Published in final edited form as:
J Org Chem. 2011 June 3; 76(11): 4358–4370. doi:10.1021/jo2003506.

Total Synthesis of Dolabelide C: A Phosphate-Mediated Approach

Paul R. Hanson, **Rambabu Chegondi**, **John Nguyen**, **Christopher D. Thomas**, **Joshua D. Waetzig**, and **Alan Whitehead**
Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045

Paul R. Hanson: phanson@ku.edu

Abstract

The first synthesis of dolabelide C (**1**), a cytotoxic marine macrolide, is reported utilizing a phosphate tether-mediated approach. Bicyclic phosphates (*S*,*S*,S_P)-**5** and (*R*,*R*,R_P)-**5** serve as the central building blocks for the construction of two major 1,3-*anti*-diol subunits in **1** through selective cleavage pathways, regioselective olefin reduction and cross-metathesis. Overall, phosphate-mediated processes provided copious amounts of both major subunits allowing for a detailed RCM macrocyclization study to the 24-membered macrolactone **1**.

I. Introduction: The Dolabelide Family

In 1995, the isolation and structural characterization of two new 22-membered macrolides, dolabelides A and B, from the sea hare *Dolabella auricularia* was reported (Figure 1). These compounds exhibited cytotoxicity against cervical cancer HeLa-S_3 cells with IC_{50} values of 6.3 and 1.3 μg/mL, respectively.[1] Two years later, dolabelides C and D,[2] 24-membered macrolides, were isolated from the same source and were found to possess cytotoxicity toward HeLa-S_3 cells with IC_{50} values of 1.9, and 1.5 μg/mL, respectively. To the best of our knowledge, the mechanism of action of these compounds remains unknown to date.

Common features among the dolabelide family are 11 stereogenic centers, 8 of which bear oxygen, and two *E*-configured trisubstituted olefins. Other structural features possessed by this family of macrolactones include 1,3-*anti*-diol fragments found at C7/C9 and C19/C21, along with an accompanying 1,3-*syn*-diol at C9/C11 and polypropionate fragments at C1/C4 and C21/C23. The stereochemical complexity and biological profile of this class of compounds has attracted synthetic interest from several groups[3] and in 2006, the first total synthesis of dolabelide D was reported by Leighton and coworkers.[4]

Dolabelide C (**1**) can be disconnected into C1-C14 and C15-C30 subunits, **2** and **3**, respectively (Scheme 1). The endgame for this approach is similar to Leighton's strategy towards dolabelide D,[4] employing a macrocyclization sequence to install the C14/C15 trisubstituted olefin through a late stage ring-closing metathesis (RCM) reaction. Macrocyclization, via RCM, is preceded by Yamaguchi coupling between the C1 carboxylic acid of the northern subunit **2** and the C23 carbinol center in the southern subunit **3**. Central to this approach are the 1,3 *anti*-diol motifs at C7/C9 and C19/C21, which can be assembled

Correspondence to: Paul R. Hanson, phanson@ku.edu.

Supporting Information **Available**. Experimental details and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

and elaborated from bicyclic phosphates (*R*,*R*,R_P)-**5** and (*S*,*S*,S_P)-**5**, respectively, utilizing a phosphate tether-mediate approach.

Results and Discussion

II. Construction of *P*-Chiral, Nonracemic Bicyclo[4.3.1]phosphates (*R*,*R*,R_P)-5 and (*S*,*S*,S_P)-5

The enantiomeric phosphate triester building blocks (*R*,*R*,R_P)-**5** and (*S*,*S*,S_P)-**5** (Scheme 2) were assembled via a phosphate tether, RCM desymmetrization approach[5] inspired by Burke and coworkers.[6] In this method, a phosphate tether effectively serves to mediate the tripodal coupling of *anti*-diol **8**[7] with an allylic alcohol component via either a phosphoryl monochloride or through a one-step coupling/oxidation sequence from commercially available allyl tetraisopropylphosphorodiamidite to yield pseudo-C_2-symmetric triene **9**. Desymmetrization[8] by ring-closing metathesis (RCM) using Grubbs catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh (cat-**B**)][9,10,11] affords *P*-chiral bicyclo[4.3.1]phosphate (*S*,*S*,S_P)-**5** and is based on the premise that only the terminal olefin *cis* to the phosphate-tethered olefin reacts to generate **5** possessing two sterically differentiated olefins.

III. Construction of C1–C14 Subunit

We embarked upon the synthesis of the C1–C14 subunit of dolabelide beginning with an elaborate cross methesis (CM) between bicyclic phosphate (*R*,*R*,R_p)-**5** possessing a Type III exocyclic terminal olefin and Type I olefin **10**.[12] As shown previously,[13] CM of (*R*,*R*,R_p)-**5** is high yielding with both Type I and Type II olefins in the presence of the Hoveyda-Grubbs catalyst (cat-**C**).[14] Various conditions for the desired CM of **10** and (*R*,*R*,R_p)-**5** were probed and it was found that employing 6 mol% Hoveyda-Grubbs catalyst at 90 °C in DCE gave the CM adduct **4** in 72% yield (Scheme 3). This notable CM event between two complex olefins assembles in a single operation five of the six stereocenters contained within the C1–C14 subunit of dolabelide C. Moreover, excess amounts of **10**, a Type II CM partner, could be recovered in near quantitative yield and recycled in future CM events.

Two related regioselective processes were next investigated. The first involved a regioselective removal of the exocyclic C5–C6 olefin in the CM adduct **4** in the presence of the C10–C11 internal olefin, which sets the stage for subsequent regioselective hydride opening of the bicyclic system. Upon probing several hydrogenation conditions, (Wilkinson's catalyst, Crabtree's catalyst, Pd/C) it was found that a mild diimide reduction, generated *in situ* from *o*-nitrobenzenesulfonyl-hydrazine,[15] provided the necessary hydrogenated phosphate moiety **11** with near complete regioselectivity for the exocyclic olefin. In comparison, other diimide conditions (tosylhydrazine, NaOAc, H_2O, DCE, 90 °C) gave drastically lower yields, likely due to bicyclic phosphate instability under basic medium.[16]

Having achieved the regioselectively-hydrogenated product **11**, a regioselective opening with hydride was probed as an additional method to unmask the phosphate tether. Initial studies focused on allylic copper hydride addition using various reagents (Stryker's reagent, CuCN•2LiCl/$PhSiH_3$, $CeCl_3$•$7H_2O$/$NaBH_4$) (Scheme 3). Unfortunately, all conditions probed provided only unreacted starting material or total decomposition of the reaction mixture. Pd-catalyzed formate reductions were next investigated for generation of the requisite terminal olefin.[17] Employment of 1.5 equivalents of formic acid and 5 mol % $Pd(OAc)_2$ at 40 °C in DCE selectively opened phosphate **11** to provide the desired terminal olefin in **12**. Methylation of the phosphate acid intermediate showed that a highly regioselective process was operative (>20:1 ratio of regioisomers as evident by ^{31}P NMR analysis). Purification provided phosphate **12** in 87% yield. The remarkable regioselectivity

reveals another feature of the phosphate tether, whereby orthogonal orbital alignment within **11** allows for selective Pd(0)-catalyzed ionization of C12 over the C9 allylic phosphate position. This ionization allows Pd to deliver the hydride selectively at the internal C10 position to provide the desired terminal olefin. Addition of the hydride at the terminal C12 position would afford an allylic phosphate anion that is capable of additional ionization events with the C9 phosphate. Ultimately, the success of this reaction results in a net olefin transposition expediting the route to the C1–C14 subunit, as well as showcasing an additional facet of the phosphate-mediated methodology.

Upon completion of the synthesis of phosphate **12**, work began toward the installation of the C11–C14 fragment (Scheme 4). Cleavage of the phosphate was achieved using $LiAlH_4$, which generated a diol that was subsequently protected (PPTS, 2,2-dimethoxypropane, CH_2Cl_2) to yield acetonide **13**. Subsequent ozonolysis (O_3, pyridine, CH_2Cl_2:MeOH 1:1, Me_2S) of the terminal olefin produced the requisite aldehyde, which was subjected to the corresponding Grignard[18] derived from 1-iodo-3-methyl-3-butene affording **14** in a 95% yield. Dess-Martin periodinane (DMP, $NaHCO_3$, CH_2Cl_2) oxidation of the free alcohol in **14** produced the corresponding ketone in 90% yield. Attempts to selectively reduce the acetonide-protected ketone, using an assortment of reducing agents, failed to give any diastereoselectivity at C11. This problem was circumvented by deprotection of the acetonide and subsequent *syn* reduction utilizing the C9 alcohol. Selective removal of the acetonide was achieved by the addition of $CeCl_3 \bullet 7H_2O$ and water,[19] which efficiently (86% yield) cleaved the acetonide-protecting group without loss of the primary TBS group to provide diol **15**. Final reduction of ketone **15** using Evan's conditions (Et_2BOMe, $NaBH_4$)[20] afforded triol **16** in 60% (95% *brsm*) with excellent diastereoselectivity (*ds* ≥ 20:1).

IV. First Generation Synthesis of the C15–C30 Subunit of Dolabelide C

The construction of the C15–C30 subunit of dolabelide began with the enantiomeric bicyclic phosphate (*S*,*S*,S_P)-**5** possessing unique orbital symmetry of the bicyclic phosphate (Scheme 5).[21] Initial studies probed the possibility of an oxidation of the exocyclic olefin of **5** in the presence of the cyclic olefin. After testing various conditions, a chemoselective hydroboration of (*S*,*S*,S_P)-**5** was achieved using 9-BBN followed by mild $NaBO_3$ oxidation to yield the primary alcohol. Due to the aforementioned instability of (*S*,*S*,S_P)-**5** to basic hydrolysis, a mild perborate oxidation protocol developed by Burke and coworkers was implemented. Burke has shown this protocol to be compatible with multiple acetate protecting groups;[22] optimization of this hydroboration reaction with phosphate **5** found the reaction to be highly dependent on the amount of oxidant, equivalents of H_2O, and reaction time. Subsequent PMB ether formation using *p*-methoxybenzyl trichloroacetimidate produced **17** in good yields demonstrating the acid stability of bicyclic phosphate (*S*,*S*,S_P)-**5**. Employing the previously reported regio- and diastereoselective cuprate addition protocol, displacement of **17** (CuCN•2LiCl, $ZnMe_2$, THF, -30 °C to rt) afforded the S_N2' displaced phosphate acid exclusively (*ds* ≥ 20:1), which upon methylation ($TMSCHN_2$ and MeOH) produced cyclic phosphate ester **18** in excellent overall yield (87%). This reaction again highlights the remarkable orbital alignment of the bicyclic phosphate system and its concave nature, where only one of four possible products for this S_N2' cuprate reaction is generated. Reductive cleavage, followed by sequential protection of the diol systems with TIPS and MOM groups, and final ozonolysis of the olefin afforded aldehyde **19** in good yield.

With aldehyde **19** and vinyl iodide **20** in hand, studies aimed at a diastereoselective addition to aldehyde **19** to set the C23 stereogenic carbinol center began (Scheme 5). Initial efforts to generate the C23 stereocenter by lithiate additions gave predominately the undesired 1,2-Felkin product. To overcome this problem, investigation focused on reagent-controlled, ephedrine-based asymmetric vinylzincate additions, described by Marshall.[23] Aldehyde **19** reacted with **20** under these conditions to obtain the desired 1,3-*syn* isomer **21** in an 11:1

ratio of diastereomers, in 65% yield. Successful formation of **21** provided the advance intermediate bearing the requisite stereochemistry of the C15-C30 subunit. With **21** in place, only the installation of the C14–C15 terminal olefin was needed to complete the C15–C30 subunit of dolabelide C. MOM-protection of the C23 alcohol, DDQ removal of the PMB ether, tosylation, and cuprate displacement all proceeded in good yield to afford the terminal olefin **22** and complete the C15–C30 subunit of dolabelide C. Overall, a 12-step sequence to **22** from **5** was achieved, bearing the requisite stereochemistry for the C15–C30 subunit of dolabelide C.

V. Second Generation Synthesis of the C15–C30 Subunit of Dolabelide C

A second-generation synthesis was next developed when attempts to remove the three MOM-protecting groups from **22** proved problematic. To our dismay, all conditions tested for cleavage of these groups in the presence of the more labile TIPS-protecting groups provided unreacted starting material or total decomposition of the substrate (Scheme 6). The difficulty in removing these protecting groups prompted a reevaluation of protecting groups to access a suitable C15–C30 subunit of dolabelide. This alternative strategy coincided with a planned installation of the C23 carbinol at the last step of the sequence to streamline the route.

The alternative approach to the C15–C30 subunit began by employing previously established CM/reduction methodology (Scheme 7).[12a] As anticipated, **5** underwent CM with **23** in the presence of 6 mol % cat-**C**[14] (DCE, 90 °C) providing *E*-configured (>20:1) product in 82% yield. Selective reduction of the external olefin was again achieved using *o*-nitrobenzenesulfonyl-hydrazine[15] furnishing **24** in 75% yield.[24] Compound **24** was also synthesized through a one-pot, sequential cross-metathesis/olefin reduction protocol in 59% overall yield utilizing the same reagents shown in Scheme 6 This yield averages to 77% per synthetic step over the 2-step combined transformation. Regio- and diastereoselective methyl cuprate addition into **24** and subsequent phosphate cleavage produced diol **25** in good yield.[21] Diol **25** was protected as the acetonide (PPTS, 2,2-dimethoxypropane) in 96% yield.

The terminal olefin was next converted into primary alcohol **26** by an oxidative cleavage/reduction sequence in good yields. TBS-protection of alcohol **26** proceeded in 86% yield and was followed by removal of the PMB-ether to provide the corresponding primary alcohol. Conversion of the alcohol to a terminal olefin through an iodination/elimination sequence occurred in excellent yield over the two-step sequence. Achievement of the C14/C15 olefin left only a deprotection/oxidation/nucleophilic addition sequence to obtain the necessary C15–C30 subunit. TBAF removal of the TBS-protecting group to **27** and Swern oxidation provided aldehyde **28** necessary for the addition of the C24–C30 fragment.

Despite previous success with the Marshall asymmetric zincate addition protocol,[21] difficulties in reaction reproducibility and low product yields, also recently noted by Marshall,[23] prompted investigation of an alternative addition sequence. Thus, vinyl iodide **29** was converted to the lithiate with 2 equivalents of *t*BuLi followed by the addition of aldehyde **28** to afford a 1:1 mixture of C23 epimers of alcohol **30** in 79% yield. The two diastereoisomers of **30** were easily separated by column chromatography, allowing for isolation of the correct stereoisomer of alcohol **30** as well as facile recycling (oxidation/reduction) of the undesired diastereomer (*dr* = 2.7:1).[25] Overall, this alternative 13-step route to **30** from phosphate (*S*,*S*,S_P)-**5** provided a C15–C30 fragment ready to couple with the C1–C14 subunit of dolabelide C.

VI. Completion of the Total Synthesis

Studies toward the completion of dolabelide C next commenced with the complete acetylation of triol **16** to install the proper acetylation pattern for C1–C14 subunit of dolabelide C (Scheme 8). This was accomplished by adding acetic anhydride and pyridine to triol **16** to afford triacetate **31** in excellent yield. Deprotection of the TBS protecting group provided alcohol **32** in 93% yield. Swern oxidation of **32** generated the desired aldehyde that was prone to epimerization and was taken on without purification. Pinnick oxidation of the aldehyde provided carboxylic acid **2** in 81% yield over the two-step sequence, which was ready for coupling with the C15–C30 subunit.

Final coupling of the C1–C14 carboxylic acid **2** and the C15–C30 alcohol **30** was achieved using Yamaguchi conditions,[26] as previously described by Leighton and coworkers (Scheme 9).[4] The addition of 2,4,6-trichlorobenzoyl chloride, Et_3N, and DMAP at -78 °C for 21 hours avoided epimerization at C2 and yielded the desired coupled **33** in 77% yield. Deprotection of the C27-TES protecting group was achieved with TBAF in 94% yield. Subsequent acylation provided **34** in 98% yield. The final two protecting groups were removed using PPTS in MeOH, followed by treatment with DDQ to provide metathesis precursor **35** in excellent yield over two steps. Efforts to close the ring were attempted prior to PMB ether removal and provided the desired RCM product as observed by HRMS, albeit in poor overall conversion. As a result, subsequent investigations focused on RCM of the deprotected triol **35**. Portion-wise addition of 20 mol % of $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (cat-**B**)[11] to triol **35** afforded approximately a 1:1 *E*/*Z* mixture of dolabelide C **1** and its (*Z*)-isomer in a 57-60% yield.

VII. Purification Attempts and RCM/Isomerization Side Reaction

Initial attempts utilizing repeated standard normal-phase chromatography removed the *Z*-isomer (higher R_f), leaving what was believed to be pure dolabelide C (**1)** as a single spot on TLC. ^{1}H NMR analysis, however, revealed impurities, which were originally presumed to be the *Z*-isomer. Attempted purification using preparative reverse-phase LC-MS revealed the major by-product, as seen by ^{1}H NMR to be a demethylenated analog (M-14), along with trace amounts of a constitutional isomer and two by-products resulting from formal loss of an ethylene (M-28) as seen in the total-ion chromatogram (Figure 2). These by-products (**35a** and **35b**) are presumed to occur from isomerization of **35** followed by RCM, resulting in the smaller macrocycles (Scheme 10).[27] Numerous reports are consistent with this observation[28] and to the best of our knowledge; this is the first report of a detailed LC-MS analysis of the aforementioned side reaction.

In an attempt to understand and optimize the final RCM sequence, the final metathesis precursor was scaled-up. Both syntheses to each subunit proved to be scalable, providing 300 mg of **30** and 175 mg of **32**.[29] This material was carried through the same endgame steps (Scheme 9) affording 160 mg of RCM precursor **35** to apply towards the goal of optimizing the C14/15 *E:Z* ratio and minimizing the amount of deleterious side reactions occurring in the final RCM step. For this study metathesis catalyst cat-**B** and three other candidates shown in Figure 3 were screened.[30]

Initially, the conditions shown from Scheme 9 were reproduced (Table 1, entry 1), where LC-MS analysis showed nearly complete conversion and a similar ratio to what was previously observed. Screening of other catalysts by varying the phosphine or NHC-ligand showed a significant increase of by-product formation (entries 3-5). While no significant changes in *E:Z* ratio were obtained from catalyst screening, rigorous degassing and purification of the solvent were shown to reduce deleterious side products.[31]

Due to the scalability of this synthesis,[32] ample material was provided for characterization, where all NMR spectra matched with the previous reported data.[2,33] In addition, sufficient quantities of the unnatural C14/15 *Z*-isomer[34] were generated for both NMR analysis and collection of biological data to determine its bioactivity and potential potency against cervical cancer.[35]

Conclusion

In conclusion, dolabelide C (**1)** and its non-natural C14–C15 *Z*-diastereomer were produced and isolated from a scalable phosphate-mediated synthesis. A complex mixture was generated in the final RCM step resulting in by-products, which arose from a net loss of CH_2 and C_2H_4, that proved to be difficult to separate via repeated flash chromatography (8:1 CH_2Cl_2:acetone). Since the material produced at the end of the first synthesis of **1** was sparse, a re-synthesis provided 175 mg of the C1–C14 subunit (**32**), 300 mg of the C15–C30 subunit (**30**) and 160 mg of RCM precursor **35**. This allowed a detailed optimization study through a screening of various metathesis catalysts, concluding with the originally developed conditions (20 mol % cat-**B**, 0.5 μm, 40 °C) provided the optimum results. Overall, 14 mg (21% yield) of pure dolabelide C and 10 mg (15% yield) of the pure *Z*-isomer were produced in a 24-step longest linear sequence (LLS) from commercially available material utilizing the (*R*,*R*,R_P) antipode of **5** (sequence streamlined to a 22-step LLS using one-pot, sequential protocols).

Experimental Section

General Methods

All reactions were carried out in oven- or flame-dried glassware, under an argon atmosphere, using standard gastight syringes, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. Et_2O, THF, and CH_2Cl_2 were passed through a purification system employing activated Al_2O_3. Et_3N was eluted through basic alumina and stored over KOH. Butyl lithium was titrated prior to use. All olefin metathesis catalysts were obtained commercially and used without further purification. All ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_5D_5N at 400 MHz or 500 MHz and 126 MHz, respectively, and calibrated to the solvent peak. All mass spectra were obtained using electrospray ionization (ESI) (MeOH) coupled to high-resolution mass spectrometry (HRMS). Observed rotations at 589 nm were measured using an automatic polarimeter. Infrared spectra were obtained using a Fourier transform infrared (FTIR) spectrometer.

(4*S*,6*R*)-4-((*R*)-But-3-en-2-yl)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxane (SI-1)—Diol **25** (2.00 g, 5.95 mmol) was dissolved in CH_2Cl_2 (8 mL) at rt. 2,2-Dimethoxypropane (8 mL) and PPTS (150 mg, 0.595 mmol) were added respectively and the clear solution was stirred until completion. The reaction was quenched with saturated $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were washed once with brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Compound **SI-1** was isolated using flash chromatography (19:1 hexanes/EtOAc) as a clear oil (2.18 g, 98%); $[\alpha]_D$ = -36.3 (*c* = 0.40, CH_2Cl_2); FTIR (neat) 2983, 2935, 2856, 1612, 1512, 819 $cm^{-1;}$ ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.83 (ddd, *J* =17.4, 10.5 and 7.3 Hz, 1H), 5.03 (ddd, *J* = 17.5, 11.0 and 2.6 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.74–3.66 (m, 1H), 3.63 (ddd, *J* = 9.7, 6.3 and 6.3 Hz, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.18–2.26 (m, 1H), 1.71–1.64 (m, 1H), 1.63–1.53 (m, 2H), 1.55–1.35 (m, 6H), 1.32 (s, 6H), 1.30–1.24 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 140.9, 130.7, 129.3, 114.4, 113.7, 100.3, 72.5, 70.1, 70.0, 66.8, 55.3, 42.1, 36.3, 35.9, 29.7, 26.2, 25.3, 24.7, 24.4, 15.3; HRMS calcd for $C_{23}H_{36}NaO_4$ $(M+Na)^+$ 399.2511; found 399.2498 (ESI).

(*R*)-2-((4*S*,6*R*)-6-(5-(4-Methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-1-ol (26)—Olefin **SI-1** (1.50 g, 3.99 mmol) was dissolved in *t*-BuOH:THF:H_2O (10:2:1, 20 mL) at rt. *N*-Methyl morpholine *N*-oxide (933 mg, 7.98 mmol) and OsO_4 (0.19 mL, 0.08 mmol, 4% aq) were added and the reaction was stirred for approximately 12 h until olefin was completely consumed. The mixture was then diluted with phosphate buffer pH 7 (twice the volume of *t*-BuOH) and $NaIO_4$ was added (3.41 mg, 16.0 mmol). The reaction was stirred vigorously for approximately 2 h until the diol was completely consumed (monitored by TLC). The reaction was quenched with solid Na_2SO_3 (2.0 g) and acetone was removed under reduced pressure. The residue was partitioned with EtOAc (20 mL) and H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The collected organics were washed once with brine (20 mL), dried (Na_2SO_4) and filtered. After concentrating under reduced pressure, the crude product was purified using flash chromatography (5:1 hexanes/EtOAc) to generate intermediate aldehyde as a yellow oil.

The resultant aldehyde was dissolved in EtOH (16 mL) and cooled to 0 °C. $NaBH_4$ (303 mg, 7.98 mmol) was added and the reaction was slowly brought back to rt. Upon completion (~45 min), the solution was partitioned with 2:1, Et_2O:H_2O (40 mL), the aqueous layer was extracted with Et_2O (3 × 5 mL) and the organic layers were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification with flash chromatography (1:2 hexanes/EtOAc) afforded **26** (88% over two steps, 1.35 mg) as a clear oil; $[\alpha]_D$ = - 0.26 (*c* = 0.18, CH_2Cl_2); FTIR (neat) 3442, 2933, 2856, 1612, 1512, 819 cm $^{-1;}$ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.79–3.73 (m, 1H), 3.68 (ddd, *J* = 9.2, 6.3 and 6.3 Hz, 1H), 3.58 (d, *J* = 5.1 Hz, 2H), 3.43 (t, *J* = 6.6 Hz, 2H), 3.08 (s, 1H), 1.20–1.80 (m, 11H), 1.38 (s, 3H), 1.33 (s, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 130.8, 129.2, 113.7, 100.5, 73.1, 72.5, 70.1, 68.3, 66.6, 55.3, 40.6, 37.9, 35.8, 29.7, 26.2, 25.2, 24.6, 24.6, 12.7; HRMS calcd for $C_{22}H_{36}NaO_5$ $(M+Na)^+$ 403.2460; found 403.2413 (ESI).

***tert*-Butyl((*R*)-2-((4*S*,6*R*)-6-(5-(4-methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxan-4-yl)propoxy)dimethylsilane (SI-2)—**Alcohol **26** (1.34 mg, 3.53 mmol) was dissolved in CH_2Cl_2 (23 mL) at rt. Imidazole (720 mg, 10.6 mmol), DMAP (10 mg, 0.08 mmol) and TBSCl (800 mg, 5.29 mmol) were added, respectively. The reaction was quenched upon completion (~90 min, monitored by TLC) with saturated NH_4Cl (25 mL) and diluted with Et_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the organic layers were washed with brine (25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification with flash chromatography (20:1 hexanes/EtOAc) afforded **SI-2** (1.70 g, 97%) as a yellow oil; $[\alpha]_D$ = -16.6 (*c* = 0.35, CH_2Cl_2); FTIR (neat) 2933, 2856, 2881, 1247, 835 cm $^{-1;}$ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.24 (s, 2H), 3.80 (s, 3H), 3.74–3.66 (m, 2H), 3.56 (d, *J* = 4.4 Hz, 2H), 3.44 (t, *J* = 6.6 Hz, 2H), 1.37–1.67 (m, 11H), 1.31 (s, 6H), 0.89 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 130.7, 129.2, 113.7, 100.1, 72.5, 70.1, 67.0, 66.8, 64.1, 55.2, 40.5, 36.6, 35.9, 29.7, 26.1, 25.9, 25.3, 24.6, 24.5, 18.2, 12.2, -5.5, -5.5; HRMS calcd for $C_{28}H_{50}NaO_5Si$ $(M+Na)^+$ 517.3325; found 517.3334 (ESI).

5-((4*R*,6*S*)-6-((*R*)-1-(*tert*-Butyldimethylsilyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)pentan-1-ol (SI-3)—PMB ether **SI-2** (1.65 g, 3.34 mmol) was dissolved in EtOAc (16 mL) at rt. A catalytic amount of 10% Pd/C (50 mg) and $NaHCO_3$ (280 mg, 3.34 mmol) were added sequentially and the flask was pressurized with a H_2 balloon. After 10 h the mixture was filtered through pad of Celite® and rinsed thoroughly with EtOAc. The filtrate was concentrated under reduced pressure and purified with flash chromatography (10:1 hexanes/EtOAc) to yield alcohol **SI-3** (1.12 g, 90% yield) as a clear oil; $[\alpha]_D$ = -0.11 (*c* = 0.40, CH_2Cl_2); FTIR (neat) 3357, 2933, 2858, 1379, 1251, 1224, 835, 775 cm$^{-1;}$ ^{1}H

NMR (500 MHz, $CDCl_3$)[36a] δ 3.75–3.68 (m, 2H), 3.63 (t, J = 6.6 Hz, 2H), 3.55 (dd, J = 4.7 and 1.3 Hz, 2H), 1.70–1.38 (m, 10H), 1.33 (s, 6H), 1.28–1.22 (m, 1H), 0.89 (s, 9H), 0.84 (d, J = 6.9 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 100.2, 67.1, 66.8, 64.1, 63.0, 40.5, 36.6, 35.9, 32.7, 25.9 (3), 25.7, 25.3, 24.6, 24.5, 18.2, 12.2, -5.5, -5.5; HRMS calcd for $C_{20}H_{42}NaO_4Si$ $(M+Na)^+$ 397.2750, found 397.2773 (ESI).

(*R*)-2-((4*S*,6*R*)-2,2-Dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)propan-1-ol (27)— Alcohol **SI-3** (1.12 g, 2.99 mmol) was dissolved in THF (30 mL) at rt. Triphenylphosphine (941 mg, 3.59 mmol) and imidazole (477 mg, 6.59 mmol) were added, respectively, and the solution was cooled to 0 °C. I_2 (912 mg, 3.59 mmol) was added and the reaction was stirred for approximately 30 min (monitored by TLC). The solution was diluted with hexane and filtered through a pad of silica, while washing with hexane, and concentrated under reduced pressure. The crude product was taken onto the next step.

The iodo compound was dissolved in THF (35 mL) at rt followed by stepwise addition of *t*-BuOK (1.0 g, 8.98 mmol). The reaction was stirred for ~30 min. and was quenched with H_2O. The aqueous layer was extracted with EtOAc (3 × 20 mL portions) and the organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification with flash chromatography (20:1 hexanes/EtOAc) yielded the resultant terminal olefin (1.0 g, 94%) as a clear oil.

The resultant silyl ether (1.00 g, 2.81 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. A solution of TBAF in THF (8.5 mL, 1.0 M in THF) was added dropwise. The reaction was stirred at 0 °C until completion (~45 min), quenched with saturated NH_4Cl (10 mL) and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification using flash chromatography (10:1 hexanes/EtOAc) afforded **27** (670 mg, 98%) as a clear oil; $[\alpha]_D$ = -78.6 (c = 0.50, CH_2Cl_2); FTIR (neat) 3446, 2983, 2935, 2879, 1379, 1224, 908 $cm^{-1;}$ ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86–5.75 (m, 1H), 5.07–4.93 (m, 2H), 3.82–3.76 (m, 1H), 3.69 (ddd, J = 9.2, 9.2 and 6.2 Hz, 1H), 3.61–3.55 (m, 2H), 3.08 (s, 1H), 2.06 (dd, J = 14.1 and 7.1 Hz, 2H), 1.80–1.40 (m, 7H), 1.38 (s, 3H), 1.33 (s, 3H), 0.81 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 114.7, 100.5, 73.0, 68.2, 66.6, 40.6, 37.8, 35.3, 33.6, 24.7, 24.6, 24.6, 12.6; HRMS calcd for $C_{14}H_{27}O_3$ $(M+H)^+$ 243.1960, found 243.2895 (ESI).

(2*R*,3*R*,7*R*,*E*)-2-((4*S*,6*R*)-2,2-Dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-5-methyl-7-(triethylsilyloxy)dec-4-en-3-ol (30)—A solution of oxalyl chloride (0.158 mL, 1.86 mmol) in CH_2Cl_2 (4.8 mL) was cooled to -78 °C and DMSO (0.220 mL, 3.01 mmol) was added slowly by syringe (gas evolution). After stirring for 10 min, a solution of alcohol **27** (300 mg, 1.24 mmol) in CH_2Cl_2 (3.0 mL) was added by cannula and rinsed with CH_2Cl_2 (2 × 0.5 mL). The cloudy mixture was stirred at -78 °C for 15 min at which time Et_3N (0.700 mL, 4.96 mmol) was added dropwise. The reaction mixture was stirred for 1 h at -78 °C, quenched cold with saturated $NaHCO_3$ (5 mL) and allowed to warm to rt. After diluting with CH_2Cl_2, the layers were separated and the aqueous layer was re-extracted with CH_2Cl_2 (3 × 12 mL). The organic layer was dried (Na_2SO_4), filtered through a silica plug and rinsed (3 × 25 mL) with a EtOAc/CH_2Cl_2(1:1). The filtrate was concentrated under reduced pressure to give aldehyde **28** as a yellow oil. The crude aldehyde was taken immediately to the next reaction without further purification.

To a solution of the vinyl iodide **29** (1.01 mg, 2.75 mmol) in Et_2O (10 mL) at −78 °C was added *t*-BuLi (1.7 M in pentane, 3.40 mL, 5.75 mmol), and the reaction was immediately warmed to 0 °C for 25 min. The reaction was recooled to -78 °C, and the aldehyde **28** was slowly added via syringe in Et_2O (2.5 mL, 0.60 mL rinse). After 1 h, the reaction was

quenched at -78 °C with saturated NH_4Cl, warmed to rt, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (10:1 hexanes/EtOAc) afforded a 1:1 mixture of 1,3-*syn* and 1,3-*anti* **30** (ratio determined by ^1H NMR analysis of crude reaction mixture, 464 mg, combined yield of diastereomers 77% over two steps).

Oxidation/Reduction Sequence: The 1,3-*anti* diastereomer (65 mg, 0.135 mmol) of **30** was dissolved in CH_2Cl_2 (2.6 mL) at rt. Dess-Martin periodinane (115 mg, 0.270 mmol) was added to the stirring solution, where upon completion (monitored by TLC), the reaction was diluted with Et_2O (5 mL). The organic layer was washed with saturated $NaHCO_3$ (2 × 5 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure and the residual oil was purified through a short plug of SiO_2 (1:1 hexanes/EtOAc) providing a clear oil (40 mg, 85%).

The ketone (6 mg, 0.0125 mmol) was dissolved in MeOH and cooled to 0 °C. $NaBH_4$ (11 mg, 0.035 mmol) was added slowly and the mixture was stirred until the ketone was completely consumed (monitored by TLC). The mixture was partitioned with H_2O:Et_2O (1:1, 10 mL) and the resultant aqueous layer was extracted with Et_2O (3 × 5 mL). The collected organic layers were washed with brine (5 mL) and dried (Na_2SO_4). The epimeric ratio of the crude material was determined by ^1H NMR analysis after filtration and removal of solvent under reduced pressure, (~2.7:1). Flash chromatography (5:1 hexanes/EtOAc) provided both isomers (4 mg, 89%) as a clear oil; $[\alpha]_D$ = -8.1 (*c* = 1.3, CH_2Cl_2); FTIR (neat) 3456, 2954, 2935, 2875, 1458, 1379, 1224, 908 $cm^{-1;}$ ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (dddd, *J* = 16.9, 10.1, 6.7 and 6.7 Hz, 1H), 5.16 (d, *J* = 9.1 Hz, 1H), 5.01 (ddd, *J* = 17.1, 3.4 and 1.5 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 4.27 (t, *J* = 8.7 Hz, 1H), 3.99 (s, 1H), 3.84–3.74 (m, 3H), 2.27 (dd, *J* =14.1 and 4.3 Hz, 1H), 2.16 (dd, *J* = 8.7 and 3.0 Hz, 1H), 2.06 (q, *J* = 7.0 Hz, 2H), 1.70 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.72–1.20 (m, 11H), 0.96 (t, *J* = 8.2 Hz, 9H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H), 0.59 (q, *J* = 8.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 136.0, 128.8, 114.6, 100.6, 72.9, 72.4, 70.7, 66.6, 48.5, 44.1, 38.7, 38.0, 35.2, 33.6, 24.7, 24.6, 24.5, 18.4, 17.3, 14.2, 11.6, 7.0, 5.0; HRMS calcd for $C_{28}H_{54}NaO_4Si$ $(M+Na)^+$ 505.3689; found 505.3674 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-15-(*tert*-Butyldimethylsilyloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethylpentadec-1-ene-5,7,9-triyl triacetate (31)—To a solution of triol **16** (132 mg, 0.232 mmol) in CH_2Cl_2 (3.3 mL) was added DMAP (3 mg, 0.023 mmol), pyridine (0.750 mL, 9.30 mmol), and acetic anhydride (0.45 mL, 4.65 mmol). The reaction was stirred until disappearance of starting material at rt (~2 h). The reaction was diluted with EtOAc (5 mL), quenched with saturated NH_4Cl (5 mL), and the aqueous layer was re-extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) provided **31** (151 mg, 94%) as a clear oil; $[\alpha]_D$ = +12.4 (*c* = 0.50, CH_2Cl_2); FTIR (neat) 2956, 2929, 2883, 2856, 1739, 1514, 1461, 1247 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.97 (dddd, *J* = 9.5, 6.2, 6.2 and 3.1 Hz, 1H), 4.89 (m, 2H), 4.71 (s, 1H), 4.66 (s, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.46 (d, *J* = 10.9 Hz, 1H), 3.80 (s, 3H), 3.71 (dd, *J* = 9.7 and 5.3 Hz, 1H), 3.63 (dd, *J* = 9.7 and 3.3 Hz, 1H), 3.25 (dd, *J* = 8.7 and 2.4 Hz, 1H), 2.07–1.99 (m, 2H), 2.05 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.92 (dddd, *J* = 18.7, 10.2, 4.4 and 4.4 Hz, 1H), 1.84–1.68 (m, 5H), 1.71 (s, 3H), 1.64–1.54 (m, 4H), 1.46–1.38 (m, 1H), 1.34–1.22 (m, 1H), 0.92 (s, 9H), 0.90 (d, *J* = 2.3 Hz, 3H), 0.88 (d, *J* = 2.3 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 170.7, 170.6, 159.1, 144.9, 131.7, 129.3, 113.9, 110.5, 83.3, 74.6, 70.9, 70.3, 67.5, 65.1, 55.4, 39.2, 38.7, 38.6, 35.4, 33.5, 33.1, 32.3, 30.5, 26.1, 22.6, 21.3, 21.3,

21.2, 18.5, 14.8, 13.6, -5.2, -5.2; HRMS calcd for $C_{38}H_{64}NaO_9Si$ $(M+Na)^+$ 715.4217; found 715.4213 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-15-Hydroxy-13-(4-methoxybenzyloxy)-2,12,14-trimethylpentadec-1-ene-5,7,9-triyl triacetate (32)—To a solution of **31** (150 mg, 0.216 mmol) in THF (2.3 mL) was added TBAF (0.70 mL, 1.0 M in THF). The reaction was stirred until disappearance of starting material at rt (~3 h). The reaction was diluted with EtOAc (3 mL), quenched with saturated NH_4Cl (5 mL), and the aqueous layer was re-extracted with EtOAc (2 × 5 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (2:1 hexanes/EtOAc) provided **32** (118 mg, 94%) as a clear oil; $[\alpha]_D$ = +13.1 (*c* = 2.4, CH_2Cl_2); FTIR (neat) 3502, 3072, 2964, 2935, 2875, 1737, 1514, 1454, 1245 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.98 (dddd, *J* = 9.6, 6.3, 6.3 and 3.3 Hz, 1H), 4.99–4.85 (m, 2H), 4.73 (s, 1H), 4.67 (s, 1H), 4.58 (d, *J* = 10.6 Hz, 1H), 4.51 (d, *J* = 10.6 Hz, 1H), 3.81 (s, 3H), 3.62–3.67 (m, 2H), 3.25 (dd, *J* = 7.6, 3.3 Hz, 1H), 2.71 (s, 1H), 2.07–1.99 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.95–1.86 (m, 2H) 1.84–1.68 (m, 6H), 1.72 (s, 3H), 1.64–1.56 (m, 2H), 1.54–1.44 (m, 1H), 1.34–1.22 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 170.6, 170.5, 159.3, 144.7, 130.4, 129.4 (2), 113.9 (2), 110.4, 87.6, 74.8, 70.6, 70.0, 67.3, 66.5, 55.3, 39.0, 38.4, 37.7, 36.1, 33.3, 32.8, 32.2, 30.0, 22.4, 21.2, 21.1, 21.1, 15.4, 14.3; HRMS calcd for $C_{32}H_{50}NaO_9$ $(M+Na)^+$ 601.3353; found 601.3354 (ESI).

(2*S*,3*S*,4*R*,7*S*,9*R*,11*S*)-7,9,11-Triacetoxy-3-(4-methoxybenzyloxy)-2,4,14-trimethylpentadec-14-enoic acid (2)—A solution of oxalyl chloride (0.046 mL, 0.539 mmol) in CH_2Cl_2 (1.67 mL) was cooled to -78 °C and DMSO (0.077 mL, 1.08 mmol) was added slowly by syringe (gas evolution). After stirring for 10 min a solution of alcohol **32** (125 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) was added by cannula and rinsed with CH_2Cl_2 (2 × 0.2 mL). The cloudy mixture was stirred at -78 °C for 15 min at which time Et_3N (0.18 mL, 1.29 mmol) was added dropwise. The reaction mixture was stirred for 2 h at -78 °C. The reaction was quenched at -78 °C with saturated $NaHCO_3$ (3 mL) and allowed to warm to rt. The reaction was diluted with CH_2Cl_2, and the layers were separated. The aqueous layer was re-extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give aldehyde as a yellow oil. The crude aldehyde was taken immediately to the next reaction with further purification.

To a solution of crude aldehyde was added *t*-butanol (4.5 mL) and 2-methyl-2-butene (1.5 mL). A solution of $NaClO_2$ (390 mg, 4.30 mmol) and sodium dihydrogen phosphate (470 mg, 3.01 mmol) in H_2O (2.0 mL) was prepared and added to the reaction mixture by syringe. The yellow solution was stirred vigorously for 2 h at rt, diluted with Et_2O (15 mL) and poured into H_2O (9 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combine organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (1:1 hexanes:EtOAc) provided **2** (104 mg, 81% over two steps) as a clear oil; $[\alpha]_D$ = +8.13 (*c* = 0.16, CH_2Cl_2); FTIR (neat) 3251, 3076, 2964, 2923, 2854, 1737, 1714, 1512, 1454, 1245 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.10–4.85 (m, 3H), 4.73 (s, 1H), 4.67 (s, 1H), 4.56 (d, *J* = 10.7 Hz, 1H), 4.50 (d, *J* = 10.6 Hz, 1H), 3.79 (s, 3H), 3.57 (dd, *J* = 7.2 and 3.5 Hz, 1H), 2.78 (dddd, *J* = 14.33, 7.1, 7.1 and 7.1 Hz, 1H), 2.07–1.99 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.95–1.86 (m, 2H), 1.84–1.64 (m, 5H), 1.72 (s, 3H), 1.64–1.40 (m, 3H), 1.39–1.20 (m, 2H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.9, 170.8, 170.7, 170.5, 159.4, 144.7, 130.0, 129.5 (2), 113.9 (2), 110.3, 84.2, 74.4, 70.8, 69.9, 67.3, 55.3, 42.3, 39.0, 38.1, 35.6, 33.3, 32.5, 32.3, 28.9, 22.4, 21.2, 21.1, 21.1, 14.7, 14.4; HRMS calcd for $C_{32}H_{48}NaO_{10}$ $(M+Na)^+$ 615.3145; found 615.3131 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((2*S*,3*R*,7*R*,*E*)-2-((4*S*,6*R*)-2,2-Dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-5-methyl-7-(triethylsilyloxy)dec-4-en-3-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate (33)—To a solution of alcohol **30** (77 mg, 0.159 mmol), carboxylic acid **2** (106 mg, 0.175 mmol), and DMAP (975 mg, 7.98 mmol) in toluene (32 mL) at -78 °C was added Et_3N (0.5 mL, 3.61 mmol) dropwise followed by the slow addition of 2,4,6-trichlorobenzoyl chloride (0.56 mL, 3.58 mmol), which caused the white solution to thicken. The mixture was stirred for 21 h at -78 °C ensuring that the bath temperature did not rise above -65 °C. The reaction flask was then moved to a dry ice/CH_3CN bath and stirred for 2.5 h maintaining the temperature between -30 °C to -42 °C. At the end of the 2.5 h the solution was slowly allowed to warm to rt in the bath over 1 h. The flask was placed in an ice bath for 2 h while being stirred. The reaction was quenched by the addition of sataturated $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer was back extracted with Et_2O (25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduce pressure. Purification by flash chromatography (5:1 hexanes/EtOAc) provided ester **33** (130 mg, 77%) as a colorless oil; $[\alpha]_D$ +3.63 (*c* = 0.28, CH_2Cl_2); FTIR (neat) 3076, 2954, 2935, 2875, 1739, 1515, 1442, 1244 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.82 (dddd, *J* = 17.0, 10.2, 6.8 and 6.8 Hz, 1H), 5.68 (dd, *J* = 9.9 and 5.7 Hz, 1H), 5.17 (d, *J* = 9.8 Hz, 1H), 5.02 (ddd, *J* = 17.1, 3.2 and 1.6 Hz, 1H), 5.00–4.93 (m, 3H), 4.94–4.85 (m, 2H), 4.74 (s, 1H), 4.67 (s, 1H), 4.51 (d, *J* = 10.8 Hz, 1H), 4.34 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 3.70–3.80 (m, 2H), 3.69–3.60 (m, 3H), 2.69 (dt, *J* = 14.2 and 7.1 Hz, 1H), 2.20–1.89 (m, 8H), 2.06 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.80–1.20 (m, 18H), 1.76 (s, 3H), 1.73 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.08 (d, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.93–0.84 (m, 9H) 0.58 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 170.6, 170.6, 170.5, 158.9, 144.7, 139.6, 138.8, 131.2, 129.0, 122.7, 114.6, 113.6, 110.3, 100.1, 83.1, 73.9, 71.4, 70.7, 70.2, 70.0, 67.3, 67.1, 66.5, 55.2, 53.5, 48.8, 43.5, 42.1, 39.1, 38.5, 38.5, 35.4, 34.7, 33.7, 33.3, 32.1, 30.3, 29.9, 29.7, 24.9, 24.9, 24.8, 22.4, 21.2, 21.1, 21.1, 18.3, 17.6, 15.3, 14.8, 14.2, 13.2, 9.8, 7.0 (3), 5.0 (3); HRMS calcd for $C_{60}H_{100}NaO_{13}Si$ $(M+Na)^+$ 1079.6831; found 1079.7115 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((2*S*,3*R*,7*R*,*E*)-2-((4*S*,6*R*)-2,2-Dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-7-hydroxy-5-methyldec-4-en-3-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate (SI-4)—Ester **33** (75 mg, 0.071 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. A solution of TBAF in THF (0.214 mL, 1.0 M in THF) was added dropwise. The reaction stirred at 0 °C until completion (approximately 45 min). The reaction was quenched with saturatred NH_4Cl and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded **SI-4** (63 mg, 94%) as a clear; $[\alpha]_D$ = -11.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.81 (dddd, *J* = 17.0, 10.2, 6.7 and 6.7 Hz, 1H), 5.64 (dd, *J* = 9.9 and 5.2 Hz, 1H), 5.20 (d, *J* = 9.6 Hz, 1H), 5.01 (ddd, *J* = 17.1, 3.4 and 1.6 Hz, 1H), 5.00–4.93 (m, 2H), 4.93–4.85 (m, 2H), 4.72 (s, 1H), 4.67 (s, 1H), 4.53 (d, *J* = 10.7 Hz, 1H), 4.38 (d, *J* = 10.7 Hz, 1H), 3.79 (s, 3H), 3.76–3.69 (m, 1H), 3.66–3.59 (m, 1H), 3.60–3.54 (m, 1H), 3.53 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.70 (dt, *J* = 15.2 and 7.2 Hz, 1H), 2.15–1.87 (m, 8H), 2.06 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.80–1.20 (m, 21H), 1.76 (s, 3H), 1.73 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 1.10 (d, *J* = 7.1 Hz, 3H), 0.93–0.84 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 170.7, 170.6, 170.5, 158.9, 144.7, 139.6, 138.7, 131.2, 128.8, 123.1, 114.6, 113.5, 110.3, 100.2, 83.7, 73.8, 71.8, 70.7, 70.0, 68.4, 67.3, 66.4, 55.2, 53.5, 48.1, 43.4, 42.1, 39.2, 39.1, 38.5, 36.3, 35.4, 35.1, 33.7, 33.3, 32.8, 32.2, 29.8, 29.7, 24.8, 24.6, 22.4, 21.2, 21.1, 21.0, 18.9, 17.5, 14.8, 14.2, 13.6, 9.9; HRMS calcd for $C_{54}H_{86}NaO_{13}$ $(M+Na)^+$ 965.5966; found 965.5897 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((2*S*,3*R*,7*R*,*E*)-7-Acetoxy-2-((4*S*,6*R*)-2,2-dimethyl-6-(pent-4-enyl)-1,3-dioxan-4-yl)-5-methyldec-4-en-3-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate (34)—To a solution of **SI-4** (58 mg, 0.062 mmol) in CH_2Cl_2 (3.0 mL) was added DMAP (1 crystal), pyridine (0.2 mL, 2.46 mmol) and acetic anhydride (0.117 mL, 1.23 mmol). The reaction was stirred at rt until disappearance of starting material (~2 h). The reaction was diluted with EtOAc (3 mL), quenched with saturated NH_4Cl (3 mL) and the aqueous layer was re-extracted with EtOAc (3 × 5 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (1.5:1 hexanes/EtOAc) provided **34** (60 mg, 98%) as a clear oil; $[\alpha]_D$ = +2.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.80 (dddd, *J* = 16.9, 10.2, 6.7 and 6.7 Hz, 1H), 5.67 (dd, *J* = 9.9 and 5.6 Hz, 1H), 5.16 (d, *J* = 9.7 Hz, 1H), 5.00 (ddd, *J* = 17.1, 3.4 and 1.6 Hz, 1H), 5.00–4.92 (m, 3H), 4.92–4.84 (m, 2H), 4.73 (s, 1H), 4.66 (s, 1H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.35 (d, *J* = 10.9 Hz, 1H), 3.79 (s, 3H), 3.75–3.68 (m, 1H), 3.62–3.55 (m, 2H), 2.68 (dt, *J* = 16.0 and 6.9 Hz, 1H), 2.15–1.87 (m, 8H), 2.06 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.80–1.20 (m, 20H), 1.77 (s, 3H), 1.73 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.93–0.84 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 170.6, 170.6, 170.6, 170.5, 158.9, 144.7, 138.7, 138.6, 131.3, 128.8, 122.5, 114.6, 113.5, 110.3, 100.2, 83.2, 73.8, 72.1, 71.2, 70.7, 70.0, 67.3, 66.4, 55.2, 53.5, 44.2, 42.1, 39.2, 39.1, 35.9, 35.4, 33.7, 33.3, 32.2, 31.9, 31.6, 29.9, 24.8, 24.8, 22.7, 21.3, 21.2, 21.1, 21.0, 18.4, 17.8, 14.7, 14.2, 14.2, 14.0, 13.2, 9.7; HRMS calcd for $C_{56}H_{88}NaO_{14}$ $(M+Na)^+$ 1007.6072; found 1007.6210 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((4*R*,8*R*,9*S*,10*S*,12*R*,*E*)-4-Acetoxy-10,12-dihydroxy-6,9-dimethylheptadeca-6,16-dien-8-yloxy)-13-(4-methoxybenzyloxy)-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate (SI-5)—To a solution of tetraacetate **34** (60 mg, 0.061 mmol) in MeOH (6 mL) was added PPTS (2.5 mg, 0.03 mmol). The reaction was stirred until disappearance of starting material at rt (~ 4 h). The reaction was diluted with EtOAc, quenched with saturated $NaHCO_3$ and the aqueous layer was re-extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography (1.5:1 hexanes/EtOAc) provided **SI-5** (47 mg, 82%) as a clear oil; $[\alpha]_D$ = +8.97 (*c* = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.82 (dddd, *J* = 15.8, 12.1, 5.4 and 5.4 Hz, 1H), 5.69 (dd, *J* = 9.7 and 6.0 Hz, 1H), 5.18 (d, *J* = 9.8 Hz, 1H), 5.05–4.85 (m, 6H), 4.73 (s, 1H), 4.67 (s, 1H), 4.51 (d, *J* = 10.9 Hz, 1H), 4.34 (d, *J* = 11.0 Hz, 1H), 3.92–3.86 (m, 1H), 3.80 (s, 3H), 3.71 (m, 1H), 3.58 (dd, *J* = 8.4, 2.0 Hz, 1H), 2.73 (dddd, *J* = 14.2, 6.8, 6.8 and 6.8 Hz, 1H), 2.50–1.19 (m, 28H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.82 (s, 3H), 1.72 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.86–0.81 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 170.7, 170.6, 170.6, 170.5, 158.9, 144.7, 138.7, 138.6, 131.1, 128.4, 123.4, 114.7, 113.7, 110.3, 83.5, 73.8, 73.5, 72.5, 70.7, 70.1, 68.8, 67.3, 60.4, 55.2, 44.3, 43.4, 43.0, 39.5, 39.1, 38.5, 37.1, 36.3, 34.9, 33.7, 33.3, 32.2, 31.6, 29.8, 25.1, 22.7, 21.3, 21.2, 21.1, 21.1, 18.4, 17.8, 14.2, 14.0, 13.6, 10.8; HRMS calcd for $C_{53}H_{84}NaO_{14}$ $(M+Na)^+$ 967.5759; found 967.5789 (ESI).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*S*)-15-((4*R*,8*R*,9*S*,10*S*,12*R*,*E*)-4-Acetoxy-10,12-dihydroxy-6,9-dimethylheptadeca-6,16-dien-8-yloxy)-13-hydroxy-2,12,14-trimethyl-15-oxopentadec-1-ene-5,7,9-triyl triacetate (35)—Ester **SI-5** (105 mg, 0.112 mmol) was taken up in CH_2Cl_2 (5.0 mL) followed by the addition of pH = 7 buffer solution (5.0 mL) and DDQ (51 mg, 0.224 mmol) at rt. Upon completion (~0.5 h, monitored by TLC), CH_2Cl_2 (13 mL) was added followed by saturated $NaHCO_3$ (1 mL). The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined

organic layers were washed with brine (10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (2:1 hexanes/EtOAc) afforded **35** (89 mg, 97%) as a clear oil. $[\alpha]_D$ = +4.4 (*c* = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dddd, *J* = 17.0, 10.2, 6.7 and 6.7 Hz, 1H), 5.19 (dd, *J* = 9.7 and 9.5 Hz, 1H), 5.07–4.87 (m, 6H), 4.73 (s, 1H), 4.66 (s, 1H), 4.15–4.09 (m, 2H), 3.96–3.89 (m, 1H), 3.71 (dd, *J* = 9.9 and 1.2 Hz, 1H), 2.54 (dddd, *J* = 14.1, 7.0, 7.0 and 7.0 Hz, 1H), 2.17–1.19 (m, 28H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.82 (s, 3H), 1.72 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.86–0.81 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 172.4, 170.8, 170.8, 170.6, 144.6, 138.7, 138.0, 125.3, 114.6, 110.4, 72.6, 72.6, 72.4, 71.9, 70.7, 68.1, 67.1, 66.9, 45.3, 44.2, 42.7, 39.0, 37.6, 37.3, 36.9, 36.0, 33.7, 33.6, 33.3, 32.3, 31.5, 29.0, 25.3, 22.4, 21.4, 21.3, 21.2, 21.1, 18.5, 17.8, 13.9, 13.6, 12.5, 9.5; HRMS calcd for $C_{45}H_{76}NaO_{13}$ $(M+Na)^+$ 847.5184; found 847.5183 (ESI).

Dolabelide C (1)—To a refluxing solution of ester **23** (70 mg, 0.085 mmol) in degassed CH_2Cl_2 (175 mL) was added Grubbs II catalyst (8.0 mg, 0.0085 mmol). The reaction was refluxed 2 h with the addition of more catalyst (4.0 mg, 0.00425 μmol) after 2 h. A third portion of catalyst (4.0 mg, 0.00425) was had after 2 more hours; the reaction was refluxed for 6 hours (monitored by TLC and LC-MS). The solution was cooled to rt and concentrated under reduced pressure. The resultant residue was purified via flash chromatography through two sequential columns (8:1 CH_2Cl_2/acetone) and (5:1 pentane/EtOAc) afforded **1**, (14.0 mg, 21% yield) as an analytically pure sample and its C14–C15 *Z*-configured diastereomer (10.0 mg, 15% yield) (vide infra); $[\alpha]_D$ = +2.9 (*c* = 0.63, $CHCl_3$); ^{1}H NMR (500 MHz, pyridine-d_5)[36b] δ 6.10-5.90 (br m, 1H), 5.70 (t, *J* = 9.3 Hz, 1H), 5.67 (s, 1H), 5.40 (d, *J* = 9.5 Hz, 1H), 5.38–5.31 (m, 2H), 5.30–5.23 (m, 2H), 5.16–5.10 (m, 1H), 4.88–4.82 (m, 1H), 4.37–4.32 (m, 1H), 4.03 (br d, *J* = 9.1 Hz, 1H), 2.93–2.85 (m, 1H), 2.52–2.48 (m, 1H), 2.32 (dd, *J* = 14.0 and 7.9 Hz, 1H), 2.28 (dd, *J* = 13.9 and 5.4 Hz, 1H), 2.21–2.15 (m, 1H), 2.11–2.00 (m, 6H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.96–1.92 (m, 2H), 1.90–1.80 (m, 4H), 1.79–1.58 (m, 7H), 1.59 (s, 3H), 1.53–1.49 (m, 3H), 1.32–1.28 (m, 2H), 1.19 (d, *J* = 7.3 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, pyridine-d_5) δ 173.9, 170.6, 170.5, 170.4, 170.3, 136.7, 132.6, 127.3, 127.2, 74.3, 73.5, 71.8, 69.9, 69.9, 68.0, 67.9, 67.3, 46.4, 44.5, 43.7, 38.8, 38.5, 38.0, 37.2, 36.3, 35.2, 34.1, 31.8, 31.6, 29.3, 28.0, 27.0, 21.1, 21.0, 20.9, 20.9, 18.8, 17.6, 15.2, 14.0, 13.8, 12.6, 11.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (t, *J* = 9.1 Hz, 1H), 5.10–5.05 (m, 2H), 5.04–5.00 (m, 1H), 4.98–4.92 (m, 1H), 4.88–4.82 (m, 2H), 4.08 (s, 1H), 3.93 (s, 1H), 3.57 (s, 1H), 3.24 (s, 1H), 2.60–2.54 (m, 1H), 2.54–2.47 (m, 1H), 2.25 (dd, *J* = 13.8 and 7.1 Hz, 1H), 2.21 (dd, *J* = 14.1 and 5.7 Hz, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.90–1.83 (m, 2H), 1.81 (s, 3H), 1.78–1.64 (m, 3H), 1.64–1.62 (m, 4H), 1.58 (s, 3H), 1.56 (m, 9H), 1.43–1.27 (m, 5H), 1.25 (s, 3H), 1.23–1.20 (m, 1H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.84 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 171.2, 171.0, 170.7, 170.4, 137.9, 133.1, 126.1, 125.0, 74.6, 73.1, 72.2, 69.8, 69.2, 68.7, 68.1, 67.7, 45.1, 44.3, 42.7, 39.1, 36.8, 36.1, 35.1, 34.6, 31.9, 31.7, 29.7, 28.3, 26.7, 25.0, 21.2, 21.2, 21.2, 21.1, 18.5, 17.7, 15.2, 13.9, 13.6, 12.6, 10.6; HRMS calcd for $C_{43}H_{72}NaO_{13}$ $(M+Na)^+$ 819.4871; found 819.4858 (ESI).

Non-Natural C14-C15 *Z*-Isomer of 1—$[\alpha]_D$ = +10.0 (*c* = 0.30, $CHCl_3$); ^{1}H NMR (500 MHz, pyridine-d_5)[36c] δ 6.28 (br s, 1H), 6.20–6.05 (br m, 1H), 5.85 (t, *J* = 9.4 Hz, 1H), 5.51 (d, *J* = 8.8 Hz, 1H), 5.48–5.40 (m, 2H), 5.38–5.29 (m, 2H), 5.27–5.18 (m, 1H), 4.88–4.84 (m, 1H), 4.53–4.46 (m, 1H), 4.14 (br d, *J* = 7.4 Hz, 1H), 3.03–2.97 (m, 1H), 2.64–2.56 (m, 1H), 2.43 (dd, *J* = 7.5, 13.8 Hz, 1H), 2.37 (dd, *J* = 5.3, 13.1 Hz, 1H), 2.34–2.23 (m, 3H), 2.22–2.19 (m, 1H), 2.18–2.14 (m, 12H), 2.13–2.12 (m, 2 H), 2.08 (s, 3 H), 2.06–2.02 (m, 1 H), 2.02–2.00 (m, 1 H), 1.99–1.95 (m, 2 H), 1.95–1.91 (m, 1 H), 1.91–1.86 (m, 2 H), 1.84–1.78 (m, 2 H), 1.77 (s, 3 H), 1.75–1.66 (m, 3 H), 1.64–1.58 (m, 3 H); 1.49–1.31 (m, 4 H),

1.29 (d, J = 7.0 Hz, 6 H), 1.04 (d, J = 6.6 Hz, 3 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (126 MHz, pyridine-d_5) δ 174.2, 170.9, 170.9, 170.7, 170.6, 137.2, 134.3, 127.3, 126.9, 75.2, 73.6, 72.2, 71.8, 70.1, 68.3, 68.2, 68.1, 46.6, 44.8, 44.3, 39.9, 39.2, 39.0, 37.6, 36.7, 34.4, 32.8, 32.0, 29.3, 28.4, 27.9, 27.5, 23.3, 21.4, 21.4, 21.3, 21.3, 19.1, 17.9, 14.3, 14.3, 13.0, 11.4; ^{1}H NMR (500 MHz, $CDCl_3$)[36d] δ 5.13–5.07 (m, 2H), 5.03–4.97 (m, 3H), 4.96–4.91 (m, 1H), 4.90–4.85 (m, 1H), 4.27 (s, 1H), 4.05–4.01 (m, 1H), 3.68 (d, J = 9.7 Hz, 1H), 2.54 (tt, J = 7.0 Hz, 1H), 2.31–2.20 (m, 4H), 2.13–2.11 (m, 1H), 2.11–2.08 (m, 1H), 2.06–2.04 (m, 2H), 2.04–2.03 (m, 6H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00–1.97 (m, 1H), 1.97–1.95 (m, 1H), 1.82 (s, 3H), 1.81–1.76 (m, 2H), 1.76–1.74 (m, 1H), 1.74–1.71 (m, 1H), 1.66 (s, 3H), 1.61 (s, 1H), 1.58–1.56 (m, 1H), 1.48–1.46 (m, 2H), 1.45–1.43 (m, 2H), 1.42–1.39 (m, 2H), 1.38–1.25 (m, 6H), 1.01 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 171.6, 171.3, 170.7, 170.4, 137.6, 133.9, 125.9, 125.8, 74.0, 72.8, 72.3, 71.3, 70.8, 68.0, 67.0, 66.6, 45.7, 44.1, 42.9, 38.0, 37.4, 37.0, 35.9, 34.9, 33.6, 32.2, 31.1, 28.2, 26.7, 25.9, 22.8, 21.4, 21.2, 21.2, 21.2, 21.2, 18.5, 17.8, 13.9, 13.4, 11.5, 9.36; HRMS calcd for $C_{43}H_{72}NaO_{13}$ $(M+Na)^+$ 819.4871; found 819.4877 (ESI).

HPLC-MS Analysis of 1: HPLC data was collected using the following gradient over 35 min:

Time (min)	A% (99:1 H_2O:MeCN)	B% (99:1 MeCN: H_2O)	Flow Rate (mL/min)
0.00	95.0	5.0	1.000
1.00	40.0	60.0	1.000
31.00	30.0	70.0	1.000

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This investigation was kindly supported by funds provided by NSF CHE-0503875, NIH-NIGMS RO1 GM077309, and the NIH Dynamic Aspects in Chemical Biology Training Grant (A.W., J.D.W.). The authors thank the University of Kansas Honors department for a KU Undergraduate Research Award (J.N., KU-UGRA), Dr. Marc Anderson and Dr. Todd D. Williams for LC-MS analysis, Dr. Justin T. Douglas and Sarah Neuenswander for assistance in NMR analysis, and Materia, Inc. for supplying catalyst and helpful discussion. The authors also thank Dr. Kigoshi, Dr. Ojika, and Dr. Suenaga for supplying us with a natural sample of dolabelide C.

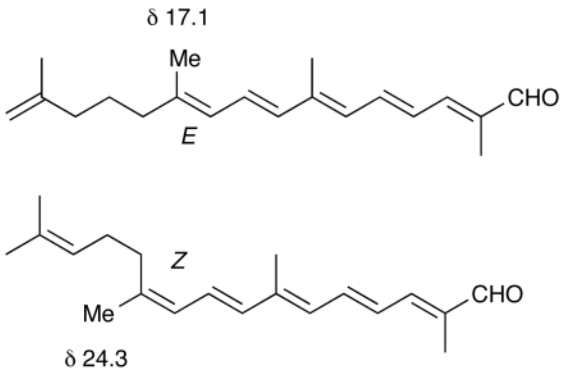
References

1. Ojika M, Nagoya T, Yamada K. Tetrahedron Lett. 1995; 36:7491–7494.
2. Suenaga K, Nagoya T, Shibata T, Kigoshi H, Yamada K. J Nat Prod. 1997; 60:155–157.
3. (a) Grimaud L, Rotulo D, Ros-Perez R, Guitry-Azam L, Prunet J. Tetrahedron Lett. 2002; 43:7477–7479.(b) Grimaud L, de Mesmay R, Prunet J. Org Lett. 2002; 4:419–421. [PubMed: 11820894] (c) Desroy N, Le Roux R, Phansavath P, Chiummiento L, Bonini C, Genêt JP. Tetrahedron Lett. 2003; 44:1763–1766.(d) Schmidt DR, Park PK, Leighton JL. Org Lett. 2003; 5:3535–3537. [PubMed: 12967318] (e) Le Roux R, Desroy N, Phansavath P, Genêt JP. Synlett. 2005:429–432.(f) Keck GE, McLaws MD. Tetrahedron Lett. 2005; 46:4911–4914. [PubMed: 16909163] (g) Vincent A, Prunet J. Synlett. 2006:2269–2271.(h) Roche C, Desroy N, Haddad M, Phansavath P, Genêt JP. Org Lett. 2008; 10:3911–3914. [PubMed: 18681446]
4. Park PK, O'Malley SJ, Schmidt JDR, Leighton L. J Am Chem Soc. 2006; 128:2796–2797. [PubMed: 16506747]
5. Both antipodes of the bicyclic phosphate **5** and diol **7** have been previously constructed, see: (a) Whitehead A, McReynolds MD, Moore JD, Hanson PR. Org Lett. 2005; 7:3375–3378. [PubMed:

16018664] Recently a 4-step synthesis from commercially available 2,4-pentanedione (see reference 5a) has been developed to bicyclic phosphate **5** see: (b) Venukadasula PKM, Chegondi R, Maitra S, Hanson PR. Org Lett. 2010; 12:1556–1559. [PubMed: 20196547] For additional methods to 1,3-*anti*-diols, see: (c) Bode SE, Wolberg M, Müller M. Synthesis. 2006:557–588.

6. (a) Burke SD, Muller N, Beaudry CM. Org Lett. 1999; 1:1827–1829. [PubMed: 10836042] (b) Burke SD, Voight EA. Org Lett. 2001; 3:237–240. [PubMed: 11430043] (c) Lambert WT, Burke SD. Org Lett. 2003; 5:515–518. [PubMed: 12583757] For desymmetrization of a C_2-symmetric diol using the Prins cyclization, see: (c) Rychnovsky SD, Yang G, Hu Y, Khire UR. J Org Chem. 1997; 62:3022–3023. [PubMed: 11671673]
7. Rychnovsky SD, Griesgraber G, Powers JP. Org Synth. 1999; 77:1–11.
8. (a) Mislow K, Siegel J. J Am Chem Soc. 1984; 106:3319–3328.(b) Eliel, EL. Stereochemistry of Carbon Compounds. McGrawHill; New York: 1962.
9. The Grubbs catalyst $(PCy_3)_2(Cl)_2Ru$=CHPh (cat-**A**),[10] was shown to be not as effective in this desymmetrization reaction as cat-**B**.[11]
10. $(PCy_3)_2(Cl)_2Ru$=CHPh (cat-**A**) (a) Schwab P, Grubbs RH, Ziller JW. J Am Chem Soc. 1996; 118:100–110.(b) Schwab P, France MB, Ziller JW, Grubbs RH. Angew Chem, Int Ed. 1995; 34:2039–2041.
11. $(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh (cat-**B**) Scholl M, Ding S, Lee CW, Grubbs RH. Org Lett. 1999; 1:953–956. [PubMed: 10823227]
12. Grubbs and co-workers have categorized various olefins by their relative rates of homodimerization correlating with the catalyst being used for CM. These types range from Type I olefins, classified by rapid, reversible, homodimerization, to Type IV olefins which are spectators to CM. Varying product ratios can be observed when pairing different olefin types; mixing Type I olefins yields a statistical mixture of CM and homodimerization, whereas CM between Type I and TypeII olefin pairs is very selective and high yielding of CM products. Using differential reactivity of olefins allows one to design selective CM by properly pairing olefin partners. Chatterjee AK, Choi TL, Sanders DP, Grubbs RH. J Am Chem Soc. 2003; 125:11360–11370. [PubMed: 16220959]
13. (a) Waetzig JD, Hanson PR. Org Lett. 2006; 8:1673–1676. [PubMed: 16597138] (b) Waetzig JD, Hanson PR. Org Lett. 2008; 10:109–112. [PubMed: 18062695]
14. Cat-**C**: Hoveyda-Grubbs 2nd Generation Catalyst Garber SB, Kingsbury JS, Gray BL, Hoveyda AH. J Am Chem Soc. 2000; 122:8168–8179.
15. (a) Meyers AG, Zheng B, Movassaghi M. J Org Chem. 1997; 62:7507. [PubMed: 11671877] (b) For recent use of NBSH as a diimide source, see Haukaas MH, O'Doherty GA. Org Lett. 2002; 4:1771–1774. [PubMed: 12000295] (c) Buszek KR, Brown N. J Org Chem. 2007; 72:3125–3128. [PubMed: 17367188] (b) For a flavin-catalyzed generation of diimide, see: Imada Y, Iida H, Naota T. J Am Chem Soc. 2005; 127:14544–14545. [PubMed: 16231886]
16. In a model study, a one-pot, sequential ring-closing, cross-metathesis and olefin reduction were also conducted to generate (R,R,R_P)-**5** in situ in 30% overall yield. This yield averages to 67% per synthetic step over the 3-step combined transformation from the pseudo-C_2-symmetric monocyclic triene phosphate (*ent*-**9**).
17. For a related study on using Pd-formate reductions to form terminal olefins see: (a) Hughes G, Lautens M, Wen C. Org Lett. 2000; 2:107–110. [PubMed: 10814258] (b) Chau A, Paquin JF, Lautens M. J Org Chem. 2006; 71:1924–1933. [PubMed: 16496977]
18. Helmboldt H, Koehler D, Hiersemann M. Org Lett. 2006; 8:1573–1576. [PubMed: 16597113]
19. Umezawa T, Hayashi T, Sakai H, Teramoto H, Yoshikawa T, Izumida M, Tamatani Y, Hirose T, Ohfune Y, Shinada T. Org Lett. 2006; 8:4971–4974. [PubMed: 17020349]
20. (a) Chen KM, Hardtmann GE, Prasad K, Repic O, Shapiro MJ. Tetrahedron Lett. 1987; 28:155–158.(b) Evans DA, Chapman KT, Carreira EM. J Am Chem Soc. 1998; 110:3560–3578.
21. Whitehead A, Waetzig JD, Thomas CD, Hanson PR. Org Lett. 2008; 10:1421–1424. [PubMed: 18324822]
22. Lucas BS, Luther LM, Burke SD. Org Lett. 2004; 6:2965–2968. [PubMed: 15330659]
23. Marshall JA, Eidam P. Org Lett. 2004; 6:445–448. [PubMed: 14748614]

24. Compound **11** was also synthesized through a one-pot protocol in 59% yield utilizing the same reagents shown in Scheme 3.
25. The low diastereoselectivity prompted additional studies where **17** was oxidized to the corresponding ketone and subjected to various reducing conditions. Initial reduction utilizing Mori's conditions ($LiAlH_4$, LiI) generated a 1:1.5 mixture of diastereomers, see: (a) Mori Y, Kuhara M, Takeuchi A, Suzuki M. Tetrahedron Lett. 1988; 29:5419–5422.(b) Ghosh AK, Lei H. J Org Chem. 2002; 67:8783–8788. [PubMed: 12467389] Other reductants such as L-selectride (*dr* = 1.7:1) and the CBS (Corey EJ, Shibata S, Bakshi RK. J Org Chem. 1988; 53:2861–2863.) reduction (*dr* = 2.2:1) gave favorable ratios as well.
26. (a) Inanaga J, Hirata K, Saeki H, Katsuki T, Yamaguchi M. Bull Chem Soc Jpn. 1979; 52:1989–1993.(b) Kawanami Y, Dainobu Y, Inanaga J, Katsuki T, Yamaguchi M. Bull Chem Soc Jpn. 1981; 54:943–944.
27. Integration of the peaks areas of each mixture component resulted in a ~2.6:1 of **1**demethyleneated product and the ratio between the title compound to the constitutional isomer as >20:1.[17] It is assumed that the constitutional isomer results from further Ru-H isomerization of dolabelide C due to a comparison of retention times with the aforementioned C14/C15 Z-configured dolabelide C analog originally separated during normal-phase flash chromatography.
28. (a) Clark JS, Kettle JG. Tetrahedron Lett. 1997; 38:123–126.(b) Overmann LE, Joe D. Tetrahedron Lett. 1997; 38:8635–8638. For references citing difficulty in constructing trisubstituted *E*-olefins using RCM, see (c) Hoye TR, Zhao H. Org Lett. 1999; 1:169–171. [PubMed: 10822555] (d) Smith AB, Mesaros EF, Meyer EA. J Am Chem Soc. 2006; 128:5292–5299. [PubMed: 16608366] (e) Jin J, Chen Y, Li Y, Wu J, Dai WM. Org Lett. 2007; 9:2585–2588. [PubMed: 17536814] (f) Becker J, Bergander K, Frölich R, Hoppe D. Angew Chem, Int Ed. 2008; 47:1654–1657.
29. Sequence was run simultaneously in two batches to obtain the quantities noted.
30. The olefin metathesis catalysts screened in Figure 2 were provided by Materia, Inc.
31. Rigorous purification and degassing of the solvent was achieved through distillation over CaH_2 and conventional freeze/thaw technique.
32. The RCM was performed on 70 mg scale providing 14 mg of an analytically pure sample of the desired *E* isomer and 10 mg of the *Z* isomer.
33. Optical rotation was measured over several trials resulting in variation of both the value and sign of analytically pure **1** (determined by LC-MS analysis, see supporting information). This phenomenon is consistent with hydrogen-bonding systems, where inconsistency is frequently observed. Abraham E, Davies SG, Roberts PM, Russell AJ, Thomson JE. Tetrahedron:Asymmetry. 2008; 19:1027–1047. and references cited within.
34. The major diastereomer determined to be *E*, due to resonances matching with listed resonances in reference 3. The *E* geometry is confirmed from comparison of ^{13}C NMR, in which the C-14 methyl has a chemical shift (15.7 ppm) and the Z-isomer (23.3 ppm), which is consistent with reference 3 and the paper cited within (Carey L, Clough JM, Pattenden G. J Chem Soc Perkin Trans I. 1983:3005–3009.) where it's stated “The ^{13}C NMR shifts of vinyl methyl and vinyl methylene carbon atoms associated with isolated trisubstituted double bonds are critically dependent on the configuration of the double bond as a result of the well-known γ-effect.” For example:



35. Purification of each isomer was achieved using 2-3 consecutive runs on normal phase flash chromatography (see supporting information).

36. (a) Spectrum integrated to 41 total H, where the unassigned H was presumed to be an O-H peak undergoing H-D exchange; (b) Spectrum integrated to 71 total H, where the unassigned H was presumed to be an O-H peak undergoing H-D exchange. Only the O-H peaks did not match exactly to the reported data; (c) Spectrum integrated to 71 total H, where the unassigned H was presumed to be an O-H peak undergoing H-D exchange; (d) Spectrum integrated to 69 total H, where the unassigned H's were presumed to be O-H peaks undergoing H-D exchange.

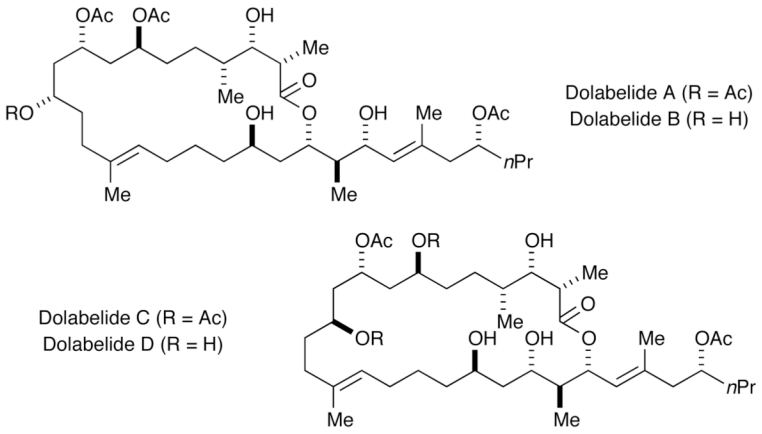


Figure 1.
The dolabelide family, isolated from *Dollabella auricularia*.

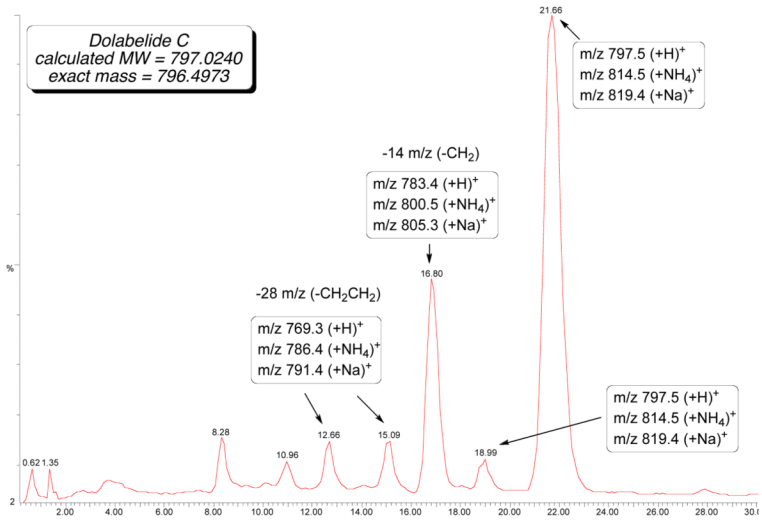


Figure 2.
LC-MS analysis of mixture from final RCM.

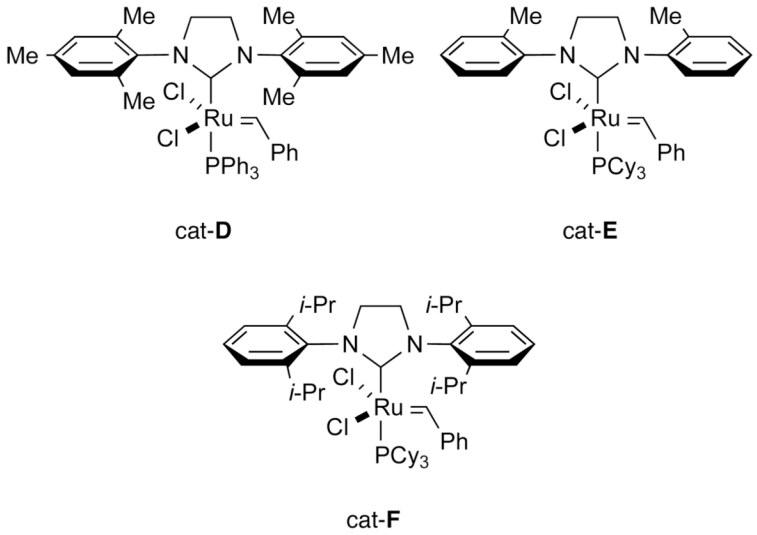
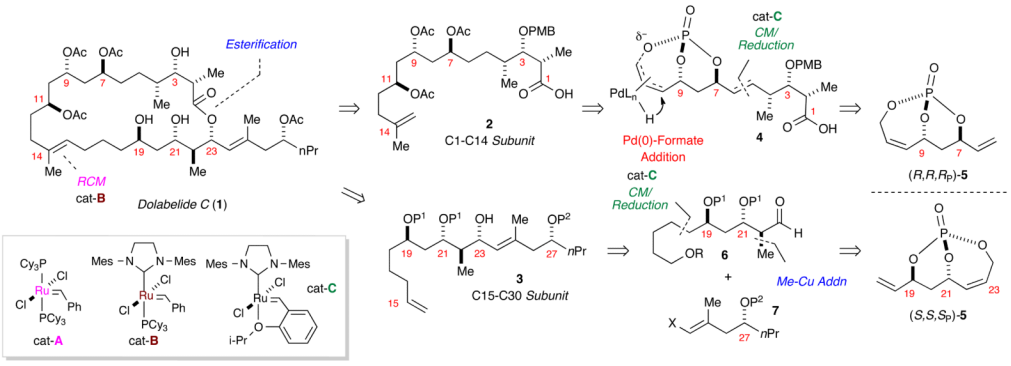
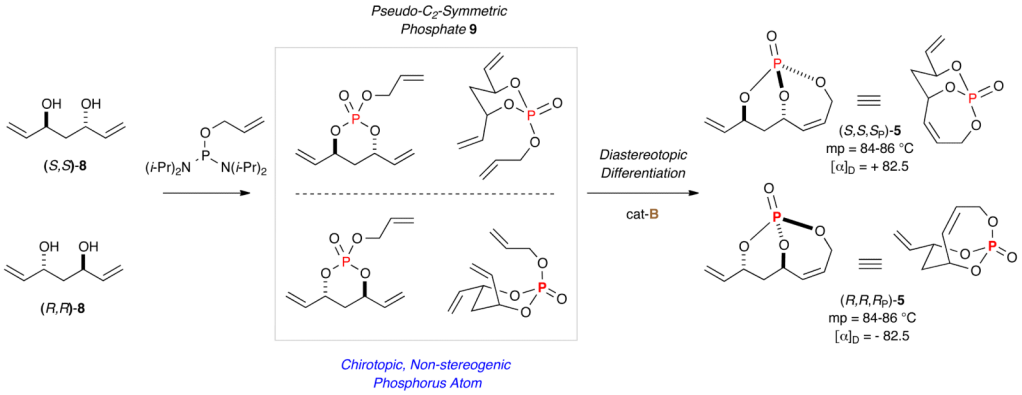


Figure 3.
Metathesis Catalysts Screened on Final RCM Step.

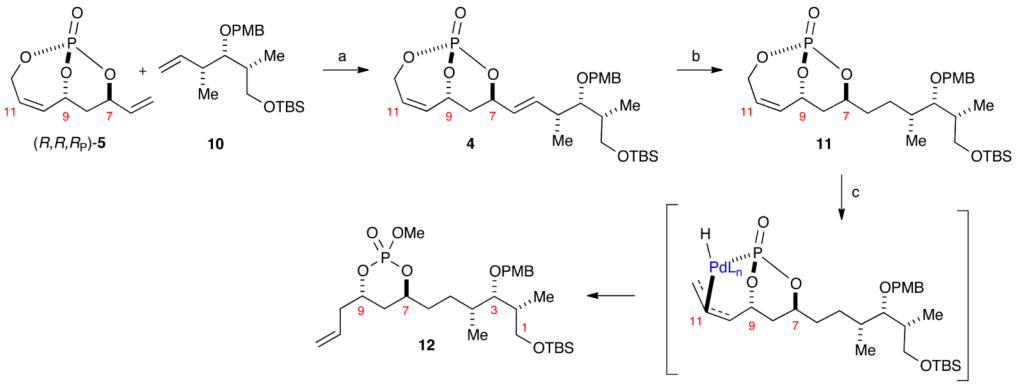


Scheme 1. Retrosynthesis of Dolabelide C



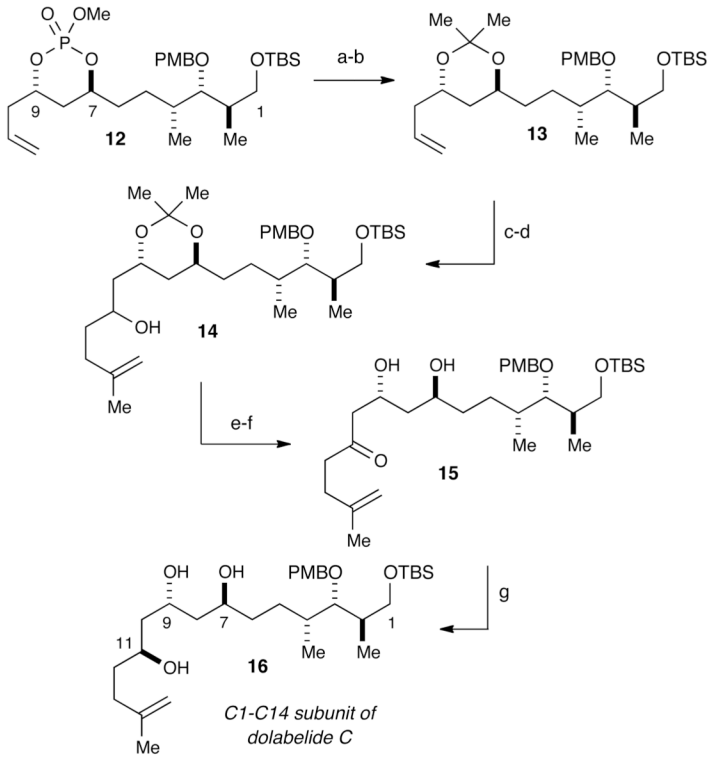
Scheme 2. Tether-Mediated Desymmetrization of C_2-Symmetric 1,3-*anti*-Diol 8[a]

[a]Reagents and Conditions: (a) Allyl tetraisopropylphosphorodiamidite, 1-*H*-tetrazole, MeCN, 2 h, rt, then *m*-CBPA, 1 h, 64%; (b) cat-**B**, CH_2Cl_2, 85-90%.



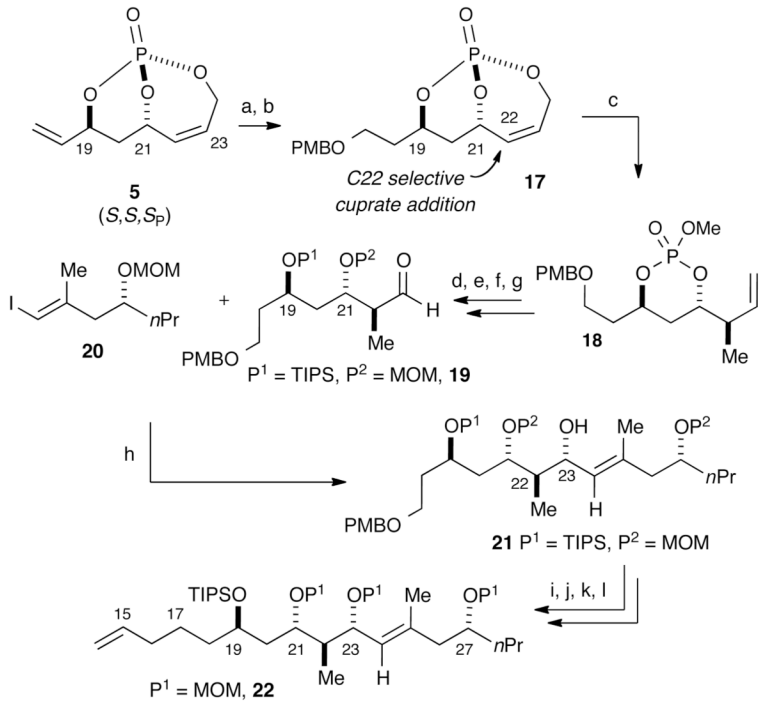
Scheme 3. Phosphate-Mediated Sequence for Assembly of the C1–C14 Subunit[a]

[a]Reagents and Conditions: (a) cat-**C** (6 mol %), DCE, 90 °C, 72%; (b) *o*-$NO_2C_6H_5SO_2NHNH_2$, Et_3N, CH_2Cl_2, 72%; (c) $Pd(OAc)_2$ (5 mol %), HCO_2H, Et_3N, DCE, 40 °C, then MeOH, $TMSCHN_2$, 87%. Abbreviations: DCE = dichloroethane.



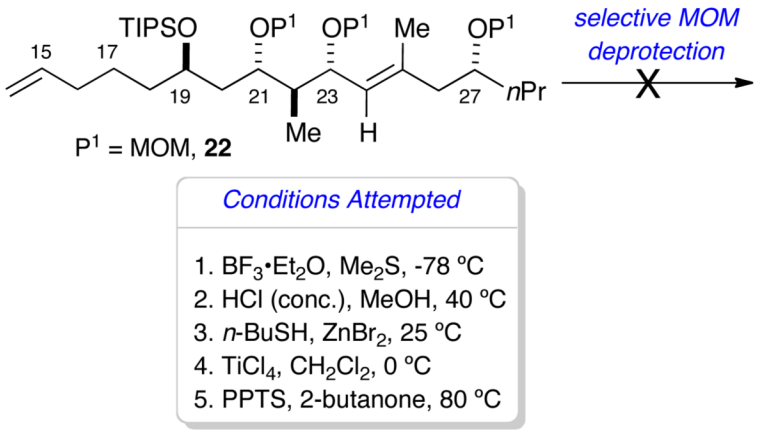
Scheme 4. Synthesis of C1–C14 Carbon Framework[a]

[a]Reagents and conditions: (a) $LiAlH_4$, Et_2O, 75%; (b) PPTS, 2,2-DMP, CH_2Cl_2, 96%; (c) O_3, pyridine, 1:1 MeOH:CH_2Cl_2, -78 °C, then Me_2S, 72%; (d) 1-Iodo-3-methyl-butene, Mg, Et_2O, -78 °C, 95%; (e) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 90%; (f) $CeCl_3$•$7H_2O$, H_2O/MeCN (1:7), 87%; (g) Et_2BOMe, $NaBH_4$, THF:MeOH 4:1, -78 °C, *ds* ≥ 20:1, 60% (95% *brsm*).

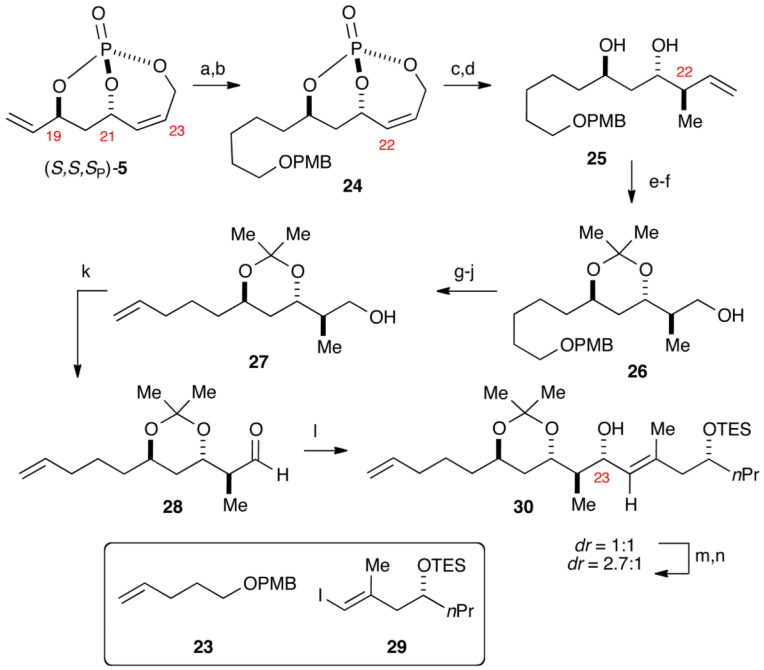


Scheme 5. First Generation Synthesis of the C15–C30 Subunit[a]

[a]Reagents and conditions: (a) 9-BBN, then H_2O, $NaBO_3$•$4H_2O$, 80%; (b) *p*-$OMeC_6H_4OCH_2OC{=}NH(CCl_3)$, PPTS, CH_2Cl_2, 89%; (c) 1. CuCN•2LiCl, Me_2Zn, THF, -30 °C to rt; 2. $TMSCHN_2$, MeOH, 87%; (d) $LiAlH_4$, Et_2O, 0 °C, 96%; (e) TIPSCl, imidazole, DMAP, CH_2Cl_2, 86%; (f) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 91%; (g) O_3, pyridine, -78 °C, Me_2S, 75%; (h) *t*-BuLi, $ZnBr_2$, **20**, then *n*-BuLi, (*R*,*S*,)-NME, then **19**, 65%, 11:1 *dr*; (i) MOMCl, *i*Pr_2NEt, DCE, 82%; (j) DDQ, pH 7 buffer, CH_2Cl_2, 92%; (k) TsCl, DABCO, CH_2Cl_2, 90%; (l) allylMgBr, CuI, -20 °C to 0 °C, 89%. Abbreviations: 9-BBN = 9-borabicyclo(3.3.1)nonane; TMS = trimethylsilyl; TIP = triisopropylsilyl; MOM = methoxymethyl; DMAP = 4-(dimethylamino)pyridine; NME = *N*-methylephedrine; DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; Ts = tosyl; DABCO = 1,4-diazabicyclo(2.2.2)octane.

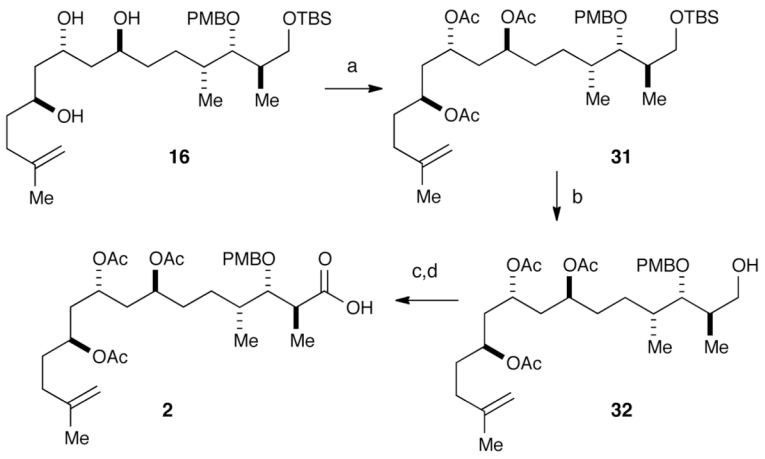


Scheme 6. MOM-deprotection Conditions



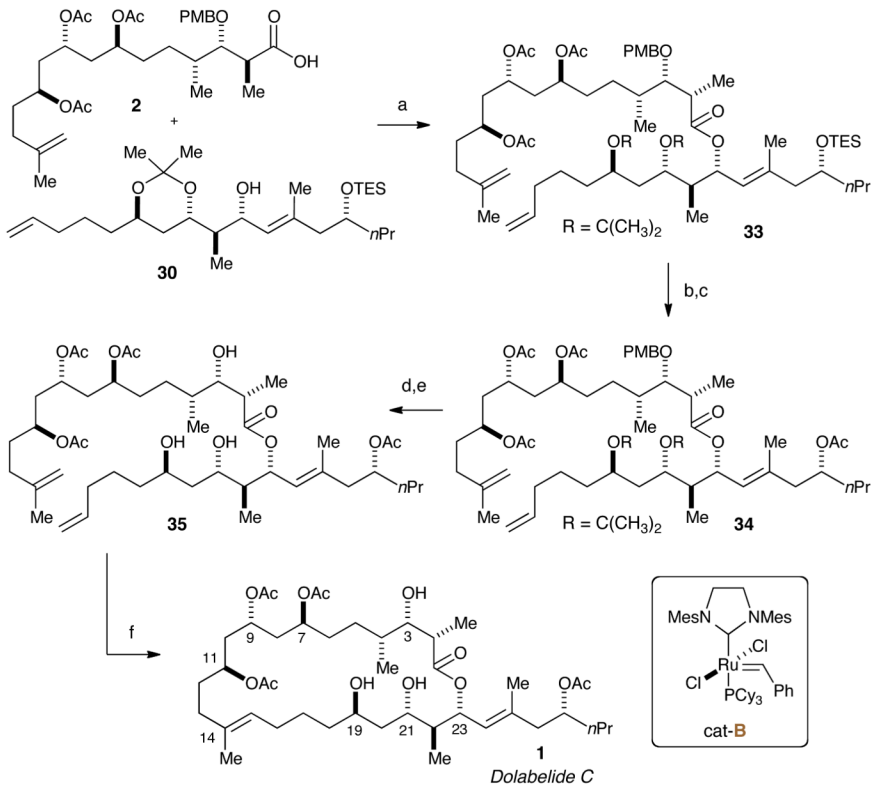
Scheme 7. Second Generation Synthesis of C15–C30 Subunit[a]

[a]Reagents and conditions: (a) cat-**C** (6 mol %), **23**, DCE, 90 °C, 82%; (b) *o*-$NO_2C_6H_5SO_2NHNH_2$, Et_3N, CH_2Cl_2, 75%; (c) 1. CuCN•2LiCl, Me_2Zn, THF, -30 °C to rt; 2. $TMSCHN_2$, MeOH, 91%; (d) $LiAlH_4$, Et_2O, 0 °C, 92%; (e) 2,2-DMP, PPTS, CH_2Cl_2, 96%; (f) OsO_4, NMO, *t*-BuOH/THF/ H_2O, then $NaIO_4$, Phosphate Buffer pH 7, then $NaBH_4$, EtOH, 0 °C, 81%; (g) TBSCl, pyridine, 95%; (h) H_2, Pd/C, EtOAc, $NaHCO_3$, 90%; (i) Ph_3P, I_2, imidazole, then *t*-BuOK, THF, 94%; (j) TBAF, THF, 98%; (k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt; (l) *t*-BuLi, Et_2O, **29**, -78 °C to 0 °C, 30 min, 28, -78 °C, ~1:1 *syn:anti*, 79% over 2 steps; (m) Dess-Martin, CH_2Cl_2, 85% n) $NaBH_4$, MeOH, 0 °C, 89%, ~2.7:1 *syn:anti*. Abbreviations: DMP = dimethoxypropane; PPTS = pyridinium *p*-toluenesulfonate; NMO = *N*-methylmorpholine *N*-oxide; TBS = *tert*-butyldimethylsilyl; TBAF = tetra-*n*-butylammonium fluoride.



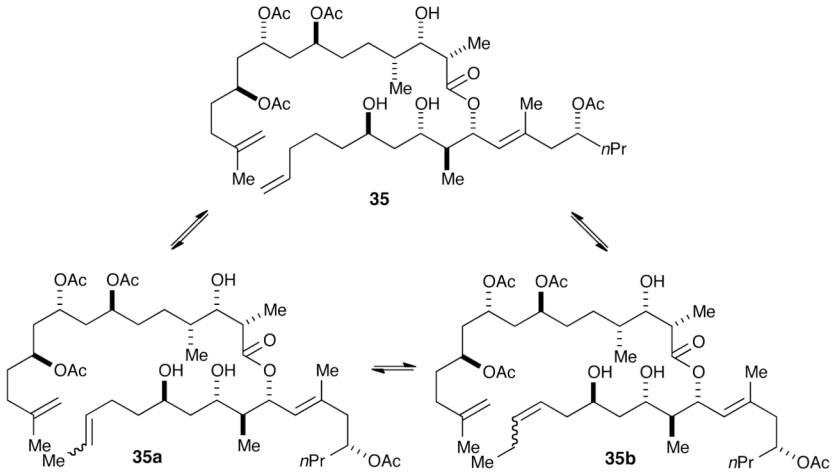
Scheme 8. Generation of ready-to-couple C1–C14 Subunit[a]

[a]Reagents and conditions: (a) Ac_2O, DMAP, pyridine, 95%; (b) TBAF, THF, 93%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (d) $NaClO_2$, 2-methyl-2-butene, H_3PO_4, 81% over 2 steps.



Scheme 9. Completion of Dolabelide C (1)[a]

[a]Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, toluene, 77%; (b) TBAF, 94%; (c) Ac_2O, pyridine, DMAP, 98%; (d) PPTS, 83%; (e) DDQ, Phosphate Buffer pH = 7, CH_2Cl_2, 95%; (f) cat-**B** (20 mol %), CH_2Cl_2 (0.5 mM), 57%, *E:Z* = ~1:1.



Scheme 10. Possible Isomerization Pathways from Metathesis Step

Table 1

Catalyst Screening of Final RCM.

Entry	Catalyst	Conversion	*E:Z*[a]	*E:Z*: By-Pdts[a]
1	cat-**B**	>99%	1:1	**1:1:0.17**
2	cat-**B**[b]	87%	1.2:1	1.2:1:0.26
3	cat-**D**	100%	1:1	1:1:0.80
4	cat-**E**	100%	1:1.1	1:1.1:0.45
5	cat-**F**	87%	1.2:1	1.2:1:0.61

[a] Ratios determined through peak area integration from LC-MS analysis of crude mixtures.

[b] Purified newly purchased catalyst through SiO_2 plug in 10:1 hexanes:EtOAc.

[c] All reactions were run with stepwise addition of 20 mol % catalyst over 6 h at 40 °C in 0.5 μM CH_2Cl_2.