Total Synthesis of (±)-Nisamycin

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We have developed a highly convergent synthesis of the manumycin-type *m*-C_7N-antibiotic nisamycin that is applicable to other members of this family of antibiotics. The synthesis features a three-step sequence to the epoxyquinol core that serves as a scaffold for the attachment of the polyene side chains. The eastern polyene side chain was constructed via a novel organozirconocene-mediated synthesis. Zirconocene methodology was also applied to the synthesis of the polyene side chains of asukamycin. The southern side chain of nisamycin was introduced via a Stille reaction that employed a vinyl bromo ketone, derived from an acid-sensitive bromo ketal. Pd-mediated coupling of the vinyl bromide with a stannyl TIPS ester gave TIPS-protected nisamycin that was readily converted to the natural product.

Nisamycin (**1**) is a recently isolated member of the manumycin family of antibiotics, which includes alisamycin,[2] asukamycin,[3] and manumycin A (Figure 1).[4,5] Nisamycin was discovered in 1993 by Hayashi and co-workers in the culture broth of *Streptomyces* sp. K106, a bacterial strain isolated from a soil sample collected in Sakai City, Japan.[6] Like other members of the manumycin family, nisamycin has a highly functionalized epoxyquinol core, known as the *m*-C_7N (meta-substituted aniline) unit.[7] This unit is thought to originate from 3-amino-4-hydroxybenzoic acid via a unique biosynthetic pathway involving a building block from the TCA cycle.[7,8] A consequence of this biosynthetic pathway is the syn orientation of the epoxide and the quinol oxygen, a feature that is common to most manumycins. Attached to the core are two polyunsaturated side chains. The southern side chain consists of a trienyl acyl unit that is found in manumycin A, alisamycin, and asukamycin. Similarly, the eastern side chain of nisamycin contains a dienyl amide moiety that is common to other manumycins. Collectively, the dense functionality of the core and the chemical sensitivity of the polyene moieties make nisamycin a challenging synthetic target.[9] We have reported the first successful synthetic route toward the manumycin *m*-C_7N core structure in 1994 and subsequently applied this strategy in an asymmetric total synthesis of the antitumor antibiotic LL-C10037α.[10,11] To date, there has been only one reported synthesis of racemic nisamycin by Taylor and co-workers in 1998 using a related strategy for *m*-C_7N synthesis.[12,13] In this

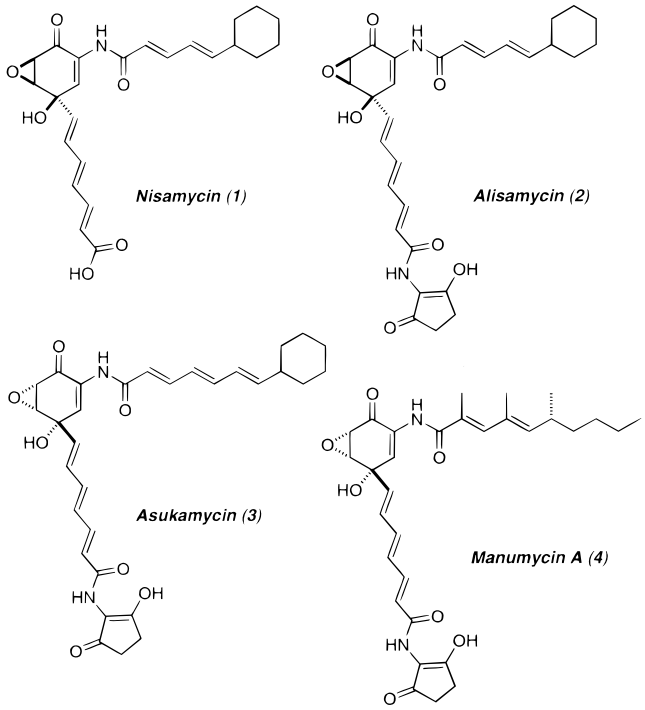

Figure 1. Some members of the manumycin family of antibiotics.

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(2) (a) Franco, C. M. M.; Maurya, R.; Vijayakumar, E. K. S.; Chatterjee, S.; Blumbach, J.; Ganguli, B. N. *J. Antibiot.* **1991**, *44*, 1289. (b) Chatterjee, S.; Vijayakumar, E.; Franco, C.; Blumbach, J.; Ganguli, B. N. *J. Antibiot.* **1993**, *46*, 1027. (c) Hayashi, K.; Nakagawa, M.; Fujita, T.; Nakayama, M. *Biosci. Biotech. Biochem.* **1994**, *58*, 1332.

(3) (a) Omura, S.; Kitao, C.; Tanaka, H.; Oiwa, R.; Takahashi, Y.; Nakagawa, A.; Shimada, M.; Iwai, Y. *J. Antibiot.* **1976**, *29*, 876. (b) Kakinuma, K.; Ikekawa, N.; Nakagawa, A.; Omura, S. *J. Am. Chem. Soc.* **1979**, *101*, 3402. (c) Cho, H. G.; Sattler, I.; Beale, J. M.; Zeeck, A.; Floss, H. G. *J. Org. Chem.* **1993**, *58*, 7925.

(4) (a) Buzzetti, F.; Gäumann, E.; Hütter, R.; Keller-Schierlein, W.; Neipp, L.; Prelog, V.; Zähner, H. *Pharm. Acta Helv.* **1963**, *38*, 871. (b) Thiericke, R.; Stellwaag, M.; Zeeck, A. *J. Antibiot.* **1987**, *40*, 1549. (c) Zeeck, A.; Schröder, K.; Frobel, K.; Grote, R.; Thiericke, R. *J. Antibiot.* **1987**, *40*, 1530. (d) Zeeck, A.; Frobel, K.; Heusel, C.; Schröder, K.; Thiericke, R. *J. Antibiot.* **1987**, *40*, 1541.

(5) For recent reviews on the chemistry of manumycin-type antibiotics, see: (a) Sattler, I.; Thiericke, R.; Zeeck, A. *Nat. Prod. Rep.* **1998**, *15*, 221. (b) Floss, H. G. *Nat. Prod. Rep.* **1997**, *14*, 433.

(6) (a) Hayashi, K.; Nakagawa, M.; Fujita, T.; Tanimori, S.; Nakayama, M. *J. Antibiot.* **1993**, *46*, 1904. (b) Hayashi, K.; Nakagawa, M.; Nakayama, M. *J. Antibiot.* **1994**, *47*, 1104. (c) Hayashi, K.; Nakagawa, M.; Fujita, T.; Tanimori, S.; Nakayama, M. *J. Antibiot.* **1994**, *47*, 1110.

(7) (a) Kim, C.-G.; Kirschning, A.; Bergon, P.; Zhou, P.; Su, E.; Sauerbrei, B.; Ning, S.; Ahn, Y.; Breuer, M.; Leistner, E.; Floss, H. G. *J. Am. Chem. Soc.* **1996**, *118*, 7486. (b) Hu, Y.; Melville, C. R.; Gould, S. J.; Floss, H. G. *J. Am. Chem. Soc.* **1997**, *119*, 4301.

(8) Dewick, P. M. *Nat. Prod. Rep.* **1993**, *10*, 233.

(9) For mechanistic studies of the reactivity pattern of epoxyquinols, see: Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351.

(10) Wipf, P.; Kim, Y. *J. Org. Chem.* **1994**, *59*, 3518.

(11) Wipf, P.; Kim, Y.; Jahn, H. *Synthesis* **1995**, 1549.

(12) Taylor, R. J. K.; Alcaraz, L.; Kapfer-Eyer, I.; Macdonald, G.; Wei, X.; Lewis, N. *Synthesis* **1998**, 775.

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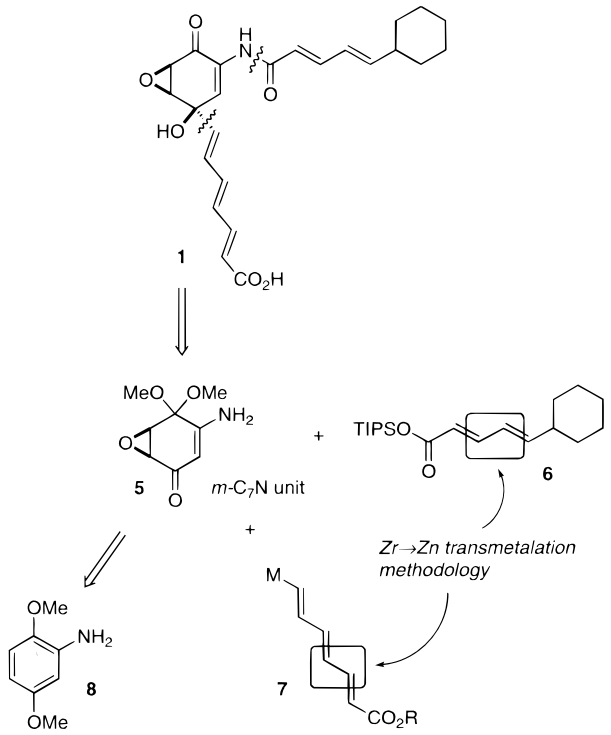
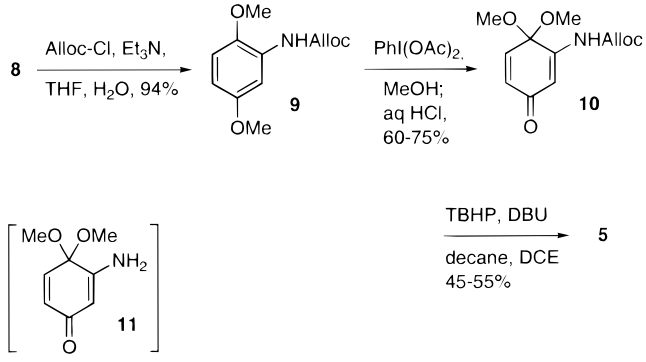
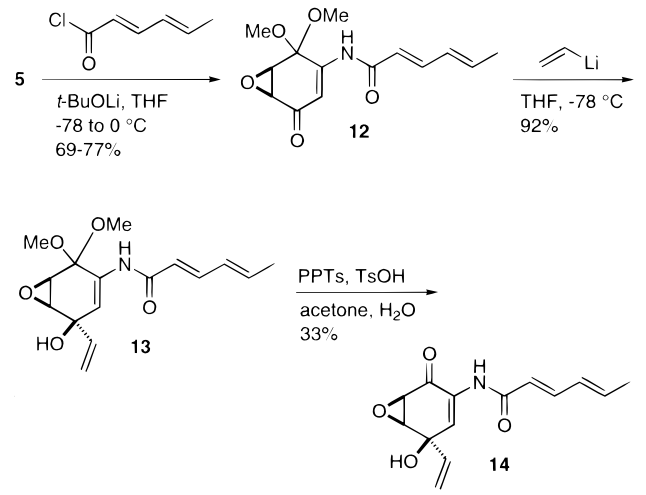
Scheme 1



Scheme 2



Scheme 3



paper, we report our approach for the successful convergent assembly of (±)-nisamycin.[14]

Our initial retrosynthetic analysis of nisamycin is shown in Scheme 1. Disconnection of the amide and allylic alcohol bonds affords three segments, the epoxyquinol core **5** and the two polyene side chains **6** and **7**. We planned to construct the polyunsaturated acid side chains using Zr−Zn transmetalation methodology,[15] which we had recently employed for the synthesis of the eastern side chain of manumycin A (vide infra).[14a] Our approach to the *m*-C_7N core **5** was closely patterned after previous work on the synthesis of LL-C10037α in our laboratories.[10,11] Further optimization of this strategy resulted in a three-step sequence to the core from commercially available 2,5-dimethoxyaniline **8**.

Results and Discussion

Protection of the aniline nitrogen of **8** provided the Alloc derivative **9** in excellent yield (Scheme 2). Subsequent hypervalent iodine oxidation[16] led to the desired quinone monoketal **10**. During isolation of **10** via radial chromatography (UV detection), we noted a second compound, presumably a diketal,[17] that was decomposing to the desired monoketal. To simplify the purification and convert any diketal to monoketal before chromatography, the crude product was washed with dilute acid. Subsequent purification provided **10** in 60−75% yield. Chemoselective epoxidation of the dienone employed a combination of DBU and TBHP to give **5**.[18] We knew from our previous work with LL-C10037α that epoxidation occurs at the electron-poor double bond, and not at the N-substituted double bond. Concurrent deprotection of the Alloc group led to the primary amine **5** as a stable solid in 45−55% yield. Careful chromatography provided pure material; however, usually a mixture containing 10−15% of vinylogous amide **11** was isolated. This was not a concern since **11** was readily removed as an acyl derivative in the next step.

Before continuing with the synthesis, we conducted a brief model study in order to test the feasibility of our retrosynthetic plan (Scheme 3). Acylation of the core **5** with sorbyl chloride using a protocol similar to that of Taylor[12] provided the desired amide **12** in high yield. 1,2-Addition of commercially available vinyllithium to the ketone functionality proceeded smoothly at low temperature and gave the tertiary alcohol **13** in 92% yield. The assignment of the relative stereochemistry of the epoxide

(13) For other syntheses of manumycin-type natural products, see: (a) Kapfer, I.; Lewis, N. J.; Macdonald, G.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 2101. (b) Alcaraz, L.; Macdonald, G.; Kapfer, I.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 6619. (c) Macdonald, G.; Lewis, N. J.; Taylor, R. J. K. *Chem. Commun.* **1996**, 2647. (d) Alcaraz, L.; Taylor, R. J. K. *Chem. Commun.* **1998**, 1157.

(14) In preliminary communications, we have reported the preparation of polyene side chains of manumycins using organozirconocene methodology: (a) Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G. *Pure Appl. Chem.* **1997**, *69*, 639. (b) Wipf, P.; Coish, P. D. G. *Tetrahedron Lett.* **1997**, *38*, 5073.

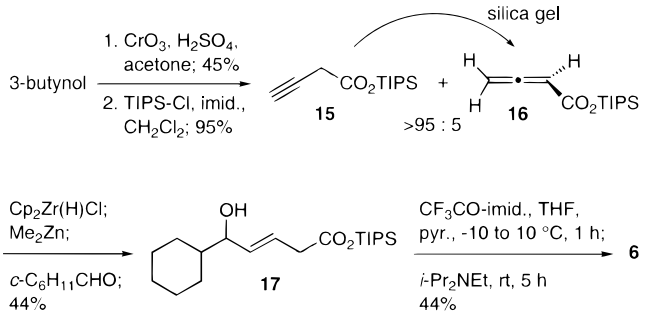
(15) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Xu, W. *Org. Synth.* **1996**, *74*, 205. (c) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.

(16) (a) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677. (b) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649. (c) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **1998**, *63*, 3530.

(17) ^{1}H NMR analysis (300 MHz, $CDCl_3$) of an impure sample supported this assumption. Peak listings characteristic for the diketal: δ 3.13 (s, 6 H), 3.26 (s, 6 H), 4.54 (d, 2 H, J = 4.5 Hz), 5.19 (d, 1 H, J = 10.5 Hz), 5.23 (d, 1 H, J = 18 Hz), 5.75 (d, 1 H, J = 10.5 Hz), 5.8−6.0 (m, 1 H), 6.25 (dd, 1 H, J = 2.5, 10 Hz), 6.62 (br s, 1 H), 6.74 (br s, 1 H).

(18) Other epoxidation protocols, including enantioselective procedures, were inefficient.

Scheme 4



and tertiary alcohol centers of **13** was based on the assumption that the vinyllithium approached from the less-hindered face of the ketone, anti to the electron-withdrawing epoxide.[19] This assignment was confirmed by an X-ray analysis of an analogue of **13** obtained by phenyllithium addition to the corresponding *N*-Alloc-protected epoxy ketone.[20]

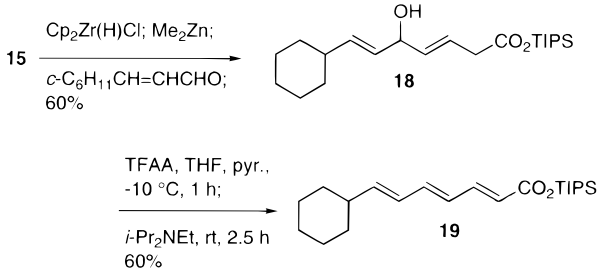
The final step in our model study was the deprotection of the ketal, which we thought would be problematic given the presence of the very acid-sensitive tertiary bis-allylic alcohol moiety in **13**. In fact, ketal hydrolysis in closely related systems has met with failure.[13b] However, treatment of **13** with PPTs/TsOH afforded the desired ketone **14**, albeit in low yield.

Encouraged by the success of this model study that yielded a compound **14** closely related to the nisamycin target molecule, we proceeded with a synthesis of the eastern side chain **6**. Our approach was based on the sequential hydrozirconation, Zr−Zn transmetalation, and 1,2-addition reactions demonstrated in our synthesis of the dienyl side chain of manumycin A.[14] Starting with TIPS 3-butynoate (**15**),[14b] derived in two steps from 3-butynol, hydrozirconation of the triple bond followed by in situ Zr−Zn transmetalation using Me_2Zn and subsequent addition of the generated vinyl zinc to commercially available cyclohexyl carboxaldehyde provided the allylic alcohol **17** in good yield (Scheme 4). It should be noted that the TIPS alkynyl ester and its acid precursor are labile intermediates. Base washing of the crude product from the Jones oxidation of 3-butynol resulted in rapid isomerization to the corresponding allenyl acid. Similarly, silica gel chromatography of the TIPS ester gave the allenyl ester.

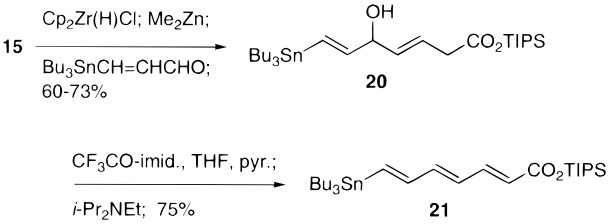
The secondary alcohol **17** was activated toward elimination by conversion to the trifluoroacetate. In situ treatment of this trifluoroacetate with diisopropylethylamine gave the all-trans diene **6** as the major product in 44% yield. Minor side products were observed but not isolated. Furthermore, the elimination product was contaminated by a small amount of a geometric isomer (possibly the 2*Z*,4*E* compound), which was removed during the next step. The elimination of the trifluoroacetate moiety was not as facile as the elimination of the *bis-allylic* acetate of **18** (vide infra) and required extended warming to room temperature in order to consume the trifluoroacetylated intermediate.

The zirconocene strategy was also applied to the synthesis of the trienyl side chain of asukamycin (Scheme 5). Hydrozirconation of butynoate **15**, followed by Zr−Zn transmetalation and 1,2-addition to 3-cyclohexyl

Scheme 5



Scheme 6



acrolein,[21] afforded the bis-allylic alcohol **18**, which was readily converted to the desired trienyl TIPS ester **19** in 60% yield. The preparation of **19**, in addition to the earlier approach toward the manumycin A dienonate,[14] demonstrates the generality of our protocol for the preparation of a broad range of conjugated polyenes present in this family of natural products.

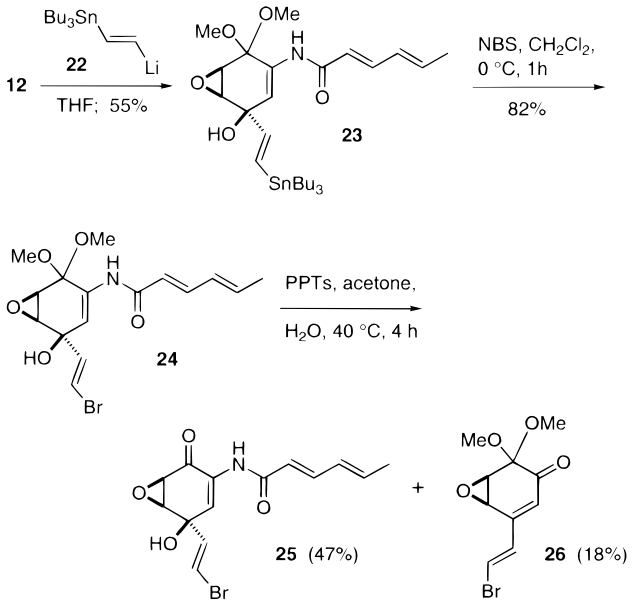
The preparation of the southern side chain segment **7** required access to a metallotriene equivalent. Hydrozirconation/transmetalation of TIPS alkynyl ester **15** provided a vinyl zinc species that was readily added to β-tributylstannylacrolein[14b] to give alcohol **20** (Scheme 6). Trifluoroacetylation with the imidazolide followed by base treatment gave the desired all-trans triene **21** in good yield. In this sequence, 1-(trifluoroacetyl)imidazole was used rather than TFAA for the protection step since the side product, imidazole, is unreactive (compared to trifluoroacetic acid derived from TFAA) toward the acid-sensitive vinyl tin moiety.

We next studied the conversion of stannyl ester **21** to the required trienyllithium reagent. Treatment of the stannane with 1.05 equiv of *n*-BuLi in THF at low temperature (−85 to −78 °C) resulted in complete decomposition of the starting material. Similarly, the generation of trienyllithium from the corresponding bromo- and iodotrienyl ester,[22] or the addition of the dianion obtained from the corresponding acid[23] to the core gave rapid decomposition. Therefore, we decided to modify our strategy for the introduction of the southern

(19) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678.
(20) Wipf, P.; Jeger, P. Unpublished results.

(21) Maeta, H.; Suzuki, K. *Tetrahedron Lett.* **1993**, *23*, 3851.
(22) The trienyl bromide was obtained in 82% yield by treating stannane **21** with 2 equiv of NBS in CH_2Cl_2 (^{1}H NMR δ 0.85−1.45 (m, 21 H), 5.96 (d, 1 H, J = 15.0 Hz), 6.34 (dd, 1 H, J = 10.5, 15.0 Hz), 6.41 (dd, 1 H, J = 10.5, 15.0 Hz), 6.55 (d, 1 H, J = 13.5 Hz), 6.81 (dd, 1 H, J = 10.5, 13.5 Hz), 7.20 (dd, 1 H, J = 10.5, 15.0 Hz)). The trienyl iodide was obtained as an approximately 1:1 mixture of presumably cis and trans isomers in 83% yield by treating stannane **21** with 2 equiv of NIS in CH_2Cl_2 (^{1}H NMR δ 1.00−1.45 (m, 21 H), 5.99 (d, 1 H, J = 15.0 Hz), 6.01 (dd, 1 H, J = 10.5, 15.0 Hz), 6.33 (dd, 1 H, J = 10.5, 14.5 Hz), 6.43 (dd, 1 H, J = 10.5, 15.0 Hz), 6.52−6.75 (m, 4 H), 6.84 (dd, 1 H, J = 7.5, 10.0 Hz), 7.10−7.48 (m, 3 H)). For a related cis−trans isomerization during tin−iodine exchange, see: Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 23.
(23) The iodo trienyl acid was prepared obtained in 84% yield by treating the TIPS ester with K_2CO_3 in MeOH/THF/H_2O (^{1}H NMR (CD_3OD) δ 5.96 (d, 1 H, J = 15.0 Hz), 6.00 (d, 1 H, J = 13.0 Hz), 6.41 (dd, 1 H, J = 11.0, 15.0 Hz), 6.54 (dd, 1 H, J = 11.0, 15.0 Hz), 6.62−6.96 (m, 5 H), 7.12−7.40 (m, 3 H)).

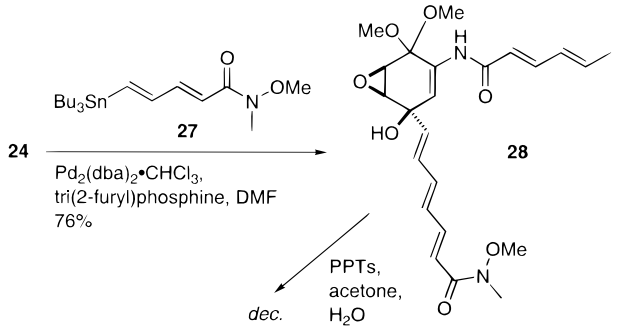
Scheme 7



side chain. From our model study, we knew that vinyllithium added readily to the acylated core **12**. Accordingly, we considered the addition of vinylstannyllithium **22,**[24] which provides a stannylated addition product that could be elongated via a Stille reaction (Scheme 7). The vinyl tin linker was successfully employed by Taylor and co-workers in their synthesis of nisamycin; however, in their approach, addition to a quinone core structure was not chemoselective and required separation of regioisomers.[12] In our strategy, vinylstannane **23** was subjected to tin−bromide exchange.[25] The presence of the bromide substituent allowed the deprotection of the ketal moiety of **24** under acidic conditions to access epoxy ketone **25**, which would then serve as a coupling partner in the Stille reaction. The tin−bromide exchange reaction represents an Umpolung of the reactivity of the vinyl linker segment that was crucial for acetal hydrolysis and thus for a successful realization of our strategy toward nisamycin. Nonetheless, the yield for the hydrolysis of the acid-sensitive dimethyl acetal **24** was modest even after reaction optimization (47% based on recovered starting material), and elimination product **26** was isolated in 18%.

We decided to study the cross-coupling reaction of the advanced model **24** with amide **27** (Scheme 8). This amide was quite similar in structure to the electrophile required for completion of nisamycin. A degassed solution of bromo ketal and dienyl stannane **27**[26] was stirred at room temperature for 5.5 h with catalytic $Pd_2(dba)_2$·$CHCl_3$ in the presence of tri(2-furyl)phosphine according

Scheme 8



to the procedure of Farina et al.[27] Repeated chromatography of the crude product provided the desired coupling product **28** in 76% yield. However, treatment of **28** with PPTs in acetone/H_2O resulted in decomposition of the starting material. This negative result was analogous to that of Taylor et al., who attempted the ketal deprotection of a fully functionalized precursor of alisamycin.[12] Pd-catalyzed coupling of ketone **25** with stannane **27** did not provide a viable alternative, since the coupling product was only obtained in 24% yield after a difficult purification.

For the successful completion of the total synthesis of nisamycin, core enamine **5** was treated with acid chloride **29**, prepared in situ by exposure of TIPS ester **6** to oxalyl chloride in the presence of a catalytic amount of DMF (Scheme 9). Enone **30** was obtained in 50% yield and subjected to vinyllithium reagent **22** to afford the 1,2-addition product in 52% yield. Tin−bromine exchange proceeded smoothly using conditions previously optimized for the stannane **23**; treatment with NBS provided the vinyl bromide **31** in 88% yield. In the crucial hydrolysis step, addition of PPTs to a solution of **31** in acetone/H_2O followed by heating at 40 °C for 4 h provided the ketone **32** in 39% yield based on recovered starting material. The elimination product **26** was also isolated in 23% yield. We then examined the cross coupling of the vinyl bromide **32** with dienyl stannane **33**.[28] This Stille-type reaction was performed using preformed Pd(0) catalyst, generated by DIBAL-H reduction of $PdCl_2(PPh_3)_2$.[29] The pentaene **34** was isolated in good yield (70% based on recovered starting material). The final step in the total synthesis of (±)-nisamycin was the deprotection of the TIPS ester. An initial attempt using aqueous methanolic K_2CO_3 provided a mixture of components. We next employed methanolic CsF which effected clean and rapid conversion of the ester to the acid. Aqueous acidic workup followed by concentration of the organic layer under high vacuum provided (±)-nisamycin in quantitative yield and high purity by LC-MS analysis. An analytically pure sample was also obtained by preparative TLC. The spectral data of the synthetic sample were in full agreement with the natural product.[6]

In conclusion, we have developed a convergent synthesis of (±)-nisamycin that is applicable to other members of the manumycin family of antibiotics. The syn-

(24) (a) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 3788. (b) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581.

(25) Treatment of the vinylstannane with NBS at low temperature resulted in partial conversion to the vinyl bromide. For example, stirring the stannane with 1 equiv of NBS at −40 °C for 1 h gave a 44% yield of the vinyl bromide **24** and a 34% yield of recovered starting material. However, conducting the experiment at higher temperature (0 °C) resulted in complete consumption of stannane. At this temperature, the vinyl bromide was obtained in 82% yield as a single stereoisomer (see Experimental Section).

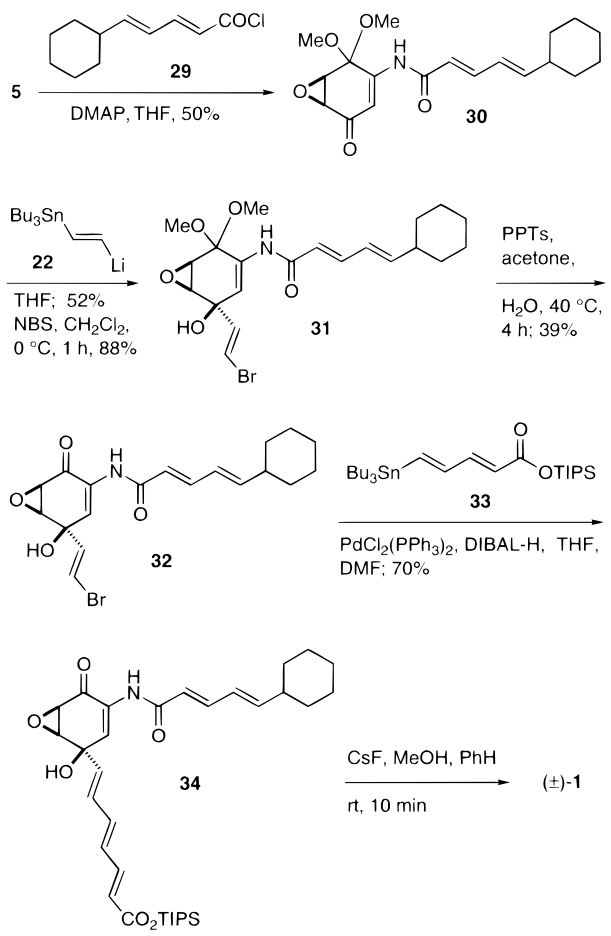
(26) This compound was prepared in 51% yield by Horner−Emmons condensation of *β*-tributylstannyl acrolein with *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (see the Experimental Section).

(27) Farina, V.; Roth, G. P. *Adv. Metal-Org. Chem.* **1996**, *5*, 1.

(28) This compound was prepared by Horner−Emmons condensation of *β*-tributylstannylacrolein with diethyl(trimethylsilyloxycarbonylmethyl)phosphorane, followed by aqueous base workup and reprotection of the acid function using TIPS−Cl and imidazole (see the Experimental Section).

(29) Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

Scheme 9



thesis features a highly functionalized cyclohexyl core **5** that was readily prepared via a three-step sequence from commercially available material. The core served as a scaffold for the attachment of the eastern and southern side chains. One-flask hydrozirconation−Zr−Zn transmetalation−1,2-addition, followed by base-mediated elimination, provided the eastern side chain of (±)-nisamycin stereoselectively. This methodology was also applied to the preparation of the eastern side chains of manumycin A and asukamycin. Umpolung of a vinylstannane addition product to the corresponding vinyl bromide allowed the crucial acetal hydrolysis to unmask the epoxyketone moiety. Subsequent Stille reaction with a dienyl stannane completed the assembly of the carbon skeleton of (±)-nisamycin, and, after TIPS ester deprotection, provided the natural product. Despite the modest overall yield of 3% for (±)-**1** due to decomposition of the acid-sensitive enamide functionality during acetal hydrolysis, the longest linear sequence is only nine steps, and thus, this strategy is well suited to gain rapid synthetic access to the manumycin class of epoxyquinol natural products.

Experimental Section

General Methods. THF and Et_2O were dried by distillation over Na/benzophenone ketyl. Dry CH_2Cl_2, DBU, DCE, and toluene were obtained by distillation from CaH_2. DMF and *t*-BuOH were dried over 4 Å sieves. BuLi (1.6 M in hexanes) was obtained from Aldrich Chemical Co. and was standandized using the procedure of Kofron and Baclawski.[30] Vinyllithium (2.2 M in THF) was obtained from Organometallics, Inc. $Pd_2(dba)_2$·$CHCl_3$, tri(2-furyl)phosphine, Me_2Zn (2 M in toluene), 1-octyne, TBHP (5.0−6.0 M in decane), *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide, cyclohexyl carboxaldehyde, and diethyl(trimethylsilyloxycarbonylmethyl)phosphonate were obtained from the Aldrich Chemical Co. $Cp_2Zr(H)Cl$ was prepared according to the procedure of Buchwald et al.[31] Cp_2ZrCl_2 was obtained from Boulder Chemicals, Inc. Other solvents or reagents were used as acquired except when otherwise noted. ^{13}C and ^1H NMR spectra were measured with 300 and 500 MHz spectrometers using $CDCl_3$ as the solvent unless stated otherwise. LCMS analysis was performed with an HP 1100 Series LC/MSD equipped with a Waters Nova-Pak C18 column and with a Finnigan LCQ (electrospray detection) equipped with a Phenomenox Luna C18 column. Column chromatography was performed using silica gel 60 (particle size 0.040−0.055 mm, 230−400 mesh). Radial chromatography was carried out on a Chromatotron using in-house plates coated with silica gel 60 (with $CaSO_4$, E. Merck, 1, 2, or 4 mm thick).

3-Amino-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-one (5). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 3.01 mL, 20.14 mmol) was added to a cold (0 °C) approximately 5 M solution of TBHP (40.25 mmol) in decane (8.05 mL). The resulting mixture was stirred for 20 min. A solution of ketone **10**[11] (1.02 g, 4.03 mmol) in 1,2-dichloroethane (10 mL) was added via cannula, giving a clear, colorless solution. The reaction mixture was allowed to warm to room temperature over a period of 5.5 h. The reaction flask was opened to the atmosphere and treated with Na_2SO_3 (3.8 g). The resulting suspension was vigorously stirred for 15 min and filtered through a pad of Celite (fritted-glass funnel, water aspirator, and elution with ethyl acetate). The filtrate was thoroughly concentrated (water aspirator) to give ∼7−8 mL of a yellow-brown solution that contained decane. The solution was filtered through a pad of silica gel (fritted-glass funnel, water aspirator, and elution with hexanes). Subsequently, the silica pad was washed with ethyl acetate (4×). The ethyl acetate extracts were concentrated to give crude product that was purified by column chromatography on SiO_2 (ethyl acetate) to afford 339 mg (45%) of solid epoxide as an approximately 85:15 mixture of **5** and **11**. Careful chromatography gave a pure sample of **5**. A similar procedure using a solution of TBHP in 1,2-dichloroethane[32] was also effective and gave a 31% yield of a 85:15 mixture of epoxide and dienone: mp 155.5−157.9 °C; IR ($CDCl_3$) 3511, 3399, 1618, 1415, 1251, 1125 cm^{-1}; ^1H NMR δ 3.30 (s, 3 H), 3.40 (dd, 1 H, J = 2.0, 4.0 Hz), 3.57 (s, 3 H), 3.73 (d, 1 H, J = 4.0 Hz), 4.96 (br s, 2 H), 5.11 (d, 1 H, J = 2.0 Hz); ^{13}C NMR δ 50.4, 51.5, 51.9, 53.0, 95.8, 96.2, 157.2, 190.8; MS (EI) *m*/*z* (rel intensity) 185 (M^+, 80), 153 (95), 126 (100); HRMS (EI) *m*/*z* calcd for $C_8H_{11}NO_4$ 185.0688, found 185.0691.

The ^1H NMR signals derived from **11** appeared in the spectrum of the mixture as follows: δ 3.17 (s, 6 H), 4.76 (br s, 2 H), 5.49 (d, 1 H, J = 2.0 Hz), 6.31 (dd, 1 H, J = 2.0, 10.0 Hz), 6.37 (d, 1 H, J = 10.0 Hz).

3-(Hexa-2′*E*,4′*E*-dienamido)-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-one (12). A 1.6 M solution of BuLi in hexanes (1.20 mL, 1.90 mmol) was added dropwise to a chilled (0 °C) solution of *t*-BuOH (182 μL, 1.90 mmol) in dry THF (2.0 mL). The resulting clear, colorless solution was stirred for 30 min and was then transferred via cannula to a −78 °C solution of ketone **5** (335 mg, 1.81 mmol) and sorbyl chloride (266 μL, 2.17 mmol) in dry THF (16.4 mL). The reaction mixture became cloudy, and then clear and yellowish, within minutes after the addition. The solution was allowed to warm to 0 °C over 30 min. Saturated aqueous NH_4Cl was added, and the mixture was warmed to room temperature. Water and ethyl acetate were added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3×). The

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combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on SiO_2 (CH_2Cl_2/EtOAc 95:5) to yield 84 mg (18%) of acylated **11** and 349 mg (69%) of the epoxy amide **12** as an oil that crystallized upon standing: mp 115.5−116.5 °C; IR ($CDCl_3$) 3402, 1693, 1666, 1608, 1236 cm^{-1}; ^1H NMR δ 1.81 (d, 3 H, J = 5.0 Hz), 3.24 (s, 3 H), 3.47 (dd, 1 H, J = 2.0, 4.0 Hz), 3.61 (s, 3 H), 3.77 (d, 1H, J = 4.0 Hz), 5.80 (d, 1 H, J = 15.0 Hz), 6.05−6.25 (m, 2 H), 7.14−7.30 (m, 2 H), 7.62 (br s, 1 H); ^{13}C NMR δ 18.8, 50.6, 51.3, 51.5, 52.1, 95.4, 108.4, 120.6, 129.4, 140.9, 144.7, 146.1, 165.3, 193.0; MS (EI) m/z (rel intensity) 279 (M^+, 3), 95 (100); HRMS (EI) m/z calcd for $C_{14}H_{17}NO_5$ 279.1107, found 279.1099.

3-(Hexa-2′*E*,4′*E*-dienamido)-4,4-dimethoxy-5,6-epoxy-1-vinylcyclohex-2-en-1-ol (13). A 2.2 M solution of vinyllithium in THF (1.97 mmol, 0.90 mL) was added to a cold (−78 °C) solution of ketone **12** (183.6 mg, 0.657 mmol) in dry THF (6.6 mL). The mixture was stirred at −78 °C for 45 min. Saturated aqueous NH_4Cl was added, and the mixture was allowed to warm to room temperature while being vigorously stirred. Et_2O and water were added, and the layers were separated. The aqueous layer was extracted with Et_2O (3×). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting oil was purified by flash chromatography on SiO_2 (CH_2Cl_2/EtOAc 8:2) to afford 186.6 mg (92%) of **13** as a colorless solid: mp 136.0−136.7 °C; IR ($CDCl_3$) 3571, 3413, 1684, 1641, 1240 cm^{-1}; ^1H NMR δ 1.80 (d, 3 H, J = 5.0 Hz), 2.23 (br s, 1 H (disappeared upon addition of D_2O)), 3.20 (s, 3 H), 3.32 (dd, 1 H, J = 2.5, 4.5 Hz), 3.51 (s, 3 H), 3.58 (d, 1 H, J = 4.5 Hz), 5.23 (dd, 1 H, J = 1.0, 10.5 Hz), 5.48 (dd, 1 H, J = 1.0, 17.0 Hz), 5.74 (d, 1 H, J = 15.0 Hz), 5.84 (dd, 1 H, J = 10.5, 17.5 Hz), 6.02−6.22 (m, 2 H), 6.58 (d, 1 H, J = 2.5 Hz), 7.12−7.35 (m, 2 H); ^{13}C NMR δ 18.6, 50.0, 50.8, 51.9, 55.9, 72.1, 95.4, 116.3, 117.0, 121.7, 128.1, 129.6, 138.3, 138.8, 142.4, 164.7; MS (EI) m/z (rel intensity) 307 (M^+, 1), 208 (55), 194 (75), 95 (100); HRMS (EI) m/z calcd for $C_{16}H_{21}NO_5$ 307.1420, found 307.1408.

2-(Hexa-2′*E*,4′*E*-dienamido)-4-hydroxy-5,6-epoxy-4-vinylcyclohex-2-en-1-one (14). A solution of ketal **13** (12 mg, 0.039 mmol) in acetone (1.1 mL) and water (137 μL) was treated at room temperature with PPTs (9.8 mg, 0.039 mmol) and $TsOH\cdot H_2O$ (2.2 mg, 0.012 mmol). The resulting clear, colorless solution was stirred at room temperature for 46 h, concentrated, and purified by radial chromatography on SiO_2 (1 mm plate, CH_2Cl_2/EtOAc, 8:2) followed by flash chromatography on SiO_2 (CH_2Cl_2/EtOAc 9:1) to afford 3.4 mg (33%) of the vinyl ketone **14** as a white solid: mp 166.3−168.7 °C; IR ($CDCl_3$) 3691, 3575, 1676, 1638, 1241 cm^{-1}; ^1H NMR δ 1.87 (d, 3 H, J = 5.0 Hz), 2.66 (br s, 1 H), 3.64 (d, 1 H, J = 4.0 Hz), 3.70 (dd, 1 H, J = 2.5, 4.0 Hz), 5.38 (d, 1 H, J = 10.5 Hz), 5.52 (d, 1 H, J = 17.0 Hz), 5.82 (d, 1 H, J = 14.5 Hz), 5.90 (dd, 1 H, J = 10.5, 17.0 Hz), 6.12−6.30 (m, 2 H), 7.20−7.30 (m, 1 H), 7.43 (d, 1 H, J = 2.5 Hz), 7.58 (br s, 1 H); ^{13}C NMR (125 MHz) δ 18.8, 53.0, 57.6, 71.5, 118.2, 120.8, 127.0, 128.2, 129.5, 137.5, 140.0, 143.6, 165.2, 188.9; MS (EI) m/z (rel intensity) 261 (M^+, 2), 206 (10), 95 (100); HRMS (EI) m/z calcd for $C_{14}H_{15}NO_5$ 261.1001, found 261.0996.

3-Butynoic Acid.[33] To a cold (0 °C) solution of concentrated H_2SO_4 (9.6 mL) and CrO_3 (1.39 g, 13.9 mmol) in distilled water (36 mL) was added a solution of 3-butyn-1-ol (0.5 g, 7.1 mmol) and acetone (7 mL) over a period of 1 h. After 3.5 h at 0 °C, the mixture was transferred to a separatory funnel and extracted with Et_2O (6×). The combined organic layers were washed with H_2O (2×), dried (Na_2SO_4), and concentrated to afford 270 mg (45%) of 3-butynoic acid as an off-white solid: ^1H NMR δ 2.25 (t, 1 H, J = 2.5 Hz), 3.38 (d, 2 H, J = 2.5 Hz).[34]

Triisopropylsilyl 3-Butynoate (15). To a solution of 3-butynoic acid (42.6 mg, 0.507 mmol) and TIPS−Cl (97.7 mg, 0.507 mmol) in CH_2Cl_2 (2.5 mL) was added imidazole (34.5 mg, 0.507 mmol). The mixture was stirred for 45 min and was then diluted with H_2O and CH_2Cl_2. The layers were separated, and the organic layer was washed with water (2×) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated to afford 115.3 mg (95%) of **15** as a colorless oil (this material contained a small amount (≤5% by ^1H NMR) of the allenyl ester **16**): IR (neat) 3295, 1728, 1274 cm^{-1}; ^1H NMR δ 1.09 (d, 18 H, J = 7.5 Hz), 1.25−1.42 (m, 3 H), 2.19 (t, 1 H, J = 2.5 Hz), 3.32 (d, 2 H, J = 2.5 Hz); ^{13}C NMR δ 12.0, 17.8, 27.3, 71.8, 76.4, 167.7; MS (EI) m/z (rel intensity) 197 ([M−C_3H_7]$^+$, 100), 153 (81), 111 (69); HRMS (EI) m/z calcd for $C_{10}H_{17}O_2Si$ (M − C_3H_7) 197.0998, found 197.0990.

Triisopropylsilyl 5-Cyclohexylpenta-2*E*,4*E*-dienoate (6). To a cold (0 °C) solution of alkyne **15** (8.715 g, 36.25 mmol) in dry, degassed CH_2Cl_2 (121 mL) was added Cp_2ZrHCl (10.3 g, 39.9 mmol) in three portions. The ice bath was removed, and the suspension was allowed to warm to room temperature over 45 min. The suspension became a clear, orange solution after approximately 6 min of warming and was subsequently chilled to −78 °C and treated with a solution of Me_2Zn in toluene (20.8 mL, 41.7 mmol) over 30 min. The −78 °C bath was replaced with a 0 °C bath, and the mixture was stirred for 25 min. A solution of cyclohexylcarboxaldehyde (4.88 g, 43.5 mmol) in dry, degassed CH_2Cl_2 (20 mL) was added dropwise via cannula. The reaction mixture was stirred at 0 °C for 3 h, transferred to a flask containing EtOAc and saturated aqueous NH_4Cl, and slowly stirred. After addition of H_2O and Et_2O, the aqueous phase was reextracted with Et_2O (3×). The combined organic extracts were washed with brine and dried (Na_2SO_4). The opaque solution was filtered through silica (55 g, EtOAc). The filtrate was concentrated, and the resulting oil was purified by flash chromatography on SiO_2 (hexanes/ethyl acetate 85:15) to afford 5.69 g (44%) of pure, oily **17**: IR (neat) 2929, 1720, 1270 cm^{-1}; ^1H NMR δ 0.68−1.40 (m, 24 H), 1.52−1.95 (m, 8 H), 3.04 (d, 2 H, J = 7.0 Hz), 3.76 (t, 1 H, J = 7.0 Hz), 5.53 (dd, 1 H, J = 7.0, 15.5 Hz), 5.68 (dt, 1 H, J = 7.0, 15.5 Hz); ^{13}C NMR δ 12.0, 17.9, 26.2, 26.3, 28.7, 29.0, 39.5, 43.7, 124.5, 135.7, 171.9; MS (EI) m/z (rel intensity) 354 (M^+, 10), 311 (100), 293 (95); HRMS (EI) m/z calcd for $C_{20}H_{38}O_3Si$ 354.2590, found 354.2597.

To a cold (−10 °C) solution of alcohol **17** (5.58 g, 15.7 mmol) in dry THF was added trifluoro-acetyl-imidazole (5.37 mL, 47.2 mmol), followed by dry pyridine (5 mL, 62 mmol). The bath was allowed to warm to approximately 10 °C over 1 h, diisopropylethylamine (13.7 mL, 78.7 mmol) was added, and the reaction mixture was allowed to warm to room temperature over 5 h. Et_2O (400 mL) and H_2O (400 mL) were added, and the organic layer was washed with saturated aqueous NH_4Cl (2×), H_2O, and brine and dried (Na_2SO_4). Flash chromatography on SiO_2 (hexanes/EtOAc 98:2) of the resulting oil afforded 2.31 g (44%) of diene **6**: IR (neat) 1692, 1250 cm^{-1}; ^1H NMR δ 0.90−1.38 (m, 24 H), 1.55−1.75 (m, 7 H), 1.96−2.12 (m, 1 H), 5.74 (d, 1 H, J = 15.0 Hz), 5.98 (dd, 1 H, J = 6.5, 15.5 Hz), 6.09 (dd, 1 H, J = 10.5, 15.5 Hz), 7.15 (dd, 1 H, J = 10.5, 15.0 Hz); ^{13}C NMR δ 12.2, 18.0, 26.0, 26.2, 32.5, 41.3, 121.3, 126.1, 146.0, 150.1, 167.1; MS (EI) m/z (rel intensity) 293 ([M − $CH(CH_3)_2$]$^+$, 100), 211 (10), 159 (10); HRMS (EI) m/z calcd for $C_{17}H_{29}O_2Si$ (M − $CH(CH_3)_2$) 293.1937, found 293.1926.

Triisopropylsilyl 7-Cyclohexylhepta-3*E*,6*E*-dienoate (18). A solution of freshly distilled **15** (534 mg, 2.22 mmol) in dry, degassed CH_2Cl_2 (22 mL) was added to a suspension of Cp_2ZrHCl (548 mg, 2.13 mmol) in CH_2Cl_2 (10 mL) while the reaction temperature was maintained near 20 °C. After 10 min, the homogeneous, orange solution was cooled to −78 °C, and a solution of Me_2Zn (2.13 mmol, 2.0 M) in toluene was added. After 5 min, the −78 °C bath was replaced with a 0 °C bath, and the reaction mixture was stirred for a further 25 min. A solution of freshly distilled (*E*)-3-cyclohexyl-2-propen-1-al[35] (267 mg, 1.93 mmol) in CH_2Cl_2 (6.4 mL) was added, and the mixture was stirred at 0 °C for 2 h and then at room temperature for 1.5 h. The mixture was cooled to 0 °C, and saturated aqueous NH_4Cl solution was added followed by, after 20 min, 2 g of $MgSO_4$. The suspension was stirred for 20 min

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and then filtered through Celite (CH_2Cl_2). Concentration of the filtrate, followed by dilution with 85:15 hexanes/EtOAc, gave a suspension that was filtered through Celite (hexanes/EtOAc 85:15). Concentration of the filtrate, followed by flash chromatography on SiO_2 (hexanes/EtOAc 85:15), afforded 443 mg (60%) of the dienyl alcohol **18** as an oil: IR ($CDCl_3$) 3511 (br), 3330, 1708, 1464, 1342, 1189, 1072, 972, 764 cm^{-1}; ^1H NMR δ 0.94−1.40 (m, 27 H), 1.57−1.78 (m, 5 H), 1.87−2.04 (m, 1 H), 3.12 (d, 2 H, J = 7 Hz), 4.57 (t, 1 H, J = 6 Hz), 5.44 (dd, 1 H, J = 6.5, 16 Hz), 5.58−5.71 (m, 2 H), 5.73−5.87 (m, 1 H); ^{13}C NMR δ 12.1, 18.0, 26.1, 26.2, 32.9, 39.5, 40.5, 73.6, 123.9, 128.6, 135.7, 138.8, 171.8; MS (EI) m/z (rel intensity) 380 (M^+, 10), 337 (55); HRMS (EI) m/z calcd for $C_{19}H_{33}O_3Si$ (M − $CH(CH_3)_2$) 337.2199, found 337.2188.

Triisopropylsilyl 7-Cyclohexylhepta-2*E*,4*E*,6*E*-trienoate (19). To a cooled (−10 °C) solution of **18** (37.7 mg, 0.099 mmol) in dry THF (1 mL) was added TFAA (41.6 mg, 0.198 mmol), followed by pyridine (15.7 mg, 0.20 mmol). The reaction mixture was allowed to warm to 5 °C over 1 h. Diisopropylethylamine (76.8 mg, 0.594 mmol) was added, and the solution was allowed to warm to room temperature over a 2.5 h period. The reaction mixture was concentrated to approximately half of the original volume and purified by chromatography on a 1 mm SiO_2 chromatotron plate (hexanes/EtOAc 98:2) to yield 21.4 mg (60%) of **19** as a yellow-brown oil: IR ($CDCl_3$) 1679, 1275 cm^{-1}; ^1H NMR δ 1.00−1.42 (m, 27 H), 1.60−1.82 (m, 4 H), 2.00−2.15 (m, 1 H), 5.78−5.95 (m, 2 H), 6.11 (dd, 1 H, J = 10.5, 15 Hz), 6.23 (dd, 1 H, J = 11.5, 15 Hz), 6.52 (dd, 1 H, J = 10.5, 15 Hz), 7.26 (dd, 1 H, J = 11.5, 15 Hz); ^{13}C NMR δ 12.3, 18.1, 26.1, 26.3, 32.7, 41.3, 121.9, 127.5, 128.1, 141.8, 145.6, 146.3, 167.1; MS (EI) m/z (rel intensity) 362 (M^+, 51), 319 (100); HRMS (EI) m/z calcd for $C_{19}H_{31}O_2Si$ (M − $CH(CH_3)_2$) 319.2093, found 319.2108.

Triisopropylsilyl 7-(Tributylstannyl)hepta-3*E*,6*E*-dienoate (20). To a suspension of Cp_2ZrHCl (1.56 g, 6.05 mmol) in dry, degassed CH_2Cl_2 (37 mL) was added at 0 °C a solution of freshly distilled **15** (1.60 g, 6.66 mmol) in CH_2Cl_2 (24 mL). After 20 min, the homogeneous orange solution was cooled to −78 °C, and a solution of Me_2Zn (6.0 mmol, 2.0 M) in toluene was added. After 5 min, the −78 °C bath was replaced with a 0 °C bath, and the reaction mixture was stirred for another 30 min. A solution of (*E*)-3-tributylstannyl-2-propen-1-al[36] (1.89 g, 5.48 mmol) in CH_2Cl_2 (27 mL) was added, and the reaction mixture was stirred at 0 °C for 3 h. After addition of saturated aqueous NH_4Cl, the mixture was allowed to warm to room temperature over 15 min and treated with Na_2SO_4 (2 g). After 10 min, the suspension was filtered through approximately 5 g of Celite (CH_2Cl_2). Concentration of the filtrate was followed by dilution with hexanes to give a suspension that was filtered through Celite (hexanes/EtOAc 80:20). Concentration of the filtrate followed by flash chromatography on SiO_2 (hexanes/EtOAc 93:7) afforded 2.35 g (73%) of the dienyl alcohol **20** as an oil: IR (neat) 3419 (br), 1724, 1265 cm^{-1}; ^1H NMR (C_6D_6) δ 0.85−1.75 (m, 49 H), 2.91 (d, 2 H, J = 7 Hz), 4.42−4.52 (m, 1 H), 5.53 (dd, 1 H, J = 6, 15.5 Hz), 5.79−5.92 (m, 1 H), 6.17 (dd, 1 H, J = 5, 19 Hz), 6.34 (d, 1 H, J = 19 Hz); ^{13}C NMR (C_6D_6) δ 10.1, 12.6, 14.3, 18.4, 28.1, 29.8, 39.5, 76.0, 123.8, 127.7, 136.6, 150.4, 171.9; MS (EI) m/z (rel intensity) 531 ([M − C_4H_9]$^+$, 36), 529 (31); HRMS (EI) m/z calcd for $C_{24}H_{47}O_3Si^{120}Sn$ (M − C_4H_9) 531.2316, found 531.2326.

Triisopropylsilyl 7-(Tributylstannyl)hepta-2*E*,4*E*,6*E*-trienoate (21). To a cooled (−10 °C) solution of **20** (426 mg, 0.725 mmol) in dry THF was added CF_3CO-imidazole (357 mg, 2.18 mmol), followed by pyridine (201 mg, 2.54 mmol). The reaction mixture was allowed to warm to 5 °C over 1 h. Diisopropylethylamine (469 mg, 3.63 mmol) was added, and the reaction mixture was allowed to warm to 15 °C over a 2.5 h period. After addition of H_2O and Et_2O, the organic layer was washed sequentially with saturated aqueous NH_4Cl (2×), H_2O, and brine. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the crude residue by column chromatography on SiO_2 (hexanes/EtOAc 96:4) afforded 310 mg (75%) of **21** as a yellow-brown oil: IR (C_6D_6) 1685, 1267 cm^{-1}; ^1H NMR (C_6D_6) δ 0.75−1.05 (m, 15 H), 1.17 (d, 18 H, J = 7.5 Hz), 1.25−1.75 (m, 15 H), 5.90−6.05 (m, 2 H), 6.25 (dd, 1 H, J = 10, 15 Hz), 6.46 (d, 1 H, J = 18.5 Hz), 6.66 (dd, 1 H, J = 10, 18.5 Hz), 7.51 (dd, 1 H, J = 11.5, 15 Hz); ^{13}C NMR (C_6D_6) δ 10.2, 12.8, 14.3, 18.5, 28.0, 29.9, 124.1, 129.6, 141.3, 143.1, 145.6, 147.0, 166.6; MS (EI) m/z (rel intensity) 513 ([M − C_4H_9]$^+$, 100), 511 (75); HRMS (EI) m/z calcd for $C_{24}H_{45}O_2Si^{120}Sn$ (M − C_4H_9) 513.2211, found 513.2226.

3-(Hexa-2′*E*,4′*E*-dienamido)-1-(2″*E*-tributylstannylethenyl)-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-ol (23). A solution of BuLi in hexanes (201 μL, 0.322 mmol) was added dropwise over 5 min to a cold (−78 °C) solution of 1,2-di-(tributylstannyl)ethene[24] (250 mg, 0.413 mmol) in dry THF (3.3 mL). The reaction mixture was stirred at −78 °C for 30 min and was then allowed to warm to 0 °C over 1 h. The solution was rechilled to −78 °C, and a solution of ketone **12** (30.0 mg, 0.107 mmol) in dry THF (1.1 mL) was added via cannula. The resulting dark mixture was stirred at −78 °C for 45 min and quenched by addition of saturated aqueous NH_4Cl solution followed by H_2O. Ethyl acetate was added, and the aqueous phase was re-extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography on SiO_2 (1 mm plate, CH_2Cl_2/EtOAc 9:1) to afford 35.1 mg (55%) of **23** as an off-white solid: mp 87.7−88.6 °C; IR ($CDCl_3$) 3577, 3415, 1791, 1677, 1246 cm^{-1}; ^1H NMR (C_6D_6) δ 0.80−1.10 (m, 15 H), 1.25−1.75 (m, 15 H), 2.32 (s, 1 H), 3.10 (s, 3 H), 3.20 (s, 3 H), 3.25−3.35 (m, 2 H), 5.25 (d, 1 H, J = 14.5 Hz), 5.50−5.66 (m, 1 H), 5.86 (dd, 1 H, J = 10.5, 14.5 Hz), 6.31 (d, 1 H, J = 19.0 Hz), 6.85 (d, 1 H, J = 19.0 Hz), 7.23 (br s, 1 H), 7.44 (d, 1 H, J = 10.5, 14.5 Hz); ^{13}C NMR δ 9.7, 13.9, 18.9, 27.5, 29.2, 50.2, 51.1, 52.3, 56.3, 73.8, 95.8, 116.7, 121.9, 128.3, 129.7, 130.8, 139.1, 142.6, 146.4, 164.7; MS (EI) m/z (rel intensity) 540 ([M − C_4H_9]$^+$, 8), 95 (100); HRMS (EI) m/z calcd for $C_{24}H_{38}NO_5{}^{120}Sn$ (M^+ − C_4H_9) 540.1772, found 540.1802.

3-(Hexa-2′*E*,4′*E*-dienamido)-1-(2″*E*-bromoethenyl)-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-ol (24). Solid *N*-bromosuccinimide (139.6 mg, 0.785 mmol) was added in one portion to a cold (0 °C) solution of stannane **23** (445.6 mg, 0.747 mmol) in dry, degassed CH_2Cl_2 (7.5 mL). The reaction mixture was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution. CH_2Cl_2 was added, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by radial chromatography on SiO_2 (2 mm plate, followed by a 1 mm plate for impure fractions, CH_2Cl_2/EtOAc 9:1) to afford 236.5 mg (82%) of the vinyl bromide **24** as an off-white solid: mp 110−113 °C dec; IR ($CDCl_3$) 3579, 3409, 1791, 1677, 1240 cm^{-1}; ^1H NMR (C_6D_6) δ 1.43 (d, 3 H, J = 6.5 Hz), 2.04 (s, 1 H, exchanges with D_2O), 2.75 (s, 3 H), 2.95−3.02 (m, 1 H), 3.05−3.11 (m, 4 H), 5.20 (d, 1 H, J = 14.5 Hz), 5.54−5.70 (m, 1 H), 5.87 (dd, 1 H, J = 10.5, 14.5 Hz), 6.25 (d, 1 H, J = 13.5 Hz), 6.68 (d, 1 H, J = 13.5 Hz), 7.06 (d, 1 H, J = 2.0 Hz), 7.47 (dd, 1 H, J = 10.5, 14.5 Hz); ^{13}C NMR δ 18.9, 50.2, 51.0, 51.9, 55.3, 73.2, 95.5, 109.8, 115.1, 121.6, 129.2, 129.6, 137.1, 139.5, 143.0, 164.9; MS (EI) m/z (rel intensity) 385 (M^+, 1), 208 (50), 95 (100); HRMS (EI) m/z calcd for $C_{16}H_{20}NO_5Br$ 385.0525, found 385.0509.

2-(Hexa-2′*E*,4′*E*-dienamido)-4-(2″*E*-bromoethenyl)-4-hydroxy-5,6-epoxycyclohex-2-en-1-one (25). A solution of ketal **24** (33.4 mg, 0.086 mmol) and PPTS (54.3 mg, 0.216 mmol) in acetone (247 μL) and H_2O (117 μL) was heated at 40 °C for 4 h. The clear, yellow-brown solution was concentrated and subjected to radial chromatography on SiO_2 (1 mm plate, CH_2Cl_2/EtOAc 9:1) to yield 10.7 mg (36%, 47% based on recovered starting material) of the vinyl bromide **25** as a white solid: mp 85 °C dec; IR ($CDCl_3$) 3688, 3570, 1678, 1240 cm^{-1}; ^1H NMR (C_6D_6) δ 1.44 (d, 3 H, J = 6.0 Hz), 2.7 (s, 1 H), 2.88−2.95 (m, 1 H), 3.02 (d, 1 H, J = 3.5 Hz), 5.00 (d, 1 H, J = 14.5 Hz), 5.54−5.74 (m, 1 H), 5.68 (d, 1 H, J = 13.5 Hz), 5.76−5.90 (m, 1 H), 6.50 (d, 1 H, J = 13.5 Hz), 7.29 (br s, 1 H), 7.39 (dd, 1 H, J = 10.5, 14.5 Hz), 7.55 (d, 1 H, J = 2.5 Hz); ^{13}C NMR δ 18.9, 52.9, 57.1, 72.3, 111.7, 120.7, 125.9, 128.4, 129.6, 136.5,

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140.5, 144.1, 165.6, 188.6; MS (EI) *m/z* (rel intensity) 341 (0.5), 339 (M^+, 0.5), 260 (1), 243 (1), 163 (15), 135 (15), 95 (100), 67 (35); HRMS (EI) calcd for $C_{14}H_{14}NO_4Br$ 339.0106, found 339.0112. Also isolated was 4.4 mg (18%) of the elimination product **26** as a yellow solid: mp 74.7−77.4 °C; IR ($CDCl_3$) 1681, 1173 cm^{-1}; ^1H NMR δ 3.22 (s, 3 H), 3.51 (s, 3 H), 3.66 (dd, 1 H, J = 2.0, 4.0 Hz), 3.80 (d, 1 H, J = 4.0 Hz), 5.89 (d, 1 H, J = 2.0 Hz), 6.93 (d, 1 H, J = 14.0 Hz) 7.13 (d, 1 H, J = 14.0 Hz); ^{13}C NMR δ 47.0, 50.2, 50.8, 53.7, 94.0, 116.4, 126.5, 136.3, 149.2, 188.6; MS (EI) *m/z* (rel intensity) 274 (M^+, 0.5), 217 (25), 215 (25), 195 (20), 167 (80); HRMS (EI) *m/z* calcd for $C_{10}H_{11}O_4Br$ 273.9841, found 273.9854.

***N*-Methoxy-*N*-methyl-5-tributylstannyl-penta-2*E*,4*E*-dienamide (27).** *N*-Methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (212.4 mg, 0.585 mmol) was added in one portion at room temperature to a solution of (*E*)-3-tributylstannyl-2-propen-1-al (183.4 mg, 0.531 mmol) in dry THF (5.3 mL). After 5 h, the clear, colorless solution was concentrated and subjected to radial chromatography on SiO_2 (1 mm plate, hexanes/EtOAc 8:2) to give 87 mg of starting material and 104.6 mg (46%, 87% based recovered starting material) of dienyl amide **27** as an oil: IR (neat) 1654 cm^{-1}; ^1H NMR (C_6D_6) δ 0.80−1.10 (m, 15 H), 1.25−1.70 (m, 12 H), 2.96 (s, 3 H), 3.03 (s, 3 H), 6.60 (d, 1 H, J = 15.0 Hz), 6.69 (d, 1 H, J = 18.5 Hz), 6.91 (dd, 1 H, J = 10.5, 18.5 Hz), 7.78 (dd, 1 H, J = 10.5, 15.0 Hz); ^{13}C NMR δ 9.8, 13.9, 27.4, 29.3, 32.7, 62.0, 117.8, 144.9, 145.5, 146.2, 167.7; MS (EI) *m/z* (rel intensity) 374 (M^+, 100); HRMS (EI) *m/z* calcd for $C_{15}H_{28}NO_2{}^{120}Sn$ 374.1142, found 374.1145.

3-(Hexa-2′*E*,4′*E*-dienamido)-1-(*N*-methoxy-*N*-methyl-hepta-1″*E*,3″*E*,5″*E*-trienylamido)-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-ol (28). To a solution of vinyl bromide **24** (30 mg, 0.078 mmol), dienyl stannane **27** (35.1 mg, 0.0817 mmol), and tri(2-furyl)phosphine (3.6 mg, 0.016 mmol) in dry, degassed DMF (390 μL) was added at room temperature $Pd_2(dba)_2{\cdot}CHCl_3$ (8.0 mg, 0.0078 mmol). After 5.5 h, the solvent was removed under reduced pressure, and the resulting oil was purified by radial chromatography on SiO_2 (2 × 1 mm plate, EtOAc/pentane 2:8) to afford 26.5 mg (76%) of ketal **28**: mp 80 °C dec; IR (C_6D_6) 3411, 3232, 1652 cm^{-1}; ^1H NMR (C_6D_6) δ 1.43 (d, 3 H, J = 6.5 Hz), 2.36 (s, 1 H), 2.96 (s, 3 H), 2.98 (s, 3 H), 3.07 (s, 3 H), 3.12−3.28 (m, 5 H), 5.27 (d, 1 H, J = 15.0 Hz), 5.52−5.62 (m, 1 H), 5.75 (d, 1 H, J = 15.0 Hz), 5.85 (dd, 1 H, J = 10.5, 15 Hz), 6.10−6.28 (m, 2 H), 6.50 (d, 1 H, J = 15 Hz), 6.71 (dd, 1 H, J = 10.0, 15.0 Hz), 7.0−7.2 (m, 1 H), 7.24 (br s, 1 H), 7.48 (dd, 1 H, J = 10.5, 15.0 Hz), 7.71 (dd, 1 H, J = 10.5, 15.0 Hz); ^{13}C NMR (C_6D_6) δ 18.8, 32.6, 50.0, 50.8, 52.2, 56.3, 61.5, 72.6, 96.5, 117.3, 120.4, 122.7, 129.2, 130.3, 131.0, 132.2, 137.8, 138.6, 139.8, 142.9, 143.7, 164.6, 167.5; MS (FAB) *m/z* (rel intensity) 469 ([M + Na]$^+$, 100); HRMS (FAB) *m/z* calcd for $C_{23}H_{30}N_2O_7Na$ (M + Na) 469.1951, found 469.1933.

3-(5-Cyclohexylpenta-2*E*,4*E*-dienamido)-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-one (30). Dry DMF (10 μL) was added to a cold (0 °C) solution of TIPS ester **6** (1.089 g, 3.236 mmol) and oxalyl chloride (564 μL, 6.47 mmol) in dry CH_2Cl_2 (3.2 mL). The clear, colorless solution was stirred at 0 °C for 1.5 h and allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure, and after addition of dry toluene, the mixture was concentrated in vacuo. Dry THF (11 mL) was added, and the solution was cannulated under Ar to a flask containing dry epoxide **5** (509 mg, 2.75 mmol). The reaction mixture was cooled to −78 °C, and a mixture of DMAP (39.5 mg, 0.324 mmol), diisopropylethylamine (672 μL, 3.88 mmol), and dry THF (693 μL) was added. The solution was allowed to warm to room temperature over 1.5 h and diluted with EtOAc, and saturated aqueous NH_4Cl was added. The organic layer was extracted with saturated aqueous NH_4Cl (2×), H_2O, and brine, dried (Na_2SO_4), and purified by radial chromatography on SiO_2 (4 mm plate, CH_2Cl_2/EtOAc 98:2) to afford 0.48 g (50%) of the amide **30** as an off-white solid: mp 137.3−137.7 °C; IR ($CDCl_3$) 3400, 1730, 1668, 1246 cm^{-1}; ^1H NMR (C_6D_6) δ 0.85−1.24 (m, 5 H), 1.50−1.68 (m, 5 H), 1.75−1.90 (m, 1 H), 2.74 (s, 3 H), 3.08 (d, 1 H, J = 4.0 Hz), 3.15 (s, 3 H), 3.29 (dd, 1 H, J = 2.0, 4.0 Hz), 5.05 (d, 1 H, J = 14.5 Hz), 5.65 (dd, 1 H, J = 6.5, 15.5 Hz), 5.81 (dd, 1 H, J = 10.5, 15.5 Hz), 7.35 (dd, 1 H, J = 10.5, 14.5 Hz), 7.95 (d, 1 H, J = 2.0 Hz); ^{13}C NMR δ 25.9, 26.1, 32.3, 41.3, 50.9, 51.5, 51.6, 52.3, 95.6, 108.9, 120.9, 125.6, 145.4, 145.8, 151,9, 165.2, 193.0; MS (EI) *m/z* (rel intensity) 347 (M^+, 10), 225 (40), 135 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{25}NO_5$ 347.1733, found 347.1718.

3-(5-Cyclohexylpenta-2*E*,4*E*-dienamido)-1-(2″*E*-bromoethenyl)-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-ol (31). A solution of BuLi in hexanes (0.78 mL, 1.18 mmol) was added dropwise via syringe pump over 5 min to a cold (−78 °C) solution of di(tributylstannyl)ethene[24] (953 mg, 1.573 mmol) in dry THF (10.5 mL). After 30 min, the solution was stirred for 90 min at −10 °C bath and then rechilled to −78 °C. A solution of ketone **30** (136.6 mg, 0.393 mmol) in dry THF (3.9 mL) was added dropwise via syringe pump over 5 min. The reaction mixture was stirred at −78 °C for 70 min, quenched with saturated aqueous NH_4Cl, and allowed to warm to room temperature. After addition of H_2O and EtOAc, the aqueous layer was extracted with EtOAc (3×), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting liquid was filtered through a short pad of SiO_2 in (hexanes/EtOAc 95:5, followed by EtOAc). The EtOAc filtrate was concentrated, and the resulting oil was purified by flash chromatography on SiO_2 (CH_2Cl_2/EtOAc 98:2, followed by CH_2Cl_2/EtOAc 95:5) to afford 135 mg (52%, 57% based on recovered starting material) of the vinyl stannane intermediate as a white solid: mp 78.2−81.0 °C; IR ($CDCl_3$) 3695, 3577, 3415, 1678 cm^{-1}; ^1H NMR δ 0.70−1.75 (m, 37 H), 1.92−2.10 (m, 1 H), 2.62 (s, 1 H), 3.15 (s, 3 H), 3.26 (dd, 1 H, J = 2.5, 4.5 Hz), 3.47 (s, 3 H), 3.51 (d, 1 H, J = 4.5 Hz) 5.75 (d, 1 H, J = 15.0 Hz), 5.90 (d, 1 H, J = 19.5 Hz), 5.95−6.12 (m, 2 H), 6.40 (d, 1 H, J = 19.5 Hz), 6.58 (br s, 1 H), 7.12 (dd, 1 H, J = 10.0, 15.0 Hz), 7.25 (br s, 1 H); ^{13}C NMR δ 9.7, 13.8, 26.0, 26.2, 27.4, 29.0, 32.4, 41.2, 50.2, 51.0, 52.2, 56.2, 73.7, 95.8, 116.9, 122.2, 125.8, 128.2, 130.5, 142.9, 146.5, 149.7, 164.7; MS (EI) *m/z* (rel intensity) 638 ([M−C_4H_9]$^+$, 2), 251 (25); HRMS (EI) *m/z* calcd for $C_{29}H_{46}NO_5{}^{120}Sn$ (M − C_4H_9) 608.2398, found 608.2394.

To a cold (0 °C) solution of this stannane in dry, degassed CH_2Cl_2 (1.4 mL) was added solid *N*-bromosuccinimide (26.1 mg, 0.147 mmol) in one portion. The reaction mixture was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4) and purified by radial chromatography on SiO_2 (1 mm plate, CH_2Cl_2/EtOAc 9:1) to afford 55.9 mg (88%) of the vinyl bromide **31** as a white solid: mp 78−83 °C dec; IR ($CDCl_3$) 3578, 3413, 1679, 1246 cm^{-1}; ^1H NMR δ 0.95−1.32 (m, 5 H), 1.54−1.75 (m, 5 H), 1.90−2.1 (m, 1 H), 3.18 (s, 3 H), 3.28 (dd, 1 H, J = 2.5, 4.5 Hz), 3.40 (br s, 1 H), 3.47 (s, 3 H), 3.52 (d, 1 H, J = 4.5 Hz), 5.76 (d, 1 H, J = 14.5 Hz), 6.00−6.06 (m, 2 H), 6.11 (d, 1 H, J = 13.5 Hz), 6.54 (d, 1 H, J = 13.5 Hz), 6.55 (d, 1 H, J = 2.5 Hz), 7.06−7.20 (m, 1 H), 7.31 (br s, 1 H); ^{13}C NMR δ 26.0, 26.2, 32.4, 41.3, 50.1, 50.9, 51.7, 55.2, 73.2, 95.5, 109.7, 115.3, 121.7, 125.7, 129.0, 137.3, 143.5, 150.2, 164.9; MS (EI) *m/z* (rel intensity) 453 (M^+, 2), 276 (85), 262 (85); HRMS (EI) *m/z* calcd for $C_{21}H_{28}NO_5Br$ 453.1151, found 453.1173.

3-(2-Cyclohexylpenta-2*E*,4*E*-dienamido)-4-(2″-bromoethenyl)-4-hydroxy-5,6-epoxycyclohex-2-en-1-one (32). A solution of ketal **31** (114 mg, 0.251 mmol) and PPTS (158 mg, 0.627 mmol) in acetone (0.72 mL) and H_2O (0.34 mL) was heated at 40 °C for 4 h. The clear, yellow-brown solution was concentrated and subjected to radial chromatography on SiO_2 (4 mm plate, CH_2Cl_2/EtOAc 95:5) to afford 15.6 mg (23%) of the elimination product **26** and 32.8 mg (35%, 39% based on recovered starting material) of the bromo ketone **32** as a yellow solid: IR ($CDCl_3$) 3692, 3575, 3388, 1676, 1242 cm^{-1}; ^1H NMR δ 1.00−1.35 (m, 5 H), 1.55−1.80 (m, 5 H), 2.0−2.12 (m, 1 H), 3.58 (d, 1 H, J = 4.0 Hz), 3.62−3.70 (m, 1 H), 5.79 (d, 1 H, J = 15 Hz), 6.00−6.15 (m, 2 H), 6.12 (d, 1 H, J = 13.5 Hz), 6.64 (d, 1 H, J = 13.5 Hz), 7.12−7.25 (m, 1 H), 7.33 (d, 1 H, J = 2.5 Hz), 7.53 (br s, 1 H); ^{13}C NMR δ 26.0, 26.2, 32.4, 41.4, 52.9, 57.1, 72.4, 111.6, 120.9, 125.7, 126.0, 128.3, 136.6, 144.7, 151.3, 165.6, 188.7; MS (EI) *m/z* (rel intensity) 407 (M^+, 2), 274 (55),

231 (50), 203 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{22}NO_4Br$ 407.0732, found 407.0726.

Triisopropylsilyl 5-(Tributylstannyl)penta-2*E*,4*E*-dienoate (33). A solution of BuLi in hexanes (290 μL, 0.463 mmol) was added dropwise to a solution of diethyl(trimethylsilyloxycarbonylmethyl)phosphonate (124.3 mg, 0.463 mmol) in THF (4 mL). The reaction mixture was stirred at room temperature for 0.5 h. To the resulting clear, colorless solution was cannulated a solution of (*E*)-3-tributylstannyl-2-propen-1-al (143.9 mg, 0.417 mmol) in THF (154 μL). The mixture, which became slightly yellow within minutes, was stirred at room temperature for 1.5 h and quenched with saturated aqueous $NaHCO_3$, H_2O, and EtOAc. The aqueous layer was extracted with EtOAc (2×). The combined organic layers were dried (Na_2SO_4) and purified by radial chromatography on SiO_2 (1 mm plate, hexanes/EtOAc 75:25, followed by hexanes/EtOAc 50:50, EtOAc, and MeOH) to afford 114.6 mg (71%) of dienyl acid as a slightly yellow oil: IR (neat) 2969, 1691, 1231 cm^{-1}; ^1H NMR δ 0.76−1.10 (m, 15 H), 1.20−1.65 (m, 12 H), 5.75 (d, 1 H, J = 15.5 Hz), 6.64 (dd, 1 H, J = 10.5, 18.5 Hz), 6.86 (d, 1 H, J = 18.5 Hz), 7.22 (dd, 1 H, J = 10.0, 15.5 Hz), 11.5 (br s, 1 H); ^{13}C NMR δ 9.8 ($^1J_{Sn-C}$ = 338 Hz), 13.9, 27.5 ($^2J_{Sn-C}$ = 55 Hz), 29.3 ($^3J_{Sn-C}$ = 21 Hz), 119.2, 144.2, 148.7 (J_{Sn-C} = 70 Hz), 149.6, 173.4; MS (EI) *m/z* (rel intensity) 331 (M^+, 15), 275 (100), 219 (80); HRMS (EI) *m/z* calcd for $C_{13}H_{23}O_2{}^{120}Sn$ 331.0720, found 331.0719.

Imidazole (58.4 mg, 0.858 mmol) was added to a room-temperature solution of dienyl acid (332.1 mg, 0.858 mmol) and TIPS−Cl (165.4 mg, 0.858 mmol) in dry CH_2Cl_2 (2.8 mL). The resulting white suspension was stirred for 1 h and quenched with H_2O and CH_2Cl_2, and the organic layer was washed with H_2O (2×) and brine, dried (Na_2SO_4), and concentrated. Flash chromatography on SiO_2 (hexanes/EtOAc 97:3) gave 425 mg (91%) of ester **33** as a clear, colorless oil: IR (neat) 2958, 1694 cm^{-1}; ^1H NMR δ 0.80−0.95 (m, 15 H), 1.0−1.1 (m, 18 H), 1.20−1.62 (m, 15 H), 5.77 (d, 1 H, J = 15.5 Hz), 6.62 (dd, 1 H, J = 10.0, 18.5 Hz), 6.76 (d, 1 H, J = 18.5 Hz), 7.10 (dd, 1 H, J = 10.0, 15.5 Hz); ^{13}C NMR δ 9.8 (J_{Sn-C} = 330 Hz), 12.2, 13.9, 18.1, 27.5 (J_{Sn-C} = 54 Hz), 29.3 (J_{Sn-C} = 21 Hz), 122.0, 144.6, 146.9, 147.3, 167.3; MS (EI) *m/z* (rel intensity) 501 ($[M - CH(CH_3)_2]^+$, 25), 487 ($[M - C_4H_9]^+$, 100), 211 (70); HRMS (EI) *m/z* calcd for $C_{22}H_{43}O_2Si^{120}Sn$ ($M - C_4H_9$) 487.2054, found 487.2051.

2-(Hexa-2′*E*,4′*E*-dienamido)-4-(triisopropylsilylhepta-1″*E*,3″*E*,5″*E*-trienoate)-4-hydroxy-5,6-epoxycyclohex-2-en-1-one (34). A solution of DIBAL-H in hexanes (114 μL, 0.114 mmol) was added to a solution of $PdCl_2(PPh_3)_2$ (38 mg, 0.054 mmol) in dry degassed THF (3.8 mL). The resulting dark brown mixture was stirred at room temperature for 20 min. A portion of this mixture (1.7 mL) was added to a degassed solution of stannane **33** (99 mg, 0.182 mmol) and bromide **32** (49.4 mg, 0.121 mmol) in dry DMF (1.2 mL). The mixture was stirred at room temperature for 14.5 h and quenched with EtOAc, H_2O, and brine. The organic layer was washed with a 3:1 mixture of H_2O/brine (3×), dried (Na_2SO_4), and concentrated. Radial chromatography on SiO_2 (1 mm plate, CH_2Cl_2/EtOAc 95:5, followed by CH_2Cl_2/EtOAc 9:1) afforded 40.8 mg (58%, 70% based on recovered starting material) of keto ester **34** as a viscous, yellow oil: IR ($CDCl_3$) 3572, 3391, 1678 cm^{-1}; ^1H NMR δ 0.96−1.40 (m, 26 H), 1.55−1.80 (m, 5 H), 2.00−2.15 (m, 1 H), 2.83 (br s, 1 H), 3.59 (d, 1 H, J = 4.0 Hz), 3.66 (dd, 1 H, J = 2.5, 4.0 Hz), 5.77 (d, 1 H, J = 14.0 Hz), 5.80 (d, 1 H, J = 15.0 Hz), 5.88 (d, 1 H, J = 15.0 Hz), 6.00−6.20 (m, 2 H), 6.3−6.6 (m, 3 H), 7.11−7.26 (m, 2 H), 7.36 (d, 1 H, J = 2.5 Hz), 7.52 (br s, 1 H); ^{13}C NMR δ 12.2, 18.0, 26.0, 26.2, 32.5, 41.4, 53.1, 57.7, 71.4, 121.1, 124.4, 125.7, 126.9, 128.2, 131.9, 132.5, 135.8, 138.6, 144.3, 144.4, 151.1, 165.5, 166.7, 188.9; MS (EI) *m/z* (rel intensity) 581 (M^+, 8), 538 ($[M - CH(CH_3)_2]^+$, 100); HRMS (EI) *m/z* calcd for $C_{30}H_{40}NO_6Si$ ($M - CH(CH_3)_2$) 538.2625, found 538.2628.

(±)-Nisamycin (1). A solution of CsF (12.2 mg, 0.0804 mmol) in MeOH (2.0 mL) was added at room temperature to a solution of the TIPS ester **34** (23.4 mg, 0.0402 mmol) in benzene (2.5 mL). The resulting slighly yellow solution was stirred for 15 min and treated with CH_2Cl_2 followed by a 0.1 M aqueous KH_2PO_4 solution and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to afford a quantitative yield of (±)-nisamycin as a yellowish solid. LCMS analysis of this material was in agreement with high-purity nisamycin. An analytically pure sample was obtained by preparative TLC (CH_2Cl_2/MeOH, 95:5): IR ($CDCl_3$) 3692, 3640, 1722, 1678, 1240 cm^{-1}; ^1H NMR (500 MHz) δ 1.05−1.20 (m, 3 H, 7′ax, 9′ax, 11′ax), 1.20−1.32 (m, 2 H, 8′ax, 10′ax), 1.60−1.67 (m, 1 H, 9′eq), 1.67−1.78 (m, 4 H, 7′eq, 8′eq, 10′eq, 11′eq), 2.01−2.12 (m, 1 H, 6′), 3.3 (br s, 1 H, OH), 3.62 (d, 1 H, J = 4.0 Hz, H6), 3.69 (dd, 1 H, J = 2.5, 4.0 Hz, H4), 5.81 (d, 1 H, J = 15.0 Hz, H2′), 5.84 (d, 1 H, J = 14.5 Hz, H7), 5.90 (d, 1 H, J = 15.0 Hz, H12), 6.10−6.15 (m, 2 H, H4′, H5′), 6.35−6.45 (m, 1 H, H10), 6.50−6.62 (m, 2 H, H8, H9), 7.17−7.25 (m, 1 H, H3′), 7.32 (dd, 1 H, J = 11.0, 15.0 Hz, H11), 7.38 (d, 1 H, J = 2.5 Hz, H3), 7.55 (s, 1 H, NH); ^{13}C NMR (125 MHz) δ 25.79 (C8′, 10′), 25.97 (C9′), 32.21 (C7′, 11′), 41.14 (C6′), 52.89 (C6), 57.36 (C5), 71.17 (C4), 120.81 (C2′), 121.21 (C12), 125.46 (C4′), 126.42 (C3), 128.00 (C2), 131.57 (C8), 131.94 (C10), 136.30 (C7), 139.47 (C9), 144.32 (C3′), 145.82 (C11), 150.92 (C5′), 165.26 (C1′), 170.91 (C13), 188.61 (C1) (^{13}C and ^1H assignments were based in part on COSY, HMQC, and HMBC data); FAB HRMS *m/z* calcd for $C_{24}H_{28}NO_6$ (M + H) 426.1917, found 426.1934.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all synthetic intermediates and ^1H and ^{13}C NMR and LC-MS spectra for nisamycin. This material is available free of charge via the Internet at http://pubs.acs.org.

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