis of neopeltolide through an oxidatively generated macrocyclic oxocarbenium ion. Key steps in the sequence include fragment coupling through a BrØnsted acid-mediated etherification process and a Sonogashira reaction, and a regioselective alkyne hydration through hydrosilylation. We also report that the alkene in the cyclization product can be functionalized with good to excellent stereochemical control en route to the natural product and analogs.

2. Results and discussion

2.1. Retrosynthetic analysis

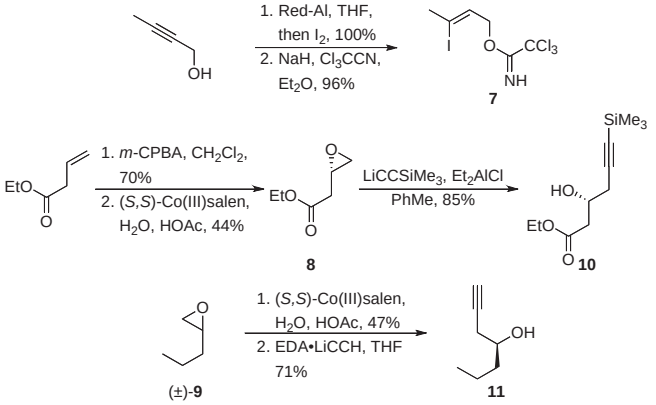
We designed our synthesis of **3** to proceed through **4**, a known precursor[5,6e] to the natural product (Scheme 2). This bridged bicycle can be accessed from **5** through oxidative cyclization and stereoselective alkene reduction. The macrocycle is derived from diester **6**, which in turn can be prepared from readily-accessible subunits **7**, **8**, and **9**.



Scheme 2. Retrosynthetic analysis of neopeltolide.

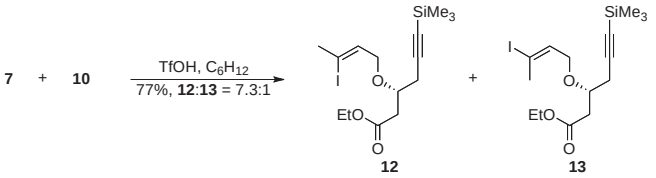
2.2. Neopeltolide synthesis

The synthesis of **7** (Scheme 3) proceeded through 2-butyn-1-ol hydroalumination with Red-Al[10] followed by quenching with I_2. The desired trichloroacetimidate was formed by exposing the iodoallylic alcohol to NaH and Cl_3CCN. Epoxide **8** is commercially available in enantiomerically pure form, though cost constraints mandate that it be synthesized rather than purchased. Epoxidation of ethyl 3-butenoate with *m*-CPBA followed by hydrolytic kinetic resolution[11] with Jacobsen's (*S*,*S*)-salenCo(III) catalyst provided **8** in suitable yield. The epoxide was opened with lithium trimethylsilylacetylide and Et_2AlCl[12] to provide alcohol **10** in 85% yield. This unit was prepared in >99% ee as determined by Mosher ester analysis.[13] Epoxide **9** is also commercially available in enantiomerically pure form but expense again dictated that it be prepared through hydrolytic kinetic resolution of the less expensive racemic epoxide with the (*S*,*S*)-salenCo(III) catalyst. Opening the epoxide with the ethylene diamine complex of lithium acetylide[14] yielded **11** in 71% yield and in >99% ee (as determined by Mosher ester analysis). Attempts to prepare **11** directly through the addition of allenyl tributyltin to butanal in the presence of (*R*)-BINOL and $Ti(O^iPr)_4$[15] were productive with respect to overall yield, though the enantiomeric excess of 67% was not suitable for the synthesis.



Scheme 3. Subunit preparation.

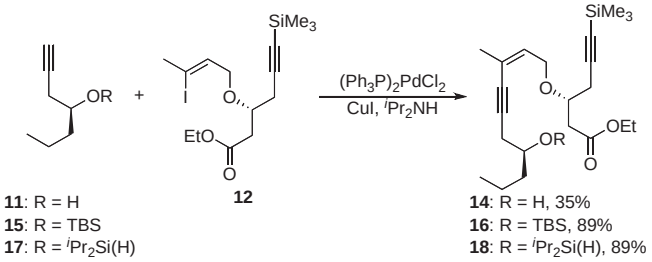
We initially attempted to use TMSOTf to promote the ether linkage formation[16] between **7** and **10** (Scheme 4) to avoid the use of harshly basic Williamson ether synthesis conditions that could cause **10** to undergo a retro aldol reaction. Significant alkene isomerization was observed, however, leading to an inseparable 4:1 mixture of geometrical isomers **12** and **13** in 74% yield. During the course of an extensive optimization effort that focused on concentration, stoichiometry, and temperature variations, we observed that the addition of 2,6-di-*tert*-butylpyridine completely suppressed the etherification reaction. This indicated that adventitious TfOH was the real catalyst for the reaction. Combining **10** with an excess of **7** in the presence of 15 mol % TfOH resulted in the isolation of a 7.3:1 mixture of **12** and **13** in 77% yield.



Scheme 4. TfOH-mediated etherification.

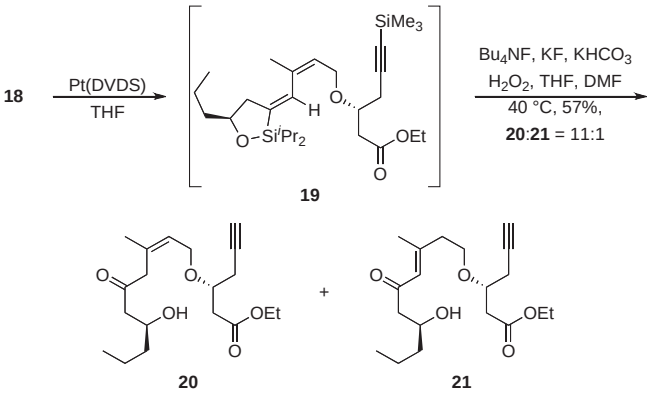
The remaining carbons for the neopeltolide macrolactone could, in principle, be introduced through a Sonogashira coupling[17] between **11** and **12** (Scheme 5). The yield of enyne **14**, however, never exceeded 35% despite repeated attempts to optimize the reaction conditions with respect to palladium catalyst, solvent, and amine. We postulated that the inefficiency derived from the free hydroxyl group in **11**, and this was confirmed when we subjected silyl ether **15** to standard Sonogashira conditions with **12** and isolated enyne **16** in 89% yield. While this yield was acceptable, the use of a silyl ether solely as a protecting group was not desirable. In consideration our plan to perform a regioselective alkyne hydration reaction through intramolecular hydrosilylation, we studied the possibility of using dialkylsilyl ethers in the coupling reaction. While the

dimethylsilyl and diphenylsilyl ethers of **11** proved to be too labile to survive the coupling, diisopropylsilyl ether **17**, prepared in 77% yield by treating **11** with $^{i}Pr_2Si(H)Cl$ and imidazole, coupled with **12** to form enyne **18** in 89% yield.



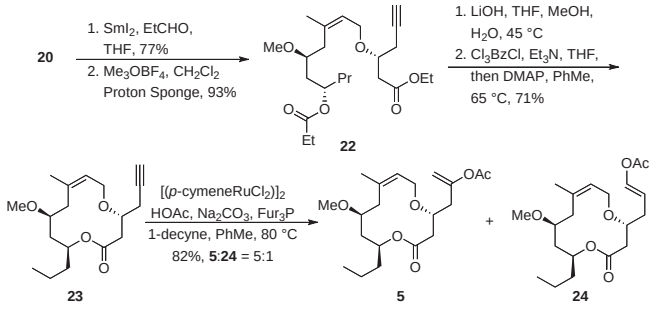
Scheme 5. Sonogashira coupling.

The regioselective alkyne hydration reaction required that the sequence[18] of intramolecular hydrosilylation and Tamao oxidation proceed without isomerization of the product β,γ-unsaturated ketone to the conjugated isomer. The hydrosilylation of **18** proceeded quite smoothly with Pt(DVDS)[19] (DVDS=divinyl dimethyldisiloxane) to form siloxane **19**. The isopropyl groups in **19** create greater steric congestion than the methyl groups that are generally used in these reactions, dictating that the Tamao oxidation[20] be conducted under unusually harsh conditions. Extensive optimization led to the identification of a suitable protocol in which **19** was exposed to a mixture of Bu_4NF, KF, $KHCO_3$, and aqueous H_2O_2 in THF and DMF at 40 °C to yield **20** in 57% yield as an acceptable 11:1 mixture with conjugated isomer **21**. These conditions also led to concomitant cleavage of the alkynylsilane group. The alkene stereoisomer that had been carried through the sequence since the etherification reaction was easily be removed at this stage. Attempts to improve the yield of the hydration by conducting a *trans*-hydrosilylation with $[(C_6H_6)RuCl_2]_2$[21] were unsuccessful (Scheme 6).



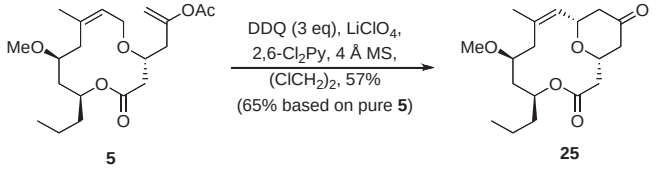
Scheme 6. Alkyne hydration through hydrosilylation.

The remainder of the sequence to form the macrolactone substrate (Scheme 7) proceeded with little incident. Reduction of **20** under Evans-Tischenko[22] conditions provided hydroxy ester **22** in 77% yield as a single stereoisomer. Conjugated isomer **21** was unreactive in this reaction and was easily separated. This transformation is ideally suited for neopeltolide synthesis, as observed in most approaches to this structure, because it establishes the appropriate stereochemical relationship between C11 and C13 while selectively protecting the C13 hydroxyl group. Selective protection allows for efficient methylation of the C11 hydroxyl group to form **22**. Cleaving both ester groups and lactonizing under Yamaguchi's conditions[23] provided **23** in 71% overall yield. Exposing **23** to HOAc and $[(p\text{-cymene})RuCl_2]_2$[24] provided cyclization substrate **5** along with regioisomer **24** as an inseparable 5:1 mixture in 82% yield. We have modified the reported protocol for enol acetate formation to include 1-decyne. This promotes greater reproducibility for the reaction by using a sacrificial alkyne to aid in the generation of the catalytically relevant ruthenium phosphine complex.



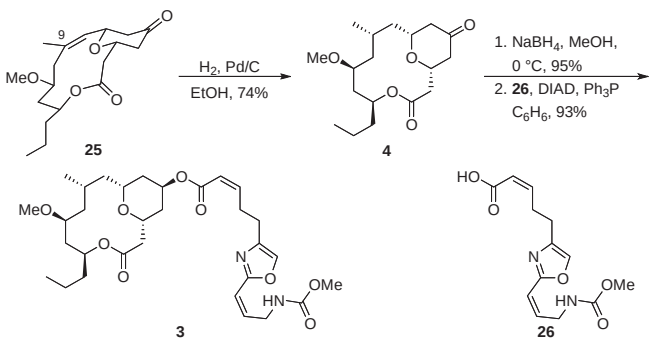
Scheme 7. Completion of the cyclization substrate synthesis.

The oxidative cyclization of **5** (Scheme 8) was significantly slower than previous cyclization reactions of acyclic allylic ethers that contain trisubstituted alkenes.[7] Two factors could lead to the slow kinetics. The proximity of the ether oxygen to the electron withdrawing carboxyl group reduces its capacity to stabilize the intermediate oxocarbenium ion. We have observed that these reactions are dependent upon the oxidation potential of the substrate and the stability of the intermediate carbocation.[25] Inductively destabilizing the cation, therefore, slows the reaction. The macrocycle also could adapt a conformation that inhibits proper alignment between the cleaving carbon–hydrogen bond and the π-bond of the alkene. Stereoelectronic effects have been established as an important kinetic factor in other oxidative cleavage reactions.[26] The reaction proceeded to completion after 18 h at room temperature by using 3 equiv DDQ. This provided a 57% yield of bicyclic tetrahydropyran **25**. In consideration of the fact that the starting material was an 84:16 mixture of enol acetate regioisomers, this yield could be extrapolated to 65% if pure **5** were used in the reaction. No 5-*endo*-cyclization product from the reaction of **24** was isolated.



Scheme 8. Oxidative cyclization.

Completing the synthesis (Scheme 9) required that the Δ **8** and **9** alkene be reduced with high facial control. A crystal structure[27] of **25** showed that the molecule prefers a curved conformation in

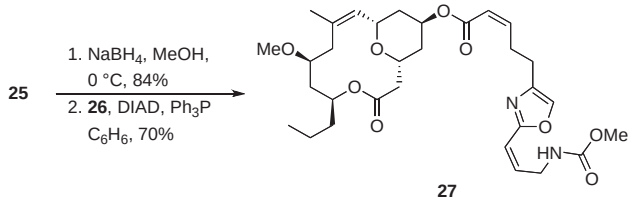


Scheme 9. Synthesis of neopeltolide.

which the sterically more-accessible convex face should react with H_2 to provide the desired stereoisomer. Indeed, subjecting **25** to H_2 and Pd/C provided **4** in 74% yield. A small amount (<10%, impure) of the stereoisomer at C9 was also isolated. The conversion of **4** to neopeltolide has been reported,[5,6f] but we completed the synthesis to have the natural product for subsequent biological studies. Reduction of **4** with $NaBH_4$ in MeOH followed by Mitsunobu esterification[28] with acid **26** (prepared according to the protocol of Wipf and Graham[29]) provided **3**.

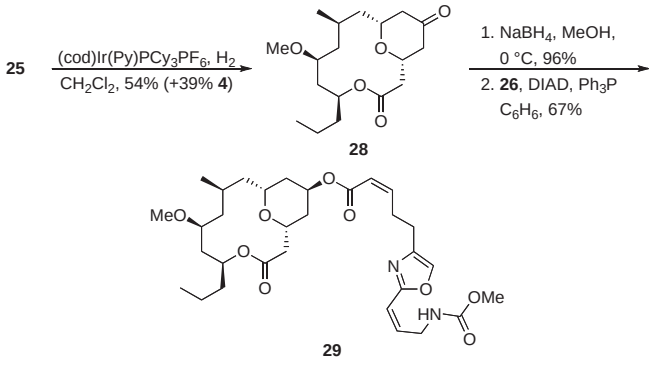
2.3. Analog synthesis

The presence of the $\Delta^{8,9}$ alkene in **25** creates opportunities for analog synthesis. Simply reducing the C5 carbonyl group of **25** with $NaBH_4$ followed by appending the side chain provided dehydroneopeltolide **27** (Scheme 10). Although this structure is not likely to differ from neopeltolide with respect to physical properties or biological activity, the removal of one step in the sequence improves analog accessibility.



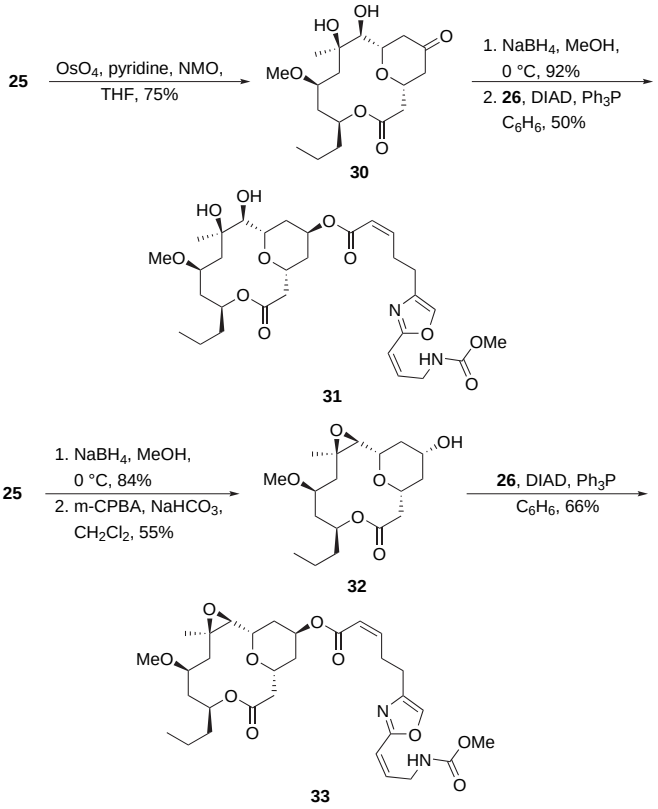
Scheme 10. Synthesis of dehydroneopeltolide.

We subjected **25** to hydrogenation in the presence of Crabtree's catalyst[30] in an effort to determine whether we could exploit reagent coordination to the tetrahydropyranyl oxygen to functionalize the alkene from the convex face (Scheme 11). While the diastereoselectivity for the reaction was low (~1.4:1), major product **28**, the C9-epimer of **4**, was isolated in a reasonable 54% yield. Despite the low selectivity, this result suggests that future analogs can be accessed through coordinated delivery of reagents[31] to the less accessible face of the alkene. Reduction of **28** with $NaBH_4$ followed by esterification with **26** provided C9-*epi*-neopeltolide **29**.



Scheme 11. Synthesis of 9-*epi*-neopeltolide.

The alkene provides opportunities for introducing polar groups that could improve physical properties, such as water solubility. Exposing **25** to OsO_4 and pyridine, followed by osmate ester cleavage with NMO yielded diol **30** in 75% yield as a single diastereomer. This reaction required stoichiometric OsO_4 to proceed at a reasonable rate, though at a larger scale the OsO_4 loading could conceivably be lowered. Ketone reduction and acylation provided a 50% yield of dihydroxyneopeltolide **31**. We approached the epoxide analog by reducing **25** with $NaBH_4$ followed by exposing the resulting alcohol to *m*-CPBA to provide **32**. Conducting the reduction prior to epoxidation averted the potential for **25** to undergo a competitive Bayer–Villiger reaction. Acylation gave epoxyneopeltolide **33** in 66% yield (Scheme 12).



Scheme 12. Synthesis of dihydroxy- and epoxyneopeltolide.

3. Summary and conclusions

We have shown that our method for oxidative carbocation formation in a macrocycle can be applied to the total synthesis of the potent cytotoxin neopeltolide. The use of a relatively inert ether as a precursor to an oxocarbenium ion obviates the need for step investment with respect to protecting groups and/or activating groups, leading to a brief overall sequence. This work also highlights the versatility of alkynes in complex molecule synthesis[32] (coupling through the Sonogashira reaction, hydration to form a ketone, and acetoxylation to form an enol acetate). While neopeltolide does not contain the alkenyl group, that is, required to conduct the oxidative cyclization, the unsaturation can be exploited to provide a number of interesting analogs. Hydrogenation can be conducted with Pd/C or Crabtree's catalyst provides the natural product or an epimer. Retaining the alkene provide a structure that can be accessed in one fewer step. Dihydroxylation and epoxidation yield analogs that are more polar than the natural product. We have initiated studies to evaluate the biological activities of these and other analogs. The results of these studies will be reported elsewhere.

4. Experimental section

4.1. General experimental

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, respectively. The chemical shifts are given

in parts per million (ppm) on the delta (δ) scale. Tetramethylsilane (TMS) or the solvent peak was used as a reference value, for ^{1}H NMR: TMS (in $CDCl_3$)=0.00 ppm, CD_3OD=3.31, for ^{13}C NMR: TMS (in $CDCl_3$)=0.00, CD_3OD=49.00. Data are reported as follows: (s=singlet; d=doublet; t=triplet; q=quartet; dd=doublet of doublets; dt=doublet of triplets; br=broad). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60 F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32–63 60 Å silica gel. Methylene chloride was distilled under N_2 from CaH_2. Reagent grade ethyl acetate, diethyl ether, pentane, and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Benzene was dried with 4A molecular sieves. THF was distilled from sodium. Other reagents were obtained from commercial source without further purification. All reactions were performed in oven or flame-dried glassware with magnetic stirring unless otherwise noted. The synthesis and characterization of compounds **4**, **5**, **7**, **10**, **12**, **18**, **20**, **22**, **23**, and **25** have previously been reported.

4.2. General procedure for macrocyclic ketone reduction

To the macrocyclic ketone (0.020 mmol) in MeOH (0.5 mL) at 0 °C was added $NaBH_4$ (0.040 mmol). After 10 min, AcOH (0.40 mmol) was added and the reaction was concentrated under vacuum. The resulting residue was purified by flash column chromatography to afford the desired macrocyclic alcohol.

4.3. General procedure for Mitsunobu acylation

Tohe macrocyclic alcohol (0.019 mmol), **26** (0.078 mmol), and PPh_3 (0.086 mmol) in benzene (0.5 mL) was added DIAD (0.086 mmol). After ten minutes the reaction was concentrated under vacuum. The resulting residue was purified by flash column chromatography to afford the desired product.

4.4. Procedures and characterization data

4.4.1. (1R,5S,7S,9S,11R,13S)-13-hydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one. The general ketone reduction protocol was followed with **4** (6.5 mg, 0.020 mmol) and $NaBH_4$ (1.6 mg, 0.042 mmol). Flash column chromatography (50% EtOAc in hexanes) yielded the desired product (6.2 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12–5.21 (m, 1H), 3.75–3.87 (m, 1H), 3.73 (ddd, *J*=2.0, 4.4, 10.9 Hz, 1H), 3.59 (t, *J*=9.4 Hz, 1H), 3.32 (s, 3H), 3.18 (t, *J*=9.3 Hz, 1H), 2.63 (dd, *J*=4.4, 14.5 Hz, 1H), 2.44 (dd, *J*=10.7, 14.5 Hz, 1H), 1.99 (ddd, *J*=1.8, 1.8, 11.5 Hz, 1H), 1.81–1.92 (m, 2H), 1.43–1.78 (m, 5H), 1.12–1.41 (m, 6H), 1.0 (d, *J*=6.7 Hz, 3H), 0.92 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 78.6, 75.6, 73.3, 72.3, 68.1, 56.2, 44.1, 42.2, 42.2, 41.9, 40.7, 40.0, 36.9, 31.2, 25.5, 19.0, 13.9; IR (film) 3416, 2918, 2871, 1730, 1650, 1459, 1087 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{32}O_5Na$ ([M+Na]$^+$) 351.2147, found 351.2159; $[\alpha]_D^{25}$ +17.1 (*c* 0.2, $CHCl_3$).

*4.4.2. Synthesis of neopeltolide (**3**).* The general Mitsunobu acylation procedure was followed with the macrocyclic alcohol (6.2 mg, 0.019 mmol), **26** (22.0 mg, 0.078 mmol), Ph_3P (11.4 mg, 0.086 mmol), and DIAD (16.8 μL, 0.086 mmol). Flash column chromatography (30% EtOAc in hexanes) yielded neopeltolide (10.5 mg, 93%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.66 (s,1H), 6.32–6.41 (m, 1H), 6.28 (dt, *J*=2.1, 13.8 Hz, 1H), 6.03 (pentet, *J*=6.0 Hz, 1H), 5.88 (d, *J*=11.6 Hz, 1H), 5.20 (t, *J*=2.8 Hz, 1H), 5.12–5.22 (m, 1H), 4.30 (dd, *J*=1.4, 4.2 Hz, 2H), 4.06 (t, *J*=9.3 Hz, 1H), 3.70 (s, 1H), 3.65 (s, 3H), 3.56 (t, *J*=9.0 Hz, 1H), 3.28 (s, 3H), 3.01 (dd, *J*=7.6, 15.1 Hz, 2H), 2.71 (s, 1H), 2.70 (dt, *J*=4.4, 14.7 Hz, 1H), 2.23 (dd, *J*=11.0, 14.7 Hz, 1H), 1.73–1.90 (m, 2H), 1.65–1.73 (m, 2H), 1.44–1.60 (m, 5H), 1.26–1.44 (m, 6H), 1.07–1.18 (m, 1H), 0.97(d, *J*=6.3, 3H), 0.92 (d, J=13.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 173.1, 166.9, 161.9, 159.5, 150.0, 142.3, 139.3, 136.0, 121.7, 116.0, 77.2, 77.1, 74.0, 71.4, 69.2, 56.4, 52.6, 45.3, 43.5, 43.3, 41.1, 38.0, 37.6, 37.4, 36.2, 32.6, 29.0, 26.4, 26.0, 20.0, 14.2; IR (film) 3357, 2954, 2922, 2854, 1719, 1646, 1537, 1458, 1376, 1342, 1249, 1178, 1064, 994, 777 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{46}N_2O_9Na$ ([M+Na]$^+$) 613.3101, found 613.3076; $[\alpha]_D^{25}$ +17.5 (*c* 0.24, MeOH).

4.4.3. (1R,5S,7S,11S,13R,Z)-13-hydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadec-9-en-3-one. The general ketone reduction protocol was followed with **25** (14.9 mg, 0.046 mmol) and $NaBH_4$ (3.6 mg, 0.095 mmol). Flash column chromatography (50% EtOAc in hexanes) yielded the desired product (12.6 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31–5.37 (m, 1H), 5.30 (d, *J*=7.2 Hz, 1H), 3.82–3.93 (m, 3H), 3.49–3.56 (m, 1H), 3.36 (s, 3H), 2.63 (dd, *J*=3.8, 15.1 Hz, 1H), 2.51 (dd, *J*=11.1, 15.1 Hz, 1H), 2.33 (d, *J*=13.3 Hz, 1H), 1.95–2.05 (m, 3H), 1.86 (d, *J*=0.6 Hz, 3H), 1.81–1.89 (m, 1H), 1.64–1.74 (m, 1H), 1.47–1.59 (m, 2H), 1.44 (s, 1H), 1.18–1.40 (m, 3H), 0.92 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 146.9, 125.1, 81.8, 74.1, 72.4, 72.0, 68.1, 57.9, 43.3, 42.1,41.8, 40.5, 40.3, 37.4, 25.2, 18.7, 13.9; IR (film) 3422, 2959, 2923, 2854, 1732, 1654, 1454, 1373, 1315, 1264, 1195, 1080, 1035, 981, 939, 842, 755 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}O_5Na$ ([M+Na]$^+$) 349.1991, found 349.1992; $[\alpha]_D^{25}$ −47.0 (*c* 0.38, $CHCl_3$).

*4.4.4. Dehydroneopeltolide (**27**).* The general Mitsunobu acylation protocol was followed with the macrocyclic alcohol (6.8 mg, 0.021 mmol), **26** (23.0 mg, 0.083 mmol), Ph_3P (23.5 mg, 0.090 mmol), and DIAD (17.8 μL, 0.090 mmol). Flash column chromatography (30% EtOAc in hexanes) yielded dehydro-neopeltolide (8.6 mg, 70%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.67 (s, 1H), 6.34–6.43 (m, 1H), 6.28 (dt, *J*=2.0, 12.0 Hz, 1H), 6.05 (pentet, *J*=6.0 Hz, 1H), 5.90 (dt, *J*=1.5, 11.5 Hz, 1H), 5.25–5.33 (m, 1H), 5.27 (t, *J*=2.8 Hz, 1H), 5.22 (d, *J*=6.7 Hz, 1H), 4.31 (d, *J*=4.7 Hz, 2H), 4.19–4.28 (m, 2H), 3.66 (s, 3H), 3.58–3.65 (m, 1H), 3.34 (s, 3H), 3.03 (ddd, *J*=1.4, 7.7, 7.7 Hz, 2H), 2.73(t, *J*=7.0 Hz, 2H), 2.69(dd, *J*=3.4, 10.2 Hz, 1H), 2.27–2.38 (m, 2H), 1.95 (dd, *J*=10.4, 13.6 Hz, 1H), 1.84 (s, 3H), 1.62–1.88 (m, 5H), 1.49–1.58 (m, 3H), 1.23–1.30 (m, 3H), 0.95 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.7, 166.9, 162.0, 159.7, 150.1, 148.0, 142.3, 139.3, 136.0, 127.0, 121.8, 116.0, 83.4, 75.2, 71.3, 71.1, 69.1, 58.2, 52.7, 44.2, 43.3, 42.5, 41.1, 38.5, 36.3, 35.9, 29.1, 26.5, 25.8, 19.9, 14.3; IR (film) 3351, 2957, 2923, 1719, 1521, 1458, 1268, 1170, 1097, 1072, 892, 818, 776 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{44}N_2O_9Na$ ([M+Na]$^+$) 611.2945, found 611.2997; $[\alpha]_D^{25}$ −44.1 (*c* 0.56, MeOH).

*4.4.5. (1S,5S,7S,9R,11R)-7-methoxy-9-methyl-5-propyl-15-oxabicyclo[9.3.1]pentadecane-3,13-dione (**28**).* To **25** (6.1 mg, 0.019 mmol) in CH_2Cl_2 (0.2 mL) was added Crabtree's catalyst (3.2 mg, 0.004 mmol). The flask was quickly evacuated and backfilled with H_2, and this process was repeated three times. The reaction mixture was stirred at room temperature for 30 min., then was filtered through Celite, concentrated, and purified by flash chromatography (5% Et_2O in CH_2Cl_2) to afford the desired product (3.3 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14–5.22 (m, 1H), 3.93–4.02 (m, 1H), 3.69 (m, 1H), 3.32 (s, 3H), 3.23–3.31 (m, 1H), 2.72 (dd, *J*=4.5, 14.4 Hz, 1H), 2.46 (dd, *J*=8.5, 14.4 Hz, 1H), 2.42 (dd, *J*=4.1, 7.0 Hz, 1H), 2.31 (d, *J*=7.8 Hz, 2H), 1.92 (dt, *J*=2.2, 14.8 Hz, 1H), 1.74–1.83 (m, 1H), 1.43–1.73 (m, 4H), 1.16–1.39 (m, 6H), 0.94 (d, *J*=6.8 Hz, 3H), 0.92 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 179.8, 80.4, 75.0, 73.8, 72.6, 56.3, 48.2, 46.8, 41.7, 41.6, 40.1, 39.0, 37.7, 28.6, 20.9, 18.7,

13.9; IR (film) 2956, 2923, 2853, 1723, 1459, 1370, 1330, 1252, 1185, 1105, 1081, 844, 799 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}O_5Na$ ($[M+Na]^+$) 349.1991, found 349.1974; $[\alpha]_D^{25}$ −7.9 (*c* 0.17, $CHCl_3$).

4.4.6. (1R,5S,7S,9R,11R,13S)-13-hydroxy-7-methoxy-9-methyl-5-propyl-15-oxabicyclo[9.3.1]pentadecan-3-one. The general reduction protocol was followed with **28** (3.3 mg, 0.010 mmol) and $NaBH_4$ (1.1 mg, 0.029 mmol). Flash column chromatography (35% EtOAc in hexanes) yielded the desired product (3.2 mg, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.11–5.20 (m, 1H), 3.80–3.86 (m, 1H), 3.69 (tdd, *J*=1.9, 4.6, 11.0 Hz, 1H), 3.78 (tt, *J*=2.4, 8.7 Hz, 1H), 3.31 (s, 3H), 3.27 (dt, *J*=2.0, 9.1 Hz, 1H), 2.64 (dd, *J*=4.6, 14.3 Hz, 1H), 2.41 (dd, *J*=9.0, 14.3 Hz, 1H), 1.90–1.99 (m, 2H), 1.83–1.88 (m, 2H), 1.60–1.80 (m, 3H), 1.43–1.60 (m, 3H), 1.13–1.40 (m, 4H), 0.89–0.93 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 80.5, 74.6, 72.4, 71.5, 68.4, 56.4, 41.8, 41.7, 41.5, 40.3, 39.6, 39.4, 37.7, 28.7, 21.1, 18.7, 13.9; IR (film) 3363, 3296, 2916, 2852, 1718, 1490, 1457, 1364, 1274, 1256, 1220, 1160, 1108, 1074, 1036, 931 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{32}O_5Na$ ($[M+Na]^+$) 351.2147, found 351.2166; $[\alpha]_D^{25}$ −9.6 (*c* 0.32, $CHCl_3$).

*4.4.7. 9-epi-Neopeltolide (**29**).* The general Mitsunobu acylation protocol was followed with the alcohol (3.1 mg, 0.0095 mmol), **26** (10.5 mg, 0.038 mmol), Ph_3P (10.7 mg, 0.041 mmol), and DIAD (8.1 μL, 0.041 mmol). Flash column chromatography (30% EtOAc in hexanes) yielded C9-*epi*-neopeltolide (3.8 mg, 67%). ^1H NMR (300 MHz, CD_3OD) δ 7.65 (s, 1H), 6.36 (dt, *J*=7.4, 11.6 Hz, 1H), 6.26 (dt, *J*=2.0, 11.8 Hz, 1H), 6.02 (pentet, *J*=6.1 Hz, 1H), 5.86 (dt, *J*=1.6, 11.5 Hz, 1H), 5.22 (t, *J*=2.8 Hz, 1H), 5.11–5.20 (m, 1H), 4.29 (dd, *J*=1.5, 5.8 Hz, 2H), 3.95–4.05 (m, 1H), 3.76 (t, *J*=6.0 Hz, 1H), 3.64 (s, 3H), 3.29 (s, 3H), 2.99 (dd, *J*=7.1, 7.1 Hz, 2H), 2.69 (t, *J*=7.7 Hz, 2H), 2.65 (dd, *J*=4.4, 9.4 Hz, 1H), 2.24 (dd, *J*=9.2, 14.4 Hz, 1H), 1.90 (d, *J*=8.9 Hz, 1H), 1.75–1.84 (m, 3H), 1.39–1.68 (m, 4H), 1.23–1.39 (m, 6H), 1.22 (t, *J*=7.2 Hz, 2H), 1.09–1.19 (m, 1H), 0.91 (t, *J*=7.3 Hz, 3H), 0.89 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.6, 166.9, 161.9, 159.6, 150.0, 142.2, 139.2 135.9, 121.7, 115.9, 82.1, 75.8, 70.8, 70.6, 69.4, 68.9, 56.5, 52.6, 42.6, 41.0, 40.9, 40.5, 38.8, 37.0, 35.8, 30.0, 29.0, 26.4, 21.5, 19.8, 14.2; IR (film) 2923, 2854, 1716, 1519, 1458, 1375, 1249, 1179, 1103, 817 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{46}N_2O_9Na$ ($[M+Na]^+$): 613.3101, found 613.3075; $[\alpha]_D^{25}$ +0.2 (*c* 0.20, MeOH).

*4.4.8. (1R,5S,7R,9R,10S,11S)-9,10-dihydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxa-bicyclo[9.3.1]pentadecane-3,13-dione (**30**).* To OsO_4 (6.1 mg, 0.024 mmol) and pyridine (61 μL, 0.76 mmol) in THF (0.2 mL) at 0 °C was added **25** (5.3 mg, 0.016 mmol) in THF (0.2 mL). After 10 min, NMO·H_2O (4.3 mg, 0.032 mmol) was added and the reaction was allowed to room temperature over 30 min. The reaction was quenched by 1 mL saturated $Na_2S_2O_3$ at 0 °C and extracted with three 2 mL portions of EtOAc. The organic layer was concentrated under vacuum and purified by flash column chromatography (5% MeOH in CH_2Cl_2) to afford the diol (4.4 mg, 75%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.03–5.14 (m, 1H), 4.04 (tt, *J*=3.4, 11.2 Hz, 1H), 3.66 (tt, *J*=3.0, 11.2 Hz, 1H), 3.59 (s, 1H), 3.54–3.58 (m, 1H), 3.39 (s, 3H), 3.28 (t, *J*=7.4 Hz, 1H), 2.84 (d, *J*=7.2 Hz, 1H), 2.71 (dt, *J*=1.8, 15.0, 1H), 2.65 (dd, *J*=3.8, 14.5 Hz, 1H), 2.50 (dd, *J*=11.1, 14.3 Hz, 2H), 2.40 (dd, *J*=12.2, 15.1 Hz, 1H), 2.27 (dd, *J*=11.5, 13.5 Hz, 1H), 2.15 (ddd, *J*=1.3, 3.5, 14.4 Hz, 1H), 1.92 (dd, *J*=2.9, 15.2 Hz, 1H), 1.63 (dd, *J*=10.5, 14.8 Hz, 2H), 1.42–1.62 (m, 2H), 1.15–1.39 (m, 5H), 0.92 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 169.5, 77.8, 77.7, 73.3, 73.0, 72.9, 56.2, 47.1, 45.0, 42.7, 41.5, 38.2, 37.5, 24.8, 18.4, 13.9; IR (film) 3441, 2923, 1721, 1555, 1460, 1377, 1267, 1183, 1100, 1069, 964, 934, 817 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}O_7Na$ ($[M+Na]^+$) 381.1889, found 381.1902; $[\alpha]_D^{25}$ −28.5 (*c* 0.13, MeOH).

4.4.9. (1R,5S,7R,9R,10S,11S,13R)-9,10,13-trihydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one. The general reduction protocol was followed with **30** (3.6 mg, 0.010 mmol) and $NaBH_4$ (1.1 mg, 0.029 mmol). Flash column chromatography (5% MeOH in CH_2Cl_2) yielded the desired triol (3.3 mg, 92%). ^1H NMR (300 MHz, CD_3OD) δ 5.09–5.18 (m, 1H), 3.70–3.83 (m, 2H), 3.49–3.55 (m, 1H), 3.46 (ddd, *J*=1.7, 7.1, 11.1, 1H), 3.32 (s, 3H), 3.28 (s, 1H), 2.76 (dd, *J*=4.6, 14.1 Hz, 1H), 2.30 (dd, *J*=8.8, 14.1 Hz, 1H), 2.12 (dt, *J*=2.2, 12.4 Hz, 1H), 1.97 (t, *J*=14.8 Hz, 2H), 1.91–1.95 (m, 1H), 1.68 (dd, *J*=10.8, 14.7 Hz, 2H), 1.50–1.65 (m, 3H), 1.20–1.40 (m, 8H), 0.97 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 171.2, 77.0, 76.6, 76.5, 74.1, 74.0, 72.0, 67.5, 55.0, 45.4, 41.2, 40.6, 39.9, 37.6, 37.4, 25.6, 18.2, 12.8; IR (film) 3397, 2924, 1729, 1457, 1373, 1263, 1195, 1099, 1044, 937, 731 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{32}O_7Na$ ($[M+Na]^+$): 383.2046, found 383.2034; $[\alpha]_D^{25}$ −8.6 (*c* 0.32, MeOH).

*4.4.10. Dihydroxyneopeltolide (**31**).* The general Mitsunobu acylation protocol was followed with the triol (3.5 mg, 0.01 mmol), **26** (4.1 mg, 0.015 mmol), Ph_3P (4.2 mg, 0.016 mmol), and DIAD (3.2 μL, 0.016 mmol) in benzene (0.2 mL). Flash chromatography (5% MeOH in CH_2Cl_2) yielded the desired product (3.0 mg, 50%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 6.26–6.34 (m, 2H), 6.09 (pentet, *J*=6.4 Hz, 1H), 5.90 (dt, *J*=1.7, 11.5 Hz, 1H), 5.57 (br, 1H), 5.32 (t, *J*=2.8 Hz, 1H), 5.06–5.14 (m, 1H), 4.31 (t, *J*=6.1 Hz, 2H), 4.00 (tdd, *J*=1.9, 1.9, 9.3 Hz, 1H), 3.69 (s, 3H), 3.59–3.67 (m, 2H), 3.40 (s, 1H), 3.37 (s, 3H), 3.35 (s, 1H), 3.16 (dd, *J*=5.7, 8.4 Hz, 1H), 3.04 (ddt, *J*=1.9, 7.4, 7.4 Hz, 2H), 2.90 (d, *J*=6.0 Hz, 1H), 2.72 (t, *J*=7.2 Hz, 2H), 2.54 (dd, *J*=3.8, 14.4 Hz, 1H), 2.36 (dd, *J*=11.2, 14.4 Hz, 1H), 2.01–2.11 (m, 3H), 1.83 (d, *J*=9.6 Hz, 1H), 1.68 (dt, *J*=3.0, 11.5 Hz, 1H), 1.50–1.65 (m, 5H), 1.35 (t, *J*=7.3 Hz, 2H), 1.27 (s, 3H), 0.91 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 171.5, 165.5, 148.6, 140.8, 137.8, 134.6, 120.3, 114.5, 77.3, 76.8, 74.0, 73.9, 73.6, 69.5, 67.6, 54.9, 45.1, 41.1, 40.1, 37.4, 34.5, 32.5, 27.5, 25.6, 24.9, 18.2, 12.8; IR (film) 3358, 2957, 2922, 2853, 2500, 1715, 1635, 1553, 1460, 1396, 1262, 1169, 1095, 1052, 1019, 816, 795, 780 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{46}N_2O_{11}Na$ ($[M+Na]^+$) 645.2999, found 645.2996; $[\alpha]_D^{25}$ −2.1 (*c* 0.16. MeOH).

*4.4.11. (1S,2S,4R,6R,8S,12R,14R)-14-Hydroxy-6-methoxy-4-methyl-8-propyl-3,9,16-trioxatricyclo[10.3.1.0^{2,4}]hexadecan-10-one (**32**).* To the unsaturated lactone (5.9 mg, 0.018 mmol) and $NaHCO_3$ (5.8 mg, 0.069 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added recrystallized *m*-CPBA (4.5 mg, 0.026 mmol). The reaction was stirred at 0 °C for 4 h and then warmed to room temperature and stirred overnight. The reaction was quenched by the addition of 0.7 mL saturated $Na_2S_2O_3$ and 0.7 mL saturated $NaHCO_3$ at 0 °C and extracted with three 1 mL portions of ethyl acetate. Flash chromatography (50% EtOAc in hexanes) afforded the epoxy alcohol (3.4 mg, 55%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.32–5.42 (m, 1H), 3.8 (br, 1H), 3.76 (tdd, *J*=1.5, 3.8, 10.9 Hz, 1H), 3.65 (dd, *J*=5.4, 8.9 Hz, 1H), 3.06 (ddd, *J*=2.0, 8.0, 10.9 Hz, 1H), 2.71 (d, *J*=7.8 Hz, 1H), 2.58 (dd, *J*=3.8, 15.1 Hz, 1H), 2.50 (dd, *J*=10.8, 15.2 Hz, 1H), 2.25 (dt, *J*=2.4, 12.4 Hz, 1H), 2.12 (dd, *J*=11.2, 14.6 Hz, 1H), 1.86–2.00 (m, 3H), 1.43–1.62 (m, 5H), 1.34 (s, 3H), 1.24–1.39 (m, 6H), 0.91 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 73.9, 73.4, 67.4, 64.6, 61.8, 57.2, 44.4, 41.8, 41.6, 39.8, 39.3, 37.3, 23.3, 22.7, 18.7, 13.9; IR (film) 3435, 2924, 2854, 1732, 1459, 1374, 1262, 1200, 1078, 942, 799 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}O_6Na$ ($[M+Na]^+$) 365.1940, found 365.1932; $[\alpha]_D^{25}$ −23.5 (*c* 0.33, $CHCl_3$).

*4.4.12. Epoxyneopeltolide (**33**).* The general Mitsunobu acylation protocol was followed with **32** (3.1 mg, 0.009 mmol), **26** (11.2 mg, 0.040 mmol), Ph_3P (11.4 mg, 0.044 mmol), and DIAD (8.6 μL, 0.044 mmol). Flash column chromatography (30% EtOAc in CH_2Cl_2) yielded epoxyneopeltolide (3.6 mg, 66%). ^1H NMR (300 MHz, CD_3OD) δ 7.65 (s, 1H), 6.36 (dt, *J*=4.1, 7.3 Hz, 1H), 6.27 (dt, *J*=2.1, 11.9 Hz, 1H), 6.03 (pentet, *J*=6.0 Hz, 1H), 5.89 (dt, *J*=1.6, 11.6 Hz, 1H), 5.27–5.39 (m, 1H), 5.28 (t, *J*=3.0 Hz, 1H), 4.30 (dd, *J*=1.8, 6.1 Hz, 2H), 4.08–4.18 (m, 1H), 3.72 (dd, *J*=5.3, 10.0 Hz, 1H), 3.65 (s, 3H), 3.34–3.42 (m, 1H), 3.37 (s, 3H), 3.00 (ddd, *J*=1.7, 7.4, 7.4 Hz, 2H), 2.71 (t,

J=7.1 Hz, 2H), 2.63–2.70 (m, 2H), 2.33 (dd, J=11.6, 15.2 Hz, 1H), 2.04 (dd, J=10.4, 14.7 Hz, 2H), 1.74–1.96 (m, 4H), 1.47–1.66 (m, 4H), 1.26–1.40 (m, 4H), 1.30 (s, 3H), 0.93 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.4, 166.7, 161.9, 150.2, 142.2, 139.1, 136.0, 121.6, 116.0, 77.8, 74.9, 72.2, 68.2, 66.1, 63.0, 57.0, 44.8, 42.7, 42.0, 38.4, 35.4, 34.9, 29.0, 26.4, 23.7, 19.7, 14.1; IR (film) 3352, 2960, 2924, 1724, 1644, 1521, 1440, 1380, 1266, 1253, 1173, 1126, 1077, 1006, 968, 778 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{46}N_2O_{10}Na$ ([M+Na]$^+$) 627.2894, found 627.2910; $[\alpha]_D^{25}$ −11.3 (c 0.34, MeOH).

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.066.

References and notes

1. Wright, A. E.; Botelho, J. C.; Guzman, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412.
2. (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51; (b) D'Ambrosio, M.; Tató, M.; Poscfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347.
3. (a) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894; (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420; (c) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066; (d) Fettes, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4098; (e) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274; (f) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670; (g) Wang, Y.; Janjic, J.; Kozmin, S. A. *Pure Appl. Chem.* **2005**, *77*, 1161; (h) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343; (i) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833; (j) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3934; (k) Williams, D. R.; Patnaik, S.; Plummer, S. V. *Org. Lett.* **2003**, *5*, 5035; (l) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641; (m) Su, Q.; Panek, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1223; (n) Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem.* **2007**, *72*, 2; (o) Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2007**, *9*, 2461; (p) Van Orden, L. J.; Patterson, B. D.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 5784; (q) Jung, H. H.; Seiders, J. R., II; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8464; (r) Ferrié, L.; Boulard, L.; Pradaux, F.; Bouzbouz, S.; Reymond, S.; Capdevielle, P.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 1864; (s) Evans, P. A.; Andrews, W. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5426.
4. Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 9211.
5. Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804.
6. (a) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3242; (b) Vintonyak, V. V.; Maier, M. E. *Org. Lett.* **2008**, *10*, 1239; (c) Fuwa, H.; Naito, S.; Goto, T.; Sasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4737; (d) Ulanovskaya, O. A.; Janjic, J.; Suzuki, M.; Sabharwal, S. S.; Schumaker, P. T.; Kron, S. J.; Kozmin, S. A. *Nature Chem. Biol.* **2008**, *4*, 418; (e) Paterson, I.; Miller, N. A. *Chem. Commun.* **2008**, 4708; (f) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047; (g) Vintonyak, V. V.; Kunze, B.; Sasse, F.; Maier, M. E. *Chem.—Eur. J.* **2008**, *14*, 11132; (h) Custar, D. W.; Zabawa, T. P.; Hines, J.; Crews, C. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 12406; (i) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577; (j) Guinchard, X.; Roulland, E. *Org. Lett.* **2009**, *11*, 4700; (k) Fuwa, H.; Saito, A.; Naito, S.; Konoki, K.; Yotsu-Yamashita, M.; Sasaki, M. *Chem.—Eur. J.* **2009**, *15*, 12807; (l) Yadav, J. S.; Krishna, G. G.; Kumar, S. N. *Tetrahedron* **2010**, *66*, 480; (m) Gallon, J.; Reymond, S.; Cossy, J. *Comp. Rend. Chim.* **2008**, *11*, 1463.
7. (a) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184; (b) Liu, L.; Floreancig, P. E. *Org. Lett.* **2009**, *11*, 3152.
8. For a preliminary account of a portion of the material in this paper, see: Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567.
9. (a) Schulteelte, K. H.; Hauser, A.; Ohloff, G. *Helv. Chim. Acta* **1979**, *62*, 2673; (b) Wender, P. A.; De Brabander, J.; Harran, P. G.; Jimenez, J. M.; Koehler, M. F. T.; Lippa, B.; Park, C. M.; Shiozaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4534; (c) Wender, P. A.; DeChristopher, B. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 6658; (d) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177.
10. Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.
11. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
12. Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650.
13. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
14. Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535.
15. Yu, C.-M.; Choi, H.-S.; Yoon, S.-K.; Jung, W.-H. *Synlett* **1997**, 889.
16. (a) Wei, S. Y.; Tomooka, K.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 5973; (b) Maleczka, R. E., Jr.; Geng, F. *Org. Lett.* **1999**, *1*, 1111; (c) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773.
17. (a) Sonogashira, K.; Todah, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467; (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.
18. (a) Marshall, J. A.; Yanik, M. M. *Org. Lett.* **2000**, *2*, 2173; (b) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495; (c) Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028; (d) Robles, O.; McDonald, F. E. *Org. Lett.* **2008**, *10*, 1811.
19. Denmark, S. E.; Wang, Z. *Org. Lett.* **2001**, *3*, 1073.
20. Tamao, K.; Maeda, K.; Tanaka, T.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 6955.
21. Denmark, S. E.; Pan, W. *Org. Lett.* **2002**, *4*, 4163.
22. Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
23. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
24. (a) Goossen, L. J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706; (b) Neveux, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1197.
25. Jung, H. H.; Floreancig, P. E. *Tetrahedron* **2009**, *65*, 10830.
26. (a) Tolbert, L. M.; Khanna, R. K.; Popp, A. E.; Gelbaum, L.; Bottomley, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 2373; (b) Perrott, A. L.; de Lijser, H. J. P.; Arnold, D. R. *Can. J. Chem.* **1997**, *75*, 384; (c) Freccero, M.; Pratt, A.; Albini, A.; Long, C. *J. Am. Chem. Soc.* **1998**, *120*, 284; (d) Floreancig, P. E. *Synlett* **2007**, 191.
27. CCDC721650 contains the supplimentary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
28. Mitsunobu, O. *Synthesis* **1981**, 1.
29. Wipf, P.; Graham, T. H. *J. Org. Chem.* **2001**, *66*, 3242.
30. Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.
31. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
32. For recent discussions, see: (a) Trost, B. M.; Weiss, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7664; (b) Trost, B. M.; Sieber, J. D.; Qian, W.; Dhawan, R.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 5478.