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ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 11437–11449

Domino intramolecular enyne metathesis/cross metathesis approach to the xanthanolides. Enantioselective synthesis of (+)-8-*epi*-xanthatin

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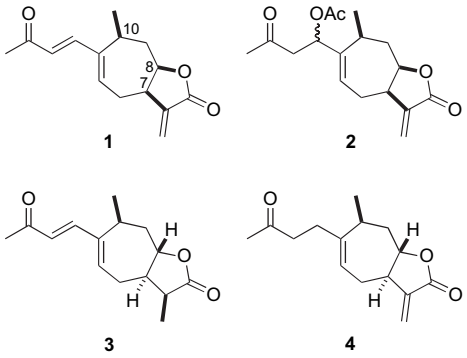
Received 14 April 2006; accepted 9 May 2006
Available online 2 June 2006

Abstract—The first total synthesis of (+)-8-*epi*-xanthatin (**1**) has been achieved in 14 steps starting from the commercially available ester **24**, which was converted into aldehyde **23** in six steps. An enantioselective aldol reaction of **23** gave **30**, which was transformed into triflate **22** in four steps, setting the stage for a palladium-catalyzed carbonylation reaction to form acrylate **34**. Compound **34** was then subjected to a deprotection/lactonization sequence to furnish enyne **21**, which underwent a domino enyne ring-closing metathesis/cross metathesis process to form a seven-membered carbocycle and (*E*)-conjugated dienone, thereby completing the synthesis of **1**. This domino ruthenium-catalyzed metathesis reaction thus serves as an efficient method to construct the core of xanthanolide and other sesquiterpene lactones.

1. Introduction

The xanthanolide sesquiterpene lactones are isolated primarily from the genus *Xanthium* (family Compositae). The phytochemical composition of this genus is quite homogeneous, and xanthanolides are isolated from every species.[1] The xanthanolides can be divided into two structural classes depending upon the stereochemistry at C(8), although both are characterized by a five-membered γ-butyrolactone that is fused to a seven-membered carbocycle. The xanthumin class is exemplified by (+)-8-*epi*-xanthatin (**1**) and xanthumin (**2**), which comprise a *cis*-fused γ-butyrolactone, whereas (−)-dihydroxanthatin (**3**) and 8-*epi*-tomentosin (**4**) are representative of the xanthinin class and incorporate a *trans*-fused lactone. 8-*epi*-Xanthatin has not only been isolated from various species in the genus *Xanthium*,[1c,2] but it has also been obtained by elimination of acetic acid from **2**.[3]

The structures of numerous xanthanolides are well documented, and many, including **1**, exhibit interesting biological profiles. For example, xanthanolides **1** and **2** have been shown to halt the larval growth of *Drosophila melanogaster* (fruit fly) at doses as small as 1.3 mg of **1** or **2** in 2 g of growth medium.[2b] Compounds **1** and **2** also display antimalarial activity against the chloroquine resistant *Plasmodium falciparum* strain K1 with IC_{50} values of 125 and 31 μg/mL, respectively.[4] More recently, **1** has been shown to inhibit the in vitro proliferation of several cultured human tumor cell lines, including A-549 (lung adenocarcinoma), SK-OV-3 (ovarian adenocarcinoma), SK-MEL-2 (malignant melanoma), XF-498 (central nervous system carcinoma), and HCT-15 (colon adenocarcinoma) with ED_{50} values ranging between 0.2 and 1.5 μg/mL (IC_{50} values ranging between 0.8 and 6.1 μM).[5] Because **4** was found to be inactive toward these tumor cell lines, it is apparent that the α-methylene-γ-butyrolactone and the conjugated enone functionalities contribute to cytotoxicity.[5a,6] In conjunction with these tumor inhibition studies, **1** was found to inhibit the in vitro farnesylation of human lamin-B by farnesyltransferase in a dose-dependent manner (IC_{50}=64 μM).[5b]



Keywords: Cross metathesis; Ring-closing metathesis; Enantioselective; Domino reactions.
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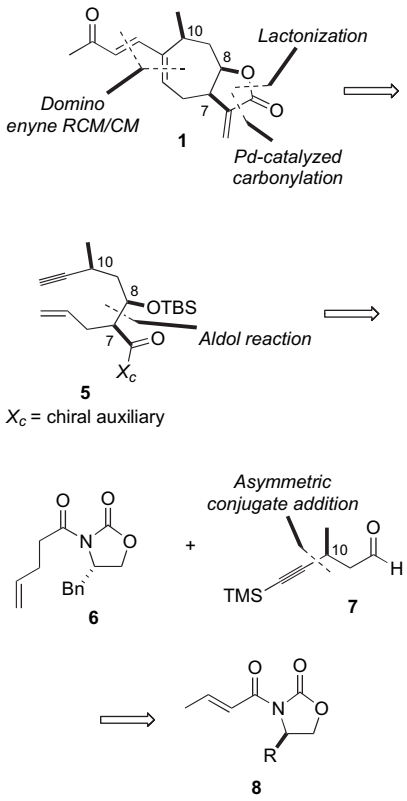
0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.05.019

Despite their promising biological activities and interesting structures, there have been few accounts of synthetic efforts directed toward the xanthanolide core.[7] In the first reported total synthesis of a xanthanolide, Morken utilized a stereoselective Oshima–Utimoto reaction[8] and sequential ruthenium-catalyzed metathesis reactions to synthesize **3**.[9] Our contemporaneous interest in 8-*epi*-xanthatin arose as a result of our ongoing efforts to expand the scope of ruthenium-catalyzed ring-closing metathesis (RCM) reactions in the context of natural product total synthesis. We have recently applied RCM cyclizations to the syntheses of a number of complex targets including dihydrocorynantheol[10] as well as the anticancer alkaloids manzamine A,[11] FR900482,[12] and (−)-peduncularine[13] together with the potent nicotinic acetylcholine receptor (+)-anatoxin-a.[14] In the context of these studies, we envisioned that an attractive strategy for constructing the xanthanolide core and the (*E*)-conjugated dienone present in many of the members of this class of natural products might feature a domino enyne RCM/cross metathesis (CM) process. Despite the extensive use of enyne RCM reactions in organic synthesis,[15] there are few applications of this reaction coupled with a subsequent CM in a domino sequence.[16] Coupled with the biological activity profiles of the xanthanolides and a lack of synthetic approaches for their construction, we undertook the total synthesis of (+)-8-*epi*-xanthatin (**1**), the details of which we report in this account.[17]



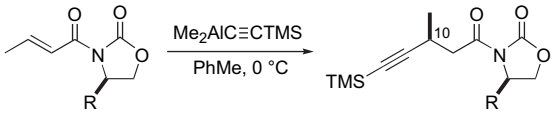
Scheme 1.

2. Results and discussion

2.1. First generation approach

In our first approach to **1**, we targeted enyne **5** as a versatile gateway because it contains the requisite absolute stereochemistry at C(7)–C(8) and C(10) as well as the appropriate functional handles for completing the synthesis (Scheme 1). This advanced intermediate would allow for the construction of the seven-membered cycloheptene ring and (*E*)-conjugated dienone moieties via a domino enyne RCM/CM sequence prior to installing the reactive α-methylene-γ-butyrolactone functionality. We envisaged the assembly of enyne **5** via an asymmetric aldol reaction[18] between the known oxazolidinone **6**[19] and the functionalized aldehyde **7**, which in turn would be assembled using an asymmetric conjugate addition of an appropriate metal acetylide to the chiral *N*-enoyloxazolidinone **8**. For example, Kunz has shown that dialkylaluminum chlorides as well as mixed organoaluminum reagents participate in diastereoselective conjugate additions to *N*-enoyloxazolidinones derived from amino acids and carbohydrates.[20,21]

In accordance with the above retrosynthetic analysis, we began to explore reaction conditions for constructing aldehyde **7** via a diastereoselective conjugate addition of an aluminum acetylide species to the chiral *N*-enoyloxazolidinones **8a–c** (Scheme 2). In a preliminary experiment, we found that reaction of **8a**[22] and the organoaluminum species derived from the transmetalation of lithium (trimethylsilyl)acetylene with Me_2AlCl at 0 °C delivered the desired 1,4-addition product **9a** in 93% yield (dr=1.9:1)[23] (Scheme 2).[24] Inspired by these results, we reasoned that increasing the steric bulk at the 4-position of the oxazolidinone might improve the diastereoselectivity of the pivotal conjugate addition. The known acyl oxazolidinone **8b**[25] and the new acyl oxazolidinone **8c** were therefore prepared (Scheme 3). The synthesis of **8c** commenced with the treatment of L-serine methyl ester hydrochloride (**10**) with phosgene to afford a known intermediate oxazolidinone,[26] which was allowed to react with excess 2-naphthyllithium to provide tertiary alcohol **11**. Alcohol **11** was deoxygenated according to the method of Gribble to afford **12**,[27] which was acylated with (*E*)-crotonyl chloride to provide **8c**. The conjugate addition reactions employing **8b** and **8c** provided the adducts **9b** and **9c** with roughly a twofold enhancement in the diastereomeric ratio obtained with **8a** (Scheme 2). Although the yield of **9b** was comparable to that of **9a**, the yield of **9c** was somewhat lower.



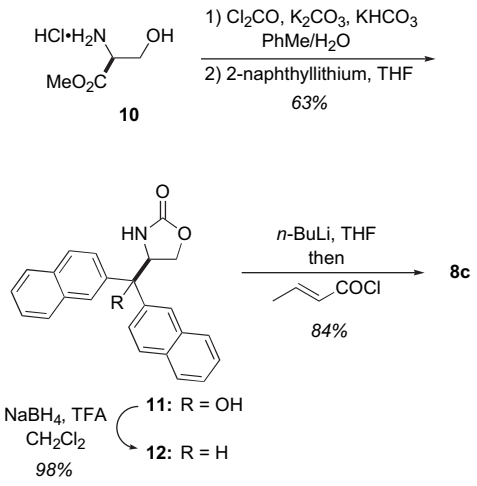
8a: R = Ph
b: R = $CH(Ph)_2$
c: R = $CH(2\text{-naphthyl})_2$

9a: *93%* (*dr* = 1.9:1)[a]
b: *92%* (3.4:1)
c: *78%* (3.2:1)

[a]The *dr* reflects the ratio of C(10*S*:10*R*) (see ref 24).

Scheme 2.

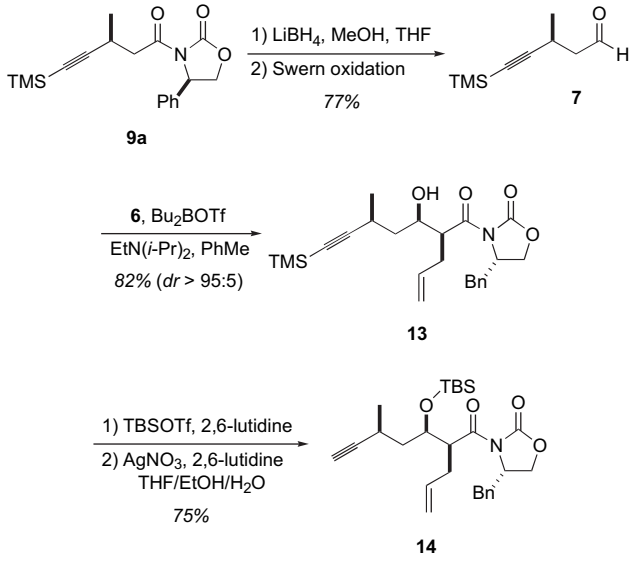
Although the stereoinduction provided by the chiral oxazolidinones in **8a–c** was modest, these auxiliaries did indeed afford the addition products with the appropriate stereochemistry at C(10).[24] In an effort to improve upon the diastereoselectivity obtained during these addition reactions, we turned our attention to the method of Schwartz, who



Scheme 3.

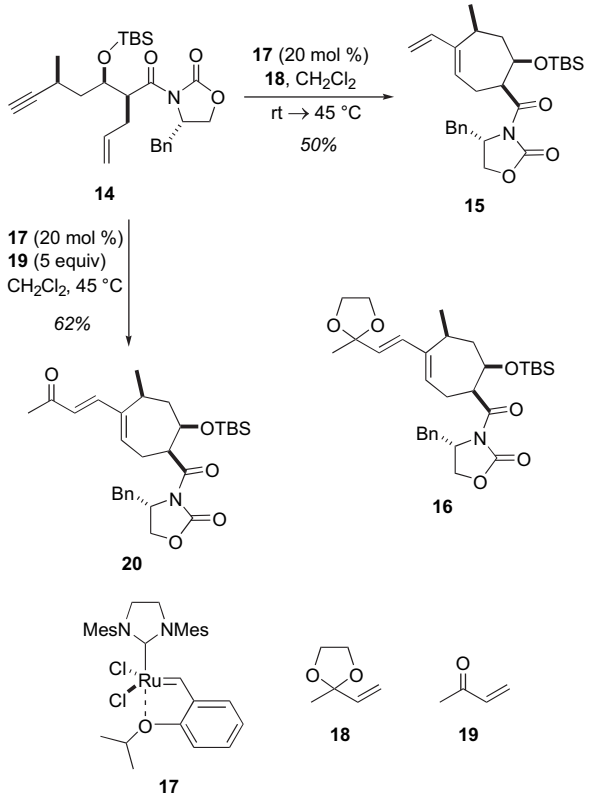
developed a procedure for the nickel(I)-catalyzed conjugate addition of aluminum acetylides to achiral enones.[28] We queried whether use of a nickel acetylide species might lead to improved diastereoselection. However, when we applied the Schwartz protocol without added chiral ligands to additions to **8a–c**, **9a–c** were formed in lower yields (<70%) with no diastereoselectivity.[29]

Although we had not been able to secure **9a** with high diastereoselectivity, it was possible to separate it from the minor C(10) epimer so we could examine the viability of the key domino enyne RCM/CM reaction.[24] Toward this end, imide **9a** was reduced, and the resulting alcohol was oxidized under Swern conditions to provide aldehyde **7** (Scheme 4).[30] The boron-mediated asymmetric aldol reaction between **7** and oxazolidinone **6** proceeded in 82% yield and excellent diastereoselectivity (dr>95:5)[23] to afford **13**. This aldol reaction proceeded in highest yield when toluene was used as the solvent and EtN(*i*-Pr)$_2$ as the base; employing CH_2Cl_2 as the solvent and Et_3N as the base consistently gave **13** in 10–20% lower yield. Protection of the secondary alcohol as a *tert*-butyldimethylsilyl ether followed by deprotection of the alkyne provided **14**.[31]



Scheme 4.

With **14** in hand, we explored conditions to effect the key enyne RCM/CM transformation. The phosphine-free ruthenium catalyst **17**[32] was employed owing to its reported superiority in tandem RCM/CM reactions.[16b] We first conducted the domino enyne RCM/CM sequence using dioxolane **18**,[33] which has been found to participate in CM reactions,[34] because its use would introduce the requisite enone moiety in a suitably protected form. In this way, subsequent transformation of the oxazolidinone moiety in **15** to the α-methylene-γ-butyrolactone could be performed without additional protection/deprotection steps (Scheme 5). However, the enyne RCM/CM reaction of **14** and **18** gave only the cyclic diene **15** (50%) with the remainder of the mass balance corresponding to the homodimer of **15**;[35] none of the desired **16** was isolated. When the metathesis reaction was conducted under an atmosphere of ethylene, **15** was produced in 59% yield, but **16** was still not detected in the reaction mixture. Interestingly, formation of the homodimer of **15** was completely suppressed under these conditions. Failing in these attempts to perform a domino RCM/CM, we examined the simple CM reaction of **15** with **18** as a route to **16**, but all such experiments were unavailing, even when large excesses of **18** were used; only **15** was recovered. These results led us to the inescapable conclusion that the protected enone **18** was not a suitable coupling partner for this particular CM reaction.



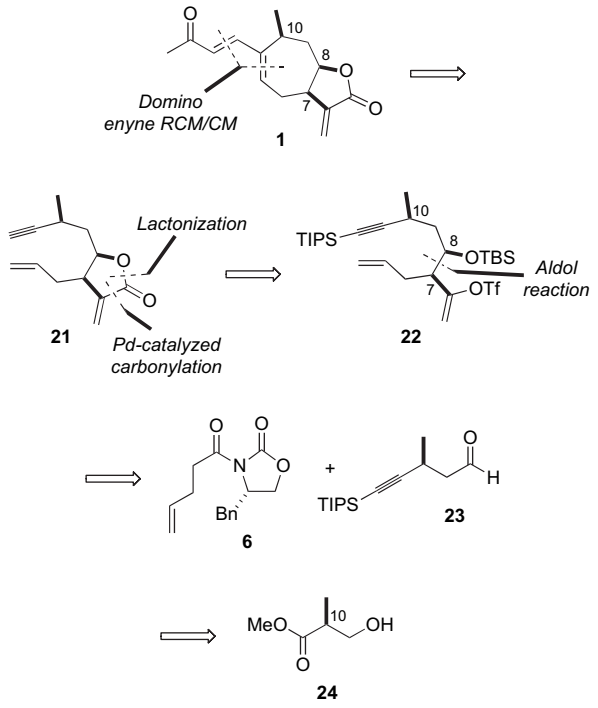
Scheme 5.

In the wake of these disappointments, we were pleased to discover that the domino RCM/CM reaction of enyne **14** and methyl vinyl ketone (**19**) proceeded cleanly to provide **20** in 62% yield.[36] This result was indeed promising as it nicely supported our original hypothesis that we could induce a domino enyne RCM/CM reaction to assemble the

seven-membered ring and pendant enone found in the xanthanolides.

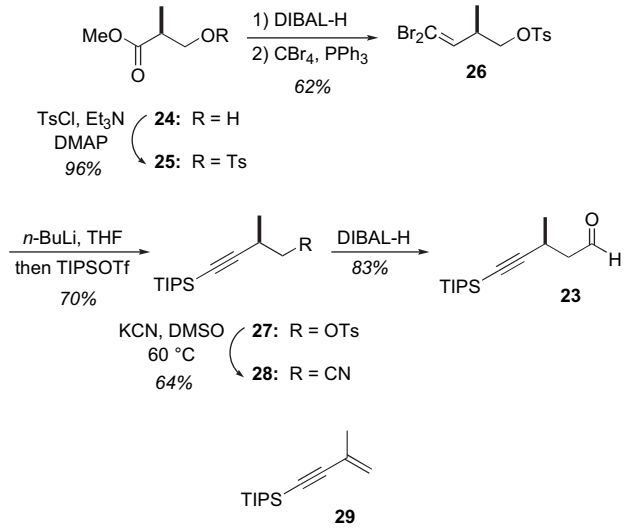
2.2. Second-generation approach

Inasmuch as the conjugate additions of aluminum acetylides to *N*-enoyloxazolidinones proceeded with modest diastereoselectivity, we queried whether an alternative route to the synthesis of **1** would prove viable. Moreover, it occurred to us that incorporating the α-methylene-γ-butyrolactone prior to the key domino RCM/CM sequence would enable us to minimize unproductive functional group manipulations. Indeed, Paquette had shown that the α-methylene-γ-butyrolactone functionality is stable to the conditions of ruthenium-catalyzed RCM reactions.[37] A second-generation strategy was thus designed in which the lactone moiety in **21** would be elaborated via a palladium-catalyzed carbonylation of the enol triflate **22** followed by a lactonization (Scheme 6). The stereocenters at C(7)–C(8) in **22** would be assembled by an asymmetric aldol reaction of oxazolidinone **6** and aldehyde **23**, whereas the remaining stereocenter at C(10) would be obtained from enantiomerically pure **24**, which is commercially available.



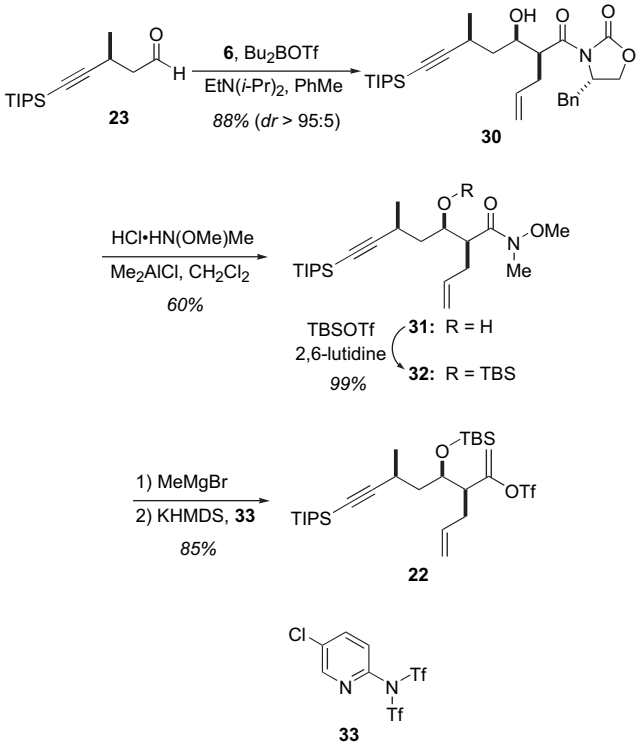
Scheme 6.

The first step in reducing the strategy in Scheme 6 to practice involved converting the ester **24** into the tosylate **25** (Scheme 7). Reduction of the ester moiety and application of the Corey–Fuchs homologation[38] protocol to the resulting aldehyde delivered vinyl dibromide **26**, which upon treatment with *n*-BuLi and trapping the lithium acetylide generated in situ with TIPSOTf afforded alkyne **27**. Displacement of the primary tosylate in **27** with potassium cyanide afforded the corresponding nitrile **28** in modest yield (64%) owing to competitive β-elimination to form enyne **29** (20%). Reduction of nitrile **28** with DIBAL-H afforded aldehyde **23**.[39]



Scheme 7.

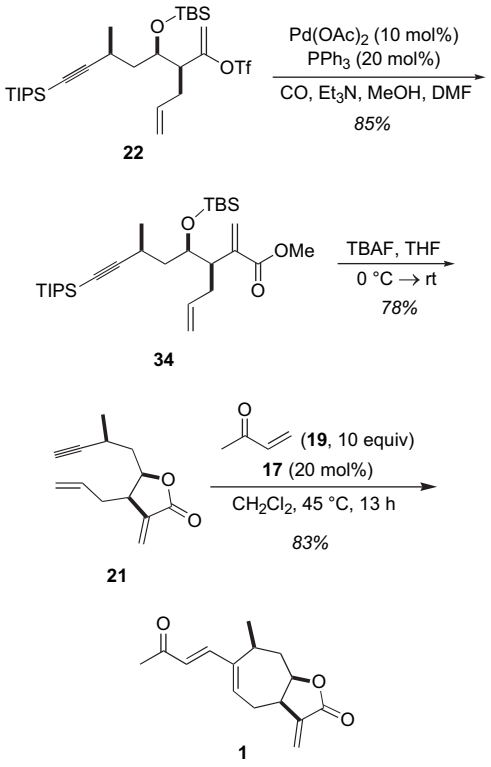
The aldol coupling reaction between **23** and **6** proceeded in good yield to afford **30** with excellent diastereoselectivity (dr>95:5)[23] (Scheme 8). The secondary alcohol group of the *N*,*O*-dimethyl amide **31**, which was prepared from **30** using the method of Weinreb,[40] was protected as its *tert*-butyldimethylsilyl ether to deliver **32**. Subsequent treatment of amide **32** with MeMgBr provided the corresponding ketone, which was readily transformed into the requisite enol triflate **22** in 85% overall yield by kinetic deprotonation using KHMDS and trapping of the resultant enolate with *N*-(5-chloro-2-pyridyl)triflimide (**33**).[41]



Scheme 8.

The final phase of the synthesis was initiated with the palladium-catalyzed carbonylation of **22** in the presence of

MeOH to deliver acrylate **34** in 85% yield (Scheme 9).[42] Simultaneous removal of the two silyl protecting groups and intramolecular lactonization was effected with TBAF to afford **21** in 78% yield,[43] thereby setting the stage for the pivotal domino enyne RCM/CM sequence. In the event, reaction of enyne **21** and enone **19** in the presence of catalyst **17** provided **1** in 83% yield. The ^{1}H and ^{13}C NMR spectral data of the synthetic **1** thus obtained were consistent with those previously reported.[2b,5a,b,44,45] Moreover, it exhibited an optical rotation $\{[\alpha]_D^{24}$ +23.4 (*c* 0.333, $CHCl_3$)} in close accord with the previously reported value $\{[\alpha]_D^{20}$ +25 (*c* 0.5, $CHCl_3$)}.[5b]



Scheme 9.

3. Conclusions

The first total synthesis of the sesquiterpene lactone (+)-8-*epi*-xanthatin has been completed by a route that required only 14 steps in the longest linear sequence and proceeded in an overall yield of 5.5%. The essential elements of the approach comprise a sequence for palladium-catalyzed carbonylation and lactonization to construct the α-methylene-γ-butyrolactone functionality and a domino enyne RCM/CM process to elaborate the seven-membered carbocycle with its pendant enone array. Indeed, the synthesis underscores the significant utility of domino ruthenium-catalyzed metathesis reactions for the rapid construction of functionalized, polycyclic ring systems that are found in natural products. During the course of these studies, we also investigated aluminum-mediated conjugate addition reactions to chiral α,β-unsaturated imides. Other applications of olefin metathesis to solve challenging problems in total synthesis are under active investigation in our laboratories, and the results of these studies will be disclosed in due course.

4. Experimental

4.1. General

Unless otherwise indicated, all starting materials and solvents were obtained from commercial suppliers and used without further purification. All solvents contained less than 50 ppm H_2O by Karl Fisher coulometric moisture analysis. Tetrahydrofuran (THF) was dried by passage through two columns of activated neutral alumina and stored under argon. Methanol (MeOH) and dimethylformamide (DMF) were dried by passage through two columns of activated molecular sieves and stored under argon. Toluene (PhMe) was first passed through a column of neutral alumina, then through a column of Q5 reactant and stored under argon. Methylene chloride (CH_2Cl_2), triethylamine (Et_3N), 2,6-lutidine, Hünig's base ($EtN(i\text{-}Pr)_2$), trimethylsilyl chloride (TMSCl), triisopropyl silyltrifluoromethanesulfonate (TIPSOTf), and dimethylsulfoxide (DMSO) were distilled from calcium hydride and used immediately. Reactions involving air or moisture-sensitive reagents or intermediates were performed in flame-dried glassware under an atmosphere of dry nitrogen or argon. All reaction temperatures are reported as the temperature of the surrounding bath. Flash chromatography was performed following the Still[46] protocol with ICN Silitech 32-63 D 60A silica gel with the indicated solvents. Analytical thin layer chromatography was performed using Merck 250 micron 60F-254 silica plates. The plates were visualized with ultraviolet light, potassium permanganate, or ceric ammonium molybdate. Proton (^{1}H) and carbon (^{13}C) NMR spectra were obtained using a Varian Unity Plus (400 MHz) or Varian Unity Plus (500 MHz) spectrometer as solutions in $CDCl_3$, unless otherwise indicated. Chemical shifts are reported as parts per million (ppm, δ) and referenced to the residual protic solvent. Coupling constants are reported in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet; comp, complex multiplet; app, apparent. Low-resolution chemical ionization mass spectra (CI) were obtained on a Finnigan TSQ-70 instrument in positive ionization mode. High-resolution mass spectra (HRMS) were obtained on a VG Analytical ZAB-2E instrument in positive ionization mode. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR either neat or as solutions in $CDCl_3$ on sodium chloride plates or as a KBr pellet and are reported in wavenumbers (cm^{-1}). Melting points are uncorrected. Percent yields are given for compounds that were ≥95% pure as judged by ^{1}H NMR spectroscopy.

4.1.1. (3*S*)-(3-Methyl-5-trimethylsilanylpent-4-ynoyl)-(4*R*)-phenyloxazolidin-2-one (9a). A solution of *n*-BuLi (2.46 M in hexane, 4.4 mL, 11.0 mmol) was added dropwise to a solution of (trimethylsilyl)acetylene (1.5 mL, 11.0 mmol) in PhMe (80 mL) at 0 °C. The mixture was stirred at this temperature for 0.5 h, whereupon the cooling bath was removed and stirring continued at room temperature for an additional 0.5 h. The solution was then cooled to 0 °C, whereupon Me_2AlCl (1.0 M in hexane, 11.0 mL, 11.0 mmol) was added dropwise and stirring continued for 0.5 h. To this mixture was added a solution of **8a** (998 mg, 4.32 mmol) in PhMe (30 mL), and stirring was continued at 0 °C for 0.5 h. The reaction was then slowly quenched by the sequential addition of saturated aqueous Rochelle's

salt (40 mL), H_2O (40 mL), and EtOAc (50 mL). The resulting mixture was stirred at room temperature overnight and then extracted with EtOAc (3×20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_2O/pentane (2:1) to afford 873 mg (61%) of the desired major diastereomer **9a** as a colorless solid and 458 mg (32%) of the undesired adduct (10*R*)-**9a** as a colorless solid.

Major diastereomer (**9a**): mp=24–25 °C; ^{1}H NMR (500 MHz) δ 7.38–7.26 (comp, 5H), 5.44–5.38 (m, 1H), 4.69–4.65 (m, 1H), 4.27–4.24 (m, 1H), 3.22 (app d, *J*=6.1 Hz, 1H), 3.06–2.94 (comp, 2H), 1.17 (d, *J*=6.8 Hz, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz) δ 170.3, 153.6, 138.9, 129.2, 128.7, 125.9, 109.8, 84.5, 70.0, 57.7, 42.4, 22.7, 20.8, 0.1; IR ($CDCl_3$) 2958, 2173, 1784, 1713, 1384, 1197, 843 cm^{-1}; mass spectrum (CI) *m*/*z* 330.1542 [$C_{18}H_{24}NO_3Si$ (M+1) requires 330.1526], 330 (base), 314.

Minor diastereomer (10*R*)-**9a**: mp=25–26 °C; ^{1}H NMR (500 MHz) δ 7.38–7.26 (comp, 5H), 5.42 (dd, *J*=8.8, 3.8 Hz, 1H), 4.67 (t, *J*=8.8 Hz, 1H), 4.26 (dd, *J*=8.8, 3.8 Hz, 1H), 3.21–3.14 (m, 1H), 3.04–2.95 (comp, 2H), 1.14 (d, *J*=6.8 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (125 MHz) δ 170.3, 153.7, 139.0, 129.2, 128.7, 125.9, 109.7, 84.7, 70.0, 57.6, 42.2, 23.0, 20.8, 0.1; IR (neat) 2959, 2171, 1786, 1708, 1386, 1198, 843 cm^{-1}; mass spectrum (CI) *m*/*z* 330.1537 [$C_{18}H_{24}NO_3Si$ (M+1) requires 330.1526], 330 (base), 314.

4.1.2. (4*R*)-Benzhydryl-3-[(3*S*)-methyl-5-trimethylsilanylpent-4-ynoyl]oxazolidin-2-one (9b). Prepared as a white foam in 71% yield along with 21% yield of the undesired adduct (10*R*)-**9b** as a white foam according to the procedure described above for **9a**.

Major diastereomer (**9b**): mp=24–25 °C; ^{1}H NMR (500 MHz) δ 7.34–7.27 (comp, 5H), 7.26–7.24 (m, 1H), 7.12–7.10 (comp, 2H), 7.08–7.06 (comp, 2H), 5.32–5.29 (m, 1H), 4.75 (d, *J*=5.0 Hz, 1H), 4.46–4.39 (comp, 2H), 3.11–2.94 (comp, 3H), 1.19 (app dd, *J*=6.9, 1.7 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz) δ 170.6, 153.3, 139.5, 137.9, 129.4, 128.9, 128.7, 128.3, 127.9, 127.1, 110.2, 84.5, 64.7, 56.2, 50.2, 42.5, 22.6, 20.8, 0.2; IR (neat) 2962, 2165, 1784, 1704, 1389, 1280, 1249, 1212, 838, 756, 697 cm^{-1}; mass spectrum (CI) *m*/*z* 420.1986 [$C_{25}H_{30}NO_3Si$ (M+1) requires 420.1995], 420 (base), 404, 326, 254, 167.

Minor diastereomer (10*R*)-**9b**: mp=25–26 °C; ^{1}H NMR (500 MHz) δ 7.34–7.26 (comp, 5H), 7.24–7.20 (m, 1H), 7.17–7.14 (comp, 2H), 7.10–7.07 (comp, 2H), 5.34–5.30 (m, 1H), 4.67 (d, *J*=5.8 Hz, 1H), 4.43–4.36 (comp, 2H), 3.04 (dd, *J*=15.9, 6.8 Hz, 3H), 2.96 (app sext, *J*=6.7 Hz, 1H), 2.87 (dd, *J*=15.9, 6.4 Hz, 1H), 1.13 (app d, *J*=6.6 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (125 MHz) δ 170.4, 153.3, 139.5, 138.0, 129.3, 128.9, 128.7, 128.4, 127.9, 127.1, 109.8, 84.9, 65.2, 56.3, 51.0, 42.3, 22.9, 20.9, 0.1; IR (neat) 2966, 2167, 1784, 1702, 1496, 1455, 1390, 1367, 1249, 1208, 1114, 844, 756, 703 cm^{-1}; mass spectrum (CI) *m*/*z* 420.1985 [$C_{25}H_{30}NO_3Si$ (M+1) requires 420.1995], 420 (base), 404, 326, 167.

4.1.3. (4*R*)-[(Dinaphthalen-2-yl)methyl]-3-[(3*S*)-methyl-5-trimethylsilanylpent-4-ynoyl]oxazoldin-2-one [(10*S*)-9c] and [(10*R*)-9c]. Prepared as a white foam in 78% yield according to the procedure described above for **9a** (dr= 3.2:1); mp (mixture)=24–25 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (mixture of diastereomers) δ 7.95–7.82 (comp, 6.5H), 7.76 (br s, 1H), 7.70 (br s, 1H), 7.56–7.48 (comp, 4H), 7.32 (dd, *J*=8.6, 1.8 Hz, 0.28H), 7.27 (dd, *J*=8.5, 1.7 Hz, 0.78H), 7.21 (overlapping pair of dd, *J*=8.3, 1.8 Hz for the minor set, and *J*=8.6, 1.8 Hz for the major set, total integral is 1H), 5.45–5.50 (m, 1H), 4.91 (d, *J*=4.1 Hz, 0.76H), 4.86 (d, *J*=5.1 Hz, 0.26H), 4.78–4.71 (m, 1H), 4.55 (dd, *J*=9.2, 2.3 Hz, 0.72H), 4.51 (dd, *J*=9.2, 2.3 Hz, 0.25H), 3.11 (dd, *J*=16.7, 6.6 Hz, 0.73H), 2.98–2.82 (comp, 2.23H), 1.11 (d, *J*=6.8 Hz, 2.33H), 0.98 (d, *J*=6.2 Hz, 0.75H), 0.13 (s, 6.3H), 0.11 (s, 2.1H); ^{13}C NMR (125 MHz, DMSO-d_6) (mixture of diastereomers) δ 170.4, 169.9, 153.6, 153.5, 137.6, 137.5, 136.4, 136.3, 133.2, 133.1, 133.0, 132.5, 132.1, 128.7, 128.6, 128.5, 128.3, 128.2, 127.9, 127.9, 127.7, 127.6, 126.8, 126.6, 126.5, 126.4, 126.2, 111.6, 110.8, 85.5, 84.2, 65.2, 64.8, 55.8, 50.7, 50.1, 42.3, 23.0, 22.5, 20.7, 20.5, 0.4, 0.3 δ; IR (neat) 2962, 2164, 1782, 1704, 1385, 1249, 1212, 842, 759 cm^{-1}; mass spectrum (CI) *m*/*z* 520.2306 [$C_{33}H_{34}NO_3Si$ (M+1) requires 520.2308], 520, 267 (base).

4.1.4. (4*R*)-[Hydroxy(dinaphthalen-2-yl)methyl]oxazolidin-2-one (11). A solution of *tert*-BuLi (1.7 M in pentane, 2.8 mL, 4.7 mmol) was added dropwise via syringe to a solution of 2-bromonaphthalene (0.49 g, 2.4 mmol) in THF (5 mL) at −78 °C. The resulting yellowish-green slurry was stirred at −78 °C for 10 min, whereupon the mixture was transferred to a 0 °C bath and stirring continued for 10 min. The mixture was cooled to −78 °C, whereupon a solution of the oxazolidinone derived from **10**[25] (0.11 g, 0.76 mmol) in THF (2 mL) was added via cannula. The mixture was stirred at −78 °C for 1 h, whereupon a saturated aqueous solution of NH_4Cl (10 mL) was added and the cooling bath removed. The mixture was poured into brine (30 mL), and the biphasic mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was dissolved in a minimal volume of DMSO and purified by flash chromatography eluting with EtOAc/hexanes (4:1) to afford 188 mg (67%) of **11** as a white solid (63% from **10**); mp=197–199 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15–8.14 (m, 1H), 8.10–8.09 (m, 1H), 7.92 (br t, *J*=7.8 Hz, 2H), 7.83–7.81 (comp, 2H), 7.77 (dd, *J*=9.0, 3.8 Hz, 2H), 7.70 (br s, 1H), 7.52–7.45 (comp, 6H), 6.30 (s, 1H), 5.29–5.26 (m, 1H), 4.32 (t, *J*=8.8 Hz, 1H), 4.21 (dd, *J*=8.6, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.1, 142.0, 141.9, 132.6, 132.5, 131.9, 131.8, 128.3, 128.2, 127.7, 127.4, 127.3, 127.2, 126.1, 126.0, 125.9, 125.8, 125.4, 125.1, 124.7, 124.3, 77.9, 65.0, 57.5; IR (KBr) 3402, 1732, 1416, 1236, 1033, 754 cm^{-1}; mass spectrum (CI) *m*/*z* 370. 1453 [$C_{24}H_{20}NO_3$ (M+1) requires 370.1443], 370 (base), 352, 283, 169.

4.1.5. (4*R*)-[(Dinaphthalen-2-yl)methyl]oxazolidin-2-one (12). TFA (3 mL) was added dropwise via syringe to a slurry of **11** (185 mg, 0.501 mmol) and $NaBH_4$ (95 mg, 2.5 mmol) in CH_2Cl_2 (7 mL) at room temperature, during which time a vigorous evolution of H_2 was observed. The reaction mixture was stirred at room temperature for 21 h, diluted with

H_2O (10 mL), and neutralized (pH=7) by the addition of solid KOH pellets. The resulting biphasic mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude yellow solid thus obtained was purified by recrystallization from MeOH–hexanes. The crystals were collected by vacuum filtration, rinsed with cold hexanes (2×5 mL), and dried under reduced pressure to afford 173 mg (98%) of **12** as an off-white crystalline solid; mp=120–122 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (br d, J=3.6 Hz, 2H), 7.91–7.86 (comp, 3H), 7.84–7.80 (comp, 4H), 7.53–7.42 (comp, 6H), 5.06–5.01 (m, 1H), 4.40–4.36 (comp, 2H), 4.04–3.98 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.7, 139.0, 138.6, 133.1, 133.0, 132.0, 131.9, 128.2, 128.1, 127.8, 127.7, 127.5, 127.4, 126.8, 126.7, 126.6, 126.4, 126.3, 126.1, 125.9, 125.7, 67.9, 56.3, 54.2; IR (neat) 3274, 3053, 1756, 1404, 1239, 1026, 756 cm^{-1}; mass spectrum (CI) m/z 354.1492 [$C_{24}H_{20}NO_2$ (M+1) requires 354.1494], 355 (base), 267, 129.

4.1.6. 3-But-2-enoyl-(4*R*)-(dinaphthalen-2-ylmethyl)oxazolidin-2-one (8c). A solution of *n*-BuLi (2.36 M in hexanes, 63 μL, 0.15 mmol) was added to a solution of **12** (44 mg, 0.13 mmol) in THF (0.5 mL) at −78 °C, whereupon the mixture was stirred for an additional 0.5 h. To this mixture was added freshly distilled *trans*-crotonyl chloride (18 μL, 0.19 mmol). The solution was allowed to warm to room temperature over a 2 h period and then quenched by adding a solution of saturated aqueous NH_4Cl (2 mL). The resulting layers were separated, and the aqueous phase was extracted with EtOAc (3×2 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (2:3) to afford 44 mg (84%) of **8c** as a white solid; mp=48–51 °C; ^{1}H NMR (400 MHz) δ 7.88–7.74 (comp, 6H), 7.66–7.57 (comp, 2H), 7.54–7.45 (comp, 4H), 7.35–7.24 (comp, 3H), 7.20–7.08 (m, 1H), 5.62–5.58 (m, 1H), 5.14 (d, J=5.1 Hz, 1H), 4.57–4.48 (comp, 2H), 1.93 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 164.7, 153.2, 146.9, 137.1, 135.4, 133.2, 133.0, 132.6, 132.2, 128.5, 128.3, 127.7, 127.6, 127.5, 127.4, 127.1, 126.3, 126.2, 126.1, 126.0, 121.5, 64.7, 56.1, 50.8, 18.4; IR (neat) 3054, 2957, 2932, 2870, 1779, 1682, 1634, 1340, 1208, 749, 668 cm^{-1}; mass spectrum (CI) m/z 422.1752 [$C_{28}H_{24}NO_3$ (M+1) requires 422.1756], 422 (base), 354, 267.

4.1.7. (3*S*)-Methyl-5-trimethylsilanylpent-4-yn-1-ol. Solid $LiBH_4$ (49 mg, 2.1 mmol) and dry MeOH (78 μL, 1.9 mmol) were sequentially added to a solution of **9a** (637 mg, 1.93 mmol) in THF (19 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, whereupon the cooling bath was removed and stirring continued at room temperature for 8 h. The reaction was poured into a mixture of 25% aqueous NaOH (40 mL) and Et_2O (10 mL), and the resulting biphasic mixture was extracted with Et_2O (3×15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated at atmospheric pressure. The residue was purified by flash chromatography eluting with Et_2O/pentane (4:1) to afford 270 mg (82%) of the product as a yellow oil; ^{1}H NMR (400 MHz) δ 3.83–3.70 (comp, 2H), 2.66–2.55 (m, 1H), 1.93 (br s, 1H), 1.73–1.58 (comp, 2H), 1.17 (d, J=6.8 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (100 MHz) δ 111.2, 85.2, 61.2, 39.3, 23.9, 21.1, 0.1; IR (neat) 3350, 2961, 2167, 1250, 841, 760 cm^{-1}; mass spectrum (CI) m/z 171.1207 [$C_9H_{19}OSi$ (M+1) requires 171.1205], 171 (base), 155, 139.

4.1.8. (3*S*)-Methyl-5-trimethylsilanylpent-4-ynal (7). To a solution of oxalyl chloride (410 μL, 4.66 mmol) in CH_2Cl_2 (58 mL) at −78 °C DMSO (0.67 mL, 9.4 mmol) was added via syringe. The mixture was stirred at −78 °C for 15 min, whereupon a solution of the above alcohol (264 mg, 1.55 mmol) in CH_2Cl_2 (4 mL) was added via cannula and stirring continued for 1 h. Et_3N (2.6 mL, 19 mmol) was added via syringe, and the reaction mixture was transferred to a 0 °C bath and stirring continued for 0.5 h. The reaction was quenched by adding H_2O (15 mL) and poured into 1 N HCl (70 mL). The biphasic mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were dried ($MgSO_4$), filtered through a 0.5-in. plug of neutral Al_2O_3 rinsing with CH_2Cl_2 (300 mL) and Et_2O (200 mL), and concentrated at atmospheric pressure. The resulting crude residue was triturated with pentane (5 mL) and filtered. Concentration of the filtrate at atmospheric pressure afforded 246 mg (94%) of **7** as a yellow oil; ^{1}H NMR (400 MHz) δ 9.76 (t, J=2.1 Hz, 1H), 2.97 (app sext, J=6.8 Hz, 1H), 2.63–2.41 (comp, 2H), 1.21 (d, J=6.8 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (100 MHz) δ 201.1, 109.1, 85.7, 49.8, 21.5, 20.9, 0.1; IR (neat) 2962, 2169, 1714, 1410, 1250, 842, 760 cm^{-1}; mass spectrum (CI) m/z 169.1050 [$C_9H_{17}OSi$ (M+1) requires 169.1049], 169 (base).

4.1.9. 3-[(2*S*)-Allyl-(3*R*)-hydroxy-(5*S*)-methyl-7-trimethylsilanylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one (13). To a solution of oxazolidinone **6** (594 mg, 2.29 mmol) and EtN(*i*-Pr)$_2$ (400 μL, 2.29 mmol) in anhydrous PhMe (12 mL) at −78 °C was added Bu_2BOTf (570 μL, 2.30 mmol).[47] The mixture was stirred at −78 °C for 1 h, whereupon aldehyde **7** (285 mg, 1.69 mmol) in anhydrous PhMe (2 mL) was added dropwise via cannula. The mixture was stirred at −78 °C for 30 min and then at room temperature for 6 h. The mixture was cooled to 0 °C, whereupon pH 7.0 phosphate buffer (2 mL), MeOH (1 mL), and 30% H_2O_2 (500 μL) were added successively, and stirring was continued for 1 h. The mixture was poured into H_2O (30 mL), and the resulting biphasic mixture extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (3:2) to give 615 mg (82%) of **13** as a colorless oil (dr>95:5 by ^{1}H NMR); ^{1}H NMR (500 MHz) δ 7.33–7.29 (comp, 2H), 7.27–7.23 (m, 1H), 7.21–7.18 (comp, 2H), 5.89–5.80 (m, 1H), 5.13–5.09 (m, 1H), 5.05–5.02 (m, 1H), 4.72–4.67 (m, 1H), 4.25–4.19 (comp, 2H), 4.17–4.09 (comp, 2H), 3.28 (dd, J=13.5, 3.4 Hz, 1H), 2.75–2.69 (m, 1H), 2.68–2.55 (comp, 3H), 2.44–2.38 (m, 1H), 1.63–1.50 (comp, 2H), 1.18 (d, J=7.0 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (125 MHz) δ 174.8, 153.7, 135.3, 135.2, 129.4, 129.0, 127.4, 117.3, 110.9, 85.2, 70.4, 66.0, 55.6, 47.3, 40.5, 38.0, 32.1, 23.8, 21.4, 0.1; IR (neat) 3524, 2963, 2165, 1782, 1698, 1386, 1249, 1208, 1102, 842, 760, 701 cm^{-1}; mass spectrum (CI) m/z 428.2254 [$C_{24}H_{34}NO_4Si$ (M+1) requires 428.2257], 428 (base), 412, 356, 250.

4.1.10. 3-[(2*S*)-Allyl-(3*R*)-(*tert*-butyldimethylsilanyloxy)-(5*S*)-methyl-7-trimethylsilanylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one. To a solution of alcohol **13** (463 mg,

1.08 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C was added 2,6-lutidine (1.2 mL, 10.0 mmol) and TBDMSOTf (720 μL, 3.1 mmol). The resulting solution was stirred at 0 °C for 2 h, whereupon MeOH (3 mL) was added and the cooling bath removed. After warming to room temperature, the mixture was poured into H_2O (20 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (3:2) to give 536 mg (92%) of the product as a yellow oil; ^{1}H NMR (500 MHz) δ 7.32–7.28 (comp, 2H), 7.26–7.22 (m, 1H), 7.22–7.19 (comp, 2H), 5.90–5.81 (m, 1H), 5.14–5.09 (m, 1H), 5.04–5.01 (m, 1H), 4.64–4.59 (m, 1H), 4.25–4.21 (m, 1H), 4.17–4.14 (m, 1H), 4.12–4.03 (m, 1H), 3.28 (dd, J=13.3, 3.1 Hz, 1H), 2.67 (dd, J=13.3, 10.0 Hz, 1H), 2.58–2.48 (comp, 2H), 2.34–2.26 (m, 1H), 1.81–1.75 (m, 1H), 1.68–1.63 (m, 1H), 1.18 (d, J=6.9 Hz, 3H), 0.84 (s, 9H), 0. 13 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz) δ 174.0, 153.1, 135.5, 135.3, 129.5, 128.9, 127.3, 117.1, 111.4, 85.5, 71.9, 65.7, 56.0, 48.1, 41.5, 37.7, 33.1, 25.7, 24.0, 21.6, 18.0, 0.2, −4.4, −4.7; IR (neat) 2955, 2167, 1784, 1696, 1384, 1248, 1207, 1095, 837, 778 cm^{-1}; mass spectrum (CI) m/z 542.3120 [$C_{30}H_{48}NO_4Si_2$ (M+1) requires 542.3122], 542 (base), 526, 484, 410.

4.1.11. 3-[(2*S*)-Allyl-(3*R*)-(*tert*-butyldimethylsilanoxyl)-(5*S*)-methylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one (14). Solid $AgNO_3$ (3.30 g, 19.0 mmol) was added in one portion to a solution of the preceding alkyne (695 mg, 1.28 mmol) in THF/EtOH/H_2O/2,6-lutidine (1:1:1:0.1) (65 mL) at room temperature. The resulting solution was stirred for 30 min and filtered through a pad of Celite (3 cm) rinsing with Et_2O (300 mL). The combined filtrate and washings were washed with brine (200 mL) and H_2O (100 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3×75 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure The residue was purified by flash chromatography eluting with pentane/Et_2O (2:1) to afford 493 mg (82%) of **14** as a yellow oil; ^{1}H NMR (500 MHz) δ 7.32–7.28 (comp, 2H), 7.26–7.23 (m, 1H), 7.22–7.19 (comp, 2H), 5.89–5.80 (m, 1H), 5.12–5.08 (m, 1H), 5.04–5.00 (m, 1H), 4.65–4.60 (m, 1H), 4.28–4.24 (m, 1H), 4.15–4.04 (comp, 3H), 3.28 (dd, J=13.4, 3.2 Hz, 1H), 2.64 (dd, J=13.5, 10.2 Hz, 1H), 2.55–2.47 (comp, 2H), 2.39–2.33 (m, 1H), 2.05 (d, J=2.2 Hz, 1H), 1.78–1.67 (comp, 2H), 1.21 (d, J=7.0 Hz, 3H), 0.83 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz) δ 174.0, 153.1, 135.5, 135.2, 129.5, 128.9, 127.3, 117.1, 88.6, 71.9, 69.3, 65.7, 56.0, 48.0, 41.7, 37.8, 33.4, 25.8, 22.8, 21.8, 18.0, −4.4, −4.6; IR (neat) 3307, 2931, 1784, 1696, 1384, 1249, 1208, 1096, 837, 779 cm^{-1}; mass spectrum (CI) m/z 470.2720 [$C_{27}H_{40}NO_4Si$ (M+1) requires 470.2727], 470 (base), 454, 412, 338.

4.1.12. (4*S*)-Benzyl-(3*S*)-[(7*R*)-(*tert*-butyldimethylsilanyloxy)-(5*S*)-methyl-4-vinylcyclohept-3-enecarbonyl]oxazolidin-2-one (15). A solution of **14** (20 mg, 0.0426 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was degassed by bubbling with a stream of argon for 10 min, whereupon dioxolane **18** (15 mg, 0.128 mmol) and catalyst **17** (5 mg, 0.009 mmol) were added. The mixture was stirred at 45 °C for 22 h and then cooled to room temperature, whereupon DMSO (50 μL) was added and stirring continued for 12 h. The mixture was concentrated under reduced pressure and purified by flash chromatography eluting with pentane/Et_2O (2:1) to give 10 mg (50%) of **15** as a yellow oil; ^{1}H NMR (500 MHz) δ 7.33–7.29 (comp, 2H), 7.27–7.25 (m, 1H), 7.21–7.19 (comp, 2H), 6.21 (dd, J=17.4, 10.9 Hz, 1H), 5.74–5.71 (m, 1H), 5.09 (d, J=17.4 Hz, 1H), 4.91 (d, J=10.9 Hz, 1H), 4.61–4.56 (m, 1H), 4.24–4.21 (m, 1H), 4.19–4.16 (m, 1H), 4.14–4.07 (comp, 2H), 3.27 (dd, J=13.3, 3.2 Hz, 1H), 3.03–2.96 (m, 1H), 2.83–2.76 (m, 1H), 2.72 (dd, J=13.3, 9.8 Hz, 1H), 2.25–2.14 (comp, 2H), 1.78 (ddd, J=14.7, 6.1, 2.0 Hz, 1H), 1.21 (d, J=7.4 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (125 MHz) δ 173.9, 153.3, 145.5, 140.2, 135.5, 129.5, 128.9, 128.4, 127.3, 110.4, 71.9, 65.8, 55.8, 45.8, 38.3, 37.9, 31.2, 25.8, 24.0, 20.5, 17.9, −4.4, −5.5; IR (neat) 2929, 1784, 1698, 1388, 1350, 1242, 1210, 1099, 1072, 835, 776 cm^{-1}; mass spectrum (CI) m/z 470.2728 [$C_{27}H_{40}NO_4Si$ (M+1) requires 470.2727], 470 (base), 338.

4.1.13. (4*S*)-Benzyl-(3*S*)-[7(*R*)-(*tert*-butyldimethylsilanyloxy)-5(*S*)-methyl-4-(3-oxobut-1-enyl)cyclohept-3-enecarbonyl]oxazolidin-2-one (20). A solution of **14** (364 mg, 0.775 mmol) in anhydrous CH_2Cl_2 (155 mL) was degassed with argon for 10 min, whereupon freshly distilled methyl vinyl ketone (320 μL, 3.88 mmol) and catalyst **17** (97 mg, 0.160 mmol) were added. The mixture was stirred at 45 °C for 20 h and cooled to room temperature, whereupon DMSO (600 μL) was added and stirring continued for 6 h. The mixture was concentrated under reduced pressure and purified by flash chromatography eluting with pentane/Et_2O (1:1) to give 245 mg (62%) of **20** as a white solid; mp=24–26 °C; ^{1}H NMR (500 MHz) δ 7.34–7.30 (comp, 2H), 7.28–7.24 (m, 1H), 7.20–7.18 (comp, 2H), 7.02 (d, J=16.1 Hz, 1H), 6.20 (m, 1H), 6.08 (d, J=16.1 Hz, 1H), 4.61–4.56 (m, 1H), 4.27–4.25 (m, 1H), 4.16–4.07 (comp, 3H), 3.27 (dd, J=13.4, 3.3 Hz, 1H), 3.13–3.06 (m, 1H), 2.82–2.75 (m, 1H), 2.73 (d, J=13.3, 9.7 Hz, 1H), 2.32–2.27 (comp, 4H), 2.23–2.17 (m, 1H), 1.80 (ddd, J=14.7, 5.6, 1.8 Hz, 1H), 1.23 (d, J=7.2 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (125 MHz) δ 198.9, 173.3, 153.3, 147.6, 144.7, 138.8, 135.3, 129.4, 129.0, 127.4, 124.8, 71.7, 65.9, 55.8, 45.7, 38.0, 37.8, 31.8, 27.3, 25.8, 24.4, 20.4, 17.8, −4.3, −5.6; IR (neat) 2928, 2856, 1778, 1702, 1667, 1590, 1386, 1354, 1256, 1195, 985, 837, 774 cm^{-1}; mass spectrum (CI) m/z 512.2833 [$C_{29}H_{42}NO_5Si$ (M+1) requires 512.2832], 512 (base), 494, 454, 380, 362, 205, 163.

4.1.14. (2*S*)-Methyl-3-(toluene-4-sulfonyloxy)propionic acid methyl ester (25). To a solution of alcohol **24** (5.36 g, 45.4 mmol) in anhydrous CH_2Cl_2 (65 mL) at 0 °C was added Et_3N (7.60 mL, 54.4 mmol), DMAP (1.10 g, 9.07 mmol), and TsCl (10.4 g, 54.4 mmol) successively. The cooling bath was removed after 1 h, and the mixture was stirred at room temperature for 20 h. The mixture was poured into water (50 mL), and the resulting biphasic solution was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a volume of approximately 15 mL. This solution was filtered through a pad of

silica (2 cm) rinsing with CH_2Cl_2 (100 mL). The filtrate was concentrated under reduced pressure to afford 11.8 g (96%) of **25** as a light yellow oil with spectral characteristics identical to those previously reported.[48]

4.1.15. 4,4-Dibromo-(2*R*)-methyl-1-(toluene-4-sulfonyloxy)but-3-ene (26). To a solution of ester **25** (2.0 g, 7.34 mmol) in anhydrous PhMe (36.5 mL) at −78 °C was added DIBAL-H (1 M in PhMe, 8.1 mL, 8.08 mmol) dropwise via syringe. The mixture was stirred for 1.5 h at −78 °C, whereupon EtOAc (30 mL) was added and the cooling bath removed. Once the mixture had warmed to room temperature, saturated aqueous Rochelle's salt (100 mL) was added, and the biphasic mixture was stirred vigorously for 3 h. The layers were separated, and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organics were washed with water (2×30 mL) and brine (2×30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure (20 mmHg) to afford the crude aldehyde (ca. 2.0 g) as a yellow oil that was used in the next step without further purification.

Solid CBr_4 (4.88 g, 14.7 mmol) was added in one portion to a solution of PPh_3 (7.70 g, 29.4 mmol) in anhydrous CH_2Cl_2 (37 mL) at 0 °C. After stirring for 10 min, a solution of the preceding aldehyde (ca. 2.0 g) and 2,6-lutidine (1.7 mL, 14.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise via syringe. Stirring was continued at 0 °C for 1 h, whereupon saturated aqueous NH_4Cl (6 mL) was added and the cooling bath removed. The reaction mixture was poured into saturated aqueous NH_4Cl (40 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_2O/pentane (2:1) to give 1.82 g (62% from **25**) of **26** as a white solid; mp 74–76 °C; ^{1}H NMR (400 MHz) δ 7.79–7.77 (m, 2H), 7.37–7.35 (m, 2H), 6.13 (d, J=9.2 Hz, 1H), 3.92–3.90 (comp, 2H), 2.83–2.73 (m, 1H), 2.45 (s, 3H), 1.02 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 145.3, 138.5, 132.9, 130.2, 128.2, 91.3, 72.2, 38.1, 21.9, 15.7; IR ($CDCl_3$) 2973, 1598, 1458, 1360, 1176, 1097, 973, 813, 784, 666 cm^{-1}; mass spectrum (CI) m/z 396.9119 [$C_{12}H_{15}O_3SBr_2$ (M+1) requires 396.9109], 401, 399 (base), 397.

4.1.16. Toluene-4-sulfonic acid-(2*R*)-methyl-4-triisopropylsilanylbut-3-ynyl ester (27). *n*-BuLi (2.47 M in hexane, 4.10 mL, 10.1 mmol) was added dropwise via syringe to a solution of the preceding dibromide (1.61 g, 4.04 mmol) in anhydrous THF (13.3 mL) at −78 °C. After 1 h at −78 °C, the reaction mixture was allowed to warm to −20 °C, and stirring was continued at this temperature for 1 h. The reaction mixture was cooled to −78 °C, whereupon TIPSOTf (3.30 mL, 12.1 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 4 h, whereupon MeOH (4 mL) was added and stirring continued for 10 min. The reaction mixture was poured into saturated aqueous NH_4Cl (30 mL), and the resulting biphasic mixture was extracted with Et_2O (3×10 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with pentane/Et_2O (3:1) to give 1.11 g (70%) of **27** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.79–7.77 (comp, 2H), 7.35–7.33 (comp, 2H), 4.06 (dd, J=9.2, 5.8 Hz, 1H), 3.87 (dd, J=9.2, 7.8 Hz, 1H), 2.87–2.78 (m, 1H), 2.45 (s, 3H), 1.19 (d, J=6.8 Hz, 3H), 1.04–0.96 (comp, 21H); ^{13}C NMR (125 MHz) δ 144.8, 133.1, 129.8, 127.9, 107.4, 82.9, 72.6, 27.2, 21.6, 18.5, 17.7, 11.1; IR (neat) 2942, 2865, 2170, 1599, 1463, 1365, 1190, 1178, 1098, 980, 667, 554 cm^{-1}; mass spectrum (CI) m/z 395.2075 [$C_{21}H_{35}O_3SiS$ (M+1) requires 395.2076], 395, 351, 329, 285 (base).

4.1.17. (3*S*)-Methyl-5-triisopropylsilanylpent-4-ynenitrile (28). To a solution of tosylate **27** (1.11 g, 2.81 mmol) in anhydrous DMSO (11.2 mL) was added anhydrous KCN (385 mg, 5.91 mmol). The mixture was stirred at 60 °C for 3 h and then allowed to cool to room temperature, whereupon it was slowly poured into a 15% brine (40 mL). The resulting mixture was extracted with Et_2O (3×10 mL), and the combined organics were dried (Na_2SO_4), filtered, and concentrated at atmospheric pressure. The residue was purified by flash chromatography eluting with pentane/Et_2O (4:1) to give 451 mg (64%) of the nitrile **28** and 125 mg (20%) of enyne **29** as colorless oils; ^{1}H NMR (400 MHz) δ 2.91–2.83 (m, 1H), 2.58–2.47 (comp, 2H), 1.35 (d, J=6.8 Hz, 3H), 1.08–1.02 (comp, 21H); ^{13}C NMR (125 MHz) δ 117.4, 108.5, 83.2, 25.4, 24.4, 20.6, 18.5, 11.1; IR (neat) 2943, 2866, 2173, 1463, 1382, 1331, 1120, 996, 883, 667 cm^{-1}; mass spectrum (CI) m/z 250.1991 [$C_{15}H_{28}NSi$ (M+1) requires 250.1991], 250 (base), 206, 157.

Enyne **29**: ^{1}H NMR (500 MHz) δ 5.34–5.33 (m, 1H), 5.24–5.22 (m, 1H), 1.91–1.90 (comp, 3H), 1.08–1.07 (comp, 21H); ^{13}C NMR (125 MHz) δ 127.2, 122.2, 108.5, 89.3, 23.5, 18.6, 11.3; IR (neat) 2944, 2865, 2253, 1465, 1383, 1096 cm^{-1}; mass spectrum (CI) m/z 223.1875 [$C_{14}H_{27}Si$ (M+1) requires 223.1882], 223 (base), 181, 157.

4.1.18. (3*S*)-Methyl-5-triisopropylsilanylpent-4-ynal (23). DIBAL-H (1 M in CH_2Cl_2, 5.4 mL, 5.35 mmol) was added dropwise via syringe to a solution of nitrile **28** (445 mg, 1.78 mmol) in anhydrous CH_2Cl_2 (18 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 3 h, whereupon 1 N HCl (5 mL) was added and the cooling bath was removed. The mixture was poured into 1 N HCl (25 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organics were washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated at atmospheric pressure. The residue was purified by flash chromatography eluting with pentane/Et_2O (3:1) to give 371 mg (83%) of **23** as a yellow oil; ^{1}H NMR (500 MHz) δ 9.81 (t, J=2.1 Hz, 1H), 2.99 (app sext., J=6.9 Hz, 1H), 2.54 (ddd, J=16.5, 7.4, 2.1 Hz, 1H), 2.48 (ddd, J=16.5, 6.9, 2.1 Hz, 1H), 1.24 (d, J=6.9 Hz, 3H), 1.05–0.98 (comp, 21H); ^{13}C NMR (125 MHz) δ 201.2, 111.0, 81.7, 50.0, 21.8, 21.2, 18.6, 11.2; IR (neat) 2943, 2866, 2167, 1730, 1463, 996, 883, 676 cm^{-1}; mass spectrum (CI) m/z 253.1990 [$C_{15}H_{29}OSi$ (M+1) requires 253.1988], 253 (base), 209, 157.

4.1.19. 3-[(2*S*)-Allyl-(3*R*)-hydroxy-(5*S*)-methyl-7-triisopropylsilanylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one (30). Bu_2BOTf (470 μL, 1.88 mmol)[47] was added via syringe to a solution of oxazolidinone **6** (407 mg, 1.57 mmol) and EtN(*i*-Pr)$_2$ (330 μL, 1.88 mmol) in anhydrous PhMe

(11 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h, whereupon aldehyde **23** (475 mg, 1.88 mmol) in anhydrous PhMe (2 mL) was added dropwise via syringe. The mixture was stirred at −78 °C for 30 min and then at room temperature for 6 h. The mixture was cooled to 0 °C, whereupon pH 7.0 phosphate buffer (2 mL), MeOH (1 mL), and 30% H_2O_2 (500 μL) were added successively; stirring was continued for 1 h. The mixture was poured into H_2O (30 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (2:1) to give 705 mg (88%) of **30** as a colorless oil (dr>95:5 by ^1H NMR); ^1H NMR (500 MHz) δ 7.33–7.30 (comp, 2H), 7.27–7.24 (m, 1H), 7.21–7.19 (comp, 2H), 5.88–5.80 (m, 1H), 5.12–5.08 (m, 1H), 5.03–5.01 (m, 1H), 4.68 (ddt, *J*=10.2, 7.0, 3.6 Hz, 1H), 4.28–4.25 (comp, 2H), 4.15–4.09 (comp, 2H), 3.27 (dd, *J*=13.3, 3.2 Hz, 1H), 2.80–2.72 (m, 1H), 2.65–2.56 (comp, 2H), 2.42–2.37 (m, 1H), 1.65–1.60 (m, 1H), 1.54–1.50 (m, 1H), 1.20 (d, *J*=6.8 Hz, 3H), 1.06–0.97 (comp, 21H); ^{13}C NMR (125 MHz) δ 174.8, 153.6, 135.3, 135.2, 129.4, 128.9, 127.3, 117.2, 112.8, 80.8, 70.6, 65.9, 55.6, 47.4, 40.8, 38.0, 32.1, 23.9, 21.7, 18.6, 11.2; IR (neat) 3523, 2942, 2162, 1782, 1698, 1462, 1386, 1350, 1237, 1208, 1102, 997, 918, 883, 702 cm^{-1}; mass spectrum (CI) *m/z* 512.3195 [$C_{30}H_{45}NO_4Si$ (M+1) requires 512.3196], 512 (base), 468, 318.

4.1.20. (2*S*)-Allyl-(3*R*)-hydroxy-(5*S*)-methyl-7-triisopropylsilanylhept-6-ynoic acid methoxymethylamide (31). Me_2AlCl (1 M in hexane, 5.25 mL, 5.25 mmol) was added dropwise via syringe to a solution of HCl·HN(OMe)Me (512 mg, 5.25 mmol) in anhydrous CH_2Cl_2 (8.0 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min, the cooling bath was removed, and stirring was continued at room temperature for 30 min. The mixture was cooled to 0 °C, whereupon alcohol **30** (671 mg, 1.31 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise via syringe. The mixture was stirred at 0 °C for 30 min and then at room temperature for 6 h. The reaction was quenched at 0 °C with 1 N HCl (5 mL). The mixture was poured into 1 N HCl (20 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (3:2) to give 311 mg (60%) of **31** as a colorless oil; ^1H NMR (500 MHz) δ 5.75 (ddt, *J*=17.1, 10.0, 7.0 Hz, 1H), 5.06 (dd, *J*=17.1, 1.6 Hz, 1H), 4.97 (dd, *J*=10.0, 0.8 Hz, 1H), 4.16–4.13 (m, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 3.08–3.00 (br s, 1H), 2.76 (dtd, *J*=10.9, 7.0, 4.1, 1H), 2.55–2.48 (m, 1H), 2.38–2.33 (m, 1H), 1.69 (ddd, *J*=13.4, 10.0, 4.1 Hz, 1H), 1.42 (ddd, *J*=13.4, 10.9, 2.4 Hz, 1H), 1.20 (d, *J*=7.0 Hz, 3H), 1.05–0.96 (comp, 21H); ^{13}C NMR (125 MHz) δ 176.2, 136.1, 116.7, 113.2, 80.5, 70.3, 61.5, 45.3, 42.0, 31.9, 30.9, 24.0, 21.8, 18.6, 11.2; IR (neat) 3449, 2941, 2865, 2161, 1640, 1463, 1384, 994, 817, 883, 676 cm^{-1}; mass spectrum (CI) *m/z* 396.2934 [$C_{22}H_{42}NO_3Si$ (M+1) requires 396.2934], 397 (base), 352.

4.1.21. (2*S*)-Allyl-(3*R*)-(*tert*-butyldimethylsilanyloxy)-(5*S*)-methyl-7-triisopropylsilanylhept-6-ynoic acid methoxymethylamide (32). To a solution of the preceding amide (262 mg, 0.662 mmol) in anhydrous CH_2Cl_2 (9.5 mL) at 0 °C was added 2,6-lutidine (460 μL, 3.97 mmol) and TBDMSOTf (300 μL, 1.32 mmol). The resulting solution was stirred at 0 °C for 1 h, whereupon MeOH (3 mL) was added and the cooling bath removed. After warming to room temperature, the mixture was poured into H_2O (20 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (3:1) to give 334 mg (99%) of **32** as a yellow oil; ^1H NMR (500 MHz) δ 5.74 (ddt, *J*=17.1, 10.0, 7.1 Hz, 1H), 5.07–5.02 (m, 1H), 4.97–4.94 (m, 1H), 4.11–4.07 (m, 1H), 3.62 (s, 3H), 3.15 (s, 3H), 3.08–3.00 (br s, 1H), 2.55–2.49 (m, 1H), 2.45–2.40 (m, 1H), 2.26–2.21 (m, 1H), 1.67–1.62 (comp, 2H), 1.18 (d, *J*=7.0 Hz, 3H), 1.06–0.96 (comp, 21H), 0.86 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz) δ 174.4, 136.5, 116.4, 113.5, 80.6, 72.2, 61.1, 47.5, 42.7, 33.3, 32.0, 26.0, 24.1, 22.2, 18.6, 18.1, 11.3, −4.2; IR (neat) 2941, 2864, 2163, 1668, 1463, 1382, 1253, 1096, 996, 883, 838, 776, 676 cm^{-1}; mass spectrum (CI) *m/z* 510.3798 [$C_{28}H_{56}NO_3Si_2$ (M+1) requires 510.3799], 510 (base), 466, 452.

4.1.22. (3*S*)-Allyl-(4*R*)-(*tert*-butyldimethylsilanyloxy)-(6*S*)-methyl-8-triisopropylsilanyloct-7-yn-2-one. MeMgBr (3 M in Et_2O, 1.10 mL, 3.27 mmol) was added dropwise via syringe to a solution of the preceding amide (333 mg, 0.653 mmol) in anhydrous THF (6.6 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and then at 0 °C for 1.5 h, whereupon saturated aqueous NH_4Cl (5 mL) was added. The mixture was poured into a 15% brine solution (20 mL), and the resulting biphasic mixture was extracted with EtOAc (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to give 292 mg (96%) of the ketone as a yellow oil; ^1H NMR (500 MHz) δ 5.72 (ddt, *J*=17.1, 10.3, 7.2 Hz, 1H), 5.05–4.96 (comp, 2H), 4.12–4.08 (m, 1H), 2.83–2.79 (m, 1H), 2.59–2.50 (m, 1H), 2.45–2.38 (m, 1H), 2.22 (s, 3H), 2.04–1.97 (m, 1H), 1.51–1.44 (m, 1H), 1.29–1.22 (m, 1H), 1.18 (d, *J*=6.8 Hz, 3H), 1.08–1.01 (comp, 21H), 0.92 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz) δ 210.1, 136.2, 116.5, 113.0, 81.0, 72.1, 58.9, 41.2, 32.8, 32.3, 25.9, 24.2, 22.2, 18.6, 18.1, 11.5, −4.0, −4.6; IR (neat) 2942, 2865, 2162, 1714, 1642, 1463, 1253, 1171, 1085, 837, 776, 677 cm^{-1}; mass spectrum (CI) *m/z* 465.3582 [$C_{27}H_{53}O_2Si_2$ (M+1) requires 465.3584], 465, 449, 421 (base), 407, 367, 199.

4.1.23. Trifluoromethanesulfonic acid (2*S*)-allyl-(3*R*)-(*tert*-butyldimethylsilanyloxy)-(5*S*)-methyl-1-methylene-7-triisopropylsilanylhept-6-ynyl ester (22). A solution of the preceding ketone (48 mg, 0.103 mmol) in anhydrous THF (200 μL) was added dropwise via cannula to a solution of KHMDS (0.5 M in PhMe, 410 μL, 0.207 mmol) in THF (200 μL) at −78 °C. The solution was stirred at −78 °C for 20 min, whereupon triflimide **33** (100 mg, 0.258 mmol) in anhydrous THF (300 μL) was added via cannula. The resulting mixture was stirred at −78 °C for 1 h, 0 °C for 1 h, then at room temperature for 1 h. The reaction was quenched at 0 °C with saturated aqueous NH_4Cl (2 mL). The mixture was poured into a 15% brine solution (10 mL), and the resulting biphasic mixture was extracted with Et_2O (3×5 mL).

The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with pentane/Et_2O (20:1) to give 55 mg (89%) of **22** as a yellow oil; ^1H NMR (500 MHz) δ 5.75 (ddt, J=17.1, 10.2, 6.8 Hz, 1H), 5.24 (d, J=4.0 Hz, 1H), 5.11–5.04 (comp, 2H), 4.91 (d, J=4.0 Hz, 1H), 4.08–4.05 (m, 1H), 2.60–2.52 (m, 1H), 2.51–2.48 (m, 1H), 2.29–2.19 (comp, 2H), 1.54–1.45 (comp, 2H), 1.19 (d, J=7.0 Hz, 3H), 1.06–0.99 (comp, 21H), 0.87 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H); ^{19}F NMR (470 MHz) δ −74.59 (s, 3F); ^{13}C NMR (125 MHz) δ 155.9, 134.9, 118.4 (J_{CF}=320.3 Hz), 117.4, 112.8, 105.7, 81.1, 71.7, 51.1, 41.5, 32.5, 25.9, 24.1, 22.2, 18.6, 18.1, 11.2, −4.1, −4.4; IR (neat) 2942, 2865, 2162, 1660, 1422, 1251, 1213, 1143, 936, 838, 776, 677 cm^{-1}; mass spectrum (CI) m/z 597.3078 [$C_{28}H_{52}O_4Si_2F_3$ requires 597.3077], 597, 441, 367 (base).

4.1.24. (3*R*)-Allyl-(4*R*)-(*tert*-butyl-dimethyl-silanyloxy)-(6*S*)-methyl-2-methylene-8-triisopropylsilanyl-oct-7-ynoic acid methyl ester (34). A solution of **22** (54 mg, 0.091 mmol) in anhydrous DMF (400 μL) was degassed by bubbling with a stream of CO for 5 min and then added to a solution of similarly degassed anhydrous MeOH (150 μL, 3.62 mmol), Et_3N (25 μL, 0.181 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and PPh_3 (4 mg, 0.0181 mmol). The mixture was stirred under an atmosphere of CO (balloon) at room temperature for 3.5 h. The reaction mixture was poured into H_2O (10 mL), and the resulting biphasic mixture was extracted with Et_2O (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with pentane/Et_2O (20:1) to give 39 mg (85%) of **34** as a yellow oil; ^1H NMR (500 MHz) δ 6.27–6.26 (m, 1H), 5.47–5.46 (m, 1H), 5.72–5.64 (m, 1H), 4.99–4.92 (comp, 2H), 3.95 (ddd, J=9.2, 5.0, 2.7 Hz, 1H), 3.71 (s, 3H), 2.95–2.91 (m, 1H), 2.58–2.50 (m, 1H), 2.42–2.37 (m, 1H), 2.22–2.16 (m, 1H), 1.56–1.51 (m, 1H), 1.40–1.35 (m, 1H), 1.16 (d, J=6.8 Hz, 3H), 1.06–1.00 (comp, 21H), 0.85 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz) δ 168.1, 140.5, 136.7, 126.0, 116.1, 113.5, 80.5, 72.7, 51.8, 46.0, 42.3, 34.2, 26.0, 23.9, 22.1, 18.6, 18.2, 11.3, −4.0, −4.1; IR (neat) 2943, 2864, 2163, 1724, 1463, 1253, 1155, 1090, 1058, 996, 883, 837, 775, 660 cm^{-1}; mass spectrum (CI) m/z 507.3688 [$C_{29}H_{55}O_3Si_2$ (M+1) requires 507.3690], 507 (base), 449, 375.

4.1.25. (4*R*)-Allyl-(5*R*)-[(2*S*)-methylbut-3-ynyl]-3-methylenedihydrofuran-2-one (21). A solution of TBAF·$3H_2O$ (74 mg, 0.233 mmol) in THF (500 μL) was added via syringe to a solution of acrylate **34** (38 mg, 0.075 mmol) in anhydrous THF (1 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then at room temperature for 6 h. The mixture was poured into saturated aqueous NH_4Cl (10 mL), and the resulting biphasic mixture was extracted with Et_2O (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with pentane/Et_2O (3:1) to give 12 mg (78%) of **21** as a yellow oil; ^1H NMR (400 MHz) δ 6.23 (d, J=2.2 Hz, 1H), 5.77 (ddt, J=17.1, 10.3, 6.8 Hz, 1H), 5.57 (d, J=2.2 Hz, 1H), 5.17–5.09 (comp, 2H), 4.89 (ddd, J=10.9, 7.2, 2.4 Hz, 1H), 3.20–3.13 (m, 1H), 2.82–2.73 (m, 1H), 2.37–2.22 (comp, 2H), 2.09 (d, J=2.4 Hz, 1H), 1.69–1.62 (m, 1H), 1.59–1.52 (m, 1H), 1.23 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 170.4, 138.6, 134.4, 122.3, 118.3, 87.3, 79.1, 69.9, 42.3, 38.1, 32.6, 23.0, 21.7; IR (neat) cm^{-1}; mass spectrum (CI) m/z 205.1229 [$C_{13}H_{17}O_2$ (M+1) requires 205.1229], 409 (dimer), 205 (base).

4.1.26. 8-*epi*-Xanthatin (1). A solution of lactone **21** (7 mg, 0.034 mmol) in anhydrous CH_2Cl_2 (6.9 mL) was degassed by bubbling through a stream of argon for 10 min, whereupon freshly distilled methyl vinyl ketone (29 μL, 0.34 mmol) and catalyst **17** (4.3 mg, 0.007 mmol) was added. The mixture was stirred at 45 °C for 12 h and then cooled to room temperature, whereupon DMSO (50 μL) was added and stirring continued for 6 h. The mixture was concentrated and then purified by flash chromatography eluting with Et_2O to give 7 mg (83%) of **1** as a colorless oil; $[\alpha]_D^{24}$ +23.4 (c 0.333, $CHCl_3$); ^1H NMR (400 MHz) δ 6.97 (d, J=16.1 Hz, 1H), 6.32 (d, J=3.4 Hz, 1H), 6.20 (dd, J=9.0, 6.3 Hz, 1H), 6.13 (d, J=16.1 Hz, 1H), 5.57 (d, J=2.9 Hz, 1H), 4.68–4.62 (m, 1H), 3.45–3.37 (m, 1H), 2.87–2.78 (m, 1H), 2.65–2.56 (m, 1H), 2.53–2.46 (m, 1H), 2.29 (s, 3H), 2.17 (ddd, J=14.2, 7.1, 2.2 Hz, 1H), 1.95–1.86 (m, 1H), 1.17 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 198.7, 170.0, 146.7, 143.1, 138.3, 135.9, 126.1, 122.8, 78.4, 41.4, 36.5, 31.9, 27.9, 27.2, 21.7; IR (neat) 2957, 2360, 1761, 1664, 1619, 1592, 1274, 1256, 980 cm^{-1}; mass spectrum (CI) m/z 247.1333 [$C_{15}H_{19}O_3$ (M+1) requires 247.1334], 247 (base), 249.

Acknowledgements

We thank the National Institutes of Health (GM31077), Pfizer, Inc., Merck Research Laboratories, and the Robert A. Welch Foundation for their generous support of this research. We are also grateful to Dr. Richard Fisher (Materia, Inc.) for catalyst support and helpful discussions. We additionally thank Dr. Shi Yong Ryu of the Korea Research Institute of Chemical Technology for providing ^1H and ^{13}C NMR spectra of natural **1**. D.A.K. thanks Pfizer, Inc. for an undergraduate research fellowship.

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6, 2.5 Hz), 1.91 (ddd, J=14, 12, 12 Hz), 1.18 (d, J=7 Hz).[44] ^{13}C NMR ($CDCl_3$) δ 198.3, 169.6, 146.4, 142.7, 138.0, 135.6, 125.8, 122.4, 78.1, 41.1, 36.2, 31.6, 27.6, 26.9, 21.4.[2b]

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