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Total synthesis of erythromycin B

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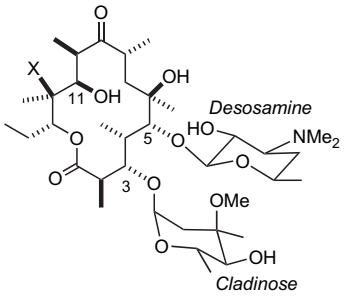
Abstract—We report the details of the first total synthesis of erythromycin B using two different strategies for the end game. The first of these follows a classical approach in which the desosamine and cladinose residues are sequentially appended to a macrocyclic lactone, which was formed by cyclization of a seco acid derivative, to give a bis-glycosylated macrolide intermediate that is converted into erythromycin B. The second strategy features an abiotic approach in which a seco acid bearing a desosamine residue is cyclized to give a monoglycosylated macrocyclic lactone that is then transformed into erythromycin B via a sequence of steps involving refunctionalizations and a glycosylation to introduce the cladinose moiety. Attempts to prepare a bis-glycosylated seco acid by de novo synthesis were unsuccessful. The syntheses of the key seco acid intermediates feature the oxidative transformation of a furan containing C(3)–C(10) to provide a dioxabicyclo[3.3.1]-nonenone that served as a template on which to create the stereocenters at C(6) and C(8). A stereoselective aldol reaction was used to establish the C(11)–C(15) segment, and a stereoselective crotylation was implemented to introduce the propionate subunit comprising C(1)–C(2).

1. Introduction

Isolated and discovered in the early 1950s in the fermentation broth of the fungus *Saccharopolyspora erythraea*,[1] erythromycin A (**1**) and erythromycin B (**2**) are the best known members of the clinically important macrolide class of antibiotics.[2] Indeed, erythromycin A and several of its derivatives remain the antibiotics of choice for the clinical treatment of numerous pathogenic bacteria. These macrolides block ribosomal protein biosynthesis by inhibiting peptidyl transferase,[3] and structures of various erythromycins complexed with the 50S ribosomal subunit provide useful insights into the basis for their remarkable biological activity.[4]

Erythromycin A (**1**) and erythromycin B (**2**), which differ by a hydroxyl group at C(11), are bis-glycosylated macrocyclic lactones bearing a desosamine residue on the hydroxyl group at C(5) and a cladinose group on the hydroxyl function at C(3). Although the desosamine residue is critical for activity, the cladinose group is not. For example, the ketolides comprise a potent family of erythromycin-derived antibiotics in which the cladinosyl glycoside appended to the alcohol function at C(3) is replaced by a carbonyl group. The macrocyclic 14-membered ring of the erythromycins is the product of propionate biosynthesis and is punctuated by 10 stereogenic centers.



1: X = OH
2: X = H

Given the unusual combination of powerful antibiotic activity and stereochemically complex architecture, it is not surprising that the erythromycins have been popular targets for synthesis. As such, they have provided an exquisite testing ground for developing new strategies and methods for the stereoselective formation of carbon–carbon bonds and introduction of functional groups. Despite the numerous elegant efforts directed toward the erythromycins,[5] the only total synthesis of **1** was reported by the Woodward group in

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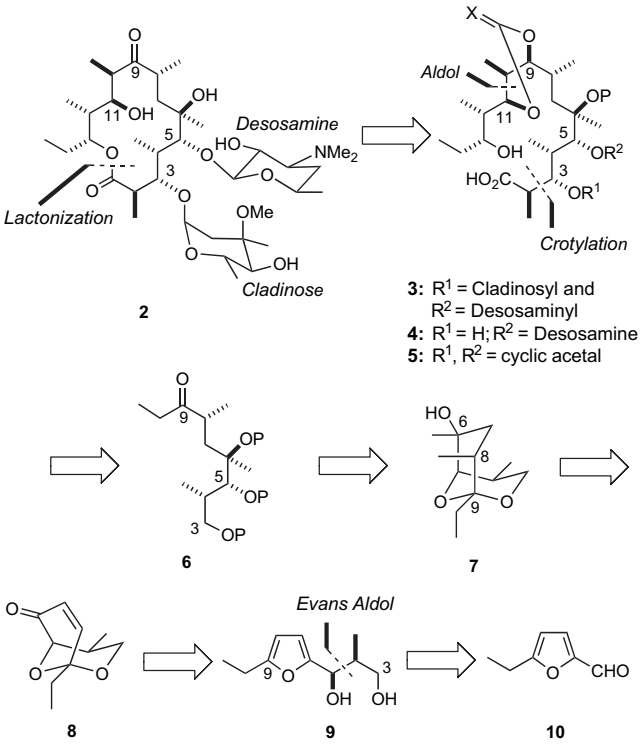
1981.[6] This landmark achievement was followed by the singular report of a formal total synthesis of **1** by Oishi and co-workers in 1988.[7] Perhaps inspired by the proposed biosynthesis of the erythromycins,[8] the Woodward approach featured the initial construction of a suitably protected macrolide ring that was then elaborated by introducing the carbohydrate residues; sequential deprotections and refunctionalizations then led to erythromycin A. The targets of all of the synthetic work that has subsequently emerged from other laboratories have been either macrolide aglycones or related seco acid derivatives. Herein we provide a historical account of our endeavors in this area that resulted in the first syntheses of erythromycin B by two strategies having conceptually different end games.[9,10]

2. Results and discussion

2.1. Preliminary strategic planning

In designing a novel strategy for the erythromycin antibiotics, we were attracted to a completely different, abiotic approach featuring the macrolactonization of a glycosylated derivative of an erythromycin seco acid such as **3** or **4** (Scheme 1). Inasmuch as the carbohydrate groups might obviate the need for protecting the hydroxyl groups at C(3) and C(5), it was conceivable that this plan might result in more concise syntheses of the erythromycins. It did not escape notice, however, that this was a rather daring plan as Woodward and others had clearly shown that successful macrolactonizations of seco acid derivatives relied upon rather specific structural requirements. In particular, reduction of the conformational space available to the seco acid backbone in two different regions was considered essential. Rigidifying the C(9)–C(12) portion of the backbone most commonly involved forming a six-membered ring incorporating the functional groups at C(9) and C(11) as illustrated by the carbonate or acetal moiety in **3**–**5** (X=O; R, R′),[5c,d,g–k,m–o,6,7] but the presence of double bonds in this segment has also proven to be effective.[5a,f] Following the lead of the Woodward group, the absolute stereochemistry at C(9) of the seco acids in the vast majority of these studies was *S*. Notable exceptions to this rule, include work performed by the Mulzer group, which cyclized a seco acid having a protected 9(*R*)-hydroxyl group and a free hydroxyl group at C(11),[5l] and the Carreira group, which reported the successful cyclization of a seco acid in which an isoxazoline ring bridged C(9)–C(11).[5p] Preorganization of the C(2)–C(6) segment of the seco acid backbones has been universally enforced by introducing a cyclic protecting group such as an acetal between the hydroxyl groups at C(3) and C(5) as shown in **5**.



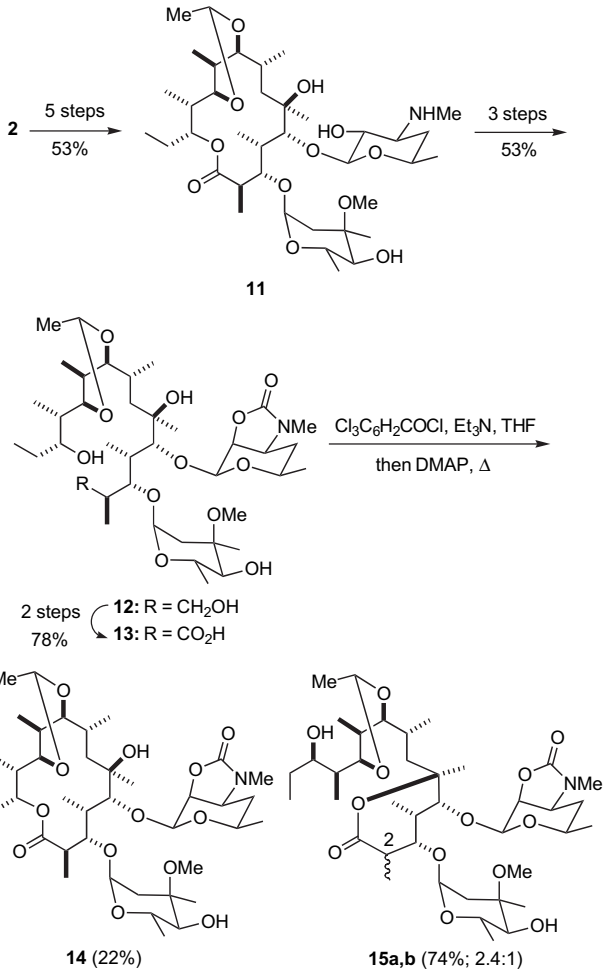
Scheme 1.

Having adopted the unconventional strategy of cyclizing a glycosylated seco acid derivative, we envisioned that the requisite cyclization substrates **3** and/or **4** might be assembled from the C(3)–C(10) ketone **6**. The C(11)–C(15) subunit would be affixed to **6** via a diastereoselective aldol reaction, which was nicely precedented at the time we initiated this study by the work of Masamune.[5b] Introducing the remaining backbone carbon atoms C(1)–C(2) would be achieved via a stereoselective crotylation or aldol reaction. Based upon our prior synthesis of tirandamycin,[11] we realized that **6** was simply an acyclic variant of the bridged bicyclic intermediate **7**, which might be accessed by the stereoselective introduction of the two methyl groups at C(8) and C(6) by sequential nucleophilic additions onto **8**. In further accord with that art, it followed that the synthesis of **8** would entail the oxidative transformation of the furan **9**, the absolute stereochemistry of which would be established by an Evans aldol reaction of the furaldehyde **10**.

2.2. Macrocyclization of a glycosylated seco acid

Owing to the unprecedented and thus highly risky nature of our plan to cyclize a glycosylated seco acid derivative, it seemed prudent to establish the underlying feasibility of such a transformation before undertaking the arduous task of total synthesis. The prior art in the area had clearly defined some of the key structural features that must be embodied within the seco acid matrix for a successful macrolactonization. Drawing upon this knowledge, we decided to convert erythromycin B (**2**) into a derivative of **3**.[12] Rigidity is imparted to the C(9)–C(13) segment of **3** by forming a cyclic derivative between the C(11) and C(9*S*) hydroxyl groups. It was then our hope that the steric buttressing between the protected cladinose and desosamine residues at C(3) and C(5), respectively, of **3** would reduce the conformational mobility along the C(1)–C(8) subunit of the backbone to facilitate cyclization. Although this possibility was supported by preliminary modeling studies, one might equally envision that unfavorable steric interactions between the two sugar residues would disfavor conformers of **3** capable of cyclizing. The issue would have to be resolved by experiment, so we initiated a study to examine cyclizations of bis-glycosylated seco acid derivatives of erythromycin.[12]

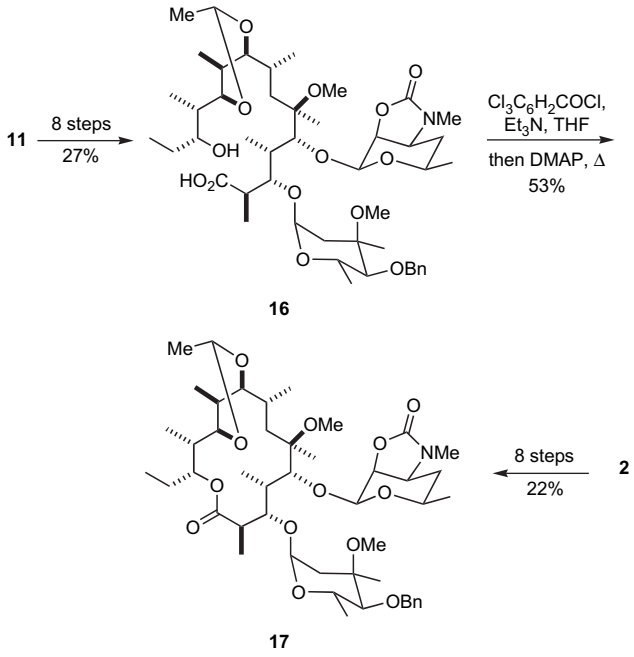
Using modifications of known procedures for effecting N-demethylation, carbonyl reduction, and acetal formation in the erythromycin series,[13,14] erythromycin B was converted into **11** in five steps and 53% overall yield (Scheme 2). Owing to facile hydrolysis of the cladinose residue under acidic conditions, our options for opening the lactone ring of **11** were limited. A number of attempts to hydrolyze the lactone ring under basic conditions were unsuccessful. Eventually, we found that hydride reduction of the lactone proceeded smoothly, and subsequent protection of the *vicinal* amino alcohol array on the desosamine residue as a cyclic carbamate furnished the tetraol **12** in three steps and 53% yield.[15] Selective oxidation of the primary hydroxyl group at C(1) then gave the seco acid **13** in 78% yield,[16,17] thereby setting the stage to test the crucial macrocyclization.



Scheme 2.

Several methods for inducing the macrocyclization of **13** were examined, but the Yamaguchi protocol proved to be the best,[18] yielding a separable mixture (1:2.4:1) of the desired 14-membered lactone **14** together with two isomeric lactones, which were *tentatively* identified as the seven-membered lactones **15a**,**b**, which are epimeric at C(2), but it was not possible to verify this assignment. The formation of the seven-membered lactones **15a**,**b** as the major products from the cyclization of **13** was somewhat unexpected, since there were several reports of cyclizations of erythronolide seco acid derivatives bearing an unprotected hydroxyl group at C(6) to provide 14-membered lactones as the exclusive products.[5d,h,j,6] Lactonization of **13** via its 2-pyridyl thioester was much less efficient,[19] providing a mixture composed primarily of the two seven-membered lactones **15a**,**b** together with only a small amount of **14** (49% combined yield). An authentic sample of **14** for comparison purposes was prepared directly from **11** in two straightforward steps (71% yield).[20]

In order to obviate forming a seven-membered lactone, the fully protected seco acid derivative **16** was prepared in eight steps (27% overall yield) from **11** (Scheme 3).[21] The success of this sequence lay in the significant difference in the chemical reactivity of the four hydroxyl groups, which followed the known order of C(1)>>C(4″)>C(13)>>C(6), thereby allowing selective protection and manipulation of each hydroxyl function. When **16** was subjected to the conditions of the Yamaguchi lactonization procedure,[18] the protected erythromycin B derivative **17** was isolated in 53% yield. An authentic sample of **17** for comparison was prepared independently from erythromycin B (**2**) in eight steps,[22] and the two compounds thus obtained were identical by ^{1}H and ^{13}C NMR. Several preliminary attempts to effect the cyclization of **16** under conditions previously defined by Corey[19] or Keck[23] were unavailing.



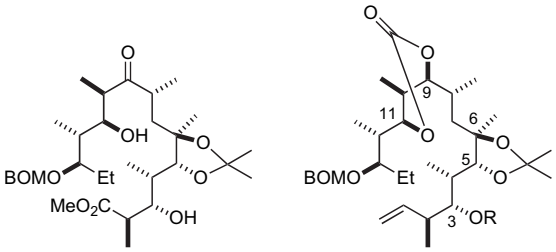
Scheme 3.

The novel macrolactonizations of **13** and **16** to give **14** and **17**, respectively, convincingly established the feasibility of cyclizing seco acid derivatives in which the cyclic protecting groups on the hydroxyl functions at C(3) and C(5) were replaced with carbohydrate residues. This critical discovery set the stage for the continuation of our efforts toward developing a novel approach to the erythromycin antibiotics.

2.3. Synthesis of seco acids: first generation approach

Concurrent with undertaking these experiments involving cyclizations of glycosylated seco acid derivatives of

erythromycin B, we were engaged in parallel investigations to evaluate the efficacy of the basic elements of the synthetic plan outlined in Scheme 1. These investigations were directed toward preparing compounds related to **5** that might serve as viable precursors of **3** or **4**. We had thus discovered that intermediates of the general type **6**, which comprise the C(3)–C(10) subunit of the erythromycins, could indeed be prepared from the substituted dioxabicyclo[3.3.1]nonane **7**, which was readily accessible in excellent yield and only five steps from commercially available **10**.[24] Furthermore, concise syntheses of **18** and **19**, both of which are potential precursors of glycosylated seco acid derivatives of erythromycin B, were completed.

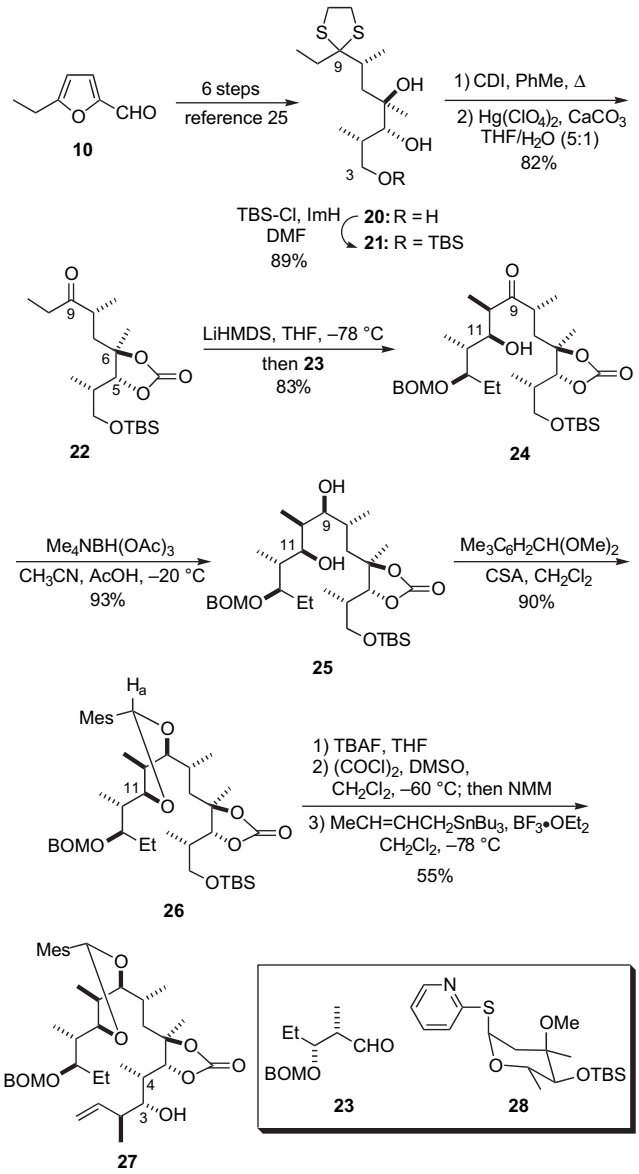


18 **19:** R = H, Ac, CO_2Bn

Because the Woodward group had shown that a C(9)–C(11) carbamate could be cyclized,[6] we reasoned that the C(9)–C(11) carbonate moiety in **19** would induce the necessary constraint into that portion of a seco acid. It then remained to introduce the carbohydrate residues onto **19**. Unfortunately, we discovered that removal of the acetonide protecting group from the C(5)–C(6) diol array of **19** (R=Ac, CO_2Bn) was surprisingly difficult and required rather forcing acidic conditions under which other hydroxyl protecting groups were labile. We did not explore the possibility of introducing a cladinose residue onto **19** (R=H), because cladinose is easily removed from the natural erythromycins under mild acidic conditions. Recognizing that **19** was thus not a viable intermediate en route to erythromycin B, we initiated studies to prepare a suitable seco acid using a different protecting group strategy.

2.4. Early efforts to prepare glycosylated seco acids

After exploring several possible options, it occurred to us that a cyclic carbonate might be a suitable protecting group for the vicinal diol array at C(5)–C(6). Accordingly, the primary alcohol group in **20**, which was available in six steps from **10** following procedures developed toward the syntheses of **18** and **19**,[24] was selectively protected to give **21** (Scheme 4). The corresponding TES ether of **20** was too labile to survive subsequent transformations. Conversion of **21** into the protected ketone **22** was achieved by sequential carbonate formation and hydrolysis of the thioacetal. It was essential to remove the dithiolane under mild, buffered conditions in order to avoid concomitant cleavage of the TBS ether and epimerization at C(8). In analogy with our previous work, we found that the lithium enolate generated by deprotonation of the ketone **22** using lithium hexamethyldisilazide underwent a highly stereoselective aldol reaction with the protected aldehyde **23** to give **24**, thereby completing the synthesis of the C(3)–C(15) portion of the erythromycin B backbone. Comparison of this and several related aldol reactions[5b,k,25] suggests that the diastereofacial selectivities in such processes may be affected by subtle differences in substitution on the enolate that are more than five atoms from the reacting center.[26] We had considerable difficulty in scaling up this reaction, and when the reaction was conducted on amounts of the ketone greater than 75–100 mg, there was a significant erosion in yield and stereoselectivity. This problem was later solved with a related ketone (vide infra).



Scheme 4.

With **24** in hand, it remained to introduce a constraint into the C(9)–C(12) subunit in anticipation of the eventual macrolactonization step. Toward this end, the carbonyl group at C(9) of **24** was stereoselectively reduced with $Me_4NBH(OAc)_3$ to give the *anti*-diol **25**,[27] which was protected as a cyclic mesitylene acetal (Mes) to provide **26**. Use of a mesitylene acetal as a constraining ring was predicated upon the pioneering work of Yonemitsu, who had shown

that a seco acid having such a cyclic acetal incorporating the C(9) and C(11) hydroxyl groups underwent facile cyclization.[5j] Support for the assigned stereochemistry of the carbon atom bearing the aryl group on the acetal moiety of **26** was obtained by an NOE experiment that showed a strong NOE between H_a and the proton at C(11).

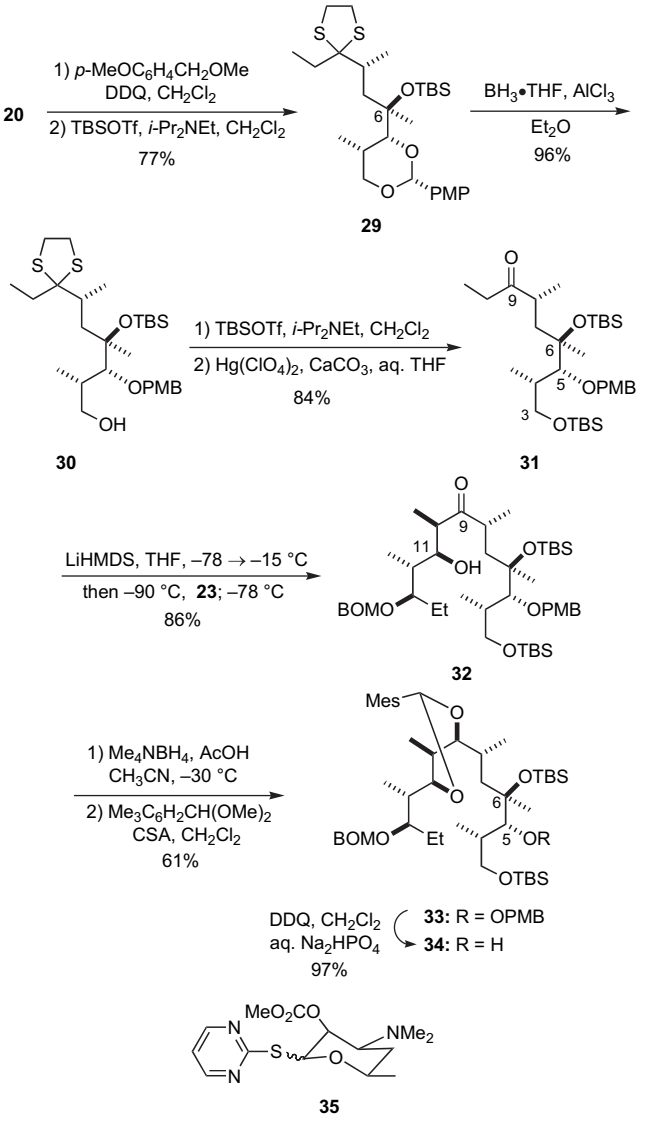
It then remained to complete the construction of the erythromycin B backbone. In the event, deprotection of the primary alcohol group of **26** followed by Swern oxidation and reaction of the aldehyde thus produced with tri-*n*-butylcrotylstannane in the presence of $BF_3\cdot OEt_2$, a transformation established in our earlier route to **19**,[24] furnished **27** together with minor quantities of diastereomeric adducts. *N*-Methylmorpholine (NMM) was used as the base rather than the more conventional triethylamine in the Swern oxidation in order to minimize side reactions such as β-elimination of the cyclic carbonate in the unstable intermediate aldehyde.

The stage was now nicely set for experiments directed toward introducing a cladinose residue onto the C(3) hydroxyl group of **27**. Disappointingly, several preliminary attempts to glycosylate **27** with **28**[6] in the presence of a number activators gave at best miniscule quantities of the desired cladinose derivative. We reluctantly recognized that it was time to reconsider our options.

2.5. Alternate entry to a glycosylated seco acid

Given our unsuccessful foray into accessing a seco acid derivative of erythromycin B bearing a cladinose residue, we turned our attention to an alternative approach in which desosamine would first be appended to a precursor of a seco acid. Such a strategy would again necessitate modifying the protecting group strategy applied to the trihydroxy ketal **20**. Because the criteria for selecting the specific hydroxyl protecting groups were crucial to the eventual success of the synthesis, they merit brief discussion. Based upon previous work with the cyclizations of **13** and **16**, we surmised that the C(6) alcohol must remain protected until after the macrolactonization step. The acid-labile nature of the glycosyl moieties, especially the cladinose residue, suggested that selective deprotection of late stage intermediates under basic or neutral conditions would be required. The TBS group thus emerged as a reasonable choice for the C(6) hydroxyl group. The TBS group was also selected as a protecting group for the C(3) hydroxyl group in anticipation that it could be selectively removed in the presence of the more hindered TBS group on the C(6) hydroxy group to enable eventual chain extension at C(3). Finally, the *p*-methoxybenzyl group (PMB)[28] was chosen to protect the C(5) hydroxyl function. This analysis led to our identifying **31** as the initial subgoal toward preparing a more advanced intermediate such as **34**, which bears a free hydroxyl group at C(5) (Scheme 5).

The first step toward preparing compound **31** entailed forming a cyclic *p*-methoxybenzylidene acetal involving the primary and secondary alcohol groups at C(3) and C(5) of **20**; the remaining tertiary hydroxyl group at C(6) was then silylated to give **29** (Scheme 5). Reductive cleavage of the acetal moiety in **29** with $BH_3\cdot THF$ in the presence of $AlCl_3$ in Et_2O, which was a better solvent than the more Lewis basic solvent THF, effected the selective release of



Scheme 5.

the less hindered primary hydroxyl group to furnish **30**. Interestingly, a similar hydride reduction of the acetal moiety in the tertiary alcohol precursor of **29** proceeded in the opposite regiochemical sense to give a C(5)–C(6) vicinal diol in which the C(3) hydroxyl group was protected as a PMB ether. This alternate mode of acetal cleavage presumably arose from preferential complexation of the Lewis acid with the tertiary alcohol at C(6) *prior* to its coordination with and activation of the proximal oxygen at C(5). On the other hand, the Lewis acid simply activates the less hindered acetal oxygen in **29** to furnish **30**. Subsequent protection of the hydroxyl group at C(3) of **30** as its TBS ether followed by hydrolysis of the thioacetal in the presence of $Hg(ClO_4)_2$ and in aqueous THF saturated with $CaCO_3$ delivered **31** in excellent overall yield from **20**. If this reaction was not conducted under buffered conditions, some loss of the TBS group from the primary alcohol was observed.

The stage was now appropriately set for the stereoselective aldol reaction to introduce the C(11)–C(15) portion of the backbone. In analogy with the aldol reaction of **22**, addition

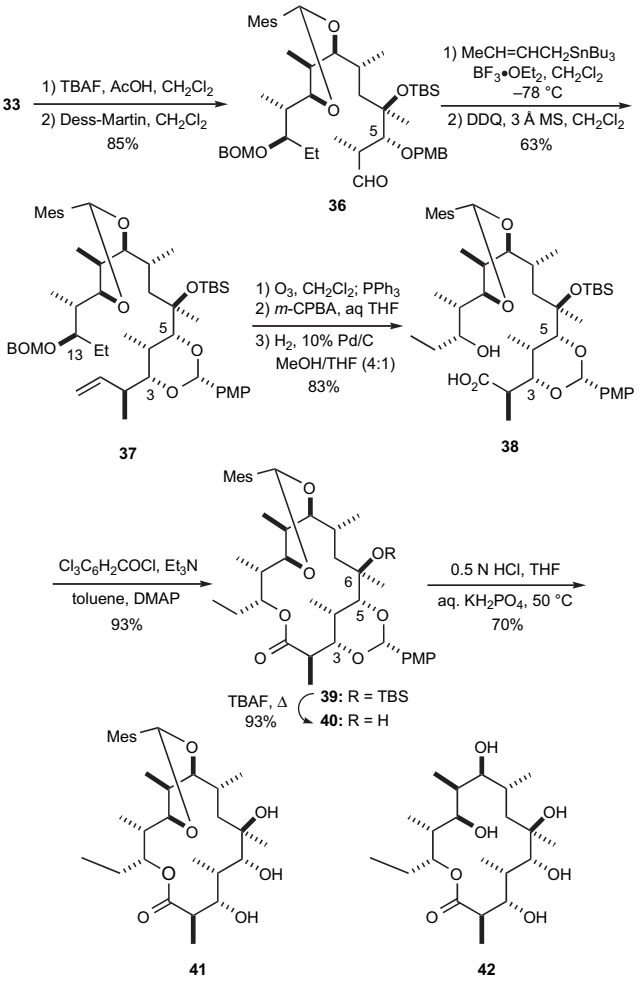
of the enolate generated from **31** to the protected aldehyde **23** furnished **32** with excellent *syn* and *anti* Felkin-Anh stereoselectivity (>40:1). Although we had encountered considerable difficulty in scaling up the aldol reaction of **22**, we discovered that the aldol reaction of **31** could be readily performed on several grams, *provided* the solution of the enolate was aged briefly at −15 °C and the aldol reaction was initiated at −90 °C before warming to −78 °C. Reduction of the hydroxy ketone **32** with $Me_4NBH(OAc)_3$ proceeded stereoselectively (ca. 10:1) to give the C(9)–C(11) *anti*-diol that was protected as a cyclic mesitylene acetal to provide **33**. Oxidative removal of the PMB protecting group from **33** using DDQ then delivered **34**.

The plan now required introducing a desosamine moiety onto **34**. However, much to our continued dismay, a number of attempts to glycosylate the free hydroxyl group at C(5) of **34** with **35**[6] or the corresponding glycosyl bromide were unsuccessful. We had thus once again been thwarted in our attempt to prepare a glycosylated seco acid derivative of erythromycin B that might be subsequently cyclized as a key step in a novel entry to these antibiotics.

2.6. Regrouping: first synthesis of erythromycin B

Despite the significant disappointment of being unable to introduce a desosamine group on **34**, it was evident that **33** might nevertheless be a viable intermediate in a synthesis of erythromycin B via the well-established approach involving glycosylation of a macrocyclic lactone.[9] We had already expended considerable effort in getting to this juncture, and the possibility of completing the first synthesis of erythromycin B was alluring. Toward this new objective, it only remained to add a propionate group to C(3) and incorporate a cyclic protecting group between the C(3)–C(5) alcohol pair to give a seco acid derivative of erythromycin B that would be a reasonable candidate for macrolactonization. In the event, selective deprotection of the primary alcohol of **33** followed by oxidation with the Dess–Martin periodinane[29] gave the aldehyde **36** (Scheme 6). Reaction of **36** with tri-*n*-butylcrotylstannane in the presence of $BF_3\cdot OEt_2$ delivered a separable mixture (% yield ratio of 69:6:12:6) of all four possible diastereomeric homoallylic alcohols. As expected, the major, and desired, product was the *syn*-isomer arising from nucleophilic attack according to the Felkin-Anh model. The free hydroxyl group at C(3) of the major adduct was then incorporated into a cyclic *p*-methoxyphenyl (PMP) acetal by oxidative cyclization to give **37**.[28a] A two-step oxidative cleavage of the carbon–carbon double bond in **37** and removal of the C(13) hydroxyl protecting group by hydrogenolysis, the selectivity of which was critically dependent upon solvent, furnished the seco acid derivative **38**.

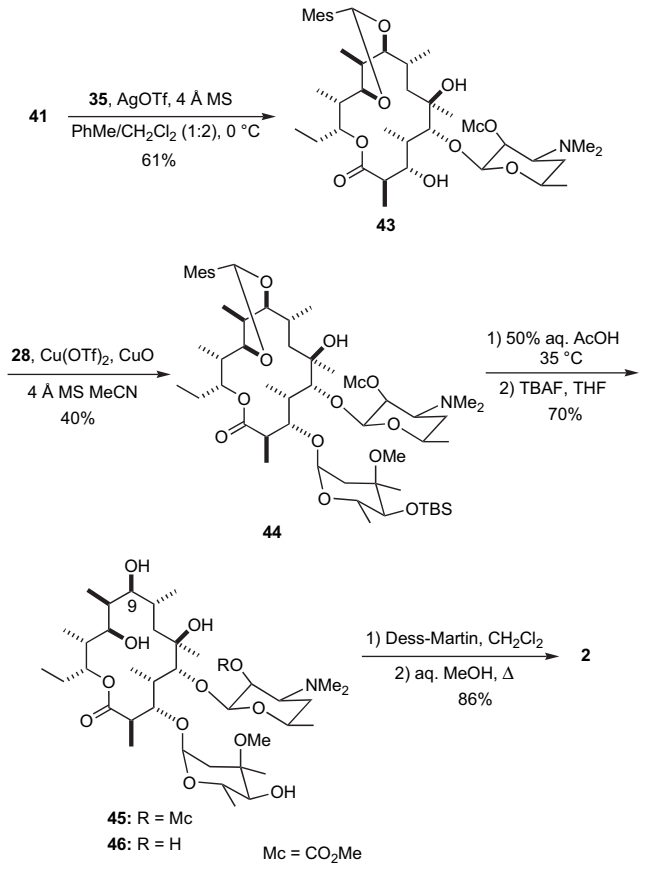
Macrolactonization of **38** following the Yamaguchi protocol proceeded with high efficiency to give the erythronolide B derivative **39**. Although fluoride-induced deprotection of the C(6) tertiary hydroxyl group proceeded smoothly to give **40**, the subsequent removal of the *p*-methoxybenzylidene acetal from the hydroxyl groups at C(3) and C(5) proved somewhat troublesome. Attempts to remove this acetal by hydrogenolysis were unselective and led to mixtures containing products arising from cleavage of the C(9)–C(11) acetal. Hydrolytic removal of the cyclic C(3)–C(5) protecting group proved to be the method of choice, but under the best conditions, the triol **41** was isolated in 70% yield (84% based upon recovered **40**) together with starting material **40** (17%) and 9(*S*)-dihydroerythronolide (**42**) (7%). A more expeditious route to **42** involved the global deprotection of **39** by heating in methanolic HCl and THF, whereby **42**. The 9(*S*)-dihydroerythronolide, which was thus obtained in only 23 steps from commercially available **10**, was identical (TLC, ^1H and ^{13}C NMR, and IR) with an authentic sample prepared by degradation of natural erythromycin B.[24]



Scheme 6.

The next phase of the plan required glycosylating the C(5) and C(3) hydroxyl groups of **41** to append the D-desosamine and L-cladinose residues, respectively, and we relied upon ample precedent in the literature. Accordingly, reaction of **41** with the pyrimidyl thioglycoside **35** in the presence of silver triflate according to a slight modification of a method developed by Tatsuta furnished **43** as a single isomer (Scheme 7).[30] Introducing a protected L-cladinose moiety onto **19** implementing the Woodward protocol,[6] in which lead(II) perchlorate was used to activate the glycosyl donor, failed in our hands. However, we discovered that treating **43** with **28** in the presence of a mixture of copper(II) triflate and copper(II) oxide in acetonitrile provided **44** in 40% yield (65% yield based upon recovered starting glycosyl acceptor

43).[31] Approximately 10% of the corresponding β-anomeric cladinose derivative was also isolated as a side product. Selective hydrolysis of the mesitylene acetal in **44** followed by fluoride-induced removal of the silyl protecting group on the L-cladinose moiety then gave the tetraol **45**. Gratifyingly, oxidation of **45** with 1 equiv of the Dess–Martin periodinane reagent proceeded *exclusively* at the C(9) hydroxyl group. Subsequent removal of the methyl carbonate moiety from the desosamine residue on **45** then delivered erythromycin B (**2**). The synthetic erythromycin B, which was thus obtained via a longest linear sequence of only 30 chemical steps from commercially available **10**, was identical to a natural sample by comparison of TLC, ^{1}H and ^{13}C NMR, and HRMS.



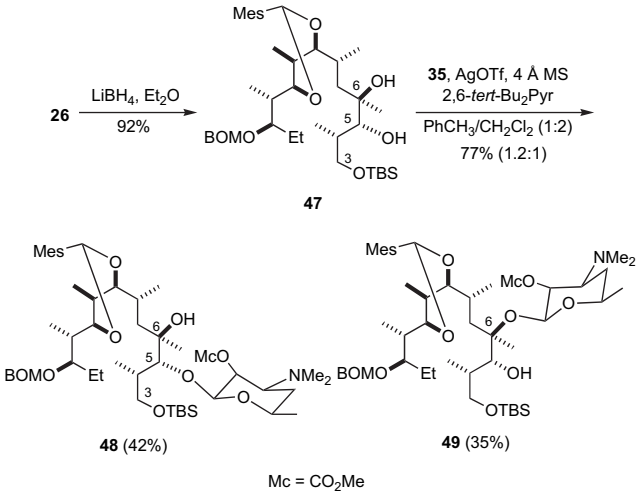
Scheme 7.

As a footnote to the final stage in this first synthesis of erythromycin B, the unusual ability of the Dess–Martin reagent to selectively oxidize secondary alcohols, even in the presence of *unprotected* tertiary amines, based on slight variations in their steric environments is virtually unprecedented. The only reaction that rivals this one is Tatsuta's report of the oxidation of the *N*-oxide of a related compound using a combination of bromine and bis(tributyltin) oxide.[30] However, the need to protect the basic nitrogen atom as its *N*-oxide added two steps to that sequence. In this context, we also discovered that 9(*S*)-dihydroerythronolide B (**46**), which was prepared by heating **45** in aqueous MeOH, may be selectively oxidized using Dess–Martin reagent to give **2**, albeit in somewhat lower overall yield. The scope of selective oxidations of sterically differentiated secondary alcohols using the Dess–Martin reagent certainly merits further study as it could find significant application in the synthesis of complex molecules.

2.7. Re-evaluating glycosylations of seco acid precursors

Our success in completing the first total synthesis of erythromycin B (**2**) notwithstanding, it was difficult to abandon our original goal of preparing **2** by cyclizing a glycosylated seco acid derivative. Our inability to append a desosamine residue onto an advanced intermediate (Scheme 5) did, however, provide some useful insights that led to developing another approach in which a desosamine moiety was introduced onto a different seco acid precursor. We reasoned that our failure to glycosylate **34** with **35** might be a consequence of steric hindrance arising from the bulky TBS protecting group on the hydroxyl function at C(6). It therefore occurred to us that a substrate bearing free hydroxyl groups at C(5) and C(6) might be suitable for additional glycosylation studies. After considering various possibilities, the carbonate **26** reemerged as a possible key intermediate for a renewed endeavor.

It was first necessary to cleave the carbonate moiety in **26**, but this ostensibly simple transformation proved to be more challenging than expected (Scheme 8).[10] Base-induced hydrolysis of the carbonate was sluggish, and heating **26** in aqueous dioxane containing NaOH required forcing conditions under which the TBS protecting group was lost. Reaction of **26** with MeLi gave a C(5) acetate that was also difficult to hydrolyze. Reductive cleavage of the carbonate with $LiAlH_4$ gave **47** in 81% yield, but the 3,5,6-triol, which could be easily separated, was also produced in 13% yield. Cleavage of the carbonate using K-Selectride was slow and somewhat variable in efficiency, although the reaction did occasionally proceed to give **47** in >90% yield. We eventually discovered that the carbonate could be quickly and reproducibly removed to give **47** in excellent yield using $LiBH_4$ in ether.



Scheme 8.

The Woodward group had shown that an erythronolide A derivative having free hydroxy groups at C(5) and C(6) underwent glycosylation with the desosamine derivative **35** to give exclusive reaction at the C(5) hydroxyl group.[6] We

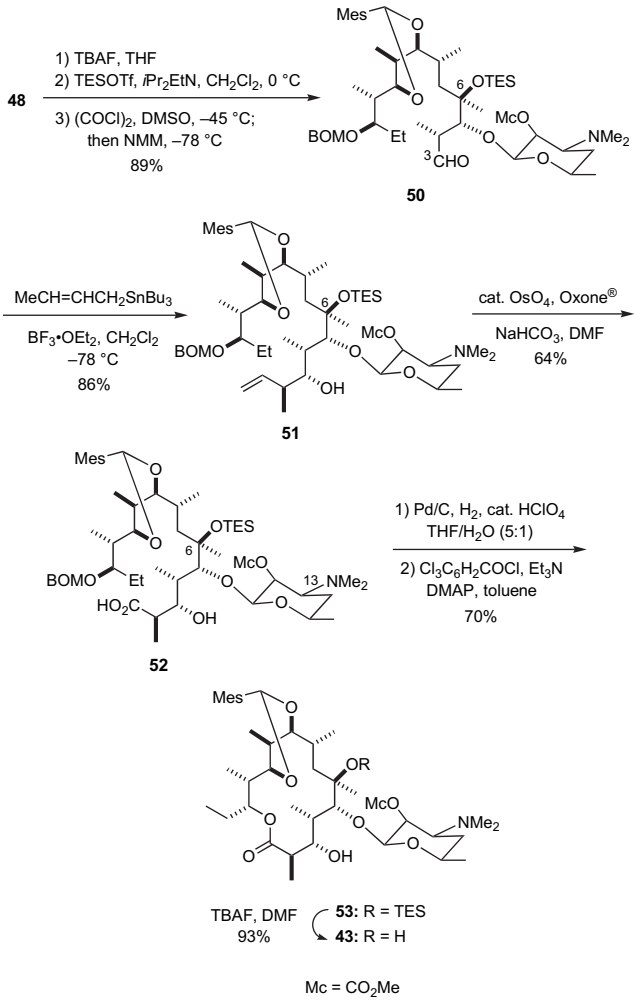
were thus surprised to find that reaction of **47** with **35** under similar conditions in the presence of AgOTf typically gave a separable mixture (1.2:1) of **48** and **49** in 77% yield together with 20–25% of recovered starting **47**. We investigated the use of other glycosyl donors including thioglycosides and glycosyl sulfoxides, trichloroacetimidates and fluorides, but none of these led to any improvements in the reaction. Lower yields of products were obtained, and significant quantities of **49** arising from the remarkably facile glycosylation of the tertiary alcohol at C(6) were invariably isolated. Attempts to improve the regioselectivity by using a stannylene derivative of **47** were equally unsuccessful.[32] Nevertheless, we had finally prepared a glycosylated derivative of a seco acid precursor, so we were obliged to be content with separating the isomeric C(5)- and C(6)-glycosylated products and continuing the synthesis with **48**.

2.8. Cyclization of a glycosylated seco acid: vindication

In order to introduce the remaining three-carbon unit of the erythromycin backbone into **48**, it was first necessary to oxidize the C(3) alcohol of **48** to an aldehyde. Not surprisingly, we found that if the C(6) hydroxyl group was not protected prior to generating the aldehyde at C(3), a five-membered lactol that could not be advanced in the synthesis was unavoidably formed. The most expeditious solution to this problem involved deprotecting the primary alcohol at C(3) of **48** followed by reaction of the resultant diol with excess TES–OTf. The resulting C(3)–C(5) diprotected diol then underwent selective desilylation and Swern oxidation of the primary TES-protected alcohol at C(3) to give **50** (Scheme 9).[33] It was necessary to maintain strict control of the temperature during the course of this reaction to avoid loss of the TES group on the C(6) hydroxyl group. Reaction of **50** with crotylstannane in the presence of $BF_3 \cdot OEt_2$ proceeded in analogy with our previous work to furnish **51** in 86% yield together with about 12% of a mixture of the other three diastereomeric adducts.

Prior to continuing the synthesis, we briefly explored the feasibility of several alternative tactics to introduce the C(1)–C(2) propionate subunit via different aldol reactions involving **50**.[34] However, these efforts did not yield significant quantities of the desired adduct. In the context of preparing a fully glycosylated seco acid, we also conducted a number of experiments to introduce the cladinose residue onto the masked seco acid **51** using **28**, and various derivatives thereof. Owing to a shortage of material, we were unable to fully explore such glycosylations, but these investigations were not encouraging.

Returning to the task at hand, it then remained to oxidize the terminal carbon–carbon double bond of **51** to generate the C(1) carboxylic acid. In our previous work (Scheme 6 and Ref. 24), we had developed two- and three-step protocols for effecting this transformation. Seeking a more expeditious approach, we found that oxidation of **51** to give **52** using a procedure involving an 'organometallic ozonolysis' provided an efficient one-step alternative to those tactics.[35] Removal of the C(13) hydroxyl protecting group by hydrogenolysis under carefully defined conditions gave an unstable hydroxy acid that was cyclized according to the



Scheme 9.

Yamaguchi protocol to furnish **53** in very good overall yield. Deprotection of the C(6) hydroxyl group then delivered **43**. Because we had previously converted **43** into erythromycin B (**2**) (Scheme 7), we had thus finally completed a synthesis of erythromycin B (**2**) that featured cyclization of a glycosylated seco acid derivative as a key step. Our original goal had thus been achieved and our perseverance had been amply rewarded. As we had originally anticipated, this approach to erythromycin B was three steps shorter than our first synthesis.

3. Conclusions

We have thus completed the first total synthesis of erythromycin B (**2**) using two different strategies in the final stages. The first of these followed the classical approach in which a protected macrocyclic lactone was formed by cyclization of a seco acid derivative, and then the desosamine and cladinose residues were sequentially appended to the macrolide leading to erythromycin B. This synthesis was relatively concise and required only 30 steps in the longest linear sequence from the commercially available starting aldehyde **10**. During the course of this work, we also completed a 23-step synthesis of 9(*S*)-dihydroerythronolide B (**42**).

The end game of the second synthesis featured an abiotic approach in which a seco acid bearing a desosamine residue was cyclized to give a monoglycosylated macrocyclic lactone that was then transformed into erythromycin B via a sequence of steps involving refunctionalizations and a glycosylation to introduce the cladinose moiety. This synthesis of **2**, which required a mere 27 steps in the longest linear sequence, represents the first time any macrolide antibiotic has been prepared via an approach wherein a sugar residue was appended prior to the macrolactonization step. This latter strategy was predicated upon our exploratory work that established that both sugars might in principle be introduced prior to the macrolactonization step. However, attempts to prepare a bis-glycosylated seco acid by de novo synthesis have thus far proven unsuccessful.

The ability to cyclize the hydroxy acids derived from **13**, **16**, and **52** clearly illustrates that more structural flexibility in the backbone can be tolerated in the cyclization step than was heretofore recognized. The syntheses of the requisite seco acid derivatives for each of these approaches featured the oxidative transformation of a furan containing C(3)–C(10) to a dioxabicyclo[3.3.1]nonenone that served as a template upon which to create the stereocenters at C(6) and C(8). A stereoselective aldol reaction was used to establish the C(11)–C(15) segment, and a stereoselective crotylation was implemented to introduce C(1)–C(2).

Although our work spanned considerably more than a decade, the journey was ultimately rewarding as it led to a number of exciting new discoveries. That there are still unsolved problems in the area is evident from the fact that the erythromycins and other macrolides continue to be targets of interest in a number of laboratories. These and other investigations directed toward the synthesis of complex molecules reveal that there remains much to learn. Indeed, despite what is widely, albeit erroneously, perceived, our ability as organic chemists to prepare such targets is anything but straightforward. Such endeavors still require extensive experimentation, and the continued development of new and efficient methods for forming carbon–carbon bonds and manipulating functionality fully justifies the effort.

4. Experimental

4.1. General

Solvents and reagents were reagent-grade and used without purification unless otherwise noted. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), and diisopropylamine were distilled from calcium hydride and stored under nitrogen. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were either distilled from potassium/benzophenone ketyl under nitrogen or passed through a column of neutral alumina and stored under argon. Methanol (MeOH) and dimethylformamide (DMF) were passed through a column of molecular sieves and stored under argon. Toluene was either distilled from sodium or passed through a column of Q5 reactant and stored under argon. All reactions were done in flame-dried glassware under nitrogen or argon unless otherwise indicated. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained as solutions in $CDCl_3$ unless otherwise indicated. ^{13}C NMR were obtained as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in parts per million (ppm, δ) and referenced from the solvent. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex; and br, broad. Fourier transform infrared (IR) spectra were obtained as solutions or using sodium chloride plates as indicated, and reported as wave numbers. Analytical thin layer chromatography was performed using Merck 250 micron $60F_{254}$ silica gel plates. The plates were visualized with UV light, ninhydrin, phosphomolybdic acid, *p*-anisaldehyde, and potassium permanganate. Flash column chromatography was performed according to Still's procedure[36] using ICN Silitech 32-63 D 60A silica gel.

4.1.1. (2*S*,3*R*,4*R*,6*R*)-7,7-(Ethylenedithio)-1,3-{[(*R*)-4-methoxybenzylidene]dioxy}-2,4,6-trimethylnonan-4-ol. To a solution of triol **20** (1.95 g, 6.29 mmol) in CH_2Cl_2 (200 mL) were added 4-methoxyphenylmethyl methyl ether (3.75 mL, 25.1 mmol) and DDQ (3.14 g, 13.8 mmol). After stirring for 30 min at room temperature, the mixture was filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (50:1 to 10:1) to give 2.28 g (85%) of acetal as a white solid; mp 107–109 °C; ^{1}H NMR (300 MHz) δ 7.44 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 5.55 (s, 1H), 4.06 (dd, J=11.1, 2.1 Hz), 3.98 (dd, J=11.1, 1.2 Hz), 3.81 (s, 3H), 3.61 (d, J=2.1 Hz, 1H), 3.22–3.02 (comp, 4H), 2.61 (s, 1H), 2.45–2.30 (comp, 2H), 2.10–1.78 (comp, 3H), 1.34 (d, J=6.9 Hz, 3H), 1.24 (m, 1H), 1.19 (s, 3H), 1.17 (d, J=7.1 Hz, 3H), 1.06 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 159.9, 131.4, 127.3, 113.5, 101.7, 84.2, 80.2, 75.2, 73.5, 55.3, 44.3, 40.0, 39.5, 37.1, 34.9, 30.4, 21.6, 21.2, 13.2, 10.6; IR ($CHCl_3$) ν 3564, 2972, 1616, 1518 cm^{-1}; mass spectrum (CI) m/z 426.1889 ($C_{22}H_{34}O_4S_2$ requires 426.1899), 409, 391, 371, 333, 197, 133 (base).

4.1.2. (2*S*,3*R*,4*R*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-7,7-(ethylenedithio)-1,3-{[(*R*)-4-methoxybenzylidene]-dioxy}-2,4,6-trimethylnonane (29). To a solution of the preceding acetal (1.92 g, 4.50 mmol) in CH_2Cl_2 (80 mL) were added diisopropylethylamine (5.10 mL, 29.3 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.10 mL, 13.5 mmol) at 0 °C. After the mixture was stirred 18 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C. The layers were separated and the organic layer was washed with 0.5 M aqueous HCl (60 mL) and saturated aqueous NaCl (40 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1) to afford 2.22 g (91%) of **29** as a colorless oil; ^{1}H NMR (300 MHz) δ 7.47 (d, J=8.7 Hz, 2H), 6.92 (d, J=8.7 Hz, 2H), 5.47 (s, 1H), 4.07 (dd, J=11.0, 2.1 Hz, 1H), 3.96 (d, J=11.0 Hz, 1H), 3.84 (s, 3H), 3.71 (d, J=2.1 Hz, 1H), 3.30–3.15 (comp, 4H), 2.23 (m, 1H), 2.15–1.80 (comp, 4H), 1.60 (m, 1H), 1.35 (s, 3H), 1.31 (d, J=6.8 Hz, 3H), 1.22 (d, J=6.6 Hz, 3H), 1.10 (t, J=7.2 Hz,

3H), 0.87 (s, 9H), 0.02 (s, 3He), 0.00 (s, 3H); ^{13}C NMR (75 MHz) δ 159.8, 131.4 (128.3, 127.6 one of them may be benzene), 113.4, 102.3, 85.2, 80.0, 78.1, 75.6, 55.2, 43.7, 39.9, 39.5, 38.2, 34.5, 30.1, 26.1, 24.4, 19.9, 18.5, 13.7, 10.6, −1.8, −2.1; IR (film) ν 2953, 2930, 2837, 1616, 1512, 1243, 1115, 830 cm^{-1}; mass spectrum (CI) *m*/*z* 541.2826 [$C_{28}H_{49}O_4S_2Si$ (M+H) requires 541.2842] (base), 409.

4.1.3. (2*S*,3*R*,4*R*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-7,7-(ethylenedithio)-3-[(4-methoxybenzyl)oxy]-2,4,6-trimethylnonanol (30). To a solution of **29** (2.22 g, 4.10 mmol) in ether (110 mL) was added a solution of $BH_3\cdot$THF in THF (1.0 M, 24.6 mL, 24.6 mmol) at 0 °C. After stirring for 5 min, $AlCl_3$ (1.10 g, 8.25 mmol) was added and the mixture was stirred for 1 h at 0 °C and for 3 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL), and the organic layer was washed with saturated NaCl (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1 to 10:1) to afford 2.14 g (96%) of **30** as a colorless oil; ^{1}H NMR (500 MHz) δ 7.26 (d, *J*=8.7 Hz, 2H), 6.87 (d, *J*=8.7 Hz, 2H), 4.57 (d, *J*=11.1 Hz, 1H), 4.51 (d, *J*=11.1 Hz, 1H), 3.81 (s, 3H), 3.59–3.48 (m, 2H), 3.23–3.12 (comp, 5H), 2.32 (m, 1H), 2.20 (m, 1H), 2.13 (d, *J*=14.0 Hz, 1H), 2.04 (m, 1H), 1.87 (m, 1H), 1.51 (dd, *J*=14.0, 9.0 Hz, 1H), 1.38 (s, 3H), 1.18 (d, *J*=6.6 Hz, 3H), 1.07 (t, *J*=7.2 Hz, 3H), 1.03 (d, *J*=6.9 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz) δ 159.0, 131.1, 129.0, 113.6, 86.8, 80.4, 80.0, 74.3, 68.7, 55.3, 41.5, 40.0, 39.6, 37.7, 36.0, 35.0, 29.7, 26.4, 20.0, 18.6, 13.0, 10.7, −1.2, −1.3; IR (film) ν 3440, 2926, 1612, 1516, 1464, 1253, 1087, 1042 cm^{-1}; mass spectrum (CI) *m*/*z* 543.2971 [$C_{28}H_{51}O_4S_2Si$ (M+1) requires 543.2998], 307 (base).

4.1.4. (2*R*,3*R*,4*R*,6*R*)-1,4-Bis[(*tert*-butyldimethylsilyl)oxy]-7,7-(ethylenedithio)-3-[(4-methoxybenzyl)oxy]-2,4,6-trimethylnonane. To a solution of **30** (1.02 g, 1.88 mmol) in CH_2Cl_2 (40 mL) were added diisopropylethylamine (1.64 mL, 9.41 mmol) and TBSOTf (0.864 mL, 3.76 mmol) at 0 °C. After the mixture was stirred 1 h at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the organic layer was washed with 0.2 M aqueous HCl (50 mL) and saturated aqueous NaCl (30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (100:1, 50:1) to provide 1.22 g (99%) of product as a colorless oil; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.36 (d, *J*=8.5 Hz, 2H), 6.82 (d, *J*=8.5 Hz, 2H), 4.78 (d, *J*=11.2 Hz, 1H), 4.61 (d, *J*=11.2 Hz, 1H), 3.70 (dd, *J*=9.4, 5.9 Hz, 1H), 3.58 (dd, *J*=9.4, 6.3 Hz, 1H), 3.47 (d, *J*=1.4 Hz, 1H), 3.30 (s, 3H), 2.86–2.74 (comp, 4H), 2.60 (m, 1H), 2.55–2.36 (comp, 2H), 2.10 (m, 1H), 1.95 (m, 1H), 1.86 (m, 1H), 1.34 (d, *J*=6.6 Hz, 3H), 1.28 (d, *J*=6.8 Hz, 3H), 1.20 (t, *J*=7.0 Hz, 3H), 1.08 (s, 9H), 1.00 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H), 0.11 (s, 6H); ^{13}C NMR (75 MHz) δ 159.2, 128.9, 114.5, 86.3, 80.5, 79.7, 73.8, 68.6, 63.0, 55.3, 41.4, 40.0, 39.6, 37.8, 35.4, 26.42, 26.37, 26.0, 25.9, 25.7, 19.9, 12.7, 10.7, −1.2, −1.3, −2.9, −5.3; IR (film) ν 2938, 2850, 1610, 1511, 1462, 1247, 1093, 834, 768 cm^{-1}; mass spectrum (CI) *m*/*z* 657.3858 [$C_{34}H_{65}O_4S_2Si_2$ (M+1) requires 657.3863], 643, 526, 388, 333, 311 (base).

4.1.5. (2*R*,3*R*,4*R*,6*R*)-1,4-Bis[(*tert*-butyldimethylsilyl)oxy]-3-[(4-methoxybenzyl)oxy]-2,4,6-trimethylnonan-7-one (31). To a suspension of thioketal from the preceding experiment (2.55 g, 3.88 mol) and $CaCO_3$ (1.55 g, 15 .5 mmol) in THF (35 mL) and water (7 mL) was added an aqueous solution of $Hg(ClO_4)_2$ (4.0 M, 1.94 mL, 7 76 mmol) dropwise over 5 min at 0 °C. After stirring for 15 min at room temperature, the reaction mixture was diluted with ether (150 mL) and filtered through Celite. The precipitates were washed with ether (200 mL). The filtrates were combined and washed with saturated aqueous NaCl (150 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1) to give 1.92 g (85%) of **31** as a white solid; mp 49–49.5 °C; ^{1}H NMR (300 MHz) δ 7.24 (d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 4.61 (d, *J*=10.9 Hz, 1H), 4.34 (d, *J*=10.9 Hz, 1H), 3.81 (s, 3H), 3.54 (dd, *J*=9.4, 5.9 Hz, 1H), 3.44 (dd, *J*=9.4, 6.6 Hz, 1H), 3.21 (d, *J*=1.8 Hz, 1H), 2.91 (m, 1H), 2.45–2.10 (comp, 4H), 1.46 (m, 1H), 1.17 (s, 3H), 0.99 (t, *J*=7.2 Hz, 3H), 0.91 (d, *J*=7.7 Hz, 3H), 0.89 (d, *J*=7.1 Hz, 3H), 0.90 (s, 9H), 0.85 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 213.1, 159.8, 131.6, 129.5, 114.1, 87.0, 79.1, 75.2, 68.9, 54.8, 41.64, 41.60, 36.2, 34.6, 26.7, 26.4, 26.2, 20.0, 18.59, 18.56, 12.8, 8.0, −1.4, −5.2; IR ($CHCl_3$) ν 2957, 2931, 1712, 1514, 1472, 1463, 1252 cm^{-1}; mass spectrum (CI) *m*/*z* 579.3893 [$C_{32}H_{59}O_5Si_2$ (M−1) requires 579.3901], 566 (base), 449, 154.

4.1.6. (2*R*,3*R*,4*R*,6*R*,8*R*,9*S*,10*R*,11*R*)-11-[(Benzyloxy)methoxy]-1,4-bis[(*tert*-butyldimethylsilyl)oxy]-9-hydroxy-3-[(4-methoxybenzyl)oxy]-2,4,6,8,10-pentamethyltridecan-7-one (32). To a solution of lithium hexamethyldisilazide (2.69 mmol) in THF (24 mL) was added ketone **31** (1.20 g, 2.07 mmol) in THF (12 mL) via cannula over 15 min at −78 °C. The mixture was allowed to warm to −15 °C over 1.5 h and stirred for 30 min. To the mixture cooled to −95 °C aldehyde **23** (880 mg, 3.72 mmol) in THF (12 mL) was added via cannula over 25 min, and then stirred for 1 h at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl (25 mL), and the mixture was allowed to warm to room temperature. After concentration under reduced pressure to remove THF, the residue was extracted with ether (2×60 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1, 10:1) to afford 1.46 g (86%) of **32** as a colorless oil together with small amounts (ca. 2%) of diastereoisomeric adducts; ^{1}H NMR (500 MHz) δ 7.37–7.24 (comp, 5H), 7.24 (d, *J*=8.6 Hz, 2H), 6.85 (d, *J*=8.6 Hz, 2H), 4.84 (d, *J*=6.7 Hz, 1H), 4.78 (d, *J*=6.7 Hz, H), 4.62 (s, 2H), 4.59 (d, 1H, *J*=11.0 Hz, H), 4.37 (d, 1H, *J*=11.0 Hz, 1H), 3.92 (td, *J*=7.0, 1.9 Hz, 1H), 3.87 (dt, *J*=9.7, 2.0 Hz, 1H), 3.80 (s, 3H), 3.63 (d, *J*=2.2 Hz, 1H), 3.55 (dd, *J*=9.5, 5.8 Hz, 1H), 3.46 (dd, *J*=9.5, 6.6 Hz, 1H), 3.19 (d, *J*=1.8 Hz, 1H), 3.10 (m, 1H), 2.72 (qd, *J*=7.1, 2.7 Hz, 1H), 2.22 (qd, *J*=6.5, 1.8 Hz, 1H), 2.15 (dd, *J*=14.3, 7.7 Hz, 1H), 1.72 (m, 1H), 1.65 (m,

1H), 1.53 (dd, *J*=14.3, 3.5 Hz, 1H), 1.47 (m, 1H), 1.16 (s, 3H), 1.04 (d, *J*=7.2 Hz, 3H), 0.98 (d, *J*=7.0 Hz, 3H), 0.94 (d, *J*=7.1 Hz, 3H), 0.91 (t, *J*=7.4 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.72 (d, 3H, *J*=7.0 Hz, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.043 (s, 3H), 0.039 (s, 3H); ^{13}C NMR (125 MHz) δ 219.3, 159.0, 137.9, 131.3, 129.2, 128.4, 127.8, 127.6, 113.6, 95.0, 86.6, 80.0, 78.4, 74.4, 71.4, 69.7, 68.5, 55.2, 45.9, 40.7, 40.5, 37.8, 35.6, 26.5, 26.1, 26.0, 25.0, 20.0, 18.4, 18.3, 12.4, 10.7, 9.7, 8.5, −1.6, −1.7, −5.4; IR (film) ν 3503, 2939, 2856, 1700, 1512, 1459, 1247, 1100, 1036, 830 cm^{-1}; mass spectrum (FAB) *m/z* 815.5304 [$C_{46}H_{79}O_8Si_2$ (M−1) requires 815.5314], 799, 613, 460 (base), 439, 409.

4.1.7. (2*R*,3*R*,4*R*,6*R*,7*S*,8*S*,9*R*,10*R*,11*R*)-11-[(Benzyloxy)-methoxy]-1,4-bis[(*tert*-butyldimethylsilyl)oxy]-3-[(4-methoxybenzyl)oxy]-2,4,6,8,10-pentamethyltridecan-7,9-diol. Acetic acid (3.27 mL, 57.1 mmol) was added slowly to Me_4NBH_4 (1.02 g, 11.5 mmol) at 0 °C. After stirring for 1 h at room temperature, CH_3CN (50 mL) was added and the mixture was cooled to −40 °C. To the mixture was added a solution of **32** (1.17 g, 1.43 mmol) in CH_3CN (30 mL) and stirred for 70 h at −6 to −10 °C. The reaction was quenched by adding saturated $NaHCO_3$ (560 mL) and saturated aqueous potassium sodium tartrate (50 mL) and the mixture was stirred for 30 min at room temperature. After concentration under reduced pressure to remove CH_3CN, the residue was extracted with ether (3×50 mL). The combined organic layers were washed with saturated aqueous potassium sodium tartrate (50 mL) and saturated NaCl (50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (10:1, 7:1) to afford 93 mg (7.9%) of *syn*-diol as a colorless oil and 858 mg (73%) of *anti*-diol as a white solid; mp 84–85 °C; ^{1}H NMR (500 MHz) δ 7.36–7.26 (comp, 7H), 7.24 (d, *J*=8.6 Hz, 2H), 6.58 (d, *J*=8.6 Hz, 2H), 4.86 (d, *J*=7.0 Hz, 1H), 4.78 (d, *J*=7.0 Hz, 1H), 4.73 (d, *J*=12.0 Hz, 1H), 4.64 (d, *J*=12.0 Hz, 1H), 4.61 (d, *J*=11.2 Hz, 1H), 4.42 (d, *J*=11.2 Hz, 1H), 4.01 (br d, *J*=10.2 Hz, 1H), 3.80 (s, 3H), 3.80 (m, 1H), 3.60 (br d, *J*=9.1 Hz, 1H), 3.53 (dd, *J*=9.4, 5.4 Hz, 1H), 3.45 (m, 1H), 3.42 (dd, *J*=9.4, 5.2 Hz, 1H), 3.21 (d, *J*=1.5 Hz, 1H), 2.29 (m, 1H), 1.95 (m, 1H), 1.92–1.81 (comp, 2H), 1.72–1.63 (comp, 3H), 1.52 (m, 1H), 1.32 (s, 3H), 0.96 (d, *J*=7.0 Hz, 3H), 0.94 (t, *J*=7.4 Hz, 3H), 0.88 (s, 9H), 0.86 (d, *J*=6.8 Hz, 3H), 0.84 (s, 9H), 0.78 (d, *J*=7.0 Hz, 3H), 0.76 (d, *J*=7.0 Hz, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz) δ 158.9, 137.6, 131.4, 129.1, 128.4, 127.8, 127.7, 113.6, 94.9, 85.8, 83.2, 80.1, 76.1, 73.9, 71.2, 69.9, 68.8, 55.2, 41.5, 38.1, 37.2, 35.3, 30.3, 26.3, 26.0, 25.4, 24.2, 18.42, 18.39, 14.3, 12.9, 11.4, 11.1, 9.2, −1.3, −1.4, −5.4; IR (film) ν 3480, 2958, 2931, 1514, 1464, 1252 cm^{-1}; mass spectrum (CI) *m/z* 817.5471 [$C_{46}H_{81}O_8Si_2$ (M−1) requires 817.5470], 733, 697, 410, 354, 204, 153 (base).

4.1.8. (2*R*,3*R*,4*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*)-11-[(Benzyloxy)-methoxy]-1,4-bis[(*tert*-butyldimethylsilyl)oxy]-3-[(4-methoxybenzyl)oxy]-2,4,6,8,10-pentamethyl-7,9-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}tridecane (33). To a solution of *anti*-diol from the preceding experiment (807 mg, 0.985 mmol) and mesitaldehyde dimethyl acetal (0.883 mL, 3.94 mmol) in CH_2Cl_2 (30 mL) was added (+)-10-camphorsulfonic acid (114 mg, 0.490 mmol) and the mixture was stirred for 3 h at room temperature. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (30 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (30 mL), and combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (100:1, 30:1) to afford 774 mg (83%) of **33** as a colorless oil; ^{1}H NMR (500 MHz) δ 7.32–7.20 (comp, 7H, Ar), 6.85 (d, *J*=8.7 Hz, 2H), 6.77 (s, 2H), 5.88 (s, 1H), 4.75 (d, *J*=6.5 Hz, 1H), 4.66–4.61 (comp, 3H), 4.45 (d, *J*=12.0 Hz, 1H), 4.41 (d, *J*=11.1 Hz, 1H), 3.89–3.82 (comp, 2H), 3.79 (s, 3H), 3.58 (dd, *J*=9.5, 5.8 Hz, 1H), 3.48 (dd, *J*=9.5, 5.8 Hz, 1H), 3.29 (d, *J*=2.5 Hz, 1H), 3.29 (d, *J*=11.0 Hz, 1H), 2.57 (m, 1H), 2.42 (s, 6H), 2.22 (s, 3H), 2.20 (m, 1H), 1.84 (qd, *J*=7.0, 2.0 Hz, 1H), 1.78–1.65 (comp, 2H), 1.62 (d, *J*=13.4 Hz, 1H), 1.46 (m, 1H), 1.41 (s, 3H), 1.41 (m, 1H), 1.24 (d, *J*=7.0 Hz, 3H), 1.06 (d, *J*=6.4 Hz, 3H), 0.99 (d, *J*=7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.82 (t, *J*=7.5 Hz, 3H), 0.78 (d, *J*=7.0 Hz, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz) δ 158.9, 138.2, 137.8, 136.8, 131.8, 131.4, 129.8, 128.9, 128.32, 128.26, 127.6, 127.4, 113.6, 95.5, 94.7, 86.3, 85.5, 78.7, 76.1, 73.9, 69.3, 68.1, 55.2, 41.5, 37.1, 36.0, 28.8, 28.3, 27.7, 26.4, 26.0, 25.9, 20.9, 20.5, 18.5, 18.3, 18.0, 14.4, 13.0, 10.4, 7.2, −1.2, −1.5, −5.4; IR (film) ν 2942, 2845, 1612, 1460, 1249, 1098, 1038 cm^{-1}; mass spectrum (CI) *m/z* 949.6405 [$C_{56}H_{93}O_8Si_2$ (M+1) requires 949.6409] (base).

4.1.9. (2*S*,3*R*,4*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*)-11-[(Benzyloxy)-methoxy]-4-[(*tert*-butyldimethylsilyl)oxy]-3-[(4-methoxybenzyl)oxy]-2,4,6,8,10-pentamethyl-7,9-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}tridecanol. To a solution of **33** (687 mg, 0.724 mmol) in THF (10 mL) were added acetic acid (0.456 mL, 7.97 mmol) and a solution of tetrabutylammonium fluoride in THF (1.0 M, 7.24 mL, 7.24 mmol). The mixture was stirred for 40 h at room temperature. After concentration under reduced pressure to remove THF, the residue was suspended in water (20 mL) and extracted with ether (2×30 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL) and saturated NaCl (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (10:1, 7:1) to afford 535 mg (88%) of alcohol as a white foam; ^{1}H NMR (500 MHz) δ 7.29–7.23 (comp, 7H), 6.86 (d, *J*=8.7 Hz, 2H), 6.78 (s, 2H), 5.93 (s, 1H), 4.73 (d, *J*=6.0 Hz, 1H), 4.71 (d, *J*=11.2 Hz, 1H), 4.66 (d, *J*=6.0 Hz, 1H), 4.62 (d, *J*=12.0 Hz, 1H), 4.59 (d, *J*=11.2 Hz, 1H), 4.51 (d, *J*=12.0 Hz, 1H), 3.97 (dd, *J*=10.2, 2.0 Hz, 1H), 3.82 (m, 1H), 3.79 (s, 3H), 3.57 (d, *J*=1.8 Hz, 1H), 3.51 (t, *J*=6.0 Hz, 2H), 3.27 (d, *J*=11.0 Hz, 1H), 2.75 (m, 1H), 2.45 (s, 6H), 2.45 (t, *J*=6.0 Hz), 2.23 (s, 3H), 1.97 (m, 1H), 1.82–1.66 (comp, 3H), 1.58 (br d, *J*=13.5 Hz, 1H), 1.43 (s, 3H), 1.56–1.33 (comp, 2H), 1.27 (d, *J*=6.9 Hz, 3H), 1.17 (d, *J*=6.4 Hz, 3H), 0.99 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.81 (t, *J*=7.5 Hz, 3H), 0.79 (d, *J*=7.0 Hz, 3H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz) δ 158.9, 137.8, 136.9, 131.7, 131.5, 129.8, 128.7, 128.3, 127.7, 127.5, 113.6, 95.3, 94.9, 85.6, 84.5, 80.3, 78.2, 76.0, 74.9, 69.7, 67.3, 55.2, 43.6, 36.9, 36.9, 28.8, 27.5, 27.2, 26.6, 25.5, 20.9, 20.6, 18.7,

17.7, 14.1, 12.3, 10.3, 7.1, −1.2, −1.2; IR ($CHCl_3$) ν 2963, 2934, 1612, 1513, 1462, 1251, 1099, 1034 cm^{-1}; mass spectrum (CI) *m/z* 835.5523 [$C_{50}H_{79}O_8Si$ (M+1) requires 835.5544] (base).

4.1.10. (2*R*,3*R*,4*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*)-11-[(Benzyloxy)methoxy]-4-[(*tert*-butyldimethylsilyl)oxy]-3-[(4-methoxybenzyl)oxy]-2,4,6,8,10-pentamethyl-7,9-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}tridecanal (36). To a suspension of the Dess–Martin periodinane (757 mg, 1.78 mmol) in CH_2Cl_2 (8 mL) was added pyridine (0.359 mL, 4.44 mmol). After stirring for 10 min at room temperature, a solution of alcohol from the preceding experiment (741 mg, 0.887 mmol) in CH_2Cl_2 (4 mL) was added at 0 °C, and the mixture was stirred for 2 h at room temperature. To the reaction mixture were added saturated $NaHCO_3$ (10 mL), $Na_2S_2O_3\cdot 5H_2O$ (2.0 g) and ether (40 mL). After stirring the mixture for 15 min at room temperature, layers were separated and the aqueous layer was extracted with ether (20 mL). The combined organic layers were washed with 0.5 M HCl (10 mL) and saturated $NaHCO_3$ (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (10:1) to afford 712 mg (96%) of aldehyde **36** as a colorless oil; ^1H NMR (500 MHz) δ 9.68 (d, *J*=1.8 Hz, 1H), 7.31–7.20 (comp, 5H), 7.20 (d, *J*=8.7 Hz, 2H), 6.83 (d, *J*=8.7 Hz, 2H), 6.77 (s, 2H), 5.85 (s, 1H), 4.72 (d, *J*=6.5 Hz, 1H), 4.64 (d, *J*=11.9 Hz, 1H), 4.62 (d, *J*=6.5 Hz, 1H), 4.44 (d, *J*=11.9 Hz, 1H), 4.40 (d, *J*=10.9 Hz, 1H), 4.34 (d, *J*=10.9 Hz, 1H), 3.87–3.82 (comp, 2H), 3.77 (s, 3H), 3.73 (d, *J*=4.4 Hz, 1H), 3.28 (d, *J*=11.1 Hz, 1H), 2.89 (m, 1H), 2.52 (m, 1H), 2.41 (s, 6H), 2.23 (s, 3H), 1.84–1.66 (comp, 3H), 1.44 (s, 3H), 1.53–1.41 (comp, 3H), 1.27 (d, *J*=7.0 Hz, 3H), 1.26 (d, *J*=7.3 Hz, 3H), 1.08 (d, *J*=6.4 Hz, 3H), 0.87 (s, 9H), 0.82 (t, *J*=7.5 Hz, 3He), 0.80 (d, *J*=7.1 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz) δ 203.4, 159.2, 138.1, 137.8, 136.8, 131.7, 130.1, 129.9, 129.0, 128.3, 127.7, 127.4, 113.7, 95.5, 94.8, 85.3, 84.2, 78.6, 78.6, 76.0, 73.8, 69.4, 55.2, 47.1, 42.4, 37.2, 28.8, 27.8, 27.4, 26.3, 25.9, 20.9, 20.5, 18.4, 18.1, 14.3, 10.5, 10.4, 7.3, −1.5; IR ($CHCl_3$) ν 2935, 1718, 1612, 1513, 1462, 1378, 1251, 1101, 1036 cm^{-1}; mass spectrum (CI) *m/z* 833.5370 [$C_{50}H_{77}O_8Si$ (M+1) requires 833.5388] (base).

4.1.11. (3*S*,4*R*,5*S*,6*R*,7*R*,9*R*,10*S*,11*S*,12*S*,13*S*,14*R*)-14-[(Benzyloxy)methoxy]-7-[(*tert*-butyldimethylsilyl)oxy]-6-[(4-methoxybenzyl)oxy]-3,5,7,9,11,13-hexamethyl-10,12-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}hexadec-1-ene-4-ol. To a solution of aldehyde **36** (550 mg, 0.660 mmol) in CH_2Cl_2 (11 mL) at −78 °C was added a solution of $BF_3\cdot OEt_2$ in CH_2Cl_2 (1.0 M, 0.990 mL, 0.990 mmol). After stirring for 15 min at −78 °C, tri-*n*-butylcrotylstannane (0.438 mL, 1.32 mmol) was added and the mixture was stirred for 5 h at −78 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), warmed to room temperature and extracted with ether (2×50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1, 10:1) to afford 405 mg (69%) of the desired *syn*/Felkin-Anh adduct, together with 132 mg (22%) of the other three diastereomeric adducts; ^1H NMR (500 MHz) δ 7.32–7.20 (comp, 7H), 6.83 (d, *J*=8.7 Hz, 2H), 6.78 (s, 2H), 5.86 (s, 1H), 5.64 (ddd, *J*=17.2, 10.3, 8.9 Hz), 5.06 (m, 1H), 4.97 (dd, *J*=10.3, 1.8 Hz, 1H), 4.72 (d, *J*=6.5 Hz, 1H), 4.67 (d, *J*=10.9 Hz, 1H), 4.65 (d, *J*=12.0 Hz, 1H), 4.63 (d, *J*=6.5 Hz, 1H), 4.51 (d, *J*=10.9 Hz, 1H), 4.45 (d, *J*=12.0 Hz, 1H), 3.89–3.81 (comp, 2H), 3.78 (s, 3H), 3.49 (ddd, *J*=9.6, 4.8, 1.7 Hz, 1H), 3.31 (d, *J*=4.1 Hz, 1H), 3.27 (d, *J*=11.1 Hz, 1H), 2.53 (m, 1H), 2.43 (s, 6H), 2.36–2.26 (comp, 2H), 2.24 (d, *J*=4.8 Hz, 1H), 2.23 (s, 3H), 1.83 (m, 1H), 1.80–1.67 (comp, 2H), 1.61 (br d, *J*=13.8 Hz, 1H), 1.47 (s, 3H), 1.48–1.37 (comp, 2H), 1.26 (d, *J*=7.0 Hz, 3H), 1.11 (d, *J*=6.6 Hz, 3H), 1.07 (d, *J*=6.4 Hz, 3H), 0.97 (d, *J*=7.1 Hz), 0.89 (s, 9H), 0.82 (t, *J*=7.5 Hz, 3H), 0.79 (d, *J*=7.0 Hz, 3H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz) δ 159.0, 140.9, 138.1, 137.8, 136.8, 131.7, 130.9, 129.9, 128.8, 128.3, 127.7, 127.4, 114.8, 113.7, 95.5, 94.7, 90.2, 85.4, 79.8, 78.7, 78.4, 76.1, 74.0, 69.4, 55.2, 42.6, 42.0, 37.2, 36.4, 28.8, 28.7, 27.9, 26.4, 25.9, 20.9, 20.5, 18.5, 18.0, 18.0, 14.4, 10.4, 8.3, 7.3, −1.2, −1.3; IR ($CHCl_3$) ν 3509, 2962, 2934, 1612, 1514, 1463, 1252, 1099, 1035 cm^{-1}; mass spectrum (CI) *m/z* 888.5928 ($C_{54}H_{84}O_8Si$ requires 888.5935), 770, 343 (base).

4.1.12. (3*S*,4*R*,5*S*,6*R*,7*R*,9*R*,10*S*,11*S*,12*S*,13*S*,14*R*)-14-[(Benzyloxy)methoxy]-7-[(*tert*-butyldimethylsilyl)oxy]-4,6-{[(*R*)-4-methoxybenzylidene]dioxy}-3,5,7,9,11,13-hexamethyl-10,12-{[(*R*)-2,4,6-trimethylbenzylidene]-dioxy}hexadecene (37). To a solution of the homoallylic alcohol from the preceding experiment (195 mg, 0.219 mmol) in CH_2Cl_2 (5 mL) was added powdered molecular sieves 3 Å (400 mg). After stirring 30 min at room temperature, DDQ was added and the mixture was stirred for 30 min at room temperature. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (5 mL), and filtered through Celite. The precipitates were washed with ether (25 mL), and the filtrates were combined. The layers were separated and the aqueous layer was extracted with ether (10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1) to give 177 mg (91%) of **37** as a white foam; ^1H NMR (500 MHz) δ 7.44 (d, *J*=8.7 Hz, 2H), 7.34–7.24 (comp, 5H), 6.88 (d, *J*=8.7 Hz, 2H), 6.78 (s, 2H), 5.92 (s, 1H), 5.56 (ddd, *J*=17.2, 10.3, 8.7 Hz, 1H), 5.46 (s, 1H), 5.12 (m, 1H), 5.04 (dd, *J*=10.3, 1.7 Hz, 1H), 4.76 (d, *J*=6.5 Hz, 1H), 4.68 (d, *J*=6.5 Hz, 1H), 4.64 (d, *J*=12.0 Hz, 1H), 4.54 (d, *J*=12.0 Hz, 1H), 3.90 (dd, *J*=10.1, 2.1 Hz, 1H), 3.86 (m, 1H), 3.81 (s, 3H), 3.49 (d, *J*=2.0 Hz, 1H), 3.36 (dd, *J*=10.0, 1.8 Hz, 1H), 3.31 (d, *J*=11.1 Hz, 1H), 2.45 (s, 6H), 2.50–2.34 (comp, 2H), 2.23 (s, 3H), 1.85 (m, 1H), 1.80–1.65 (comp, 3H), 1.60–1.40 (comp, 3H), 1.34 (s, 3H), 1.28 (d, *J*=7.6 Hz, 3H), 1.10 (d, *J*=6.5 Hz, 3H), 1.08 (d, *J*=6.8 Hz, 3H), 1.04 (d, *J*=6.4 Hz, 3H), 0.86 (s, 9H), 0.83 (t, *J*=7.5 Hz, 3H), 0.81 (d, *J*=7.1 Hz, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz) δ 159.7, 139.2, 138.1, 137.9, 136.9, 131.8, 131.7, 129.9, 128.3, 127.6, 127.5, 127.4, 115.6, 113.4, 101.5, 95.7, 94.8, 85.7, 85.6, 85.3, 78.9, 77.4, 76.1, 69.5, 55.3, 43.7, 39.5, 37.3, 31.5, 28.6, 28.1, 26.3, 26.1, 26.0, 20.9, 20.6, 18.5, 18.2, 17.5, 14.4, 10.4, 8.2, 7.3, −1.5, −1.7; IR ($CHCl_3$) ν 2957, 2930, 1614, 1517, 1458, 1249,

1108, 1035 cm^{-1}; mass spectrum (CI) *m/z* 886.5765 ($C_{54}H_{82}O_8Si$ requires 886.5779) 835, 117 (base).

4.1.13. (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*,9*S*,10*S*,11*S*,12*S*,13*R*)-13-[(Benzyloxy)methoxy]-6-[(*tert*-butyldimethylsilyl)oxy]-3,5-{[(*R*)-4-methoxybenzylidene]dioxy}-2,4,6,8,10,12-hexamethyl-9,11-{[(*R*)-2,4,6-trimethylbenzylidene]-dioxy}pentadecanal. Ozone was passed over the surface of a solution of olefin **37** (115 mg, 0.131 mmol) in CH_2Cl_2 (40 mL) and pyridine (0.4 mL) containing 0.5 mg of Sudan III at −78 °C until the red color began to fade. Triphenylphosphine (170 mg, 0.65 mmol) was added and the mixture was stirred for 2 h at room temperature. The mixture was washed with 0.5 M HCl (15 mL) and saturated aqueous $NaHCO_3$ (15 mL), dried (Na_2SO_4) and then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1, 10:1) to afford 99 mg (85%) of aldehyde as a white foam; ^1H NMR (500 MHz) δ 9.71 (d, J=2.0 Hz, 1H), 7.43 (d, J=8.8 Hz, 2H), 7.40–7.25 (comp, 5H), 6.89 (d, J=8.8 Hz, 2H), 6.78 (s, 2H), 5.92 (s, 1H), 5.55 (s, 1H), 4.79 (d, J=6.5 Hz, 1H), 4.69 (d, J=6.5 Hz, 1H), 4.65 (d, J=12.0 Hz, 1H), 4.53 (d, J=12.0 Hz, 1H), 3.93–3.87 (comp, 2H), 3.85 (m, 1H), 3.81 (s, 3H), 3.58 (d, J=2.1 Hz, 1H), 3.30 (d, J=11.1 Hz, 2H), 2.83 (m, 1H), 2.46 (s, 6H), 2.37 (m, 1H), 2.23 (s, 3H), 1.90 (m, 1H), 1.85 (m, 1H), 1.77 (m, 1H), 1.72 (m, 1H), 1.61 (m, 1H), 1.48–1.42 (comp, 2H), 1.33 (s, 3H), 1.28 (d, J=7.0 Hz, 3H), 1.21 (d, J=7.0 Hz, 3H), 1.11 (d, J=6.9 Hz, 3H), 1.04 (d, J=6.4 Hz, 3H), 0.86 (s, 9H), 0.83 (t, J=7.5 Hz, 3H), 0.81 (d, J=7.0 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz) δ 202.7, 159.9, 138.2, 137.9, 136.9, 131.7, 131.2, 129.9, 128.3, 127.6, 127.5, 127.4, 113.5, 101.8, 95.7, 94.8, 85.2, 84.7, 81.8, 78.8, 77.4, 76.1, 69.6, 55.3, 48.1, 43.8, 37.2, 31.8, 28.6, 28.1, 26.1, 26.0, 25.9, 20.9, 20.7, 18.5, 18.3, 14.4, 11.2, 10.4, 8.9, 7.3, −1.5, −1.7; IR ($CHCl_3$) ν 2963, 2934, 1722, 1614, 1517, 1458, 1378, 1249, 1105, 1035 cm^{-1}; mass spectrum (CI) *m/z* 889.5637 [$C_{53}H_{81}O_9Si$ (M+1) requires 889.5650] (base).

4.1.14. (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*,9*S*,10*S*,11*S*,12*S*,13*R*)-13-[(Benzyloxy)methoxy]-6-[(*tert*-butyldimethylsilyl)oxy]-3,5-{[(*R*)-4-methoxybenzylidene]dioxy}-2,4,6,8,10,12-hexamethyl-9,11-{[(*R*)-2,4,6-trimethylbenzylidene]-dioxy}pentadecanoic acid. To a solution of aldehyde from the preceding experiment (87 mg, 0.061 mmol) in THF (5 mL) and 0.1 M aqueous Na_2HPO_4 (0.5 mL) was added *m*-CPBA (50–60% purity, 135 mg, 0.39 mmol). The mixture was stirred for 15 h at room temperature. $Na_2S_2O_3\cdot 5H_2O$ (150 mg, mmol) was added, and the resulting mixture was stirred for 30 min at room temperature. After concentration under reduced pressure to remove THF, the residue was suspended in ether (30 mL), and washed with saturated aqueous $NaHCO_3$ (2×10 mL), 0.5 M HCl (10 mL), and saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue obtained was purified by flash chromatography, eluting with hexanes/EtOAc (5:1) to afford 89 mg (ca. 100%) of acid as a white film; ^1H NMR (500 MHz) δ 7.45 (d, J=8.7 Hz, 2H), 7.29–7.18 (comp, 5H), 6.91 (d, J=8.7 Hz, 2H), 6.77 (s, 2H), 5.99 (s, 1H), 5.59 (s, 1H), 5.05 (d, J=6.9 Hz, 1H), 4.66 (d, J=6.9 Hz, 1H), 4.62 (d, J=11.7 Hz, 1H), 4.41 (d, J=11.7 Hz, 1H), 3.98–3.94 (comp, 2H), 3.91 (dd, J=10.5, 1.2 Hz, 1H), 3.82 (s, 3H), 3.78 (dd, J=10.3, 1.9 Hz), 3.27 (d, J=10.7 Hz, 1H), 2.80 (m, 1H), 2.54 (m, 1H), 2.47 (s, 6H), 2.22 (s, 3H), 1.98–1.80 (comp, 3H), 1.77 (m, 1H), 1.62–1.53 (comp, 2H), 1.34 (s, 3H), 1.32 (m, 1H), 1.30 (d, J=6.3 Hz, 3H), 1.28 (d, J=7.0 Hz, 3H), 1.19 (d, J=6.4 Hz, 3H), 1.13 (d, J=6.8 Hz, 3H), 0.83 (t, J=7.5 Hz, 3H), 0.81 (d, J=7.0 Hz, 3H), 0.78 (s, 9H), −0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (125 MHz) δ 175.7, 160.0, 137.9, 137.5, 136.8, 131.4, 131.1, 129.8, 128.3, 127.8, 127.6, 113.5, 102.8, 95.2, 95.0, 86.5, 86.1, 83.8, 80.3, 78.6, 76.4, 69.7, 55.3, 44.4, 41.2, 35.9, 32.3, 28.8, 28.5, 27.1, 26.1, 25.4, 20.9, 20.6, 18.4, 17.2, 14.8, 14.6, 10.1, 8.2, 7.0, −2.0, −2.2; IR ($CHCl_3$) ν 2954, 2933, 1728, 1614, 1517, 1458, 1378 cm^{-1}; mass spectrum (CI) *m/z* 905.5580 [$C_{53}H_{81}O_{10}Si$ (M+1) requires 905.5599] (base), 798.

4.1.15. (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*,9*S*,10*S*,11*S*,12*S*,13*R*)-6-[(*tert*-Butyldimethylsilyl)-oxy]-13-hydroxy-3,5-{[(*R*)-4-methoxybenzylidene]dioxy}-2,4,6,8,10,12-hexamethyl-9,11-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}pentadecanoic acid (38). To a solution of acid from the preceding experiment (61 mg, 0.067 mmol) in a mixture of methanol (9.6 mL) and THF (2.4 mL) was added 10% palladium on charcoal (61 mg). The mixture was stirred under an atmosphere of hydrogen for 3.5 h at room temperature. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue obtained was purified by flash chromatography, eluting with hexanes/EtOAc (4:1, 2:1, 1:1) to afford 53 mg (99%) of **38** as a white foam; ^1H NMR (500 MHz) δ 7.46 (d, J=8.7 Hz, 2H), 6.91 (d, J=8.7 Hz, 2H), 6.83 (s, 2H), 6.02 (s, 1H), 5.61 (s, 1H), 4.03 (m, 1H), 4.00 (br s, 1H), 3.89 (dd, J=10.3, 1.0 Hz, 1H), 3.82 (s, 3H), 3.71 (dd, J=10.4, 1.8 Hz, 1H), 3.31 (d, J=10.6 Hz, 1H), 2.75 (m, 1H), 2.63 (m, 1H), 2.52 (s, 6H), 2.25 (s, 3H), 1.94 (m, 1H), 1.82–1.72 (comp, 2H), 1.59–1.50 (comp, 2H), 1.36–1.24 (comp, 2H), 1.34 (s, 3H), 1.30 (d, J=6.8 Hz, 3H), 1.28 (d, J=7.0 Hz, 3H), 1.24 (d, J=6.4 Hz, 3H), 1.12 (d, J=6.8 Hz, 3H), 0.93 (t, J=7.4 Hz, 3H), 0.78 (s, 9H), 0.75 (d, J=7.0 Hz, 3H), −0.06 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (125 MHz) δ 177.1, 160.0, 138.1, 137.2, 131.5, 131.1, 129.8, 127.9, 113.5, 103.1, 94.9, 86.7, 86.3, 84.1, 78.4, 76.9, 72.4, 55.2, 43.7, 41.7, 38.2, 32.3, 28.4, 27.9, 27.2, 26.9, 26.1, 20.9, 20.5, 18.4, 17.3, 15.0, 14.5, 10.7, 8.1, 7.3, −2.1, −2.3; IR ($CHCl_3$) ν 3534, 2937, 1723, 1614, 1518, 1460 cm^{-1}; mass spectrum (CI) *m/z* 785.5017 [$C_{45}H_{73}O_9Si$ (M+1) requires 785.5024], 257 (base).

4.1.16. (9*S*)-6-*O*-*tert*-Butyldimethylsilyl-3,5-*O*-[(*R*)-4-methoxybenzylidene]-9,11-*O*-[(*R*)-2,4,6-trimethylbenzylidene]-9-dihydroerythronolide B (39). To a solution of **38** (30 mg, 0.038 mol) in toluene (2.0 mL) were added 4-dimethylaminopyridine (2.0 mg, 0.020 mmol), triethylamine (26 μL, 0.19 mmol), and 2,3,4-trichlorobenzoyl chloride (9.0 μL, 0.057 mmol). After stirring for 15 min at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the mixture was extracted with ether (2×10 mL). The combined organic layers were washed with 0.5 M HCl (5 mL) and saturated aqueous $NaHCO_3$ (15 mL), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1) to afford 27 mg (93%) of **39** as a white film; ^1H NMR (500 MHz) δ 7.47

(d, J=8.7 Hz, 2H), 6.92 (d, J=8.7 Hz, 2H, 6.83 (s, 2H), 6.03 (s, 1H), 5.65 (s, 1H), 5.38 (dd, J=10.5, 3.6 Hz, 1H), 3.98 (br s, 1H), 3.88 (d, J=10.7 Hz, 1H), 3.82 (s, 3H), 3.60 (br d, J=9.3 Hz, 1H), 3.28 (d, J=10.9 Hz, 1H), 2.86 (m, 1H), 2.57 (s, 6H), 2.57 (m, 1H), 2.24 (s, 3H), 1.87 (m, 1H), 1.75 (m, 1H), 1.73–1.64 (comp, 2H), 1.51 (d, J=14.2 Hz, 1H), 1.55–1.32 (comp, 2H), 1.33 (s, 3H), 1.30 (d, J=6.6 Hz, 3H), 1.24 (d, J=6.6 Hz, 3H), 1.23 (d, J=6.2 Hz, 3H), 1.15 (d, J=6.6 Hz, 3H), 0.88 (d, J=7.2 Hz, 3H), 0.81 (t, J=7.3 Hz, 3H), 0.80 (s, 9H), −0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz) δ 175.3, 160.0, 138.0, 137.3, 131.4, 131.0, 129.8, 127.8, 113.5, 103.4, 95.3, 87.3, 85.7, 84.9, 78.5, 76.7, 75.9, 55.3, 43.2, 41.9, 39.6, 32.3, 28.4, 27.0, 26.9, 26.2, 25.4, 20.9, 20.7, 18.4, 17.7, 14.1, 13.6, 10.3, 8.4, 7.5, −2.0, −2.2; IR ($CHCl_3$) ν 2970, 2936, 1715, 1614, 1518, 1457, 1251 cm^{-1}; mass spectrum (CI) m/z 767.4916 [$C_{45}H_{71}O_8Si$ (M+1) requires 767.4918] (base).

4.1.17. (9*S*)-3,5-*O*-[(*R*)-4-Methoxybenzylidene]-9,11-*O*-[(*R*)-2,4,6-trimethylbenzylidene]-9-dihydroerythronolide B (40). A solution of **39** (145 mg, 0.189 mmol) was stirred with tetrabutylammonium fluoride (3.78 mL of 1.0 M, 3.78 mmol) in 10 mL of THF at 60 °C for 28 h. After cooling to room temperature, the reaction was quenched with 0.5 M HCl (5 mL), and the mixture was extracted with ether (2×10 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (8:1, 4:1) to afford 117 mg (93%) of **40** as a white foam; ^{1}H NMR (500 MHz) δ 7.47 (d, J=8.7 Hz, 2H), 6.94 (d, J=8.7 Hz, 2H), 6.84 (s, 2H), 6.05 (s, 1H), 5.72 (s, 1H), 5.40 (dd, J=10.4, 3.5 Hz, 1H), 4.10 (br s, 1H), 3.89 (d, J=10.6 Hz, 1H), 3.83 (s, 3H), 3.61 (d, J=9.0 Hz, 1H), 3.35 (d, J=10.9 Hz, 1H), 2.89 (m, 1H), 2.57 (s, 6H), 2.57 (m, 1H), 2.39 (s, 1H), 2.25 (s, 3H), 1.92 (q, J=6.7 Hz, 1H), 1.79 (q, J=6.7 Hz, 1H), 1.73–1.67 (comp, 2H), 1.56 (d, J=14.2 Hz, 1H), 1.44–1.35 (comp, 2H), 1.33 (s, 3H), 1.32 (d, J=6.7 Hz, 3H), 1.27 (d, J=6.5 Hz, 3H), 1.25 (d, J=6.6 Hz, 3H), 1.16 (d, J=6.7 Hz, 3H), 0.88 (d, J=7.2 Hz, 3H), 0.81 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz) δ 175.2, 160.1, 138.1, 137.2, 131.3, 130.8, 129.8, 127.5, 113.6, 103.2, 95.3, 87.2, 85.7, 85.0, 76.8, 75.8, 75.0, 55.3, 41.7, 40.0, 39.4, 31.9, 28.3, 27.0, 26.7, 25.4, 20.9, 20.6, 17.4, 13.9, 13.6, 10.2, 8.0, 7.5; IR ($CHCl_3$) ν 3580, 2933, 1718, 1615, 1518, 1457, 1374, 1246, 1179, 1102 cm^{-1}; mass spectrum (CI) m/z 653.4051 [$C_{39}H_{57}O_8$ (M+1) requires 653.4053] (base).

4.1.18. (9*S*)-9,11-*O*-[(*R*)-2,4,6-Trimethylbenzylidene]-9-dihydroerythronolide B (41). A solution of **40** (46 mg, 0.070 mmol), 5% KH_2PO_4 (0.9 mL), and 0.5 M HCl (1.8 mL) was stirred in THF at 50 °C for 14 h. After concentration under reduced pressure to remove THF, the residue was suspended in ether (30 mL), and washed with saturated aqueous $NaHCO_3$ (2×10 mL) and saturated aqueous NaCl (10 mL). The organic layer was concentrated under reduced pressure, and the residue obtained was purified by flash chromatography, eluting with hexanes/EtOAc (10:1, 4:1, 2:1, 1:1) to afford 26 mg (70%) of **41** as a white foam, and 8 mg of **40** (17%); ^{1}H NMR (500 MHz) δ 6.81 (s, 2H), 6.06 (s, 1H), 5.29 (dd, J=10.3, 3.6 Hz, 1H), 4.12 (d, J=2.2 Hz, 1H), 4.05 (d, J=10.3 Hz, 1H), 3.54 (d, J=9.7 Hz, 1H), 3.52 (s, 1H), 3.29 (d, J=10.8 Hz, 1H), 3.00 (s, 1H), 2.76–2.70 (m, 1H), 2.54 (s, 6H), 2.23 (s, 3H), 2.04 (s, 1H), 1.73–1.63 (comp, 5H), 1.42–1.32 (comp, 2H), 1.31 (s, 3H), 1.29 (d, J=7.1 Hz, 3H), 1.28 (d, J=6.7 Hz, 3H), 1.25 (d, J=6.9 Hz, 3H), 1.23 (d, J=6.2 Hz, 3H), 1.02 (d, J=6.8 Hz, 3H), 0.81 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz) δ 175.9, 138.1, 137.4, 131.4, 129.9, 95.1, 85.5, 80.9, 79.8, 76.8, 75.8, 75.1, 43.6, 41.7, 39.3, 36.1, 28.4, 26.9, 26.3, 25.3, 20.9, 20.6, 17.1, 15.1, 13.1, 10.3, 7.6, 6.0; IR ($CHCl_3$) ν 3694, 2976, 1724, 1467, 1301, 1095 cm^{-1}; mass spectrum (CI) m/z 535.3615 [$C_{31}H_{51}O_7$ (M+1) requires 535.3635], 517, 415.

4.1.19. (9*S*)-9-Dihydro-5-*O*-(2-*O*-(methoxycarbonyl)-β-D-desosaminyl)-9,11-*O*-[(*R*)-2,4,6-trimethylbenzylidene]erythronolide B (43). To a stirred suspension of silver triflate (289 mg, 1.12 mmol) and powdered 4 Å molecular sieves (200 mg) in dry CH_2Cl_2/toluene (1:1, 1 mL) at 0 °C were added a solution of **41** (40 mg, 0.075 mmol) in dry CH_2Cl_2 (0.5 mL) and a solution of **35** (122 mg, 0.37 mmol) in dry CH_2Cl_2 (0.5 mL) under argon. After stirring for 1 h at 0 °C in the dark, the reaction was quenched with saturated $NaHCO_3$ (2 mL). EtOAc (10 mL) was added and the suspension was filtered through a pad of Celite (20 mmHg). The layers were separated, and the aqueous layer was extracted with EtOAc (2×5 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with toluene/acetone (9:1, 5:1) to afford 25 mg (61%) of **43** as a white foam; ^{1}H NMR (500 MHz) δ 6.80 (s, 2H), 6.07 (s, 1H), 5.21 (dd, J=10.8, 3.6 Hz, 1H), 4.71 (d, J=7.7 Hz, 1H), 4.59 (dd, J=10.4, 7.7 Hz, 1H), 4.54 (br s, 1H), 4.02 (d, J=2.0 Hz, 1H), 3.94 (d, J=10.0 Hz, 1H), 3.80 (s, 3H), 3.72–3.66 (m, 1H), 3.61 (d, J=9.4 Hz, 1H), 3.25 (d, J=10.4 Hz, 1H), 2.79–2.73 (m, 1H), 2.68 (br s, 1H), 2.66–2.60 (m, 1H), 2.55 (s, 6H), 2.51–2.45 (m, 1H), 2.21 (s, 6H), 2.02 (s, 3H), 1.81–1.74 (comp, 2H), 1.70–1.58 (comp, 3H), 1.46–1.40 (m, 1H), 1.35 (m, 1H), 1.28 (d, J=7.6 Hz, 3H), 1.27 (d, J=7.6 Hz, 3H), 1.26 (s, 3H), 1.24 (m, 3H), 1.22 (d, J=7.2 Hz, 3H), 0.96 (d, J=6.5 Hz, 3H), 0.79 (t, J=7.3 Hz, 3 H); ^{13}C NMR (125 MHz) δ 175.9, 155.1, 137.9, 137.4, 131.5, 129.8, 103.2, 95.0, 93.9, 85.9, 77.9, 75.7, 75.4, 75.3, 75.0, 70.4, 63.9, 55.1, 44.3, 41.2, 40.7, 39.6, 37.5, 29.3, 28.5, 27.9, 26.9, 25.2, 20.8, 20.8, 16.9, 15.7, 14.2, 13.1, 10.3, 7.5; IR ($CHCl_3$) ν 3667, 3575, 2975, 2937, 1756, 1724, 1612, 1455, 1442, 1269, 1173, 1094, 1040, 995 cm^{-1}; mass spectrum (CI) m/z 750.4792 [$C_{41}H_{68}NO_{11}$ (M+1) requires 750.4792] (base), 631, 279.

4.1.20. (9*S*)-3-*O*-(4-*O*-(*tert*-Butyldimethylsilyl)-α-L-cladinosyl)-9-dihydro-5-*O*-(2-*O*-(methoxycarbonyl)-β-D-desosaminyl)-9,11-*O*-[(*R*)-2,4,6-trimethylbenzylidene]-erythronolide B (44). To a stirred suspension of **43** (45 mg, 0.060 mmol), **28** (184 mg, 0.48 mmol), copper oxide (347 mg, 4.34 mmol), and powdered 4 Å molecular sieves (800 mg) in dry acetonitrile (1 mL) was added copper(II) trifluoromethanesulfonate (347 mg, 0.96 mmol) as a solid under argon at room temperature. After stirring for 2 h at room temperature, the reaction was quenched with saturated $NaHCO_3$ (2 mL). EtOAc (10 mL) was added, and the suspension was filtered through a pad of Celite. The layers were separated,

and the aqueous layer was extracted with EtOAc (2×5 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with toluene/acetone (15:1, 10:1, 5:1) to afford 25 mg (40%) of **44** together with 6.3 mg (10%) of the corresponding β-anomer, and 17 mg (38%) of starting material; ^{1}H NMR (500 MHz) δ 6.80 (s, 2H), 6.07 (s, 1H), 5.32 (d, J=4.8 Hz, 1H), 5.19 (dd, J=10.4, 3.6 Hz, 1H), 4.72–4.62 (comp, 2H), 4.17–4.14 (m, 1H), 4.12–4.06 (m, 1H), 3.94 (d, J=2.6 Hz, 1H), 3.78 (br s, 3H), 3.38 (s, 3H), 3.37 (d, J=8.2 Hz, 1H), 3.29 (d, J=9.6 Hz, 1H), 3.16 (d, J=9.0 Hz, 1H, C9-H), 2.95–2.85 (m, 1H), 2.77–2.73 (m, 1H), 2.70–2.64 (m, 1H), 2.52 (s, 6H), 2.44 (d, J=13.2 Hz, 1H), 2.30 (br s, 6H), 2.23 (s, 3H), 1.82–1.78 (m, 1H), 1.70–1.62 (comp, 3H), 1.53 (dd, J=15.1, 5.1 Hz, 1H), 1.44–1.36 (m, 1H), 1.28–1.25 (comp, 9H), 1.20 (d, J=8.0 Hz, 3H), 1.14 (d, J=6.2 Hz, 3H), 1.08 (s, 3H), 0.94–0.91 (comp, 5H), 0.90 (s, 9H), 0.83 (d, J=7.0 Hz, 3H), 0.82 (t, J=7.2 Hz, 3H), 0.13 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz) δ 178.0, 155.2, 137.8, 137.7, 131.5, 129.8, 97.5, 95.2, 94.8, 86.9, 80.7, 78.4, 75.5, 75.2, 75.1, 73.6, 67.9, 65.6, 62.1, 55.5, 45.3, 43.9, 40.5, 39.1, 38.4, 35.4, 29.7, 29.3, 27.5, 26.3, 25.1, 25.0, 22.9, 22.7, 21.0, 20.9, 19.5, 18.4, 17.9, 14.1, 13.8, 13.1, 10.3, 8.0, 7.5, −2.6, −4.1; IR ($CHCl_3$) ν 2931, 2856, 1748, 1727, 1461, 1442, 1383, 1272, 1183, 1106, 1096, 1037, 993 cm^{-1}; mass spectrum (CI) m/z 1022.6623 [$C_{55}H_{96}NO_{14}Si$ (M+1) requires 1022.6600] (base), 750, 630, 285.

4.1.21. (9*S*)-3-*O*-(α-L-Cladinosyl)-9-dihydro-5-*O*-(2-*O*-(methoxycarbonyl)-β-D-desosaminyl)erythronolide B (45). A solution of **44** (16 mg, 0.016 mmol) in acetic acid (1 mL) and water (1 mL) was stirred for 14 h at 35 °C. The reaction was cooled to room temperature, and poured into a mixture of ether (5 mL) and iced saturated $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with ether (2×5 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and then concentrated under reduced pressure to provide the C(9)/C(11) diol as an opaque film; mass spectrum (CI) m/z 891.5733 [$C_{45}H_{85}NO_{14}Si$ (M+1) requires 891.5739] 620, 241, 156. The crude diol thus obtained was dissolved in dry THF (1 mL) and cooled to 0 °C, whereupon a solution of tetrabutylammonium fluoride in THF (1.0 mL of 1.0 M, 1.0 mmol) was added and the reaction stirred for 3 h at room temperature. After addition of ether (10 mL), the reaction was quenched with 0.1 M HCl (5 mL) at 0 °C, and the layers were separated. The aqueous layer was extracted with ether (2×5 mL), and the combined organic layers were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with MeOH/CH_2Cl_2 (2% MeOH/CH_2Cl_2, 5% MeOH/CH_2Cl_2, 10% MeOH/CH_2Cl_2) to afford 8.7 mg of **45** as a white foam (70%); ^{1}H NMR (500 MHz) δ 5.07–5.04 (m, 1H), 4.97 (d, J=4.2 Hz, 1H), 4.68–4.60 (comp, 2H), 4.45 (br s, 1H), 4.19 (br s, 1H), 4.15 (dd, J=7.6, 1.3 Hz, 1H), 4.01–3.95 (comp, 2H), 3.77–3.71 (m, 1H), 3.72 (s, 3H), 3.64 (d, J=14.7 Hz, 1H), 3.60–3.54 (m, 1H), 3.50–3.45 (m, 1H), 3.35 (s, 3H), 3.03 (dd, J=9.7, 9.2 Hz, 1H), 2.90–2.81 (comp, 2H), 2.35 (br s, 6H), 2.35–2.30 (m, 1H), 2.27 (d, J=9.8 Hz, 1H), 2.17–2.11 (m, 1H), 1.93–1.85 (comp, 2H), 1.81–1.67 (comp, 2H), 1.60–1.53 (comp, 2H), 1.51–1.44 (m, 1H), 1.42–1.36 (comp, 2H), 1.30 (d, J=6.2 Hz, 3H), 1.27 (s, 3H), 1.24 (s, 3H), 1.23 (d, J=6.2 Hz, 3H), 1.18 (d, J=7.2 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H), 1.02 (d, J=7.2 Hz, 3H), 0.92 (d, J=7.4 Hz, 3H), 0.88 (t, J=7.2 Hz), 0.81 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 177.9, 155.1, 100.3, 96.1, 83.3, 82.0, 79.8, 77.9, 77.0, 75.5, 75.3, 74.6, 72.8, 71.1, 68.4, 65.8, 63.3, 54.7, 49.3, 44.7, 40.8, 40.5, 40.0, 36.4, 35.0, 34.3, 31.0, 26.3, 25.3, 21.6, 21.0, 20.1, 18.5, 14.9, 12.5, 10.4, 9.07, 8.56; IR ($CHCl_3$) ν 3424, 2974, 2882, 1751, 1708, 1460, 1442, 1379, 1343, 1320, 1270, 1186, 1166, 1124, 1054, 997, 908 cm^{-1}; mass spectrum (CI) m/z 778.4948 [$C_{39}H_{72}NO_{14}$ (M+1) requires 778.4953] (base), 620.

4.1.22. (9*S*)-3-*O*-(α-L-Cladinosyl)-5-*O*-(2-*O*-(methoxycarbonyl)-β-D-desosaminyl)erythronolide B. To a solution of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (5.2 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of **45** (8.7 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) over 3 min at room temperature. After stirring for 14 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and saturated aqueous sodium thiosulfate (1 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×3 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with methanol/dichloromethane (2% MeOH/CH_2Cl_2, 5% MeOH/CH_2Cl_2, 10% MeOH/CH_2Cl_2) to afford 7.8 mg (90%) of keto lactone as a white foam; ^{1}H NMR (500 MHz) δ 5.31 (dd, J=10.4, 3.6 Hz, 1H), 4.85 (d, J=4.2 Hz, 1H), 4.54–4.49 (comp, 2H), 3.97 (d, J=10.0 Hz, 1H), 3.96–3.92 (m, 1H), 3.75–3.73 (m, 1H), 3.74 (s, 3H), 3.51 (d, J=7.0 Hz, 1H), 3.48–3.44 (m, 1H), 3.30 (s, 3H), 3.13 (br s, 1H), 3.00–2.92 (comp, 2H), 2.85–2.80 (m, 1H), 2.70–2.61 (comp, 2H), 2.34–2.31 (m, 1H), 2.25 (br s, 6H), 2.25–2.21 (m, 1H), 2.01–1.97 (comp, 2H), 1.86–1.81 (m, 1H), 1.73–1.52 (comp, 5H), 1.47–1.42 (m, 1H), 1.41 (s, 3H), 1.30–1.26 (m, 1H), 1.24 (d, J=6.4 Hz, 3H), 1.21 (s, 3H), 1.19 (d, J=6.0 Hz, 3H), 1.14 (d, J=6.0 Hz, 3H), 1.12 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.91 (d, J=7.2 Hz, 3H), 0.86–0.82 (comp, 6H); ^{13}C NMR (125 MHz) δ 219.9, 176.1, 155.3, 100.8, 96.4, 83.6, 80.3, 77.9, 75.8, 75.4, 75.0, 72.6, 69.4, 68.5, 65.7, 63.4, 54.6, 49.4, 44.8, 44.7, 40.7, 39.9, 39.2, 39.0, 37.7, 35.0, 30.4, 27.4, 25.6, 21.5, 21.1, 18.7, 18.4, 15.5, 10.4, 9.3, 9.1, 8.7; IR ($CHCl_3$) ν 3540, 2972, 2939, 1748, 1723, 1692, 1457, 1442, 1378, 1343, 1272, 1178, 1111, 1055, 998 cm^{-1}; mass spectrum (CI) m/z 776.4796 [$C_{39}H_{70}NO_{14}$ (M+1) requires 776.4796], 758 (base), 618, 600, 282.

4.1.23. Erythromycin B (2). A solution of keto lactone from the preceding experiment (7.0 mg, 0.009 mmol) in methanol (1.8 mL) and water (0.2 mL) was heated under reflux for 8 h. The reaction was cooled to room temperature, diluted with ether (5 mL), and washed with saturated aqueous NaCl (5 mL). The layers were separated, and the aqueous layer was extracted with ether (2×3 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with methanol/dichloromethane (10% MeOH/CH_2Cl_2)

to afford 6.1 mg (95%) of erythromycin B (**2**) as a white solid. The melting point (mp 196–197 °C) and spectroscopic data (^{1}H and ^{13}C NMR in deuterated benzene, IR, and mass) were identical with an authentic sample of erythromycin B.

4.1.24. (2*S*,3*R*,4*R*,6*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3,4-(carbonyldioxy)-7,7-ethylenedithio-2,4,6-trimethylnonane. To a solution of triol **20** (2.0 g, 6.5 mmol) and imidazole (0.662 g, 9.7 mmol) in anhydrous DMF (22 mL) at 0 °C was added *tert*-butyldimethylchlorosilane (1.03 g, 6.8 mmol). After stirring at 0 °C for 8 h, saturated aqueous $NaHCO_3$ (20 mL) and Et_2O (20 mL) were added. The layers were separated, and the aqueous was extracted with additional Et_2O (3×20 mL). The combined organic layers were washed with brine (1×25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was then filtered through a pad of silica gel, eluting with hexanes/EtOAc (1:1). Concentration of the filtrate under reduced pressure gave 2.49 g (89%) of the monoprotected triol as a yellow oil. The crude diol thus obtained was dissolved in benzene (64 mL), and 1,1′-carbonyldiimidazole (9.39 g, 58 mmol) was added. The solution was heated under reflux for 12 h and then cooled to room temperature. After adding Et_2O (40 mL), the solution was filtered through a silica gel plug and concentrated under reduced pressure to give a residue that was purified by flash chromatography, eluting with hexanes/EtOAc (4:1) to give 2.53 g (98%) of the titled carbonate as a colorless oil; ^{1}H NMR (300 MHz) δ 4.53 (d, J=5.0 Hz, 1H), 3.47 (m, 2H), 3.22–3.12 (comp, 4H), 2.25 (d, J=14.7 Hz, 1H), 2.15 (qd, J=8.6, 6.6 Hz, 1H), 2.01–1.79 (comp, 3H), 1.67 (dd, J=14.7, 8.6 Hz, 1H), 1.43 (s, 3H), 1.16 (d, J=6.6 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz) δ 154.2, 86.3, 83.4, 78.6, 64.8, 44.3, 40.0, 39.6, 38.2, 36.4, 34.2, 25.8, 21.0, 19.7, 18.2, 12.1, 10.4, −5.5; IR ($CDCl_3$) ν 1788, 1463, 1254 cm^{-1}; mass spectrum (CI) m/z 449.2223 [$C_{21}H_{41}O_4SiS_2$ (M+1) requires 449.2216].

4.1.25. (4*R*,6*R*,7*R*,8*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-6,7-(carbonyldioxy)-4,6,8-trimethylnonan-3-one (22). To a stirred suspension of the carbonate from the previous experiment (0.50 g, 1.1 mmol) and calcium carbonate (0.44 g, 4.4 mmol) in THF/water (5:1) (8 mL) was added mercury(II) perchlorate (4 M solution in water, 0.56 mL, 2.2 mmol) dropwise. After the addition was complete, the mixture was stirred for 5 min and then diluted with ether (25 mL) and then filtered through silica gel plug, dried (Na_2SO_4), and concentrated under reduced pressure to give an oil. Purification by flash column chromatography, eluting with hexane/EtOAc (9:1) gave 0.35 g (84%) of **22** as a white solid; mp 59–60 °C; ^{1}H NMR (300 MHz) δ 4.32 (d, J=5.6 Hz, 1H), 3.52–3.37 (m, 2H), 2.85–2.73 (m, 1H), 2.60–2.39 (comp, 3H), 1.96–1.88 (m, 1H), 1.57 (dd, J=14.6, 3.2 Hz, 1H), 1.39 (s, 3H), 1.08 (d, J=7.0 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H), 0.96 (d, J=6.7 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz) δ 213.4, 153.8, 85.5, 85.0, 64.7, 42.4, 41.0, 36.1, 34.4, 25.8, 19.8, 19.1, 18.2, 12.3, 7.8, −5.5; IR ($CHCl_3$) ν 1793, 1714, 1462, 1254, 838 cm^{-1}; mass spectrum (CI) m/z 373.2400 [$C_{19}H_{37}O_5Si$ (M+1) requires 373.2420]; $[\alpha]_D^{24}$ +47.4 (c 2.95, $CHCl_3$); Anal. Calcd for $C_{19}H_{36}O_5Si$: C, 61.25; H, 9.74. Found: C, 61.22; H, 9.78.

4.1.26. (2*S*,3*R*,4*R*,6*R*,8*R*,9*S*,10*R*,11*R*)-11-(Benzyloxymethoxy)-1-[(*tert*-butyldimethylsilyl)oxy]-3,4-(carbonyldioxy)-9-hydroxy-2,4,6,8,10-pentamethyltridecan-7-one (24). To a stirred solution of lithium hexamethyldisilazide (0.376 mmol) in THF (1.6 mL) at −78 °C was added a solution of ketone **22** (70 mg, 0.188 mmol) in THF (1.6 mL) via cannula. After stirring at −78 °C for 2 h, a solution of freshly prepared aldehyde **23** (102 mg, 0.432 mmol) in THF (1.6 mL) was added via cannula, and the resulting solution was stirred at −78 °C for 1.5 h. After warming to −20 °C over 30 min, saturated aqueous NH_4Cl (ca. 2 mL) was added, and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (7:1 to 5:1), to provide 95 mg (83%) of **24** as a clear colorless oil; ^{1}H NMR (500 MHz) δ 7.33–7.24 (m, 5H), 4.84 (d, J=6.7 Hz, 1H), 4.77 (d, J=6.7 Hz, 1H), 4.63 (d, J=11.9 Hz, 1H), 4.60 (d, J=11.9 Hz, 1H), 4.31 (d, J=5.6 Hz, 1H), 4.03 (ddd, J=9.8, 2.7, 2.1 Hz, 1H), 3.88 (ddd, J=8.0, 6.5, 2.1 Hz, 1H), 3.55 (d, J=2.7 Hz, 1H), 3.48 (dd, J=10.3, 4.8 Hz, 1H), 3.44 (dd, J=10.3, 7.3 Hz, 1H), 3.03 (dqd, J=8.8, 7.0, 3.2 Hz, 1H), 2.80 (qd, J=7.0, 2.1 Hz, 1H), 2.46 (dd, J=14.6, 8.8 Hz, 1H), 1.96–1.91 (m, 1H), 1.78 (dqd, J=9.8, 7.0, 2.1 Hz, 1H), 1.71 (dqd, J=14.0, 8.0, 7.4 Hz, 1H), 1.55 (dd, J=14.6, 3.2 Hz, 1H), 1.51 (dqd, J=14.0, 7.4, 6.5 Hz, 1H), 1.42 (s, 3H), 1.11 (d, J=7.0 Hz, 3H), 1.09 (d, J=7.0 Hz, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.92 (t, J=7.4 Hz, 3H), 0.88 (s, 9H), 0.83 (d, J=7.0 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz) δ 216.6, 153.6, 137.7, 128.4, 127.7, 127.6, 94.9, 85.3, 85.2, 80.8, 71.5, 69.8, 64.7, 47.6, 43.0, 39.0, 37.8, 36.1, 25.9, 24.6, 19.7, 19.4, 18.3, 12.3, 10.7, 10.4, 8.2, −5.5, −5.5; IR (neat) ν 3430, 2900, 1800, 1700, 1460, 1390, 1050, 850, 790 cm^{-1}; mass spectrum (CI) m/z 501.32452 [$C_{26}H_{49}O_7Si$ (M−$PhCH_2O$) requires 501.32476]; $[\alpha]_D^{25}$ +27.1 (c 2.3, $CHCl_3$).

4.1.27. (2*S*,3*R*,4*R*,6*R*,7*S*,8*S*,9*R*,10*R*,11*R*)-11-(Benzyloxymethoxy)-1-*O*-*tert*-butyldimethylsilyl-3,4-(carbonyldioxy)-2,4,6,8,10-pentamethyltridecan-1,7,9-triol (25). To a solution of tetramethylammonium triacetoxyborohydride (476 mg, 1.81 mmol) in anhydrous CH_3CN (1.13 mL) was added anhydrous acetic acid (2.26 mL) slowly via syringe. After stirring at room temperature for 30 min, the solution was cooled to −20 °C, and a solution of β-hydroxy ketone **24** (110 mg, 0.181 mmol) in CH_3CN (1.13 mL) was added. The solution was stirred at −20 to −25 °C for 12 h. After warming to −10 °C, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and stirred at room temperature for 30 min. The resulting mixture was extracted with CH_2Cl_2 (3×10 mL), and the combined organic extracts were washed with brine (1×5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (5:1) to give 102 mg (93%) of *anti*-diol **25** as a colorless oil; ^{1}H NMR (500 MHz) δ 7.36–7.26 (comp, 5H), 4.85 (d, J=6.9 Hz, 1H), 4.76 (d, J=6.9 Hz, 1H), 4.70 (d, J=11.9 Hz, 1H), 4.62 (d, J=11.9 Hz, 1H), 4.39 (d, J=5.9 Hz, 1H), 4.00 (ddd, J=10.2, 2.0, 1.7 Hz, 1H), 3.88 (d, J=1.7 Hz, 1H), 3.72 (ddd, J=7.1,

4.3, 2.7 Hz, 1H), 3.52 (dd, *J*=10.3, 4.4 Hz, 1H), 3.51–3.48 (m, 1H), 3.47 (dd, *J*=10.3, 6.8 Hz, 1H), 2.60 (d, *J*=6.1 Hz, 1H), 1.98–1.89 (comp, 4H), 1.70–1.62 (comp, 3H), 1.57–1.52 (m, 1H), 1.44 (s, 3H), 1.03 (d, *J*=6.7 Hz, 3H), 0.96 (t, *J*=7.3 Hz, 3H), 0.95 (d, *J*=5.8 Hz, 3H), 0.87 (s, 9H), 0.86 (d, *J*=6.9 Hz, 3H), 0.76 (d, *J*=7.0 Hz, 3H), 0.38 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (125 MHz) δ 154.3, 137.4, 128.5, 127.8, 127.7, 94.8, 86.8, 85.1, 83.7, 76.6, 71.7, 70.1, 64.7, 44.2, 37.9, 36.4, 36.0, 31.2, 25.9, 23.6, 19.3, 18.2, 12.7, 11.8, 11.1, 9.9, −5.5, −5.5; IR (neat) ν 3460, 3060, 1800, 1460, 1390, 1260, 850 cm^{-1}; mass spectrum (CI) *m/z* 503.34062 [$C_{26}H_{51}O_7Si$ (M−$PhCH_2O$) requires 503.34041]; $[\alpha]_D^{25}$ +26.6 (*c* 1.59, $CHCl_3$).

4.1.28. (2*S*,3*R*,4*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*)-11-(Benzyloxymethoxy)-1-[(*tert*-butyldimethylsilyl)oxy]-3,4-(carbonyldioxy)-2,4,6,8,10-pentamethyl-7,9-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}tridecane (26). A solution of 1,3-*anti*-diol **25** (335 mg, 0.549 mmol), mesitylaldehyde dimethyl acetal (426 mg, 2.20 mmol), and CSA (64 mg, 0.274 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ (ca. 4 mL) was added, and the layers were separated; the aqueous layer was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (20:1) to provide 367 mg (90%) of acetal **26** as a white foam; ^{1}H NMR (500 MHz) δ 7.33–7.22 (comp, 5H), 6.79 (s, 2H), 5.95 (s, 1H), 4.72 (s, 2H), 4.72 (d, *J*=12.5 Hz, 1H), 4.66 (d, *J*=12.5 Hz, 1H), 4.32 (d, *J*=6.0 Hz, 1H), 4.01 (dd, *J*=10.2, 2.0 Hz, 1H), 3.82 (td, *J*=7.1, 1.0 Hz, 1H), 3.53 (dd, *J*=10.3, 4.2 Hz, 1H), 3.46 (dd, *J*=10.3, 6.4 Hz, 1H), 3.29 (d, *J*=11.1 Hz, 1H), 2.64–2.50 (m, 1H), 2.47 (s, 6H), 2.23 (s, 3H), 1.94 (qddd, *J*=6.8, 6.4, 6.0, 4.2 Hz, 1H), 1.77 (qd, *J*=7.0, 2.0 Hz, 1H), 1.73–1.64 (comp, 3H), 1.54 (dd, *J*=14.9, 7.6 Hz, 1H), 1.43–1.34 (m, 1H), 1.32 (s, 3H), 1.26 (d, *J*=7.0 Hz, 3H), 1.06 (d, *J*=6.6 Hz, 3H), 1.04 (d, *J*=6.8 Hz, 3H), 0.87 (s, 9H), 0.85 (d, *J*=7.0 Hz, 3H), 0.81 (t, *J*=7.4 Hz, 3H), 0.36 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (125 MHz) δ 153.6, 138.5, 138.0, 136.9, 131.6, 129.9, 128.2, 128.2, 127.4, 127.3, 95.9, 95.0, 86.5, 85.8, 84.6, 79.6, 76.2, 69.4, 64.7, 44.5, 37.6, 35.8, 38.5, 27.7, 26.3, 25.8, 20.9, 20.6, 19.2, 19.1, 18.3, 14.3, 13.1, 10.5, 7.4, −5.5, −5.6; IR (neat) ν 1800, 1600, 1455, 1380, 1250, 840 cm^{-1}; mass spectrum (CI) *m/z* 740.4674 [$C_{43}H_{68}O_8Si$ (M+1) requires 740.4684]; $[\alpha]_D^{23}$ +25.5 (*c* 1.78, $CHCl_3$).

4.1.29. (2*S*,3*R*,4*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*)-11-(Benzyloxymethoxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2,4,6,8,10-pentamethyl-7,9-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}tridecan-3,4-diol (47). $LiBH_4$ (7 mg, 0.314 mmol) was added to a solution of the cyclic carbonate **26** (193 mg, 0.26 mmol) in anhydrous ether (25 mL) at room temperature under Ar. After stirring 5 h, the reaction was cooled to 0 °C, and saturated aqueous NH_4Cl (ca. 6 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography with hexanes/ethyl acetate (4:1) to give 170 mg (92%) of **47** as a white foam; ^{1}H NMR (500 MHz) δ 7.30–7.23 (comp, 5H), 6.76 (s, 2H), 5.98 (s, 1H), 4.73 (d, *J*=6.6 Hz, 1H), 4.69 (d, *J*=6.6 Hz, 1H), 4.68 (d, *J*=12.3 Hz, 1H), 4.62 (d, *J*=12.3 Hz, 1H), 4.01 (dd, *J*=10.2, 2.0 Hz, 1H), 3.84 (ddd, *J*=7.2, 7.1, 1.2 Hz, 1H), 3.77 (dd, *J*=9.7, 3.0 Hz, 1H), 3.62 (dd, *J*=9.7, 4.1 Hz, 1H), 3.61 (s, 1H), 3.50 (d, *J*=1.8 Hz, 1H), 3.30 (d, *J*=11.3 Hz, 1H), 2.64–2.54 (m, 1H), 2.45 (s, 6H), 2.40 (s, 1H), 2.21 (s, 3H), 1.91 (qd, *J*=7.1, 2.0 Hz, 1H), 1.84–1.78 (m, 1H), 1.74–1.62 (comp, 2H), 1.56 (d, *J*=14.4 Hz, 1H), 1.44–1.36 (m, 1H), 1.25 (d, *J*=7.0 Hz, 3H), 1.19 (dd, *J*=14.4, 6.5 Hz, 1H), 1.12 (s, 3H), 1.06 (d, *J*=6.5 Hz, 3H), 1.04 (d, *J*=7.0 Hz, 3H), 0.90 (s, 9H), 0.81 (d, *J*=7.5 Hz, 3H), 0.80 (d, *J*=6.9 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz) δ 138.4, 137.8, 136.9, 132.0, 129.8, 128.3, 127.6, 127.4, 95.5, 94.6, 85.6, 78.9, 78.8, 76.5, 74.2, 70.3, 69.5, 44.8, 37.4, 35.163, 28.1, 26.5, 26.2, 25.9, 22.3, 20.9, 20.6, 19.8, 18.2, 14.3, 10.8, 10.5, 7.4, −5.6, −5.6; IR (neat) ν 3430, 1450, 1255, 1110 cm^{-1}; mass spectrum (CI) *m/z* 715.49678 [$C_{42}H_{71}O_7Si$ (M+1) requires 715.49691], 407, 393, 365 (base); $[\alpha]_D^{25}$ −25.7 (*c* 0.72, $CHCl_3$).

4.1.30. (2*S*,3*R*,4*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*)-11-(Benzyloxymethoxy)-1-[(*tert*-butyldimethylsilyl)oxy]-3-[(2′-*O*-methoxycarbonyl-α-D-desosaminyl)oxy]-2,4,6,8,10-pentamethyl-7,9-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}tridecan-4-ol (48). To a suspension of freshly activated 4 Å molecular sieves (2.2 g) and AgOTf (1.03 g, 4.0) in CH_2Cl_2 (3.3 mL) and toluene (3.3 mL), was added a solution of diol **47** (145 mg, 0.203 mmol), desosamine thioglycoside **35** (398 mg, 1.22 mmol), and 2,6-di-*tert*-butylpyridine (0.275 mL, 1.22 mmol) in CH_2Cl_2 (3.3 mL) by syringe pump (0.052 mL/min). The reaction flask was wrapped with aluminum foil to protect the mixture from light, and the reaction was stirred at room temperature for 4 h after the completion of addition. After adding Et_3N (ca. 3 mL), the resulting mixture was filtered through Celite, eluting with EtOAc. The filtrate was washed with saturated aqueous $NaHCO_3$ (4×4 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (2:1), to provide 36 mg (25%) of starting **47**, 69 mg (42%) of **48**, and 57 mg (35%) of **49** as colorless oils; ^{1}H NMR (500 MHz) δ 7.33–7.23 (comp, 5H), 6.75 (s, 2H), 5.98 (s, 1H), 4.70 (d, *J*=6.6 Hz, 1H), 4.67 (dd, *J*=10.6, 7.6 Hz, 1H), 4.66 (d, *J*=6.6 Hz, 1H), 4.66 (d, *J*=12.4 Hz, 1H), 4.63 (d, *J*=12.4 Hz, 1H), 4.36 (d, *J*=7.6 Hz, 1H), 4.09 (s, 1H), 4.08 (dd, *J*=9.7, 1.8 Hz, 1H), 3.82 (ddd, *J*=7.2, 7.1, 0.95 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 1H), 3.59–3.47 (m, 1H), 3.41 (dd, *J*=10.0, 9.9 Hz, 1H), 3.33 (dd, *J*=9.9, 5.4 Hz, 1H), 3.24 (d, *J*=11.4 Hz, 1H), 2.93–2.81 (m, 1H), 2.74 (ddd, *J*=12.2, 10.6, 4.4 Hz, 1H), 2.42 (s, 6H), 2.29 (s, 6H), 2.20 (s, 3H), 2.07 (qd, *J*=7.2, 1.8 Hz, 1H), 1.88–1.72 (comp, 2H), 1.69–1.60 (comp, 2H), 1.42–1.35 (comp, 2H), 1.24 (d, *J*=6.1 Hz, 3H), 1.20 (d, *J*=7.1 Hz, 3H), 1.17 (s, 3H), 1.10 (dd, *J*=13.9, 4.6 Hz, 1H), 1.04 (d, *J*=6.7 Hz, 3H), 0.90 (s, 9H), 0.80 (t, *J*=7.5 Hz, 3H), 0.77 (d, *J*=7.0 Hz, 3H), 0.72 (d, *J*=6.9 Hz, 3H), 0.62 (s, 3H), 0.43 (s, 3H); ^{13}C NMR (125 MHz) δ 155.3, 138.5, 137.6, 137.0, 132.2, 129.7, 128.2, 127.7, 127.3, 103.2, 95.2, 94.5, 87.5, 86.2, 78.5, 76.0, 75.3, 73.2, 69.7, 69.4, 65.1, 63.1, 54.6, 44.0, 40.6, 37.5, 36.5, 30.5, 27.5, 26.2, 25.8, 25.6, 22.8, 20.9, 20.7, 20.6, 20.3, 18.1, 14.3, 10.5, 9.9, 7.2, −5.3; IR (neat) ν 3420, 1750, 1440, 1270, 1100 cm^{-1}; mass spectrum

(CI) *m/z* 929.60241 [$C_{52}H_{87}NO_{11}Si$ (M+1) requires 929.60484]; $[\alpha]_D^{20}$ −14.1 (*c* 1.4, $CHCl_3$).

4.1.31. (2*S*,3*R*,4*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*)-11-(Benzyloxymethoxy)-3-[(2′-*O*-methoxycarbonyl-α-D-desosaminyl)oxy]-2,4,6,8,10-pentamethyl-7,9-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}tridecan-1,4-diol. To a stirred solution of **48** (61 mg, 0.0657 mmol) in THF (1 mL) at 0 °C was added TBAF (0.33 mL, 0.33 mmol, 1 M in THF). After stirring 1.25 h, the reaction was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with EtOAc to give 54 mg (99%) of diol as a white foam; ^{1}H NMR (500 MHz) δ 7.29–7.23 (comp, 5 H), 4.70 (d, *J*=6.0 Hz, 1H), 4.69 (dd, *J*=10.6, 7.6 Hz, 1H), 4.66 (d, *J*=6.0 Hz, 1H), 4.63 (d, *J*=12.4 Hz, 1H), 4.60 (d, *J*=12.4 Hz, 1H), 4.43 (d, *J*=7.6 Hz, 1H), 4.32 (br s, 1H), 4.08 (dd, *J*=10.3, 1.8 Hz, 1H), 3.85 (s, 1H), 3.81 (td, *J*=7.2, 1.4 Hz, 1H), 3.68–3.58 (m, 1H), 3.56–3.44 (m, 1H), 3.45 (dd, *J*=10.6, 5.6 Hz, 1H), 3.25 (d, *J*=11.2 Hz, 1H), 2.83–2.76 (comp, 2H), 2.44 (s, 6H), 2.30 (s, 6H), 2.20 (s, 3H), 1.94 (qd, *J*=7.1, 1.8 Hz, 1H), 1.86–1.78 (m, 1H), 1.76 (ddd, *J*=13.2, 4.3, 1.8 Hz, 1H), 1.70 (dqd, *J*=10.3, 7.0, 1.5 Hz, 1H), 1.70–1.60 (m, 1H), 1.42–1.36 (comp, 2H), 1.32 (d, *J*=14.0 Hz, 1H), 1.25–1.23 (comp, 7H), 1.20 (s, 3H), 1.12 (d, *J*=6.5 Hz, 3H), 0.79 (t, *J*=7.4 Hz, 3H), 0.77 (d, *J*=6.8 Hz, 3H), 0.77 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 155.2, 137.9, 137.7, 136.9, 131.9, 129.8, 128.3, 127.8, 127.5, 103.5, 95.0, 94.7, 87.1, 85.8, 78.1, 75.8, 75.4, 74.0, 69.7, 69.7, 65.0, 63.0, 54.8, 43.4, 40.6, 37.0, 36.8, 30.4, 28.0, 26.1, 25.7, 24.9, 20.8, 20.8, 20.6, 18.8, 14.2, 10.4, 10.1, 7.0; IR (neat) ν 3420, 1750 cm^{-1}; mass spectrum (CI) *m/z* 816.52590 [$C_{46}H_{74}NO_{11}$ (M+1) requires 816.52619]; $[\alpha]_D^{24}$ −17.4 (*c* 1.6, $CHCl_3$).

4.1.32. (2*S*,3*R*,4*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*)-11-(Benzyloxymethoxy)-3-[(2′-*O*-methoxycarbonyl-α-D-desosaminyl)oxy]-2,4,6,8,10-pentamethyl-1,4-bis[(triethylsilyl)oxy]-7,9-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}tridecane. Distilled diisopropylethylamine (1.2 g, 9.3 mmol) and TESOTf (614 mg, 2.325 mmol) were added to a solution of the diol from the previous experiment (72 mg, 0.088 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After stirring 2 h, saturated aqueous $NaHCO_3$ (3.0 mL) was added and the reaction warmed to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/ethyl acetate (1:1.5) to give 90 mg (98%) of the bis-TES ether as a colorless oil; ^{1}H NMR (500 MHz) δ 7.30–7.22 (comp, 5H), 6.75 (s, 2H), 5.89 (s, 1H), 4.75 (d, *J*=6.5 Hz, 1H), 4.64 (d, *J*=6.5 Hz, 1H), 4.63 (d, *J*=11.9 Hz, 1H), (dd, *J*=10.4, 7.6 Hz, 1H), 4.50 (d, *J*=7.6 Hz, 1H), 4.43 (d, *J*=11.9 Hz, 1H), 3.89 (dd, *J*=10.2, 2.1 Hz, 1H), 3.86–3.81 (m, 1H), 3.72 (s, 3H), 3.69 (d, *J*=1.8 Hz, 1H), 3.50 (dd, *J*=9.6, 6.4 Hz, 1H), 3.45–3.43 (m, 1H), 3.42 (dd, *J*=9.6, 5.4 Hz, 1H), 3.26 (d, *J*=11.2 Hz, 1H), 2.73–2.67 (m, 1H), 2.52–2.49 (m, 1H), 2.43 (s, 6H), 2.28 (s, 6H), 2.24–2.22 (m, 1H), 2.21 (s, 3H), 1.80 (qd, *J*=7.1, 2.1 Hz, 1H), 1.77–1.69 (comp, 3H), 1.46–1.10 (comp, 2H), 1.41 (s, 3H), 1.33–1.24 (comp, 2H), 1.23 (d, *J*=7.1 Hz, 3H), 1.20 (d, *J*=6.1 Hz, 3H), 1.05 (d, *J*=6.4 Hz, 3H), 0.96 (t, *J*=7.9 Hz, 9H), 0.95 (t, *J*=7.9 Hz, 9H), 0.83 (d, *J*=7.2 Hz, 3H), 0.80 (t, *J*=7.6 Hz, 3H), 0.79 (d, *J*=7.0 Hz, 3H), 0.70–0.64 (comp, 6H), 0.62–0.56 (comp, 6H); ^{13}C NMR (125 MHz) δ 155.2, 138.2, 137.7, 136.8, 131.9, 129.8, 128.2, 127.6, 127.4, 100.6, 95.4, 94.5, 85.7, 82.5, 78.7, 78.2, 76.0, 75.6, 69.3, 68.7, 67.0, 63.1, 54.5, 40.8, 40.6, 37.1, 35.1, 31.3, 28.5, 27.7, 26.8, 25.7, 21.0, 20.8, 20.5, 18.6, 14.6, 12.1, 10.3, 7.4, 7.2, 7.0, 6.8, 4.4; IR (neat) ν 1750, 1610, 1275 cm^{-1}; mass spectrum (CI) *m/e* 1043.69076 ($C_{58}H_{101}NO_{11}Si_2$ requires 1043.69132), 626, 576, 425, 309, 216 (base).

4.1.33. (2*S*,3*R*,4*R*,6*R*,7*S*,8*S*,9*S*,10*S*,11*R*)-11-(Benzyloxymethoxy)-3-[(2′-*O*-methoxycarbonyl-α-D-desosaminyl)oxy]-2,4,6,8,10-pentamethyl-4-[(triethylsilyl)oxy]-7,9-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}tridecane (50). To a solution of freshly distilled oxalyl chloride (206 mg, 1.62 mmol) in CH_2Cl_2 (2 mL) at −60 °C was added DMSO (254 mg, 3.25 mmol). After stirring 30 min at −60 °C, the bis-TES ether from the preceding experiment (85 mg, 0.081 mmol) in CH_2Cl_2 (0.75 mL) was added dropwise, and the solution was stirred for 6 h at −45 °C. The reaction was then cooled to −78 °C, *N*-methylmorpholine (827 mg, 8.15 mmol) was added. The reaction mixture was warmed to room temperature over a period of 30 min, whereupon the resulting yellowish solution was diluted with Et_2O (10 mL), and the mixture was filtered through a plug of silica gel. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (1:1 to 1:2) to provide 91 mg (91%) of **50** as a colorless oil; ^{1}H NMR (500 MHz) δ 9.58 (d, *J*=1.5 Hz, 1H), 7.28–7.20 (comp, 5H), 6.76 (s, 2H), 5.89 (s, 1H), 4.74 (d, *J*=6.4 Hz, 1H), 4.64 (d, *J*=12.4 Hz, 1H), 4.63 (d, *J*=6.0 Hz, 1H), 4.49 (dd, *J*=10.5, 7.0 Hz, 1H), 4.45 (d, *J*=11.5 Hz, 1H), 4.20 (d, *J*=7.4 Hz, 1H), 4.03 (d, *J*=4.4 Hz, 1H), 3.88 (dd, *J*=10.0, 2.0 Hz, 1H), 3.82 (ddd, *J*=6.5, 6.5, 1.5 Hz, 1H), 3.72 (s, 3H), 3.48–3.43 (m, 1H), 3.24 (d, *J*=12.0 Hz, 1H), 2.89–2.84 (m, 1H), 2.68 (ddd, *J*=12.5, 11.0, 4.5 Hz, 1H), 2.51–2.44 (m, 1H), 2.44 (s, 6H), 2.23 (s, 6H), 2.21 (s, 3H), 1.79–1.67 (comp, 4H), 1.45 (s, 3H), 1.25 (d, *J*=7.0 Hz, 3H), 1.21 (d, *J*=6.1 Hz, 3H), 1.16 (d, *J*=7.0 Hz, 3H), 1.04 (d, *J*=6.5 Hz, 3H), 0.94 (t, *J*=7.9 Hz, 9H), 0.80 (t, *J*=7.4 Hz, 3H), 0.80 (d, *J*=7.0 Hz, 3H), 0.63 (q, *J*=7.6 Hz, 3H), 0.62 (q, *J*=8.3 Hz, 3H); ^{13}C NMR (125 MHz) δ 202.7, 155.1, 138.2, 137.8, 136.9, 131.8, 129.8, 128.3, 127.7, 127.4, 100.5, 95.4, 94.7, 85.5, 80.9, 78.8, 76.0, 75.3, 69.3, 69.3, 63.1, 54.7, 46.9, 42.0, 40.6, 37.1, 30.6, 28.5, 27.1, 27.0, 25.8, 20.9, 20.9, 20.5, 18.7, 14.5, 10.3, 10.0, 7.3, 7.1, 6.9; IR (neat) ν 2939, 1756, 1650, 1615, 1105, 1052 cm^{-1}; mass spectrum (CI) *m/z* 928.59471 [$C_{52}H_{86}NO_{11}Si$ (M+1) requires 928.59702], 696, 234, 216 (base).

4.1.34. (3*S*,4*R*,5*R*,6*R*,7*R*,9*R*,10*S*,11*S*,12*S*,13*S*,14*R*)-14-(Benzyloxymethoxy)-7-*O*-6-[(2′-*O*-methoxycarbonyl-α-D-desosaminyl)oxy]-3,5,7,9,11,13-hexamethyl-10,12-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}hexadecen-4-ol (51). To a solution of aldehyde **50** (21 mg, 0.0226 mmol) in CH_2Cl_2 (1.14 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (0.055 mL, 0.45 mmol). After stirring at −78 °C for 5 min, tributyl crotylstannane (149 mg, 0.45 mmol) was added, and the reaction was stirred at −78 °C for 10 h. Saturated aqueous $NaHCO_3$ (0.9 mL) was added, and the mixture

was allowed to warm to room temperature. 10% Aqueous NaOH (0.9 mL) was added, and the resulting mixture was stirred at room temperature for 14 h. The layers were separated, and the aqueous was extracted with CH_2Cl_2 (5×2 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (1:1, 1:2, 1:3) and $CHCl_3$/MeOH (9:1) to provide 19 mg (86%) of **51** as a colorless oil; ^{1}H NMR (500 MHz) δ 7.28–7.20 (comp, 5H), 6.75 (s, 2H), 5.87 (s, 1H), 5.62 (ddd, J=17.1, 10.2, 9.1 Hz, 1H), 5.04 (dd, J=17.1, 1.4 Hz, 1H), 4.92 (dd, J=10.2, 1.9 Hz, 1H), 4.75 (d, J=6.5 Hz, 1H), 4.70 (d, J=7.8 Hz, 1H), 4.63 (d, J=11.9 Hz, 1H), 4.62 (d, J=6.5 Hz, 1H), 4.53 (dd, J=10.4, 7.8 Hz, 1H), 4.43 (d, J=11.9 Hz, 1H), 3.88 (dd, J=10.3, 2.4 Hz, 1H), 3.84 (ddd, J=8.0, 6.6, 2.4 Hz, 1H), 3.73 (s, 3H), 3.55 (d, J=2.5 Hz, 1H), 3.52–3.46 (m, 1H), 3.23 (d, J=11.4 Hz, 1H), 2.74 (ddd, J=12.5, 9.3, 4.5 Hz, 1H), 2.53–2.48 (m, 1H), 2.43 (s, 6H), 2.27 (s, 3H), 2.21 (s, 3H), 1.84–1.68 (comp, 4H), 1.44 (s, 3H), 1.21 (d, J=7.0 Hz, 3H), 1.20 (d, J=6.3 Hz, 1H), 1.09 (d, J=6.5 Hz, 3H), 1.04 (d, J=6.4 Hz, 3H), 0.97 (t, J=7.9 Hz, 9H), 0.82–0.77 (comp, 9H), 0.70–0.64 (comp, 6H); ^{13}C NMR (125 MHz) δ 155.2, 140.8, 138.2, 136.8, 131.9, 129.8, 128.2, 127.7, 127.4, 114.4, 99.8, 95.4, 94.5, 86.1, 85.7, 79.0, 78.6, 75.9, 75.6, 69.3, 68.8, 63.2, 54.7, 43.0, 40.6, 40.3, 37.0, 35.4, 31.9, 30.2, 29.4, 28.5, 27.5, 26.6, 25.7, 22.7, 21.0, 20.9, 20.5, 18.6, 14.5, 14.2, 14.1, 10.3, 7.5, 7.3, 7.2, 7.0; IR (neat) ν 2967, 2876, 1756, 1455, 1441, 1378, 1288, 1102, 1053, 995, 910, 734 cm^{-1}; mass spectrum (CI) m/z 983.64880 [$C_{56}H_{93}NO_{11}Si$ (M+1) requires 983.65179], 154 (base).

4.1.35. (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*,9*S*,10*S*,11*S*,12*S*,13*R*)-13-[(Benzyloxy)methoxy]-6-[triethylsilyloxy]-5-*O*-[2′-*O*-(methoxycarbonyl)-β-D-desosaminyl]-2,4,6,8,10,12-hexamethyl-9,11-{[(*R*)-2,4,6-trimethylbenzylidene]dioxy}-pentadecanoic acid (52). Solid $NaHCO_3$ (3.4 mg, 0.04 mmol) and OsO_4 (0.019 mL, 0.001 mmol, 0.055 M in *t*-BuOH) were sequentially added to a solution of **51** (10 mg, 0.0102 mmol) in DMF (0.20 mL) with stirring at room temperature. Stirring was continued for 5 min, whereupon solid Oxone® (50 mg, 0.0816 mmol) was added in one portion. The mixture was stirred for 6 h at room temperature, and saturated aqueous $Na_2S_2O_3$ (0.5 mL) and EtOAc (0.5 mL) were added. The resulting mixture was stirred vigorously for 15 min. The solution was acidified by the addition of 1 N HCl (pH~3). The layers were separated, and the aqueous layer was extracted with EtOAc (3×1 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with $CHCl_3$/MeOH (9:1) to provide 6.5 mg (64%) of acid **52** as a pale yellow oil; ^{1}H NMR (300 MHz) δ 7.29–7.25 (comp, 5H), 6.78 (s, 2H), 5.93 (s, 1H), 4.87 (d, J=6.9 Hz, 1H), 4.77 (d, J=7.2 Hz, 1H), 4.68–4.55 (comp, 3H), 4.46 (d, J=12.0 Hz, 1H), 3.91–3.81 (m, 2H), 3.74 (s, 3H), 3.68 (s, 1H), 3.28 (d, J=10.8 Hz, 1H), 2.97–2.94 (m, 1H), 2.66–2.61 (m, 1H), 2.44 (s, 6H), 2.35 (s, 6H), 2.23 (s, 3H), 1.84–1.69 (comp, 4H), 1.45 (s, 3H), 1.26–1.23 (comp, 9H), 1.16 (d, J=7.2 Hz, 3H), 1.05 (d, J=6.3 Hz, 3H), 0.99 (t, J=8.4 Hz, 9H), 0.87–0.80 (comp, 6H), 0.71 (q, J=7.5 Hz, 6H); ^{13}C NMR (125 MHz) δ 155.0, 138.1, 137.8, 136.8, 131.8, 129.9, 128.4, 128.3, 127.7, 127.5, 98.9, 95.4, 94.5, 85.8, 83.6, 79.2, 78.7, 75.7, 74.9, 69.4, 68.2, 62.6, 54.9, 53.4, 42.4, 40.2, 39.9, 37.0, 35.7, 31.2, 29.7, 28.6, 27.7, 27.0, 25.7, 20.9, 20.9, 20.5, 18.4, 14.5, 14.2, 14.1, 13.4, 10.3, 9.0, 7.5, 7.3, 7.0; IR (neat) ν 3425, 2972, 1643, 1454 cm^{-1}; mass spectrum (CI) m/z 1002.6324 [$C_{55}H_{92}NO_{13}Si$ (M+1) requires 1002.6338].

4.1.36. (9*S*)-9-Dihydro-5-*O*-(2′-*O*-(methoxycarbonyl)-β-D-desosaminyl)-6-*O*-triethylsilyl-9,11-*O*-[(*R*)-2,4,6-trimethylbenzylidene]erythronolide B (53). A solution of acid **52** (3.0 mg, 0.0030 mmol) in THF/H_2O (5:1) containing 0.01 M $HClO_4$ (0.500 mL) and Pd/C (5 mg, 20 wt %) was stirred under an atmosphere of H_2 (1 atm) for 6 h. The mixture was then filtered through a plug of Celite, eluting with EtOAc. The solution was concentrated to give ~3 mg (~100%) of the intermediate hydroxy acid that was used immediately without further purification. Mass spectrum (CI) m/z 882.5772 [$C_{47}H_{84}NO_{12}Si$ (M+1) requires 882.5763]. A solution of the preceding hydroxy acid (~3 mg, 0.003 mmol) in toluene (0.40 mL) was stirred at room temperature, and Et_3N (0.005 mL, 0.036 mmol), DMAP (1 mg, 0.008 mmol), and 2,4,6-trichlorobenzoylchloride (0.005 mL, 0.032 mmol) were added sequentially. The solution was stirred 0.5 h at room temperature, whereupon saturated aqueous $NaHCO_3$ (1.0 mL) and EtOAc (0.5 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3×1 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with toluene/acetone (5:1) to give 2.0 mg (70%, two steps) of **53** as a colorless oil; ^{1}H NMR (500 MHz) δ 6.78 (s, 2H), 6.10 (s, 1H), 5.19 (dd, J=11.0, 3.5 Hz, 1H), 4.90 (br s, 1H), 4.54 (dd, J=10.5, 7.4 Hz, 1H), 4.07 (br s, 1H), 3.90 (d, J=9.6 Hz, 1H), 3.80 (s, 3H), 3.65 (d, J=9.0 Hz, 1H), 3.63–3.55 (m, 1H), 3.27 (d, J=10.4 Hz, 1H), 2.74–2.68 (m, 1H), 2.66–2.58 (m, 1H), 2.64 (dd, J=10.0, 6.5 Hz, 1H), 2.54 (s, 6H), 2.26 (s, 6H), 2.21 (s, 3H), 1.78–1.72 (comp, 2H), 1.67–1.60 (comp, 3H), 1.36–1.32 (m, 1H), 1.27 (d, J=6.5 Hz, 3H), 1.26 (d, J=6.5 Hz, 3H), 1.15 (d, J=6.5 Hz, 3H), 0.98 (t, J=7.5 Hz, 9H), 0.80–0.77 (comp, 6H), 0.70 (q, J=7.5 Hz, 6H); ^{13}C NMR (125 MHz) δ 176.0, 155.4, 138.2, 137.7, 131.9, 129.3, 100.9, 95.1, 86.3, 79.6, 76.8, 76.2, 76.0, 69.8, 63.7, 55.0, 45.0, 41.0, 40.1, 38.4, 30.6, 29.0, 27.1, 25.6, 21.7, 21.5, 21.1, 16.1, 13.6, 10.6, 8.4, 8.0, 7.7, 0.22; IR (neat) ν 2937, 1758, 1724, 1456, 1376, 1265, 1170, 1093, 1052, 993 cm^{-1}; mass spectrum (CI) m/z 864.5652 [$C_{47}H_{82}NO_{11}Si$ (M+1) requires 864.5657].

4.1.37. (9*S*)-9-Dihydro-5-*O*-(2-*O*-(methoxycarbonyl)-β-D-desosaminyl)-9,11-*O*-[(*R*)-2,4,6-trimethylbenzylidene]erythronolide B (43). A solution of TBAF (0.010 mL, 0.010 mmol, 1.0 M in THF) was added to a stirred solution of macrolactone **53** (2.0 mg, 0.0023 mmol) in DMF (0.20 mL) at room temperature. The reaction mixture was stirred for 3 h, and then saturated aqueous $NaHCO_3$ (1 mL) and EtOAc (1 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3×1 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with $CHCl_3$/MeOH (9:1) to give 1.6 mg (93%) of the

macrolactone **43** that was identical in all respects to a sample prepared previously.

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21. The sequence of reactions and the unoptimized yields for each step was as follows: (a) TBS–Cl, DMAP, CH_2Cl_2, rt (84%); (b) NaH, BnCl, Bu_4NI, THF, 0 °C to rt (91%); (c) TBS–OTf, Et_3N, CH_2Cl_2, 0 °C (86%); (d) KH, MeI, 18-crown-6, THF, 0 °C to rt (93%); (e) TBAF, THF, rt (97%); (f) PDC, CH_2Cl_2, rt (82%); (g) $NaClO_2$, 2-methyl-2-butene, aq *t*-BuOH, rt (73%); (h) TBAF, HMPA, 80 °C (76%).
22. The sequence of reactions and the unoptimized yields for each step was as follows: (a) I_2, MeOH, *hv* (96%); (b) Cbz–Cl, DMAP, CH_2Cl_2 (95%); (c) MeI, KOH, DME–DMSO (75%); (d) $NaBH_4$, MeOH, 0 °C (71%); (e) $MeCH(OEt)_2$, PPTS, CH_2Cl_2 (62%); (f) H_2, 10% Pd–C, aq EtOH/acetate buffer (pH=4.8) (85%); (g) $COIm_2$, toluene, reflux; 10% aq Na_2CO_3, THF (94%); (h) BnBr, Bu_4NI, KH, 18-crown-6, THF (92%).

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