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Total synthesis of (+)-ambruticin S

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Dedicated to Professor K. C. Nicolaou in recognition of his many contributions to organic chemistry and his receipt of the Tetrahedron Prize

Abstract—A convergent total synthesis of the novel antifungal agent ambruticin S (**1**) has been completed from the assembly of intermediates **18**, **33** and **52** that served as the respective A-, B-, and C-ring precursors. The first generation approach to a potential A-ring intermediate eventuated in the synthesis of **9a** via a route that featured oxidation of the dihydroxy furan **2** and elaboration of the dihydropyranone **3** derived therefrom. Although **9a** served as a precursor of **31***E* to complete a formal synthesis of **1**, there were several inefficiencies associated with the preparation of **9a**. A more expedient and efficient route to an A-ring subunit was devised that commenced with the carbohydrate-derived bisacetonide aldehyde **10** and produced **18** in five steps and 46% overall yield. The synthesis of the cyclopropyl sulfone **33** was initiated with the enantioselective cyclopropanation of **19** catalyzed by Rh_2[5(*S*)-MEPY]$_4$. Ring opening of the resultant lactone **20** followed by a series of refunctionalizations gave **33** in a total of seven steps and 46% yield from **19**. Coupling of the A- and B-ring precursors **18** and **33** was then achieved via a modified Julia coupling followed by deprotection and oxidation to furnish the key intermediate **35**. The dihydropyran core of the C-ring subunit precursor **49** was formed from the ring closing metathesis of the diene **48**, which was prepared in three steps from the known epoxide **45**, followed by oxidation. A chelation-controlled addition to the methyl ketone **49** set the stage for a stereoselective [2,3]-Wittig rearrangement that delivered the alcohol **51** that was then transformed in two steps to the sulfone **52**. A traditional Julia coupling of **52** and **35** proceeded with excellent stereoselectivity, and subsequent removal of the various protecting groups gave ambruticin S (**1**). The longest linear sequence was 13 steps and proceeded in 4.3% overall yield.

1. Introduction

Ambruticin S (**1**) is a structurally novel antifungal antibiotic that was isolated from the fermentation extracts of *Polyangium cellulosum var. fulvum* in 1977 by researchers at Warner–Lambert.[1] Ambruticin S was initially considered an interesting lead compound because of its low toxicity coupled with its oral activity against several systemic fungal infections.[2] Following its discovery, a combination of extensive chemical and spectral analysis was first employed to elucidate the gross structural features of **1**. However, owing to its complexity, it was necessary to determine the relative stereochemical structure of **1** by X-ray analysis of a crystalline triformate derivative that was prepared from **1** by sequential hydride reduction and exhaustive formylation.[1] The absolute configuration of **1** was later established through the independent synthesis of ozonolysis fragments.[3] The presence of a divinyl cyclopropane linking two hydropyranoid fragments in a natural product was unprecedented. It has also been shown that this divinyl cyclopropane moiety undergoes a sigmatropic rearrangement upon heating at 240°C to give a cycloheptadiene derivative that showed no biological activity, suggesting that the divinyl cyclopropane is required for biological activity.[4]

Subsequent to their initial report, Connor's group at Warner–Lambert isolated the 5-*epi*-isomer of **1**,[5] and they prepared a number of synthetic derivatives to explore the structure activity relationships of ambruticin analogues.[6] More recently, six natural ambruticins possessing quaternary amines in the place of the C5 hydroxyl group were isolated from *P. cellulosum*, and these compounds also exhibited potent in vivo antifungal activity and low toxicity.[7] Taken together, the biological studies demonstrate that the presence of polar functionality at C1, C5 and C6 was critical to the biological activity of the ambruticins. The mechanism of action of **1** has recently been studied and appears to involve interference with osmoregulation.[8] However, the narrow spectrum of antifungal activity exhibited by ambruticin S and its analogues limited the clinical utility of these compounds.

The shortcomings of its biological profile notwithstanding, ambruticin S remains an extremely attractive target for total synthesis because of its unique structural features. Indeed, a number of groups have developed synthetic approaches toward ambruticin S.[9] The first total synthesis of **1** was

Keywords: oxygen heterocycles; furan; carbohydrates; enantioselective; rearrangement; ring closing metathesis; Julia coupling.

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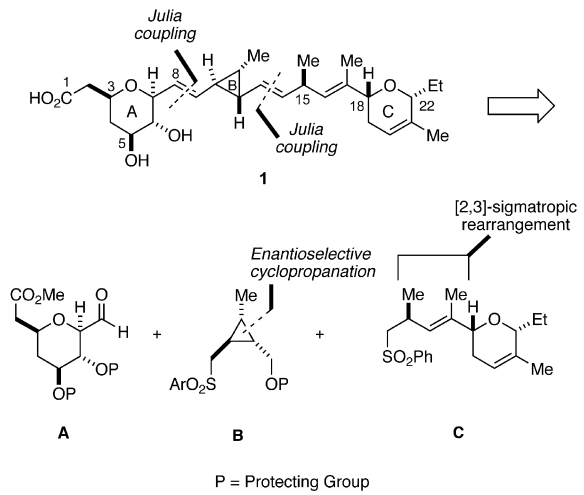
reported by Kende in 1990,[10] but three additional syntheses of **1** have recently been independently reported by ourselves[11] and the groups of Jacobsen[12] and Lee.[13]

Our analysis of the challenges posed by ambruticin S led to the retrosynthetic analysis outlined in Scheme 1 in which disconnections at the two disubstituted *E*-olefins are first performed. The three fragments obtained from these disconnections were an A-ring aldehyde **A**, a bifunctionalized B-ring cyclopropane **B** and a C-ring sulfone **C**. Each of these fragments has a similar degree of stereochemical and functional complexity, thereby endowing the approach with maximal convergency. We originally envisioned that the central **B** ring fragment would be accessible via methodology we had developed in collaboration with the Doyle group for the enantioselective synthesis of trisubstituted cyclopropanes via cyclizations of allylic diazoacetates in the presence of a chiral rhodium catalyst.[14] There were a number of options for constructing the hydropyranoid A and C ring subunits. At the outset, however, we had a particular prejudice for preparing these fragments from dihydropyranones that would be prepared via the oxidation of enantiomerically pure furans according to strategies that have been under extensive development in our laboratories.[15,16] Carbohydrates were also considered as potential precursors of the A and C rings. Although a carbohydrate was ultimately chosen as the starting material for the A ring, the C ring was eventually most readily prepared by a ring closing metathesis, a transformation that has gained considerable importance in natural product synthesis.[17] We now report the details of our studies directed toward the total synthesis of **1**.

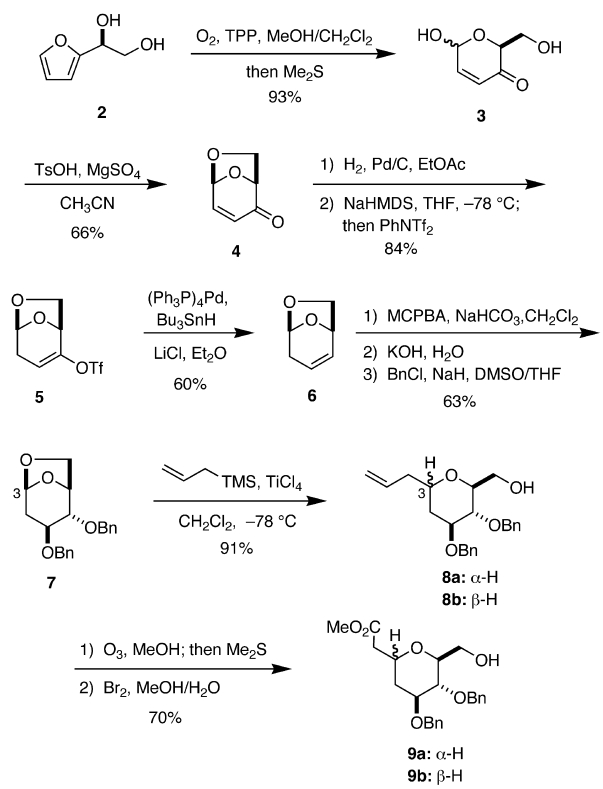


Scheme 1.

2. Results and discussion

2.1. Approaches to the A-ring

In our first approach to a protected A-ring subunit, we explored the use of the dihydropyranone **3**, which was prepared by oxidation of the hydroxy furan **2**, as a key intermediate. We had previously shown that various dihydropyranones thus obtained admirably served as intermediates in concise syntheses of highly oxygenated natural products.[16] Although we initially prepared **2** by the enantioselective reduction of 1-furyl-3-hydroxyacetone[18] using Baker's yeast,[19] this technique proved rather cumbersome on large scale, and we found that the Sharpless dihydroxylation of vinyl furan[20] provided an excellent alternative route to large quantities of **2**.[21] Oxidation of **2** with singlet oxygen then furnished a mixture of anomeric pyranones **3**, which underwent acid-catalyzed cyclization to give the bicyclic ketal **4** in 61% yield from **2** (Scheme 2). Subsequent to our developing this approach to **4**, Ogasawara and co-workers published a closely related synthesis of **4** from **2**.[22] Reduction of **4** by catalytic hydrogenation followed by reaction of the enolate of the resultant ketone with $PhNTf_2$ gave **5**, reduction of which with Bu_3SnH provided the bicyclic olefin **6** in 50% overall yield.[23,24] The double bond in **6** was oxidized with *m*-chloroperbenzoic acid (MCPBA), and the resulting mixture of α- and β-epoxides was treated with KOH to give a single diastereomeric diol that was converted to the dibenzyl ether **7**.[25] The stereochemical outcome of the epoxide opening reaction may be attributed to the preference for hydroxide to attack the epoxide from an axial direction irrespective of which diastereomeric epoxide was the substrate.



Scheme 2.

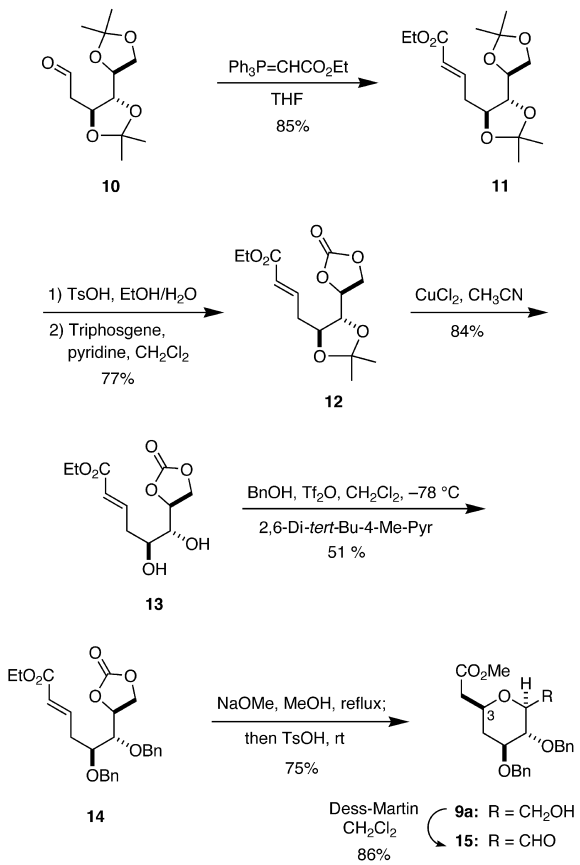
With **7** in hand, it remained to install an acetic acid side chain at C(3) to complete construction of the A-ring subunit.[26] Although **7** did react with the trimethylsilyl- and *tert*-butyldimethylsilylketene acetals derived from methyl acetate in the presence of Lewis acids,[27] the yields were poor with optimized yields being less than 15%. On the other hand, reaction of **7** with allyltrimethylsilane in the presence of $TiCl_4$ provided a mixture (1:4) of the anomeric *C*-glycosides **8a**,**b**.[28,29] These diastereomers were readily

separable and were independently subjected to ozonolysis followed by oxidation with Br_2 in aqueous methanol to furnish the esters **9a** and **9b**. Both **9a** and **9b** gave ^1H and ^{13}C NMR spectral data that were consistent with those reported by Donaldson,[30] who also showed that **9b** could be readily epimerized to provide exclusively the desired isomer **9a**.

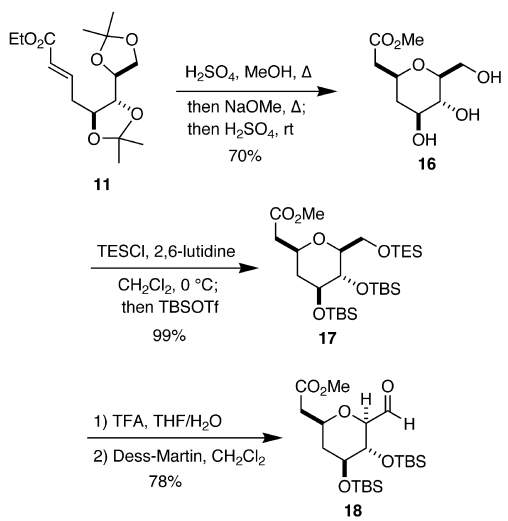
The sequence outlined in Scheme 2 provided a successful entry to the A-ring subunit of ambruticin S, but we were interested in developing a stereochemically more efficient route. After considering a number of possibilities, it occurred to us that the known aldehyde **10** (Scheme 3), which could be easily synthesized from commercially available L-glucono-1,5-lactone,[31] might be a suitable starting material. In the event, stereoselective Wittig olefination of **10** provided ester **11**. The terminal acetonide moiety was selectively removed by the action of *p*-TsOH in aqueous ethanol, and the intermediate diol was reprotected as a cyclic carbonate.[32] The subsequent deprotection of the internal acetonide of **12** to give **13** proved troublesome, as the carbonate function was too labile to withstand the standard acidic conditions required for acetonide cleavage. Eventually, we discovered that the acetonide group could be cleanly removed using $CuCl_2$ in acetonitrile to give the diol **13** in good overall yield from **10**.[33] The instability of the carbonate to relatively mild acidic conditions served as a harbinger of the difficulties that would follow as we found that the cyclic carbonate in **13** was incompatible with a number of standard conditions that are often employed to prepare *O*-benzyl ethers. For example, the use of benzyl trichloroacetimidate and benzyl bromide/silver oxide under a variety of conditions gave unsatisfactory yields of the desired dibenzyl ether **14**.[34,35] Ultimately we found that this benzylation could be most effectively achieved by reaction of **13** with benzyl triflate that was prepared in situ to furnish **14** in 51% yield.[36]

Heating **14** with NaOMe in MeOH induced a cascade of reactions involving cleavage of the cyclic carbonate group, transesterification of the ethyl ester, and intramolecular Michael reaction that led to the formation of **9a**. If this reaction was allowed to proceed for short periods of time, the C(3) epimeric ester **9b** could be observed in the mixture. However, heating the reaction mixture overnight effected the complete equilibration of any **9b** produced into **9a** via a retro-Michael/Michael process, although these conditions resulted in significant saponification of the methyl ester, a side reaction that was also observed by Donaldson.[30] Hence, the acid that was produced during this process was esterified in situ by simply adding an excess of TsOH to the cooled reaction mixture to deliver **9a** in 75% overall yield from **14**. After we completed this route to **9a**, Genêt reported a similar one-pot equilibration and esterification procedure for its preparation.[9k] Oxidation of the primary alcohol group in **9a** using Dess–Martin periodinane[37] furnished **15**, which exhibited spectral properties consistent with those previously reported,[9k] in seven steps and 18% overall yield from **10**. This stereoselective synthesis of **9a** thus represented a significant improvement over the approach outlined in Scheme 2 in which **9a** was prepared in 11 steps and 12% overall yield via a sequence that required a separation of diastereomers.

The route to the A-ring aldehyde **15** summarized in Scheme 3 was reasonably efficient and was originally employed to produce the quantities of material that were needed to explore various model Julia couplings to append the B ring (vide infra). However, the need to manipulate the hydroxyl protecting groups was viewed as a serious drawback to the approach, and so we developed an even more expeditious synthesis of a suitable A-ring precursor. Thus, **11** was heated with H_2SO_4 in MeOH to cleave both acetonides and provide a complex mixture containing the



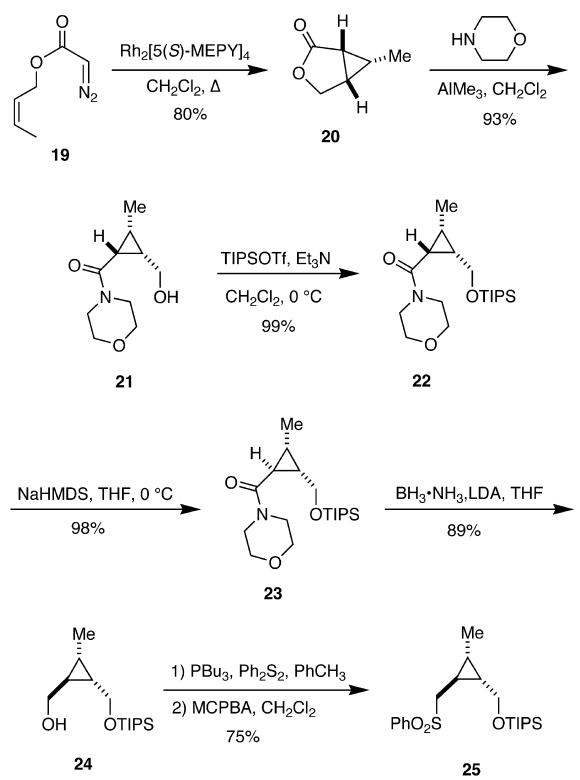
Scheme 3.



Scheme 4.

corresponding open-chain tetraol together with tetrahydrofurans and tetrahydropyrans derived from the acyclic tetraol via intramolecular Michael addition reactions (Scheme 4). Precedent suggested that tetrahydrofurans might be kinetic products,[38] but on the basis of preliminary molecular mechanics calculations,[39] we were seduced into thinking that the desired tetrahydropyran **16** would be significantly more stable than the tetrahydrofurans. Gratifyingly, **16** was isolated in 70% overall yield when this mixture was heated under reflux in methanolic NaOMe for 24 h and the resulting reaction mixture was acidified with H_2SO_4.

Transformation of **16** into an A-ring aldehyde then necessitated protection of the two secondary alcohols. Toward this objective, the primary alcohol of **16** was first selectively protected by reaction with TESCl at 0°C; however, several attempts to benzylate the secondary alcohols to prepare a precursor of **15** were unsuccessful. Another protecting group for these hydroxyl groups was thus indicated. Although we were unable to convert these alcohols cleanly into their TIPS ethers, the corresponding TBS ethers were readily formed. Indeed, the entire sequence of protecting the primary alcohol of **16** and then the two secondary alcohols with TBS groups could be conveniently performed in a one-pot procedure to provide ester **17** in nearly quantitative yield. Selective deprotection of the TES group with TFA followed by oxidation of the resulting alcohol provided the A-ring aldehyde **18** in five steps and 46% overall yield from **10**. This yield represented a significant improvement over previous routes to similar compounds.



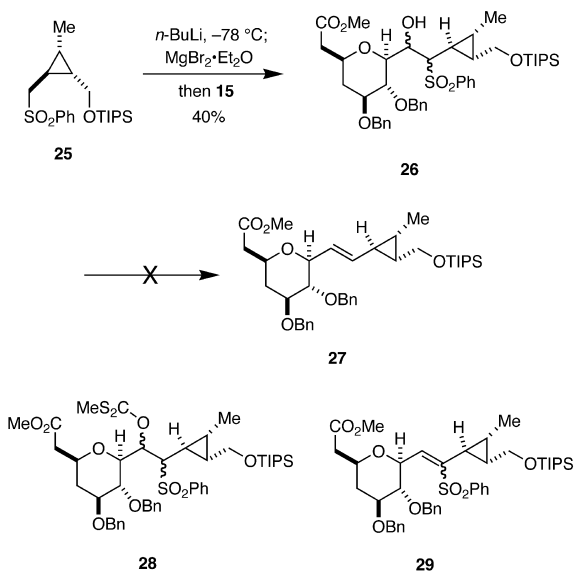
Scheme 5.

2.2. Synthesis of a B-ring subunit

At the outset of our studies we envisioned that suitable B-ring subunit precursors would be best accessed via an enantioselective cyclopropanation using a protocol that we had developed previously.[14] Thus, the known diazoacetate **19** was heated in the presence of $Rh_2[5(S)\text{-MEPY}]_4$ to provide the bicyclic lactone **20** in 80% yield and 92% enantiomeric excess (Scheme 5).[40] The lactone ring was opened using morpholine and $AlMe_3$ according to the Weinreb protocol to give alcohol **21**.[41] Inasmuch as we wanted a robust alcohol protecting group to explore various tactics for coupling the A and B rings (vide infra), the alcohol **21** was protected as its TIPS ether **22**. Base-induced epimerization of the stereocenter alpha to the carbonyl group in **22** to give **23** was driven by the conversion of the more sterically congested all *cis*-trisubstituted cyclopropane into a less strained cyclopropane ring in which the carboxamide group was *trans* to the other two substituents. Reduction of the amide moiety to give the requisite primary alcohol **24** was smoothly effected with the LDA and borane–ammonia complex reagent reported by Myers.[42] Anticipating the union of the A and B subunits via a standard Julia coupling procedure, the alcohol **24** was converted into its derived phenyl sulfide that was then oxidized with MCPBA to give the sulfone **25**.[43]

2.3. Coupling the A-ring and B-ring subunits

Preliminary experiments directed toward joining the A- and B-ring subunits **15** and **25** via a classic Julia coupling were fraught with pitfalls (Scheme 6). For example, when **15** was treated with the carbanion obtained upon deprotonation of **25** with either *n*-BuLi or NaHMDS, none of the desired adduct was obtained. Rather sulfone **25** was isolated together with an unsaturated aldehyde that appeared to arise from **15** through deprotonation followed by elimination of benzyl alkoxide. Some years ago, Lythgoe discovered a solution to this problem and reported that magnesium, rather than lithium or sodium, salts of sulfones added cleanly to highly enolizable aldehydes.[44] We found,

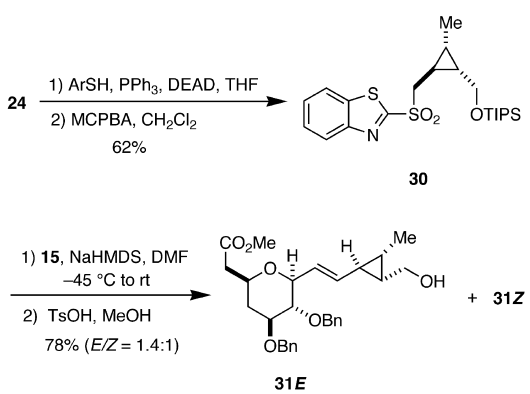


Scheme 6.

however, that direct deprotonation of **25** with EtMgBr was sluggish, even at elevated temperature, and provided only about 50% of the deprotonated sulfone as determined by quenching of the reaction mixture with CD_3OD. On the other hand, deprotonation of **25** with *n*-BuLi at −78°C proceeded quantitatively. The resulting lithiated sulfone was transmetallated by reaction with ethereal $MgBr_2{\cdot}Et_2O$ prepared according to the procedure of Seebach[45] to provide the corresponding magnesio sulfone,[46] which did react with the aldehyde **15** to furnish a mixture of diastereomeric hydroxy sulfones **26**, albeit in modest yield.

Despite this success, converting the diastereomeric hydroxy sulfones **26** into the desired olefin **27** proved to be problematic. When **26** was subjected to standard conditions using sodium amalgam to effect reductive elimination, none of the desired **27** could be detected in the reaction mixture, and no other identifiable products were isolated. We speculated that these difficulties might be a consequence of ring opening of the cyclopropyl carbinyl radical that would be generated upon homolytic scission of the carbon–sulfur bond. In one attempt to avoid forming this putative radical intermediate, **26** was transformed into the xanthate **28**, but reaction of **28** with Bu_3SnH failed to provide **27**.[47] Falck had encountered similar difficulties in related constructions, and he solved his problem by discovering that cyclopropyl vinyl sulfones could be reduced by electron transfer to give the corresponding vinyl cyclopropanes.[48] In order to explore this tactic as a possible solution to our dilemma, we converted several model cyclopropyl hydroxy sulfones into the corresponding vinyl cyclopropanes by sequential dehydration using either Tf_2O or the Martin sulfurane[49] and reduction of the resultant vinyl sulfone. However, we were unable to induce efficient elimination of **26** to the vinyl sulfone **29**.

Given these failures using a phenyl sulfone and the classic Julia procedure, we turned to modified Julia coupling methods in which the anion of either a benzothiazole sulfone[50] or a phenyl tetrazole sulfone[51] is employed as the reacting nucleophile. Aldehyde adducts derived from both of these sulfones were known to eliminate spontaneously in situ, and Charette had exploited such couplings to form vinyl cyclopropanes.[52] Toward applying this methodology to solving the problem in our synthesis, the benzothiazole **30** was first prepared from **24** (Scheme 7). The stepwise procedure of deprotonating **30** followed by adding **15** gave

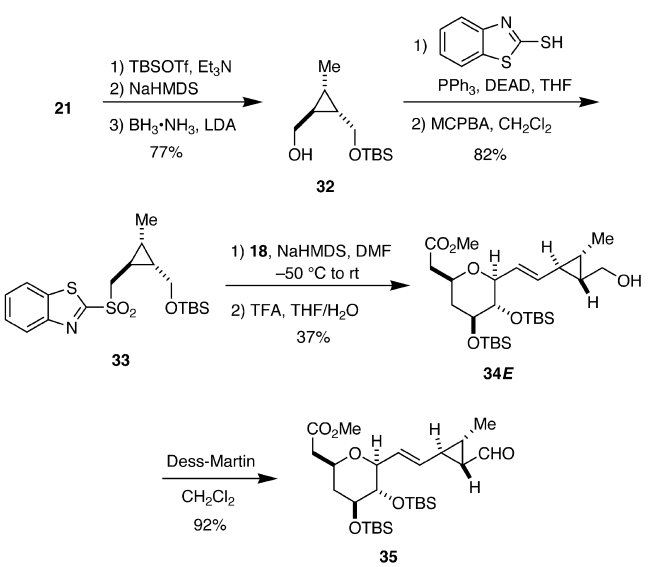


Scheme 7.

significant quantities of a bisbenzothiazole sulfone, which was presumably formed through a disproportionation reaction as described by Kocienski.[53] However, when a solution of **15** and **30** in DMF was treated with NaHMDS, the desired alkene **27** together with its *Z*-isomer were obtained. Although these isomers were inseparable, removal of the TIPS protecting group provided a separable mixture of the alcohols **31***E* and **31***Z* in a 1.4 to 1 ratio. The **31***E* thus exhibited ^1H NMR spectral characteristics consistent with those reported by Kende,[10b] thus completing a formal total synthesis of ambruticin S.[11a]

We were, of course, interested in improving the *E*/*Z* ratio in this coupling process. Julia,[54] Kocienski[51] and Charette[52] all reported that the *E*/*Z* ratio in their studies was dependent upon both the solvent and the counterion employed. In contrast, we found that changing the solvents (THF, DME, DMF and Et_2O) as well as the counterions (Na and K) had little effect upon the *E*/*Z* ratio in this reaction. Use of the phenyl tetrazole sulfone corresponding to **30** as described by Kocienski also afforded no advantage.[51] Although we briefly examined the possibility of isomerizing the undesired *cis*-isomer **31***Z* using iodine, these experiments were unavailing, and we therefore had to be content with the result.

Contemporaneous with the successful coupling of **15** with **30**, we developed the improved synthesis of the modified A-ring precursor **18** that is summarized in Scheme 4. In planning this approach, ancillary studies suggested that TBS ethers on the A-ring might not be fully compatible with the conditions required to remove the TIPS protecting group from the primary cyclopropyl carbinol in an advanced AB-ring intermediate. We thus prepared the TBS-protected benzothiazole sulfone **33** following the procedures previously developed for the synthesis of **30** (Scheme 8). The A-ring aldehyde **18** and the sulfone **33** were then coupled using the previously optimized conditions to give a mixture (2.6:1) of isomeric *E*- and *Z*-alkenes. Although the *E*/*Z* ratio was somewhat higher for this reaction than for the corresponding coupling of **30** and **15**, the overall yield

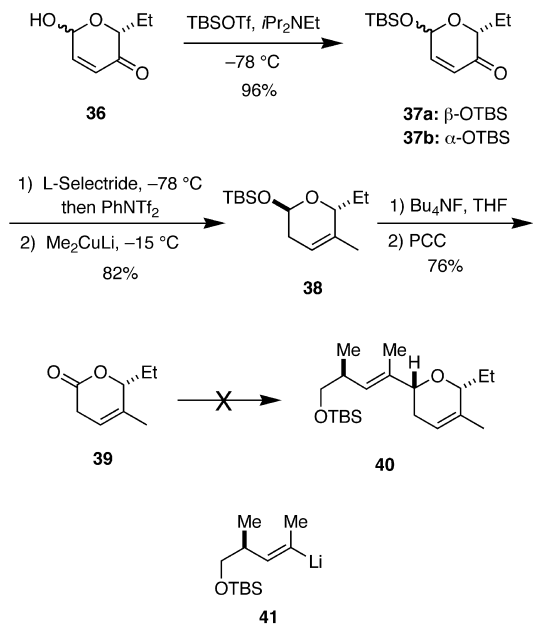


Scheme 8.

was slightly lower. This mixture of fully protected geometric isomers was separable, but the chromatography was tedious. Because the corresponding primary alcohols were easy to separate, the mixture of alkenes formed from the Julia coupling was simply treated with aqueous CF_3CO_2H to selectively remove the TBS group from the primary alcohol function to give **34***E* and **34***Z*. Oxidation of the primary hydroxyl group of **34***E* using Dess–Martin periodinane then furnished the aldehyde **35**.[37]

2.4. Synthesis of the C-ring

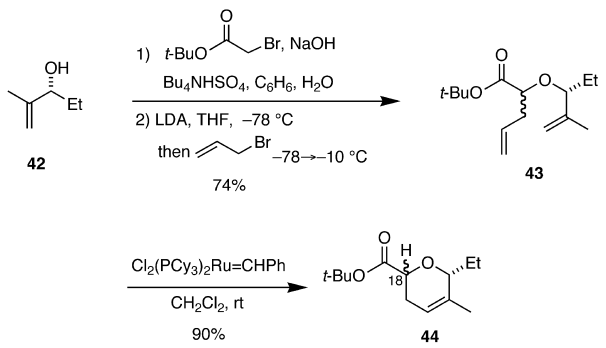
Our initial approach to the C-ring was based on the oxidative rearrangement of hydroxy furans that we had previously exploited in our laboratories.[16] We first developed a new procedure for preparing the known enone **36**[55] via the singlet oxygen oxidation of (+)-1-furyl-1-propanol,[56] which was synthesized by the TADDOL-mediated addition of Et_2Zn to furfural.[57] Silylation of **36** provided **37a**,**b** as a mixture (3:1) of anomers (Scheme 9). In principle, each of these anomers could have been transformed into the lactone **39**; however, because the ensuing 1,4-reduction of **37b** was not clean, they were separated and **37a** was used in subsequent experiments. In order to avoid epimerization of the stereocenter bearing the ethyl side chain during conjugate reduction, it was necessary to add **37a** to a solution of L-Selectride according to a protocol developed by Paquette.[58] The intermediate enolate was trapped as its triflate, which was then treated with Me_2CuLi to deliver the trisubstituted olefin **38**.[59] Removal of the silyl protecting group followed by PCC oxidation of the resultant lactol provided the lactone **39**.



Scheme 9.

We had originally envisioned that addition of an organometallic reagent such as **41**[60] to lactone **39** followed by reduction with Et_3SiH and $BF_3{\cdot}Et_2O$ would provide the C-ring subunit **40**. Unfortunately, this expectation was overly optimistic as we obtained at best low yields of adducts from reactions of **39** with either simple vinyl organometallic species or **41** under a wide variety of conditions. This inability to add organometallic reagents to lactone **39** necessitated a dramatic change in our approach to the C-ring subunit of ambruticin S.

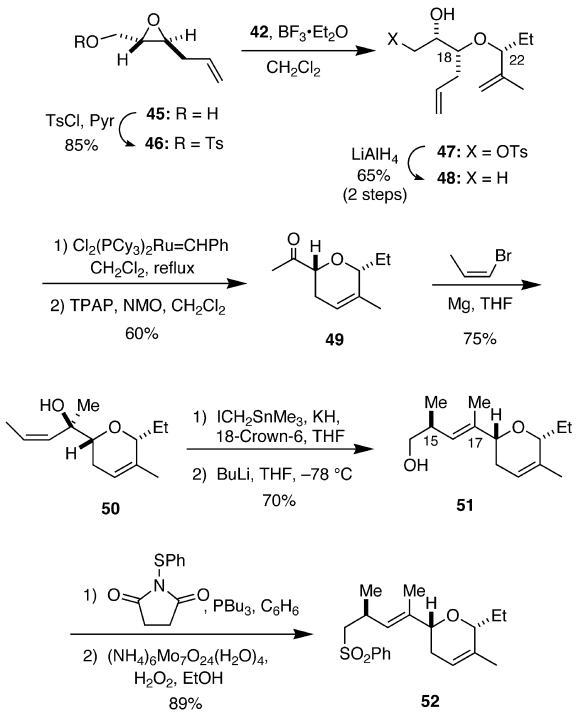
Inasmuch as we were concurrently exploiting ring closing metathesis (RCM) as a key step in several other projects,[61] it occurred to us that such a construction might constitute a useful entry to the C-ring. Toward this end, we developed an improved enantioselective synthesis of the known alcohol **42**[62] in 53% yield and 97% ee by the TADDOL-mediated addition of Et_2Zn to methacrolein.[57] This alcohol was then *O*-alkylated with *tert*-butyl bromoacetate under phase transfer conditions, and the enolate derived from the resulting ester was alkylated with allyl bromide to provide diene **43** as a mixture (1:1.3) of diastereomers (Scheme 10). Although small amounts of each diastereomer could be obtained through careful chromatography, this procedure would obviously not be amenable to preparing larger quantities of material. Hence, the mixture was stirred at room temperature in the presence of Grubbs' catalyst[63] to provide the dihydropyran **44**, also as a mixture (1:1.3) of diastereomers. We had originally anticipated that this mixture could be equilibrated using base to provide the desired *cis*-2,6-disubstituted hydropyran exclusively. Unfortunately, exposing **44** to a variety of bases in different solvents simply returned the same ratio of C(18) epimers.



Scheme 10.

Although this study clearly demonstrated the viability of using a RCM reaction to assemble the C-ring hydropyran with its trisubstituted double bond, it also revealed the necessity of correctly establishing the stereocenter at C(18) prior to ring formation. A different diene was thus required as a starting material. Toward this goal, the known epoxide **45**[64] was converted into its tosylate **46** (Scheme 11). The ring opening of the epoxide moiety of **46** with **42** in the presence of $BF_3{\cdot}Et_2O$ proceeded regioselectively as expected to give **47**,[65] and reduction of the tosylate with $LiAlH_4$ gave the requisite diene **48** in 65% overall yield from **46**. Heating **48** with Grubbs' catalyst followed by oxidation of the intermediate alcohol with catalytic TPAP provided the methyl ketone **49** as a single diastereomer.

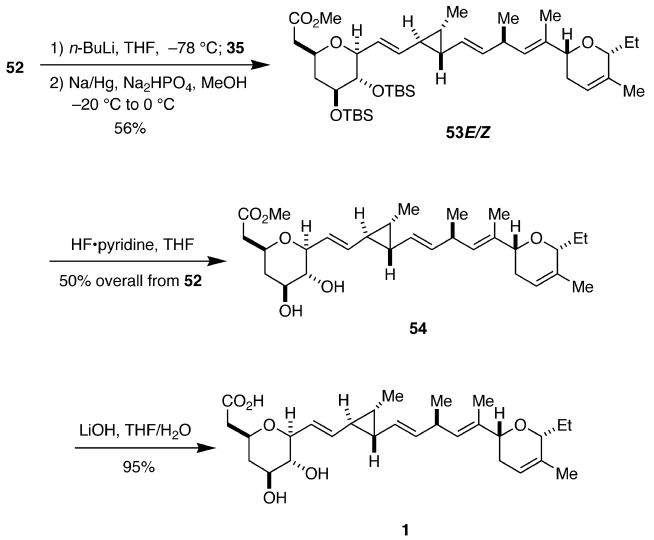
With ketone **49** in hand, it remained to append the C-14 to C-17 segment that would be linked to the AB-ring subunit **35**. We reasoned that this goal might be best achieved using a [2,3]-Wittig rearrangement. Toward this end, addition of propenylmagnesium bromide to **49** proceeded with



Scheme 11.

chelation control and with >95% diastereoselectivity to give the tertiary alcohol **50**,[66] which was alkylated with trimethyltinmethyl iodide[67] to provide an intermediate stannane. When this stannane was treated with *n*-BuLi, a highly diastereoselective (>20:1) [2,3]-Wittig rearrangement ensued to give the homoallylic alcohol **51**,[68] which possessed both the requisite *S*-configuration at C(15) and the *E*-olefin geometry at C(16)–C(17). Transformation of **51** into the sulfone **52** was achieved in 89% overall yield by sequential reaction with *N*-thiophenylsuccinimide and PBu_3, followed by oxidation of the intermediate sulfide with ammonium molybdate/H_2O_2.[69]

The stage was then set for the final assembly of the ambruticin S framework via the Julia coupling between



Scheme 12.

the aldehyde **35** and the C-ring sulfone **52** (Scheme 12). In the event, deprotonation of **52** with *n*-BuLi followed by addition of **35** provided a mixture of diastereomeric hydroxy sulfones that was not characterized. Rather, the mixture was treated directly with Na/Hg to provide **53***E*/*Z* as an inseparable mixture (*E*/*Z*≈10:1) of isomers in 56% combined yield.[70] When the TBS protecting groups were removed with HF·pyridine, the ambruticin S methyl ester (**54**) was isolated in 50% overall yield from **52**. The **54** thus obtained exhibited ^{1}H NMR spectral characteristics consistent with those previously reported.[10b] Saponification of **54** with LiOH delivered synthetic (+)-ambruticin S (**1**), which was identical with an authentic sample of natural ambruticin S by TLC, ^{1}H and ^{13}C NMR (including HMQC), MS and optical rotation.

3. Conclusions

A highly convergent synthesis of ambruticin S (**1**) was accomplished in 28 total steps with a 4.3% overall yield for the longest linear sequence, which comprised only 13 steps from the cyclopropyl lactone **20**. The synthesis featured a catalytic enantioselective cyclopropanation for the preparation of the B-ring precursor of **1**. A RCM reaction and a stereoselective [2,3]-Wittig rearrangement were utilized to construct the C-ring subunit, whereas the A-ring subunit was prepared from a carbohydrate. The synthesis also highlighted a modified Julia coupling to join the A- and B-ring fragments and a traditional Julia coupling to complete the assembly of the skeletal framework.

4. Experimental

4.1. General

All reagents and solvents were used as received, except as noted below. Tetrahydrofuran (THF), diethyl ether (Et_2O), toluene, dimethylformamide (DMF), and methanol (MeOH) were purified using solvent columns as described by Grubbs.[71] Dichloromethane (CH_2Cl_2), diisopropylamine, and triethylamine (NEt_3) were distilled from CaH_2. All moisture sensitive reactions were performed under a nitrogen or argon atmosphere in oven dried glassware. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM) according to the Still protocol.[72] Percent yields are given for compounds that were ≥95% pure as judged by ^{1}H NMR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on 300 or 500-MHz spectrometers in $CDCl_3$ unless otherwise specified; individual peaks are reported as (multiplicity, coupling constant in Hz, number of hydrogens). Spectral splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad. Melting points are uncorrected.

4.1.1. (5*S*,6*R*,7*S*)-5,6;7,8-Diisopropylidene-5,6,7,8-tetrahydroxyoct-2-enoic acid, ethyl ester (11). A solution of aldehyde **10**[31] (0.10 g, 0.41 mmol) and carboethoxymethylene triphenylphosphorane (0.21 g, 0.61 mmol) in THF (3 mL) was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the

resulting paste was filtered through a plug of silica gel using Et_2O (75 mL). The filtrate was concentrated under reduced pressure, and the resulting yellow oil was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (15:85) to provide 110 mg (85%) of **11** as a clear colorless oil: ^{1}H NMR δ 7.04 (dt, J=15.7, 7.2 Hz, 1H), 5.94 (dt, J=15.7, 1.2 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 4.15–3.90 (comp, 4H), 3.57 (t, J=8.0 Hz, 1H), 2.73 (dddd, J=16.8, 8.2, 3.4, 1.6 Hz, 1H), 2.50 (dddd, J=15.3, 8.9, 7.7, 1.6 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.29 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 166.3, 144.4, 123.6, 110.0, 109.3, 80.5, 78.8, 77.1, 67.8, 60.2, 35.8, 27.1, 26.9, 26.7, 25.2, 14.2; IR (neat) 2986, 2874, 1746, 1658, 1455, 1372 cm^{-1}; MS (CI) m/z 315.1809 [$C_{16}H_{27}O_6$ (M+1) requires 315.1808] (base), 275, 257, 217.

4.1.2. [4,6-Dideoxy-6-(methoxycarbonyl)-D-gluco-β-*C*-pyranosyl]methanol (16). A solution of H_2SO_4 (0.1 M in MeOH, 0.57 mL) was added to a solution of **11** (90 mg, 0.29 mmol) in anhydrous MeOH (3 mL), and this mixture was heated under reflux for 3 h. The reaction was cooled to room temperature and the solvent removed in vacuo. The resultant white solid was redissolved in MeOH (3 mL), and the solution heated under reflux for 3 h; this process was repeated an additional time. The reaction was then stirred for 16 h at room temperature, at which time NaOMe (0.5 M in MeOH, 0.86 mL) was added. This mixture was heated under reflux for an additional 24 h. The solution was then cooled to room temperature and H_2SO_4 (0.1 M in MeOH) was added until the solution was strongly acidic (pH≈1). The reaction was stirred for 2 h at room temperature, and saturated aqueous $NaHCO_3$ was added until the mixture was neutral. The insoluble salts were removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography over silica gel eluting with MeOH/CH_2Cl_2 (1:9) to provide a white solid. This was recrystallized using EtOAc/hexanes (2:1) to provide 44 mg (70%) of **16** as a white solid: mp 114–115°C; ^{1}H NMR (CD_3OD) δ 3.92–3.77 (comp, 2H), 3.66 (s, 3H), 3.64–3.50 (comp, 2H), 3.17 (d, J=1.8 Hz, 1H), 3.15 (s, 1H), 2.59 (dd, J=15.6, 7.7 Hz, 1H), 2.48 (dd, J=15.6, 5.5 Hz, 1H), 2.00 (ddd, J=12.7, 5.1, 1.9 Hz, 1H), 1.33 (q, J=11.5 Hz, 1H); ^{13}C NMR (CD_3OD) δ 173.2, 81.6, 73.5, 73.1, 73.0, 62.9, 52.2, 41.1, 39.9; MS (CI) m/z 221.1020 [$C_9H_{17}O_6$ (M+1) requires 221.1025], 185 (base), 171, 129.

4.1.3. [1-*O*-Triethylsilyl-2,3-bis-*O*-*tert*-butyldimethylsilyl-4,6-dideoxy-6-(methoxycarbonyl)-D-gluco-β-*C*-pyranosyl]methanol (17). To a solution of **16** (50 mg, 0.23 mmol) and 2,6-lutidine (0.29 mL, 2.49 mmol) in CH_2Cl_2 (2.5 mL) at 0°C was added TESCl (0.057 mL, 0.34 mmol), and the mixture was stirred for 30 min at 0°C. Freshly distilled TBSOTf (0.21 mL, 0.91 mmol) was then added, and stirring was continued for another 30 min at 0°C. Saturated aqueous $NaHCO_3$ (2 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting clear oil was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (5:95) to provide 126 mg (99%) of **17** as a clear colorless oil: ^{1}H NMR δ 3.82–3.61 (comp, 4H), 3.66 (s, 3H), 3.33 (t, J=8.9 Hz, 1H), 3.09 (ddd, J=9.0, 5.0, 2.1 Hz, 1H), 2.56 (dd, J=15.4, 7.4 Hz, 1H), 2.35 (dd, J=15.3, 5.8 Hz, 1H), 1.97 (ddd, J=12.7, 4.8, 1.8 Hz, 1H), 1.32 (q, J=12.6 Hz, 1H), 0.93 (t, J=8.0 Hz, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.54 (q, J=8.1 Hz, 6H), 0.07 (s, 3H), 0.06 (s, 9H); ^{13}C NMR δ 171.5, 81.3, 74.8, 72.8, 71.4, 62.5, 51.5, 40.7, 40.6, 26.4, 26.2, 18.4, 18.1, 6.7, 4.6, −2.8, −2.9, −3.9, −4.7; IR (neat) 2956, 2359, 1748, 1471, 1255 cm^{-1}; MS (CI) m/z 563.3622 [$C_{27}H_{59}O_6Si_3$ (M+1) requires 563.3620] (base), 533, 505, 431, 299.

4.1.4. [2,3-Bis-*O*-*tert*-butyldimethylsilyl-4,6-dideoxy-6-(methoxycarbonyl)-D-gluco-β-*C*-pyranosyl]methanol. A solution of **17** (36 mg, 0.064 mmol) and trifluoroacetic acid (0.049 mL, 0.64 mmol) in THF (2 mL) and H_2O (0.1 mL) was stirred for 3 h at room temperature. Saturated aqueous $NaHCO_3$ (4 mL) and Et_2O (4 mL) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (2×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting clear oil was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (1:4) to provide 23 mg (81%) of alcohol as a clear colorless oil: ^{1}H NMR δ 3.93–3.88 (m, 1H), 3.81 (dd, J=11.4, 2.8 Hz, 1H), 3.75–3.69 (m, 1H) 3.72 (s, 3H), 3.60 (dd, J=11.4, 6.2 Hz, 1H), 3.34 (t, J=7.8 Hz, 1H), 3.25 (ddd, J=9.1, 6.2, 2.8 Hz, 1H), 2.58 (dd, J=15.5, 7.7 Hz, 1H), 2.44 (dd, J=15.5, 5.3 Hz, 1H), 2.02 (ddd, J=12.9, 4.8, 1.9 Hz, 1H), 1.58 (br s, 1H), 1.42 (q, J=12.9 Hz, 1H), 0.92 (s, 9H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 6H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1, 80.4, 74.4, 73.2, 71.7, 62.6, 51.7, 40.6, 40.4, 26.3, 26.1, 18.3, 18.0, −2.8, −2.9, −4.1, −4.6; IR (neat) 3506, 2964, 2353, 2334, 1745, 1467 cm^{-1}; MS (CI) m/z 449.2751 [$C_{21}H_{45}O_6Si_2$ (M+1) requires 449.2755] (base), 433, 391, 317, 301.

4.1.5. [2,3-Bis-*O*-*tert*-butyldimethylsilyl-4,6-dideoxy-6-(methoxycarbonyl)-D-gluco-β-*C*-pyranosyl] aldehyde (18). A suspension of alcohol from the preceding experiment (14 mg, 0.031 mmol) and Dess–Martin periodinane (27 mg, 0.062 mmol) in CH_2Cl_2 (0.5 mL) was stirred for 1 h at room temperature. A solution of 1 M aqueous NaOH (1 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting clear oil was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (1:4) to provide 13.5 mg (96%) of **18** as a clear, colorless oil: ^{1}H NMR δ 9.61 (d, J=1.8 Hz, 1H), 4.01–3.90 (m, 1H), 3.80–3.74 (m, 1H), 3.73 (dd, J=8.5, 1.9 Hz, 1H) 3.67 (s, 3H), 3.52 (t, J=8.3 Hz, 1H), 2.67 (dd, J=15.8, 7.3 Hz, 1H), 2.44 (dd, J=15.8, 5.8 Hz, 1H), 2.04 (ddd, J=13.2, 4.8, 2.5 Hz, 1H), 1.42 (q, J=12.1 Hz, 1H), 0.88 (s, 9H), 0.86 (s, 9H), 0.08 (s, 6H), 0.07 (s, 3H), −0.04 (s, 3H); ^{13}C NMR δ 198.4, 171.0, 84.1, 73.4, 72.9, 71.3, 51.7, 40.3, 39.5, 26.2, 25.9, 18.2, 17.9, −3.3, −3.4, −4.4, −4.5; IR (neat) 3473, 2962, 2486, 2334, 1750, 1725 cm^{-1}; MS (CI) m/z 447.2597 [$C_{21}H_{43}O_6Si_2$ (M+1) requires 447.2598] (base), 431, 389, 315, 299.

4.1.6. (1*R*,2*S*,3*R*)-2-Hydroxymethyl-3-methyl-1-(morpholino)carbonylcyclopropane (21). To a solution of morpholine (0.23 mL, 2.7 mmol) in CH_2Cl_2 (10 mL) was

added $AlMe_3$ (1.3 mL, 2.0 M in hexanes) over 15 min. This solution was stirred for 15 min, and **20**[40] (100 mg, 0.89 mmol) was added. After stirring for 72 h, the reaction was cooled to 0°C, and 1N HCl (10 mL) was slowly added. The resulting heterogeneous mixture was stirred for 1 h at room temperature, and then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography over silica gel eluting with EtOAc to provide 165 mg (93%) of **21** as a clear, colorless oil: ^{1}H NMR δ 4.07 (br s, 1H), 3.88 (dd, J=12.0, 6.2 Hz, 1H), 3.80–3.45 (comp, 9H), 1.71 (t, J=8.8 Hz, 1H), 1.57–1.34 (comp, 2H), 1.05 (d, J=6.5 Hz, 3H); ^{13}C NMR δ 169.5, 66.8, 58.7, 46.1, 41.9, 23.1, 22.8, 16.0, 9.4; IR ($CHCl_3$) 3540–3040, 2965, 2915, 2875, 1625, 1480 cm^{-1}; MS (CI) m/z 199.1219 [$C_{10}H_{17}NO_3$ (M) requires 199.1208] (base), 182, 168, 114.

4.1.7. (1*R*,2*S*,3*R*)-3-Methyl-1-(morpholino)carbonyl-2-(*tert*-butyldimethylsilyloxy)methylcyclopropane. To a solution of **21** (38 mg, 0.19 mmol) and 2,6-lutidine (0.089 mL, 0.76 mmol) in CH_2Cl_2 (2 mL) at 0°C was added freshly distilled TBSOTf (0.066 mL, 0.29 mmol), and the solution was stirred for 30 min at 0°C. Saturated aqueous $NaHCO_3$ (4 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide 58 mg (97%) of protected alcohol as a clear, colorless oil that was used without further purification: ^{1}H NMR δ 3.95 (dd, J=11.5, 5.4 Hz, 1H), 3.79 (dd, J=11.5, 8.1 Hz, 1H), 3.61–3.38 (comp, 8H), 1.62 (t, J=9.0 Hz, 1H), 1.41–1.12 (comp, 2H), 1.08 (d, J=6.2 Hz, 3H), 0.82 (s, 9H), −0.02 (s, 6H); ^{13}C NMR δ 169.3, 67.0, 59.1, 46.2, 41.8, 26.0, 24.1, 21.1, 18.2, 15.7, 8.3, −5.2; IR (neat) 2953, 2851, 2364, 1659, 1462 cm^{-1}; MS (CI) m/z 314.2149 [$C_{16}H_{32}NO_3Si$ (M+1) requires 314.2151] (base), 298, 256, 182.

4.1.8. (1*S*,2*S*,3*R*)-3-Methyl-1-(morpholino)carbonyl-2-(*tert*-butyldimethylsilyloxy)methylcyclopropane (23). To a solution of preceding cyclopropane amide (159 mg, 0.51 mmol) in THF at 0°C was added NaHMDS (0.56 mL, 1.0 M in THF), and the solution was stirred for 90 min at 0°C. Saturated aqueous NH_4Cl (2 mL) and Et_2O (4 mL) were then added, and the layers were separated. The aqueous layer was extracted with Et_2O (2×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (35:65) to provide 146 mg (92%) of epimerized amide as a clear, colorless oil: ^{1}H NMR δ 3.69 (dd, J=11.0, 4.4 Hz, 1H), 3.68–3.48 (comp, 9H), 1.57–1.52 (comp, 2H), 1.31 (t, J=4.7 Hz, 1H), 1.08 (d, J=6.2 Hz, 3H), 0.81 (s, 9H), −0.02 (s, 6H); ^{13}C NMR δ 171.3, 66.7, 61.0, 45.8, 42.3, 28.1, 25.7, 24.5, 19.4, 18.1, 12.0, −5.4; IR (neat) 2951, 2857, 1647, 1466 cm^{-1}; MS (CI) m/z 314.2144 [$C_{16}H_{32}NO_3Si$ (M+1) requires 314.2151] (base), 298, 256, 182.

4.1.9. (1*S*,2*S*,3*S*)-1-Hydroxymethyl-3-methyl-2-(*tert*-butyldimethylsilyloxy)methylcyclopropane (32). To a solution of *i*-Pr_2NH (0.10 mL, 0.74 mmol) in THF (2 mL) at 0°C was added *n*-BuLi (0.55 mL, 1.35 M in hexanes), and the solution was stirred for 5 min. $BH_3{\cdot}NH_3$ (26 mg, 0.74 mmol) was added, and the cloudy suspension was stirred for 15 min at 0°C and 15 min at room temperature. A solution of amide from the preceding experiment (58 mg, 0.19 mmol) in THF (1 mL) was added, and the reaction was stirred for 90 min at 0°C. A solution of 1 M HCl (2 mL) was then added dropwise until the mixture was neutral. H_2O (2 mL) and Et_2O (6 mL) were then added, and the layers were separated. The aqueous layer was extracted with Et_2O (2×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel eluting with NEt_3/EtOAc/hexanes (2:23:75) to provide 37 mg (86%) of **32** as a clear, colorless oil: ^{1}H NMR δ 3.67 (dd, J=10.9, 6.4 Hz, 1H), 3.56 (dd, J=10.9, 7.3 Hz, 1H), 3.50 (dd, J=11.1, 6.7 Hz, 1H), 3.36 (dd, J=11.1, 7.3 Hz, 1H), 1.72 (br s, 1H), 1.07 (d, J=6.0 Hz, 3H), 0.95–0.77 (comp, 2H), 0.86 (s, 9H), 0.73–0.62 (m, 1H), 0.03 (s, 6H); ^{13}C NMR δ 66.5, 62.3, 27.3, 26.0, 23.8, 18.3, 15.5, 12.7, −5.2; IR (neat) 3356, 2955, 2857, 1472, 1391, 1255 cm^{-1}; MS (CI) m/z 231.1785 [$C_{12}H_{27}O_2Si$ (M+1) requires 231.1780], 213 (base), 194, 186, 182.

4.1.10. (1*S*,2*S*,3*S*)-1-[(Benzothiazolo)thio]methyl-2-methyl-3-(*tert*-butyldimethylsilyloxy)methyl cyclopropane. A solution of **32** (71 mg, 0.31 mmol), 2-mercaptobenzothiazole (62 mg, 0.37 mmol), Ph_3P (97 mg, 0.37 mmol), and DEAD (0.058 mL, 0.37 mmol) in THF (3 mL) was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography over silica gel eluting with CH_2Cl_2/hexanes (1:4) to provide 116 mg (99%) of sulfide as a clear, colorless oil: ^{1}H NMR δ 7.84 (ddd, J=8.1, 1.1, 0.6 Hz, 1H), 7.72 (ddd, J=8.0, 1.2, 0.6 Hz, 1H), 7.38 (ddd, J=8.1, 7.3, 1.2 Hz, 1H), 7.26 (ddd, J=8.4, 7.3, 1.2 Hz, 1H), 3.75 (dd, J=11.0, 6.0 Hz, 1H), 3.50 (dd, J=8.1, 11.0 Hz, 1H) 3.35 (dd, J=12.8, 7.3 Hz, 1H), 3.30 (dd, J=12.9, 7.3 Hz, 1H), 1.13–1.05 (m, 1H), 1.08 (d, J=6.3 Hz, 3H), 1.00–0.93 (m, 1H), 0.87 (s, 9H), 0.85–0.80 (m, 1H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 167.2, 153.4, 135.3, 126.0, 124.1, 120.9, 62.1, 38.6, 26.9, 26.0, 23.4, 18.8, 18.3, 12.6, −5.2, −5.3; IR (neat) 2956, 2928, 2856, 1428, 1428, 1251 cm^{-1}; MS (CI) m/z 380.1542 [$C_{19}H_{30}NOSiS_2$ (M+1) requires 380.1538] (base), 364, 322, 248, 213.

4.1.11. (1*S*,2*S*,3*S*)-1-[(Benzothiazolo)sulfonyl]methyl-2-methyl-3-(*tert*-butyldimethylsilyloxy)methylcyclopropane (33). A suspension of sulfide from the preceeding experiment (54 mg, 0.14 mmol), MCPBA (50 mg, 0.29 mmol) and $NaHCO_3$ (60 mg, 0.72 mmol) in CH_2Cl_2 (2 mL) was stirred for 24 h at room temperature. Saturated aqueous $NaHCO_3$ (2 mL) and $Na_2S_2O_3$ (2 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (1:9) to provide 48 mg (82%) of **33** as a white solid: mp 84–86°C; ^{1}H NMR δ 8.20–8.16 (m, 1H), 8.01–7.97 (m, 1H), 7.64–7.52 (comp, 2H), 3.61 (dd, J=11.0, 5.3 Hz, 1H), 3.54 (dd, J=14.7, 6.6 Hz, 1H), 3.40 (dd, 14.7, 7.5 Hz, 1H), 3.31 (dd, J=10.9,

8.3 Hz, 1H), 0.94 (d, *J*=5.9 Hz, 3H), 0.98–0.67 (comp, 3H), 0.78 (s, 9H), −0.09 (s, 6H); ^{13}C NMR δ 166.1, 152.8, 136.7, 127.9, 127.6, 125.3, 122.3, 61.4, 59.2, 25.8, 25.2, 18.1, 17.4, 16.4, 12.1, −5.5; IR (CH_2Cl_2) 2956, 2929, 2856, 1473, 1333, 1270, 1090 cm^{-1}; MS (CI) *m/z* 412.1432 [$C_{19}H_{30}NO_3S_2Si$ (M+1) requires 412.1436], 354, 280 (base), 256.

4.1.12. Methyl (8*E*,10*S*,11*S*,12*S*)-2,3-di-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1β-[11-methyl-12-hydroxymethylcyclopropylethenyl]-D-glucoheptopyranuronate (34*E*) and methyl (8*Z*, 10*S*,11*S*,12*S*)-2,3-di-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1β-[11-methyl-12-hydroxymethylcyclopropylethenyl]-D-glucoheptopyranuronate (34*Z*). To a solution of aldehyde **18** (35 mg, 0.078 mmol) and sulfone **33** (48 mg, 0.12 mmol) in DMF (0.5 mL) at −60°C was added a solution of NaHMDS (22 mg, 0.12 mmol) in DMF (1.5 mL). The reaction was stirred for 1 h at −60°C, the cold bath was removed, and the reaction was stirred at room temperature for 30 min. Saturated aqueous NH_4Cl (5 mL) and Et_2O (6 mL) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (3×4 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting yellow-brown oil was purified by flash chromatography over silica gel eluting with EtOAc/NEt_3/hexanes (4:2:94) to provide 28 mg of the desired adduct as a clear, colorless oil that was a mixture of inseparable olefin isomers. Integration of the appropriate signals in the ^{1}H NMR spectrum of this mixture revealed the ratio of *E*- and *Z*-isomers to be 2.6:1.

A solution of the mixture of olefins (28 mg, 0.044 mmol) and trifluoroacetic acid (0.034 mL, 0.44 mmol) in THF/H_2O (1 mL/0.1 mL) was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ (2 mL) and Et_2O (5 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (2×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting clear oil was purified by flash chromatography over silica gel eluting with Et_2O/CH_2Cl_2 (1:9) to first provide 6 mg (14%) of the *Z*-isomer **34***Z* as a clear, colorless oil followed by 15 mg (37%) of the *E*-isomer **34***E* as a clear, colorless oil:

For **34***Z*. ^{1}H NMR δ 5.38 (dd, *J*=15.3, 7.8 Hz, 1H), 5.18 (dd, *J*=15.3, 8.7 Hz, 1H), 3.81 (dtd, *J*=11.6, 6.5, 1.8 Hz, 1H), 3.76 (dd, *J*=11.5, 6.4 Hz, 1H), 3.65 (s, 3H), 3.64–3.60 (m, 1H), 3.50 (dd, *J*=11.5, 8.6 Hz, 1H), 3.49–3.44 (m, 1H), 3.16 (t, *J*=8.5 Hz, 1H), 2.61 (dd, *J*=15.6, 6.6 Hz, 1H), 2.38 (dd, *J*=15.6, 6.5 Hz, 1H), 1.99 (ddd, *J*=12.9, 4.8, 1.9 Hz, 1H), 1.38 (q, *J*=12.8 Hz, 1H), 1.29–1.23 (m, 1H), 1.22–1.15 (m, 1H), 1.12 (d, *J*=6.0 Hz, 3H), 1.00–0.91 (m, 1H), 0.89 (s, 9H), 0.85 (s, 9H), 0.062 (s, 3H), 0.061 (s, 3H), 0.056 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 171.3, 137.5, 126.6, 82.0, 76.5, 74.3, 71.4, 62.1, 51.7, 40.8, 40.5, 31.6, 27.9, 27.3, 26.3, 26.2, 18.3, 18.0, 12.4, −2.9, −3.0, −3.6, −4.2; IR (neat) 3432, 2959, 2925, 2880, 1746, 1642 cm^{-1}; MS (CI) *m/z* 529.3355 [$C_{27}H_{53}O_6Si_2$ (M+1) requires 529.3381], 511, 379, 265, 243 (base).

For **34***E*. ^{1}H NMR δ 5.27 (t, *J*=9.6 Hz, 1H), 5.06 (t, *J*=10.2 Hz, 1H), 3.95 (t, *J*=8.8 Hz, 1H), 3.89 (dtd, *J*=11.4, 6.8, 1.8 Hz, 1H), 3.79 (dd, *J*=11.4, 6.2 Hz, 1H), 3.70 (ddd, *J*=13.0, 8.2, 4.8 Hz, 1H), 3.65 (s, 3H), 3.53 (dd, *J*=11.4, 8.6 Hz, 1H), 3.26 (t, *J*=8.4 Hz, 1H), 2.62 (dd, *J*=15.7, 6.8 Hz, 1H), 2.39 (dd, *J*=15.9, 6.2 Hz, 1H), 2.01 (ddd, *J*=12.8, 4.8, 1.8 Hz, 1H), 1.40 (q, *J*=12.6 Hz, 1H), 1.31–1.26 (m, 1H), 1.15 (d, *J*=6.4 Hz, 3H), 1.13–1.10 (m, 1H), 1.01–0.96 (m, 1H), 0.89 (s, 9H), 0.83 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 171.3, 138.5, 126.6, 76.9, 76.7, 74.5, 71.5, 61.9, 51.6, 40.7, 40.5, 28.1, 26.3, 26.2, 23.9, 19.8, 18.3, 18.0, 12.3, −2.8, −2.9, −3.5, −4.1; IR (neat) 3444, 2956, 2925, 2883, 2857, 1732, 1660, 1463 cm^{-1}; MS (CI) *m/z* 529.3380 [$C_{27}H_{53}O_6Si_2$ (M+1) requires 529.3381], 511, 379, 265, 243 (base).

4.1.13. Methyl (8*E*,10*S*,11*S*,12*S*)-2,3-di-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1β-[11-methyl-12-formylcyclopropylethenyl]-D-glucoheptopyranuronate (35). A suspension of **34***E* (26 mg, 0.049 mmol) and Dess–Martin periodinane (42 mg, 0.098 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 90 min. A solution of 1 M aqueous NaOH (2 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide 24 mg (92%) of **35** as a clear, colorless oil which was used without further purification: ^{1}H NMR δ 9.46 (d, *J*=4.6 Hz, 1H), 5.56 (dd, *J*=15.3, 7.2 Hz, 1H), 5.19 (ddd, *J*=15.3, 9.0, 0.6 Hz, 1H), 3.82 (dtd, *J*=11.6, 6.6, 2.0 Hz, 1H), 3.67–3.61 (m, 1H), 3.65 (s, 3H), 3.49 (dt, *J*=8.6, 0.8 Hz, 1H), 3.16 (t, *J*=8.4 Hz, 1H), 2.59 (dd, *J*=15.5, 6.8 Hz, 1H), 2.38 (dd, *J*=15.5, 6.0 Hz, 1H), 2.10 (ddd, *J*=10.8, 6.4, 4.4 Hz, 1H), 1.99 (ddd, *J*=13.0, 4.8, 2.0 Hz, 1H), 1.97–1.94 (m, 1H), 1.56–1.51 (m, 1H), 1.38 (q, *J*=12.8 Hz, 1H), 1.26 (d, *J*=6.2 Hz, 3H), 0.88 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ 199.6, 171.3, 133.5, 129.3, 81.4, 76.5, 74.3, 71.5, 51.7, 40.7, 40.4, 36.5, 32.9, 26.5, 26.3, 26.1, 18.3, 18.0, 12.5, −2.9, −3.0, −3.7, −4.2; IR (neat) 2954, 2929, 2857, 1738, 1698 cm^{-1}; MS (CI) *m/z* 527.3202 [$C_{27}H_{51}O_6Si_2$ (M+1) requires 527.3224], 395, 263, 243 (base).

4.1.14. (2*S*,3*S*)-1-*p*-Toluenesulfoxy-2,3-epoxy-5-hexene (46). To a solution of alcohol **45**[64] (5.0 g, 44 mmol) and pyridine (6.5 mL, 80 mmol) in CH_2Cl_2 (44 mL) at 0°C was added *p*-toluenesulfonyl chloride (9.6 g, 50 mmol). The solution was then stirred at room temperature for 16 h, whereupon H_2O (100 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography over silica gel eluting with Et_2O/hexanes (3:7) to provide 10.0 g (85%) of **46** as a clear, colorless oil: ^{1}H NMR δ 7.81 (d, *J*=8.2 Hz, 2H), 7.37 (d, *J*=8.0 Hz, 2H), 5.76 (ddt, *J*=17.1, 13.2, 6.6 Hz, 1H), 5.17–4.92 (comp, 2H), 4.21 (dd, *J*=11.2, 3.2 Hz, 1H), 4.01 (dd, *J*=11.2, 5.7 Hz, 1H), 3.01 (ddd, 5.7, 3.9, 2.0 Hz, 1H), 2.90 (td, *J*=5.5, 2.0 Hz, 1H), 2.47 (s, 3H), 2.36–2.28 (m, 1H); ^{13}C NMR δ 145.0, 132.4, 132.0, 129.8, 127.7, 117.9, 69.8, 55.2, 53.8, 35.0, 21.5; IR (neat) 3079, 2981, 2926, 1637, 1598, 1448, 1363, 1190 cm^{-1}; MS (CI) *m/z* 269.0843 [$C_{13}H_{17}O_4S$ (M+1) requires 269.0848], 215, 173, 155 (base).

4.1.15. [2*S*,3*R*,3(3*R*)]-3-(4-Methyl-4-penten-3-oxy)-5-hexen-2-ol (48). To a solution of epoxide **46** (8.28 g, 30.9 mmol) and alcohol **42**[62] (4.5 g, 45.0 mmol) in CH_2Cl_2 (62 mL) was added $BF_3{\cdot}Et_2O$ (0.38 mL, 3.0 mmol). After stirring at room temperature for 16 h, the solvent was removed under reduced pressure. The resulting paste of **47** was dissolved in Et_2O (50 mL) and added via cannula to a slurry of $LiAlH_4$ (3.8 g, 100 mmol) in Et_2O (100 mL) at 0°C. The mixture was stirred for 3 h at 0°C, and then H_2O (4 mL) was added dropwise. A solution of 6 M aqueous NaOH (4 mL) and H_2O (8 mL) were added, and the resulting slurry was stirred for 2 h and then filtered through a pad of Celite. The pad was washed with Et_2O (2×100 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography over silica gel eluting with Et_2O/hexanes (3:7) to provide 4.0 g (65%) of **48** as a clear, colorless oil: ^{1}H NMR δ 5.80 (ddt, J=17.1, 14.1, 7.1 Hz, 1H), 5.10–4.86 (comp, 4H), 3.96 (dq, J=6.5, 3.2 Hz, 1H), 3.71 (dd, J=7.1, 6.8 Hz, 1H), 3.32 (ddd, J=8.4, 5.2, 3.2 Hz, 1H), 2.40–2.10 (comp, 2H), 2.08 (br s, 1H), 1.66 (d, J=0.9 Hz, 3H), 1.66–1.40 (comp, 2H), 1.15 (d, J=6.5 Hz, 3H), 0.87 (t, J=7.5 Hz, 3H); ^{13}C NMR δ 144.6, 135.7, 116.5, 114.1, 84.4, 79.6, 67.2, 33.8, 26.3, 17.5, 16.4, 10.2; IR (neat) 3474, 2963, 2933, 2874, 1647, 1598, 1458, 1369, 1190 cm^{-1}; MS (CI) m/z 199.1695 [$C_{12}H_{23}O_2$ (M+1) requires 199.1698], 181, 177, 163, 127, 117, 115, 100 (base).

4.1.16. (2*R*,6*R*)-Methyl-(6-ethyl-5-methyl-3,6-dihydropyran-2-yl)ketone (49). A solution of **48** (2.0 g, 10.0 mmol) in CH_2Cl_2 (100 mL) containing dichlorobis-(tricyclohexylphosphine)ruthenium benzylidene (0.82 g, 1.0 mmol) was heated under reflux for 16 h. The mixture was cooled, and the solvent was removed under reduced pressure. The resulting brown oil was purified by flash chromatography over silica gel eluting with Et_2O/hexanes (1:9) to provide the desired dihydropyran as a brown oil. The crude alcohol thus obtained was dissolved in CH_2Cl_2 (20 mL) containing 4 Å molecular sieves (5 g). NMO (1.4 g, 12.0 mmol) and TPAP (0.18 g, 0.5 mmol) were added, and the solution was stirred at room temperature for 2 h. The black solution was then filtered through a pad of silica gel, and the filtrate was concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography over silica gel eluting with Et_2O/hexanes (1:9) to provide 1.0 g (60%) of **49** as a clear, colorless oil: ^{1}H NMR δ 5.57 (br s, 1H), 4.11 (br s, 1H), 3.93 (dd, J=10.5, 4.6 Hz, 1H), 2.26 (s, 3H), 2.21–2.08 (m, 1H), 1.89–1.76 (m, 1H), 1.62 (d, J=0.9 Hz, 3H), 1.60–1.40 (comp, 2H), 0.96 (t, J=7.5 Hz, 3H); ^{13}C NMR δ 210.0, 135.6, 119.6, 78.8, 78.3, 27.3, 25.7, 25.6, 18.9, 8.6; MS (CI) m/z 169.1229 [$C_{10}H_{17}O_2$ (M+1) requires 169.1229].

4.1.17. [2*R*,6*R*,2(2′*R*)]-2-[2′-Hydroxy-3′-penten-2′(*Z*)-yl]-5-methyl-6-ethyl-3,6-dihydropyran (50). To a solution of ketone **49** (0.20 g, 1.2 mmol) in THF (10 mL) at −78°C was slowly added dropwise *cis*-propenylmagnesium bromide (1.0 M in THF, 5.0 mL), and the mixture was stirred for 1 h at −78°C. The reaction was warmed to 0°C and poured into saturated aqueous NH_4Cl (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (4×5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography over silica gel eluting with Et_2O/hexanes (1:9) to provide 189 mg (75%) of **50** as a clear, colorless oil: ^{1}H NMR δ 5.60–5.35 (comp, 3H), 4.08 (br s, 1H), 3.46 (dd, J=10.7, 3.2 Hz, 1H), 2.64 (br s, 1H), 2.19–2.09 (m, 1H), 1.89 (dd, J=7.1, 1.1 Hz, 1H), 1.82–1.71 (m, 1H), 1.60 (t, J=1.1 Hz, 3H), 1.57–1.44 (comp, 2H), 1.29 (s, 3H), 0.90 (t, J=7.3 Hz, 3H); ^{13}C NMR δ 135.0, 134.1, 127.0, 120.6, 79.0, 78.5, 74.9, 25.6, 25.3, 18.8, 14.3, 8.5; IR (neat) 3568, 2967, 2934, 2875, 1719, 1654, 1458, 1375, 1329, 1292, 1116, 1056 cm^{-1}; MS (CI) m/z 211.1699 [$C_{13}H_{23}O_2$ (M+1) requires 211.1698], 194, 193 (base), 169, 151.

4.1.18. [2*R*,6*R*,2(2′*S*,3′*E*)]-2-(1-Hydroxy-2-methyl-3-penten-4-yl)-5-methyl-6-ethyl-3,6-dihydropyran (51). A suspension of alcohol **50** (0.22 g, 1.1 mmol), 18-crown-6 (0.28 g, 1.1 mmol), and KH (150 mg of 35% dispersion in mineral oil, 1.3 mmol) in THF (10 mL) was stirred at 0°C for 5 min, whereupon trimethylstannyl methyliodide (3.2 g, 11 mmol) was added. The solution was allowed to warm to room temperature and stirred for 3 h. H_2O (10 mL) was then added, and the layers were separated. The aqueous layer was extracted with Et_2O (4×5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography over silica gel eluting with Et_2O to provide crude trimethylstannylmethyl ether that was not purified but dissolved in THF (10 mL). The solution was cooled to −78°C, *n*-BuLi (1.6 M in hexanes, 1.0 mL) was added slowly, and the reaction was stirred for 2 h at −78°C. The reaction was then warmed to room temperature, and H_2O (10 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (4×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography over silica gel eluting with Et_2O/hexanes (1:1) to provide 162 mg (70%) of **51** as a clear, colorless oil: ^{1}H NMR δ 5.58 (d, J=4.8 Hz, 1H), 5.23 (d, J=9.6 Hz, 1H), 4.11 (br s, 1H), 3.86 (dd, J=10.5 Hz, 3.0 Hz, 1H), 3.49 (dd, J=10.5, 6.1 Hz, 1H), 3.38 (dd, J=10.2, 7.7 Hz, 1H), 2.73–2.61 (m, 1H), 2.18–2.06 (m, 1H), 1.99–1.88 (m, 1H), 1.84–1.72 (m, 1H), 1.72 (d, J=1.1 Hz, 3H), 1.64–1.48 (comp, 2H) 1.61 (d, J=1.1 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR δ 138.4, 135.1, 127.0, 120.7, 78.0, 77.5, 67.8, 35.0, 30.3, 25.6, 18.9, 16.9, 13.0, 8.3; IR (neat) 3382, 2935, 2854, 1712, 1667, 1453, 1374, 1350, 1266, 1204 cm^{-1}; MS (CI) m/z 225.1857 [$C_{14}H_{25}O_2$ (M+1) requires 225.1855] (base), 207, 129, 117, 109.

4.1.19. [2*R*,6*R*,2(2′*S*,3′*E*)]-2-(1-Phenylthioxy-2-methyl-3-penten-4-yl)-5-methyl-6-ethyl-3,6-dihydropyran. To a solution of *N*-phenylthiosuccinimide (62 mg, 0.30 mmol) in C_6H_6 (2 mL) was added PBu_3 (0.075 mL, 0.30 mmol). After stirring for 5 min, a solution of alcohol **51** (50 mg, 0.22 mmol) in C_6H_6 (1 mL) was added, and the reaction was stirred for 1 h. The solution was concentrated under reduced pressure, and the residue was purified by flash chromatography over silica gel eluting with Et_2O/hexanes (1:4) to provide 63 mg (91%) of sulfide as a clear, colorless oil: ^{1}H NMR δ 7.36–7.14 (comp, 5H), 5.58 (d, J=4.6 Hz, 1H), 5.31 (d, J=9.1 Hz, 1H), 4.11 (br s, 1H), 3.85 (dd, J=10.9, 3.2 Hz,

1H), 2.93 (dd, *J*=12.5, 6.6 Hz, 1H), 2.82 (dd, *J*=12.3, 7.3 Hz, 1H), 2.76–2.64 (m, 1H), 2.19–2.04 (m, 1H), 2.00–1.70 (comp, 3H), 1.65–1.50 (comp, 6H), 1.12 (d, *J*=6.6 Hz, 3H), 0.92 (t, *J*=7.3 Hz, 3H); ^{13}C NMR δ 137.2, 136.4, 135.0, 129.1, 128.9, 128.7, 125.6, 120.8, 77.8, 77.7, 41.0, 31.9, 30.1, 25.6, 20.1, 18.9, 12.4, 8.2; IR (neat) 2935, 2852, 1576, 1475, 1440, 1084 cm^{-1}; MS (CI) *m/z* 317.1945 [$C_{20}H_{29}OS$ (M+1) requires 317.1939] (base), 299, 275, 221, 207.

4.1.20. [2*R*,6*R*,2(2′*S*,3*E*)]-2-(1-Phenylsulfonyl-2-methyl-3-penten-4-yl)-5-methyl-6-ethyl-3,6-dihydropyran (52). A solution of ammonium molybdate tetrahydrate (0.12 g, 0.10 mmol) in 30% aqueous H_2O_2 (2 mL) was added dropwise to a solution of the preceding sulfide (80 mg, 0.25 mmol) in EtOH (2 mL) at −10°C, and the reaction was stirred for 30 min. Saturated aqueous $NaHCO_3$ (5 mL) and Et_2O (5 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3×20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography over silica gel eluting with Et_2O/hexanes (1:4) to provide 85 mg (98%) of **52** as a clear, colorless oil: ^{1}H NMR δ 7.90–7.48 (comp, 5H), 5.53–5.46 (m, 1H), 5.13 (d, *J*=8.7 Hz, 1H), 4.03–3.95 (m, 1H), 3.67 (dd, *J*=10.0, 2.7 Hz, 1H), 3.12–2.96 (comp, 3H), 2.01–1.87 (m, 1H), 1.87–1.65 (m, 1H), 1.56 (d, *J*=1.1 Hz, 3H), 1.52 (d, *J*=1.1 Hz, 3H), 1.52–1.41 (comp, 2H), 1.12 (d, *J*=6.4 Hz, 3H), 0.84 (t, *J*=7.3 Hz, 3H); ^{13}C NMR δ 139.9, 136.6, 135.0, 133.4, 129.1, 127.8, 127.1, 120.5, 77.8, 77.0, 62.4, 29.9, 27.7, 25.5, 20.8, 18.8, 12.5, 8.3; IR (neat) 3063, 2935, 2848, 1586, 1447, 1374, 1305, 1149, 1085 cm^{-1}; MS (CI) *m/z* 349.1837 [$C_{20}H_{29}O_3S$ (M+1) requires 349.1837] (base), 331, 253, 241.

4.1.21. Methyl 5β,6α-di-*tert*-butyldimethylsilyloxypolyangioates (53*E*/*Z*). A solution of 1.25 M *n*-BuLi in hexanes (0.08 mL, 0.1 mmol) was added to a solution of sulfone **52** (34 mg, 0.097 mmol) in THF (0.2 mL) at −78°C, and the resulting solution was stirred for 30 min. A solution of aldehyde **35** (17 mg, 0.032 mmol) in THF (0.25 mL) was then added, and the solution was stirred at −78°C for an additional 2 h. Saturated aqueous NH_4Cl (2 mL) and CH_2Cl_2 (6 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography over silica gel eluting first with CH_2Cl_2/hexanes (1:3) and then with EtOAc/CH_2Cl_2 (1:9) to provide 15 mg of recovered **52** and 31 mg of hydroxy sulfones as a mixture of diastereomers. The hydroxy sulfones (31 mg, 0.035 mmol) were dissolved in MeOH (1.5 mL) containing Na_2HPO_4 (0.25 g, 1.8 mmol) at −30°C, and sodium amalgam (1.0 g, 2.1 mmol Na) was added. The mixture was stirred for 3 h at −30°C, whereupon saturated aqueous NH_4Cl (10 mL) and CH_2Cl_2 (8 mL) were added. The supernatant was decanted, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the resulting oil was purified by flash chromatography over silica gel eluting with $PhCH_3$/hexanes (1:1) to provide 13 mg (56% from **35**) of an inseparable mixture (*E*/*Z*≈10:1) of **53***E* and its *Z*-isomer **53***Z* as a clear, colorless oil. For >**53***E*. ^{1}H NMR δ 5.56–5.53 (m, 1H), 5.41 (dd, *J*=15.7, 6.8 Hz, 1H), 5.35 (dd, *J*=15.3, 8.0 Hz, 1H), 5.22 (dt, *J*=9.0, 1.2 Hz, 1H), 5.17 (dd, *J*=15.3, 9.2 Hz, 1H), 5.05 (ddd, *J*=1.2, 8.8, 15.3 Hz, 1H), 4.07 (br s, 1H), 3.81 (dd, *J*=11.3, 3.4 Hz, 1H), 3.82–3.77 (m, 1H), 3.67 (m, 1H), 3.65 (s, 3H), 3.47 (t, *J*=7.0 Hz, 1H), 3.16 (t, *J*=8.4 Hz, 1H), 3.07–3.00 (m, 1H), 2.62 (dd, *J*=15.7, 6.4 Hz, 1H), 2.38 (dd, *J*=15.5, 6.6 Hz, 1H), 2.12–1.97 (m, 1H), 1.99 (ddd, *J*=12.8, 4.8, 1.8 Hz, 1H), 1.89–1.81 (m, 1H), 1.62 (d, *J*=1.2 Hz, 3H), 1.57 (br s, 3H), 1.52–1.44 (comp, 2H), 1.43–1.37 (m, 1H), 1.04–0.96 (comp, 2H), 1.03 (d, *J*=6.4 Hz, 3H), 1.02 (d, *J*=6.8 Hz, 3H), 0.89–0.85 (m, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.06 (s, 6H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 171.3, 138.1, 135.4, 135.0, 129.8, 126.1, 125.3, 121.0, 82.3, 78.1, 77.8, 76.5, 74.3, 71.3, 51.6, 40.8, 40.5, 35.0, 30.9, 30.2, 28.5, 26.3, 26.2, 25.6, 21.2, 20.7, 18.9, 18.3, 18.0, 13.0, 12.1, 8.2, −2.8, −3.0, −3.6, −4.2; IR (CH_2Cl_2) 2958, 2929, 2857, 1763, 1463, 1114, 837 cm^{-1}; MS (CI) *m/z* 717.4942 [$C_{41}H_{73}O_6Si_2$ (M+1) requires 717.4946] (base), 585, 453, 243 (base).

4.1.22. Methyl 5β,6α-dihydroxypolyangioate (54). A solution of the preceding mixture of **53***E*/*Z* (16 mg, 0.022 mmol) in THF (1 mL) and HF·pyridine (0.2 mL) was stirred for 16 h at room temperature. Saturated aqueous $NaHCO_3$ (4 mL) and CH_2Cl_2 (4 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (35:65) followed by HPLC using two μ-porasil columns and eluting with EtOAc/hexanes (50:50) to provide 9 mg (89%) of **54** as a clear colorless oil. The ^{1}H NMR spectrum of **54** was consistent with that reported.[1,10b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56–5.54 (m, 1H), 5.44 (ddd, *J*=15.5, 6.0, 0.6 Hz, 1H), 5.41–5.39 (comp, 2H), 5.23 (dt, *J*=8.8, 1.2 Hz, 1H), 5.06 (ddd, *J*=15.3, 8.8, 1.4 Hz, 1H), 4.08 (br s, 1H), 3.92–3.87 (m, 1H), 3.70–3.65 (m, 1H), 3.67 (s, 3H), 3.53–3.50 (m, 1H), 3.11 (t, *J*=8.8 Hz, 1H), 3.07–3.02 (m, 1H), 2.64 (dd, *J*=15.7, 6.8 Hz, 1H), 2.43 (dd, *J*=15.7, 6.2 Hz, 1H), 2.33 (br s, 1H), 2.14–2.02 (comp, 2H), 1.91 (br s, 1H), 1.87–1.82 (m, 1H), 1.80–1.72 (m, 1H), 1.62 (d, *J*=1.4 Hz, 3H), 1.57 (m, 3H), 1.55–1.40 (comp, 3H), 1.20–1.05 (comp, 2H), 1.04 (comp, 6H), 0.88 (t, *J*=7.2 Hz, 3H).

4.1.23. Ambruticin S (1). A solution of diol **54** (6 mg, 0.12 mmol) in THF (1 mL) containing 0.3 M aqueous LiOH (0.21 mL) was stirred for 3.5 h at room temperature. A solution of 1N HCl (4 mL) and $CHCl_3$ (6 mL) were added, and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3×2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide 5 mg (95%) of (+)-ambruticin S (**1**) as an off-white gum. The synthetic sample was identical with an authentic sample of natural ambruticin S by TLC, ^{1}H and ^{13}C NMR (including HMQC), MS, and optical rotation. ^{1}H NMR ($CDCl_3$) δ 5.55 (dd, *J*=6.2, 1.6 Hz, 1H), 5.48–5.41 (comp, 3H), 5.23 (dt, *J*=8.8, 1.2 Hz, 1H), 5.06 (ddd, *J*=15.3, 8.8, 1.4 Hz, 1H), 4.08 (br s, 1H), 3.92–3.87 (m, 1H), 3.82 (dd, *J*=10.6, 3.0 Hz, 1H), 3.69 (ddd, *J*=13.7, 8.6,

5.0 Hz, 1H), 3.56 (dd, J=9.0, 6.0 Hz, 1H), 3.15 (t, J=9.0 Hz, 1H), 3.09–3.03 (m, 1H), 2.65 (dd, J=16.1, 7.6 Hz, 1H), 2.53 (dd, J=16.1, 5.0 Hz, 1H), 2.13–2.07 (comp, 2H), 1.89–1.80 (m, 1H), 1.78–1.68 (m, 1H), 1.63 (d, J=1.2 Hz, 3H), 1.57 (br s, 3H), 1.56–1.45 (comp, 3H), 1.12–1.06 (comp, 2H), 1.05 (br s, 3H), 1.03 (d, J=7.0 Hz, 3H), 0.88 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.2, 140.1, 135.8, 135.2, 135.1, 129.5, 125.0, 123.3, 120.9, 80.9, 78.0, 77.9, 75.6, 72.0, 71.6, 40.1, 38.0, 35.0, 30.4, 30.2, 29.2, 25.6, 21.7, 21.1, 18.9, 13.0, 12.3, 8.2; MS (CI) m/z 475.3053 [$C_{28}H_{43}O_6$ (M+1) requires 475.3060]; $[\alpha]_D^{22}$=+32° (c 0.11, $CHCl_3$); {lit.[10b] for synthetic **1**, $[\alpha]_D^{22}$=+37° (c 0.10, $CHCl_3$); for natural **1**, $[\alpha]_D^{22}$=+42° (c 0.22, $CHCl_3$)}.

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