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Formal Synthesis of (−)-Neopeltolide Featuring a Highly Stereoselective Oxocarbenium Formation/Reduction Sequence

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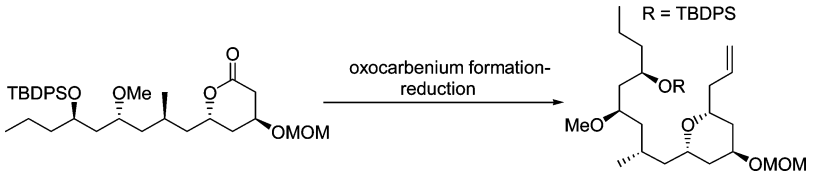

The formal synthesis of the unnatural (−)-neopeltolide core is discussed in detail. Efficient application of the Evans' protocol for the synthesis of 1,3-*syn*-diols via an intramolecular hetero-Michael addition followed by reductive deprotection of the resulting benzylidene acetal allowed for swift access to the δ-lactone. Central to the synthetic approach is a tandem nucleophilic addition−diastereoselective axial reduction of an in situ generated oxocarbenium cation to assemble the β-*C*-glycoside moiety of the neopeltolide core.

Introduction

Marine-derived secondary metabolites have rendered a myriad of molecular architectures that have proven an invaluable source of therapeutically promising leads. One such compound is (+)-neopeltolide, which was first isolated from deep-water sponges most closely related to the genus *Daedalopelta Sollas* and subsequently disclosed in 2007 by Wright as shown in Figure 1.[1] Neopeltolide is an extremely potent inhibitor of in vitro proliferation of A-549 human lung adenocarcinoma, NCI/ADR-RES ovarian sarcoma, and P388 murine leukemia cell lines with IC_{50} values in the nanomolar range (1.2, 5.1, and 0.56 nM, respectively). This polyketide natural product also demonstrates inhibitory effects in PANC-1 pancreatic and DLD-1 colorectal cell lines as well as potent inhibition (MIC = 0.625 μg/mL) of the fungal pathogen *Candida albicans*, which can greatly threaten the health of advanced AIDS patients.[2]

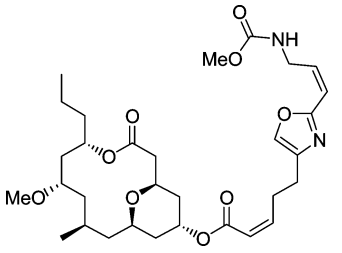

FIGURE 1. Structure of (+)-neopeltolide.

Due to its unique structure, exceptional potency, and line-selective anticancer activity, (+)-neopeltolide has been the subject of numerous synthetic studies.[3−6] Panek was the first to disclose the total synthesis of (+)-neopeltolide exploiting

(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) Wright, A. E.; Pomponi, S. A.; McCarthy, P. J. U.S. Patent 7179828B2, 2007; European Patent 1644380, 2007.

(3) (a) Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 9211. (b) Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804. (c) Fuwa, H.; Naito, S.; Goto, T.; Sasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4737. (d) Paterson, I.; Miller, N. A. *Chem. Commun.* **2008**, 4708. (e) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3242. (f) Guinchard, X.; Roulland, E. *Org. Lett.* **2009**, 4700. (g) Fuwa, H.; Saito, A.; Sasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3041. For a review, see: (h) Gallon, J.; Reymond, S.; Cossy, J. *Chemie* **2008**, *11*, 1463.

(4) (a) Vintonyak, V. V.; Maier, M. A. *Org. Lett.* **2008**, *10*, 1239. (b) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047. (c) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577. (d) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567. (e) Yadav, J. S.; Krishana, G. G.; Kumar, S. N. *Tetrahedron.* **2010**, *66*, 480.

(5) (a) Fuwa, H.; Saito, A.; Naito, S.; Konoki, K.; Yotsu-Yamashita, M.; Sasaki, M. *Chem.—Eur. J.* **2009**, *15*, 12807. (b) Custar, D. W.; Zabawa, T. P.; Hines, J.; Crews, C. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 12406. (c) Vintonyak, V. V.; Kunze, B.; Sasse, F.; Maier, M. A. *Chem.—Eur. J.* **2008**, *14*, 11132.

(6) Ulanovskaya, O. A.; Janjic, J.; Suzuki, M.; Sabharwal, S. S.; Schumacker, P. T.; Kron, S. J.; Kozmin, S. A. *Nat. Chem. Biol.* **2008**, *4*, 418.

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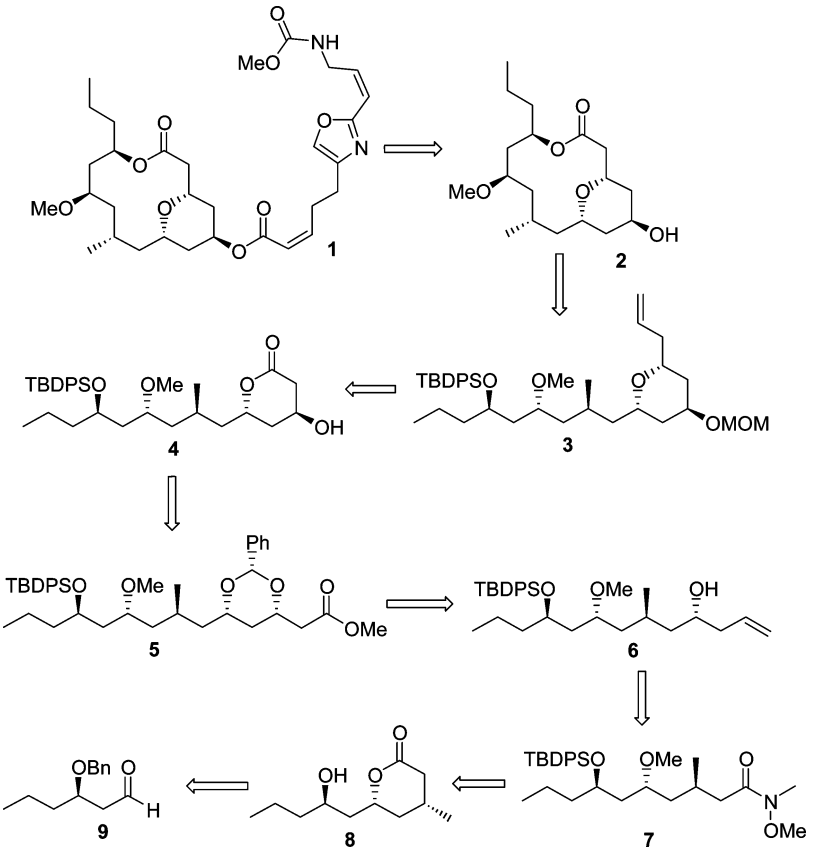
SCHEME 1. Retrosynthetic Analysis of (−)-Neopeltolide (1)



an elegant [4 + 2]-allylsilane annulation as the key step and led to stereochemical revisions of the originally proposed structure.[3a] A subsequent report by Scheidt confirmed the stereochemical reassignments and utilized an innovative Lewis acid catalyzed cyclization to generate the *cis*-tetrahydropyran ring and the macrocycle concomitantly.[3b] Most recently, Fuwa reported a very efficient synthesis (12 steps in 14% yield to the macrocycle) of (+)-neopeltolide featuring a chemo- and diastereoselective cross-metathesis reaction followed by an oxy-Michael addition to forge the β-*C*-glycoside subunit.[3g] In addition to their total synthesis, the Scheidt group has also helped shed light on the structure−activity relationships of (+)-neopeltolide.[5b] Their studies determined that both the ester side chain and the macrolide core bound together are needed for biological activity, since neither are active independently. Furthermore, the group found that stereochemistry on the macrolide is crucial for potency as the originally proposed structure for (+)-neopeltolide is 84- to 100-fold less potent than the natural product. Maier's SAR studies have found that shortening the distance between the lactone and the oxazole side chain greatly reduces the biological activity.[5c] Further SAR studies of this promising compound should give clues as to the mode of action and what key pharmacophore(s) are crucial for its impressive biological activity.

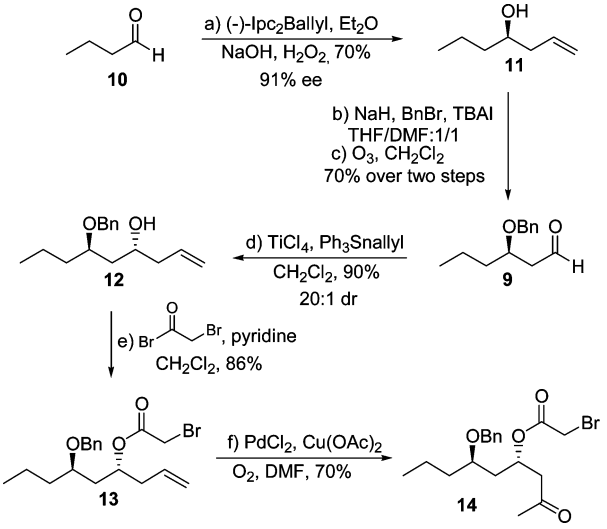
Results and Discussion

Not withstanding its impressive biological profile, our attraction to neopeltolide stemmed from the β-*C*-glycoside moiety embedded within the macrolactone core. We have successfully demonstrated in a variety of previous synthetic ventures, the efficient formation of these building blocks capitalizing on a stereoselective oxocarbenium cation formation/reduction protocol starting from δ-lactones.[7] We were hopeful that this synthetic approach would deliver the targeted β-*C*-glycoside, which in principle, could be transformed to the neopeltolide core. To the best of our knowledge, no biological testing of unnatural (−)-neopeltolide (**1**) has been performed, and based on our previous experience with (−)-dactylolide,[8] we thought it might be prudent to synthesize the antipode of the natural product core in order to potentially advance SAR studies of this promising compound. Along this line, recall that the unnatural (−)-dactylolide is roughly 2- to 3-fold more active against the SK-OV-3 line than that of (+)-dactylolide. Also, (−)-dactylolide exhibited GI_{50} values in the nanomolar (25−99 ng/mL) range against the four cell lines HL-60, K-562, HCC-2998, and SF-539 while displaying modest LC_{50} values. Our previous results with (−)-dactylolide illustrate the need for synthetic natural product molecules (or in this case the antipode) for the undertaking of more comprehensive in vitro biological screening. The following work describes the formal synthesis of **1**.

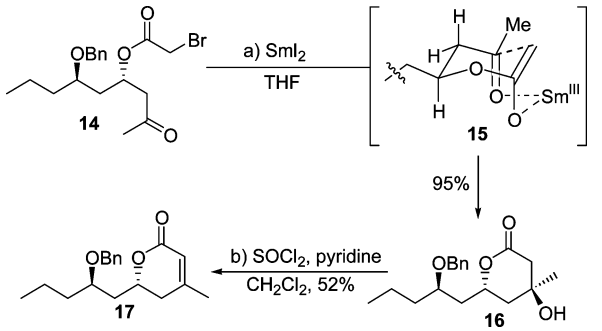
(7) (a) Jennings, M. P.; Clemens, R. T. *Tetrahedron Lett*. **2005**, *46*, 2021. (b) Ding, F.; Jennings, M. P. *Org. Lett*. **2005**, *7*, 2321. (c) Clemens, R. T.; Jennings, M. P. *Chem. Commun*. **2006**, 2720. (d) Sawant, K. B.; Jennings, M. P. *J. Org. Chem*. **2006**, *71*, 7911. (e) Sawant, K. B.; Ding, F.; Jennings, M. P. *Tetrahedron Lett*. **2006**, *47*, 939. (f) Sawant, K. B.; Ding, F.; Jennings, M. P. *Tetrahedron Lett*. **2007**, *48*, 5177. (g) Carrick, J. D.; Jennings, M. P. *Org. Lett*. **2009**, *11*, 769.

(8) Ding, F.; Jennings, M. P. *J. Org. Chem*. **2008**, *73*, 5965.

SCHEME 2. Synthesis of the Reformatsky Precursor Ketone 14



SCHEME 3. SmI_2-Mediated Molander−Reformatsky Reaction of 14

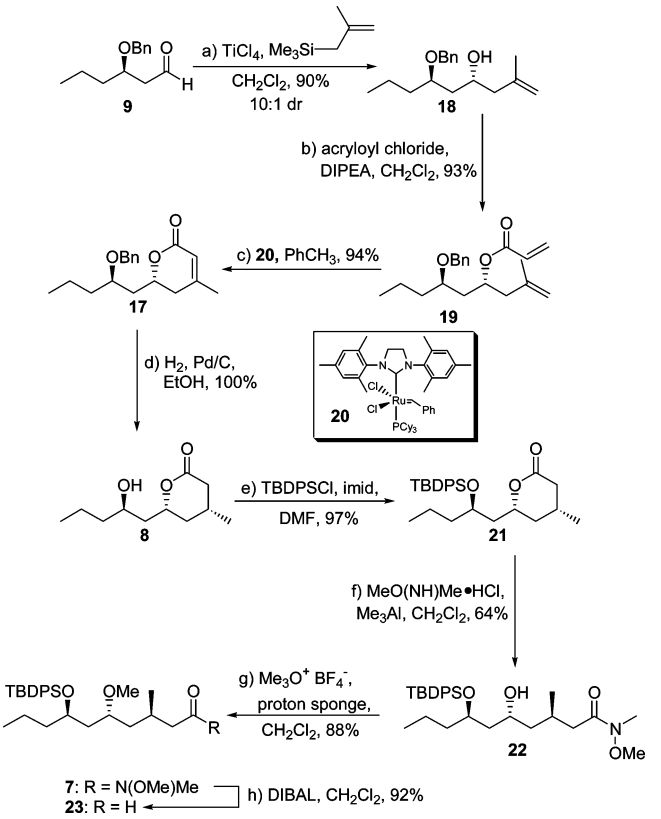


Retrosynthetic Analysis of (−)-Neopeltolide (1). Our retrosynthetic analysis of **1** followed Panek's initial disconnection of the oxazole-containing side chain in that it could be introduced via a two-step procedure involving a Still−Gennari olefination as delineated in Scheme 1.[3a] As our key step, we envisaged the β-*C*-glycoside (**3**) would emerge from a stereoselective reduction of an endocyclic oxocarbenium cation mediated by the treatment of an appropriate hemiketal with a Lewis acid. This hemiketal could be derived from a nucleophilic addition of the allyl Grignard reagent to the appropriate δ-lactone (**4**). Working backward, lactone **4** would be derived from acetal **5** and access to **5** was envisioned to arise from the precursor homoallylic alcohol **6** and methyl acrylate via a cross-metathesis. Alcohol **6** would evolve from an asymmetric allylation of the corresponding aldehyde, which would be provided by means of the Weinreb amide **7**. Along this line, amide **7** would potentially be furnished via ring-opening of lactone **8** which could be synthesized via a variety of synthetic strategies by way of the benzyl-protected β-hydroxy aldehyde **9**.

Initially, our synthetic strategy enlisted a Wacker oxidation/intramolecular Molander−Reformatsky sequence en route to the construction of the required hydroxy lactone **8**, as shown in Scheme 2.[9] Thus, the synthesis commenced

(9) (a) Yokokawa, F.; Asano, T.; Shioiri, T. *Tetrahedron* **2001**, *57*, 6311. (b) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.

SCHEME 4. Synthesis of Aldehyde 23 via Partial DIBAL Reduction of Amide 7



with an asymmetric allylation−oxidation of **10** utilizing Brown's (−)-Ipc_2Ballyl reagent to provide the homoallylic alcohol **11** in 70% yield and 91% ee.[10] The ensuing benzyl protection under basic conditions (NaH, BnBr, and TBAI) of **11** followed by ozonolysis of the corresponding alkene moiety delivered the previously reported aldehyde **9** with a 70% yield over two steps from **11**.[3e] As first reported by Keck,[11] chelation-controlled TiCl-mediated allylation of **9** was carried out at −78 °C, and a 20:1 dr resulted in favor of the desired benzyl protected 1,3-*anti*-diol **12** in 90% yield.

Subsequent treatment of **12** with bromoacetyl bromide and pyridine provided the corresponding ester **13** in 86% yield in anticipation of the intramolecular Molander−Reformatsky reaction. Much to our delight, an ensuing Wacker oxidation of **13** under the standard aerobic O_2−Pd^{II}−Cu^{II} catalysis protocol in DMF/H_2O (7:1) afforded the desired ketone **14** in 70% yield and set the stage for the intramolecular SmI_2-mediated cyclization.

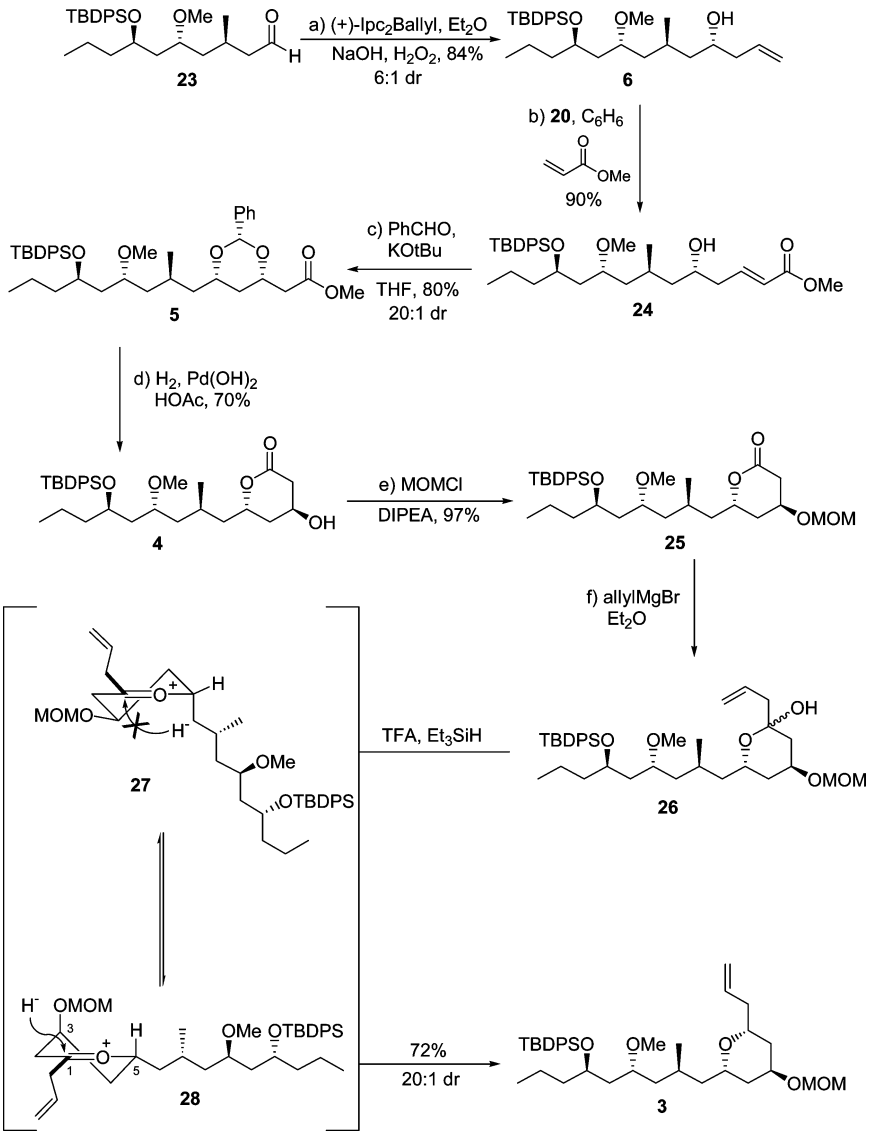
As first described by Molander,[12] treatment of bromo ester **14** with SmI_2 in THF at −78 °C formed a Sm(III) enolate which subsequently underwent an intramolecular aldol reaction with the pendant ketone via the highly ordered double six-membered transition state, depicted as **15** in Scheme 3, to provide the β-hydroxy lactone **16** in 95% yield

(10) (a) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

(11) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478.

(12) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8036.

SCHEME 5. Stereocontrolled Synthesis of β-*C*-Glycoside 3 via Oxocarbenium Reduction



and excellent diastereoselectivity at the newly generated stereocenter (>20:1 by ^{1}H NMR). In order to arrive at the desired α,β-unsaturated lactone **17**, an elimination of the newly generated stereocenter was then performed. Thus, treatment of **16** with thionyl chloride and pyridine furnished **17** in a 52% yield. Although this synthetic sequence was viable, our necessity for gram quantities of **17** forced us to pursue an alternative and more efficient strategy.

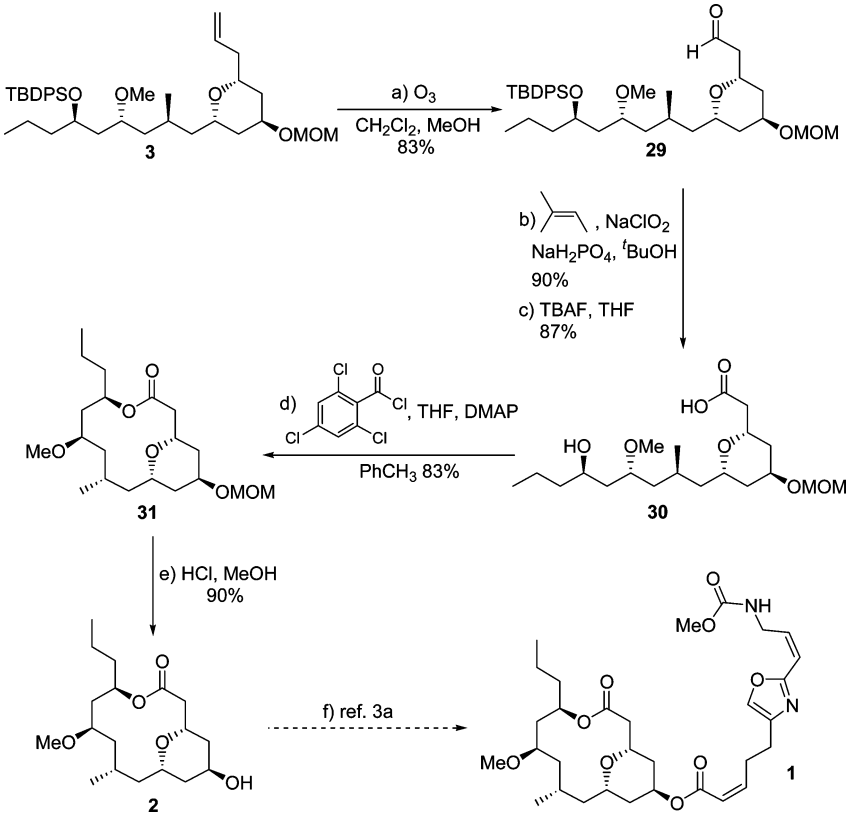
With our reformulated synthetic blueprint as described in Scheme 4, previously synthesized aldehyde **9** was subjected to $TiCl_4$-mediated methallylation and provided the homoallylic alcohol **18** (10:1 dr by ^{1}H NMR) in 90% yield.[3e] Ensuing treatment of **18** with acryloyl chloride and Hunig's base furnished acrylate ester **19** which was sequentially treated with Grubbs' second-generation catalyst[13] **20** to afford the requisite α,β-unsaturated lactenone **17** in 94% yield via a ring-closing metathesis reaction. As skillfully described by Roulland on a very similar substrate, diastereoselective reduction of the resulting alkene in **17** with concomitant removal of the benzyl protecting group was accomplished by means of a Pd/C-catalyzed hydrogenation and delivered lactone **8** in quantitative yield as a single diastereomer.[3f]

The secondary hydroxyl moiety of **8** was reprotected as a TBDPS ether with imidazole and a catalytic amount of DMAP to afford **21** in 97% yield. Subsequently, lactone **21** was subjected to transamidation conditions (MeO(NH)Me·HCl and Me_3Al)[14] and provided the unstable Weinreb amide **22**, which tended to relactonize back to **21** during purification. Therefore, the resulting free hydroxyl group of amide **22** was immediately treated with Meerwein's salt (Me_3O^+ BF_4^-), 1,8-bis(dimethylamino)naphthalene (proton sponge), and 4 Å molecular sieves to provide methoxy ether **7** in 55% yield over three steps from **8**.[3f] An ensuing partial DIBAL reduction of **7** furnished aldehyde **23** in 92% yield and set the stage for chain elongation en route to macrocycle **2**.

(13) (a) For a very recent review, see: Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(14) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

SCHEME 6. Formal Synthesis of (−)-Neopeltolide



As shown in Scheme 5, a mismatched Brown allylation of **23** afforded the homoallylic alcohol **6** with a 6:1 dr at the newly generated stereocenter in 84% yield. An ensuing highly diastereoselective cross-metathesis of the resulting alkene moiety resident in **6** with methyl acrylate and **20** as described by O'Doherty provided the *E*-α,*β*-unsaturated ester **24** in 90% yield.[15] Following the Evans' protocol for the diastereoselective synthesis of 1,3-*syn*-diols, ester **24** was treated with benzaldehyde and catalytic amounts of K-*t*-OBu in THF at 0 °C and provided **5** in 80% yield with an excellent level of diastereoselectivity (>20:1) for the *syn*-benzylidine acetal.[16] We surmised that upon reductive deprotection of the benzylidene acetal moiety resident in **5**, coupled with acidic reaction conditions, the ensuing substrate should readily cyclize to the desired *β*-hydroxy lactone **4**. Upon dissolution of **5** in HOAc and in the presence of Pearlman's catalyst [$Pd(OH)_2$] under an atmosphere of H_2, deprotection occurred, but cyclization of the resultant diol to lactone **4** was slow. Once the crude material was filtered to remove the catalyst and the filtrate refluxed (70 °C) in HOAc and H_2O (4:1), lactone **4** was isolated in 70% yield from acetal **5**. Ensuing MOM protection of the free hydroxyl group of **4** using Hunig's base in CH_2Cl_2 furnished the highly desired *δ*-lactone **25** in nearly quantitative yield. Hence, the stage was set for the oxocarbenium formation−reduction sequence as shown in Scheme 5. Upon treatment of **25** with excess allylmagnesium bromide at −78 °C, the resultant lactol **26** was formed as determined by the consumption of **25** by TLC analysis, and with the subsequent addition of TFA, **26** presumably was transformed to the corresponding oxocarbenium cation (**27** and **28**) which was consequently reduced stereoselectively (via reactive conformer **28**) with Et_3SiH to deliver the *β*-*C*-glycoside subunit **3** in 72% yield and excellent dr (>20:1).

Consistent with our previous observations and based on Woerpel's models, the observed product was assumed to arise from the more reactive conformer (i.e., **28**) that places the alkyl side chain at C5 in the pseudoequatorial position and the MOM-protected hydroxyl moiety at C3 in the axial position.[7,17] This reactive conformer allows for the stereoselective axial approach of the nucleophilic hydride via a chairlike transition state. With **3** in hand, attention was directed to the completion of the formal synthesis of **1** via stepwise transformations analogous to those previously reported.[3,4]

As shown in Scheme 6, ozonolysis of the terminal alkene of **3** followed by reductive workup with PPh_3 resulted in the production of aldehyde **29** in 83% yield. The corresponding aldehyde moiety of **29** was immediately subjected to a Lindgren−Kraus−Pinnick oxidation followed by TBAF-mediated cleavage of the TBDPS ether to furnish the Yamaguchi precursor hydroxy acid **30**.[18] The *seco*-acid **30** was then subjected to the previously reported conditions to provide

(15) O'Doherty, G. A.; Hunter, T. J. *Org. Lett.* **2001**, *3*, 1049.
(16) (a) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446. (b) Rotulo-Sims, D.; Prunet, J. *Org. Lett.* **2007**, *9*, 4147.
(17) (a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168. (b) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521.
(18) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (c) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825. (d) Pinnick, H. W.; Childers, W. E.; Bal, B. S. *Tetrahedron* **1981**, *37*, 2091.

the MOM-protected macrolide ester **31** in 83% yield.[19] Final deprotection of the MOM acetal of **31** was accomplished using Maier's conditions (concd HCl in MeOH) to afford **2** in 90% yield, thus constituting a formal synthesis of **1**.[3a,4a]

Conclusion

In closing, a formal synthesis of (−)-neopeltolide (**2**) has been achieved in 19 linear steps from the previously reported aldehyde **9** in a total overall yield of 5.6%. Efficient application of the Evans' protocol for the synthesis of 1,3-*syn* diols via an intramolecular hetero-Michael addition followed by reductive deprotection of the resulting benzylidene acetal allowed for swift access to the δ-lactone **4**. Central to the synthetic approach was a tandem nucleophilic addition-diastereoselective axial reduction of an in situ generated oxocarbenium cation to assemble the β-*C*-glycoside moiety of the neopeltolide core.

Experimental Section

All of the reactions were performed under an inert atmosphere of Ar in flame-dried glassware. Anhydrous tetrahydrofuran (THF) and dimethoxyethane (DME) were obtained from commercial sources and used without purification. Deuterated chloroform ($CDCl_3$) was stored over molecular sieves (4 Å). All of the NMR spectra were recorded on either a 360 or 500 MHz spectrometer. ^{1}H NMR spectra were obtained using $CDCl_3$ as the solvent with either tetramethylsilane (TMS: 0 ppm) or chloroform ($CHCl_3$: 7.26 ppm) as the internal standard. Column chromatography was performed using 60−200 μm silica gel. Analytical thin-layer chromatography was performed on silica coated glass plates with F-254 indicator. Visualization was accomplished by UV light (254 nm), $KMnO_4$, or ceric sulfate−PMA stain.

(*R*)-Hept-1-en-4-ol (11). To a stirred solution of (−)-Ipc$_2$BOMe (8.20 g, 25.9 mmol, 1.40 equiv) in Et_2O (75.0 mL) at −78 °C under Ar was added allylmagnesium bromide (1.0 M in Et_2O, 24.1 mL, 1.30 equiv). The reaction mixture was allowed to reach rt and stirred for 1 h, after which time the mixture was recooled to −78 °C. Butanal (1.67 mL, 18.5 mmol) was then added dropwise to the reaction mixture, which was allowed to stir for 2 h. The reaction was warmed to 0 °C. To this mixture were added 3 M NaOH (5.40 mL) and 30% aq H_2O_2 (9.40 mL) sequentially. The reaction mixture was allowed to stir at rt for 6 h, after time which the aqueous layer was extracted with Et_2O (3 × 75.0 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was distilled to give homoallylic alcohol **11** as a clear oil (1.48 g, 70% yield):[12] R_f at 10% ethyl acetate in hexanes 0.3; ^{1}H NMR (360 MHz, $CDCl_3$), δ 5.80 (m, 1H), 5.11 (m, 1H), 5.07 (m, 1H), 3.62 (m, 1H), 2.25 (m, 1H), 1.87 (s, 1H), 1.39 (m, 4H), 0.90 (t, 3H, J = 7.1 Hz).

3(*R*)-(Benzyloxy)hexanal (9). NaH (60% dispersion in mineral oil, 820 mg, 34.2 mmol, 3.00 equiv) was suspended in a 1:1 mixture of DMF/THF (40.0 mL) and cooled to 0 °C under argon. To this mixture was added dropwise alcohol **11** (1.30 g, 11.4 mmol, 1.0 equiv) dissolved in THF (9.00 mL) and the resulting mixture stirred for 30 min. Benzyl bromide was then added (2.05 mL, 17.1 mmol, 1.5 equiv) followed by tetrabutylammonium iodide (421 mg, 1.14 mmol, 0.100 equiv). The reaction mixture was allowed to reach rt and stirred for 16 h. An aqueous solution of NH_4Cl (50.0 mL) was added to the reaction mixture at 0 °C. The aqueous layer was extracted with EtOAc (3 × 50.0 mL), and the organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 1% ethyl acetate in hexanes) afforded the benzyl ether as yellowish oil (2.15 g, 92% yield): R_f at 1% ethyl acetate in hexanes 0.35.

A stream of ozone was bubbled through a solution of the benzyl ether (2.15 g, 10.5 mmol, 1.00 equiv) dissolved in a 4:1 mixture of CH_2Cl_2/MeOH (100 mL) at −78 °C until complete consumption of starting material was observed by TLC analysis (30 min). To the reaction mixture was added PPh_3 (8.30 g, 31.6 mmol, 3.00 equiv) at −78 °C, and the resulting mixture was stirred initially for 30 min and then for an additional 2.5 h at rt. The solution was concentrated in vacuo, and flash chromatography (silica, 5% ethyl acetate in hexanes) afforded aldehyde **9** as a yellow oil (1.74 g, 80% yield):[3e] R_f at 5% ethyl acetate in hexanes 0.3; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.81 (t, 1H, J = 2.1 Hz), 7.32 (m, 5H), 4.56 and 4.52 (ABq, 2H, J = 11.3 Hz), 3.95 (m, 1H), 2.68 (dd, 1H, J = 7.1, 7.3 Hz), 2.56 (dd, 1H, J = 4.7, 5.1 Hz), 1.68 (m, 1H), 1.54 (m, 1H), 1.41 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz).

6(*R*)-(Benzyloxy)non-1-en-4(*R*)-ol (12). To a stirred solution of aldehyde **9** (700 mg, 3.39 mmol, 1.00 equiv) in CH_2Cl_2 (17.0 mL) at −78 °C under Ar was slowly added $TiCl_4$ (1.00 M solution in CH_2Cl_2, 3.39 mmol, 1.00 equiv). The resulting yellow solution was allowed to stir for 10 min. To this mixture was added allyltriphenylstannane (2.66 g, 6.79 mmol, 2.00 equiv) dissolved in CH_2Cl_2 (4.00 mL) dropwise over a 15 min period. After 4 h, the reaction was quenched at −78 °C by a dropwise addition of a saturated solution of $NaHCO_3$ (20.0 mL) and allowed to reach rt. The mixture was then diluted with CH_3CN (50.0 mL) and stirred with the addition of KF (1.23 g, 20.9 mmol, 6.15 equiv) for 12 h. The suspension was then filtered through a pad of Celite, and the aqueous layer was extracted with EtOAc (3 × 75.0 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 5% ethyl acetate in hexanes) afforded the homoallylic alcohol **12** as a clear viscous oil (750 mg, 90% yield):[20] R_f at 10% ethyl acetate in hexanes 0.25; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.83 (m, 1H), 5.12 (m, 1H), 5.08 (t, 1H, J = 1.2 Hz), 4.57 and 4.53 (ABq, 2H, J = 11.2 Hz), 3.97 (m, 1H), 3.72 (m, 1H), 2.77 (d, 1H, J = 3.4 Hz), 2.22 (m, 2H), 1.67 (m, 3H), 1.51 (m, 1H), 1.36 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz).

Bromoacetic Acid 1(*R*)-[2(*R*)-(benzyloxy)pentyl]but-3-enyl Ester (13). To a solution of alcohol **12** (750 mg, 3.02 mmol, 1.00 equiv) in CH_2Cl_2 (12.0 mL) at 0 °C under Ar were slowly added pyridine (0.200 mL, 2.42 mmol, 2.00 equiv) and bromoacetyl bromide (0.210 mL, 2.42 mmol, 2.00 equiv). After 6 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30.0 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 1% ethyl ether in hexanes) afforded bromoacetyl bromide **13** as a yellow oil (940 mg, 86% yield): R_f at 5% ethyl acetate in hexanes 0.15; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.28 (m, 1H), 5.75 (m, 1H), 5.26 (m, 1H), 5.10 (d, 1H, J = 5.1 Hz), 5.07 (s, 1H), 4.53 and 4.40 (ABq, 2H, J = 11.1 Hz), 3.72 (s, 2H), 3.47 (m, 1H), 2.37 (m, 2H), 1.75 (m, 2H), 1.56 (m, 2H), 1.38 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 138.5, 132.9, 128.3, 128.1, 127.6, 118.2, 74.9, 72.6, 71.2, 39.1, 38.6, 35.9, 26.1, 18.1, 14.2; IR (CH_2Cl_2) 696, 734, 920, 993, 1106, 1278, 1357, 1456, 1734, 2874, 2928, 2958, 3030, 3065 cm^{-1}; $[\alpha]^{20}_D$ = +131 (*c* 0.43, CH_2Cl_2); HRMS (EI) calcd for $C_{18}H_{25}BrO_3$ (M^+) 368.0987, found 368.0983.

Bromoacetic Acid 3-(Benzyloxy)-1-(2-oxopropyl)hexyl Ester (14). A suspension of bromoacetyl bromide **13** (73.0 mg, 0.198 mmol, 1.00 equiv), $PdCl_2$ (3.50 mg, 0.020 mmol, 0.100 equiv), and Cu(OAc)$_2$ (7.30 mg, 0.0400 mmol, 0.200 equiv) in DMF/H_2O (7:1, 2.00

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mL) was placed under O_2 balloon pressure and stirred at rt for 48 h. The reaction was then diluted with Et_2O (10.0 mL) and water (10.0 mL). The aqueous layer was extracted with Et_2O (3 × 10.0 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded ketone **14** as a yellow viscous oil (51.0 mg, 70% yield): R_f at 10% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.33 (m, 4H), 7.27 (m, 1H), 5.49 (m, 1H), 4.55 and 4.39 (ABq, 2H, J = 11.3 Hz), 3.90 (m, 2H), 3.48 (m, 1H), 2.74 (m, 2H), 2.12 (s, 3H), 1.80 (m, 2H), 1.56 (m, 2H), 1.36 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$), δ 205.1, 166.7, 138.4, 128.4, 127.6, 74.9, 70.8, 70.2, 48.2, 40.9, 38.8, 35.7, 30.3, 18.1, 14.2; IR (CH_2Cl_2) 453, 696, 742, 977, 1073, 1183, 1293, 1357, 1411, 1453, 1723, 1742, 2870, 2958; $[\alpha]^{20}_D$ = −77.2 (*c* 0.3, CH_2Cl_2); HRMS (EI) calcd for $C_{18}H_{25}BrO_4$ ($M - H^+$) 384.0936, found 384.0922.

6-[2-(Benzyloxy)pentyl]-4-hydroxy-4-methyltetrahydropyran-2-one (16). To a stirred solution of ketone **14** (720 mg, 1.87 mmol, 1.00 equiv) in deoxygenated THF (18.7 mL) at −78 °C under Ar was added a SmI_2 solution (0.100 M solution in THF, 9.34 mmol, 93.5 mL, 5.00 equiv) dropwise. The dark blue mixture was allowed to stir at −78 °C for 6 h, at which time the reaction was quenched with a saturated aqueous solution of NH_4Cl (150 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 × 75.0 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 30% ethyl acetate in hexanes) afforded β-hydroxy lactone **16** as a white crystalline solid (530 mg, 95% yield): R_f at 50% ethyl acetate in hexanes 0.4; ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.33 (m, 4H), 7.27 (m, 1H), 4.86 (m, 1H), 4.62 and 4.49 (ABq, 2H, J = 11.3 Hz), 3.82 (m, 1H), 2.61 (d, 1H, J = 17.4 Hz), 2.42 (d, 1H, J = 17.4 Hz), 1.86 (dt, 1H, J = 2.8, 14.1 Hz), 1.76 (m, 1H), 1.68 (m, 2H), 1.58 (m, 2H), 1.51 (m, 1H), 1.39 (m, 2H), 1.33 (s, 3H), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$), δ 170.5, 138.7, 128.4, 127.9, 127.6, 75.1, 73.9, 71.9, 68.3, 44.1, 42.5, 41.3, 36.7, 30.3, 18.2, 14.3; IR (CH_2Cl_2) 457, 703, 738, 1057, 1122, 1267, 1376, 1453, 1723, 2870, 2928, 2962, 3053, 3410 cm^{-1}; $[\alpha]^{20}_D$ = −155.1 (*c* 0.13, CH_2Cl_2); HRMS (EI) calcd for $C_{18}H_{26}O_4$ ($M + H^+$) 306.1831, found 306.1838.

6-[2-(Benzyloxy)pentyl]-4-methyl-5,6-dihydropyran-2-one (17). To a stirred solution of β-hydroxy lactone **16** (65.0 mg, 0.213 mmol, 1.00 equiv) in CH_2Cl_2 (2.20 mL) under Ar at 0 °C were added pyridine (0.350 mL, 4.24 mmol, 20.0 equiv) and $SOCl_2$ (0.003 mL, 0.424 mmol, 2.00 equiv) dropwise. The reaction mixture was allowed to stir for 2 h and then quenched with a saturated solution of aqueous $NaHCO_3$ (10.0 mL). The aqueous layer was extracted with EtOAc (3 × 10.0 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded lactenone **17** as a clear oil (32.0 mg, 52% yield): R_f at 10% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.29 (m, 4H), 7.24 (m, 1H), 5.75 (s, 1H), 4.59 and 4.43 (ABq, 2H, J = 11.3 Hz), 4.55 (m, 1H), 3.80 (m, 1H), 2.25 (m, 1H), 2.13 (m, 1H), 1.90 (s, 3H), 1.85 (m, 1H), 1.68 (m, 1H), 1.59 (m, 1H), 1.48 (m, 1H), 1.37 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$), δ 165.1, 157.2, 138.6, 128.3, 127.8, 127.6, 116.4, 74.8, 74.2, 71.8, 40.5, 36.5, 35.2, 22.8, 18.1, 14.3; IR (CH_2Cl_2) 691, 739, 849, 1020, 1066, 1150, 1250, 1307, 1389, 1452, 1723, 2874, 2952, 3031, 3505 cm^{-1}; $[\alpha]^{20}_D$ = −10.8 (*c* 0.3, CH_2Cl_2); HRMS (EI) calcd for $C_{18}H_{24}O_3$ (M^+) 288.1725, found 288.1723

6(*R*)-(Benzyloxy)-2-methylnon-1-en-4(*R*)-ol (18). To a solution of aldehyde **9** (3.81 g, 18.5 mmol, 1.00 equiv) in CH_2Cl_2 (50 mL) at −78 °C under Ar was added $TiCl_4$ (1.00 M in CH_2Cl_2, 20.3 mL, 1.10 equiv) dropwise. The solution was allowed to stir for 0.5 h. The methyl-allylating reagent, $CH_2C(CH_3)CH_2TMS$ (16.2 mL, 92.4 mmol, 5.00 equiv), was then added dropwise. The reaction mixture was stirred for 8 h at −78 °C, at which time the reaction was carefully quenched with a saturated $NaHCO_3$ solution (50.0 mL) and then allowed to reach rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 50.0 mL), and the organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (silica, 3% ethyl acetate in hexanes) afforded homomethallylic alcohol **18** as a clear viscous oil (4.35 g, 90% yield): R_f at 10% ethyl acetate in hexanes 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.82 (s, 1H), 4.76 (s, 1H), 4.57 and 4.52 (ABq, 2H, J = 11.3 Hz), 4.06 (m, 1H), 3.74 (m, 1H), 2.69 (s, 1H), 2.17 (m, 2H), 1.75 (s, 3H), 1.65 (m, 3H), 1.51 (m, 1H), 1.38 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 138.5, 128.3, 127.8, 127.6, 112.9, 76.8, 71.3, 65.9, 46.3, 40.1, 35.9, 22.4, 18.6, 14.2; IR (CH_2Cl_2) 700, 736, 891, 1071, 1201, 1376, 1454, 1650, 2869, 2931, 3034, 3070, 3458 cm^{-1}; $[\alpha]^{20}_D$ = −88.7 (*c* 0.14, CH_2Cl_2); HRMS (EI) calcd for $C_{17}H_{26}O_2$ (M^+) 262.1933, found 262.1937.

Acrylic Acid 1(*R*)-[2(*R*)-(Benzyloxy)pentyl]-3-methylbut-3-enyl Ester (19). To a stirred solution of homomethallylic alcohol **18** (8.74 g, 33.3 mmol, 1.00 equiv) in CH_2Cl_2 (166 mL) were added DMAP (814 mg, 6.66 mmol, 0.200 equiv), DIPEA (29.0 mL, 166 mmol, 5.00 equiv), and acryloyl chloride (8.01 mL, 99.9 mmol, 3.00 equiv) at 0 °C under Ar. The reaction mixture was stirred for 18 h at rt, at which time the reaction temperature was lowered to 0 °C and carefully quenched with a saturated $NaHCO_3$ solution (200 mL) and then allowed to reach rt. The aqueous layer was extracted with Et_2O (3 × 150 mL), and the organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 1% ethyl acetate in hexanes) afforded acrylate ester **19** as a clear viscous oil (9.77 g, 93% yield): R_f at 1% ethyl acetate in hexanes 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 4H), 7.25 (m, 1H), 6.36 (dd, 1H, J = 1.3, 17.4 Hz), 6.08 (dd, 1H, J = 10.4, 17.3 Hz), 5.77 (dd, 1H, J = 1.7, 10.4 Hz), 5.41 (m, 1H), 4.81 (s, 1H), 4.72 (s, 1H), 4.49 and 4.41 (ABq, 2H, J = 11.1 Hz), 3.44 (m, 1H), 2.36 (m, 1H), 2.24 (m, 1H), 1.75 (m, 5H), 1.53 (m, 2H), 1.37 (m, 2H), 0.92 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 141.5, 138.6, 130.2, 128.8, 128.2, 127.9, 127.7, 127.4, 112.5, 75.5, 71.5, 69.8, 43.6, 39.2, 36.3, 22.4, 18.2, 14.2; IR (CH_2Cl_2) 700, 741, 813, 901, 988, 1066, 1190, 1268, 1299, 1407, 1459, 1634, 1727, 2874, 2925, 2967, 3034, 3076 cm^{-1}; $[\alpha]^{20}_D$ = −141.3 (*c* 0.22, CH_2Cl_2); HRMS (EI) calcd for $C_{20}H_{28}O_3$ (M^+) 316.2038, found 316.2029.

6-[2-(Benzyloxy)pentyl]-4-methyl-5,6-dihydropyran-2-one (17). To a refluxing solution of acrylate ester **19** (410 mg, 1.30 mmol, 1.00 equiv) in toluene (130 mL, 80 °C) under Ar was added a solution of Grubbs' second-generation catalyst **20** (165 mg, 0.194 mmol, 0.150 equiv) in toluene (19.5 mL) dropwise over a period of 2 h. The reaction mixture was allowed to stir at 80 °C for 18 h at which time the reaction was concentrated in vacuo. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded lactenone **17** as a clear viscous oil (352 mg, 94% yield).

6-(2-Hydroxypentyl)-4-methyltetrahydropyran-2-one (8). To a solution of lactenone **17** (90.0 mg, 0.312 mmol, 1.00 equiv) in EtOH (1.60 mL) was added Pd/C (45.0 mg) in one portion. The reaction vessel was evacuated under vacuum and placed under atmospheric H_2 balloon pressure. The reaction mixture was allowed to stir at rt for 48 h until complete consumption of the starting material was observed via TLC analysis. The reaction was filtered through a plug of Celite and concentrated in vacuo. Flash chromatography (silica, 40% ethyl acetate in hexanes) afforded lactone **8** as a clear viscous oil (60.0 mg, 100% yield): R_f at 35% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (m, 1H), 3.93 (m, 1H), 2.62 (m, 1H), 2.46 (s, 1H), 2.02 (m, 2H), 1.86 (m, 1H), 1.68 (ddd, 1H, J = 2.1, 9.7, 14.5 Hz), 1.55 (ddd, 1H, J = 2.6, 14.2, 17.1 Hz), 1.36 (m, 4H), 1.19 (m, 1H), 0.98 (d, 3H, J = 7.1 Hz), 0.88 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 77.4, 66.7, 43.5, 40.1, 37.8, 37.4, 26.6, 21.6, 18.6, 13.9; IR (CH_2Cl_2) 572, 634, 791, 931, 984,

1025, 1092, 1233, 1380, 1458, 1729, 2874, 2958, 3432 cm^{-1}; $[\alpha]^{20}_D$ = −76.4 (*c* 1.23, CH_2Cl_2); HRMS (EI) calcd for $C_{11}H_{20}O_3$ (M + H) 201.1484, found 201.1484.

6-[2-(*tert*-Butyldiphenylsilanyloxy)pentyl]-4-methyltetrahydropyran-2-one (21). To a solution of lactone **8** (4.20 g, 21.0 mmol, 1.00 equiv) in DMF (105 mL) under Ar at 0 °C were added imidazole (4.30 g, 62.9 mmol, 3.00 equiv), DMAP (512 mg, 4.19 mmol, 0.200 equiv), and TBDPSCl (8.00 mL, 31.5 mmol, 1.50 equiv). The reaction mixture was allowed to stir at rt for 48 h and quenched with H_2O (200 mL), and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (silica, 5% ethyl acetate in hexanes) afforded the TBDPS-protected lactone **21** (8.76 g, 95% yield): R_f at 5% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70, (m, 4H), 7.38 (m, 6H), 4.23 (m, 1H), 4.12 (m, 1H), 4.46 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.69 (m, 3H), 1.43 (m, 2H), 1.26 (m, 3H), 1.06 (s, 9H), 0.94 (d, 3H, *J* = 6.3 Hz), 0.74 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 135.8, 129.5, 127.4, 69.4, 43.3, 39.8, 37.6, 37.3, 27.0, 26.4, 21.7, 19.4, 17.6, 13.9; IR (CH_2Cl_2) 509, 619, 713, 739, 817, 931, 1072, 1114, 1239, 1380, 1426, 1468, 1739, 2865, 2958, 3073, 3442; $[\alpha]^{20}_D$ = −66.2 (*c* 0.7, CH_2Cl_2); HRMS (EI) calcd for $C_{23}H_{29}O_3Si$ (M − C_4H_9) 381.1886, found 381.1890.

7-(*tert*-Butyldiphenylsilanyloxy)-5-hydroxy-3-methyldecanoic Acid Methoxymethylamide (22). To a solution of MeO(NH)Me·HCl (116 mg, 1.19 mmol, 5.00 equiv) in CH_2Cl_2 (2.65 mL) at −78 °C was added Me_3Al (0.600 mL, 1.11 mmol, 5.10 equiv) dropwise. The reaction mixture was allowed to warm to rt and stirred to 2 h before the solution was recooled to 0 °C, and the TBDPS-protected lactone **21** (95.0 mg, 0.217 mmol, 1.00 equiv) was added dropwise as a solution in CH_2Cl_2 (1.45 mL). The reaction mixture was allowed to stir for 18 h at rt before it was carefully quenched at 0 °C with a 1 M solution of Rochelle's salt (10 mL). After 1 h, the mixture was extracted with ethyl acetate (3 × 20.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (silica, 35% ethyl acetate in hexanes) afforded the hydroxy Weinreb amide **22** (65.1 mg, 64% yield) along with the recovered starting material **21** (30.4 mg): R_f at 35% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69, (m, 4H), 7.39 (m, 6H), 3.95 (m, 2H), 3.66 (s, 3H), 3.17 (s, 3H), 2.39 (m, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 1.51 (m, 5H), 1.15 (m, 2H), 1.06 (s, 10H), 0.91 (d, 3H, *J* = 6.7 Hz), 0.67 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 133.9, 133.6, 129.7, 127.5, 77.3, 76.7, 71.8, 66.0, 61.1, 45.1, 42.7, 38.5, 27.0, 26.5, 19.9, 19.2, 18.3, 13.9; IR (CH_2Cl_2) 615, 705, 737, 823, 906, 1008, 1110, 1386, 1427, 1466, 1650, 2859, 2935, 2957, 3434; $[\alpha]^{20}_D$ = +26.1 (*c* 0.4, CH_2Cl_2).

7-(*tert*-Butyldiphenylsilanyloxy)-5-methoxy-3-methyldecanoic Acid Methoxymethylamide (7). To a solution of hydroxy amide **22** (1.21 g, 2.40 mmol, 1.00 equiv) in CH_2Cl_2 (30.0 mL) protected from light was added Me_3OBF_4 (1.25 g, 8.40 mmol, 3.50 equiv), proton sponge (2.57 g, 12.0 mmol, 5.00 equiv), and 4 Å molecular sieves (2.50 g) at rt under Ar. The reaction mixture was allowed to stir for 8 h, at which time the reaction was transferred to a separatory funnel, diluted with CH_2Cl_2 (70.0 mL), and washed with a 1 M HCl solution (6 × 100 mL) and saturated $NaHCO_3$ (100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded methyl ether amide **7** as a yellow viscous oil (1.05 g, 88% yield): R_f at 10% ethyl acetate in hexanes 0.25; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69, (m, 4H), 7.37 (m, 6H), 3.88 (m, 1H), 3.65 (s, 3H), 3.36 (m, 1H), 3.17 (s, 3H), 3.11 (s, 3H), 2.35 (m, 1H), 2.17 (m, 2H), 1.69 (m, 1H), 1.50 (m, 1H), 1.40 (m, 3H), 1.26 (m, 2H), 1.05 (s, 9H), 0.90 (d, 3H, *J* = 7.1 Hz), 0.71 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 135.9, 134.9, 134.4, 129.4, 129.4, 127.4, 127.3, 75.5, 70.5, 61.0, 55.4, 41.9, 41.5, 39.5, 27.0, 26.6, 20.1, 19.4, 17.7, 13.9; IR (CH_2Cl_2) 622, 710, 823, 999, 1108, 1382, 1428, 1464, 1671, 2859, 2947, 3070; $[\alpha]^{20}_D$ = +15.1 (*c* 0.2, CH_2Cl_2); HRMS (EI) calcd for $C_{26}H_{38}NO_4Si$ (M − C_4H_9) 456.2570, found 456.2574.

7(*R*)-(*tert*-Butyldiphenylsilanyloxy)-5(*R*)-methoxy-3(*R*)-methyldecanal (23). To a solution of compound **7** (1.05 g, 2.04 mmol, 1.00 equiv) in CH_2Cl_2 (13.6 mL) at −78 °C was added a solution of DIBAL-H (1.00 M in toluene, 3.20 mL, 1.55 equiv) dropwise. The resulting solution was stirred at −78 °C for 1 h and quenched carefully with MeOH (3 mL). The reaction was poured into CH_2Cl_2 (20.0 mL) and washed with 1 M HCl (50.0 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 5% ethyl acetate in hexanes) afforded aldehyde **23** as a clear viscous oil (860 mg, 92% yield): R_f at 20% ethyl acetate in hexanes 0.65; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (t, 1H, J = 2.1 Hz), 7.71 (m, 4H), 7.39 (m, 6H), 3.86 (m, 1H), 3.28 (m, 1H), 3.10 (s, 3H), 2.30 (m, 1H), 2.14 (m, 2H), 1.72 (m, 1H), 1.45 (m, 3H), 1.31 (m, 3H), 1.23 (m, 1H), 1.06 (s, 9H), 0.90 (d, 3H, *J* = 7.1 Hz), 0.76 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 135.9, 134.5, 129.5, 127.4, 75.5, 70.5, 55.6, 51.2, 41.8, 41.3, 39.4, 26.9, 24.9, 19.9, 19.3, 17.7, 13.9; IR (CH_2Cl_2) 611, 700, 746, 819, 1113, 1422, 1454, 1733, 2709, 2859, 2941, 3070 cm^{-1}; $[\alpha]^{20}_D$ = +27.3 (*c* 1.01, CH_2Cl_2); HRMS (EI) calcd for $C_{24}H_{33}O_3Si$ (M − C_4H_9) 397.2199, found 397.2211.

10(*R*)-(*tert*-Butyldiphenylsilanyloxy)-8(*R*)-methoxy-6(*S*)-methyltridec-1-en-4(*R*)-ol (6). To a stirred solution of (+)-Ipc_2Ballyl (1.00 M solution in pentane, 0.320 mL, 1.20 equiv) in Et_2O (0.200 mL) at −78 °C under argon was added a solution of aldehyde **23** (120 mg, 0.264 mmol, 1.00 equiv) in Et_2O (1.30 mL) dropwise. The reaction mixture was stirred for 2 h, at which time a solution of 3 M NaOH (0.500 mL) and 30% aqueous H_2O_2 was added slowly at 0 °C. The mixture was allowed to stir for 12 h at rt. The aqueous layer was extracted with Et_2O (3 × 10.0 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (silica, 5% ethyl acetate in hexanes) afforded homoallylic alcohol **6** as a clear viscous oil (110 mg, 84% yield): R_f at 5% ethyl acetate in hexanes 0.25; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.39 (m, 6H), 5.82 (m, 1H), 5.14 (s, 1H), 5.12 (d, 1H, *J* = 3.6 Hz), 3.87 (m, 1H), 3.70 (m, 1H), 3.32 (m, 1H), 3.12 (s, 3H), 2.24 (m, 1H), 2.13 (m, 1H), 1.75 (m, 1H), 1.68 (m, 1H), 1.52 (m, 2H), 1.32 (m, 6H), 1.16 (m, 1H), 1.05 (s, 9H), 0.97 (m, 1H), 0.85 (d, 3H, *J* = 7.1 Hz), 0.72 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 134.9, 134.4, 129.4, 127.4, 117.9, 75.8, 70.5, 68.4, 55.8, 44.7, 42.7, 42.4, 42.0, 39.5, 26.1, 19.6, 19.4, 17.8, 14.1; IR (CH_2Cl_2) 619, 702, 827, 901, 1114, 1380, 1432, 1473, 2219, 2932, 3067, 3453, 3693 cm^{-1}; $[\alpha]^{20}_D$ = +16.1 (*c* 0.062, CH_2Cl_2); HRMS (EI) calcd for $C_{27}H_{39}O_3Si$ (M − C_4H_9) 439.2668, found 439.2657.

11(*R*)-(*tert*-Butyldiphenylsilanyloxy)-5(*S*)-hydroxy-9(*R*)-methoxy-7(*S*)-methyltetradec-2-enoic Acid Methyl Ester (24). To a stirred solution of homoallylic alcohol **6** (100 mg, 0.201 mmol, 1.00 equiv) in benzene (1.00 mL) at rt under Ar were added methyl acrylate (0.0600 mL, 0.403 mmol, 3.00 equiv) and Grubbs' second-generation catalyst **20** (3.40 mg, 0.00400 mmol, 0.0200 equiv). The reaction mixture was allowed to stir at rt for 24 h at which time the reaction was concentrated in vacuo. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded ester **24** as a clear viscous oil (100 mg, 90% yield): R_f at 15% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.38 (m, 6H), 6.98 (m, 1H), 5.89 (dt, 1H, *J* = 15.7 Hz), 3.82 (m, 2H), 3.73 (s, 3H), 3.29 (m, 1H), 3.11 (s, 3H), 2.32 (m, 2H), 1.86 (s, 1H), 1.71 (m, 2H), 1.31 (m, 9H), 1.05 (s, 9H), 0.94 (m, 1H), 0.83 (d, 3H, *J* = 7.1 Hz), 0.73 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 145.9, 135.9, 134.5, 129.5, 127.4, 123.2, 75.9, 70.6, 67.7, 55.9, 51.4, 44.8, 42.4, 41.8, 40.9, 40.4, 39.2, 27.1, 26.2, 20.9, 19.6, 17.8, 14.1; IR (CH_2Cl_2) 699, 820, 1040, 1108, 1427, 1654, 1722, 2858, 2935, 2958, 3439 cm^{-1}; $[\alpha]^{20}_D$ = +11.2 (*c* 0.14, CH_2Cl_2); HRMS (EI) calcd for $C_{29}H_{41}O_5Si$ (M − C_4H_9) 497.2723, found 497.2720.

[6-[6-(*tert*-Butyldiphenylsilanyloxy)-4-methoxy-2-methylnonyl]-2-phenyl-1,3-dioxan-4-yl]acetic Acid Methyl Ester (5). To a solution of ester **24** (100 mg, 0.180 mmol, 1.00 equiv) in THF (2.00 mL) at 0 °C under Ar was added freshly distilled benzaldehyde (0.0200 mL, 0.198 mmol, 1.10 equiv) followed by KO-*t*-Bu (2.00 mg, 0.0180 mmol, 0.100 equiv). The addition of base and benzaldehyde was repeated (three times for benzaldehyde and eight times for KO-*t*-Bu) at 15-min intervals until consumption of the starting material was complete as observed by TLC analysis. The reaction was then quenched with a solution of pH 7 buffered phosphate solution (5.00 mL). The aqueous layer was extracted with Et_2O (3 × 10.0 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 5% ethyl acetate in hexanes) afforded benzylidene acetal **5** as a yellow viscous oil (95.0 mg, 80% yield): R_f at 20% ethyl acetate in hexanes 0.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (t, 4H, J = 6.9 Hz), 7.40 (m, 11H), 5.55 (m, 1H), 4.32 (m, 1H), 3.89 (m, 2H), 3.72 (s, 3H), 3.56 (m, 1H), 3.11 (s, 3H), 2.74 (m, 1H), 2.52, (m, 1H), 1.87 (m, 1H), 1.66 (m, 3H), 1.52 (m, 1H), 1.40 (m, 4H), 1.26 (m, 4H), 1.06 (s, 9H), 0.98 (m, 1H), 0.89 (d, 3H, J = 6.7 Hz), 0.72 (t, 3H, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 138.6, 134.4, 129.4, 128.1, 127.4, 126.1, 100.1, 75.6, 74.4, 73.2, 70.5, 55.7, 51.7, 43.4, 41.9, 40.8, 39.5, 37.1, 27.1, 25.4, 19.4, 17.7, 14.1; IR (CH_2Cl_2) 460, 517, 609, 700, 738, 818, 901, 1026, 1110, 1210, 1349, 1384, 1426, 1456, 1738, 2856, 2932, 2954, 3042, 3068 cm^{-1}; $[\alpha]^{20}_D$ = −10.6 (c 0.6, CH_2Cl_2); HRMS (EI) calcd for $C_{36}H_{47}O_6Si$ (M − C_4H_9) 603.3142, found 603.3129.

6-[6-(*tert*-Butyldiphenylsilanyloxy)-4-methoxy-2-methylnonyl]-4-hydroxytetrahydropyran-2-one (4). A stirred solution of benzylidene acetal **5** (780 mg, 1.18 mmol, 1.00 equiv) in HOAc (11.8 mL) was hydrogenated over 10% $Pd(OH)_2$ on carbon (780 mg) for 24 h under H_2 at atmospheric pressure. Once complete, the catalyst was filtered off over a pad of Celite and the filtrate was concentrated under vacuo to afford a mixture of lactone **4** and straight-chained diol. The crude mixture was redissolved in HOAc (9.00 mL) and H_2O (3.00 mL) and refluxed (70 °C) for 4 h until complete consumption of the diol was observed by TLC analysis. The mixture was concentrated under reduced pressure and redissolved in EtOAc (40.0 mL). The organic layer was then quenched at 0 °C with a saturated solution of $NaHCO_3$ (20.0 mL), and the aqueous layer was extracted with EtOAc (3 × 30.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 40% ethyl acetate in hexanes) afforded lactone **4** as a clear viscous oil (450 mg, 70% yield): R_f at 40% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (t, 4H, J = 7.5 Hz), 7.39 (m, 6H), 4.74 (m, 1H), 4.34 (m, 1H), 3.85 (m, 1H), 3.30 (m, 1H), 3.11 (s, 3H), 2.70 (dd, 1H, J = 7.2, 15.8 Hz), 2.59, (dd, 1H, J = 6.3, 15.7 Hz), 1.89 (m, 2H), 1.67 (m, 3H), 1.35 (m, 8H), 1.04 (s, 9H), 0.94 (m, 1H), 0.87 (d, 3H, J = 6.7 Hz), 0.72 (t, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$), δ 170.7, 135.9, 134.3, 129.4, 127.4, 75.7, 73.6, 70.5, 62.5, 55.9, 43.2, 41.9, 39.4, 38.6, 36.4, 26.9, 25.3, 19.3, 17.8, 13.9; IR (CH_2Cl_2) 611, 698, 732, 819, 1076, 1105, 1253, 1385, 1427, 1461, 1714, 2855, 2931, 2957, 3047, 3071, 3425 cm^{-1}; $[\alpha]^{20}_D$ = −9.8 (c 0.65, CH_2Cl_2); HRMS (EI) calcd for $C_{28}H_{39}O_5Si$ (M − C_4H_9) 483.2567, found 483.2576.

6-[6-(*tert*-Butyldiphenylsilanyloxy)-4-methoxy-2-methylnonyl]-4-(methoxymethoxy)tetrahydropyran-2-one (25). To a stirred solution of lactone **4** (200 mg, 0.370 mmol, 1.00 equiv) in CH_2Cl_2 (1.85 mL) at 0 °C under Ar were added DMAP (14.0 mg, 0.111 mmol, 0.300 equiv), DIPEA (0.390 mL, 2.22 mmol, 6.00 equiv), and MOMCl (0.110 mL, 1.48 mmol, 4.00 equiv). The reaction mixture was allowed to stir at rt for 18 h, at which time the reaction was recooled to 0 °C and quenched with a solution of saturated $NaHCO_3$ (10.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 20% ethyl acetate in hexanes) afforded MOM/TBDPS lactone **25** as a yellow viscous oil (210 mg, 97% yield): R_f at 40% ethyl acetate in hexanes 0.55; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (t, 4H, J = 7.3 Hz), 7.37 (m, 6H), 4.66 (s, 3H), 4.13 (m, 1H), 3.86 (m, 1H), 3.35 (s, 3H), 3.31 (m, 1H), 3.11 (s, 3H), 2.68 (m, 2H), 1.99 (d, 1H, J = 14.3 Hz), 1.90 (m, 1H), 1.68 (m, 3H), 1.47 (m, 1H), 1.38 (m, 2H), 1.27 (m, 4H), 1.04 (s, 9H), 0.94 (m, 2H), 0.87 (d, 3H, J = 6.3 Hz), 0.72 (t, 3H, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$), δ 169.9, 135.9, 134.6, 129.4, 127.4, 95.1, 75.5, 73.8, 70.5, 68.0, 55.8, 55.6, 43.3, 41.9, 39.5, 36.4, 34.6, 27.0, 25.4, 19.4, 17.8, 13.9; IR (CH_2Cl_2) 607, 700, 744, 817, 917, 1039, 1102, 1146, 1235, 1361, 1375, 1424, 1464, 1738, 2935, 2961, 3049, 3072 cm^{-1}; $[\alpha]^{20}_D$ = −19.1 (c 0.43, CH_2Cl_2); HRMS (EI) calcd for $C_{30}H_{43}O_6Si$ (M − C_4H_9) 527.2829, found 527.2830.

[6-[6-Allyl-4-(methoxymethoxy)tetrahydropyran-2-yl]-3-methoxy-5-methyl-1-propylhexyloxy]-*tert*-butyl-diphenylsilane (3). To a solution of lactone **25** (100 mg, 0.171 mmol, 1.00 equiv) in Et_2O (1.70 mL) was added allylmagnesium bromide (1.00 M solution in Et_2O, 0.550 mL, 3.10 equiv) at −78 °C under Ar. The reaction mixture was stirred until the starting material had been consumed as indicated by TLC analysis, quenched with a saturated solution of NH_4Cl (5 mL), and extracted with Et_2O (3 × 10.0 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo and used directly in the next step without further purification.

The resultant crude hemiketal **26** (130 mg, 0.208 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (2.10 mL) and cooled to −78 °C under argon. To the solution were added Et_3SiH (0.330 mL, 2.08 mmol, 10.0 equiv) and TFA (0.100 mL, 1.04 mmol, 5.00 equiv). The temperature was allowed to warm to −40 °C and the reaction mixture stirred for 0.5 h. The reaction was quenched with $NaHCO_3$ (10.0 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 2% ethyl acetate in hexanes then 10% ethyl acetate in hexanes) afforded β-*C*-glycoside **3** as a yellow viscous oil (74.0 mg, 72% yield): R_f at 15% ethyl acetate in hexanes 0.55; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (t, 4H, J = 7.2 Hz), 7.39 (m, 6H), 5.85 (m, 1H), 5.07 (dd, 1H, J = 17.2 Hz), 4.99 (dd, 1H, J = 10.2 Hz), 4.67 (s, 2H), 4.02 (m, 1H), 3.90 (m, 1H), 3.73 (m, 2H), 3.38 (m, 1H), 3.37 (s, 3H), 3.11 (s, 3H), 2.28 (m, 1H), 2.12 (m, 1H), 1.73 (m, 4H), 1.36 (m, 9H), 1.06 (s, 9H), 0.96 (m, 1H), 0.85 (d, 3H, J = 6.3 Hz), 0.70 (t, 3H, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 135.2, 134.8, 134.5, 129.4, 127.4, 116.3, 94.9, 75.6, 71.7, 70.5, 70.3, 69.8, 55.5, 55.3, 43.9, 41.9, 40.7, 39.6, 36.9, 36.1, 27.1, 25.8, 19.7, 19.4, 17.7, 13.9; IR (CH_2Cl_2) 611, 700, 740, 825, 847, 917, 1039, 1098, 1146, 1357, 1383, 1428, 1460, 2821, 2932, 3049, 3072, 3452 cm^{-1}; $[\alpha]^{20}_D$ = +24.8 (c 0.23, CH_2Cl_2); HRMS (EI) calcd for $C_{33}H_{49}O_5Si$ (M − C_4H_9) 553.3349, found 553.3343.

[6-[6-(*tert*-Butyldiphenylsilanyloxy)-4-methoxy-2-methylnonyl]-4-(methoxymethoxy)tetrahydropyran-2-yl]acetaldehyde (29). A solution of β-*C*-glycoside **3** (74.0 mg, 0.121 mmol, 1.00 equiv) in CH_2Cl_2/MeOH (1:1, 2.00 mL) was cooled to −78 °C, and a stream of O_3 was bubbled through the reaction mixture for 15 min until the starting material had been consumed as indicated by TLC analysis. The reaction was then quenched by the addition of SMe_2 (0.0500 mL, 0.604 mmol, 5.00 equiv) and allowed to stir at rt for 4 h at which time the reaction was concentrated in vacuo. Flash chromatography (silica, 15% ethyl acetate in hexanes) afforded aldehyde **29** as a clear viscous oil (61.0 mg, 83% yield): R_f at 15% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, 1H, J = 2.1 Hz), 7.69 (m, 4H), 7.38 (m, 6H), 4.68 (s, 2H), 4.25 (m, 1H), 4.03 (m, 1H), 3.89 (m, 1H), 3.82 (m, 1H), 3.35 (m, 5H), 3.09 (s, 3H), 2.52 (ddd, 1H, J = 2.4, 8.4, 16.1 Hz), 2.37 (ddd, 1H, J = 2.2, 4.4, 16.0 Hz), 1.71 (m, 4H), 1.47 (m, 2H), 1.35 (m, 4H), 1.23 (m, 2H), 1.05 (s, 10H), 0.95 (m, 1H), 0.83 (d, 3H, J = 6.3 Hz), 0.69 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 135.9, 134.8, 134.4, 129.4, 127.3, 94.9, 75.5, 70.5, 69.9, 69.7, 67.8, 55.6, 55.4, 49.6, 43.6, 42.1, 39.6, 36.7, 36.2, 27.1, 25.6, 19.6, 19.4,

17.7, 13.9; IR (CH_2Cl_2) 609, 701, 737, 821, 914, 1038, 1106, 1155, 1375, 1431, 1467, 1728, 2723, 2932, 3048, 3073, 3438 cm^{-1}; $[\alpha]^{20}_D = +28.1$ (*c* 0.05, CH_2Cl_2); HRMS (EI) calcd for $C_{32}H_{47}O_6Si$ (M − C_4H_9) 555.3142, found 555.3135.

[6-(6-Hydroxy-4-methoxy-2-methylnonyl)-4-(methoxymethoxy)-tetrahydropyran-2-yl]acetic Acid (30). To a solution of aldehyde **29** (60.0 mg, 0.0980 mmol, 1.00 equiv) in *tert*-butyl alcohol (1.20 mL) and H_2O (0.500 mL) cooled to 0 °C was added 2-methylbutene (1.01 mL, 9.80 mmol, 100.0 equiv) in one portion. A freshly prepared solution of $NaClO_2$ (53.0 mg, 0.588 mmol, 6.00 equiv) and NaH_2PO_4 (118 mg, 0.980 mmol, 10.0 equiv) in *tert*-butyl alcohol (0.500 mL) and H_2O (0.500 mL) was then added dropwise. The reaction mixture was then allowed to stir at rt for 5 h, at which time the reaction was quenched by addition of a saturated solution of NH_4Cl (10.0 mL) and extracted with EtOAc (3 × 10.0 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 25% ethyl acetate in hexanes and 1% acetic acid) afforded the TBDPS acid as a yellow viscous oil (55 mg, 90% yield): R_f at 30% ethyl acetate in hexanes 0.25.

To a stirred solution of the TBDPS acid (55.0 mg, 0.088 mmol, 1.00 equiv) in THF (0.300 mL) at 0 °C was added TBAF (1.00 M solution in THF, 0.900 mL, 10.0 equiv). The reaction mixture was allowed to stir at rt for 72 h at which time the mixture was quenched with H_2O (5.00 mL) and extracted with EtOAc (3 × 10.0 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 60% ethyl acetate in hexanes and 1% acetic acid) afforded acid **30** as yellow viscous oil (27.0 mg, 87% yield): R_f at 60% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (s, 2H), 4.18 (m, 1H), 4.01 (m, 1H), 3.94 (m, 1H), 3.84 (t, 1H, J = 9.7 Hz), 3.53 (m, 1H), 3.36 (s, 3H), 3.34 (s, 3H), 2.43 (d, 2H, J = 6.2 Hz), 1.76 (m, 5H), 1.40 (m, 9H), 1.14 (m, 2H), 0.90 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 95.0, 78.2, 71.6, 69.8, 69.5, 68.9, 56.8, 55.3, 43.7, 41.3, 40.9, 40.1, 39.1, 36.9, 35.8, 27.3, 20.6, 18.8, 14.2; IR (CH_2Cl_2) 696, 734, 920, 993, 1106, 1278, 1357, 1456, 1734, 2874, 2928, 2958, 3030, 3065 cm^{-1}; $[\alpha]^{20}_D = -72.3$ (*c* 0.05, CH_2Cl_2); HRMS (EI) calcd for $C_{20}H_{39}O_7$ (M + H) 391.2696, found 391.2701.

7-Methoxy-13-(methoxymethoxy)-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (31). To a stirred solution of acid **30** (19.0 mg, 0.0487 mmol, 1.00 equiv) in THF (0.500 mL) at 0 °C under Ar was added Hunig's base (0.0600 mL, 0.300 mmol, 6.00 equiv) followed by 2,4,6-trichlorobenzoyl chloride (0.0400 mL, 0.250 mmol, 5.00 equiv). The reaction mixture was stirred at rt for 4 h, after which time toluene was added (1.22 mL). This solution was added over 8 h by syringe pump to a refluxing solution of DMAP (150 mg, 1.22 mmol, 25.0 equiv) in toluene (38.0 mL). Upon addition, stirring was continued for an additional 16 h. The mixture was then allowed to cool to ambient temperature and concentrated in vacuo. The crude product was filtered over a pad short pad of silica using 60% ethyl acetate in hexanes and then concentrated in vacuo. Flash chromatography (silica, 10% ethyl acetate in hexanes) provided macrolactone **31** as a clear oil (27.0 mg, 87% yield): R_f at 10% ethyl acetate in hexanes 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (m, 1H), 4.67 (s, 2H), 4.12 (m, 1H) 4.02 (t, 1H, J = 2.9 Hz), 3.59 (m, 2H), 3.37 (s, 3H), 3.30 (s, 3H), 2.57 (dd, 1H, J = 4.1, 14.5 Hz), 2.33 (dd, 1H, J = 10.9, 14.5 Hz), 1.71 (m, 5H), 1.40 (m, 8H), 1.22 (m, 1H), 1.13 (m, 1H), 0.97 (d, 3H, J = 6.6 Hz), 0.90 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 94.9, 75.6, 75.4, 72.9, 69.9, 69.6, 56.2, 55.4, 44.2, 42.5, 42.3, 40.2, 37.2, 36.9, 35.9, 31.3, 25.6, 18.9, 13.9; IR (CH_2Cl_2) 727, 793, 922, 984, 992, 1039, 1087, 1150, 1197, 1249, 1274, 1345, 1440, 1458, 1656, 1730, 2927, 3441 cm^{-1}; $[\alpha]^{20}_D = -98.1$ (*c* 0.1, CH_2Cl_2); HRMS (EI) calcd for $C_{19}H_{33}O_6$ (M − CH_3) 357.2277, found 357.2290.

(−)-Neopeltolide Macrocyclic Core (2). To a stirred solution of macrolactone **31** (12.0 mg, 0.0322 mmol, 1.00 equiv) in MeOH (0.500 mL) at 0 °C was added concentrated HCl (0.0200 mL). The reaction mixture was allowed to stir at rt for 24 h, at which time the reaction was cooled to 0 °C and quenched with a saturated solution of $NaHCO_3$ (5.00 mL). The aqueous layer was extracted with EtOAc (3 × 10.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 25% ethyl acetate in hexanes) afforded (−)-neopeltolide core **2** as a clear viscous oil (9.00 mg, 90% yield): R_f at 30% ethyl acetate in hexanes 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (m, 1H), 4.24 (t, 1H, J = 2.9 Hz), 4.19 (m, 1H), 3.68 (m, 1H), 3.59 (t, 1H, J = 9.8 Hz), 3.31 (s, 3H), 2.57 (m, 1H), 2.34 (m, 1H), 1.85 (1H), 1.65 (m, 2H), 1.51 (m, 5H), 1.37 (m, 4H), 1.24 (m, 2H), 0.97 (d, 3H, J = 7.1 Hz), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 75.6, 74.8, 72.8, 69.1, 64.9, 56.2, 44.2, 42.5, 42.3, 40.1, 39.4, 38.3, 36.9, 31.4, 25.7, 18.9, 13.9; IR (CH_2Cl_2) 734, 797, 988, 1032, 1079, 1164, 1197, 1274, 1345, 1381, 1432, 1461, 1730, 2872, 2920, 3438 cm^{-1}; $[\alpha]^{20}_D = -48.4$ (*c* 0.05, CH_2Cl_2); HRMS (EI) calcd for $C_{18}H_{32}O_5$ (M^+) 328.2250, found 328.2246.

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Supporting Information Available: Additional experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.