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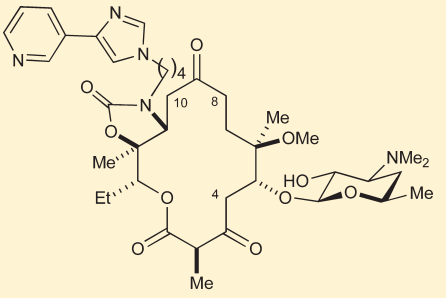
Total Synthesis of (−)-4,8,10-Tridesmethyl Telithromycin

Venkata Velvadapu, Tapas Paul, Bharat Wagh, Ian Glassford, Charles DeBrosse, and Rodrigo B. Andrade*

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, United States

Supporting Information

ABSTRACT: Novel sources of antibiotics are required to address the serious problem of antibiotic resistance. Telithromycin (**2**) is a third-generation macrolide antibiotic prepared from erythromycin (**1**) and used clinically since 2004. Herein we report the details of our efforts that ultimately led to the total synthesis of (−)-4,8,10-tridesmethyl telithromycin (**3**) wherein methyl groups have been replaced with hydrogens. The synthesis of desmethyl macrolides has emerged as a novel strategy for preparing bioactive antibiotics.



(-)-4,8,10-Tridesmethyl Telithromycin

1. INTRODUCTION

The incessant rise in antibiotic-resistant bacteria is a serious public health issue.[1,2] To address this need, we have initiated a structure-based drug design program wherein desmethyl analogues (i.e., $CH_3 \rightarrow H$) of the third-generation macrolide antibiotic telithromycin (**2**) are prepared via chemical synthesis (Figure 1). Inspiration for desmethylation came from Steitz's analysis of X-ray crystal structures of **1** and **2** bound to the 50S ribosomal subunits of *H. marismortui*, which explains how ribosomal point mutations at critical residues (i.e., A2058G, *E. coli* numbering) confer antibiotic resistance.[3]

Most modern macrolide antibiotics are semisynthetic analogues of erythromycin A, of which clarithromycin, azithromycin, and telithromycin are examples.[4] As a part of our desmethylation approach to address antibiotic resistance, herein we report the details of our synthetic efforts culminating in the total synthesis of (−)-4,8,10-tridesmethyl telithromycin (**3**).[5] We have employed a de novo synthetic strategy to access this simplified ketolide scaffold.

2. RESULTS AND DISCUSSION

2.1. Retrosynthesis. Our approach toward the synthesis of (−)-4,8,10-tridesmethyl telithromycin (**3**) is shown in Scheme 1. The retrosynthetic strategy employed was guided by prior art in the field. Specifically, we envisioned the use of a sequential one-pot carbamoylation/intramolecular aza-Michael method developed by Baker and co-workers at Abbott to install the C11−C12 oxazolidinone with pendant butylarene to access **4** from **5**.[6] In fact, this tactic was employed by Hoechst Marion Roussel (HMR) with **6** in their synthesis of HMR-3647 (i.e., telithromycin).[7] Glycosylation of a C5 hydroxyl acceptor derived from **5** would be accomplished with known desosamine donor **7**.[8] To prepare macroketolactone **5**, we utilized two tactics employed in the synthesis of the related ketolide, narbonolide: (1) the intramolecular Nozaki−Hiyama−Kishi (NHK) reaction employed by Sherman and Fecik[9] and (2) the intramolecular ring-closing metathesis (RCM) strategy employed by Kang and co-workers.[10] The NHK and RCM substrates could be accessed by an intermolecular Yamaguchi esterification,[11] which then leads to fragments **8**, **9** and **10**, the latter of which will be subjected to the Evans aldol reaction to set stereocenters at C2 and C3.[12] Finally, the Sharpless asymmetric dihydroxylation (AD) reaction[13] of olefin **11**, which is prepared via a Johnson−Claisen orthoester rearrangement, would establish the requisite configurations and oxidation states at both C5 and C6.

2.2. Synthesis. The preparation of fragments **8** and **9** was accomplished from aldehyde **15**, which was synthesized from **12** (Scheme 2). Kinetic resolution of *rac*-**12** via the Sharpless asymmetric epoxidation protocol provided enantioenriched alcohol **13** in 32% yield (92% ee).[14] Regioselective ring opening with pivalic acid and $Ti(O\text{-}iPr)_4$, acetonide formation, and treatment with MeLi afforded alcohol **14** (59% over three steps).[15] Swern oxidation of **14** to aldehyde **15**[16] proceeded without incident. At this point, **15** was subjected to the Corey−Fuchs alkynylation protocol (59% yield from **14**).[17] Hydrostannation of the intermediary alkyne with Bu_3SnH and catalytic AIBN proceeded with excellent stereocontrol to afford an (*E*)-vinyl stannane,[18] which was converted to vinyl iodide **16** with I_2 in 80% over two steps. Removal of the acetonide in **16** with 1 M HCl (aq) furnished fragment **8** (72% yield). Access to fragment **9** was accomplished by (1) Wittig methylenation of **15** and (2) removal of the acetonide in **17** under acidic conditions in 53% yield from **14**.[16]

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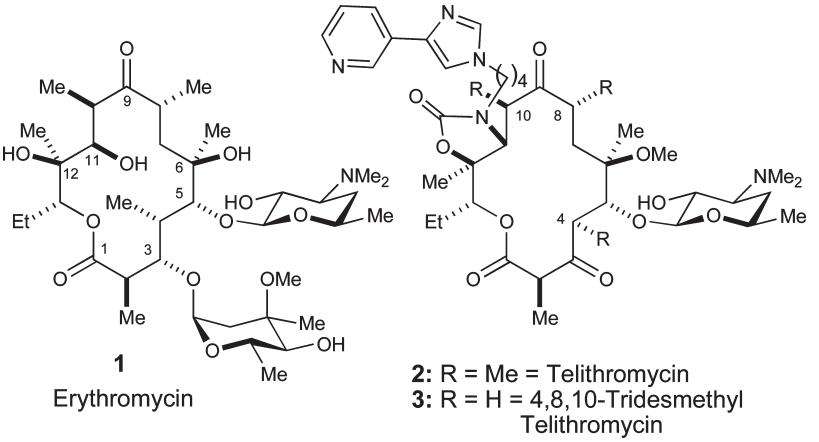
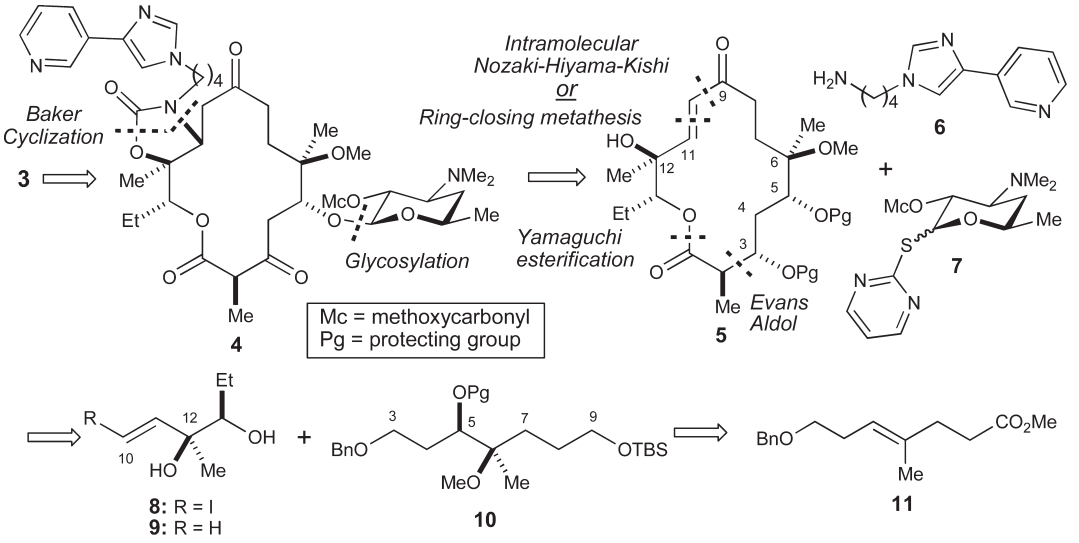


Figure 1. Structures of erythromycin (**1**), telithromycin (**2**), and novel analogue (−)-4,8,10-tridesmethyl telithromycin (**3**).

Scheme 1. Retrosynthesis of (−)-4,8,10-Tridesmethyl Telithromycin (3)



With fragments **8** and **9** in hand, attention was turned to the preparation of fragment **10** (Scheme 1). To this end, commercially available 3-benzyloxy-propanol (**18**) was oxidized using the Swern protocol (Scheme 3). Addition of 2-propenyl MgBr and subsequent Johnson−Claisen orthoester rearrangement afforded enoate **11** in 48% overall yield. Reduction of the ester and protection of the newly formed alcohol as its *tert*-butyldimethylsilyl (TBS) ether provided **19** (78% yield over two steps).[19] Sharpless dihydroxylation (AD mix-β) established the requisite stereochemistry of the hydroxyls at C5 and C6 in 91% yield (er >20:1).[13] Selective protection of the secondary C5 alcohol with TBSOTf and 2,6-lutidine followed by treatment with NaH and MeI resulted in the formation of **24** as opposed to the desired regioisomer **23** in 70% over two steps via a 1,4 silyl O→O migration (Scheme 3).[20] This migration came to light when we succeeded in obtaining a single crystal X-ray structure of cyclized product **35** (see Scheme 5). A survey of the literature revealed this to be a common undesired pathway that attends the generation of a nucleophilic alkoxide bearing a tethered trialkylsilyl ether.[21] With the undesired regioisomer in hand, we pressed forward.

Hydrogenolysis of benzyl ether **24** afforded alcohol **25** in 80% yield (Scheme 4). Swern oxidation of **25** to aldehyde **26** was followed by the Evans aldol reaction with propionimide **27**, which set the stereochemistry at C2 and C3 positions in 78% yield (dr >20:1) over two steps. Protection of the C3 hydroxyl in **28** with TBSOTf and removal of the auxiliary with LiOOH delivered acid **30** in 85% yield over two steps. Chemoselective Yamaguchi esterification of **30** and diol **8** afforded ester **31** in 74% yield.

To prepare the intramolecular NHK substrate **33**, the primary TBS ether of **31** was selectively removed under acidic conditions in 85% yield (Scheme 5). Oxidation of alcohol **32** with the Dess−Martin periodinane (DMP)[22] and $NaHCO_3$ proceeded smoothly to furnish **33** in 80% yield. The key step was thus effected by adding excess $CrCl_2$ and catalytic $NiCl_2$ to **33** in degassed DMSO (0.0025 M) at rt for 16 h, affording a 50% yield of **34** as a 1:1 mixture of diastereomeric allylic alcohols at C9. Subsequent oxidation of **34** with DMP and pyridine furnished macroketolactone **35**, which fortunately was a solid. Recrystallization of **35** from Et_2O by slow evaporation resulted

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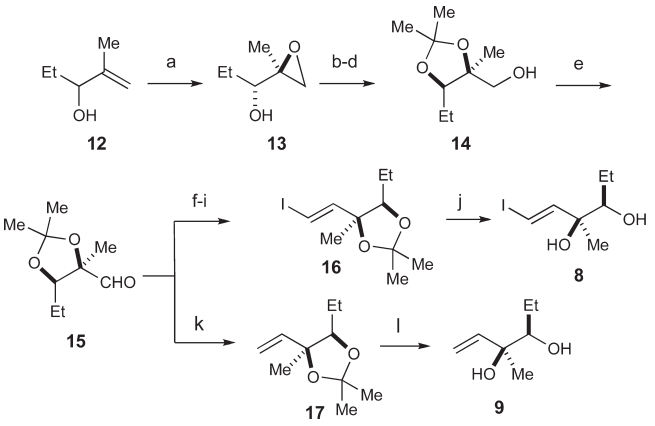
in crystals suitable for X-ray analysis. To our surprise, the groups on C5 and C6 positions in regioisomeric **33** had been transposed.

Scheme 2. Synthesis of Fragments 8 and 9 from Aldehyde 15[a]

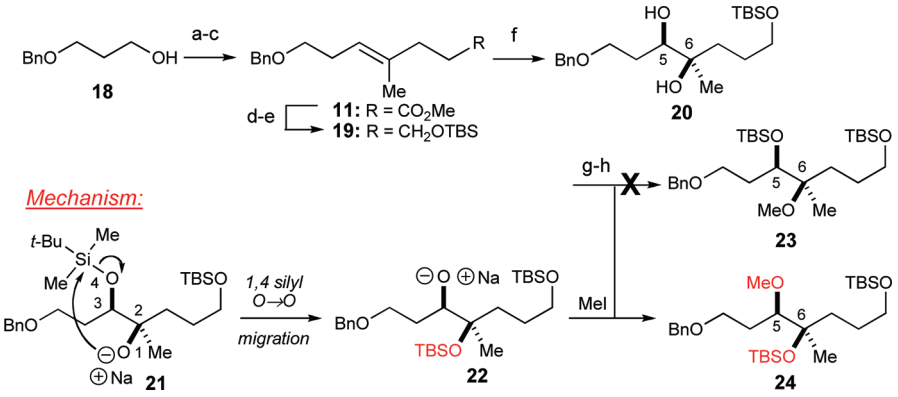


[a] Reagents and conditions: (a) (−)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 32% (92% ee); (b) PivOH, Ti(O*i*-Pr)$_4$; (c) $Me_2C(OMe)_2$, PPTS; (d) MeLi, 59% over three steps; (e) $(COCl)_2$, DMSO, Et_3N; (f) CBr_4, Ph_3P, CH_2Cl_2, 65% over two steps; (g) *n*-BuLi, THF, 90%; (h) cat. AIBN, Bu_3SnH, C_6H_6; (i) I_2, CH_2Cl_2, 80% over two steps; (j) 1 N HCl (aq), 72%; (k) $Ph_3P{=}CH_2$; (l) 1 N HCl (aq), 53% over three steps from **14**.

To rectify this issue, we revisited the methylation reaction responsible for the attendant transposition. We reasoned that employing a more reactive methylating agent (e.g., Meerwein's salt) would avoid the unwanted 1,4 O→O silyl migration enabled by reactive metal alkoxide **21** (Scheme 3). In addition, we recruited the TES protecting group to establish an orthogonal set at C3 and C5 and offer recourse in the event a regioselective glycosylation was unsuccessful (Scheme 6). To prepare substrate **36**, we protected the secondary C5 hydroxyl as a TES ether under standard conditions (90% yield). Methylation of **36** with Me_3OBF_4 (i.e., Meerwein's salt) and proton sponge in CH_2Cl_2 afforded desired regioisomer **38**.[23] Moreover, subjection to rearrangement conditions (i.e., NaH and MeI) furnished the expected, undesired regioisomer **37**.

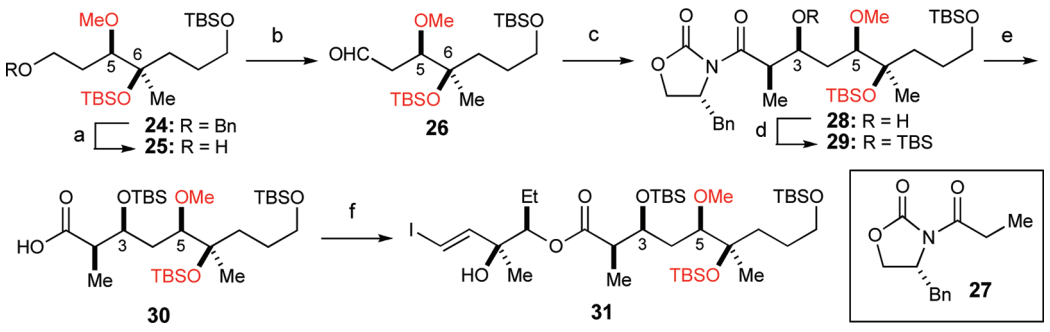
With correct regioisomer **38** in hand, we reiterated the sequence employed in Schemes 4 and 5. Thus, removal of the benzyl ether in **38** afforded alcohol **39** in 85% yield (Scheme 7). Oxidation of **39** with the Swern protocol followed by the Evans aldol reaction furnished **41** in 78% yield (dr >20:1). Protection of the C3 hydroxyl with TBSOTf and removal of the auxiliary with LiOOH resulted in acid **43** in 85% yield over two steps. Yamaguchi esterification of **43** and **8** delivered ester **44** in 75% yield. Removal of the primary TBS group with TBAF/AcOH (60% yield) and subsequent DMP oxidation (78% yield) set the stage for the intramolecular NHK on **46**. In the event, a 50% yield of **47** was obtained. Oxidation of the ~1:1 diastereomeric mixture of allylic alcohols at C9 furnished desired macroketolactone **48** in 80% yield.

Scheme 3. Unexpected Synthesis of Regioisomeric Fragment 24[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N; (b) 2-propenyl MgBr, THF; (c) $(MeO)_3CCH_3$, $EtCO_2H$, 48% over three steps; (d) $LiAlH_4$, Et_2O; (e) TBSCl, imidazole, 78% over two steps; (f) AD mix-β, 91% (er >20:1); (g) TBSOTf, 2,6-lutidine; (h) NaH, MeI, 70% over two steps.

Scheme 4. Elaboration of 24 into Macrocyclization Precursor 31[a]



[a] Reagents and conditions: (a) H_2, Pd/C, 80%; (b) $(COCl)_2$, DMSO, Et_3N; (c) **27**, Bu_2BOTf, Et_3N, 78% (dr >20:1) over two steps; (d) TBSOTf, 2,6-lutidine; (e) LiOOH, THF, H_2O, 85% over two steps. (f) $Cl_3PhCOCl$, Et_3N, DMAP, **8**, 74%.

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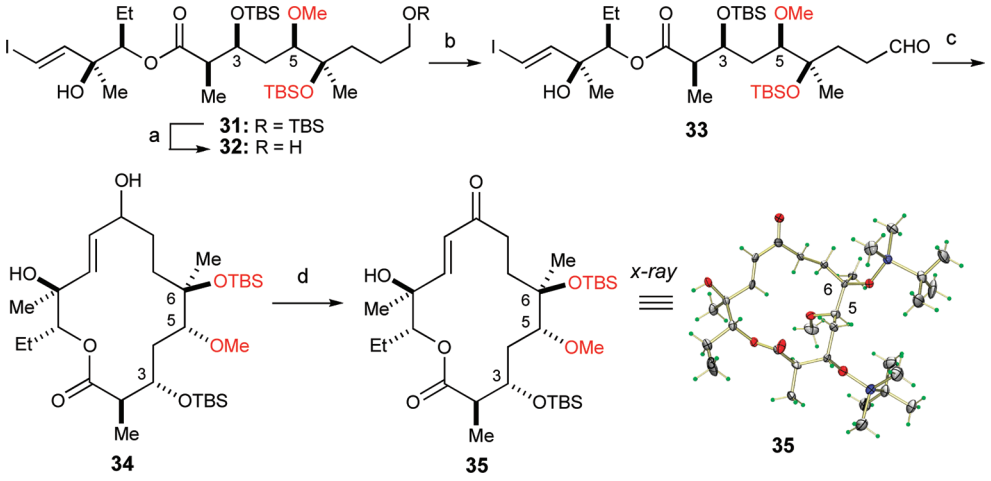
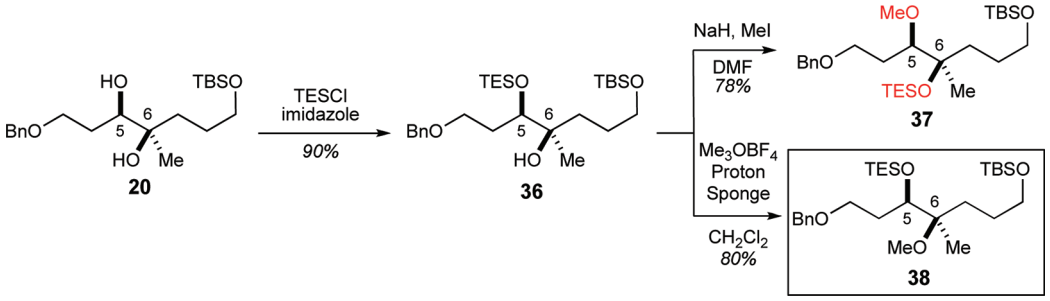
Scheme 5. Macrocyclization of 33 and X-ray Structure of Macroketolactone 35[a]



[a] Reagents and conditions: (a) CSA, MeOH, 85%; (b) DMP, $NaHCO_3$, 80%; (c) $CrCl_2$, cat. $NiCl_2$, DMSO, 50%; (d) DMP, Pyridine, 82%.

Scheme 6. Synthesis of Both Regioisomeric Fragments 37 and 38 (Desired)



In parallel, we developed a scalable RCM route inspired by Kang's synthesis of narbonolide (Scheme 8).[24] To this end, we employed Yamaguchi's method to couple acid **43** and diol **9** to access ester **49** in 75% yield. Selective removal of the primary TBS ether with TBAF/AcOH afforded alcohol **50** (65% yield). Oxidation of **50** with DMP, treatment with vinyl MgBr, and subsequent oxidation with DMP furnished RCM substrate **51** in 60% over three steps. The RCM reaction proceeded smoothly in CH_2Cl_2 (0.01 M) at rt for 20 h with 20 mol % Grubbs second generation catalyst to provide **48** in 60% yield.[25]

With macroketolactone **48** in hand, attention was directed at the installation of the desosamine moiety onto the C5 hydroxyl. To this end, the C5 TES ether was removed under various conditions (e.g., *p*-TsOH, PPTS, HF). Unfortunately, this was accompanied by ketalization at the C9 position (Scheme 9) as a consequence of the acidic conditions employed to remove the TES group

Treatment of **48** with TBAF (i.e., basic conditions) resulted in the removal of both silyl groups, affording triol **54** in 70% yield (Scheme 10). Studies by Martin[26] and Toshima and Tatsuta[27] both demonstrated the viability of regioselective glycosylations in closely related erythronolide systems. Attempted regioselective glycosylation of **54** at C5 in the presence of C3 with donor **7** under the agency of AgOTf and 2,6-di-*t*-Bu-4-Me-pyridine (DTBMP) led exclusively to the decomposition of starting material.

Recourse at this point was made to a more conservative strategy. Specifically, we chose to install desosamine with the C3 position blocked, assuming the secondary C5 hydroxyl would be more reactive than the hindered tertiary C12 hydroxyl. To test this plan, the C9 ketone of **48** was first subjected to a Luche reduction to give an inseparable 7:1 mixture of diastereomers that was carried throughout the synthesis (Scheme 11).[28] Treatment with *p*-TsOH in methanol selectively removed the C5 TES ether in the presence of the C3 TBS ether to afford triol **55**. Regioselective protection of the more reactive allylic C9 hydroxyl with TESCl and imidazole furnished diol **56**. Glycosylation of **56** with donor **7**, AgOTf, and DTBMP resulted in the desosamine at the C12 position, as opposed to the desired C5. This was confirmed by (1) 2D NMR experiments, particularly an HMBC correlation between the anomeric proton in desosamine with the C12 carbon and (2) removal of C9 TES and oxidation of product with DMP resulted in a triketo species (structure not shown).

We speculate that glycosylation at the more hindered C-12 hydroxyl is due to two factors. First, the C-12 hydroxyl in **56** is allylic and therefore more nucleophilic (and less sterically demanding) than Tatsuta's C-12 substrate, which was flanked by a 9,11-isopropylidene ketal.[27] Second, conformational properties of macrolactone acceptor **56** may render C-5 more sterically shielded. The unexpected glycosylation at the more hindered position necessitated protection at this position as well (Scheme 12). Accordingly, macroketolactone **48** was first reduced under Luche conditions. Silylation of *both* C9 and C12 hydroxyls with TESOTf and 2,6-lutidine and subsequent

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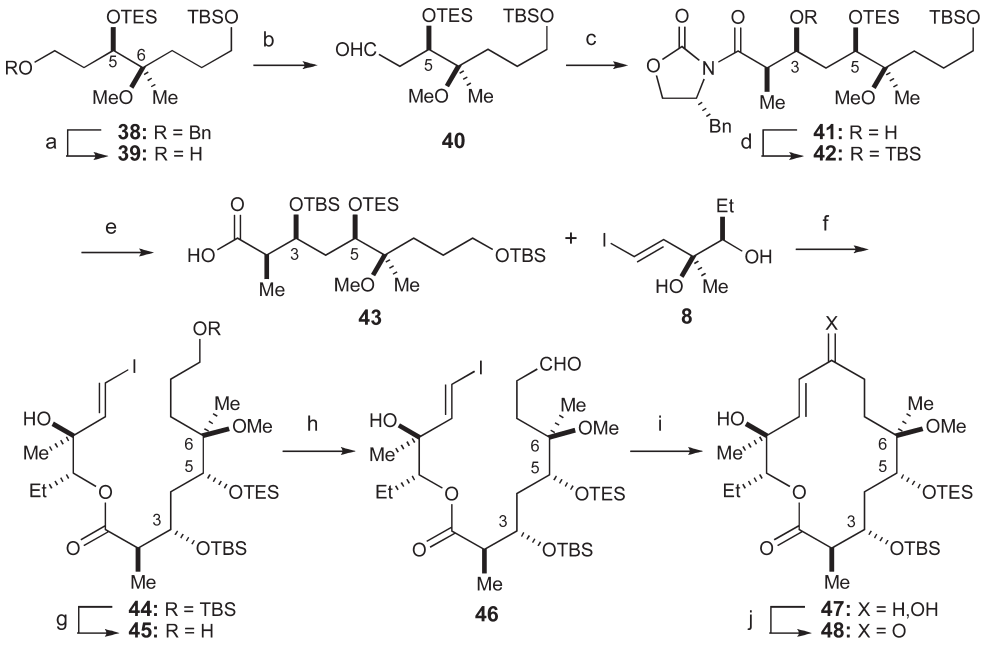
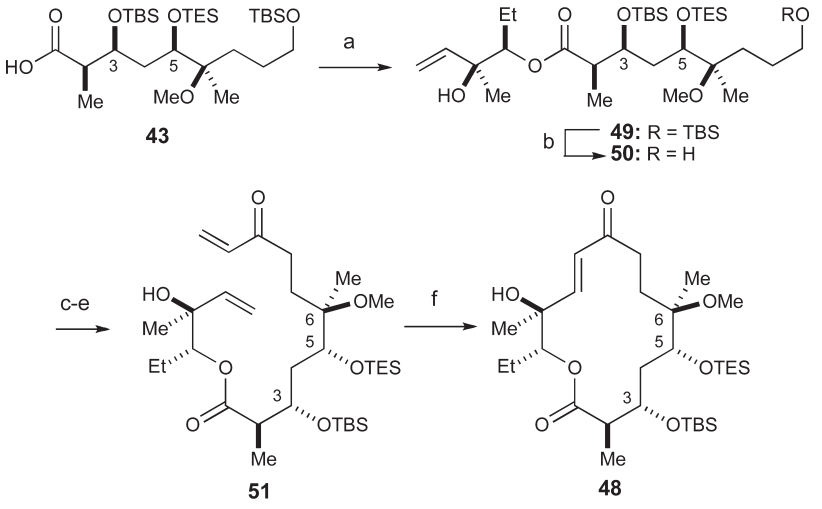
Scheme 7. Intramolecular Nozaki–Hiyama–Kishi (NHK) Route to Macroketolactone 48[a]



[a] Reagents and conditions: (a) H_2, Pd/C, 85%; (b) $(COCl)_2$, DMSO, Et_3N; (c) **27**, Bu_2BOTf, Et_3N, dr >20:1, 78% over 2 steps; (d) TBSOTf, 2,6-lutidine; (e) LiOOH, THF, H_2O, 85% over two steps; (f) $Cl_3PhCOCl$, Et_3N, DMAP, 75%; (g) TBAF, AcOH, 60%; (h) DMP, $NaHCO_3$, 78%; (i) $CrCl_2$, cat. $NiCl_2$, DMSO, 50%; (j) DMP, 80%

Scheme 8. Alternate Ring-Closing Metathesis (RCM) Route to Macroketolactone 48[a]



[a] Reagents and conditions: (a) $Cl_3PhCOCl$, Et_3N, DMAP, **9**, 78%; (b) TBAF, AcOH, 65%; (c) Dess–Martin periodinane, $NaHCO_3$; (d) vinyl MgBr, THF; (e) Dess–Martin periodinane, CH_2Cl_2, 60% over three steps; (f) 20 mol % Grubbs II cat., 60%.

treatment with *p*-TsOH selectively afforded **58** wherein only the tertiary C12 hydroxyl remained protected (52% yield over three steps). Regioselective silylation of the allylic C9 alcohol with TESCl furnished **59**. Glycosylation at the C5 position with donor **7** was accomplished in 50% yield over two steps. Fluoride-mediated cleavage of silyl ethers at C9, C12 with TBAF followed by DMP oxidation at C9 afforded glycosylated macroketolactone **62** (84% yield over two steps). The structure of **62** was rigorously confirmed by 2D NMR experiments (see Supporting Information).

The endgame for (−)-4,8,10-tridesmethyl telithromycin (**3**) began with a sequence employed by HMR to prepare C11–C12 oxazolidinones, originally developed by Baker and co-workers at Abbott.[6] Activation of the C12 alcohol in **62** with NaH and carbonyldiimidazole (CDI) followed by treatment with butylamine **6**[7] effected a tandem carbamoylation/intramolecular aza-Michael sequence to stereoselectively afford oxazolidinone **63** in 35% overall yield (Scheme 13). Removal of the C3 TBS ether with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F) proceeded in 70% yield.[29] Alternative fluoride-mediated methods

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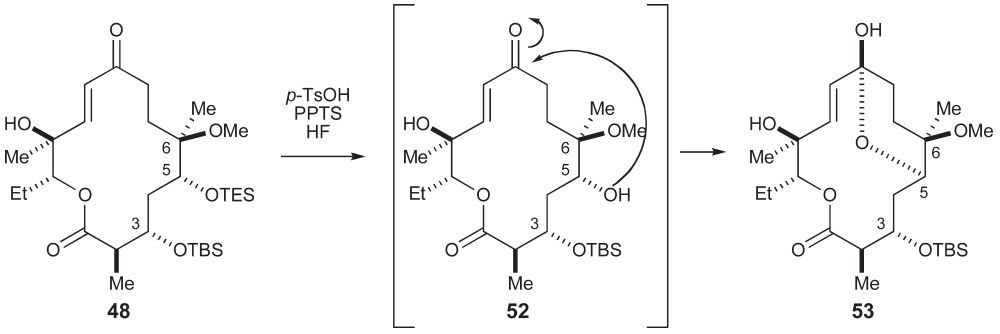
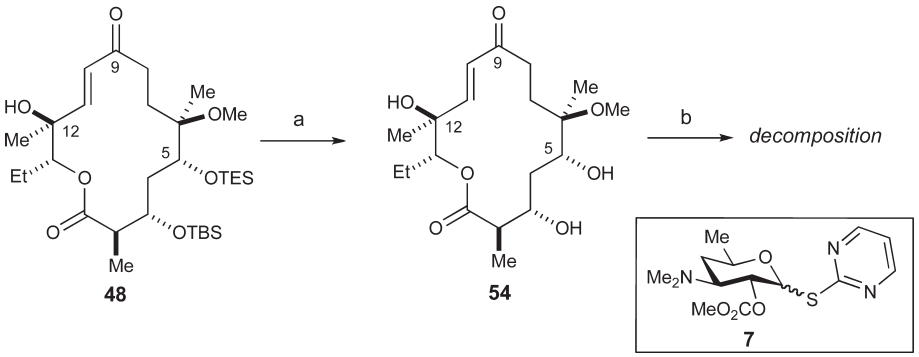
Scheme 9. Selective Removal of C5 TES Group and Attendant Ketalization

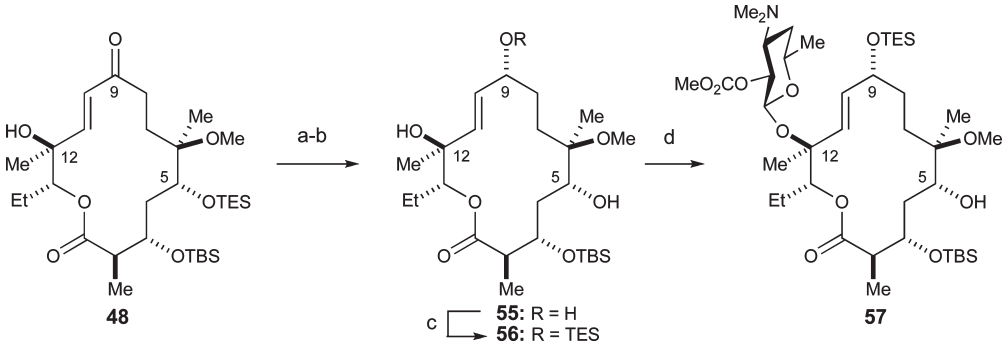


Scheme 10. Unsuccessful Regioselective Glycosylation of Diol 54 with Donor 7[a]



[a] Reagents and conditions: (a) TBAF, 4 Å MS, THF, 70%; (b) **7**, AgOTf, DTBMP.

Scheme 11. Unexpected Glycosylation of Tertiary C12 Hydroxyl in the Presence of Secondary C5 Hydroxyl[a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, dr = 7:1; (b) *p*-TsOH, MeOH, 75%; (c) TESCl, imidazole; (d) **7**, AgOTf, DTBMP, 42% over two steps.

(e.g., TBAF, HF·pyridine, HF) were all inferior. Corey–Kim oxidation furnished the C3 ketone **4**.[30] Finally, methanolysis removed the methyl carbonate from the C2′ position of desosamine to deliver (−)-4,8,10-tridesmethyl telithromycin (**3**) in 45% overall yield.

3. CONCLUSION

In conclusion, we have prepared (−)-4,8,10-tridesmethyl telithromycin (**3**), a desmethyl analogue of FDA-approved ketolide antibiotic telithromycin (**2**), by total synthesis. Both the intramolecular NHK and RCM reactions were used to prepare the 14-membered ring. Glycosylation using known desosamine donor **7** and Baker's sequential one-pot carbamoylation/intramolecular aza-Michael method with amine **6** were representative key steps. Ultimately, we were able to prepare a total of 12.1 mg of analogue **3** in 42 steps (31 steps in the longest linear sequence), which was active against several wild type and resistant bacterial strains.[5]

4. EXPERIMENTAL SECTION

(*R*)-5-((*R*)-3-(Benzyloxy)-1-methoxypropyl)-2,2,3,3,5,10,10,11,11-nonamethyl-4,9-dioxa-3,10-disiladodecane (24). To a solution of diol **20** (2.5 g, 18.29 mmol) in CH_2Cl_2 (30 mL) at −20 °C were added 2,6-lutidine (2.10 g, 19.59 mmol) and TBSOTf (2.07 g,

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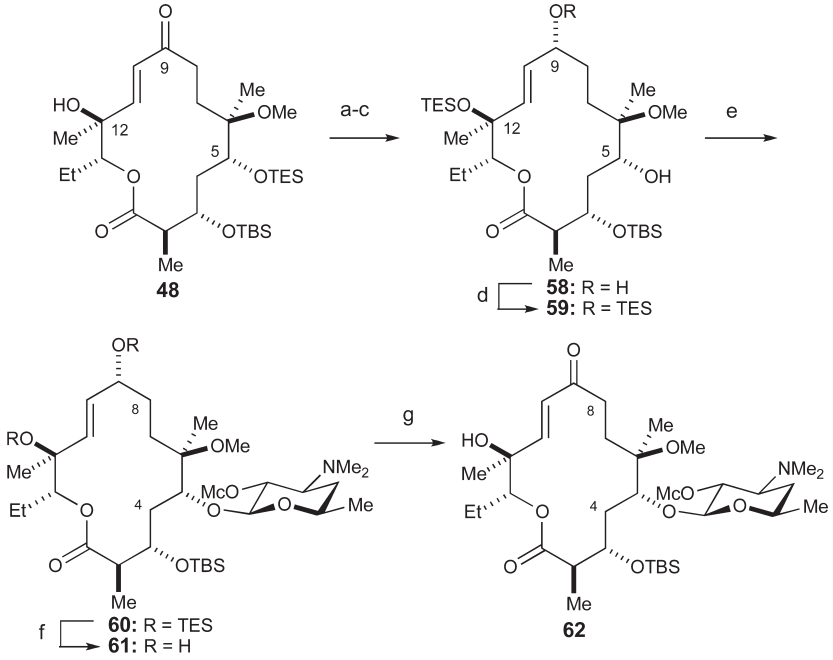
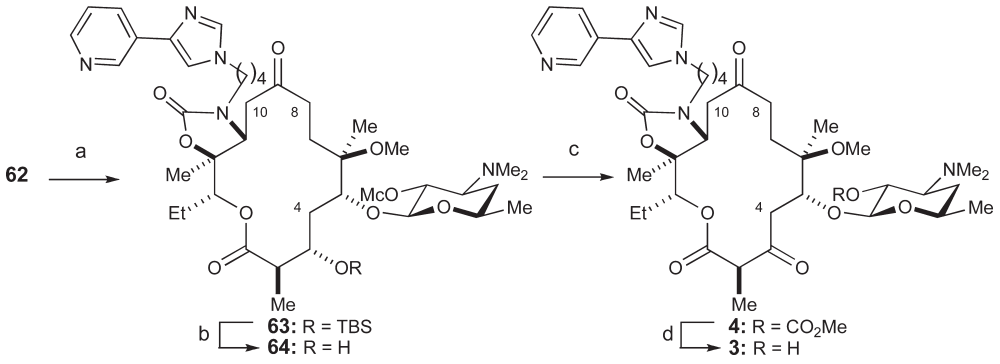
Scheme 12. Synthesis of Macroketolactone 62[a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, dr = 7:1; (b) TESOTf, 2,6-lutidine; (c) *p*-TsOH, 52% over three steps; (d) TESCl, imidazole; (e) **7**, AgOTf, DTBMP, 50% over two steps; (f) 1 M TBAF, THF, 95%; (g) DMP, CH_2Cl_2, 88%.

Scheme 13. Endgame for (−)-4,8,10-Tridesmethyl Telithromycin (3)[a]



[a] Reagents and conditions: (a) NaH, CDI, THF/DMF then **6**, 35%; (b) TASF, DMF/H_2O, 70%; (c) NCS, DMS, Et_3N; (d) MeOH, 45% over two steps.

7.83 mmol). After 2 h, the reaction was quenched by adding satd aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, azeotroped with toluene (20 mL), and dried under high vacuum. The residue was dissolved in THF (130 mL), MeI (2.01 g, 32.65 mmol) was added, and the solution was cooled to 0 °C. Sodium hydride (0.78 g, 32.65 mmol) was added slowly in portions. The reaction mixture was warmed to rt and stirred for 16 h. The reaction mixture was quenched by adding MeOH (30 mL) followed by H_2O (50 mL) at 0 °C. The reaction mixture was diluted with Et_2O (150 mL), and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.4:1) to afford 2.9 g (70%) of **24** as colorless oil. $[\alpha]^{23}_D$ +9.4° (*c* 1.8, CH_2Cl_2); IR (film) 2880, 1475, 1422, 1361, 1055, 733, 696 cm^{-1}; ^1H NMR (400 MHz) δ 7.27−7.17 (m, 5H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 3.53−3.47 (m, 4H), 3.33 (s, 3H), 3.08 (dd, *J* = 10.0, 2.2 Hz, 1H), 1.90−1.87 (m, 1H), 1.55−1.34 (m, 5H), 1.14 (s, 3H), 0.82 (s, 9H), 0.80 (s, 9H), 0.02 (s, 6H), −0.04 (s, 6H); ^{13}C NMR (100 MHz) δ 138.6, 128.3 (2), 127.5 (2), 127.4, 84.9, 78.4, 72.8, 67.8, 63.7, 60.7, 35.1, 30.8, 27.0, 26.1 (3C), 26.0 (3C), 24.0, 18.4, 18.3, −1.8, −1.9, −5.3 (2); HRMS (FAB) calcd for $C_{28}H_{54}O_4Si_2$ + Na 533.3458, found 533.3442.

(3*R*,4*R*)-4,7-Bis((*tert*-butyldimethylsilyl)oxy)-3-methoxy-4-methylheptan-1-ol (25). To a solution of ether **24** (2.9 g, 5.67 mmol) in EtOH (56 mL) was added 10% Pd/C (0.6 g, 0.56 mmol) under an atmosphere of H_2. The reaction mixture was followed 4−8 h (TLC control). The reaction mixture was filtered through a Celite plug, which had been previously washed with EtOAc. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.8:1) to afford 1.9 g (80%) of **25** as a colorless oil. $[\alpha]^{23}_D$ +6.0° (*c* 6.8, CH_2Cl_2); IR (film) 3306, 2953, 2928, 2885, 1471, 1462, 1253, 1098, 1055, 831, 811, 770 cm^{-1}; ^1H NMR

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(400 MHz) δ 3.78−3.72 (m, 2H), 3.57−3.52 (m, 2H), 3.48 (s, 3H), 3.20 (dd, J = 10.0, 2.8 Hz, 1H), 2.40 (bs, 1H), 1.82−1.76 (m, 1H), 1.65−1.39 (m, 5H), 1.21 (s, 3H), 0.87 (m, 9H), 0.84 (s, 9H), 0.95 (m, 6H), 0.02 (s, 6H); ^{13}C NMR (100 MHz) δ 86.6, 78.6, 63.6, 61.0, 60.8, 35.4, 33.0, 26.9, 26.0 (3C), 25.9 (3C), 23.9, 18.3, 18.2, −1.8, −1.9, −5.4 (2C); HRMS (FAB) calcd for $C_{21}H_{48}O_4Si_2$ + Na 443.2989, found 443.2973.

(*R*)-4-Benzyl-3-((2*R*,3*S*,5*R*,6*R*)-6,9-bis((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-5-methoxy-2,6-dimethylnonanoyl)oxazolidin-2-one (28). To a solution of oxalyl chloride (0.61 g, 4.86 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added DMSO (0.79 g, 10.12 mmol) dropwise. After 10 min of stirring, alcohol **25** (1.70 g, 4.05 mmol) in CH_2Cl_2 (10 mL) was added via cannula, and the reaction mixture was stirred at −78 °C for 45 min. Triethylamine (1.02 g, 10.12 mmol) was added dropwise by cannula, and the reaction mixture was slowly warmed to rt. After 2 h, the reaction was quenched with dropwise addition of H_2O (10 mL). The organic layer was separated and washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was dissolved in Et_2O (50 mL), filtered through a plug of silica gel using ether, concentrated, and dried under high vacuum. This material was used directly without further purification. To a solution of (*R*)-4-benzyl-3-propionyl-2-oxazolidinone (**27**) (0.94 g, 4.05 mmol) in CH_2Cl_2 (20 mL) were added dibutylborontriflate (5.30 mL of a 1.0 M solution in CH_2Cl_2, 5.26 mmol) and triethylamine (0.61 g, 6.07 mmol) dropwise at 0 °C. The solution was cooled to −78 °C, and to this was added the aldehyde (1.70 g, 4.05 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The resulting solution was stirred for 20 min at −78 °C. After warming the solution to 0 °C, the reaction mixture was stirred an additional hour. The reaction was terminated by adding a pH 7 aq phosphate buffer solution (0.2 M aq sodium hydrogen phosphate/0.1 M aq citric acid, 82:18, 8.0 mL) and MeOH (24.2 mL). To this cloudy solution was added a solution of MeOH and 30% H_2O_2 (2:1, 24.2 mL), and the resulting solution was stirred for 1 h at 0 °C. The solution was concentrated and extracted with EtOAc (3 × 60 mL). The organic layer was washed with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (2:1) to afford 1.50 g (78%) of **28** as colorless oil. $[\alpha]^{23}_D$ −39.2° (*c* 3.75, CH_2Cl_2); IR (film) 3500, 2953, 2885, 2856, 1781, 1696, 1382, 1359, 1252, 1208, 1195, 1097, 1051, 1004, 832, 771, 700 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.30−7.14 (m, 5H), 4.65−4.60 (m, 1H), 4.17−4.10 (m, 2H), 4.07−4.04 (m, 1H), 3.82−3.79 (m, 2H), 3.63 (d, J = 1.2 Hz, 1H), 3.52 (t, J = 5.8 Hz, 2H), 3.46 (s, 3H), 3.25−3.20 (m, 2H), 2.71 (dd, J = 13.4, 9.4 Hz, 1H), 1.74−1.34 (m, 6H), 1.22 (d, J = 7.2 Hz, 3H), 1.19 (s, 3H), 0.83 (s, 9H), 0.80 (s, 9H), 0.05 (s, 6H), −0.01 (s, 6H); ^{13}C NMR (100 MHz) δ 175.8, 153.1, 135.2, 129.4 (2C), 128.9 (2C), 127.3, 88.7, 78.7, 71.8, 66.0, 63.6, 60.7, 55.3, 43.0, 37.7, 36.3, 35.1, 34.2, 26.9, 26.0 (3C), 25.9 (3C), 24.1, 18.3, 11.4, −1.8, −1.8, −5.3; HRMS (FAB) calcd for $C_{34}H_{61}NO_7Si_2$ + Na 674.3884, found 674.3868.

(2*R*,3*S*,5*R*,6*R*)-3,6,9-Tris((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2,6-dimethylnonanoic acid (30). To a stirred solution of aldol **28** (1.41 g, 2.16 mmol) in CH_2Cl_2 (15 mL) at 0 °C were added 2,6-lutidine (0.41 g, 3.89 mmol) and TBSOTf (0.85 g, 3.24 mmol). The reaction mixture was stirred for 15 min at 0 °C and quenched with satd aq $NaHCO_3$ (10 mL). The organic layer was separated, washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the crude product dissolved in THF/H_2O (4:1, 31 mL). To this were added 30% aq H_2O_2 (1.14 mL, 10.07 mmol) and 0.8 M aq LiOH (4.6 mL, 3.65 mmol) at 0 °C. The reaction was warmed to rt and stirred for 16 h. The reaction was quenched by adding aq Na_2SO_3 (1.33 M, 10 mL) and aq NH_4Cl solution (10 mL). The reaction mixture was then diluted with EtOAc (40 mL). The organic layer was separated, and the aqueous layer was back-extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue purified by flash chromatography eluting with EtOAc/hexanes (0.4/1) to yield 1.11 g (85%) of **30** as a colorless oil. $[\alpha]^{23}_D$ +5.4° (*c* 2.5, CH_2Cl_2); IR (film) 3538, 2953, 2928, 2886, 2856, 1709, 1471, 1462, 1252, 1097, 1053, 1003, 832, 803 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.35−4.32 (m, 1H), 3.60−3.52 (m, 2H), 3.50 (s, 3H), 2.98 (d, J = 9.6 Hz, 1H), 2.69−2.64 (m, 1H), 1.82−1.76 (m, 1H), 1.67−1.40 (m, 5H), 1.21 (s, 3H), 1.14 (d, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 18H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (100 MHz) δ 180.1, 84.7, 78.8, 70.7, 63.5, 60.5, 43.4, 35.8, 35.8, 27.1, 26.1 (3C), 25.9 (3C), 25.8 (3C), 24.1, 18.3, 17.9, 9.5, −1.7, −1.8, −2.0, −4.2, −5.1, −5.3 (2C); HRMS (FAB) calcd for $C_{30}H_{66}O_6Si_3$ + Na 629.4065, found 629.4047.

(2*R*,3*S*,5*R*,6*R*)-(3*R*,4*S*,*E*)-4-Hydroxy-6-iodo-4-methylhex-5-en-3-yl 3,6,9-tris((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2,6-dimethylnonanoate (31). To a solution of acid **30** (0.22 g, 0.36 mmol) in THF (4 mL) at rt was added Et_3N (0.04 g, 0.38 mmol) and 2,4,6-trichlorobenzoyl chloride (0.01 g, 0.40 mmol). The reaction mixture was stirred for 3 h at rt, and the solids were filtered and washed with hexanes (10 mL). The combined filtrates were concentrated under reduced pressure, dried under vacuum, and dissolved in toluene (5 mL). To this solution were added iododiol **8** (0.11 g, 0.43 mmol) in toluene (2 mL) and DMAP (0.06 g, 0.49 mmol). After being stirred for 16 h at rt, the reaction mixture was diluted with EtOAc (20 mL), washed with satd aq $NaHCO_3$ (10 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.4/1) to afford 0.24 g (74%) of **31** as a colorless oil. $[\alpha]^{23}_D$ +11.2° (*c* 1.2, CH_2Cl_2); IR (film) 3445, 2951, 2936, 2909, 2877, 2857, 1729, 1461, 1251, 1192, 1095, 1004, 950, 836, 775 cm^{-1}; ^{1}H NMR (400 MHz) δ 6.68 (d, J = 14.6 Hz, 1H), 6.43 (d, J = 14.6, 1H), 4.81 (dd, J = 10.4, 2.8 Hz, 1H), 4.14−4.10 (m, 1H), 3.58−3.50 (m, 2H), 3.50 (s, 3H), 3.25 (dd, J = 9.6, 3.2 Hz, 1H), 3.18 (bs, 1H), 2.74−2.61 (m,1H), 1.68−1.35 (m, 8H), 1.25 (s, 3H), 1.21 (d, J = 4.8 Hz, 3H), 1.17 (s, 3H), 0.90 (s, 9H), 0.89−0.86 (m, 21H), 0.11 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz) δ 175.8, 148.0, 83.9, 80.2, 79.3, 77.7, 71.2, 63.4, 60.7, 44.3, 36.5, 35.2, 26.7, 26.2 (3C), 26.1, 25.9 (6C), 24.8, 23.5, 23.2, 18.4, 18.3, 18.0, 14.4, 10.7,-1.6, −1.7, −3.8, −4.5, −5.4 (2C); HRMS (FAB) calcd for $C_{37}H_{77}IO_7Si_3$ + Na 867.3920, found 867.3934.

(2*R*,3*S*,5*R*,6*R*)-(3*R*,4*S*,*E*)-4-Hydroxy-6-iodo-4-methylhex-5-en-3-yl 3,6-bis((*tert*-butyldimethylsilyl)oxy)-9-hydroxy-5-methoxy-2,6-dimethylnonanoate (32). To a solution of alcohol **31** (0.27 g, 0.32 mmol) in MeOH (7 mL) was added CSA (0.015 g, 0.065 mmol) at 0 °C. After stirring for 1 h, the reaction was quenched with $NaHCO_3$ (0.040 g). The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1/5) to afford 0.20 g (85%) of **32** as a colorless oil. $[\alpha]^{23}_D$ +14.5° (*c* 0.9, CH_2Cl_2); IR (film) 3458, 2952, 2936, 2908, 2877, 1724, 1461, 1251, 1194, 1094, 1045, 1005, 836, 775, 735 cm^{-1}; ^{1}H NMR (400 MHz) δ 6.67 (d, J = 11.6 Hz, 1H), 6.42 (d, J = 11.6, 1H), 4.80 (dd, J = 8.4, 2.0 Hz, 1H), 4.80 (dt, J = 5.6, 2.0 Hz, 1H), 3.59 (t, J = 4.4 Hz, 2H), 3.47 (s, 3H), 3.32−3.27 (m, 2H), 2.74−2.70 (m, 1H), 1.75−1.40 (m, 8H), 1.24 (s, 3H), 1.21 (d, J = 4.8 Hz, 3H), 1.21 (s, 3H), 0.90 (s, 9H), 0.88−0.85 (m, 12H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s,3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz) δ 175.8, 147.8, 84.3, 80.2, 78.9, 77.7, 77.4, 77.3, 63.3, 60.4, 44.6, 35.8, 34.9, 29.6, 26.2 (3C), 25.9 (3C), 24.5, 24.1, 23.2, 18.4, 18.0, 15.0, 10.6, −1.6, −1.7, −3.9, −4.5; HRMS (FAB) calcd for $C_{31}H_{63}IO_7Si_2$ + Na 753.3055, found 753.3053.

(2*R*,3*S*,5*R*,6*R*)-(3*R*,4*S*,*E*)-4-Hydroxy-6-iodo-4-methylhex-5-en-3-yl 3,6-bis((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2,6-dimethyl-9-oxononanoate (33). Dess−Martin periodinane (0.53 g, 0.31 mmol) and $NaHCO_3$ (0.13 g, 1.57 mmol) were suspended in CH_2Cl_2 (3 mL). Alcohol **32** (0.23 g, 0.31 mmol) in CH_2Cl_2 (3 mL) was added dropwise via cannula into the reaction mixture. After 1 h at rt, the reaction mixture was added to a mixture of satd aq $NaHCO_3$ (5 mL),

satd aq Na_2SO_3 (5 mL), and H_2O (10 mL). The mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.4/1) to afford 0.18 g (80%) of **33** as a foam. $[\alpha]^{23}_D$ +14.9° (*c* 0.75, CH_2Cl_2); IR (film) 2962, 2886, 2853, 1736, 1695, 1461, 1401, 1250, 1190, 1094, 1050 cm^{-1}; ^1H NMR (400 MHz) δ 9.8 (s, 1H), 6.67 (d, *J* = 14.4 Hz, 1H), 6.43 (d, *J* = 14.4 Hz, 1H), 4.81 (dd, *J* = 10.4, 2.8 Hz, 1H), 4.11 (dt, *J* = 6.8, 3.2 Hz, 1H), 3.47 (s, 3H), 3.21 (d, *J* = 9.6 Hz, 2.4, 1H), 3.11 (bs, 1H), 1.85−1.50 (m, 8H), 1.25 (s, 3H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.21 (s, 3H), 0.90 (s, 9H), 0.89−0.85 (m, 12H), 0.12 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz) δ 202.1, 175.7, 148.0, 84.1, 80.2, 78.4, 77.7, 71.1, 60.7, 44.5, 38.7, 35.2, 31.4, 26.1 (3C), 25.9 (3C), 24.6, 23.5, 23.1, 18.4, 18.0, 14.6, 10.7, −1.6, −1.8, −3.9, −4.6; HRMS (FAB) calcd for $C_{31}H_{61}IO_7Si_2$ + Na 751.2898, found 751.2892.

(3*R*,4*S*,6*R*,7*R*,13*S*,14*R*,*E*)-4,7-Bis((*tert*-butyldimethylsilyl)oxy)-14-ethyl-10,13-dihydroxy-6-methoxy-3,7,13-trimethyloxacyclotetradec-11-en-2-one (34). To a solution of aldehyde **33** (0.20 g, 0.27 mmol) in DMSO (125 mL) at rt were added $CrCl_2$ (0.33 g, 2.75 mmol) and $NiCl_2$ (0.004 mg, 0.027 mmol). The reaction was stirred for 16 h and quenched by the addition of H_2O (60 mL). The mixture was diluted with EtOAc (500 mL), and the layers were separated. The organic layer was washed with H_2O (3 × 50 mL). The combined aqueous layers were back-extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1/2) to afford 0.06 g (dr = 1:1 at C9) (50%) of **34** as a foam. IR (film) 3465, 2953, 2909, 1731, 1461, 1251, 1095, 1252, 1118, 1093, 1067 cm^{-1}; ^1H NMR (400 MHz) δ 6.85 (d, *J* = 16.4 Hz, 1H), 6.19 (d, *J* = 16.4 Hz, 1H), 4.83 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.33 (t, *J* = 8.4 Hz, 1H), 3.76 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.23 (dt, *J* = 12.8, 3.5 Hz, 1H), 3.12 (s, 3H), 2.83 (bs, 1H), 2.46−2.38 (m, 1H), 1.99−1.90 (m, 2H), 1.81−1.52 (m, 5H), 1.33 (s, 3H), 1.19 (d, *J* = 8.0 Hz, 3H), 1.18 (s, 3H), 0.94 (t, *J* = 8.2 Hz, 9H), 0.89 (s, 9H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.60 (q, *J* = 7.8 Hz, 6H), 0.13 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz) δ 204.1, 175.7, 151.8, 127.7, 80.1, 78.9, 74.1, 73.2, 71.2, 49.0, 48.3, 44.7, 34.6, 31.1, 26.2, 21.9, 21.0, 19.7, 18.4, 16.1, 10.3, 6.7, 5.1, −3.0, −4.8; HRMS (FAB) calcd for $C_{31}H_{62}O_7Si_2$ + Na 625.3932, found 625.3925

(3*R*,4*S*,6*R*,7*R*,13*S*,14*R*,*E*)-4,7-Bis((*tert*-butyldimethylsilyl)oxy)-14-ethyl-13-hydroxy-6-methoxy-3,7,13-trimethyloxacyclotetradec-11-ene-2,10-dione (35). Dess−Martin periodinane (0.07 g, 0.15 mmol) was added to alcohol **34** (0.03 g, 0.05 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.15 mL). After 1 h at rt, the reaction mixture was added to a mixture of satd aq $NaHCO_3$ (5 mL), satd aq Na_2SO_3 (5 mL), and H_2O (10 mL). The mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1.2/1) to afford 0.024 g (82%) of **35** as a white solid (mp = 192−195 °C); $[\alpha]^{23}_D$ +6.7° (*c* 2.7, CH_2Cl_2); IR (film) 3443, 2956, 2930, 2893, 2883, 2857, 1733, 1658, 1461, 1262, 1126, 1095, 1066, 1053, 1001, 835 cm^{-1}; ^1H NMR (400 MHz) δ 7.08 (d, *J* = 16.4 Hz, 1H), 6.14 (d, *J* = 16.4 Hz, 1H), 4.77 (dd, *J* = 10.0, 2.8 Hz, 1H), 4.05 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.46 (s, 3H), 3.40−3.31 (m, 2H), 3.02−2.95 (m, 1H), 2.52 (bs, 1H), 2.09−1.52 (m, 10H), 1.34 (s, 3H), 1.30 (s, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.95−0.89 (m, 12H), 0.80 (s, 3H), 0.07 (s, 3H), 0.07 (m, 6H), 0.05 (s, 3H); ^{13}C NMR (100 MHz) δ 203.7, 176.2, 152.5, 127.5, 86.6, 77.3, 76.6, 73.7, 71.7, 59.8, 45.4, 44.7, 34.8, 33.7, 32.7, 26.0 (6C), 25.5, 22.4, 21.5, 18.1, 17.4, 10.6, −1.7, −1.8, −3.9, −4.6; HRMS (FAB) calcd for $C_{31}H_{60}O_7Si_2$ + Na 623.3775 found 623.3736.

(5*R*,6*R*)-5-(2-(bBenzyloxy)ethyl)-3,3-diethyl-6,11,11,12,12-pentamethyl-4,10-dioxa-3,11-disilatridecan-6-ol (36). To a solution of diol **20** (1.0 g, 2.61 mmol) in DMF (26 mL) at 0 °C were added imidazole (0.25 g, 3.65 mmol) and TESCl (0.47 g, 3.13 mmol). The reaction mixture was warmed to rt. After 1.5 h, the reaction was quenched by with H_2O (40 mL). The aqueous layer was extracted with ether (4 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1/5) to afford 1.16 g (90%) of **36** as a colorless oil. $[\alpha]^{23}_D$ +7.7° (*c* 8.3, CH_2Cl_2); IR (film) 3443, 2956, 2930, 2893, 2883, 2857, 1733, 1658, 1461, 1262, 1126, 1095, 1066, 1053, 1001, 835 cm^{-1}; ^1H NMR (400 MHz) δ 7.29−7.18 (m, 5H), 4.43 (s, 2H), 3.61 (dd, *J* = 7.2, 3.6 Hz, 1H), 3.54 (t, *J* = 6.4 Hz, 2H), 3.50−3.47 (m, 1H), 2.47(s, 1H), 1.88−1.80 (m, 1H), 1.65−1.36 (m, 5H), 1.02(s, 3H), 0.88 (t, *J* = 6.4 Hz, 9H), 0.82 (s, 9H), 0.55 (q, *J* = 7.6 Hz, 6H), −0.02 (s, 6H); ^{13}C NMR (100 MHz) δ 138.3, 128.3 (2), 127.6 (2), 127.5, 76.0, 74.1, 72.9, 67.3, 63.8, 34.9, 33.1, 26.8, 25.9 (3C), 21.8, 18.2, 6.9 (3C), 5.2 (3C), −5.3 (2C); HRMS (FAB) calcd for $C_{27}H_{52}O_4Si_2$ + Na 519.3302 found 519.3286.

(*R*)-8-((*R*)-3-(Benzyloxy)-1-methoxypropyl)-10,10-diethyl-2,2,3,3,8-pentamethyl-4,9-dioxa-3,10-disiladodecane (37). To a solution of **36** (0.50 g, 1.00 mmol) in THF (10 mL) was added MeI (2.01 g, 32.65 mmol), and the reaction mixture was cooled to 0 °C. Sodium hydride (0.78 g, 32.65 mmol) was then added in small portions. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was quenched by adding MeOH (3 mL) followed by H_2O (5 mL) at 0 °C. The reaction mixture was diluted with Et_2O (15 mL), and the aqueous layer was back-extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.4:1) to afford 0.4 g (78%) of **37** as a colorless oil. $[\alpha]^{23}_D$ +8.4° (*c* 3.8, CH_2Cl_2); IR (film) 2880, 1475, 1422, 1361, 1055, 733, 696 cm^{-1}; ^1H NMR (400 MHz) δ 7.35−7.26 (m, 5H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.61−3.55 (m, 4H), 3.42 (s, 3H), 3.17 (dd, *J* = 10.4, 2.4 Hz, 1H), 1.93−1.89 (m, 1H), 1.65−1.39 (m, 5H), 1.20 (s, 3H), 0.95 (t, *J* = 8 Hz, 9H), 0.89 (s, 9H), 0.59 (q, *J* = 8 Hz, 6H), 0.04 (s, 6H); ^{13}C NMR (100 MHz) δ 138.6, 128.3 (2C), 127.6 (2C), 127.4, 84.6, 78.2, 72.8, 67.8, 63.7, 60.8, 35.4, 30.8, 27.0, 26.0 (3C), 24.2, 18.3, 7.2 (3C), 6.9 (3C), −5.3 (2C); HRMS (FAB) calcd for $C_{28}H_{54}O_4Si_2$ + Na 533.3458, found 533.3455.

(8*R*,9*R*)-9-(2-(bBenzyloxy)ethyl)-11,11-diethyl-8-methoxy-2,2,3,3,8-pentamethyl-4,10-dioxa-3,11-disilatridecane (38). To a solution of **36** (9.08 g, 18.29 mmol) in CH_2Cl_2 (90 mL) at 0 °C were added proton sponge (11.74 g, 54.87 mmol) and Me_3OBF_4 (8.11 g, 54.87 mmol). The reaction mixture was warmed to rt and stirred for 16 h. The reaction mixture was concentrated and quenched with satd aq NH_4Cl (50 mL). The reaction mixture was diluted with Et_2O (100 mL), and the aqueous layer was back-extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with 1 N aq HCl solution (60 mL), satd aq $NaHCO_3$ (80 mL), H_2O (80 mL), and brine (50 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1/25) to afford 7.4 g (80%) of **38** as an oil. $[\alpha]^{23}_D$ = +11.5° (c 2.6,CH_2Cl_2); IR (film) 1255, 1361, 1471, 2857, 2953, 3398, 1096, 899, 733, 696 cm^{-1}; ^1H NMR (400 MHz) δ 7.27−7.20 (m, 5H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 3.74 (dd, *J* = 9.8, 2.2 Hz, 2H), 3.54−3.48 (m, 4H), 3.07 (s, 3H), 1.84−1.76 (m, 1H), 1.60−1.28 (m, 4H), 0.98 (s, 3H), 0.88−0.84 (m, 9H), 0.83 (s, 9H), 0.55−0.49 (m, 6H), −0.02 (s, 6H); ^{13}C NMR (100 MHz) δ 138.6, 128.3 (2C), 127.6 (2C), 127.4, 78.8, 73.7, 72.9, 67.9, 63.5, 48.7, 32.7, 29.9, 26.0, 25.9 (3C), 18.2, 18.0, 7.1 (3C), 5.3 (3C), −5.3 (2C); HRMS (FAB) calcd for $C_{28}H_{54}O_4Si_2$ + Na 533.3458, found 533.3445.

(2*R*,3*S*,5*R*,6*R*)-(3*R*,4*S*,*E*)-4-Hydroxy-6-iodo-4-methylhex-5-en-3-yl 3,9-bis((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2,6-dimethyl-5-((triethylsilyl)oxy)nonanoate (44). To a solution of acid **43** (0.60 g, 0.98 mmol) in THF (10 mL) at rt were added Et_3N (0.1 g, 1.03 mmol) and 2,4,6-trichlorobenzoyl chloride (0.26 g, 1.08 mmol). The reaction mixture was stirred for 3 h at rt, and the solids were filtered and washed with hexanes (20 mL). The combined filtrates were concentrated under reduced pressure, dried under vacuum, and dissolved in toluene (15 mL). To this solution were added diol **8** (0.26 g, 0.98 mmol) in toluene (5 mL) and DMAP (0.16 g, 1.33 mmol). After stirring for 16 h at rt, the reaction mixture was diluted with EtOAc (50 mL), washed with satd aq $NaHCO_3$ (20 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.4/1) to afford 0.68 g (75%) of **44** as a colorless oil. $[\alpha]^{23}_D$ +27.4° (*c* 0.7, CH_2Cl_2); IR (film) 3460, 2951, 2933, 2878, 1732, 1471, 1462, 1381, 1254, 1199, 1095, 1073, 1044, 1005, 949, 834, 774, 736 cm^{-1}; ^1H NMR (400 MHz) δ 6.54 (d, *J* = 14.4 Hz, 1H), 6.41 (d, *J* = 14.4, 1H), 4.78 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.48 (dt, *J* = 9.6, 3.2 Hz, 1H), 3.60−3.55 (m, 3H), 3.10 (s, 3H), 2.67−2.62 (m, 1H), 2.33 (bs, 1H), 1.79−1.34 (m, 8H), 1.23 (s, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 3H), 0.94 (t, *J* = 8 Hz, 9H), 0.88−0.86 (m, 12H), 0.84 (s, 9H), 0.66−0.55 (m, 6H), 0.06 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz) δ 175.0, 147.6, 80.0, 79.0, 77.6, 77.2, 73.6, 69.6, 63.2, 48.3, 42.7, 37.3, 29.4, 26.0, 25.9 (6C), 25.2, 22.6, 18.2, 18.0, 17.4, 10.6, 9.6, 7.2 (3C), 5.4 (3C), −3.8, −4.6, −5.4 (2C); HRMS (FAB) calcd for $C_{37}H_{77}IO_7Si_3$ + Na 867.3920 found 867.3900.

(2*R*,3*S*,5*R*,6*R*)-(3*R*,4*S*,*E*)-4-Hydroxy-6-iodo-4-methylhex-5-en-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-9-hydroxy-6-methoxy-2,6-dimethyl-5-((triethylsilyl)oxy)nonanoate (45). To a solution of TBAF·$3H_2O$ (0.90 g, 2.86 mmol) in DMF (28 mL) was added AcOH (0.70 g, 2.01 mmol). After 30 min of stirring, the solution was added to **44** (0.68 g, 0.95 mmol), and the reaction mixture was stirred for 20 h at rt. The reaction was quenched with H_2O (20 mL), and the aqueous layer was back-extracted with Et_2O (4 × 60 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1/5) to afford 0.35 g (60%) of **45** as a colorless oil. $[\alpha]^{23}_D$ +30.8° (*c* 0.6, CH_2Cl_2); IR (film) 3458, 2951, 2936, 2909, 2877, 1729, 1461, 1251, 1192, 1095, 1069, 1044, 1004, 950, 940, 836, 775 cm^{-1}; ^1H NMR (400 MHz) δ 6.55 (d, *J* = 14.4 Hz, 1H), 6.41 (d, *J* = 14.4, 1H), 4.77 (dd, *J* = 10.0, 3.2 Hz, 1H), 4.45 (dt, *J* = 9.6, 3.2 Hz, 1H), 3.66 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.62−3.58 (m, 2H), 3.14 (s, 3H), 2.67 (dq, *J* = 4.8, 2.4 Hz, 1H), 2.55 (bs, 1H), 2.03 (m, 1H), 1.82−1.42 (m, 8H), 1.23 (s, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.05 (s, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.86−0.84 (m, 12H), 0.66−0.55 (m, 6H), 0.77 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz) δ 175.0, 147.6, 80.1, 79.3, 77.5, 77.3,73.5, 69.8, 63.2, 48.6, 43.4, 37.7, 30.2, 26.2, 25.9 (3C), 24.9, 22.7, 18.1, 17.4, 10.6, 10.3, 7.1 (3C), 5.4 (3C), −3.9, −4.7; HRMS (FAB) calcd for $C_{31}H_{63}IO_7Si_2$ + Na 753.3055 found 753.3032.

(2*R*,3*S*,5*R*,6*R*)-(3*R*,4*S*,*E*)-4-Hydroxy-6-iodo-4-methylhex-5-en-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2,6-dimethyl-9-oxo-5-((triethylsilyl)oxy)nonanoate (46). Dess−Martin periodinane (0.23 g, 0.54 mmol) and $NaHCO_3$ (0.19 g, 2.25 mmol) were suspended in CH_2Cl_2 (3 mL). Alcohol **45** (0.33 g, 0.45 mmol) in CH_2Cl_2 (4 mL) was added dropwise via cannula into the reaction mixture. After 1 h at rt, the reaction mixture was added to a mixture of satd aq $NaHCO_3$ (5 mL), satd aq Na_2SO_3 (5 mL), and H_2O (10 mL). The mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1/5) to afford 0.28 g (78% yield) of **46** as a colorless oil. $[\alpha]^{23}_D$ +32.8° (*c* 0.7, CH_2Cl_2); IR (film) 2952, 2879, 2877, 1733, 1684, 1463, 1411, 1379, 1250, 1190, 1094, 1050 cm^{-1}; ^1H NMR (400 MHz) δ 9.76 (m, 1H), 6.55 (d, *J* = 14.4 Hz, 1H), 6.41 (d, *J* = 14.4 Hz, 1H), 4.78 (dd, *J* = 10.0, 3.2 Hz, 1H), 4.44 (dt, *J* = 8.8, 3.6 Hz, 1H), 3.59 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.10 (s, 3H), 2.67 (dq, *J* = 4.8, 2.4 Hz, 1H), 2.53−2.35 (m, 3H), 1.99−1.91 (m, 1H), 1.77−1.47 (m, 6H), 1.24 (s, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 0.95 (t, *J* = 8.4 Hz, 9H), 0.87−0.85 (m, 12H), 0.66−0.55 (m, 6H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz) δ 202.1, 174.8, 147.6, 80.1, 78.6, 77.5, 77.2, 73.4, 69.8, 48.8, 43.3, 38.0, 37.6, 25.8 (3C), 25.6, 24.9, 22.7, 18.1, 17.7, 10.6, 10.2, 7.1 (3C), 5.4 (3C), −3.9, −4.6; HRMS (FAB) calcd for $C_{31}H_{61}IO_7Si_2$ + Na 751.2898 found 751.2892.

(3*R*,4*S*,6*R*,7*R*,13*S*,14*R*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-14-ethyl-10,13-dihydroxy-7-methoxy-3,7,13-trimethyl-6-((triethylsilyl)oxy)oxacyclotetradec-11-en-2-one (47). To a solution of aldehyde **46** (0.28 g, 0.27 mmol) in DMSO (158 mL) at rt were added $CrCl_2$ (0.47 g, 3.84 mmol) and $NiCl_2$ (0.005 mg, 0.038 mmol). The reaction mixture was stirred for 16 h and then quenched by the addition of H_2O (90 mL). The mixture was diluted with EtOAc (600 mL), and the layers were separated. The organic layer was washed with H_2O (3 × 100 mL). The combined aqueous layers were back-extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (2/5) to afford 0.12 g (dr = 1:1 at C9) (50%) of **47** as a foam. IR (film) 3443, 2953, 2936, 2909, 2878, 1731, 1461, 1251, 1095, 1057, 1005, 972, 854, 831, 815, 774 cm^{-1}; ^1H NMR (400 MHz) δ 5.75−5.60 (m, 2H), 4.81 (td, *J* = 10.6, 2.0 Hz, 1H), 4.30−4.12 (m, 1H), 4.07−3.98 (m, 1H), 3.14 (s, 3H), 2.69−2.46 (m, 2H), 2.19−1.73 (m, 2H), 1.53−133 (m, 4H), 1.29−1.26 (m, 3H), 1.21−1.16 (m, 3H), 1.12 −1.03 (m, 3H), 0.97−0.89 (m, 12H), 0.87−0.84 (s, 9H), 0.64−0.53 (m, 6H), 0.10−0.01 (m, 6H); ^{13}C NMR (100 MHz) δ 175.7, 175.3, 136.2, 133.7, 133.2, 132.4, 80.3, 79.6, 79.4, 79.3, 74.4, 73.9, 73.7, 73.4, 72.9, 72.6, 70.5, 70.3, 48.7, 48.3, 42.5, 40.4, 30.6, 30.5, 29.6, 27.5, 26.1, 25.8, 23.3, 22.1, 20.6, 19.1, 18.3, 18.0, 17.4, 15.5, 15.0, 10.6, 10.6, 7.1, 7.0, 5.3, 5.1, −3.4,-4.1,-4.8, −5.0; HRMS (FAB) calcd for $C_{31}H_{62}O_7Si_2$ + Na 625.3932, found 625.3911.

(1*R*,3*S*,4*R*,7*R*,8*S*,14*R*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-7-ethyl-8,11-dihydroxy-14-methoxy-4,8,14-trimethyl-6,15-dioxabicyclo[9.3.1]pentadec-9-en-5-one (53). To a solution of **48** (0.030 g, 0.05 mmol) in MeOH (7 mL) was added *p*-TsOH (2 mg, 0.01 mmol) at 0 °C. After 3 h at this temperature, the reaction was quenched by adding satd aq $NaHCO_3$ (5 mL). The reaction mixture was diluted with EtOAc (20 mL), and the aqueous layer was back-extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure and purified directly by flash chromatography eluting with hexanes/EtOAc (4:1) to afford 12 mg (52%) of **53** as a foam. $[\alpha]^{23}_D$ +10.7° (*c* 0.8, CH_2Cl_2); IR (film) 3441, 2954, 2934, 2882, 1729, 1461, 1374, 1264, 1178, 1145, 1072, 1006, 961, 834, 775, 702 cm^{-1}; ^1H NMR (400 MHz) δ 6.07 (d, *J* = 16.4 Hz, 1H), 5.95 (d, *J* = 16.4 Hz, 1H), 4.85 (t, *J* = 3.6 Hz, 1H), 4.54 (dd, *J* = 11.2, 2.4 Hz, 1H), 4.29 (d, *J* = 9.6 Hz, 1H), 3.94−3.90 (m, 1H), 3.21 (s, 3H), 2.90−2.82 (m, 1H), 2.06−1.95 (m, 3H), 1.85−1.71 (m, 2H), 1.57−1.46 (m, 2H), 2.59 (bs, 2H), 1.30 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.27 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz) δ 175.4, 146.1, 136.3, 122.8, 102.9, 83.2, 74.7, 73.6, 71.7, 70.9, 49.1, 44.4, 31.3, 29.3, 25.9 (3C), 21.6, 21.2, 18.0, 16.4, 10.5, −4.1, −4.7; HRMS (FAB) calcd for $C_{25}H_{46}O_7Si$ + K 525.2650, found 525.2667.

(3*R*,4*S*,6*R*,7*R*,13*S*,14*R*,*E*)-14-Ethyl-4,6,13-trihydroxy-7-methoxy-3,7,13-trimethyloxacyclotetradec-11-ene-2,10-dione (54). To a solution of **48** (34 mg, 0.05 mmol) in THF (2.2 mL) was added TBAF·$3H_2O$ (54 mg, 0.17 mmol) at 0 °C, and the mixture was allowed to

slowly warm to 10 °C and stirred for 6 h. The reaction mixture was quenched by slowly adding satd aq $NaHCO_3$ (3 mL). The mixture was diluted with EtOAc (5 mL), and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (3:2) to afford 13 mg of **54** (70%) as a foam. $[\alpha]^{23}_D$ +3.5° (*c* 0.9, CH_2Cl_2); IR (film) 3441, 2956, 2878, 1727, 1462, 1372, 1265, 1178, 1093 cm^{-1}; ^1H NMR (400 MHz) δ 6.74 (d, *J* = 16.0 Hz, 1H), 6.19 (d, *J* = 16.0 Hz, 1H), 4.87 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.00 (t, *J* = 8.8 Hz, 1H), 3.86 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.72 (bs, 1H), 3.20 (s, 3H), 2.88 (bs, 1H), 2.65−2.53 (m, 3H), 2.31−2.23 (m, 1H), 12.95−1.84 (m, 2H), 1.74−1.46 (m, 5H), 1.33 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 202.2, 175.9, 150.4, 128.3, 79.9, 78.7, 73.8, 73.2, 48.9, 46.8, 37.1, 33.5, 30.6, 22.0, 21.8, 20.8, 16.2, 14.1, 10.4; HRMS (FAB) calcd for $C_{19}H_{32}O_7$ + Na 395.2046 found 395.2024.

(3*R*,4*S*,6*R*,7*R*,10*R*,13*S*,14*R*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-14-ethyl-6,10,13-trihydroxy-7-methoxy-3,7,13-trimethyloxacyclotetradec-11-en-2-one (55). To a solution of **48** (0.075 g, 0.12 mmol) in MeOH (3 mL) at rt was added $CeCl_3 \cdot 7H_2O$ (53 mg, 0.14 mmol). The reaction mixture was cooled to −60 °C after which $NaBH_4$ (5.3 mg, 0.14 mmol) was added. After 30 min at this temperature, the reaction was quenched by adding satd aq NH_4Cl (2 mL). Ethyl acetate (10 mL) was added, and the aqueous layer was back-extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with 1 N HCl solution (5 mL), satd aq $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was dried under vacuum. The residue was dissolved in MeOH (17 mL) and cooled to 0 °C after which *p*-TsOH (4.5 mg, 0.024 mmol) was added. The reaction mixture was stirred at 0 °C for 3 h after which the reaction was quenched by adding $NaHCO_3$ (10 mg). The mixture was concentrated and purified directly by flash chromatography eluting with EtOAc/hexanes (2/5) to afford 44 mg of **55** (75%) as a foam (dr = 7:1 dr at C9 by ^1H NMR). Major 9-(*R*) isomer: IR (film) 3441, 2956, 2878, 1727, 1462, 1372, 1265, 1178, 1093 cm^{-1}; ^1H NMR (400 MHz) δ 5.90−5.84 (m, 1H), 5.71 (m, 1H), 4.87−4.84 (m, 1H), 4.13−4.04 (m, 2H), 3.75−3.73 (m, 1H), 3.20 (s, 3H), 2.80−2.70 (m, 2H), 2.52 (bs, 1H), 2.13 (bs, 1H), 2.02−1.96 (m, 1H), 1.83−1.42 (m, 5H), 1.30 (s, 3H), 1.22 (m, 1H), 1.26 (s, 3H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.07 (s, 3H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (100 MHz) δ 175.4, 133.7, 133.2, 81.5, 78.6, 73.9, 72.6, 72.1, 71.7, 49.4, 48.0, 37.2, 31.0, 29.6, 27.6, 25.8 (3C), 24.5, 23.5, 17.5, 15.1, 10.8, −4.6, −4.7; HRMS (FAB) calcd for $C_{25}H_{48}O_7Si$ + Na 511.3067, found 511.3042.

(2*S*,3*R*,4*R*,6*S*)-2-(((2*R*,3*S*,6*R*,9*R*,10*R*,12*S*,13*R*,*E*)-12-((*tert*-Butyldimethylsilyl)oxy)-2-ethyl-10-hydroxy-9-methoxy-3,9,13-trimethyl-14-oxo-6-((triethylsilyl)oxy)oxacyclotetradec-4-en-3-yl)oxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl Methyl Carbonate (57). To a solution of **55** (70 mg, 0.14 mmol) in DMF (1.5 mL) and CH_2Cl_2 (1.5 mL) at rt were added imidazole (12 mg, 0.16 mmol) and DMAP (2 mg). The reaction mixture was cooled to −78 °C, and TESCl (25 mg, 0.15 mmol) was added. After stirring for 3 h at −78 °C the reaction was quenched by adding satd aq NH_4Cl (3 mL). The mixture was diluted with EtOAc (10 mL), and the aqueous layer was back-extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with H_2O (5 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure and azeotroped with toluene (5 mL), and the crude alcohol was taken to the next step. To a suspension of freshly activated 4 Å molecular sieves (1.55 g) and AgOTf (0.72 g, 2.82 mmol) in CH_2Cl_2/toluene (5 mL, 1:1) was added dropwise by cannula a mixture of C5 alcohol (0.14 mmol), desosamine donor **7** (0.28 g, 0.85 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (0.18 g, 0.85 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. The reaction flask was wrapped with aluminum foil, warmed to rt, and stirred for an additional 20 h. The reaction was quenched with Et_3N (4.0 mL), filtered through Celite, and eluted with EtOAc (50 mL). The filtrate was washed with satd aq $NaHCO_3$ (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:2) to afford 42% of **57** as a foam (dr = 7:1 dr at C9 by ^1H NMR). Major 9-(*R*) isomer: IR (film) 3441, 2956, 2878, 1727, 1462, 1372, 1265, 1178, 1093 cm^{-1}; ^1H NMR (400 MHz) δ 5.80 (m, 1H), 5.48 (d, *J* = 16.4 Hz, 1H), 5.15 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.55 (dd, *J* = 10.4, 7.6 Hz, 1H), 4.48 (d, *J* = 7.6 Hz, 1H), 3.96−3.93 (m, 2H), 3.77 (s, 3H), 3.72−3.68 (m, 1H), 3.47−3.43(m, 1H), 3.18 (s, 3H), 2.75−2.56 (m, 2H), 2.27 (m, 9H), 2.33−2.30 (m, 1H), 1.26 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.04 (s, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.88 (s, 9H), 0.85 (t, *J* = 11.4 Hz, 3H), 0.62−0.52 (m, 6H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz) δ 174.3, 153.3, 135.8, 131.2, 96.6, 79.7, 78.7, 77.8, 75.1, 73.9, 73.6, 73.0, 68.8, 63.0, 54.6, 49.1, 48.6, 40.6 (2C), 37.7, 31.7, 30.8, 29.6, 28.1, 25.8(3C), 22.9, 21.2, 20.6, 18.0, 15.6, 10.6, 6.9 (3C), 5.0 (3C), −4.2, −4.4; HRMS (FAB) calcd for $C_{41}H_{79}NO_{11}Si_2$ + Na 840.5089, found 840.5081.

■ ASSOCIATED CONTENT

Supporting Information. General experimental procedures and NMR spectra (^1H and ^{13}C) for **24**, **25**, **28**, **30**−**38**, **44**−**47**, **53**−**55**, and **57**; crystallographic details of **35**; complete structural assignments (2D NMR analysis) of **62**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: randrade@temple.edu.

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