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Total Synthesis of (+)-Ambruticin S: Probing the Pharmacophoric Subunit†

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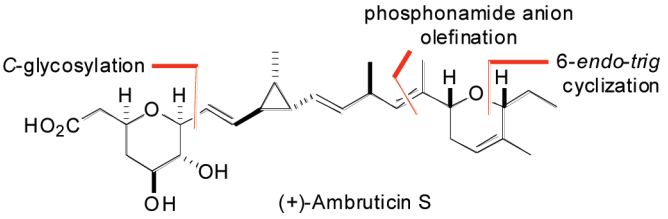

An enantioselective synthesis of the antifungal natural product (+)-ambruticin S has been accomplished starting with the readily available methyl α-D-glucopyranoside, (*R*)-Roche ester, and (*S*)-glycidol as chirons, which encompassed seven of the 10 stereogenic centers of the target molecule. The remaining three centers were set by a highly diastereoselective, asymmetric cyclopropanation employing a chiral, nonracemic phosphonamide reagent. Our strategy for the construction of the dihydropyran subunit involved a highly *syn*-selective Lewis acid catalyzed 6-*endo*-*trig* cyclization. Other key steps in the synthesis featured an epoxide opening with a dithiane anion, two efficient phosphonamide-anion based olefinations, and a late-stage *C*-glycosylation.

Introduction

(+)-Ambruticin S (**1a**) is an antifungal natural polyketide isolated in 1977 from myxobacterium *Polyangium cellulosum*[1,2] and belongs to a family that now consists of eight naturally occurring members (Figure 1).[3−5] The amino analogues in the VS-series **1c**−**h** were later isolated from a closely related myxobacterium strain, *Sorangium cellulosum* So ce10.[4]

The ambruticins show potent antifungal activity against a broad range of pathogens, such as *Aspergillus flavus*, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Hansenula anomala*, with MICs (minimal inhibition concentration) of 0.03−1.6 μg/mL, and no observed toxicity in mice.[2] Further biological testing resulted in oral activity against histoplasmosis and coccidioidomycosis. The compounds inhibit fungal growth presumably by interfering with the osmoregulatory system. It is suggested that the ambruticins induce the high osmolarity glycerol (HOG) signaling pathway by targeting hik1, a histidine kinase.[6]

The structure and absolute stereochemistry of (+)-ambruticin S was determined through a series of degradative studies, aided by a single crystal X-ray of the triformate ester of the alcohol obtained from reduction of the natural product.[1,7] The unique structural features of ambruticin S (**1a**) include 10 stereocenters, three *E*-double bonds, a tetrasubstituted

† Dedicated to Professor Eric Jacobsen on the occasion of his 50th birthday.

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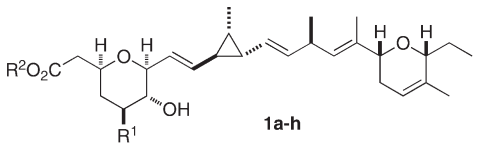

	R^1	R^2	Ambruticin
1a	OH	H	S
1b	OH (epimer)	H	F
1c	NH_2	H	VS-5
1d	NHMe	H	VS-4
1e	NMe_2	H	VS-3
1f	NMe_3^+	H	VS-1
1g	NMe_2O	H	VS-3 N-oxide
1h	NMe_3^+	Me	VS-2

FIGURE 1. The ambruticin family.

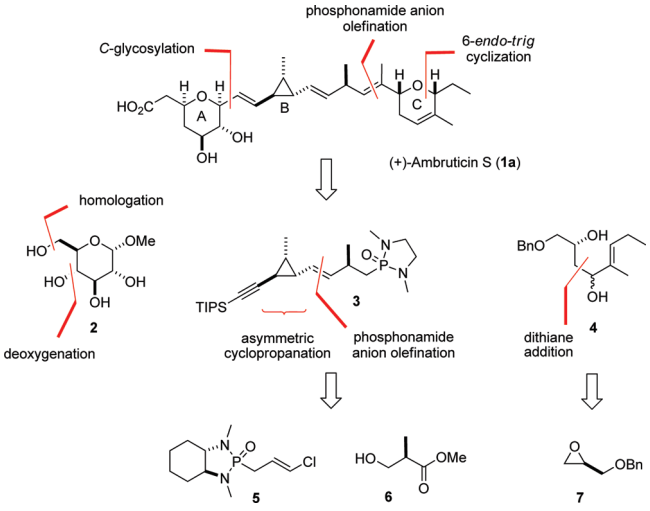

FIGURE 2. Retrosynthetic analysis and bond construction strategies of (+)-ambruticin S.

tetrahydropyran, a trisubstituted dihydropyran, and a trisubstituted cyclopropane, all encompassed in a linear array. The intriguing structure of ambruticin S has led to four total syntheses to date and some methodology studies.[5] The first total synthesis was achieved by Kende and co-workers in 1990.[8] Since then, total syntheses have been reported by the Martin,[9] Lee,[10] and Jacobsen[11] groups. Syntheses and biological evaluation of several structural analogues of the ambruticins have been published.[3,12] These structure–activity relationship studies were mainly limited to modifications of the tetrahydropyran subunit, as all of the analogues were actually derived from the ambruticins themselves through semisynthesis.

Herein we report our efforts leading to the total synthesis of (+)-ambruticin S and a crystal structure of the previously reported triformate ester. On the basis of this data, we designed and synthesized selected truncated analogues with the intention to exploit the pharmacophore believed to be associated with ring C and the trisubstituted olefin (Figure 2).

Results

In our synthetic strategy outlined in Figure 2, we envisaged a convergent, late stage assembly of three advanced fragments through a phosphonamide anion based olefination reaction and a *C*-glycosylation, respectively. It was thought that the ring A tetrahydropyran diol could be derived from methyl α-D-glucopyranoside (**2**) through a C-4 deoxygenation of the hydroxyl group and a one-carbon homologation of the C-6 side chain. The synthesis of the middle fragment **3** containing the trisubstituted cyclopropane would arise from our phosphonamide-anion methodologies for cyclopropanation[13,14] and olefination.[15,16] Thus, phosphonamide **5**[13] could provide enantioselective and diastereoselective access to the cyclopropane ring of ambruticin S, while the second phosphonamide anion based olefination in our synthetic plan would be carried out using a reagent prepared from (*R*)-Roche ester (**6**). The construction of the ring C *syn*-dihydropyran would employ a highly diastereoselective Lewis acid catalyzed 6-*endo*-*trig* cyclization recently developed in our laboratories.[17] The requisite diol **4** was anticipated to come from a dithiane anion addition to (*R*)-glycidol benzyl ether (**7**).

As shown in Scheme 1, our initial approach to build subunit A started from methyl α-D-glucopyranoside (**2**) and took advantage of an efficient, regioselective chlorination–reductive dechlorination sequence to remove the superfluous C-4 hydroxyl group.[18] Thus, treatment of **2** with sulfuryl chloride in the presence of pyridine, followed by hydrolysis with sodium iodide in aqueous methanol, delivered **8** in 86% yield.[19] Selective removal of the secondary chloride was achieved by hydrogenation in the presence of Raney nickel to yield diol **9**,[20] which was converted to the dibenzyl ether **10** (67%

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(14) (a) For a review on asymmetric cyclopropanation, see: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (b) For a review on *trans*-1,2-diamino-cyclohexane derivatives in asymmetric synthesis, see: Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3195.

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(16) Asymmetric olefination with cyclic phosphonamides: (a) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655–7658. (b) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7659–7662. (c) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754–5756.

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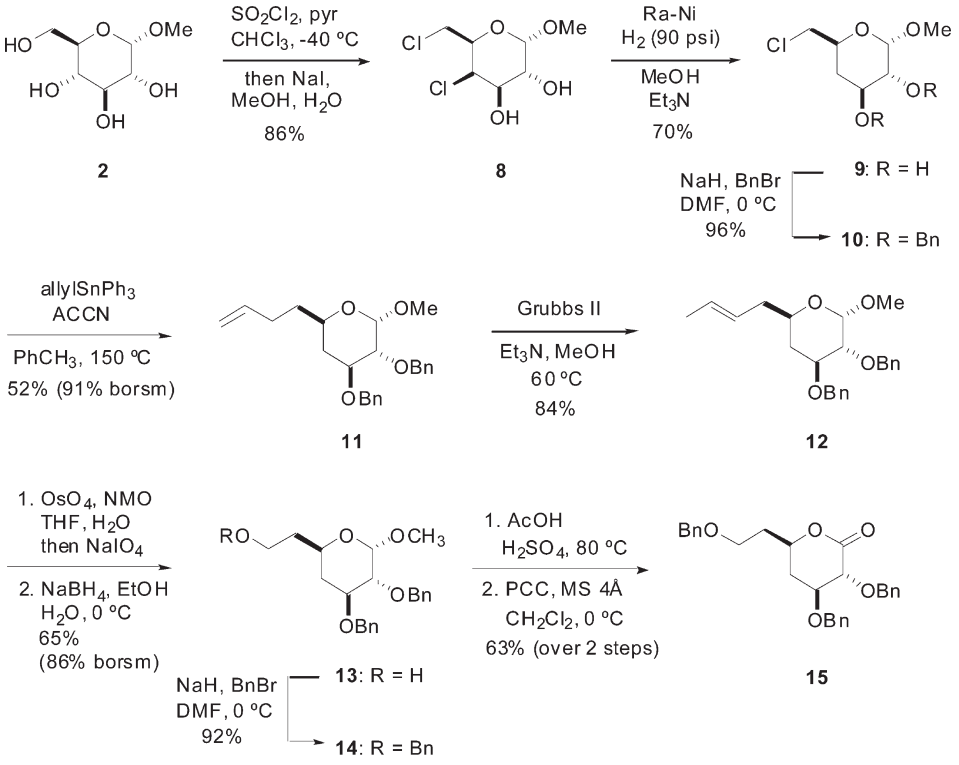
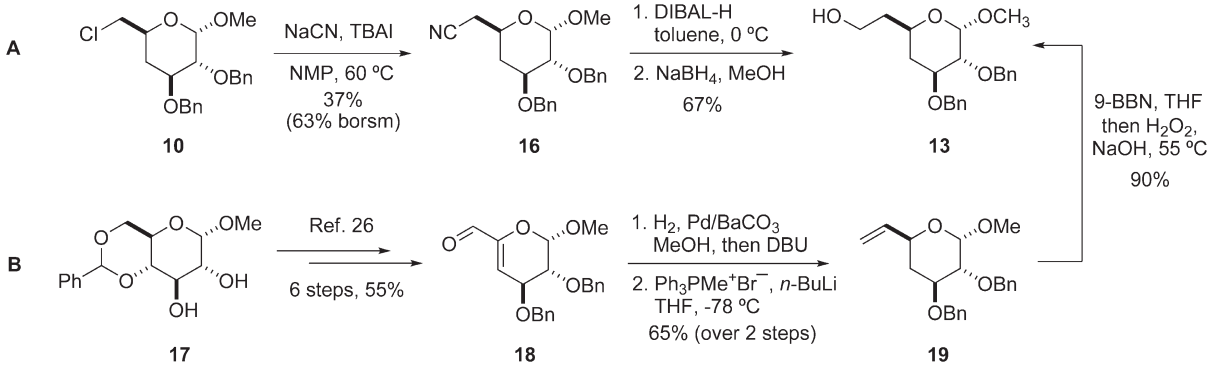
SCHEME 1. Synthesis of Ring A from Methyl α-D-Glucopyranoside (2)



SCHEME 2. Alternative Approaches to Intermediate 13



yield, two steps). After some experimentation, we found that selective substitution of the C-6 chloride could be achieved under free-radical conditions.[21] Thus, treatment of **10** with allyltriphenylstannane in the presence of ACCN (1,1′-azobis-(cyclohexanecarbonitrile) led to the *C*-allyl derivative **11** in 52% yield with recovery of starting material (43%). Isomerization of **11** in the presence of Grubbs' second generation catalyst[22] according to our recently reported method[23] afforded **12** in 84% yield, which was dihydroxylated with osmium tetroxide followed by oxidation and subsequent reduction to give alcohol **13** in 65% yield (last two steps). After protection of the free hydroxyl group with benzyl bromide, hydrolysis of the methyl glycoside under acidic conditions, and PCC oxidation, the desired lactone **15** was obtained in 58% yield (three steps).[24] The entire sequence was realized in 10 steps from commercially available and inexpensive **2** in 10% overall yield (seven steps to intermediate **13**, 16% overall yield).

Two alternative syntheses of intermediate **13** were also explored (Scheme 2A). Displacement of the chloride **10** with NaCN was notoriously slow, leading to the homologated nitrile **16** in 37% yield with recovery of starting material (41%).[25] Nevertheless, reduction with DIBAL-H to the aldehyde, followed by treatment with $NaBH_4$ furnished **13** in 67% yield (two steps). A third approach to alcohol **13** is shown in Scheme 2B. Starting from the known intermediate **18**, available from **17** in six steps and 55% overall

(21) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829–5831.
(22) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (c) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
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(24) Sánchez, M. E. L.; Michelet, V.; Besnier, I.; Genêt, J. P. *Synlett* **1994**, 705–708.
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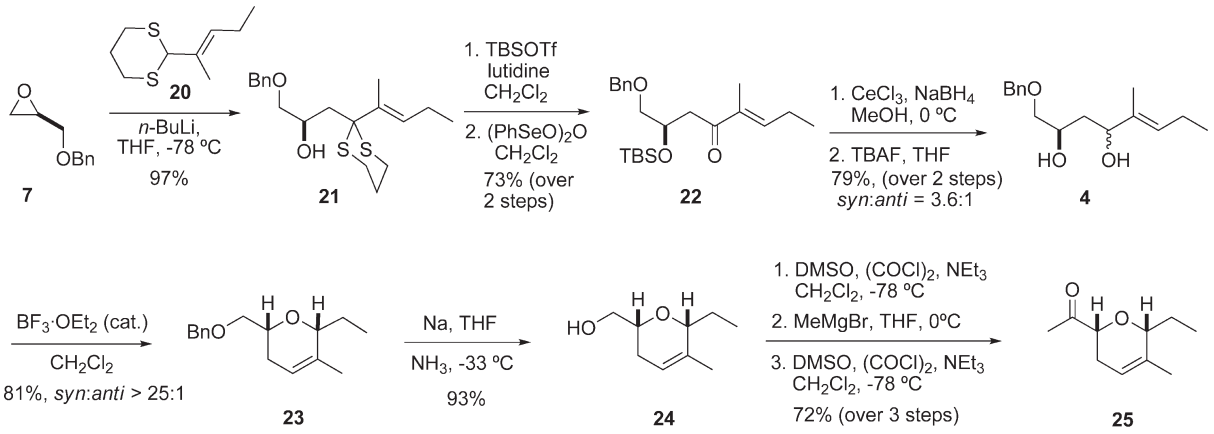
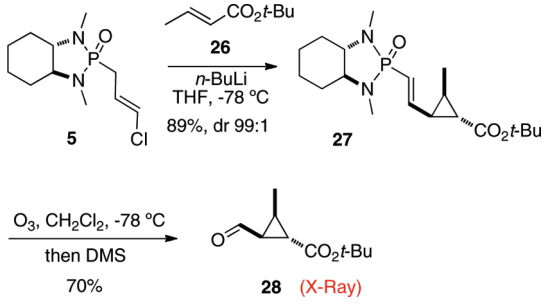
SCHEME 3. Synthesis of Ring C via 6-*endo-trig* Cyclization of Diol 4



yield,[26] we proceeded with the reduction of the α,β-unsaturated aldehyde using $Pd/BaCO_3$ and subsequent epimerization in the presence of DBU. Treatment of the saturated aldehyde thus obtained with the ylid generated from methyltriphenylphosphonium bromide gave vinyl tetrahydropyran **19**. Hydroboration of the double bond under oxidative conditions yielded primary alcohol **13** (59% yield, last three steps). These two approaches afforded intermediate **13** in six steps (14% overall yield) and nine steps (32% overall yield), respectively, from commercially available and inexpensive starting materials.

The construction of ring C of ambruticin S started from (*R*)-glycidol benzyl ether (**7**) and dithiane **20** and proceeded as shown in Scheme 3. The required dithiane **20** was obtained as a 9:1 mixture of *E*/*Z* isomers from treatment of 2-methyl-2-pentenal with 1,3-propanedithiol and $BF_3 \cdot OEt_2$.[27] Interestingly, only the anion derived from the *E*-isomer by deprotonation with butyllithium reacted with epoxide **7** to give adduct **21** in 97% yield. Protection of the hydroxyl group in **21** proved to be necessary in order to unmask the α,β-unsaturated system. Thus, exposure of adduct **21** to TBSOTf in the presence of 2,6-lutidine provided the corresponding TBS-ether in 93% yield. After some optimization, we found that the dithiane moiety could be removed conveniently from the latter compound by treatment with benzeneseleninic acid anhydride,[28] giving the relatively unstable enone **22** in 79% yield. Other methods screened for this conversion from **21** (Dess−Martin periodinane,[29a] $HgO/HgCl_2$,[29b] $HgCl_2/CaCO_3$,[29c] $HgClO_4$,[29d] $PhI(O_2CCF_3)_2$,[29e] and H_5IO_6[29f]) either gave a lower yield or led to decomposition. Luche reduction of enone **22** and treatment with TBAF furnished diol **4** as a 3.6:1 mixture of diastereomers in 79% yield (over two steps.) However, it was shown from preliminary studies that the configuration of the newly formed stereocenter is irrelevant for the subsequent 6-*endo-trig* cyclization forming dihydropyran **23**.[17] Thus, conversion of diol **4** in the presence of catalytic amounts of $BF_3 \cdot OEt_2$ proceeded smoothly on a multigram scale, furnishing the desired dihydropyran **23** in 81% yield. The benzyl group was then removed under Birch conditions, giving rise to alcohol **24** in 93% yield.[11] Oxidation under Swern conditions and reaction of the resulting aldehyde with MeMgBr, followed by a second Swern oxidation, provided the desired ketone **25** in 72% yield for three steps.[9,30]

SCHEME 4. Synthesis of Ring B



With a facile access to ring C ketone **25**, we turned our attention to the synthesis of the cyclopropane unit, which was accomplished through a highly stereoselective cyclopropanation of *tert*-butyl crotonate (**26**) using the *trans*-chloroallyl phosphonamide **5** (Scheme 4).[13b] Thus, deprotonation of **5** with *n*-butyllithium at low temperature followed by addition of *tert*-butyl crotonate gave the desired cyclopropane adduct **27** as a single diastereomer in 89% yield. The stereochemical outcome of the cyclopropanation was based on our previous study[13b] and NMR analysis and ultimately proven by single-crystal X-ray analysis. Removal of the chiral auxiliary by ozonolysis of **27** afforded the crystalline cyclopropyl aldehyde **28** in 70% yield.

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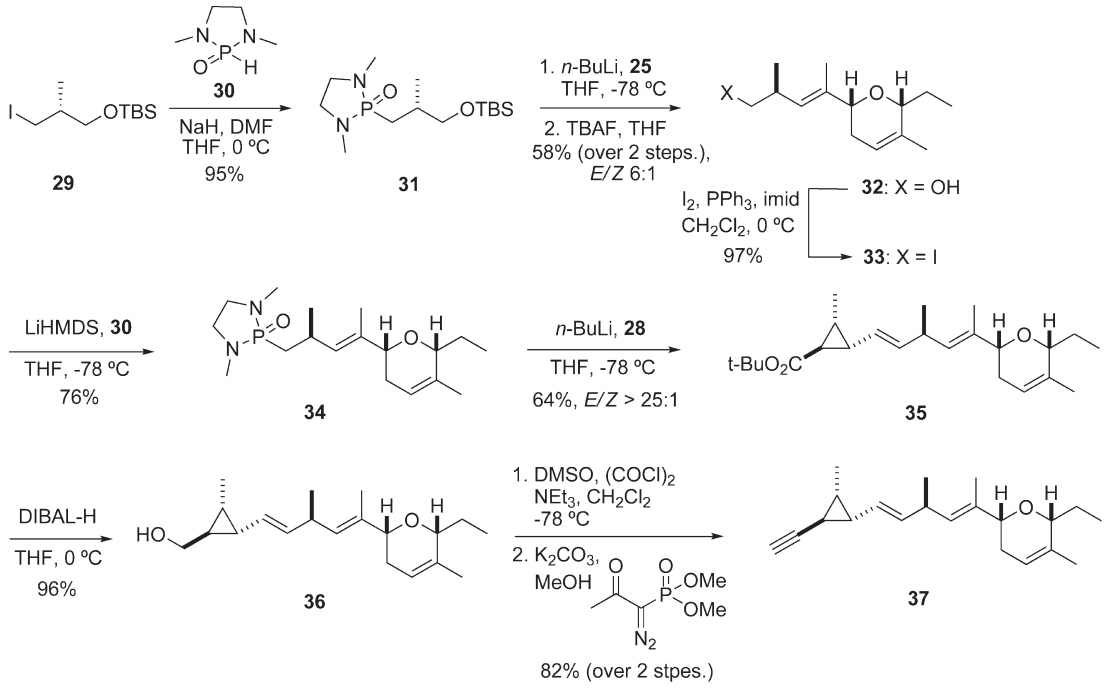
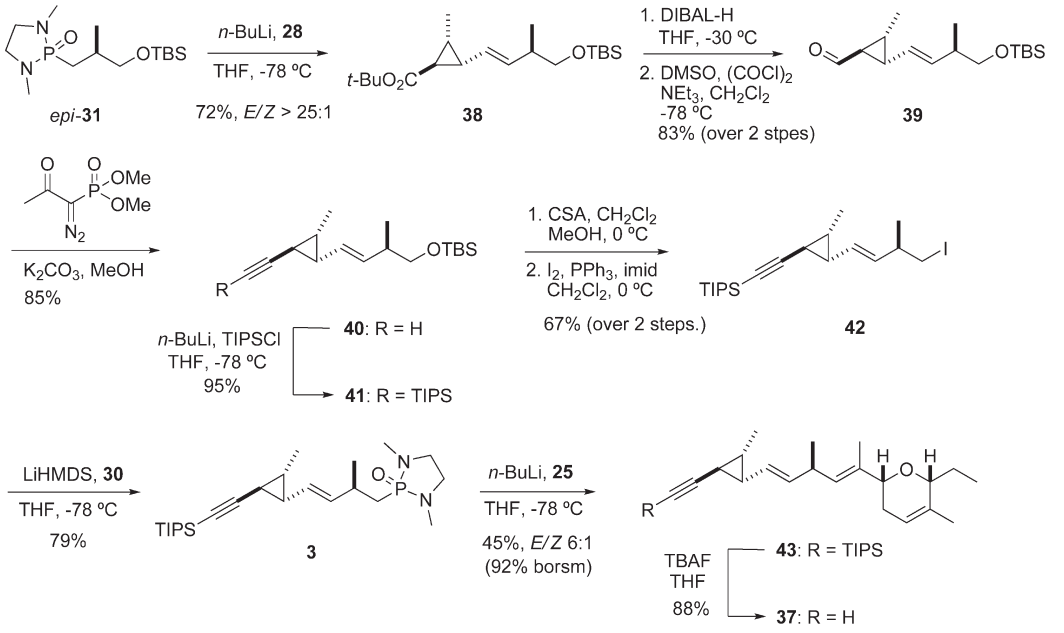
SCHEME 5. Synthesis of Middle Segment, First Approach



SCHEME 6. Synthesis of Middle Segment, Second Approach



The synthesis of the middle segment containing the cyclopropane ring was first realized in a linear fashion commencing from ketone **25** (Scheme 5). The latter was reacted with phosphonamide **31**, which is derived from alkylation of 1,3-dimethyl-2-oxo-1,3,2-diazaphospholidine (**30**)[31a,b] with (*R*)-3-*tert*-butyldimethylsilyloxy-2-methylpropyl iodide (**29**).[32] Deprotonation of **31** at low temperature followed by addition of ketone **25** and quenching with AcOH furnished a separable 6:1 mixture of *E*/*Z* isomers, with the desired compound as the major one.[17] Subsequent removal of the TBS group with TBAF afforded the known alcohol **32** in 58% yield (two steps).[9,10,30a] The latter was then converted into the corresponding iodide by treatment with iodine and PPh_3, followed by displacement of the iodide with the anion of phosphorus acid diamide **30** to give phosphonamide **34** (76% yield, two steps). Olefination of cyclopropyl aldehyde **28** with the lithium anion of **34** proceeded with excellent

(31) (a) Pudovik, M. A.; Pudovik, A. N. *Zh. Obshch. Khim.* **1973**, *43*, 2147–2149. (b) For alkylation of phosphorous acid diamides, see: Koeller, K. J.; Spilling, C. D. *Tetrahedron Lett.* **1991**, *32*, 6297–6300.

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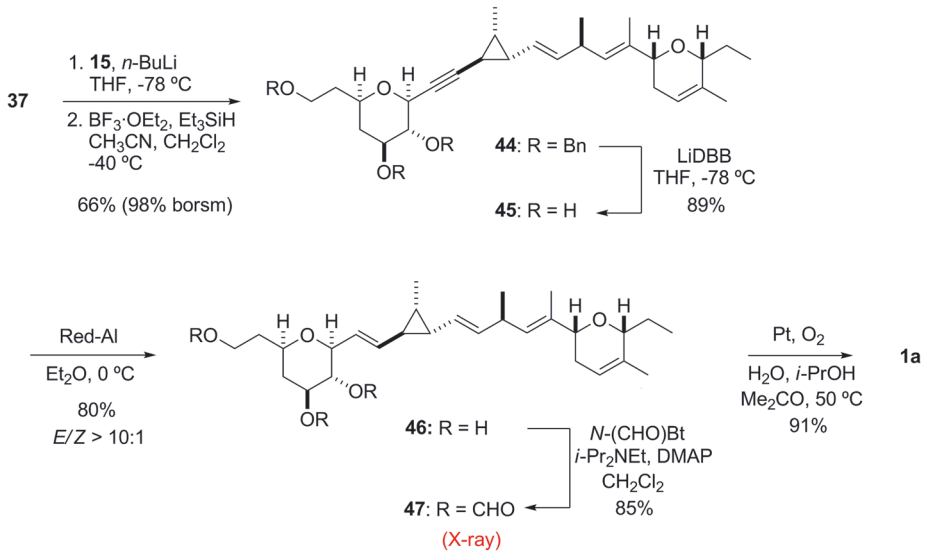
SCHEME 7. Completion of Synthesis of (+)-Ambruticin S (1a)



selectivity (E/Z > 25:1) to give diene **35** in 64% yield. Reduction of the *tert*-butyl ester to alcohol **36**, followed by oxidation under Swern conditions to the corresponding aldehyde, and treatment with the Ohira−Bestmann reagent[33] provided alkyne **37** (79%, last three steps).

An alternative, more convergent synthesis of advanced alkyne **37** was also explored using a reversed sequence of steps (Scheme 6). Thus, reaction of the crystalline aldehyde **28** with the anion prepared from phosphonamide *epi*-**31** afforded **38** with excellent E/Z selectivity (>25:1). Conversion into alkyne **40** was achieved through a three-step sequence consisting of a DIBAL-H reduction to the alcohol, Swern oxidation to **39**, and homologation with the Ohira−Bestmann reagent (71% overall yield). The alkyne moiety in **40** was then converted to its TIPS derivative **41**, followed by selective cleavage of the TBS-ether using CSA in MeOH and CH_2Cl_2 at 0 °C. Treatment of the resulting alcohol with iodine and PPh_3 gave iodide **42** (64% yield for three steps). Conversion to **3** was achieved in 79% yield by treatment with the lithium anion of 1,3-dimethyl-2-oxo-1,3,2-diazaphospholidine (**30**) at low temperature. Phosphonamide **3** was then transformed into the corresponding lithium anion, and coupled with ketone **25** to give triene **43** as a separable 6:1 mixture of E/Z isomers in 45% yield (92% based on recovered starting material), with the desired *E*-olefin as major isomer. Finally, deprotection of **43** with TBAF furnished alkyne **37** in 88% yield.

With alkyne **37** in hand, we could now commence the final assembly of (+)-ambruticin S (**1a**), as shown in Scheme 7. Deprotonation of **37** with *n*-butyllithium, followed by addition of lactone **15**, led to a 1:1 diastereomeric mixture of the desired adduct. The removal of the anomeric hydroxyl group was subsequently achieved by treatment with triethylsilane and $BF_3 \cdot OEt_2$ at low temperature.[24,34] Gratifyingly, the *C*-glycoside **44** was obtained in 66% yield as a single diastereomer with the desired *syn*-stereochemistry of the newly formed tetrahydropyran. Next, we planned to perform a stereoselective reduction of the triple bond with concomitant removal of the three benzyl-protecting groups under dissolved metal conditions. Despite extensive experimentation, all of our attempts remained unsuccessful when using either lithium or sodium in liquid ammonia, leading to over-reduced compounds. To circumvent this problem, we then decided to employ a two-step sequence instead: (a) reductive cleavage of the three benzyl-protecting groups, and (b) hydroxyl-directed *trans*-reduction of the triple bond. We were pleased to find that the use of lithium 4,4-di-*tert*-butylbiphenylide (LiDBB)[35] led to selective removal of the benzyl groups without adverse reactions to deliver alkyne **45** in 89% yield. *Trans*-reduction of the homopropargylic system was then cleanly achieved with sodium bis(2-methoxyethoxy)aluminum hydride in diethyl ether to furnish the known triol **46** (80% yield, E/Z > 10:1).[11,36] For the final oxidation of the primary hydroxyl group of triol **46** in the presence of the two secondary ones we chose a method already employed by Liu and Jacobsen in the same context.[11,37] Thus, platinum-catalyzed oxidation of **46** with oxygen in aqueous solution at 50 °C provided (+)-ambruticin S (**1a**) in 91% yield. The spectral data (^1H and ^{13}C NMR) of synthetic (+)-ambruticin S (**1a**) thus obtained were identical with those reported for the natural product.[38]

Little is known regarding the 3-dimensional nature of ambruticin S in the solid state despite an X-ray crystal structure of the triformate ester **47** prepared from triol **46**, as the pertinent data are no longer accessible.[1] Still, an appreciation of the 3-dimensional topology of ambruticin S was needed before truncated and simplified analogues

(33) (a) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (c) Procedure for preparation: William, R. F.; Goundry, W. R. F.; Baldwin, J. E.; Lee, V. *Tetrahedron* **2003**, *59*, 1719–1729.

(34) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.

(35) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930.

(36) For other examples of sodium bis(2-methoxyethoxy)aluminum hydride reductions of homopropargylic systems in natural product synthesis, see: (a) Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 9011–9014. (b) Goekjian, P. G.; Wu, T.-C.; Kang, H.-Y.; Kishi, Y. *J. Org. Chem.* **1991**, *56*, 6422–6434.

(37) (a) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, *14*, 3899–3902. (b) See also: Heyns, K.; Paulsen, H. *Chem. Ber.* **1955**, *88*, 188–195.

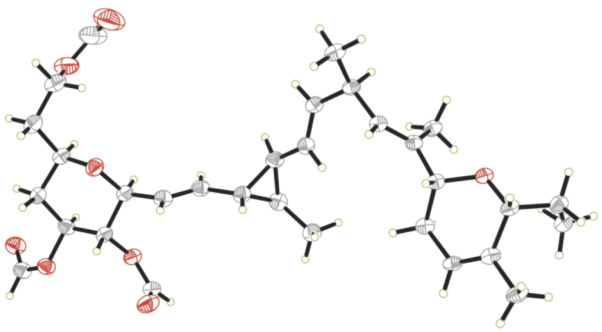
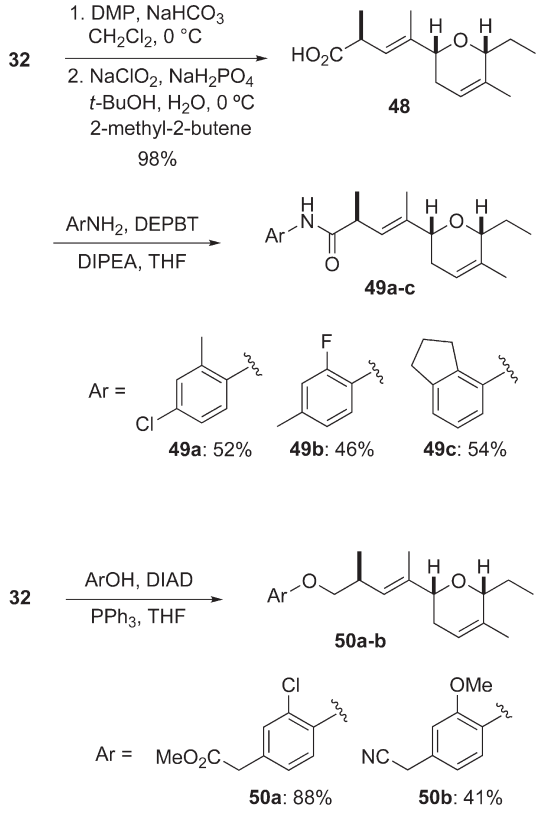


FIGURE 3. ORTEP drawing of X-ray crystal structure of triformate **47**.

SCHEME 8. Synthesis of Truncated Analogues of Ambruticin S



could be designed. Therefore, we decided to generate new crystals of triformate ester **47** to perform another X-ray analysis. Thus, treatment of triol **46** with *N*-formyl benzotriazole ((*N*-CHO)Bt) gave **47** in 85% yield. Recrystallization from ethanol provided single crystals suitable for X-ray analysis (Figure 3).[38]

While analogues of ambruticin S with variations in substituents on ring A still exhibit antifungal activity,[12] little is known regarding the functional requirements of the other subunits. We therefore prepared a series of truncated analogues of ambruticin S based on the ring C subunit, as a common scaffold, replacing the cyclopropane and ring A components with simple aromatic surrogates as shown in Scheme 8.[38] Oxidation of alcohol **32** to the corresponding aldehyde with Dess–Martin periodinane (DMP),[39] followed by Pinnick oxidation,[40] provided the carboxylic acid **48** in excellent yield with no detectable epimerization of the sensitive allylic stereocenter. Coupling with aniline derivatives using 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT)[41] provided crystalline amides **49a–c** in moderate yields. Reaction of **32** with phenols under Mitsunobu conditions gave rise to aromatic ethers **50a,b**. However, preliminary testing of compounds **49a–c** and **50a,b**[38] showed no activity using ambruticin S as a control. Further studies on a larger panel of amides and ethers are in progress and will be reported in due course.

Discussion

As previously mentioned, there are four published total syntheses of ambruticin S, each involving a number of distinctive features. Key disconnections and methods employed in bond constructions are shown in Figure 4. For the elaboration of ring A of ambruticin S, Kende,[8] Martin,[9] and Lee[10] started with carbohydrate precursors, which possessed the required diol unit, and then proceeded to manipulate existing functionality to effect deoxygenation and chain extension. Jacobsen, however, relied on a catalytic asymmetric hetero-Diels–Alder cyclization between a suitably functionalized diene and an aldehyde.[11] While Kende and Lee utilized a Yamamoto dianion-mediated formation of the trisubstituted cyclopropane (ring B),[42] Martin relied on methodology developed with Doyle,[43] and Jacobsen applied the Charette cyclopropanation[14a,44] protocol to achieve the same. Access to ring C of ambruticin S was realized in a variety of ways including ring-closing metathesis (Martin, Lee, Markó[30a,b]) and catalytic (Jacobsen) or noncatalytic (Kende, Donaldson[30c]) hetero-Diels–Alder cyclization. The three *trans*-configured olefinic appendages were introduced by a combination of well-established methods.[5] Of the four total syntheses of ambruticin S, arguably that of Liu and Jacobsen is most innovative in terms of conceptual design. Other approaches to various subunits have been reviewed by Michelet and Genêt.[5]

Inherent in our design strategy toward the total synthesis of ambruticin S was the desire to introduce flexibility in the nature of the components to be assembled with the intention to probe structure activity relationships of analogues. Having chosen a lactone branching strategy to create the *C*-glycoside corresponding to ring A, we found it practical to take advantage of the two-step synthesis of the 4-deoxy glycoside **9** from readily available methyl α-D-glucopyranoside (**2**)

(38) See Supporting Information.
(39) (a) Zhdankin, V. V.; Stang, P. *J. Chem. Rev.* **2002**, *102*, 2523–2584. (b) Speicher, A.; Bomm, V.; Eicher, T. *J. Prakt. Chem.* **1996**, *338*, 588–590. (c) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. (d) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
(40) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
(41) Li, H.; Jiang, X.; Ye, Y.-h.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91–93.
(42) Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 3343–3345.
(43) (a) Doyle, M. P.; Austin, R. E.; Bailey, S. A.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763–5775. (b) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423–1424.
(44) (a) Charette, A. B.; Lemay, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1090–1092. (b) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952.

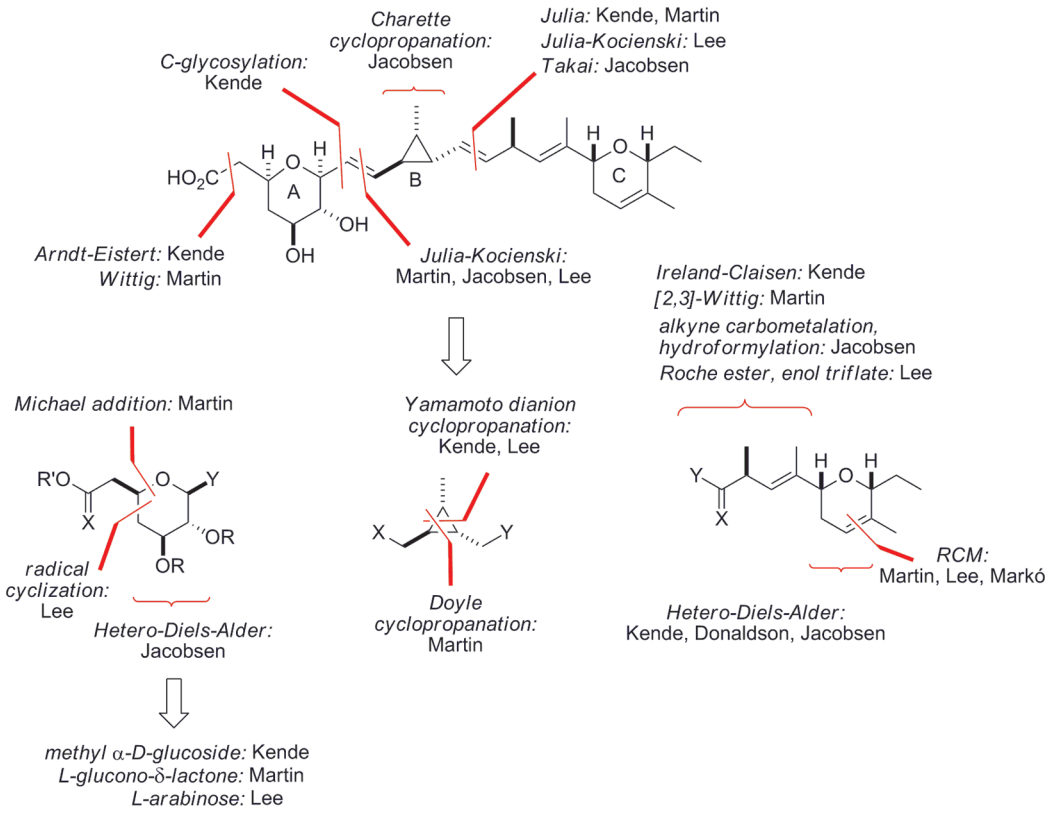


FIGURE 4. Overview of the four previous syntheses of ambruticin S and key bond construction strategies.

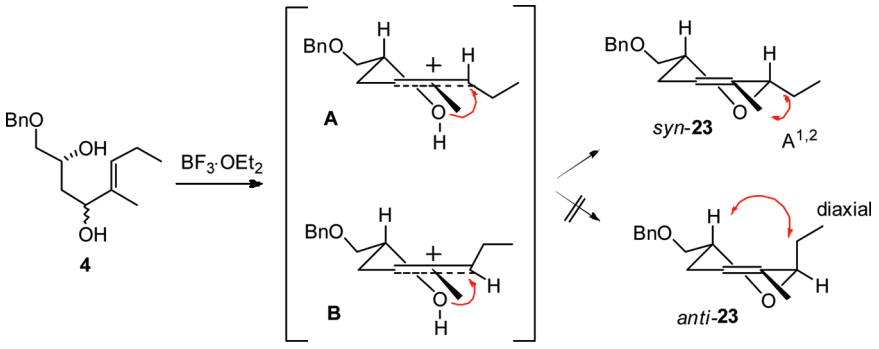


FIGURE 5. Formation of *syn*-dihydropyran **23** from diols **4**.

(Scheme 1).[45] Intermediates **11** and **12** were viewed as potential precursors to ring A-modified analogues. Likewise, the 6-*endo-trig* Lewis acid mediated cycloetherification approach to ring C would allow the synthesis of a variety of substituted analogues (Scheme 3).[17] The diol precursor to ring C was conveniently prepared from the commercially available glycidol **7**. Remarkably, the stereochemistry of the allylic alcohol was of no consequence in the cyclization reaction, strongly suggesting a cationic mechanism. Indeed, subjecting the individual diastereomers of **4** to the conditions of cycloetherification ($BF_3 \cdot OEt_2$ in CH_2Cl_2) afforded the same product **23** in excellent yields.[46] It should be noted that the observed *syn*-isomer **23** is formed in high yields even though it is subject to $A^{1,2}$ strain (Figure 5). The results can be rationalized considering a transition state model A leading to the preponderant formation of the *syn*-isomer **23**, despite the inherent $A^{1,2}$ strain effect experienced by the juxtaposition of the vicinal methyl and ethyl groups. Although $A^{1,2}$ strain can be avoided in transition state model B, there may be a more significant energetic penalty associated with a 1,3-diaxial interaction, hence the prevalence of the *syn*-isomer **23**.

Our elaboration of the trisubstituted cyclopropane ring B was admirably suited to test a methodology relying on the highly stereocontrolled conjugate addition of a chiral phosphonamide lithium anion to an α,β-unsaturated ester followed by an intramolecular attack of the resulting enolate upon the intermediate allylic chloride.[13] Remarkably, the reaction furnished a single diastereomer **27**, which was

(45) For a related approach, see: Hanessian, S.; Mi, X. *Synlett* **2010**, 761–764.

(46) For a recent Lewis acid mediated synthesis of 2,6-disubstituted pyrans, see: Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808–1811.

converted to the crystalline aldehyde **28**. The formation of *trans*-olefins linking rings C and B was achieved by relying on phosphonamide anion methodology, which provided a practical solution in delivering the *trans*-olefins **32** as a preponderant isomer and **38** quasi-exclusively. Extension to the acetylene **40** was achieved uneventfully, following which the iodide **42** was converted to phosphonamide **3**. Conversion to its lithium anion and condensation with the methyl ketone **25** gave a 6:1 *E*/*Z* ratio of chromatographically separable olefins albeit in modest yields with recovery of starting materials. In our hands, a corresponding Julia−Kocienski olefination[47] employing a phenyltetrazole sulfone gave, at best, a 3:1 ratio of olefins. Employing the classical Julia−Lythgoe conditions[48] reportedly gave an *E*/*Z* ratio of 95:1.[30a] The fully elaborated acetylene **37** was then used as the *C*-glycosylation component to access the coupled product **44**. Further functional group manipulations led to ambruticin S (**1a**) in excellent yields.

In summary, we have accomplished an enantioselective, highly convergent total synthesis of ambruticin S (**1a**) in 17 steps and 5% yield (15% based on recovered starting material) in the longest linear sequence starting from glycidol **7**. With an emphasis on late stage couplings of highly advanced fragments, our approach provides a flexible and convenient access to a variety of ambruticin derivatives.

Experimental Section

Methyl 4,6-Dichloro-4,6-dideoxy-α-D-glucopyranoside (8). To a suspension of methyl α-D-glucopyranoside (**2**) (1.0 g, 5.15 mmol) in pyridine (4.4 mL, 54.4 mmol) and chloroform (10 mL) was added dropwise under vigorous stirring sulfuryl chloride (2.6 mL, 32.4 mmol) at −40 °C. The reaction mixture was stirred for 3 h at that temperature, after which it was allowed to warm to room temperature and stirred overnight. The mixture was diluted with chloroform and washed with 10% aqueous H_2SO_4 solution, followed by saturated $NaHCO_3$ solution, water, and brine. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to yield an oily residue, which was dissolved in methanol (15 mL). To this mixture was added a solution of sodium iodide (1.12 g, 7.5 mmol) in MeOH/water (2 mL, 1:1). The resulting solution was left to stand for 8 h and then neutralized with $NaHCO_3$. Evaporation of all volatiles gave a residue, which was extracted with hot chloroform and hot ethyl acetate. The combined organic layers were dried ($MgSO_4$) and recrystallized (ethyl acetate/hexanes) to give dichloride **8** as colorless needles (1.02 g, 86%): mp 156−157 °C;[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (d, J = 5.2 Hz, 1H), 4.45 (d, J = 4.8 Hz, 1H), 4.15 (t, J = 4.86 Hz, 1H), 3.99 (dd, J = 13.2, 4.8 Hz, 1H), 3.78 (dd, J = 13.2, 5.2 Hz, 1H), 3.68 (dd, J = 7.6, 2.8 Hz, 2H), 3.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.6, 71.0, 70.0, 69.7, 65.0, 55.9, 44.5; IR (film, NaCl) 3429, 2067, 1641, 1363, 1261, 1196, 1135, 1076, 1045, 1032, 986 cm^{-1}; $[\alpha]_D$ + 187.8° (*c* 2.00, H_2O); LRMS (ESI) calcd for $C_7H_{13}Cl_2O_4$ $(M + H)^+$ 231.0, 233.0, found 231.1, 233.1.

Methyl 6-Chloro-4,6-dideoxy-α-D-glucopyranoside (9). A solution of dichloride **8** (1.00 g, 4.35 mmol) in MeOH (30 mL) containing triethylamine (1.3 mL, 9.3 mmol) and Raney-nickel (Raney2800, 2.00 g) was subjected to a hydrogen pressure of 90 psi for 24 h. Raney-nickel was filtered off, and the filtrate was concentrated *in vacuo*. Brine was added to the residue and the aqueous layer was extracted with warm ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue thus obtained was purified by column chromatography (hexanes/EtOAc, 1:1) to give **9** as a white solid (596 mg, 70%): mp 106−107 °C;[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (d, J = 4.0 Hz, 1H), 3.99 (ddt, J = 17.2, 5.6, 2.0 Hz, 1H), 3.89 (ddd, J = 11.4, 9.2, 4.8 Hz, 1H), 3.58 (d, J = 5.2 Hz, 2H), 3.47 (s, 3H), 3.43 (dd, J = 9.2, 3.6 Hz, 1H), 2.10 (ddd, J = 12.4, 4.8, 2.0 Hz, 1H), 1.53 (q, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.3, 73.9, 68.3, 67.6, 55.1, 46.2, 35.1; IR (film, NaCl) 3306, 2955, 2920, 1645, 1468, 1451, 1382, 1355, 1339, 1190, 1130, 1081, 1047, 906, 775, 729 cm^{-1}; $[\alpha]_D$ +159.0° (*c* 0.50, CH_3OH); LRMS (ESI) calcd for $C_7H_{14}ClO_4$ $(M + H)^+$ 196.1, 198.0, found 196.2, 198.1.

Methyl 6-Chloro-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside (10). Sodium hydride (500 mg of a 60% dispersion in mineral oil, 12.5 mmol) was added portionwise to a solution of diol **9** (980 mg, 5.0 mmol) and benzyl bromide (1.50 mL, 12.5 mmol) in DMF (12.5 mL) at 0 °C. The resulting suspension was allowed to warm up to room temperature and stirred overnight. The reaction mixture was then diluted with ether, and saturated NH_4Cl solution was added carefully. The organic layer was separated and washed with saturated NH_4Cl solution, brine (10 mL), and dried (Na_2SO_4). Concentration *in vacuo* gave a yellowish oil, which was purified by column chromatography (hexanes/EtOAc, 4:1) to yield 1.80 g (96%) of dibenzyl ether **10** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.30 (m, 10H), 4.87 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 11.6 Hz, 1H), 4.73−4.69 (m, 3H), 4.00−3.94 (m, 2H), 3.53 (d, J = 5.2 Hz, 2H), 3.50 (dd, J = 9.2, 3.6 Hz, 1H), 3.42 (s, 3H), 2.16 (ddd, J = 12.8, 4.8, 2.0 Hz, 1H), 1.52 (q, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.1, 128.0, 128.0, 127.7, 127.4, 127.3, 127.2, 98.7, 79.9, 74.5, 73.0, 72.3, 67.0, 54.9, 46.3, 34.5; IR (film, NaCl) 3030, 2919, 1496, 1454, 1372, 1354, 1199, 1182, 1111, 1047, 999, 914, 737, 697 cm^{-1}; $[\alpha]_D$ +47.4° (*c* 2.00, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{25}ClNaO_4$ $(M + Na)^+$ 399.1334, found 399.1330.

Methyl 6-*C*-(1-Propenyl)-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside (11). To a solution of dibenzyl ether **10** (1.00 g, 2.7 mmol) in toluene (15 mL) was added allyltriphenyltin (8.34 g, 21.3 mmol) and 1,1′-azobis(cyclohexanecarbonitrile) (714 mg, 2.9 mmol). The reaction mixture was heated in a sealed tube to 150 °C for 1 h. Evaporation of all volatiles gave a residue, which was redissolved in ethyl acetate and filtered from any insoluble material. The syrup obtained after concentration *in vacuo* was purified by flash chromatography (hexanes/ethyl acetate, 95:5) to provide 427 mg (43%) of starting material **10** and 528 mg (52%) of alkene **11** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.30 (m, 10H), 5.89−5.79 (m, 1H), 5.06 (d, J = 16.8 Hz, 1H), 5.00 (d, J = 10.4 Hz, 1H), 4.87 (d, J = 12.0 Hz, 1H), 4.80 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.68 (d, J = 3.6 Hz, 1H), 3.94 (ddd, J = 11.2, 9.6, 4.8 Hz, 1H), 3.78−3.72 (m, 1H), 3.49 (dd, J = 9.2, 3.6 Hz, 1H), 3.39 (s, 3H), 2.28−2.19 (m, 1H), 2.15−2.06 (m, 2H), 1.65−1.53 (m, 2H), 1.60 (q, J = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.3, 137.8, 128.0, 127.7, 127.3, 127.3, 127.1, 114.4, 98.6, 80.4, 75.0, 72.9, 72.1, 66.2, 54.7, 37.2, 34.2, 29.5; IR (film, NaCl) 3390, 2928, 2855, 1721, 1496, 1454, 1381, 1355, 1273, 1195, 1114, 1048, 930, 913, 738, 698 cm^{-1}; $[\alpha]_D$ +41.7° (*c* 2.26, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{30}NaO_4$ $(M + Na)^+$ 405.2036, found 405.2037.

Methyl 6-*C*-(2*E*-Propenyl)-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside (12). To a solution of alkene **11** (833 mg, 2.18 mmol) and triethylamine (0.43 mL, 3.05 mmol) in methanol (75 mL) was added Grubbs second generation catalyst (187 mg, 0.22 mmol), and the reaction mixture was heated to 60 °C for 18 h. After removal of all volatiles *in vacuo,* the residue thus

(47) (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585. (b) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.

(48) (a) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829–834. (b) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836.

obtained was purified by flash chromatography (hexanes/EtOAc, 95:5) to yield 700 mg (84%) of alkene **12** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.29 (m, 10H), 5.57−5.41 (m, 2H), 4.85 (d, J = 12.4 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 4.74−4.67 (m, 3H), 3.98−3.92 (m, 1H), 3.78−3.72 (m, 1H), 3.50 (dd, J = 11.2, 3.6 Hz, 1H), 3.40 (s, 3H), 2.28−2.21 (m, 1H), 2.17−2.08 (m, 2H), 1.74−1.64 (m, 3H), 1.39 (q, J = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.3, 128.0, 127.7, 127.4, 127.3, 127.2, 127.1, 126.4, 98.6, 80.4, 75.1, 72.9, 72.1, 66.9, 54.6, 38.1, 36.6, 17.6; IR (film, NaCl) 3499, 2926, 2872, 1722, 1496, 1454, 1372, 1358, 1276, 1190, 1106, 1048, 733, 698 cm^{-1}; $[\alpha]_D$ +35.1° (*c* 1.66, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{30}NaO_4$ $(M + Na)^+$ 405.2036, found 405.2041.

Methyl 6-*C*-(Hydroxymethyl)-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside (13). Method A (from **12**): To a stirred solution of OsO_4 (0.35 mL of a 2.5 wt % solution in *t*-BuOH, 0.0276 mmol) and *N*-methylmorpholine-*N*-oxide (485 mg, 4.14 mmol) in THF and water (15 mL, 9:1) was added a solution of alkene **12** (527 mg, 1.38 mmol) in THF (8 mL). The reaction mixture was stirred overnight and then cooled to 0 °C. A solution of $NaIO_4$ (886 mg, 4.14 mmol) in THF (4 mL) and water (4 mL) was added dropwise to the mixture. After stirring for 30 min at 0 °C, ethyl acetate was added, and the solution was filtered through a pad of Celite. The filtrate was washed with saturated $Na_2S_2O_3$ solution, water, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude aldehyde thus obtained was then dissolved in ethanol (16 mL) and water (4 mL), to which $NaBH_4$ (131 mg, 3.45 mmol) was added in one portion at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After addition of ice-cold water, the aqueous layer was extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude alcohol by flash chromatography (hexanes/EtOAc, 3:2) afforded 335 mg (65%) of **13** as a colorless oil. In addition, 128 mg (24%) of starting material **12** was recovered.

Method B (from **16**): To a 0 °C solution of nitrile **16** (184 mg, 0.5 mmol) in toluene (5 mL) was added DIBAL-H (0.6 mL of a 1 M in hexanes, 0.6 mmol). After stirring for 30 min at that temperature, the reaction mixture was quenched by addition of methanol. Aqueous HCl solution (2 N, 1.0 mL) was then added, and the mixture stirred for 45 min and filtered. After phase separation of the filtrate, the aqueous layer was extracted with diethyl ether. The combined organic phase was washed with 2 N HCl solution, saturated $NaHCO_3$ solution, and water, dried (Na_2SO_4), and concentrated *in vacuo* to afford a colorless syrup. This residue was dissolved in methanol (5 mL), and sodium borohydride (38 mg, 1.0 mmol) was added to it. The mixture was stirred at room temperature for 30 min, before excess sodium borohydride was destroyed by the addition of acetone. Evaporation *in vacuo* gave a residue, which was coevaporated three times with methanol to remove boron byproduct. The residue was dissolved in ethyl acetate, washed with 2 N HCl solution, saturated $NaHCO_3$ solution, and water, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 1:1) afforded 125 mg (67%) of alcohol **13** as a colorless oil.

Method C (from **19**): To a solution of **19** (545 mg, 1.54 mmol) in THF (10 mL) was added a 9-BBN (24.6 mL of a 0.5 M solution in THF, 12.3 mmol), and the reaction mixture was stirred overnight at room temperature. Hydrogen peroxide (3.2 mL of a 30% aqueous solution, 30.8 mmol) and 3 M NaOH solution (5.1 mL, 15.4 mmol) were then added, and the resulting mixture was heated for 2 h at 55 °C. After phase separation, the aqueous phase was extracted with EtOAc. The combined organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to give 516 mg (90%) of **13** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 10H), 4.86 (d, J = 12.0 Hz, 1H), 4.78 (d, J = 11.6 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 2.4 Hz, 1H), 4.00−3.91 (m, 2H), 3.79−3.76 (m, 2H), 3.48 (dd, J = 9.6, 3.2 Hz, 1H), 3.38 (s, 3H), 2.07 (ddd, J = 12.8, 4.8, 2.0 Hz, 1H), 1.78−1.72 (m, 2H), 1.48 (q, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.1, 128.0, 128.0, 127.6, 127.4, 127.3, 127.1, 98.6, 80.1, 74.8, 73.0, 72.2, 66.7, 60.5, 54.8, 37.7, 36.9; IR (film, NaCl) 3435, 3062, 3030, 2923, 1604, 1496, 1454, 1356, 1200, 1186, 1099, 1048, 996, 911, 736, 698 cm^{-1}; $[\alpha]_D$ + 39.1° (*c* 3.00, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{28}NaO_5$ $(M + Na)^+$ 395.1829, found 395.1820.

Methyl 6-*C*-(Benzyloxymethyl)-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside (14). To a 0 °C solution of alcohol **13** (320 mg, 0.86 mmol) and benzyl bromide (0.52 mL, 4.3 mmol) in DMF (7 mL) was added sodium hydride (86 mg of a 60% dispersion in mineral oil, 2.15 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. After diluting the mixture with diethyl ether, it was quenched by careful addition of saturated NH_4Cl solution. The organic layer was separated, washed with saturated NH_4Cl solution and brine, and dried (Na_2SO_4). Concentration *in vacuo* gave a residue that was purified by flash chromatography (hexanes/EtOAc, 4:1) to yield 364 mg (92%) of tribenzyl ether **14** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.28 (m, 15H), 4.89 (d, J = 12.2 Hz, 1H), 4.80 (d, J = 11.7 Hz, 1H), 4.74−4.68 (m, 2H), 4.68 (d, J = 3.6 Hz, 1H), 4.53 (br s, 2H), 3.97−3.91 (m, 2H), 3.66−3.57 (m, 2H), 3.51 (dd, J = 9.4, 3.6 Hz, 1H), 3.38 (s, 3H), 2.11 (ddd, J = 12.8, 5.0, 2.1 Hz, 1H), 1.84−1.78 (m, 2H), 1.43 (q, J = 12.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.3, 138.0, 128.0, 127.97, 127.6, 127.3, 127.29, 127.3, 127.2, 127.1, 98.5, 80.3, 75.1, 72.9, 72.7, 72.1, 66.3, 63.8, 54.5, 37.3, 35.1; IR (film, NaCl) 3062, 3030, 2922, 2861, 1604, 1586, 1496, 1454, 1357, 1245, 1204, 1188, 1099, 1048, 913, 783, 735, 698 cm^{-1}; $[\alpha]_D$ +40.0° (*c* 1.00, $CHCl_3$); HRMS (ESI) calcd for $C_{29}H_{34}O_5Na$ $(M + Na)^+$ 485.2299, found 485.2275.

(3*R*,4*S*,6*R*)-3,4-Bis(benzyloxy)-6-(2-(benzyloxy)ethyl)-tetrahydropyran-2-one (15). A solution of tribenzylether **14** (600 mg, 1.3 mmol) in a mixture of acetic acid (130 mL) and diluted sulfuric acid (2 M, 34 mL) was heated for 18 h to 80 °C. After removal of all volatiles *in vacuo*, the residue was dissolved in dichloromethane (150 mL). The organic phase was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue thus obtained was purified by flash chromatography (hexanes/EtOAc, 7:3) to give the hemiacetal as a colorless oil (524 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 15H), 5.23 (d, J = 3.6 Hz, 1H), 4.95−4.85 (m, 2H), 4.76−4.69 (m, 2H), 4.61−4.58 (m, 1H), 4.52−4.50 (m, 2H), 3.66−3.56 (m, 3H), 3.52−3.47 (m, 1H), 2.16−2.06 (m, 1H), 1.89−1.77 (m, 2H), 1.49−1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 138.2, 138.1, 138.09, 137.9, 128.1, 128.0, 127.7, 127.6, 127.44, 127.4, 127.36, 127.3, 127.24, 127.2, 127.17, 97.0, 91.7, 83.6, 80.2, 78.2, 74.9, 74.5, 72.9, 72.6, 71.7, 71.7, 68.4, 66.2, 65.8, 64.6, 53.0, 36.6, 35.0; IR (film, NaCl) 3392, 3062, 3030, 2921, 2862, 1496, 1454, 1362, 1207, 1096, 911, 736, 697 cm^{-1}; $[\alpha]_D$ +23.1° (*c* 2.00, $CHCl_3$); LRMS (ESI) calcd for $C_{28}H_{32}NaO_5$ $(M + Na)^+$ 471.2, found 471.2.

To a solution of the hemiacetal (400 mg, 0.89 mmol) in CH_2Cl_2 (10 mL) was added 4 Å molecular sieves (1.0 g), and the resulting mixture was stirred for 15 min. It was then was cooled to 0 °C, PCC (880 mg, 4.02 mmol) was added, and the reaction mixture was stirred for 2 h at 0 °C. After dilution with diethyl ether (10 mL) and pentane (10 mL), the mixture was filtered over Celite. The filter cake was washed with Et_2O/pentane (1:1), and the combined filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes/EtOAc, 4:1) yielded 280 mg (70%) of lactone **15** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.31 (m, 15H), 50.7 (d, J = 11.6 Hz, 1H), 4.77 (d, J = 11.6 Hz, 1H),

4.69−4.60 (m, 3H), 4.56 (d J = 11.8 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 4.07 (d, J = 6.8 Hz, 1H), 3.96−3.90 (m, 1H), 3.74−3.67 (m, 1H), 3.65−3.60 (m, 1H), 2.33 (ddd, J = 14.0, 5.6, 3.2 Hz, 1H), 2.06−1.89 (m, 2H), 1.77 (q, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 137.8, 137.4, 136.9, 128.1, 128.07, 128.0, 127.6, 127.4, 127.3, 127.28, 79.0, 75.3, 73.7, 73.3, 72.8, 71.6, 65.3, 35.5, 34.6; IR (film, NaCl) 3063, 3030, 2924, 2865, 1745, 1496, 1454, 1392, 1212, 1179, 1101, 1028, 911, 737, 698 cm^{-1}; $[\alpha]_D$ +69.4° (c 2.00, $CHCl_3$); HRMS (ESI) calcd for $C_{28}H_{31}O_5$ $(M + H)^+$ 447.2166, found 447.2155.

Methyl 6-Cyano-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside (16). To a solution of chloride **10** (376 mg, 1.0 mmol) in *N*-methylpyrrolidone (10 mL) were added NaCN (490 mg, 10.0 mmol) and *n*-Bu_4NI (3.70 g, 10.0 mmol). The reaction mixture was heated to 60 °C for 48 h, after which it was diluted with ether and saturated $NaHCO_3$ solution was added. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes/EtOAc, 4:1) gave as the first fraction 154 mg (41%) of chloride **10** and as the second fraction 136 mg (37%) of **16** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 10H), 4.85 (d, J = 12.4 Hz, 1H), 4.77 (d, J = 11.6 Hz, 1H), 4.69 (d, J = 12.4 Hz, 1H), 4.68 (d, J = 11.6 Hz, 1H), 4.66 (d, J = 3.6 Hz, 1H), 4.03−3.90 (m, 2H), 3.48 (dd, J = 9.6, 3.6 Hz, 1H), 3.40 (s, 3H), 2.52−2.50 (m, 2H), 2.16 (ddd, J = 12.8, 5.2, 2.4 Hz, 1H), 1.50 (q, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.1, 128.3, 128.28, 127.9, 127.7, 127.5, 116.7, 99.0, 79.8, 74.3, 73.3, 72.6, 63.1, 55.4, 36.5, 23.7; IR (film, NaCl) 3063, 3031, 2925, 2252, 1722, 1602, 1496, 1454, 1356, 1275, 1190, 1107, 1044, 919, 804, 739, 714, 699 cm^{-1}; $[\alpha]_D$ + 23.2° (c 1.75, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{26}NO_4$ $(M + H)^+$ 368.1856, found 368.1838.

(2*S*,3*R*,4*S*,6*S*)-3,4-Bis(benzyloxy)-2-methoxy-6-vinyl-tetrahydro-2*H*-pyran (19). A mixture of methyl 2,3-di-*O*-benzyl-4-dexoy-β-L-threo-hex-4-endodialdopyranoside (**18**) (500 mg, 1.41 mmol) and 5% palladium on barium carbonate (540 mg) in methanol (16 mL) was stirred under an atmosphere of hydrogen (14.5 psi) for 12 h. Palladium was then removed by filteration through a pad of Celite, the filtrate was concentrated *in vacuo* to a volume of approximately 8 mL, and 1,8-diazabicycloundec-7-ene (1.2 mL, 8.5 mmol) was added to it. The reaction mixture was stirred for additional 12 h, before it was concentrated to dryness *in vacuo*. The residue was dissolved in dichloromethane, washed with 2 M aqueous HCl solution, saturated $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes/EtOAc, 4:1 to 3:1) gave 432 mg (86%) of methyl 2,3-di-*O*-benzyl-4-deoxy-α-D-*xylo*-hexodialdopyranoside as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.34−7.29 (m, 10 H), 4.87 (d, J = 12.4 Hz, 1H), 4.77−4.74 (m, 3H), 4.69 (d, J = 2.0 Hz, 1H), 4.18 (dd, J = 12.4, 2.8 Hz, 1H), 3.98 (ddd, J = 10.8, 9.2, 5.2 Hz, 1H), 3.48 (dd, J = 9.2, 3.2 Hz, 1H), 3.41 (s, 3H), 2.36 (ddd, J = 13.2, 5.2, 2.8 Hz, 1H), 1.48 (q, J = 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 138.3, 138.1, 128.3, 128.2, 127.9, 127.7, 127.5, 99.3, 79.7, 74.5, 73.5, 72.4, 72.2, 55.6, 31.6; $[\alpha]_D$ +35.0° (c 1.05, $CHCl_3$); LRMS (ESI) calcd for $C_{21}H_{25}O_5$ $(M + H)^+$ 357.2, found 357.1.

To a suspension of methyltriphenylphosphonium bromide (6.0 g, 16.9 mmol) in THF (60 mL) was added slowly *n*-BuLi (10.5 mL of a 1.6 M solution in hexanes, 16.9 mmol) at −78 °C. After 10 min of stirring at that temperature, the resulting solution was warmed to 0 °C and stirred for 1 h. A solution of methyl 2,3-di-*O*-benzyl-4-deoxy-α-D-*xylo*-hexodialdopyranoside (2.0 g, 5.6 mmol) in THF (60 mL) was then added slowly to the ylide at 0 °C. The reaction mixture was allowed to warm to temperature, stirred overnight, and subsequently quenched by addition of saturated NH_4Cl solution. After extraction of the aqueous layer with diethyl ether, the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes/EtOAc, 10:1 to 8:1) yielded 1.51 g (76%) of **19** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 10H), 5.82 (ddd, J = 17.6, 9.6, 6.0 Hz, 1H), 5.76 (dt, J = 17.2, 1.6 Hz, 1H), 5.14 (dt, J = 10.4, 1.2 Hz, 1H), 4.86 (d, J = 12.0 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.70 (d, J = 11.4 Hz, 1H), 4.69 (d, J = 3.6 Hz, 1H), 4.21 (dd, J = 11.6, 5.6 Hz, 1H), 3.97 (ddd, J = 11.2, 9.2, 4.8 Hz, 1H), 3.49 (dd, J = 5.6, 3.6 Hz, 1H), 3.39 (s, 3H), 2.14 (ddd, J = 12.8, 4.8, 2.0 Hz, 1H), 1.49 (q, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.4, 138.3, 128.2, 127.9, 127.6, 128.5, 127.4, 115.7, 99.0, 80.3, 75.1, 73.2, 72.4, 67.6, 55.1, 37.1; $[\alpha]_D$ +34.1° (c 0.50, $CHCl_3$); IR (film, NaCl) 3063, 3030, 2922, 2854, 1683, 1650, 1604, 1496, 1454, 1358, 1259, 1192, 1099, 1044, 924, 813, 733, 696 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}NaO_4$ $(M + Na)^+$ 377.1723, found 377.1722.

2-((*E*)-Pent-2-en-2-yl)-1,3-dithiane (20). A mixture of 1,3-propanedithiol (7.50 mL, 75.0 mmol), boron trifluoride etherate (9.5 mL, 75.0 mmol), and glacial acetic acid (18.0 mL, 0.32 mol) in dichloromethane (125 mL) was cooled to −20 °C. To the vigorously stirred mixture was added slowly a solution of 2-methyl-2-pentenal (8.55 mL, 75.0 mmol) in CH_2Cl_2 (50 mL) while maintaining the temperature between −20 to −15 °C. The reaction mixture was stirred for 1 h at −20 °C and then siphoned into ice-cold 10% aqueous KOH solution. The temperature should be maintained below 5 °C during the quench. After dilution with diethyl ether, the organic phase was separated, washed with 10% KOH, water (3×), brine, and dried (Na_2SO_4). Concentration *in vacuo* yielded 13.9 g (99%) of the crude dithiane **20** as a 10:1 mixture of *E*/*Z* isomers. The dithiane was used without further purification in the next step: ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ 5.65−5.61 (m, 1H), 4.56 (s, 1H), 2.98−2.90 (m, 3H), 2.87−2.81 (m, 2H), 2.08−2.01 (m, 2H), 1.78 (d, J = 3.1 Hz, 4H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 132.3, 131.6, 55.3, 31.6, 25.5, 21.3, 14.9, 13.7; IR (film, NaCl) 2957, 2935, 2891, 1457, 1424, 1422, 1378, 1275, 1172, 745, 679 cm^{-1}; LRMS (ESI) calcd for $C_9H_{17}S_2$ $(M + H)^+$ 189.1, found 189.1.

(*R*,*E*)-1-(Benzyloxy)-3-(2-(pent-2-en-2-yl)-1,3-dithian-2-yl)-propan-2-ol (21). To a −78 °C solution of dithiane **20** (11.5 g, 61.0 mmol) in THF (60 mL) was added *n*-BuLi (33.3 mL of a 1.6 M solution in hexanes, 53.3 mmol) dropwise. The reaction mixture was stirred for 5 min at that temperature, warmed to 0 °C, and stirred for 30 min, before it was recooled to −78 °C. A solution of (*R*)-benzyl glycidol (**7**) (5.0 g, 30.5 mmol) in THF (40 mL) was then added slowly. The reaction mixture was stirred for 30 min and quenched by addition of saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, and the combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 10:1 to 4:1) to give 10.5 g (97%) of dithiane adduct **21** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5H), 6.05 (tq, J = 7.1, 1.2 Hz, 1H), 4.55 (s, 2H), 4.07−3.98 (m, 1H), 3.44 (dd, J = 9.6, 4.8 Hz, 1H), 3.39 (dd, J = 9.6, 6.3 Hz, 1H), 2.88−2.65 (m, 5H), 2.25−2.04 (m, 4H), 2.00−1.88 (m, 2H), 1.77 (d, J = 0.6 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 133.8, 132.5, 128.3, 127.6, 127.6, 74.1, 73.2, 67.5, 58.3, 42.8, 27.3, 27.2, 25.0, 22.1, 14.0, 13.5; IR (film, NaCl) 2957, 2935, 2909, 2870, 1453, 1422, 1100, 1089, 736, 699 cm^{-1}; $[\alpha]_D$ −6.3° (c 1.58, $CHCl_3$); HRMS (ESI) calcd for $C_{19}H_{28}NaO_2S_2$ $(M + Na)^+$ 375.1423, found 375.1434.

(*R*,*E*)-1-(Benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-5-methyloct-5-en-4-one (22). A cold (0 °C) solution of dithiane adduct **21** (10.4 g, 29.5 mmol) and 2,6-lutidine (8.6 mL, 74.1 mmol) in CH_2Cl_2 (380 mL) was treated with TBSOTf (13.6 mL, 59.2 mmol) for 1 h. The reaction mixture was quenched with saturated

NH_4Cl solution, the aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 20:1 to 9:1) to yield 12.8 g (93%) of the TBS-ether as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 4H), 7.32−7.26 (m, 1H), 6.05−6.00 (m, 1H), 4.53 (s, J = 12.2 Hz, 1H), 4.51 (d, J = 12.4 Hz, 1H), 3.99−3.93 (m, 1H), 3.42 (dd, J = 9.9, 4.1 Hz, 1H), 3.36 (dd, J = 9.9, 5.6 Hz, 1H), 2.86−2.71 (m, 2H), 2.70−2.60 (m, 2H), 2.33 (dd, J = 14.9, 6.4 Hz, 1H), 2.18−2.09 (m, 2H), 2.06 (dd, J = 14.9, 3.9 Hz, 1H), 2.02−1.84 (m, 2H), 1.74 (s, 3H), 1.06 (t, J = 7.5 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 134.1, 131.7, 128.2, 127.5, 127.3, 74.9, 73.1, 68.6, 58.6, 44.1, 27.5, 27.3, 26.0, 25.2, 22.2, 18.1, 14.2, 13.7, −4.0, −4.5; IR (film, NaCl) 2957, 2928, 2855, 1478, 1456, 1454, 1251, 1097, 1004, 836, 776, 733, 697 cm^{-1}; $[\alpha]_D$ −6.4° (c 0.94, $CHCl_3$); LRMS (ESI) calcd for $C_{25}H_{43}O_2S_2Si$ (M + H)$^+$ 467.3, found 467.3.

To a solution of the TBS-ether (5.0 g, 10.7 mmol) in CH_2Cl_2 (140 mL) was added benzeneseleninic acid anhydride (70%, 5.51 g, 10.7 mmol) and propylene oxide (1 mL). The reaction mixture was stirred for 16 h at room temperature, and solid $NaHCO_3$ (5.0 g) was added. The solvent was removed, and the residue was purified by flash chromatography (hexane/EtOAc, 10:1 to 4:1) to give enone **22** (3.20 g, 79%) as a colorless to light yellowish oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 6.67 (dt, J = 7.0, 0.9 Hz, 1H), 4.56 (s, 2H), 4.43 (dddd, J = 7.4, 5.2, 5.2, 5.2 Hz, 1H), 3.49 (dd, J = 9.8, 5.1 Hz, 1H), 3.42 (dd, J = 9.7, 5.4 Hz, 1H), 2.95 (dd, J = 15.3, 7.4 Hz, 1H), 2.82 (dd, J = 15.3, 4.9 Hz, 1H), 2.27 (dq, J = 7.4, 7.4 Hz, 2H), 1.78 (s, 3H), 1.10 (t, J = 7.6 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 145.0, 138.3, 137.4, 128.3, 127.5, 127.47, 74.4, 73.2, 69.0, 42.0, 25.8, 22.4, 18.0, 13.0, 11.1, −4.6, −5.0; IR (film, NaCl) 2957, 2930, 2857, 1668, 1252, 1112, 836 cm^{-1}; $[\alpha]_D$ +28.5° (c 2.0, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{37}O_3Si$ (M + H)$^+$ 377.2506, found 377.2526.

(2*R*,4*S*,*E*)-1-(Benzyloxy)-5-methyloct-5-ene-2,4-diol (4). To a stirred solution of **22** (13.27 g, 35.2 mmol) and cerium chloride heptahydrate (15.74 g, 42.2 mmol) in 300 mL of methanol was added sodium borohydride (1.6 g, 42.2 mmol) portionwise at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, after which acetone was added to destroy residual sodium borohydride. All volatiles were evaporated *in vacuo*, and the residue was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated *in vacuo* to give crude mono-TBS diol (13.3 g, 100%, dr = 3.6:1 by ^{1}H NMR), which was used in the next step without further purification. To a solution of crude mono-TBS diol (12.3 g, 32.5 mmol) in THF (300 mL) was added TBAF (42.2 mL of a 1 M solution in THF, 42.2 mmol). The reaction mixture was stirred for 2 h, and subsequently quenched by addition of saturated NH_4Cl solution. After evaporation of all volatiles and extraction of the remaining aqueous layer with EtOAc, the combined organic phase was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc, 4:1 to 1:1) gave 7.30 g (79% over 2 steps) of diol **4** as a colorless oil (dr 3.6:1 by ^{1}H NMR). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.42 (bt, J = 7.0 Hz, 1H), 4.55 (s, 2H), 4.25 (dd, J = 9.2, 3.6 Hz, 1H), 4.06−3.99 (m, 1H), 3.45 (dd, J = 9.5, 4.1 Hz, 1H), 3.40 (dd, J = 9.5, 6.9 Hz, 1H), 3.29 (br s, OH), 2.99 (br s, OH), 2.08−1.95 (m, 2H), 1.73−1.58 (m, 2H), 1.60 (dt, J = 1.4, 0.8 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.1, 128.4, 128.2, 127.8, 127.7, 77.5, 74.4, 73.3, 70.9, 37.9, 20.7, 14.0, 11.4; IR (film, NaCl) 3391, 2960, 2930, 2917, 2871, 1454, 1364, 1306, 1091, 1074, 1028, 999, 860 cm^{-1}; $[\alpha]_D$ −11.0° (c 1.7, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{24}NaO_3$ (M + Na)$^+$ 287.1618, found 287.1611.

(2*R*,6*R*)-2-(Benzyloxymethyl)-6-ethyl-5-methyl-3,6-dihydro-2*H*-pyran (23). To a solution of diol **4** (4.53 g, 17.1 mmol, dr 3.6:1) in CH_2Cl_2 (220 mL) was added $BF_3\cdot OEt_2$ (0.22 mL, 1.7 mmol) in one portion. The reaction mixture was stirred for 18 h at room temperature. After evaporation of all volatiles *in vacuo*, the residue was purified by flash chromatography (hexanes/EtOAc, 20:1 to 10:1) to give 3.40 g (81%) of diastereomerically pure *syn*-pyran **23** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.34 (m, 4H), 7.34−7.27 (m, 1H), 5.60−5.56 (m, 1H), 4.68 (d, J = 12.3 Hz, 1H), 4.61 (d, J = 12.3 Hz, 1H), 4.12 (br s, 1H), 3.78 (dddd, J = 10.2, 6.4, 3.8, 3.8 Hz, 1H), 3.60 (dd, J = 10.3, 6.4 Hz, 1H), 3.50 (dd, J = 10.3, 4.2 Hz, 1H), 2.10−1.88 (m, 2H), 1.83 (ddq, J = 14.7, 7.4, 3.6 Hz, 1H), 1.63 (br s, 3H), 1.54 (ddq, J = 14.2, 7.2, 7.2 Hz, 1H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 135.4, 128.3, 127.6, 127.4, 120.1, 77.9, 73.3, 73.2, 72.8, 28.1, 25.5, 19.0, 8.4; IR (film, NaCl) 2964, 2934, 2858, 1454, 1368, 1118, 1062, 1028, 1005 cm^{-1}; $[\alpha]_D$ +74.7° (c 1.96, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{22}NaO_2$ (M + Na)$^+$ 269.1512, found 269.1514.

((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)methanol (24). To a −78 °C solution of sodium (0.70 g, 30.4 mmol) in liquid ammonia (50 mL) was added a solution of benzyloxymethyl pyran **23** (1.50 g, 6.1 mmol) in THF (10 mL). The reaction was warmed to −33 °C and stirred for 1 h. Subsequently, the mixture was recooled to −78 °C and quenched by addition of solid NH_4Cl. The resulting mixture was allowed to warm to room temperature and evaporated to dryness. Remaining traces of ammonia were removed *in vacuo*. The residue was dissolved in the minimum amount of water, adjusted to pH 7 with 1 N HCl, and extracted with dichloromethane. The combined organic phase was dried over sodium sulfate, and all volatiles were removed *in vacuo*. Purification of the residue by flash chromatography (hexanes/EtOAc, 4:1 to 2:1) yielded hydroxymethyl pyran **24** as a colorless oil (0.887 g, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (ddd, J = 5.7, 3.1, 1.6 Hz, 1H), 4.07 (br s, 1H), 3.66−3.58 (m, 2H), 3.57−3.51 (m, 1H), 2.46 (s, OH), 2.07−1.90 (m, 1H), 1.84−1.80 (m, 1H), 1.75 (ddq, J = 14.7, 7.3, 3.5 Hz, 1H), 1.59 (dd, J = 2.2, 1.1 Hz, 3H), 1.54 (ddq, J = 14.2, 7.3, 7.3 Hz, 1H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 120.0, 77.8, 73.7, 65.7, 26.9, 25.4, 18.9, 8.3; IR (film, NaCl) 3415, 2965, 2936, 2880, 1455, 1438, 1374, 1117, 1056, 1023, 1002 cm^{-1}; $[\alpha]_D$ +108.2° (c 2.5, $CHCl_3$). HRMS (ESI) calcd for $C_9H_{16}NaO_2$ (M + Na)$^+$ 179.1043, found 179.1043.

1-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)ethanone (25). To a −78 °C solution of DMSO (1.0 mL, 14.1 mmol) in CH_2Cl_2 (40 mL) was added dropwise oxalyl chloride (4.65 mL of a 2 M solution in CH_2Cl_2, 9.3 mmol). After 15 min, a solution of hydroxymethyl pyran **24** (1.11 g, 7.16 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred for 1 h −78 °C. Triethylamine (4.0 mL, 28.7 mmol) was then added, and the mixture maintained for 15 min at −78 °C before it was warmed to 0 °C. After another 15 min at 0 °C, the reaction mixture was diluted with Et_2O, water was added, and the layers were separated. The organic layer was washed with water and brine and dried ($MgSO_4$). Concentration *in vacuo* yielded crude (2*R*,6*R*)-6-ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-carbaldehyde as a yellowish oil (1.10 g, 100%), which was used in the next step without further purification: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.72 (s, 1H), 5.64 (s, 1H), 4.20 (s, 1H), 3.99 (dd, J = 8.7, 6.1 Hz, 1H), 2.17−2.11 (m, 2H), 1.86 (ddq, J = 14.7, 7.4, 3.4 Hz, 1H), 1.66 (s, 3H), 1.65−1.55 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 202.0, 136.0, 119.1, 78.2, 77.6, 25.8, 25.5, 18.8, 8.1; IR (film, NaCl) 2965, 2934, 2877, 1738, 1455, 1435, 1116, 1057, 1025 cm^{-1}; HRMS (ESI) calcd for $C_9H_{15}O_2$ (M + H)$^+$ 155.1067, found 155.1062.

To a solution of the crude aldehyde (1.10 g, 7.16 mmol) in THF (60 mL) was added slowly methylmagnesium bromide

(7.2 mL of a 3 M solution in Et_2O, 21.6 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C before it was quenched by addition of wet acetone followed by saturated NH_4Cl solution. After evaporation of all volatiles, the remaining aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue thus obtained (1.22 g, 100%) was pure enough to be used in the next step without further purification (1:1 mixture of diastereomers by ^{1}H NMR): ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 5.60−5.54 (m, 1H), 5.54−5.49 (m, 1H), 4.07 (br s, 1H), 4.03 (br s, 1H), 3.94−3.86 (m, 1H), 3.66−3.58 (m, 1H), 3.41 (ddd, J = 10.8, 3.4, 3.4 Hz, 1H), 3.26−3.19 (m, 1H), 2.94 (d, J = 1.5 Hz, OH), 2.35 (d, J = 3.8 Hz, OH), 2.21−2.09 (m, 1 H), 1.94−1.68 (m, 5H), 1.63−1.57 (m, 6H), 1.56−1.43 (m, 2H), 1.14 (d, J = 7.0 Hz, 6H), 0.91 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 135.4, 134.9, 120.4, 119.8, 78.03, 78.0, 76.0, 70.4, 69.1, 27.2, 25.5, 24.3, 18.83, 18.8, 17.8, 17.4, 8.6, 8.4; LRMS (ESI) calcd for $C_{10}H_{19}O_2$ $(M+H)^+$:171.1, found 171.2

To a −78 °C solution of DMSO (1.0 mL, 14.1 mmol) in CH_2Cl_2 (40 mL) was added dropwise oxalyl chloride (4.6 mL of a 2 M solution in CH_2Cl_2, 9.2 mmol). After 15 min, a solution of crude 1-[(2*R*,6*R*)-6-ethyl-5-methyl-3,6-dihydro-2*H*-2-pyranyl]ethan-1-ol (1.22 g, 7.16 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred for 1 h −78 °C. Triethylamine (4.0 mL, 28.7 mmol) was then added, and the mixture was maintained for 15 min at −78 °C before it was warmed to 0 °C. After another 15 min at 0 °C, the reaction mixture was diluted with Et_2O, water was added, and the layers were separated. The organic layer was washed with water and brine and dried ($MgSO_4$). After careful concentration *in vacuo*, the residue was purified by flash chromatography (pentane/Et_2O, 1:0 to 10:1) to yield ketone **25** as a volatile, light yellow liquid (0.87 g, 72% over three steps from hydroxymethyl pyran **21**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61−5.54 (m, 1H), 4.15−4.07 (m, 1H), 3.93 (dd, J = 10.5, 4.2 Hz, 1H), 2.26 (s, 3H), 2.22−2.01 (m, 2H), 1.83 (ddq, J = 14.6, 7.4, 3.4 Hz, 1H), 1.61 (br s, 3H), 1.54 (ddq, J = 14.3, 7.15, 7.15 Hz, 1H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 135.6, 119.5, 78.7, 78.3, 27.3, 25.7, 25.6, 18.9, 8.6; IR (film, NaCl) 2968, 2937, 1722, 1435, 1354, 1117, 1058 cm^{-1}; $[\alpha]_D$ +191.7° (*c* 1.97, $CHCl_3$); HRMS (ESI) calcd for $C_{10}H_{17}O_2$ $(M+H)^+$ 169.1223, found 169.1222.

(1*S*,2*S*,3*R*)-*tert*-Butyl 2-((*E*)-2-((3a*S*,7a*S*)-1,3-Dimethyl-2-oxidohexahydro-1*H*-benzo[*d*][1,3,2]diazaphosphol-2(3*H*)-yl)vinyl)-3-methylcyclopropanecarboxylate (27). To a −78 °C solution of chloroallylphosphonamide **5** (0.788 g, 3.0 mmol) in THF (25 mL) was added *n*-butyl lithium (2.44 mL of a 1.6 M solution in hexanes, 3.90 mmol). Subsequently, a −78 °C solution of *tert*-butyl crotonate (0.597 g, 4.20 mmol) in THF (5 mL) was added slowly via cannula. The reaction mixture was stirred for 2 h at −78 °C and then quenched by addition of a saturated ammonium chloride solution. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography (short plug of silica gel, EtOAc/EtOH, 1:0 to 4:1) provided adduct **27** (0.98 g, 89%) as a light yellow solid: mp 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (ddd, J = 19.8, 16.5, 9.6 Hz, 1H), 5.56 (dd, J = 20.9, 16.5 Hz, 1H), 2.75−2.67 (m, 1H), 2.45 (d, J = 11.1 Hz, 3H), 2.44 (d, J = 11.1 Hz, 3H), 2.42−2.34 (m, 1H), 2.13 (ddd, J = 9.5, 4.3 Hz, 1H), 2.02−1.89 (m, 2H), 1.73−1.70 (m, 2H), 1.68−1.58 (m, 1H), 1.52 (t, J = 4.7 Hz, 1H), 1.40 (s, 9H), 1.33−1.16 (m, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.08−0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 149.5 (d, J = 4.9 Hz), 120.7 (d, J_{P-C} = 153.7 Hz), 80.5, 64.5 (d, J = 7.4 Hz), 63.5 (d, J = 5.4 Hz), 30.9, 30.6 (d, J = 24.8 Hz), 28.6 (d, J = 5.0 Hz), 28.5 (d, J = 7.9 Hz), 28.5, 28.0, 27.9, 24.1, 24.0, 23.2, 12.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.4; IR (film, NaCl) 2936, 2865, 1717, 1448, 1367, 1322, 1251, 1215, 1157, 1010, 818, 759 cm^{-1}; $[\alpha]_D$ +114.1° (*c* 1.49, $CHCl_3$); HRMS (ESI) calcd for $C_{19}H_{34}N_2O_3P$ $(M+H)^+$ 369.2302, found 369.2297.

(1*S*,2*S*,3*R*)-*tert*-Butyl 2-Formyl-3-methylcyclopropanecarboxylate (28). A −78 °C solution of phosphonamide **27** (477 mg, 1.29 mmol) in CH_2Cl_2 (20 mL) was treated with a stream of ozone for 1−2 h until a light blue color persisted and starting material could no longer be detected by TLC. The reaction mixture was flushed with argon to remove excess ozone, dimethyl sulfide was added at −78 °C, and the mixture was allowed to warm to room temperature. After dilution with dichloromethane, the organic phase was washed with saturated ammonium chloride solution and brine and dried over Na_2SO_4. Concentration *in vacuo* gave a residue, which was purified by column chromatography (hexanes/Et_2O, 4:1). The product (166 mg, 70%) was obtained as a colorless oil, which slowly crystallized upon standing in the cold to give thick, colorless needles: mp 31−32 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (d, J = 4.0 Hz, 1H), 2.42 (ddd, J = 9.3, 4.2, 4.2 Hz, 1H), 2.22 (dd, J = 5.9, 4.6 Hz, 1H), 1.96 (ddq, J = 9.4, 6.4, 6.3 Hz, 1H), 1.44 (s, 9H), 1.26 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 170.3, 81.3, 35.8, 30.2, 28.0, 25.5, 11.6; IR (film, NaCl) 2979, 1721, 1369, 1311, 1292, 1215, 1158 cm^{-1}; $[\alpha]_D$ +155.8° (*c* 0.95, $CHCl_3$); HRMS (ESI) calcd for $C_{10}H_{16}NaO_3$ $(M+Na)^+$ 207.0992, found 207.1000.

1,3-Dimethyl-1,3,2-diazaphospholidine 2-Oxide (30). To a cold (0 °C) solution of *N*,*N*′-dimethylethylenediamine (2.69 mL, 25 mmol) and NEt_3 (13.9 mL, 100 mmol) in a mixture of benzene (30 mL) and THF (30 mL) was added dropwise phosphorus trichloride (2.18 mL, 25 mmol) under vigorous stirring. The suspension was allowed to warm to room temperature and stirred for 1 h, after which it was recooled to 0 °C. Water (0.45 mL, 25 mmol) was then added slowly under vigorous stirring, and the reaction mixture was stirred for 16 h at room temperature. Filtration through a small pad of $MgSO_4$ and concentration gave an oily residue, which was redissolved in benzene/THF and filtered again (Celite). After concentration *in vacuo*, the crude phosphorus acid diamide **30** (2.18 g, 65%) was obtained as an yellowish oil, which was used without further purification:[31] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J_{P-H} = 603.4 Hz, 1H), 3.33−3.26 (m, 2H), 3.19−3.12 (m, 2H), 2.73 (dd, J = 10.6, 0.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.9 (d, J = 9.3 Hz), 31.8 (d, J = 3.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.9; IR (film, NaCl) 2917, 2826, 2329, 2228, 1472, 1352, 1269, 1224, 1166, 1033, 934, 927, 890, 730, 692 cm^{-1}; LRMS (ESI) calcd for $C_5H_{16}N_2O_2P$ $(M+H+MeOH)^+$ 167.1, found 167.1.

(*R*)-2-(3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropyl)-1,3-dimethyl-1,3,2-diazaphospholidine 2-Oxide (31). To a cold (0 °C) solution of phosphorus acid diamide **30** (3.07 g, 22.9 mmol) and (*R*)-3-*tert*-butyldimethylsilyloxy-2-methylpropyl iodide (**29**) (3.14 g, 10.0 mmol) in a mixture of THF (40 mL) and DMF (10 mL) was added portionwise NaH (0.8 g of a 60% dispersion in mineral oil, 20.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. After careful addition of saturated NH_4Cl solution, the aqueous layer was extracted with EtOAc. The combined organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. After purification of the residue by flash chromatography (EtOAc, then EtOAc/EtOH, 9:1), 3.05 g (95%) of phosphonamide **31** was obtained as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (ddd, J = 9.4, 5.7, 2.2 Hz, 1H), 3.34 (dd, J = 9.6, 6.7 Hz, 1H), 3.23−3.15 (m, 2H), 3.12−3.02 (m, 2H), 2.64 (d, J = 9.5 Hz, 3H), 2.63 (d, J = 9.4 Hz, 3H), 2.10 (ddd, J = 17.1, 16.0, 3.7 Hz, 1H), 1.85−1.70 (m, 1H), 1.53 (ddd, J = 15.7, 15.7, 8.7 Hz, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.4 (d, J = 14.7 Hz), 48.2 (d, J = 7.9 Hz), 48.0 (d, J = 7.7 Hz), 31.9 (d, J = 5.2 Hz), 31.7 (d,

J = 5.3 Hz), 31.5 (d, J = 4.0 Hz), 29.8 (d, J = 117 Hz), 25.8, 18.1, 17.7 (d, J = 4.9 Hz), −5.4, −5.5. ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.0; IR (film, NaCl) 2954, 2929, 2856, 1472, 1251, 1225, 1157, 1087, 1035, 942, 836, 806, 776 cm^{-1}; $[\alpha]_D$ −6.3° (c 3.6, $CHCl_3$); LRMS (ESI) calcd for $C_{14}H_{34}N_2O_2PSi$ $(M + H)^+$ 321.2, found 321.2.

(*S*,*E*)-4-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)-2-methylpent-3-en-1-ol (32). To a solution of phosphonamide **31** (3.4 g, 10.6 mmol) in THF (30 mL) was added *n*-BuLi (5.6 mL of a 1.6 M solution in hexanes, 8.96 mmol) at −78 °C. The mixture was stirred for 2 h at −78 °C, and then ketone **25** (800 mg, 4.76 mmol) was added to it. The reaction mixture was stirred for 1 h at −78 °C, after which it was allowed to warm to room temperature, AcOH (3.0 mL) was added, and stirring was continued for 20 min. After addition of saturated $NaHCO_3$ solution and extraction with CH_2Cl_2, the combined organic phase was dried and concentrated. The residue was purified by flash chromatography (hexanes/Et_2O, 10:1 to 4:1) to give a 1.01 g (62%) of a E/Z-mixture of TBS-olefins as a colorless oil (E/Z = 6:1 by ^{1}H NMR). As second fraction, 220 mg of ketone **25** (28%) was recovered. An analytical pure sample of the *E*-TBS-olefin was obtained by flash chromatography (hexanes/Et_2O, 100:1 to 20:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61−5.57 (m, 1H), 5.23 (d, J = 9.3 Hz, 1H), 4.12 (br s, 1H), 3.85 (dd, J = 10.7, 2.8 Hz, 1H), 3.47 (dd, J = 9.7, 6.0 Hz, 1H), 3.37 (dd, J = 9.7, 7.4 Hz, 1H), 2.66−2.54 (m, 1H), 2.19−2.08 (m, 1H), 1.93−1.84 (m, 1H), 1.84−1.72 (m, 1H), 1.62−1.60 (m, 3H), 1.70 (d, J = 1.17 Hz, 3H), 1.60−1.50 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 0.91 (s, 9H), 0.053 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 135.1, 128.0, 121.0, 77.94, 77.9, 67.8, 35.0, 30.1, 25.9, 25.6, 19.0, 18.3, 17.2, 12.6, 8.2, −5.3, −5.4; IR (film, NaCl) 2958, 2929, 2895, 2856, 1471, 1462, 1255, 1118, 1091, 1051, 1030, 836, 774, 665 cm^{-1}; $[\alpha]_D$ +47.7° (c 1.37, $CHCl_3$); LRMS (ESI) calcd for $C_{20}H_{39}O_2Si$ $(M + H)^+$ 339.3, found 339.2.

To a cold (0 °C) solution of the *E*-TBS-olefin (1.76 g, 5.2 mmol) in THF (50 mL) was added TBAF (7.8 mL of a 1 M solution in THF, 7.8 mmol). The mixture was stirred for 3 h at room temperature, and then saturated NH_4Cl solution was added. After evaporation of all volatiles *in vacuo*, the remaining aqueous layer was extracted with EtOAc. The combined organic phase was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc, 10:1 to 4:1) gave 1.09 g (93%) of alcohol **32** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61−5.57 (m, 1H), 5.24 (d, J = 9.5 Hz, 1H), 4.11 (br s, 1H), 3.87 (dd, J = 10.7, 3.0 Hz, 1H), 3.54−3.46 (m, 1H), 3.39 (dd, J = 10.4, 7.8 Hz, 1H), 2.74−2.62 (m, 1H), 2.19−2.07 (m, 1H), 2.00−1.88 (m, 1H), 1.85−1.75 (m, 1H), 1.73 (d, J = 1.4 Hz, 3H), 1.62 (ddd, J = 2.4, 2.4, 1.2 Hz, 3H), 1.60−1.48 (m, 2H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 135.1, 127.1, 120.7, 78.0, 77.5, 67.7, 35.0, 30.3, 25.6, 18.9, 16.9, 13.1, 8.3; IR (film, NaCl) 3392, 2963, 2932, 2872, 1454, 1378, 1337, 1116, 1054, 1031, 847 cm^{-1}; $[\alpha]_D$: +57.1° (c 1.52, $CHCl_3$); LRMS (ESI) calcd for $C_{14}H_{25}O_2$ $(M + H)^+$ 225.2, found 225.1.

(2*R*,6*R*)-6-Ethyl-2-((*S*,*E*)-5-iodo-4-methylpent-2-en-2-yl)-5-methyl-3,6-dihydro-2*H*-pyran (33). A solution of triphenylphosphine (1.23 g, 4.69 mmol) and imidazole (0.53 g, 7.78 mmol) in CH_2Cl_2 (10 mL) was treated with iodine (1.19 g, 4.69 mmol) at 0 °C under exclusion of light. To this mixture was then added slowly a solution of alcohol **32** (0.35 g, 1.56 mmol) in Et_2O (10 mL). The reaction mixture was allowed to warm to room temperature, stirred for 2 h, diluted with Et_2O, and subsequently quenched by addition of a 1:1 mixture of saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ solutions. The organic phase was separated, washed with water and brine, and dried over $MgSO_4$. Concentration gave a residue that was purified by flash chromatography (short plug of silica gel, hexanes/Et_2O, 20:1). The title compound **33** was obtained as a colorless oil (505 mg, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (d, J = 4.9 Hz, 1H), 5.24 (d, J = 9.1 Hz, 1H), 4.12 (s, 1H), 3.88 (dd, J = 10.8, 1.9 Hz, 1H), 3.18−3.11 (m, 1H), 3.11−3.05 (m, 1H), 2.71−2.62 (m, 1H), 2.19−2.08 (m, 1H), 1.96−1.87 (m, 1H), 1.85−1.73 (m, 1H), 1.70 (s, 3H), 1.61 (s, 3H), 1.60−1.49 (m, 1H), 1.12 (d, J = 6.6 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.1, 128.5, 120.7, 77.8, 77.6, 34.3, 30.1, 25.6, 21.2, 18.9, 15.2, 12.6, 8.2; IR (film, NaCl) 2962, 2929, 2972, 2868, 1453, 1373, 1192, 1115, 1050 cm^{-1}; $[\alpha]_D$ −6.3° (c 1.43, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{23}INaO$ $(M + Na)^+$ 357.0686, found 357.0683.

2-((*S*,*E*)-4-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)-2-methylpent-3-en-1-yl)-1,3-dimethyl-1,3,2-diazaphospholidine 2-Oxide (34). To a mixture of iodide **33** (505 mg, 1.51 mmol) and phosphorus acid diamide **30** (1.22 g, 9.1 mmol) in THF (5.0 mL) was added LiHMDS (6.0 mL of a 1 M solution in THF, 6.0 mmol) at −78 °C. The reaction mixture was stirred for 15 min at that temperature, after which it was slowly warmed to room temperature. Purification by flash chromatography (EtOAc, then EtOAc/EtOH, 9:1) gave 391 mg (76%) of **34** as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (d, J = 4.9 Hz, 1H), 5.19 (d, J = 9.3 Hz, 1H), 3.98 (br s, 1H), 3.70 (dd, J = 10.5, 2.3 Hz, 1H), 3.18−3.02 (m, 2H), 3.02−2.90 (m, 2H), 2.62−2.50 (m, 7H), 2.06−1.90 (m, 1H), 1.90−1.72 (m, 3H), 1.71−1.61 (m, 1H), 1.57 (s, 3H), 1.50 (s, 3H), 1.48−1.36 (m, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 134.0, 130.2 (d, J = 7.5 Hz), 120.5, 77.9, 76.9, 47.8 (d, J = 7.8 Hz), 47.4 (d, J = 8.6 Hz), 34.2 (d, J = 115.2 Hz), 31.8 (d, J = 5.3 Hz), 31.3 (d, J = 5.9 Hz), 29.8, 27.5 (d, J = 3.9 Hz), 25.4, 22.5 (d, J = 13.1 Hz), 18.7, 12.7, 8.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.5; IR (film, NaCl) 2961, 2918, 1450, 1376, 1349, 1263, 1226, 1210, 1163, 1115, 1036, 942, 798 cm^{-1}; $[\alpha]_D$ +31.0° (c 0.97, $CHCl_3$); LRMS (ESI) calcd for $C_{18}H_{34}N_2O_2P$ $(M + H)^+$ 341.2, found 341.2.

(1*S*,2*S*,3*R*)-*tert*-Butyl 2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)-3-methylhexa-1,4-dien-1-yl)-3-methylcyclopropanecarboxylate (35). To a solution of phosphonamide **34** (107 mg, 0.31 mmol) in THF (2 mL) was added *t*-BuLi (0.24 mL of a 1.7 M solution in hexanes, 8.96 mmol) at −78 °C. The mixture was stirred for 2 h at −78 °C, and then aldehyde **28** (91 mg, 0.49 mmol) was added to it. The reaction mixture was stirred for 1 h at −78 °C, AcOH (0.3 mL) was then added, and the reaction mixture was allowed to warm to room temperature. After addition of saturated $NaHCO_3$ solution and extraction with CH_2Cl_2, the combined organic phase was dried and concentrated. The residue was purified by flash chromatography (hexanes/Et_2O, 20:1 to 10:1) to give 74 mg (64%) of triene **35** as a colorless oil (E/Z > 20:1 by ^{1}H NMR): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62−5.54 (m, 2H), 5.28 (d, J = 8.9 Hz, 1H), 5.09 (dd, J = 15.3, 8.8 Hz, 1H), 4.11 (br s, 1H), 3.86 (dd, J = 10.5, 2.3 Hz, 1H), 3.16−3.05 (m, 1H), 2.19−2.07 (m, 1H), 2.00 (ddd, J = 9.0, 9.0, 4.3 Hz, 1H), 1.93−1.84 (m, 1H), 1.83−1.73 (m, 1H), 1.66 (s, 3H), 1.61 (s, 3H), 1.59−1.48 (m, 2H), 1.46 (s, 9H), 1.27 (dd, J = 4.4, 4.4 Hz, 1H), 1.09 (d, J = 6.4 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 137.0, 135.3, 135.1, 129.0, 123.8, 120.8, 80.1, 77.8, 77.77, 35.0, 30.2, 29.8, 29.6, 28.2, 25.6, 22.1, 21.0, 18.9, 12.5, 12.4, 8.2; IR (film, NaCl) 2963, 2917, 1718, 1366, 1154, 1117, 1062, 1049 cm^{-1}; $[\alpha]_D$ +154.5° (c 0.49, $CHCl_3$); LRMS (ESI) calcd for $C_{24}H_{38}NaO_3$ $(M + Na)^+$ 397.3, found 397.2.

((1*S*,2*S*,3*R*)-2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)-3-methyl-hexa-1,4-dien-1-yl)-3-methylcyclopropyl)methanol (36). To a solution of *tert*-butyl ester **35** (47 mg, 0.126 mmol) in CH_2Cl_2 (2 mL) was added DIBAL-H (0.38 mL of a 1 M solution in CH_2Cl_2, 0.38 mmol) at 0 °C. The reaction mixture was stirred for 2 h at that temperature and subsequently quenched with saturated NaK tartrate solution.

The resulting mixture was warmed to room temperature and stirred vigorously until two clear layers were obtained. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes/EtOAc, 4:1) yielded hydroxymethyl vinyl cyclopropane **36** (37 mg, 96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60−5.57 (m, 1H), 5.49 (ddd, J = 15.4, 6.4, 0.5 Hz, 1H), 5.28 (dddd, J = 9.0, 2.4, 1.2, 1.2 Hz, 1H), 5.13 (ddd, J = 15.4, 8.6, 1.3 Hz, 1H), 3.86 (dd, J = 10.7, 2.8 Hz, 1H), 4.12 (br s, 1H), 3.53−3.50 (m, 2H), 3.15−3.05 (m, 1H), 2.19−2.09 (m, 1H), 1.93−1.83 (m, 1H), 1.83−1.74 (m, 1H), 1.67 (d, J = 1.3 Hz, 3H), 1.62−1.60 (m, 3H), 1.60−1.50 (m, 1H), 1.36−1.29 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 5.9 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H), 0.91−0.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 135.1, 135.0, 129.5, 125.7, 120.9, 77.9, 77.8, 66.6, 34.9, 30.1, 29.7, 25.6, 24.3, 21.1, 19.0, 17.6, 13.1, 12.3, 8.2; IR (film, NaCl) 3368, 2962, 2929, 2871, 1452, 1411, 1368, 1115, 1089, 1071, 1054, 1049, 1022 cm^{-1}; $[\alpha]_D$ + 95.6° (*c* 0.25, $CHCl_3$); LRMS (ESI) calcd for $C_{20}H_{32}NaO_2$ (M + Na)$^+$ 327.2, found 327.2.

(2*R*,6*R*)-6-Ethyl-2-((*R*,2*E*,5*E*)-6-((1*S*,2*S*,3*R*)-2-ethynyl-3-methylcyclopropyl)-4-methylhexa-2,5-dien-2-yl)-5-methyl-3,6-dihydro-2*H*-pyran (37). Method A (from **36**): To a −78 °C solution of DMSO (25 μL, 0.356 mmol) in CH_2Cl_2 (1 mL) was added dropwise oxalyl chloride (0.12 mL of a 2 M solution in CH_2Cl_2, 0.24 mmol). After 20 min, a solution of **36** (35 mg, 0.115 mmol) in CH_2Cl_2 (1 mL) was added, and the resulting mixture was stirred for 1 h at −78 °C. Triethylamine (64 μL, 0.46 mmol) was then added, and the mixture maintained for 15 min at −78 °C before it was allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2, water was added, and the layers were separated. The organic layer was washed with water and brine and dried (Na_2SO_4). Concentration *in vacuo* yielded the crude aldehyde as a light yellow oil (35 mg, 100%), which was used in the next step without further purification. To a suspension of the aldehyde (35 mg, 0.115 mmol) and anhydrous K_2CO_3 (48 mg, 0.35 mmol) in methanol (1 mL) was added dimethyl-1-diazo-2-oxypropylphosphonate (40 mg, 0.21 mmol), and the reaction mixture was stirred overnight at room temperature. After dilution with diethyl ether, water was added, and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes/Et_2O, 100:1 to 40:1) gave alkyne **37** (28 mg, 82% over two steps from hydroxymethyl vinyl cyclopropane **36**) as a colorless oil.

Method B (from **43**): To a 0 °C solution of *E*,*E*-TIPS-alkyne **43** (101 mg, 0.22 mmol) in THF (4 mL) was added TBAF (0.33 mL of a 1 M solution in THF, 0.33 mmol). The mixture was warmed to room temperature and stirred for 1 h. After addition of saturated NH_4Cl solution and evaporation of all volatiles *in vacuo*, the remaining aqueous layer was extracted with EtOAc. The combined organic phase was washed (brine), dried (Na_2SO_4), and concentrated. The residue thus obtained was purified by flash chromatography (hexanes/Et_2O, 100:1 to 50:1) to give alkyne **37** (58 mg, 88%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61−5.55 (m, 2H), 5.28 (d, J = 8.9 Hz, 1H), 5.05 (ddd, J = 15.3, 8.6, 1.2 Hz, 1H), 4.12 (br s, 1H), 3.86 (dd, J = 10.7, 2.9 Hz, 1H), 3.15−3.05 (m, 1H), 2.19−2.08 (m, 1H), 1.92−1.83 (m, 2H), 1.83−1.73 (m, 2H), 1.66 (d, J = 1.2 Hz, 3H), 1.63−1.60 (m, 3H), 1.60−1.50 (m, 1H), 1.38−1.27 (m, 1H), 1.08 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 0.97−0.94 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 135.3, 135.1, 129.1, 123.8, 120.9, 86.6, 77.9, 77.8, 64.7, 35.0, 30.1, 29.7, 25.6, 22.6, 21.0, 19.0, 14.8, 12.8, 12.3, 8.2; IR (film, NaCl) 3315, 2963, 2930, 2872, 2119, 1454, 1368, 1115, 1050, 962 cm^{-1}; $[\alpha]_D$ +187.7° (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{31}O$ (M + H)$^+$ 299.2369, found 299.2363.

(1*S*,2*S*,3*R*)-*tert*-Butyl-2-((*R*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-3-methylbut-1-en-1-yl)-3-methyl-cyclopropanecarboxylate (38). To a −78 °C solution of phosphonamide *epi*-**31** (538 mg, 1.67 mmol) in THF (7 mL) was added *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes, 1.60 mmol), and the mixture was stirred for 2 h at that temperature. A solution of aldehyde **28** (155 mg, 0.84 mmol) in THF (3 mL) was then added, and the reaction mixture was stirred for 1 h at −78 °C. After quench with acetic acid (1.0 mL), the mixture was warmed to room temperature, diluted with CH_2Cl_2, and neutralized by addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried over Na_2SO_4. After evaporation of all volatiles *in vacuo*, the residue was purified by flash chromatography (hexanes/EtOAc, 20:1) to give ester **38** (214 mg, 72%) as a colorless oil (*E*/*Z* ratio >20:1 by ^{1}H NMR): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (dd, J = 15.4, 7.4 Hz, 1H), 5.18 (dd, J = 15.4, 8.7 Hz, 1H), 3.47 (dd, J = 9.7, 6.5 Hz, 1H), 3.41 (dd, J = 9.7, 6.8 Hz, 1H), 2.38−2.26 (m, 1H), 2.00 (ddd, J = 9.0, 9.0, 4.3 Hz, 1H), 1.59−1.49 (m, 1H), 1.45 (s, 9H), 1.28 (dd, J = 4.5, 4.5 Hz, 1H), 1.11 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 135.3, 125.4, 79.7, 67.7, 39.2, 29.6, 29.4, 27.8, 25.6, 25.4, 21.6, 18.0, 16.3, 12.2,-5.66, −5.7; IR (film, NaCl) 2958, 2931, 2858, 2867, 1720, 1367, 1258, 1155, 1107, 1088, 837, 776 cm^{-1}; $[\alpha]_D$ +83.2° (*c* 1.19, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{38}NaO_3Si$ (M + Na)$^+$ 377.2482, found 377.2480.

(1*S*,2*S*,3*R*)-2-((*R*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-methylbut-1-en-1-yl)-3-methyl-cyclopropanecarbaldehyde (39). To a −78 °C solution of *tert*-butyl ester **38** (380 mg, 1.07 mmol) in CH_2Cl_2 (10 mL) was added DIBAL-H (4.3 mL of a 1 M solution in CH_2Cl_2, 4.3 mmol). The reaction mixture was warmed to −30 °C, stirred for 2 h at that temperature, and subsequently quenched with saturated NaK tartrate solution. The resulting mixture was warmed to room temperature and stirred vigorously until two clear layers were obtained. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes/EtOAc, 4:1) yielded the hydroxymethyl vinyl cyclopropane (254 mg, 83%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (dd, J = 15.4, 7.3 Hz, 1H), 5.22 (ddd, J = 15.4, 8.5, 1.0 Hz, 1H), 3.49 (dd, J = 9.7, 6.2 Hz, 1H), 3.53−3.48 (m, 2H), 3.38 (dd, J = 9.7, 7.1 Hz, 1H), 2.36−2.25 (m, 1H), 1.59 (br s, OH), 1.33 (ddd, J = 8.5, 8.5, 5.1 Hz, 1H), 1.08 (d, J = 5.9 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.93−0.84 (m, 2H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 127.4, 67.9, 66.2, 39.2, 29.6, 29.3, 25.6, 24.1, 18.0, 17.2, 16.5, 12.8, −5.64, −5.67; IR (film, NaCl) 3339, 2956, 2930, 2886, 2858, 1472, 1463, 1386, 1256, 1116, 1087, 1025, 964, 837, 775 cm^{-1}; $[\alpha]_D$ +45.8° (*c* 1.62, $CHCl_3$); LRMS (ESI) calcd for $C_{16}H_{33}O_2Si$ (M + H)$^+$ 285.2, found 285.1.

To a −78 °C solution of DMSO (0.255 mL, 3.6 mmol) in CH_2Cl_2 (15 mL) was added dropwise oxalyl chloride (1.2 mL of a 2 M solution in CH_2Cl_2, 2.4 mmol). After 20 min, a solution of the hydroxymethyl vinyl cyclopropane (340 mg, 1.2 mmol) in CH_2Cl_2 (5 mL) was added, and the resulting mixture stirred for 1 h at −78 °C. Triethylamine (0.67 mL, 4.8 mmol) was added, and the mixture was maintained for 15 min at −78 °C before it was warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2, water was added, and the layers were separated. The organic layer was washed with water, brine, and dried (Na_2SO_4). Concentration *in vacuo* yielded the crude aldehyde **39** as a light yellow oil (340 mg, 100%), which was used in the next step without further purification. Alternatively, the crude product can be purified by flash chromatography (hexanes/Et_2O, 10:1) to give aldehyde **39** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, J = 4.8 Hz, 1H), 5.62 (dd, J = 15.5, 7.4 Hz, 1H), 5.25 (ddd, J = 15.4, 8.5, 0.6 Hz, 1H), 3.49

(dd, J = 9.7, 6.4 Hz, 1H), 3.42 (dd, J = 9.7, 6.7 Hz, 1H), 2.39−2.29 (m, 1H), 2.25 (ddd, J = 9.0, 9.0, 4.2 Hz, 1H), 1.84−1.75 (m, 1H), 1.68 (ddd, J = 4.5, 4.5, 4.5 Hz, 1H), 1.19 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 136.8, 124.2, 67.9, 39.5, 39.2, 31.1, 25.9, 22.7, 18.3, 16.6, 12.4, −5.3, −5.33; IR (film, NaCl) 2957, 2930, 2857, 1712, 1255, 1088, 836, 775 cm^{-1}; LRMS (ESI) calcd for $C_{16}H_{31}O_2Si$ $(M + H)^+$ 283.2, found 283.1.

***tert*-Butyl(((*R*,*E*)-4-((1*S*,2*S*,3*R*)-2-ethynyl-3-methylcyclopropyl)-2-methylbut-3-en-1-yl)oxy)dimethylsilane (40).** To a suspension of crude aldehyde **39** (340 mg, 1.2 mmol) and anhydrous K_2CO_3 (500 mg, 3.6 mmol) in methanol (6 mL) was added dimethyl-1-diazo-2-oxypropylphosphonate (415 mg, 2.16 mmol), and the reaction mixture was stirred overnight at room temperature. After dilution with diethyl ether, water was added, and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes/Et_2O, 20:1 to 10:1) gave alkyne **40** (286 mg, 85% over two steps from the hydroxymethyl vinyl cyclopropane) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (ddd, J = 15.4, 7.4, 0.6 Hz, 1H), 5.15 (ddd, J = 15.4, 8.5, 1.1 Hz, 1H), 3.50 (dd, J = 9.7, 6.2 Hz, 1H), 3.40 (dd, J = 9.7, 7.0 Hz, 1H), 2.38−2.26 (m, 1H), 1.89 (d, J = 2.1 Hz, 1H), 1.80 (ddd, J = 8.8, 8.5, 4.8, 0.6 Hz, 1H), 1.38−1.29 (m, 1H), 1.10 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.99−0.94 (m, 1H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 125.8, 86.6, 68.1, 64.7, 39.6, 29.8, 25.9, 22.6, 18.4, 16.7, 14.8, 12.9, −5.3, −5.33; IR (film, NaCl) 3317, 2956, 2930, 2896, 2886, 2857, 1471, 1462, 1256, 1114, 1087, 1062, 962, 837, 775 cm^{-1}; $[\alpha]_D$ +110.3° (*c* 1.94, $CHCl_3$); LRMS (ESI) calcd for $C_{17}H_{31}OSi$ $(M + H)^+$ 279.2, found 279.1.

***tert*-Butyldimethyl(((*R*,*E*)-2-methyl-4-((1*S*,2*R*,3*S*)-2-methyl-3-((triisopropylsilyl)ethynyl)cyclopropyl)but-3-en-1-yl)oxy)silane (41).** To a solution of alkyne **40** (81 mg, 0.29 mmol) in THF (3 mL) was added *n*-BuLi (0.27 mL of a 1.6 M solution, 0.43 mmol) at −78 °C. The reaction mixture was stirred for 1 h at that temperature, and then TIPSCl (140 mg, 0.73 mmol) was added. The mixture was stirred for 30 min at −78 °C, warmed to room temperature, and stirred for another 30 min. After quenching the mixture with saturated NH_4Cl solution, the layers were separated, and the aqueous one was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue thus obtained was purified by flash chromatography (hexanes/EtOAc, 80:1 to 40:1) to yield 120 mg (95%) of TIPS-alkyne **41** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (dd, J = 15.4, 7.4 Hz, 1H), 5.15 (dd, J = 15.4, 8.6 Hz, 1H), 3.50 (dd, J = 9.7, 6.3 Hz, 1H), 3.41 (dd, J = 9.7, 6.9 Hz, 1H), 2.38−2.27 (m, 1H), 1.77 (ddd, J = 8.8, 8.8, 4.7 Hz, 1H), 1.37−1.26 (m, 1H), 1.10 (d, J = 6.4 Hz, 3H), 1.08−1.01 (m, 22H), 1.00 (d, J = 6.7 Hz, 3H), 0.92 (br s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 126.3, 111.1, 76.4, 68.2, 39.6, 30.7, 25.9, 23.4, 18.6, 18.4, 16.7, 16.4, 13.0, 11.4, −5.28, −5.3; IR (film, NaCl) 2957, 2978, 2935, 2892, 2864, 2148, 1463, 1255, 1114, 1087, 883, 836, 775 cm^{-1}; $[\alpha]_D$ +120.6° (*c* 1.22, $CHCl_3$); LRMS (ESI) calcd for $C_{26}H_{51}OSi_2$ $(M + H)^+$ 435.3, found 435.3.

(((1*S*,2*S*,3*R*)-2-((*R*,*E*)-4-Iodo-3-methylbut-1-en-1-yl)-3-methylcyclopropyl)ethynyl)triisopropylsilane (42). A solution of TIPS-alkyne **41** (120 mg, 0.28 mmol) in a mixture of CH_2Cl_2 (2 mL) and MeOH (2 mL) was treated at 0 °C with camphorsulfonic acid (6 mg, 0.026 mmol) for 1 h. The reaction mixture was quenched by addition of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic phase was washed (brine), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 10:1 to 4:1) to give 73 mg (81%) of the alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (dd, J = 15.4, 7.9 Hz, 1H), 5.23 (ddd, J = 15.4, 8.7, 0.7 Hz, 1H), 3.56−3.46 (m, 1H), 3.46−3.38 (m, 1H), 2.42−2.31 (m, 1H), 1.80 (dddd, J = 9.0, 9.0, 4.7, 0.5 Hz, 1H), 1.47 (br s, OH), 1.39−1.28 (m, 1H), 1.11 (d, J = 6.4 Hz, 3H), 1.09−1.03 (m, 22H), 1.02 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 128.3, 110.7, 76.7, 67.3, 39.9, 30.4, 23.5, 18.6, 16.65, 16.6, 13.0, 11.3; IR (film, NaCl) 3346, 2957, 2942, 2891, 2865, 2146, 1462, 1034, 994, 882, 676 cm^{-1}; $[\alpha]_D$ + 171.8° (*c* 1.14, $CHCl_3$); LRMS (ESI) calcd for $C_{20}H_{37}OSi$ $(M + H)^+$ 321.3, found 321.2.

To a cold (0 °C) mixture of triphenylphosphine (120 mg, 0.46 mmol), imidazole (47 mg, 0.69 mmol), and iodine (116 mg, 0.46 mmol) in CH_2Cl_2 (4 mL) was added a solution of the alcohol (73 mg, 0.23 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was allowed to slowly warm to room temperature and stirred overnight. The mixture was the diluted with CH_2Cl_2, and 10% aqueous $Na_2S_2O_3$ solution was added. After phase separation, the organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexanes/Et_2O, 100:0 to 20:1) to yield 82 mg (83%) of iodide **42** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (dd, J = 15.3, 7.3 Hz, 1H), 5.20 (ddd, J = 15.3, 8.5, 0.7 Hz, 1H), 3.21 (dd, J = 9.5, 5.6 Hz, 1H), 3.12 (dd, J = 9.5, 6.9 Hz, 1H), 2.44−2.33 (m, 1H), 1.79 (ddd, J = 8.8, 8.8, 4.8 Hz, 1H), 1.39−1.30 (m, 1H), 1.13 (d, J = 6.7 Hz, 3H), 1.11 (d, J = 6.4 Hz, 3H), 1.09−1.03 (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 127.4, 110.7, 76.7, 38.8, 30.2, 23.6, 20.8, 18.6, 16.5, 25.4, 13.1, 11.3; IR (film, NaCl) 2958, 2942, 2864, 2147, 1462, 1194, 1057, 995, 960, 882, 666 cm^{-1}; $[\alpha]_D$ +167.8° (*c* 1.29, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{36}ISi$ $(M + H)^+$ 431.1626, found 431.1644.

1,3-Dimethyl-2-((*R*,*E*)-2-methyl-4-((1*S*,2*R*,3*S*)-2-methyl-3-((triisopropylsilyl)ethynyl)cyclopropyl)but-3-en-1-yl)-1,3,2-diazaphospholidine 2-Oxide (3). To a mixture of iodide **42** (117 mg, 0.27 mmol) and freshly prepared phosphorus acid diamide **30** (217 mg, 1.62 mmol) in THF (1 mL) was added LiHMDS (1.08 mL of a 1 M solution in THF, 1.08 mmol) at −78 °C. The reaction mixture was stirred for 10 min at that temperature, subsequently allowed to warm to room temperature, and stirred for another 30 min. After addition of saturated NH_4Cl solution and extraction with CH_2Cl_2, the combined organic phase was washed (brine), dried (Na_2SO_4), and concentrated *in vacuo*. The residue thus obtained was purified by flash chromatography (EtOAc, then EtOAc/EtOH, 9:1) to give 93 mg (79%) of phosphonamide **3** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (dd, J = 15.2, 8.1 Hz, 1H), 5.02 (dd, J = 15.2, 9.2 Hz, 1H), 3.18−3.10 (m, 2H), 3.10−3.00 (m, 2H), 2.61 (d, J = 9.6 Hz, 3H), 2.59 (d, J = 9.2 Hz, 3H), 2.44−2.31 (m, 1H), 1.93−1.74 (m, 2H), 1.68 (ddd, J = 9.1, 9.1, 4.7 Hz, 1H), 1.33−1.24 (m, 1H), 1.08−0.89 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0 (d, J = 7.7 Hz), 125.0, 110.4, 76.5, 48.0 (d, J = 7.9 Hz), 47.5 (d, J = 8.7 Hz), 34.3 (d, J = 115.9 Hz), 32.6 (d, J = 4.0 Hz), 32.0 (d, J = 5.2 Hz), (d, J = 5.8 Hz), 31.5, 30.8, 23.2, 22.9 (d, J = 12.6 Hz), 18.4, 16.7, 12.9, 11.1. ^{31}P NMR (162 MHz, $CDCl_3$) δ 39.9; IR (film, NaCl) 2942, 2892, 2865, 2144, 1463, 1263, 1225, 1162, 1035, 882, 665 cm^{-1}; $[\alpha]_D$ +153.2° (*c* 1.1, $CHCl_3$); LRMS (ESI) calcd for $C_{24}H_{46}N_2OPSi$ $(M + H)^+$ 437.3, found 437.3.

(((1*S*,2*S*,3*R*)-2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)-3-methyl-hexa-1,4-dien-1-yl)-3-methylcyclopropyl)ethynyl)triisopropylsilane (43). To a −78 °C solution of phosphonamide **3** (210 mg, 0.44 mmol) in THF (3 mL) was added *n*-BuLi (0.18 mL of a 2.5 M solution in THF, 0.45 mmol). The mixture was stirred for 3 h at that temperature, after which ketone **25** (110 mg, 0.65 mmol) was added. The reaction mixture was stirred for 1 h at −78 °C, warmed to room temperature, and subsequently quenched by addition of AcOH (0.4 mL). The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration

gave a residue that was purified by flash chromatography (hexanes/EtOAc, 20:1 to 10:1, then EtOAc/EtOH, 10:0 to 9:1). Olefin **43** (88 mg, 44%) was isolated as the first fraction as a 6:1 mixture of E/Z isomers. The isomers can be separated by flash chromatography (hexanes/EtOAc, 80:1). As second fraction, ketone **25** (56 mg, 51%), and as third fraction, phosphonamide **3** (98 mg, 45%) were recovered. *E,E*-Alkene **43**, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63−5.54 (m, 2H), 5.28 (d, J = 8.9 Hz, 1H), 5.05 (ddd, J = 15.3, 8.6, 0.8 Hz, 1H), 4.12 (br s, 1H), 3.87 (dd, J = 10.6, 2.7 Hz, 1H), 3.16−3.06 (m, 1H), 2.20−2.08 (m, 1H), 1.95−1.84 (m, 1H), 1.84−1.71 (m, 2H), 1.67 (d, J = 0.9 Hz, 3H), 1.61 (s, 3H), 1.60−1.50 (m, 1H), 1.36−1.25 (m, 1H), 1.11−0.97 (m, 28H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 135.3, 135.1, 129.2, 124.3, 120.9, 111.1, 77.9, 77.8, 76.3, 35.0, 30.4, 30.2, 25.6, 23.4, 21.0, 19.0, 18.6, 16.4, 12.9, 12.3, 11.3, 8.2; IR (film, NaCl) 2960, 2941, 2865, 2146, 1462, 1115, 1050, 883, 976, 665 cm^{-1}; $[\alpha]_D$ +176.3° (*c* 0.89, $CHCl_3$); LRMS (ESI) calcd for $C_{30}H_{51}OSi$ $(M + H)^+$ 455.4, found 455.3. *E,Z*-Alkene, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63−5.56 (m, 2H), 5.11−5.03 (m, 2H), 4.34 (dd, J = 10.7, 3.0 Hz, 1H), 4.10 (br s, 1H), 3.21−3.13 (m, 1H), 2.29−2.18 (m, 1H), 1.81−1.71 (m, 6H), 1.61 (br s, 3H), 1.59−1.50 (m, 1H), 1.34−1.26 (m, 1H), 1.10−0.97 (m, 28H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 135.3, 135.2, 130.5, 124.6, 121.0, 111.1, 77.5, 76.3, 72.1, 34.8, 30.5, 29.6, 25.5, 23.4, 21.6, 19.0, 18.6, 18.58, 16.5, 13.0, 11.3, 8.1; IR (film, NaCl) 2960, 2942, 2865, 2146, 1462, 1053, 882 cm^{-1}; LRMS (ESI) calcd for $C_{30}H_{51}OSi$ $(M + H)^+$ 455.4, found 455.4.

(2*R*,6*R*)-2-((*R*,2*E*,5*E*)-6-((1*S*,2*S*,3*R*)-2-(((2*S*,3*R*,4*S*,6*R*)-3,4-Bis(benzyloxy)-6-(2-(benzyloxy)-ethyl)tetrahydro-2*H*-pyran-2-yl)ethynyl)-3-methylcyclopropyl)-4-methylhexa-2,5-dien-2-yl)-6-ethyl-5-methyl-3,6-dihydro-2*H*-pyran (44). To a −78 °C solution of alkyne **37** (58 mg, 0.19 mmol) in THF (1 mL) was added *n*-BuLi (0.14 mL of a 1.6 M solution in hexanes, 0.22 mmol). After stirring for 2 h at that temperature, a solution of lactone **15** (100 mg, 0.22 mol) in THF (1 mL) was added to the solution of the generated anion. Stirring was continued for 1.5 h at −78 °C, and the reaction mixture subsequently quenched by addition of saturated NH_4Cl solution and then diluted with EtOAc. After phase separation, the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was partially purified by flash chromatography (hexanes/EtOAc, 20:1 to 2:1) to give unreacted alkyne **37** (19 mg, 33%) as the first fraction and the alkyne lactone adduct (136 mg) as second fraction (dr 1:1 by ^{1}H NMR). The alkyne lactone adduct was contaminated with unreacted lactone and butyl lactone adduct. The impure adduct was used in the next step without further purification.

To a −50 °C solution of the alkyne lactone adduct thus prepared in a mixture of CH_2Cl_2 (3 mL) and CH_3CN (3 mL) was added triethylsilane (0.12 mL, 0.75 mmol). After stirring for 1 h at that temperature, $BF_3 \cdot OEt_2$ (50 μL, 0.40 mmol) was added. The reaction mixture was stirred for an additional 1 h at −50 °C and then quenched by addition of triethylamine (0.14 mL, 1.0 mmol). The mixture was diluted with dichloromethane, washed with saturated NH_4Cl solution and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexanes/EtOAc, 10:1 to 4:1) yielded 91 mg (66% over two steps) of pure tribenzyl alkyne **44** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.43 (m, 2H), 7.42−7.29 (m, 13H), 5.62 (d, J = 4.9 Hz, 1H), 5.54 (dd, J = 15.3, 6.5 Hz, 1H), 5.30 (d, J = 8.8 Hz, 1H), 5.08 (dd, J = 15.3, 8.6 Hz, 1H), 4.96 (d, J = 10.6 Hz, 1H), 4.91 (d, J = 10.5 Hz, 1H), 4.71 (s, 2H), 4.54 (s, 2H), 4.16 (br s, 1H), 3.99 (dd, J = 9.5, 1.3 Hz, 1H), 3.90 (dd, J = 10.7, 2.7 Hz, 1H), 3.70−3.53 (m, 4H), 3.44 (t, J = 9.2 Hz, 1H), 3.16−3.07 (m, 1H), 2.23−2.08 (m, 2H), 1.99−1.75 (m, 5H), 1.69 (s, 3H), 1.64 (s, 3H), 1.62−1.52 (m, 1H), 1.51−1.32 (m, 2H), 1.11 (s, 3H), 1.09 (s, 3H), 1.07−1.02 (m, 1H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 138.3, 137.0, 135.3, 135.0, 129.2, 128.32, 128.3, 128.28, 128.2, 127.6, 127.57, 127.54, 127.5, 123.9, 120.8, 87.9, 83.0, 79.5, 77.9, 77.7, 75.5, 74.4, 72.9, 72.7, 71.9, 70.2, 66.4, 37.1, 35.6, 34.9, 30.1, 29.7, 25.6, 22.5, 21.0, 18.9, 15.3, 12.9, 12.2, 8.2; IR (film, NaCl) 3063, 3029, 2960, 2920, 2866, 2239, 1496, 1454, 1361, 1293, 1207, 1177, 1099, 1028, 962, 735, 697 cm^{-1}; $[\alpha]_D$ +73.2° (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{49}H_{60}NaO_5$ $(M + Na)^+$ 751.4333, found 751.4342.

(2*S*,3*R*,4*S*,6*R*)-2-(((1*S*,2*S*,3*R*)-2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)-3-methylhexa-1,4-dien-1-yl)-3-methylcyclopropyl)ethynyl)-6-(2-hydroxyethyl)tetrahydro-2*H*-pyran-3,4-diol (45). To a −78 °C solution of alkyne **44** (52 mg, 0.071 mmol) in THF (5 mL) was added freshly prepared LDBB (2.1 mL of a 0.5 M solution in THF, 1.05 mmol) until a green color persisted. After stirring for 1 h at −78 °C, analysis by TLC indicated complete conversion of tribenzyl alkyne **34**, and saturated NH_4Cl solution was added. Removal of all volatiles *in vacuo* gave an aqueous mixture, which was extracted by EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:1, then EtOAc) yielded 29 mg (89%) of triol **45** as a colorless oil: ^{1}H NMR (400 MHz, CD_3OD) δ 5.64−5.53 (m, 2H), 5.28 (d, J = 9.0 Hz, 1H), 5.14 (ddd, J = 15.2, 8.6, 1.0 Hz, 1H), 4.11 (br s, 1H), 3.85 (dd, J = 10.7, 2.9 Hz, 1H), 3.80 (dd, J = 9.5, 1.7 Hz, 1H), 3.72−3.55 (m, 3H), 3.53−3.45 (m, 1H), 3.16−3.09 (m, 2H), 2.18−2.08 (m, 1H), 1.96 (ddd, J = 12.9, 5.0, 1.7 Hz, 1H), 1.93−1.84 (m, 1H), 1.82−1.67 (m, 3H), 1.66 (d, J = 1.2 Hz, 3H), 1.62 (dd, J = 2.3, 1.2 Hz, 3H), 1.60−1.50 (m, 1H), 1.39−1.27 (m, 3H), 1.08 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.02 (ddd, J = 4.9, 4.9, 1.8 Hz, 1H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 137.9, 136.4, 136.3, 130.6, 125.6, 122.1, 88.8, 79.5, 77.2, 75.1, 74.1, 73.1, 72.7, 59.4, 40.6, 39.4, 36.3, 31.2, 31.0, 26.6, 23.8, 21.6, 19.1, 16.2, 13.2, 12.7, 8.8; IR (film, NaCl) 3391, 2963, 2928, 2872, 2238, 1453, 1368, 1303, 1065, 962, 930 cm^{-1}; $[\alpha]_D$ +138.7° (*c* 0.53, $CHCl_3$); HRMS (ESI) calcd for $C_{28}H_{42}NaO_5$ $(M + Na)^+$ 481.2925, found 481.2929.

(2*S*,3*R*,4*S*,6*R*)-2-((*E*)-2-((1*S*,2*S*,3*R*)-2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)-3-methylhexa-1,4-dien-1-yl)-3-methylcyclopropyl)vinyl)-6-(2-hydroxyethyl)tetrahydro-2*H*-pyran-3,4-diol (46). To a solution of triol **45** (30 mg, 0.065 mmol) in diethyl ether (6 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride (0.21 mL of a 65% solution in toluene, 0.7 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was then cooled to 0 °C, carefully quenched by addition of saturated Rochelle salt solution, and vigorously stirred at room temperature until two clear layers were obtained. After phase separation, the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the residue by flash chromatography (EtOAc) yielded 24 mg (80%) of triol **46** as a colorless oil: ^{1}H NMR (700 MHz, CD_3OD) δ 5.59 (ddd, J = 5.8, 3.1, 1.7 Hz, 1H), 5.51 (dd, J = 15.4, 6.7 Hz, 1H), 5.46 (dd, J = 15.2, 6.5 Hz, 1H), 5.38 (ddd, J = 15.3, 9.0, 0.7 Hz, 1H), 5.26 (dddd, J = 9.1, 2.6, 1.4, 1.4 Hz, 1H), 5.16 (ddd, J = 15.3, 8.8, 1.1 Hz, 1H), 4.09 (br s, 1H), 3.84 (dd, J = 10.7, 2.8 Hz, 1H), 3.69−3.60 (m, 3H), 3.56−3.48 (m, 2H), 3.15−3.09 (m, 1H), 2.97 (dd, J = 9.0, 9.0 Hz, 1H), 2.17−2.10 (m, 1H), 1.96 (ddd, J = 12.6, 5.0, 1.6 Hz, 1H), 1.89−1.85 (m, 1H), 1.79−1.69 (m, 2H), 1.65 (d, J = 1.3 Hz, 3H), 1.67−1.62 (m, 1H), 1.60 (dt, J = 3.4, 1.2 Hz, 3H), 1.59−1.52 (m, 1H), 1.50−1.46 (m, 1H), 1.34 (q, J = 12.1 Hz, 1H), 1.15−1.12 (m, 1H), 1.06 (d, J = 1.3 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.06−1.02 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (176 MHz, CD_3OD) δ 138.3, 136.3, 136.2, 136.1, 131.0, 127.0, 126.4, 122.1, 81.8, 79.6, 79.5, 77.3, 73.7, 73.6, 59.7, 40.9, 39.5, 36.4, 31.8, 31.2, 29.9, 26.6, 22.4, 21.7, 19.2, 13.5, 12.7,

8.7; IR (film, NaCl) 3368, 2960, 2920, 2872, 1668, 1451, 1368, 1062, 963 cm^{-1}; $[\alpha]_D$ +83.0° (*c* 1.25, $CHCl_3$); HRMS (ESI) calcd for $C_{28}H_{44}NaO_5$ $(M + Na)^+$ 483.3081, found 483.3097.

(+)-Ambruticin S (1a). A suspension of PtO_2 (20 mg) in water (15 mL) was treated with hydrogen at 100 psi using a stainless steel autoclave for 1 h. The mixture of Pt (black) in water was then added to a solution of triol **46** (10 mg, 0.022 mmol) and $NaHCO_3$ (20 mg) in acetone (12 mL) and 2-propanol (3 mL). The reaction mixture was heated to 50 °C while oxygen was bubbled through the solution, until analysis by LC-MS indicated complete conversion of triol **36** (about 2−3 h). The catalyst was filtered off, and the solution was concentrated to dryness. The residue was dissolved in EtOAc, washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue thus obtained was purified by preparative TLC (EtOAc/*i*-PrOH/H_2O, 85:10:5) to give 9.5 mg (91%) of (+)-ambruticin S (**1a**) as an amorphous, off-white solid: ^1H NMR (700 MHz, CD_3OD) δ 5.61−5.60 (m, 1H), 5.52 (dd, J = 15.4, 6.6 Hz, 1H), 5.48 (dd, J = 15.2, 6.5 Hz, 1H), 5.39 (dd, J = 15.4, 8.7 Hz, 1H), 5.27 (dq, J = 9.0, 1.1 Hz, 1H), 5.18 (ddd, J = 15.3, 8.8, 1.1 Hz, 1H), 4.11 (br s, 1H), 3.90−3.87 (m, 1H), 3.85 (dd, J = 10.8, 2.9 Hz, 1H), 3.56 (ddd, J = 11.5, 8.8, 5.0 Hz, 1H), 3.53 (dd, J = 9.2, 7.0 Hz, 1H), 3.13−3.09 (m, 1H), 2.99 (dd, J = 9.0, 9.0 Hz, 1H), 2.52 (dd, J = 15.3, 7.6 Hz, 1H), 2.46 (dd, J = 15.5, 5.3 Hz, 1H), 2.16−2.11 (m, 1H), 2.06 (ddd, J = 12.6, 5.0, 1.6 Hz, 1H), 1.91−1.86 (m, 1H), 1.81−1.75 (m, 1H), 1.66 (d, J = 1.3 Hz, 3H), 1.62 (d, J = 1.1 Hz, 3H), 1.59−1.52 (m, 1H), 1.51−1.48 (m, 1H), 1.36 (q, J = 12.0 Hz, 1H), 1.15−1.13 (m, 1H), 1.07−1.06 (m, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.06−1.04 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (176 MHz, CD_3OD) δ 174.8, 138.2, 136.20, 136.18, 136.0, 130.9, 126.9,126.1, 122.1, 81.8, 79.5, 79.4, 77.0, 73.32, 73.27, 41.6, 40.2, 36.3, 31.7, 31.1, 29.8, 26.6, 22.3, 21.7, 19.1, 13.4, 12.6, 8.7; IR (film, NaCl) 3368, 2959, 2920, 2851, 1713, 1452, 1378, 1063, 963 cm^{-1}; $[\alpha]_D$ +54.2° (*c* 0.24, $CHCl_3$); HRMS (ESI) calcd for $C_{28}H_{41}O_6$ $(M-H)^-$ 473.2909, found 473.2895.

(2*S*,3*R*,4*S*,6*R*)-2-((*E*)-2-((1*S*,2*S*,3*R*)-2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-yl)-3-methylhexa-1,4-dien-1-yl)-3-methylcyclopropyl)vinyl)-6-(2-(formyloxy)ethyl)-tetrahydro-2*H*-pyran-3,4-diyl Diformate (47). To a cold (0 °C) solution of triol **46** (6 mg, 0.013 mmol), DMAP (5 mg, 0.041 mmol), and *i*-Pr_2NEt (47 μL, 0.27 mmol) in CH_2Cl_2 (2 mL) was added *N*-formylbenzotriazole (33 mg, 0.22 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The residue obtained after concentration of the reaction mixture *in vacuo* was purified by flash chromatography (hexane/EtOAc, 4:1 to 2:1) to yield 6 mg (85%) of triformate **47** as an off-white solid. Recrystallization from ethanol gave colorless crystals: mp 93−94 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.05 (s, 2H), 5.60 (d, J = 4.7 Hz, 1H), 5.49 (dd, J = 15.1, 6.4 Hz, 1H), 5.42 (dd, J = 15.3, 8.6 Hz, 1H), 5.35 (dd, J = 15.3, 7.4 Hz, 1H), 5.28 (d, J = 8.9 Hz, 1H), 5.18−5.14 (m, 1H), 5.08 (dd, J = 15.2, 8.9 Hz, 1H), 4.94 (t, J = 9.5 Hz, 1H), 4.35−4.27 (m, 2H), 4.13 (br s, 1H), 3.87 (dd, J = 10.8, 2.4 Hz, 1H), 3.70−3.65 (m, 1H), 3.76 (dd, J = 9.1, 7.8 Hz, 1H), 3.12−3.06 (m, 1H), 2.24 (dd, J = 11.9, 4.5 Hz, 1H), 2.17−2.11 (m, 1H), 1.98−1.92 (m, 1H), 1.90−1.84 (m, 2H), 1.83−1.77 (m, 1H), 1.67 (s, 3H), 1.62 (s, 3H), 1.61−1.53 (m, 2H), 1.50−1.44 (m, 1H), 1.15−1.09 (m, 1H), 1.10−1.03 (m, 7H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 160.9, 160.1, 159.8, 140.0, 135.6, 135.08, 135.03, 129.5, 125.0, 122.2, 120.9, 79.0, 78.0, 77.8, 71.8, 71.6, 71.5, 60.4, 36.4, 35.0, 34.1, 30.1, 29.7, 29.3, 25.6, 21.3, 21.1, 19.0, 13.0, 12.2, 8.2; HRMS (ESI) calcd for $C_{31}H_{48}NO_8$ $(M + NH_4)^+$ 562.3374, found 562.3365.

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Supporting Information Available: Experimental procedures for compounds **5**, **29**, and **48**−**50**, spectroscopic data, details of the crystallographic analysis, including CIF files, of compounds **28** and **47**, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.