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Total Synthesis of the Potent Antitumor Polyketide (−)-Callystatin A†

Luiz C. Dias* and Paulo R. R. Meira

Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C. P. 6154, CEP 13084-971, Campinas, SP, Brazil

ldias@iqm.unicamp.br

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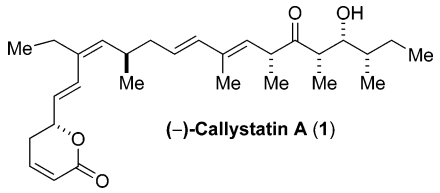

A highly convergent and efficient total synthesis of the potent antitumor polyketide (−)-callystatin A is described. The synthesis required 19 steps from *N*-propionyl oxazolidinone **23** and produced the desired product in 3.5% overall yield.

Introduction

The potent antitumor polyketide (−)-callystatin A (**1**) was isolated in 1997 by Kobayashi and co-workers from the marine sponge *Callyspongia truncata* (Figure 1).[1] (−)-Callystatin A (**1**) shows remarkable high activity (IC_{50} = 10 pg/mL) against KB tumor cell lines and IC_{50} = 20 pg/mL against L1210 cells.[2−5] In 1998, the Kobayashi group[4a] reported the first total synthesis of callystatin A, which was followed by those from Crimmins,[4b] Smith,[4c] Kalesse,[4d,h] Enders,[4e] Marshall,[4f] Lautens,[4g] and Panek.[4i] Subsequently, the Kobayashi group reported the preparation of several structural analogues of callystatin A in efforts to determine structure−activity relationships.[5]

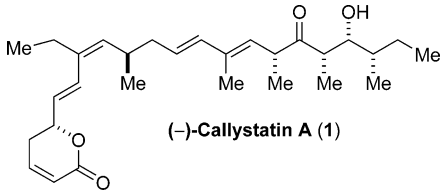

FIGURE 1. (−)-Callystatin A

(−)-Callystatin A was isolated in very small amounts (1 mg from 100 kg of sponge). Attracted by its potent cytotoxicity, and to provide material for more extensive biological evaluation, along with access to promising novel analogues, we have undertaken the total synthesis of callystatin A.[5−7] We have recently described a very efficient synthesis of the C1−C11 and C13−C22 fragments of (−)-callystatin A.[7] In this paper, we describe an improvement for the synthesis of these fragments as well as a highly convergent approach to (−)-callystatin A, which might give access to additional derivatives with potential relevance to biological studies.[8]

† Dedicated to Prof. Peter Bakuzis for his outstanding contributions to the field of synthetic organic chemistry in Brazil.

* Fax: +55-019-3788-3023.

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(4) For total syntheses of callystatin A, see: (a) Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett.* **1998**, *39*, 2349. (b) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084. (c) Smith, A. B., III.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685. (d) Kalesse, M.; Quitschalle, M.; Khandavalli, C. P.; Saeed, A. *Org. Lett.* **2001**, *3*, 3107. (e) Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M.; Enders, D. *Org. Lett.* **2002**, 4, 1023. (f) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751. (g) Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993. (h) Kalesse, M.; Chary, K. P.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem. Eur. J.* **2003**, *9*, 1129. (i) Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203.

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(8) For a previous synthesis of the C13−C22 fragment of callystatin A, see: (a) Marshall, J. A.; Fitzgerald, R. N. *J. Org. Chem.* **1999**, *64*, 4477. (b) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825. (c) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2002**, *4*, 3931.

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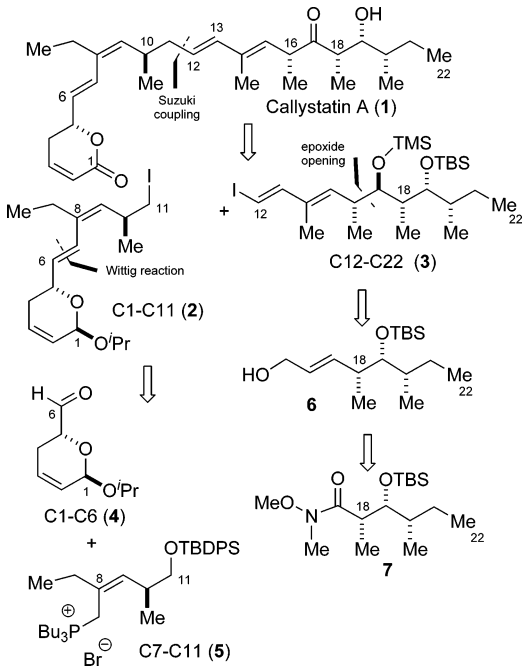
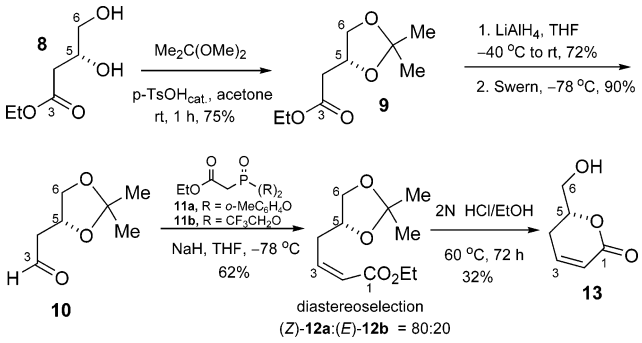
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Preparation of α,β-Unsaturated Lactone 13 from Ester 9

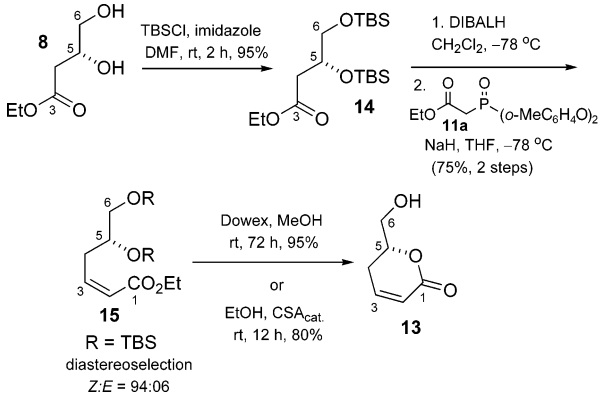


Results and Discussion

Our retrosynthetic analysis is outlined in Scheme 1, and employed a Suzuki coupling reaction to join fragments C1−C11 (**2**) and C12−C22 (**3**).[9,10] Fragment C1−C11 (**2**) is viewed as arising from coupling between aldehyde **4** (C1−C6 fragment) and phosphonium salt **5** (C7−C11 fragment). We anticipated that (*E*)-vinyl iodide **3** would be derived from allylic alcohol **6**, available from Weinreb amide **7**.

In our first attempt to prepare aldehyde **4**, diol **8**[11] was treated with 2,2-dimethoxypropane and catalytic amounts of *p*-TsOH in acetone to give ester **9** in 75% yield (Scheme 2). Reduction of ester **9** with lithium aluminum hydride in THF at −40 °C followed by oxidation of the resulting alcohol under Swern conditions at −78 °C gave aldehyde **10** in good overall yield. The unpurified aldehyde was treated with ethyl 2-((bis(*o*-tolyloxy))phosphoryl)acetate **11a** in the presence of NaH in THF at −78 °C to give (*Z*)-α,β-unsaturated ester **12a** in 62% yield, although with a disappointing selectivity ((*Z*)-**12a**:(*E*)-**12b** = 80:20).[12] Treatment of phosphonate **11b** with NaH in THF at −78 °C (using the Still−Gennari conditions), followed by addition of aldehyde **10**, led to similar results in terms of yields and selectivities (56%, (*Z*)-**12a**:(*E*)-**12b** = 78:32).[12e] Treatment of (*Z*)-ester **12a** with 2 N HCl in EtOH at 60 °C for 72 h gave lactone **13** in only 32% yield.[13,14]

SCHEME 3. Preparation of α,β-Unsaturated Lactone 13 from Ester 14



Due to the difficulties in forming lactone **13** from ester **9** and the low selectivity observed for the Horner−Wadsworth−Emmons coupling, we decided to use silicon protecting groups at C5 and C6, rendering the side chain in aldehyde **10** "less hindered" for selective (*Z*)-ester formation (Scheme 3).

Treatment of diol **8**[11] with TBSCl and imidazole in DMF gave ester **14** in 95% yield (Scheme 3). Reduction of ester **14** with diisobutylaluminum hydride in CH_2Cl_2 at −78 °C gave the intermediate aldehyde. The unpurified aldehyde was treated with ethyl 2-((bis(*o*-tolyloxy))-phosphoryl)acetate **11a** to give (*Z*)-α,β-unsaturated ester **15** (*Z*:*E* = 94:06) in 75% yield over two steps.[12] Treatment of (*Z*)-ester **15** with Dowex resin in MeOH at ambient temperature for 72 h gave lactone **13** in 95% yield.[13,14] The same ester **15** was also treated with EtOH in the presence of catalytic amounts of CSA at ambient temperature for 12 h to give lactone **13** in 80% yield. The use of Dowex resin in MeOH proved to be the best in terms of yields as well as for purposes of scale-up.

An alternative approach to lactone **13** is illustrated in Scheme 4. Treatment of (*Z*)-ester **15** with excess DIBAL-H in CH_2Cl_2 at −23 °C gave allylic alcohol **16**.

Removal of the silicon protecting groups at C5 and C6 was accomplished by treatment of **16** with Dowex resin

(9) Numbering of **1** as well as of each intermediate follows that suggested in ref 1.

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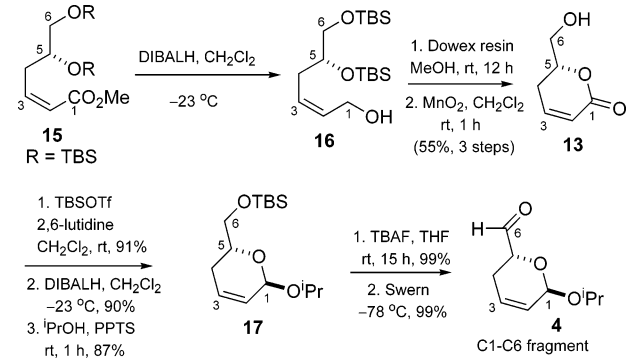
(11) (a) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933. (b) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.

(12) (a) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934. (b) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411. (c) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406. (d) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745. (e) Still, W. C.; Gennari, C. *Tetrahedron* Lett. **1983**, *24*, 4405.

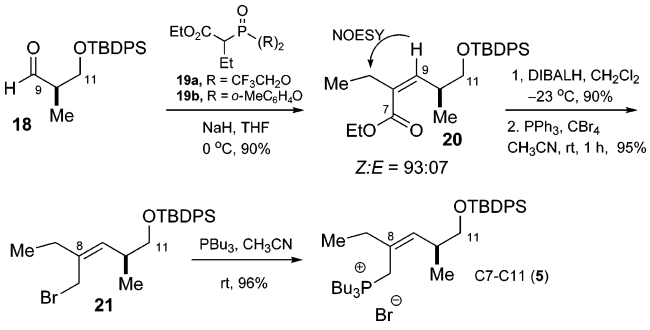
(13) (a) Hansen, T. V. *Tetrahedron: Asymmetry* **2002**, *13*, 547. (b) Boger, D. L.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161. (c) Boger, D. L.; Hikota, M.; Lewis, B. M. *J. Org. Chem.* **1997**, *62*, 1748. (d) Tsubuki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281.

(14) For a recent review with several examples of α-pyrones prepared using ring-closing metathesis (RCM), see: Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23.

SCHEME 4. Synthesis of Aldehyde 4



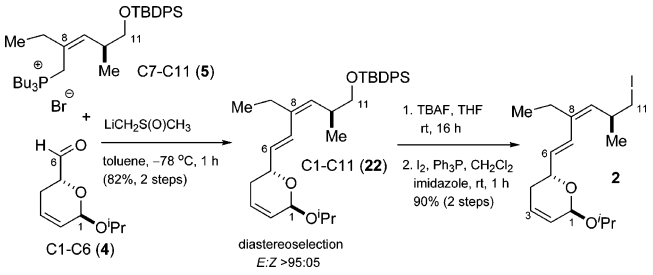
SCHEME 5. Preparation of Phosphonium Salt (5)



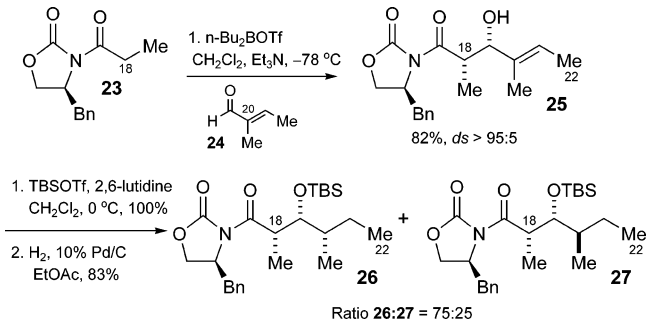
in MeOH at room temperature. Treatment of the resulting triol with activated MnO_2 in CH_2Cl_2 at ambient temperature gave lactone **13** in 55% yield (over three steps).[4,13,14] Attempts to protect the primary OH function in **13** with TBSCl, imidazole in CH_2Cl_2 or in DMF at ambient temperature failed, and the starting material was recovered. Protection of the primary alcohol functionality in **13** as its TBS ether was then accomplished by using TBSOTf in the presence of 2,6-lutidine in CH_2Cl_2 at ambient temperature (91% yield). Careful DIBAL-H reduction was followed by treatment of the intermediate lactol with ^{i}PrOH in the presence of catalytic amounts of PPTS at ambient temperature providing isopropyl acetal **17** in 78% overall yield over the two-step sequence. Cleavage of the primary TBS ether in the presence of TBAF in THF at 0 °C (99% yield) followed by Swern oxidation of the primary alcohol gave aldehyde **4** (99% yield).[4]

The synthesis of phosphonium salt **5**, starting from aldehyde **18**, is described in Scheme 5.[15] Treatment of phosphonate **19a** with KHMDS and 18-crown-6 in THF, followed by addition of aldehyde **18**, gave unsaturated ester **20** in 55% yield over two steps but with poor selectivity (*Z*:*E* = 75:25). On the basis of this result, aldehyde **18** was reacted with β-ketophosphonate **19b** in the presence of NaH in THF to give (*Z*)-α,β-unsaturated ester **20** (*Z*:*E* = 93:07) in 90% yield.[12,16–18] The (*Z*)-

SCHEME 6. Coupling between Aldehyde 4 and Phosphonium Salt (5)



SCHEME 7. Hydrogenation of Aldol Adducts



geometry for ester **20** was confirmed by NOESY interactions between the vinylic hydrogen at C9 and the hydrogens of the C8-ethyl group. Phosphonium salt **5** was prepared in excellent overall yield after a sequence involving reduction of ethyl ester **20** with DIBAL-H in CH_2Cl_2 at −23 °C, treatment of the intermediate allylic alcohol with PPh_3 and CBr_4 in CH_3CN to give bromide **21**, and reaction of **21** with PBu_3 in CH_3CN at ambient temperature.[17,18]

With fragments **4** and **5** in hand, their coupling was undertaken (Scheme 6). This was done by treatment of a mixture of aldehyde **4** and phosphonium salt **5** with $LiCH_2S(O)CH_3$ in toluene at −78 °C to give diene **22** in 82% yield (over two steps, preparation of phosphonium salt **5** and coupling with aldehyde **4**, *E*:*Z* > 95:05).[18] Removal of the TBDPS protecting group at C11 in **22** with TBAF in THF followed by treatment of the primary OH function with I_2, PPh_3, and imidazole in CH_2Cl_2 gave rapid and clean conversion to afford alkyl iodide **2**, corresponding to the C1−C11 fragment of (−)-callystatin A, in 90% yield for the two-step sequence (Scheme 6). The 12-step sequence from diol **8** to alkyl iodide **2** proceeded in an overall yield of 25%.

Our first approach to prepare Weinreb amide **7** involved double-bond hydrogenation of aldol adduct **25**, easily prepared from aldol reaction of the boron enolate of *N*-propionyloxazolidinone **23** with (*E*)-2-methylbut-2-enal **24** (Scheme 7).[19] Attempts to reduce the double bond in aldol **25** by catalytic hydrogenation with 10% Pd/C led only to a 50:50 mixture of the two possible products. Silylation of aldol **25** with TBSOTf and 2,6-lutidine in

(15) Aldehyde **18** was prepared in three steps and 77% overall yield from (*R*)-methyl-3-hydroxy-propanoate following protection with TBDPSCl and imidazole, reduction of the ester to the primary alcohol with excess DIBAL-H, followed by Swern oxidation. See Supporting Information for details. (a) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. (b) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1990**, *55*, 2138.

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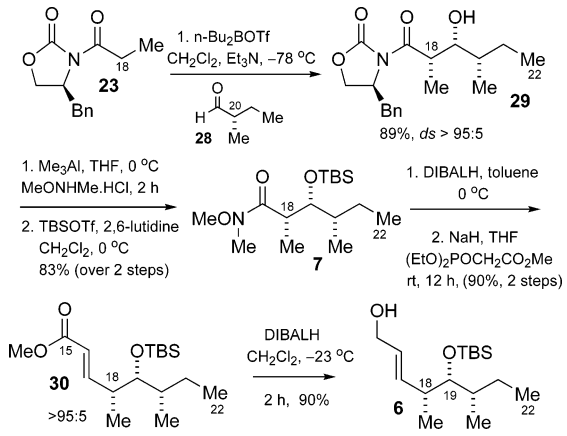
(18) (a) Smith, A. B., III; Qiu, Y. P.; Jones, D. R.; Kobayashi, J. *J. Am. Chem. Soc.* **1995**, *117*, 12011. (b) Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723.

(19) (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (c) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675.

SCHEME 8. Preparation of Allylic Alcohol 6



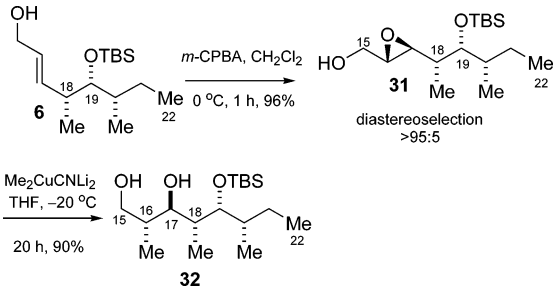
CH_2Cl_2 at 0 °C followed by catalytic hydrogenation with 10% Pd/C led to the formation of a 75:25 mixture of **26**:**27**, respectively, in good yields.

As this approach proved to be unselective, we decided to use a chiral aldehyde bearing the desired stereogenic center at C20 (Scheme 8). Synthesis of (*E*)-vinyl iodide **3** began with asymmetric aldol addition of the boron enolate derived from *N*-propionyloxazolidinone **23** with 2-(*S*)-methylbutanal **28** to give aldol adduct **29** in 89% yield (ds > 95:5).[19,20] Exchange of the oxazolidinone auxiliary in the aldol **29** with *N*,*O*-dimethylhydroxylamine in the presence of Me_3Al in THF at 0 °C[21] was followed by silylation with TBSOTf and 2,6-lutidine in CH_2Cl_2 at 0 °C to give Weinreb amide **7** (83%, two steps). Allylic alcohol **6** was obtained in a high overall yield following diisobutylaluminum hydride reduction of amide **7** to the aldehyde and its conversion to the (*E*)-α,β-unsaturated ester **30**[22] (90%, two steps), followed by reduction with excess DIBAL-H in CH_2Cl_2 at −23 °C (90% yield).

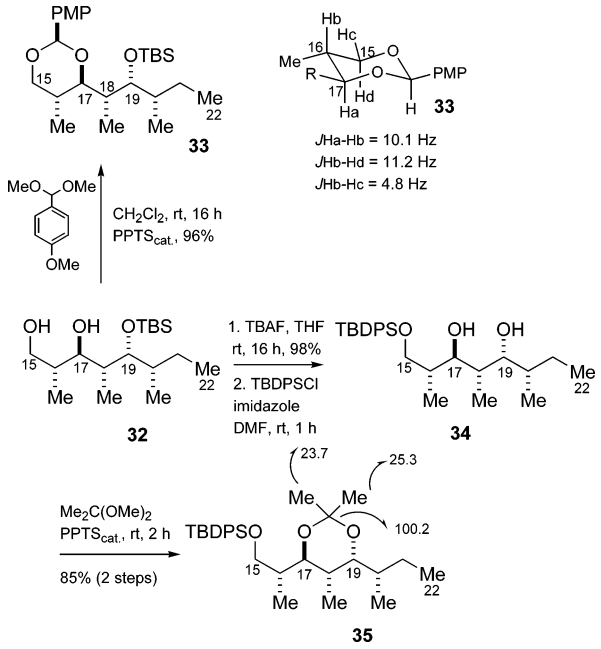
We were very pleased to find that epoxidation of allylic alcohol **6** with *m*-CPBA in CH_2Cl_2 at 0 °C proceeded smoothly to give the *anti*-epoxy alcohol **31** in 96% yield and >95:5 diastereoselectivity (Scheme 9).[7,23] Treatment of epoxy alcohol **31** with $Me_2CuCNLi_2$ in THF at −20 °C gave diol **32** in 90% yield.[4f,g,24,25]

At this point, the relative stereochemistry for 1,3-diol **32** was determined after conversion to the PMP-acetal **33** and to the acetonide **35** (Scheme 10).[26] Formation of *p*-methoxybenzylidene acetal **33** was accomplished by treatment of the diol **32** with *p*-methoxybenzaldehyde

SCHEME 9. Selective Epoxidation of Allylic Alcohol 6 and Epoxide Opening



SCHEME 10. Proof of Stereochemistry for Diol 32



dimethyl acetal and a catalytic amount of PPTS (96% yield).[4g] The preparation of acetonide **35** involved removal of the silicon protecting group in **32** with TBAF in THF at 0 °C (98% yield), selective silylation at C15 with TBDPSCl and imidazole in DMF at ambient temperature to give diol **34**, and reaction with 2,2-dimethoxypropane in the presence of catalytic amounts of PPTS (85%, two steps).

Coupling constants between Ha−Hb (10.1 Hz), Hb−Hd (11.2 Hz), and Hb−Hc (4.8 Hz) confirmed the relative stereochemistry for the C16−C17 bond in **33**.[4f,g,26] The stereochemistry at C17 and C19 was determined after analysis of acetonide **35**, which showed ^{13}C NMR resonances at 23.7, 25.3, and 100.2, characteristic of an *anti*-acetonide.[27]

Selective oxidation[28] of the primary OH function in diol **32** under Swern conditions at −78 °C followed by Wittig[21] coupling with carboethoxyethylidene-triphenylphospho-

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(26) Relative stereochemistry for **32** was further confirmed after transformation to vinyl iodide **39**, previously described by Marshall and Bourbeau in their elegant synthesis of (−)-callystatin A. See ref 4f.

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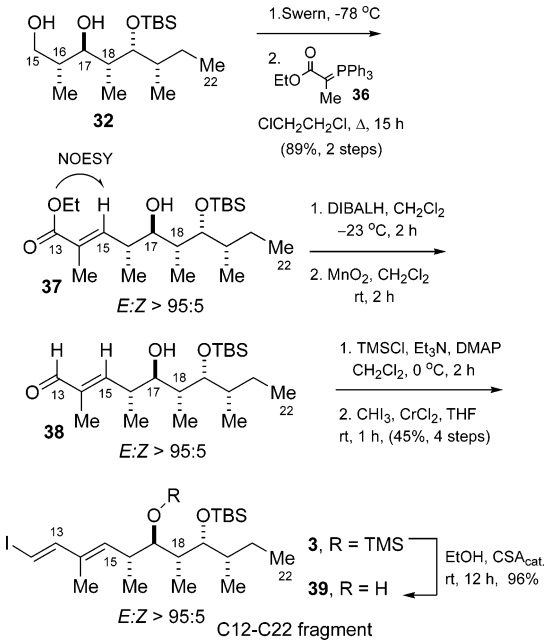
(28) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

SCHEME 11. Synthesis of (*E*)-Vinyl Iodides 3 and 39

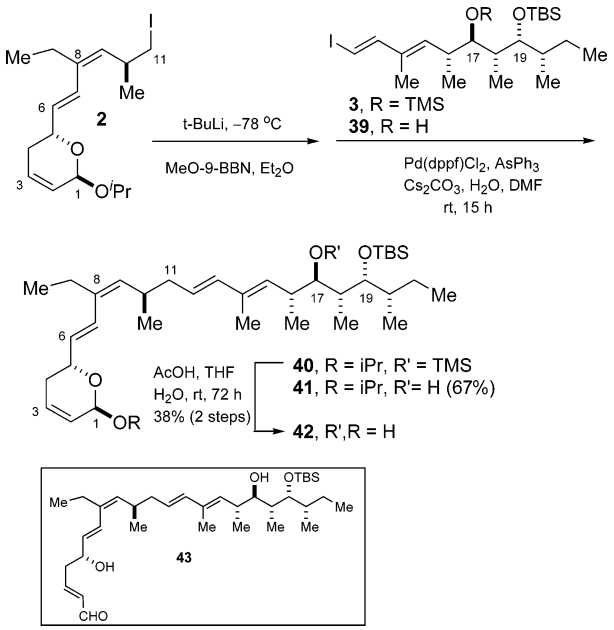


rane **36** in refluxing 1,2-dichloroethane gave α,β-unsaturated ester **37**, corresponding to the C13−C22 fragment of callystatin A (*E*:*Z* > 95:5) in 89% overall yield for the two-step sequence (Scheme 11).[4f,g] The (*E*)-geometry for ester **37** was confirmed by the illustrated NOESY interaction between the vinylic hydrogen at C15 and hydrogens of the ethyl group. Treatment of ester **37** with excess DIBAL-H in CH_2Cl_2 at −23 °C followed by oxidation of the resulting allylic alcohol with activated MnO_2 gave aldehyde **38**. Protection of the OH function at C17 in **38** as its TMS ether, followed by treatment with CHI_3 and $CrCl_2$[29] in THF, produced the (*E*)-vinyl iodide **3** (*E*:*Z* > 95:05) in 45% overall yield for the four-step sequence. It should be noted that it is essential to have the TMS-protected alcohol in order to get the (*E*)-vinyl iodide. Treatment of vinyl iodide **3** with EtOH in the presence of catalytic amounts of CSA led to deprotection of the TMS ether at C17, providing (*E*)-vinyl iodide **39** in 96% yield.[4f,26]

Overall, this route required 14 steps starting from *N*-propionyloxazolidinone **23** and resulted in 21% overall yield of vinyl iodide **3**. Notable features of this approach include an efficient syn aldol reaction and a diastereoselective epoxidation of an allylic alcohol, followed by epoxide opening with $Me_2CuCNLi_2$, a diastereoselective Wittig coupling, and a very efficient (*E*)-vinyl iodide formation.

With fragments C1−C11 and C12−C22 in hand, we attempted their coupling (Scheme 12). This was achieved through the use of a Pd-catalyzed coupling of an intermediate boronate derived from **2** with vinyl iodide **3** as well as with vinyl iodide **39**.[4f,10] Treatment of alkyl iodide **2** with *t*-BuLi in Et_2O at −78 °C, followed by addition of 9-MeO-9-BBN, gave a boronate intermediate, which participated in a Pd-catalyzed cross-coupling with vinyl iodide **3** in the presence of Pd(dppf)Cl_2, $AsPh_3$, Cs_2CO_3,

SCHEME 12. Suzuki Couplings



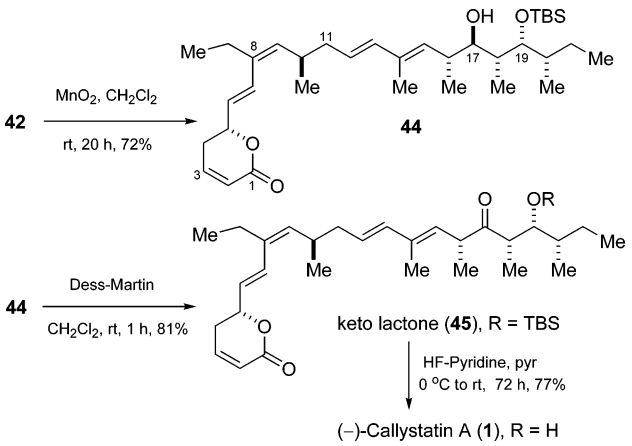
and water in DMF to give a 34:66 mixture of lactols **40** and **41** (formed by loss of the TMS protecting group at C17), respectively, in good yields, together with a byproduct, which we tentatively assigned as α,β-unsaturated aldehyde **43**, arising from opening of the lactol.[4f,g,18a] Treatment of the boronate intermediate derived from alkyl iodide **2** with vinyl iodide **39** in the presence of Pd(dppf)Cl_2, $AsPh_3$, Cs_2CO_3, and water in DMF gave lactol **41** in 67% yield, together with α,β-unsaturated aldehyde **43**.[4f] At this point we arrived at intermediates (both **40** and **41**) very close to that described by Lautens and Stammers in their synthesis of callystatin A.[4g] The last steps in the synthesis proved to be challenging and more difficult than expected. Hydrolysis of the C1 acetal in the mixture containing lactols **40** and **41** with a mixture of AcOH/THF/H_2O (1:5:1) at ambient temperature for 72 h gave lactol **42** in 38% yield (over two steps) along with α,β-unsaturated aldehyde **43**, in 25% yield. Treatment of isolated lactol **41** under the same conditions led to similar results. Although these conditions were reported to work fine for similar intermediates in a previous synthesis, we were not able to get a better yield for this transformation, and attempts to increase the yield for formation of lactol **42** were unsuccessful.[4g]

Lactol **42** was most efficiently converted to hydroxy lactone **44** after treatment with MnO_2 in CH_2Cl_2 at ambient temperature (72% yield) (Scheme 13).[4g] Dess−Martin[30] periodinane oxidation of the C17-hydroxy functionality in **44** led to the keto-lactone **45** (81% yield), which after removal of the TBS ether at C19 with HF-pyridine in THF with small amounts of pyridine added provided (−)-callystatin A (77%).[4] At this point, it should be emphasized that using HF-pyridine in THF with added pyridine avoided side reactions such as lactone opening and ketone epimerization (probably at C16, the allylic position, and α to the carbonyl group being

(29) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(30) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

SCHEME 13. Total Synthesis of (−)-Callystatin A



formed), which were observed when the reaction was conducted with HF-pyridine without excess pyridine or with TBAF in THF.

The spectroscopic and physical data for synthetic **1** [^{1}H and ^{13}C NMR, IR, $[\alpha]^{20}_D$, R_f] were identical in all respects with the published data.[1−4] In summary, a highly convergent and efficient total synthesis of (−)-callystatin A has been accomplished. The synthesis required 19 steps from oxazolidinone **23** and produced the desired product in 3.5% overall yield. This approach compares very well with other published routes, being one of the shortest approaches to (−)-callystatin A. As a result, the route to (−)-callystatin A presented here is, in principle, readily applicable for the preparation of additional analogues of callystatin A.[31]

Experimental Section

(*R*)-Ethyl 3,4-Bis(*tert*-butyldimethylsilyloxy)butanoate (14). To a stirred solution of diol **8** (3.21 g, 21.7 mmol) in DMF (15 mL) at ambient temperature were added imidazole (7.38 g, 108.4 mmol) and *tert*-butyldimethylsilyl chloride (8.50 g, 56.4 mmol), and stirring was continued for 2 h. The reaction mixture was partitioned between EtOAc and H_2O, and then the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification of the crude product on silica gel (5% EtOAc/hexane) gave the ester **14** (7.75 g, 95%) as a viscous oil: R_f 0.59 (10% EtOAc/hexane); $[\alpha]^{20}_D$ +5.2 (*c* 1.25, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 2956, 2920, 2858, 1735, 1493, 1256; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 0.06 (s, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.26 (t, 3H, *J* 7.1 Hz), 2.35 (dd, 1H, *J* 7.8, 14.8 Hz), 2.63 (dd, 1H, *J* 4.4, 14.8 Hz), 3.41 (dd, 1H, *J* 6.9, 9.8 Hz), 3.59 (dd, 1H, *J* 5.12, 9.8 Hz), 4.12 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.9, −4.3, 14.2, 18.0, 18.3, 25.7, 25.9, 40.2, 60.2, 66.9, 70.4, 171.8. HRMS calcd for $C_{18}H_{40}O_4Si_2$ [M$^+$] 376.2465, found 376.2452.

(*R*,*Z*)-Ethyl 5,6-Bis(*tert*-butyldimethylsilyloxy)hex-2-enoate (15). Ester **14** (0.628 g, 1.67 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL) under an N_2 atmosphere. The solution was cooled to −78 °C, and DIBAL-H (1.0 M in toluene, 2.0 mL) was slowly added over a period of 30 min. The reaction mixture was stirred 30 min at −78 °C before being quenched with MeOH (0.5 mL). The mixture was allowed to warm to ambient temperature before an aqueous solution of Rochelle's salt was added (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give the aldehyde (0.483, 1.5 mmol), used in the next step without further purification. R_f 0.31 (10% EtOAc/hexane). ^{1}H NMR spectroscopy of the unpurified aldehyde was very clean. To a stirred suspension of NaH (0.068 g, 1.67 mmol) in THF (5 mL) at 0 °C under argon was added ethyl 2-((bis(*o*-tolyloxy))phosphoryl)-acetate **11a** (0.582 g, 1.67 mmol). After the mixture was stirred at 0 °C for 30 min, the reaction mixture was cooled to −78 °C, and then a solution of the previously prepared aldehyde (0.483, 1.5 mmol) in THF (5 mL) was added dropwise. After the mixture was stirred for 1 h, the reaction was diluted with 5 mL of Et_2O and quenched by the slow addition of 4 mL of H_2O. The layers were separated, and the aqueous phase was extracted with two 10 mL portions of Et_2O. The combined organic extracts were washed with 10 mL of brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (20% EtOAc/hexane) to give unsaturated ester **15** (0.504 g, 75% over two steps, ratio *Z*:*E* = 94:06) as a colorless oil: R_f 0.65 (10% EtOAc/hexane); IR ν_{max} (film, cm^{-1}) 3080, 2959, 2933, 2859, 1721, 1648, 1473, 1250, 1092; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 6H), 0.06 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.26 (t, 3H, *J* 7.3 Hz), 2.87 (m, 2H), 3.44 (dd, 1H, *J* 6.2, 10.0 Hz), 3.53 (dd, 1H, *J* 5.5, 10.0 Hz), 3.81 (quint, 1H, *J* 5.86 Hz), 4.12 (q, 2H, *J* 7.3 Hz), 5.82 (dt, 1H, *J* 1.8, 11.7 Hz), 6.36 (dt, 1H, *J* 7.3, 11.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4, −5.3, −4.8, −4.3, 14.2, 18.0, 18.3, 25.8, 25.9, 33.9, 59.8, 67.1, 72.3, 120.8, 146.4, 166.4; HRMS calcd for $C_{20}H_{42}O_4Si_2$ [M$^+$] 402.2622, found 402.2618.

(*R*)-6-(Hydroxymethyl)-5,6-dihydropyran-2-one (13).[13] To a solution of ester **15** (0.169 g, 0.42 mmol) in anhydrous methanol (10 mL) at ambient temperature was added Dowex resin (0.040 g, 50wX8-200). The reaction mixture was stirred at ambient temperature for 72 h before it was concentrated in vacuo. The remaining organic residue was purified by flash chromatography on silica gel (50% EtOAc/hexane) to provide the desired lactone **13** (0.052 g, 95%) as a viscous oil: R_f 0.25 (50% EtOAc/hexane); $[\alpha]_D^{20}$ +173.1 (*c* 0.97, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3350, 3075, 2960, 1733, 1092; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (br s, 1H), 2.26−2.36 (m, 1H), 2.56−2.67 (m, 1H), 3.75 (dd, 1H, *J* 4.7, 12.4 Hz), 3.90 (dd, 1H, *J* 3.3, 12.4 Hz), 4.45 (m, 1H), 6.04 (dd, 1H, *J* 3.4, 10.2 Hz), 6.97 (ddd, 1H, *J* 1.6, 3.5, 10.2 Hz); HRMS calcd for $C_6H_8O_3$ [M$^+$] 128.0472, found 128.0467.

(*R*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-5,6-dihydropyran-2-one. To a solution of lactone **13** (0.262 g, 2.05 mmol) and 2,6-lutidine (0.28 mL, 2.35 mmol) in CH_2Cl_2 (5 mL) at ambient temperature was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (0.50 mL, 2.15 mmol) dropwise. The reaction mixture was stirred for 30 min at ambient temperature before it was diluted with CH_2Cl_2 (10 mL) and 10 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). All the organic layers were combined and dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexane) to give the desired product (0.452 g, 91%) as a white solid: R_f 0.30 (15% EtOAc/hexane); $[\alpha]_D^{20}$ +38.8 (*c* 1.00, $CHCl_3$); mp 37.0−38.0 °C; IR ν_{max} (film, cm^{-1}) 3067, 2926, 2852, 1733, 1636, 1477, 1251, 1094; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 2.37−2.58 (m, 2H), 3.80 (m, 2H), 4.46 (m, 1H), 6.04 (ddd, 1H, *J* 1.0, 2.6, 10.0 Hz), 6.89 (ddd, 1H, *J* 2.7, 5.6, 10.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −5.3, 18.3, 25.8, 37.1, 64.2, 77.7, 121.0, 144.8, 163.6; HRMS calcd for $C_{12}H_{22}O_3Si$ [M$^+$] 242.1338, found 242.1326.

***tert*-Butyl(((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)methoxy)dimethylsilane (17).** The previously prepared TBS-protected unsaturated lactone (0.082 g, 0.34 mmol) was dissolved in freshly distilled CH_2Cl_2 (5 mL) under an N_2 atmosphere. The solution was cooled to −23 °C, and DIBAL-H (1.0 M in toluene, 0.40 mL) was slowly added over a period of

(31) New compounds and the additional isolated intermediates gave satisfactory ^{1}H and ^{13}C NMR, IR, HRMS, and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.

30 min. The solution was stirred for 30 min at −23 °C before the reaction was quenched with MeOH (1 mL). The mixture was allowed to warm to ambient temperature before an aqueous solution of Rochelle's salt was added (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give an intermediate lactol (0.117 g, 90%), used in the next step without further purification. The lactol (0.117 g, 0.3 mmol) was dissolved in 2-propanol, and PPTS (0.004 g, 0.015 mmol) was added. The mixture was stirred at ambient temperature for 1 h before being diluted in Et_2O (50 mL) and washed with H_2O (5 mL) and brine (5 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (20% EtOAc/hexane) gave *i*-Pr-lactol **17** (0.121 g, 87%) as a colorless oil: R_f 0.50 (40% EtOAc/hexane); $[\alpha]^{20}_D$ +32.8 (*c* 0.70, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3077, 2959, 2929, 2859, 1469, 1255, 1110; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.16 (d, 3H, *J* 5.8 Hz), 1.24 (d, 3H, *J* 5.2 Hz), 1.99 (m, 2H), 3.61 (dd, 1H, *J* 10.6, 4.7 Hz), 3.71 (dd, 1H, *J* 10.6, 5.8 Hz), 4.04 (hept, 1H, *J* 6.2 Hz), 4.09 (m, 1H), 5.09 (br s, 1H), 5.70 (m, 1H), 5.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, 18.5, 21.9, 23.9, 25.9, 27.0, 66.1, 67.0, 69.1, 92.7, 126.0, 128.3; HRMS calcd for $C_{15}H_{30}O_3Si$ [M^+] 286.1964, found 286.1959. This intermediate was isolated as a single diastereoisomer. On the basis of literature precedents, we have assigned its stereochemistry as trans. See refs 1−4 of this manuscript.

((2*R*,6*R*)-6-Isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)methanol. To a solution of acetal **17** (0.049 g, 0.17 mmol) in 2 mL of THF at ambient temperature was added 0.34 mL (0.34 mmol) of a 1.0 M solution of TBAF in THF. The reaction mixture was stirred at ambient temperature for 15 h and then concentrated in vacuo. Purification by flash column chromatography on silica gel (40% EtOAc/hexane) gave the desired alcohol (0.027 g, 99%) as a white solid: R_f 0.50 (20% EtOAc/hexane); $[\alpha]^{20}_D$ +39.7 (*c* 0.49, CH_2Cl_2); mp 39.0−41.0 °C; IR ν_{max} (film, cm^{-1}) 3448, 3145, 2974, 2930, 1415, 1180; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 3H, *J* 5.6 Hz), 1.24 (d, 3H, *J* 5.2 Hz), 1.67 (br s, 1H), 1.90 (m, 1H), 2.10 (m, 1H), 3.60 (m, 1H), 3.75 (hept, 1H, *J* 5.6 Hz), 4.01 (m, 1H), 4.05 (m, 1H), 5.10 (br s, 1H), 5.69 (m, 1H), 5.99 (dd, 1H, *J* 10.0, 5.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 23.6, 25.8, 65.1, 66.6, 69.4, 92.7, 125.8, 128.1; HRMS calcd for $C_9H_{16}O_3$ [M^+] 172.1099, found 172.1098. This intermediate was isolated as a single diastereoisomer. On the basis of literature precedents, we have assigned its stereochemistry as trans. See refs 1−4 of this manuscript.

(2*R*,6*R*)-6-Isopropoxy-3,6-dihydro-2*H*-pyran-2-carbaldehyde (4).[4] In an oven-dried flask under an N_2 atmosphere, DMSO (0.17 mL, 2.5 mmol) was dissolved in freshly distilled CH_2Cl_2 (3 mL). The solution was cooled to −78 °C, and $(COCl)_2$ (0.10 mL, 1.25 mmol) was added dropwise. After 15 min, the previously prepared alcohol (0.172 g, 1.0 mmol) was added via cannula as a solution in CH_2Cl_2 (2.0 mL). The white slurry was stirred for 30 min at −78 °C before Et_3N (0.70 mL, 5.0 mmol) was added dropwise. The solution was allowed to warm to ambient temperature before being diluted in Et_2O (15 mL) and washed with saturated aq NH_4Cl (10 mL), $NaHCO_3$ (10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and carefully concentrated in vacuo (volatile aldehyde) to provide aldehyde **4** (0.153 g, 0.90 mmol). ^1H NMR spectroscopy of the unpurified aldehyde was very clean, and the unpurified aldehyde was used in the next step without further purification: $[\alpha]^{20}_D$ +106 (*c* 0.31, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3060, 2972, 2920, 1737, 1381, 1100; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, 3H, *J* 6.1 Hz), 1.21 (d, 3H, *J* 6.1 Hz), 2.17 (m, 2H), 4.04 (hept, 1H, *J* 6.1 Hz), 4.39 (dd, 1H, *J* 10.9, 4.8 Hz), 5.18 (br s, 1H), 5.73 (m, 1H), 5.99 (m, 1H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 23.8, 24.9, 70.2, 71.1, 93.0, 126.4, 126.9, 200.9. This intermediate was isolated as a single diastereoisomer. On the basis of literature precedents, we have assigned its stereochemistry as trans. See refs 1−4 of this manuscript.

(*S*,*Z*)-Ethyl 5-(*tert*-Butyldiphenylsilyloxy)-2-ethyl-4-methylpent-2-enoate (20). To a stirred suspension of NaH (0.057 g, 1.44 mmol) in THF (5 mL) at 0 °C under argon was added ethyl 2-((bis(*o*-tolyloxy))phosphoryl)butanoate **19b** (0.542 g, 1.44 mmol). The reaction mixture was stirred for 15 min, and then a solution of aldehyde **18** (0.470 g, 1.44 mmol) in 3 mL of THF was added dropwise. After the mixture was stirred for 2 h at 0 °C, the reaction was diluted with 10 mL of Et_2O and quenched by the slow addition of 6 mL of H_2O. The layers were separated, and the aqueous phase was extracted with two 10 mL portions of Et_2O. The combined organic extracts were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (40% EtOAc/hexane) to give unsaturated ester **20** (0.550 g, 85% over two steps, ratio *Z*:*E* = 93:07) as a colorless oil: R_f 0.60 (25% EtOAc/hexane); IR ν_{max} (film, cm^{-1}) 3074, 2962, 2931, 2856, 1715, 1467, 1428, 1219; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (m, 15H), 1.27 (t, 3H, *J* 7.1 Hz), 2.26 (q, 2H, *J* 7.3 Hz), 3.26 (m, 1H), 3.54 (d, 2H, *J* 8.5 Hz), 4.18 (q, 2H, *J* 7.1 Hz), 5.70 (d, 1H, *J* 9.8 Hz), 7.35−7.38 (m, 6H), 7.63−7.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 14.3, 17.1, 19.4, 26.8, 27.7, 36.2, 60.0, 68.4, 127.4, 129.4, 133.7, 135.4, 142.2, 168.0; HRMS calcd for $C_{26}H_{36}O_3Si$ [M^+] 424.2434, found 424.2421.

(*R*,*Z*)-5-(*tert*-Butyldiphenylsilyloxy)-2-ethyl-4-methylpent-2-en-1-ol. Unsaturated ester **20** (0.530 g, 1.25 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL) under an N_2 atmosphere. The solution was cooled to −23 °C, and DIBAL-H (1.0 M in toluene, 2.75 mL) was added. The reaction mixture was stirred for 30 min at −23 °C before being quenched with MeOH (1 mL). The mixture was allowed to warm to ambient temperature before an aqueous solution of Rochelle's salt was added (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography on silica gel (20% EtOAc/hexane) gave the desired allylic alcohol (0.430 g, 90%) as a colorless oil: R_f 0.34 (25% EtOAc/hexane); $[\alpha]^{20}_D$ +10.9 (*c* 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 3H, *J* 6.5 Hz), 1.04 (s, 9H), 1.07 (t, 3H, *J* 7.3 Hz), 1.90 (br s, 1H), 2.17 (dq, 2H, *J* 13.9, 7.3 Hz), 2.83 (m, 1H), 3.29 (dd, 1H, *J* 8.7, 9.5 Hz), 3.51 (dd, 1H, *J* 5.4, 9.5 Hz), 3.93 (d, 1H, *J* 11.7 Hz), 4.22 (d, 1H, *J* 11.7 Hz), 5.05 (br d, 1H, *J* 10.9 Hz), 7.38−7.42 (m, 6H), 7.64−7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 17.5, 19.1, 26.8, 28.9, 34.9, 60.9, 68.8, 127.5, 129.5, 130.4, 133.1, 135.5, 141.0; HRMS calcd for $C_{24}H_{34}O_2Si$ [M^+] 382.2328, found 382.2335.

(*R*,*Z*)-(4-(Bromomethyl)-2-methylhex-3-enyloxy)(*tert*-butyl)diphenylsilane (21). To a solution of the previously prepared allylic alcohol (0.291 g, 0.76 mmol) in CH_3CN (5 mL) at 0 °C were added triphenylphosphine (0.401 g, 1.53 mmol) and CBr_4 (0.507 g, 1.53 mmol). After the mixture was stirred for 1 h at ambient temperature, the solvent was removed. Purification by flash column chromatography on silica gel (20% EtOAc/hexane) gave bromide **21** (0.328 g, 95%) as a colorless oil: R_f 0.74 (10% EtOAc/hexane); IR ν_{max} (film, cm^{-1}) 3070, 2959, 2933, 2859, 1462, 1425, 1113; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 3H, *J* 6.9 Hz), 1.05 (s, 9H), 1.07 (t, 3H, *J* 7.1 Hz), 2.20 (dq, 2H, *J* 13.9, 6.9 Hz), 2.70 (m, 1H), 3.45 (m, 2H), 3.85 (d, 1H, *J* 9.8 Hz), 4.08 (d, 1H, *J* 9.8 Hz), 5.20 (d, 1H, *J* 9.8 Hz), 7.38−7.42 (m, 6H), 7.64−7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 17.1, 19.3, 26.9, 28.1, 31.2, 35.5, 68.1, 127.5, 129.4, 132.8, 134.6, 135.4, 137.3; HRMS calcd for $C_{24}H_{33}BrOSi$ [M^+] 444.1484, found 444.1472.

(*S*,*Z*)-Tributyl(5-(*tert*-butyldiphenylsilyloxy)-2-ethyl-4-methylpent-2-enyl)phosphonium Bromide (5). To a solution of bromide **21** (0.321 g, 0.70 mmol) in CH_3CN (5 mL) at ambient temperature was added *tri*-*n*-butylphosphine (0.26 mL, 1.04 mmol). The reaction was stirred for 30 min and concentrated in vacuo to give phosphonium salt **5**. This material was carried on without further purification.

***tert*-Butyl((*S*,3*Z*,5*E*)-4-ethyl-6-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)-2-methylhexa-3,5-dienyloxy)-**

diphenylsilane (22). To a solution of DMSO (0.12 mL) in freshly distilled toluene (3 mL) at ambient temperature was added *n*-BuLi (0.24 mL, 0.48 mmol). After the mixture was stirred for 1 h, the solution was cooled to −78 °C, and a solution of phosphonium salt **5** (0.084 g, 0.48 mmol) and aldehyde **4** (0.034 g, 0.20 mmol) in freshly distilled toluene (4 mL) was added. The mixture was stirred for 1 h at −78 °C before being diluted in Et_2O (10 mL). The organic phase was washed with H_2O (10 mL) and brine (10 mL) before being dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (50% EtOAc/hexane) afforded coupled material **22** (0.058 g, 82%): R_f 0.61 (20% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, 3H, *J* 6.5 Hz), 1.04 (s, 9H), 1.07 (t, 3H, *J* 7.3 Hz), 1.18 (d, 3H, *J* 6.2 Hz), 1.20 (d, 3H, *J* 6.2 Hz), 2.06 (m, 1H), 2.20 (q, 2H, *J* 7.3 Hz), 2.89 (m, 1H), 3.48 (m, 2H), 4.02 (hept, 1H, *J* 6.2 Hz), 4.52 (m, 1H), 5.15 (br s, 1H), 5.18 (d, 1H, *J* 9.6 Hz), 5.67 (m, 2H), 6.02 (m, 1H), 6.58 (d, 1H, *J* 15.7 Hz), 7.36 (m, 6H), 7.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 17.3, 19.2, 22.0, 23.8, 26.3, 26.8, 30.8, 34.5, 66.9, 68.5, 69.5, 93.1, 126.1, 127.1, 127.5, 128.4, 128.8, 129.4, 132.1, 133.9, 135.6, 137.1; HRMS calcd for $C_{33}H_{46}O_3Si$ [M^+] 518.3216, found 518.3202.

(2*R*,6*R*)-2-((*S*,1*E*,3*Z*)-3-Ethyl-5-(iodomethyl)hexa-1,3-dienyl)-6-isopropoxy-3,6-dihydro-2*H*-pyran (2). To a solution of acetal **22** (0.105 g, 0.36 mmol) in 4 mL of THF, at ambient temperature, was added 0.84 mL (0.84 mmol) of a 1.0 M solution of TBAF in THF. The reaction mixture was stirred at ambient temperature for 16 h and then concentrated in vacuo to give the desired primary alcohol (0.056 g, 99%) as a viscous oil. R_f 0.40 (25% EtOAc/hexane). This material was carried on without further purification. To a solution of triphenylphosphine (0.272 g, 1.04 mmol) in CH_2Cl_2 (3.0 mL), at 0 °C, were added imidazole (0.191 g, 2.81 mmol) and iodine (0.264 g, 1.04 mmol). The resulting solution was stirred at 0 °C for 30 min, and then a solution of the previously prepared alcohol (0.056 g, 0.2 mmol) in CH_2Cl_2 (1.0 mL) was added. After the mixture was stirred for 1 h at ambient temperature, the solvent was removed. Purification by flash column chromatography on silica gel (5% EtOAc/hexane) gave iodide **2** (0.071 g, 91%) as a colorless oil: R_f 0.75 (20% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, 3H, *J* 6.5 Hz), 1.07 (t 3H, *J* 7.3 Hz), 1.18 (d, 3H, *J* 6.2 Hz), 1.20 (d, 3H, *J* 6.2 Hz), 2.07 (m, 2H), 2.21 (q, 2H, *J* 7.3 Hz), 2.88 (m, 1H), 3.12 (m, 2H), 4.02 (sept, 1H, *J* 6.2 Hz), 4.52 (m, 1H), 5.18 (m, 2H), 5.76 (m, 2H), 6.02 (m, 1H), 6.54 (d, 1H, *J* 15.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 15.1, 21.5, 22.1, 23.9, 26.2, 30.7, 33.9, 66.9, 69.7, 93.1, 126.1, 126.7, 128.4, 129.9, 132.0, 138.0; HRMS calcd for $C_{17}H_{27}IO_2$ [M^+] 390.1056, found 390.1042.

(*S*)-4-Benzyl-3-((2*S*,3*R*,4*S*)-3-hydroxy-2,4-dimethylhexanoyl)oxazolidin-2-one (29). Di-*n*-butylboryltrifluoromethanesulfonate (5.7 mL, 22.4 mmol) was added to a solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one **23** (4.0 g, 17.2 mmol)-in 35 mL of CH_2Cl_2 at such a rate as to maintain the internal temperature below +3 °C (type K thermocouple thermometer). Triethylamine (3.2 mL, 22.4 mmol) was then added dropwise (internal temperature below +4 °C). The resulting yellow solution was then cooled to −78 °C and (*S*)-2-methyl butanal **28** (1.93 g, 22.4 mmol) (This aldehyde was prepared according to: White, J. D.; Bolton, G. L.; Dantanarayana, A. P.; Fox, C. M. J.; Hiner, R. N.; Jackson, R. W.; Sakuma, K.; Warrier, U. S. *J. Am. Chem. Soc.* **1995**, *117*, 1908. This aldehyde was found to undergo trimerization and was used promptly.) was added slowly (internal temperature below −70 °C). After 20 min, the solution was warmed to 0 °C and stirred at that temperature for 1 h. The reaction was quenched by the addition of 18 mL of pH 7.0 aqueous phosphate buffer solution and 60 mL of MeOH (internal temperature below +10 °C, bath temperature = −10 °C). A solution of 40 mL of MeOH and 20 mL of 30% aqueous H_2O_2 was added carefully (internal temperature below +10 °C), and the resulting yellow solution was stirred at 0 °C for 1 h. The volatiles were removed at aspirator pressure, and the residue was extracted with three 30 mL portions of Et_2O. The combined organic extracts were washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of brine. The organic solution was dried over anhydrous $MgSO_4$ and purified by silica gel flash column chromatography (EtOAc/hexane 25%) to give 4.9 g of the *syn*-aldol adduct **29** as a white solid (89% yield, >95:5 diastereoselectivity): R_f 0.42 (50% EtOAc/hexane); mp 87.5−88.5 °C; $[\alpha]_D^{20}$ +42.4 (*c* 1.06, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3521, 3065, 2962, 1778, 1693, 1488, 1455, 1382; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* 7.1 Hz), 0.98 (d, 3H, *J* 6.6 Hz), 1.15 (m, 1H), 1.26 (d, 3H, *J* 6.9 Hz), 1.48 (m, 2H), 2.65 (d, 1H, *J* 3.6 Hz), 2.78 (dd, 1H, *J* 9.3, 13.5 Hz), 3.25 (dd, 1H, *J* 3.3, 13.5 Hz), 3.68 (m, 1H), 3.98 (ddd, 1H, *J* 3.6, 6.9, 14.1 Hz), 4.21 (m, 2H), 4.69 (m, 1H), 7.19−7.21 (m, 2H), 7.24−7.36 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2, 11.3, 14.7, 25.6, 37.2, 37.8, 39.9, 55.1, 66.1, 74.9, 127.3, 128.8, 129.3, 134.9, 152.7, 177.4; HRMS calcd for $C_{18}H_{25}NO_4$ [M^+] 319.1783, found 365.1730.

(2*S*,3*R*,4*S*)-3-Hydroxy-*N*-methoxy-*N*,2,4-trimethylhexanamide. To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (0.401 g, 4.11 mmol) in 4 mL of THF at 0 °C was added 2.1 mL (4.15 mmol) of a 2.0 M solution of trimethylaluminum in toluene (gas evolution). The resulting solution was stirred at ambient temperature for 30 min and then cooled to −15 °C. A solution of β-hydroxy imide **29** (0.438 mg, 1.37 mmol) in 3 mL of THF was added by cannula, and the resulting mixture was stirred at 0 °C for 2 h. This solution was transferred by cannula to a well-stirred mixture of 15 mL of CH_2Cl_2 and 30 mL of 0.5 N aq HCl. After the mixture was stirred at 0 °C for 1 h, the organic phase was separated. The aqueous phase was extracted with three 25 mL portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by silica gel flash column chromatography (20% EtOAc/hexane) to give the desired Weinreb amide (0.254 g, 91%) as a colorless oil: R_f 0.23 (50% EtOAc/hexane); IR ν_{max} (film, cm^{-1}) 3445, 2964, 2936, 2877, 1781, 1640, 1462; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* 7.3 Hz), 1.00 (d, 3H, *J* 6.6 Hz), 1.17 (d, 3H, *J* 6.9 Hz), 1.40−1.58 (m, 2H), 2.60 (br s, 1H), 3.14 (br s, 1H), 3.20 (s, 3H), 3.58 (dd, 1H, *J* 7.3, 3.4 Hz), 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 11.1, 14.7, 25.6, 32.1, 36.2, 36.7, 61.5, 75.2, 178.0; HRMS calcd for $C_{10}H_{21}NO_3$ [M^+] 203.1521, found 203.1516.

(2*S*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,2,4-trimethylhexanamide (7). To a solution of the previously prepared Weinreb amide (0.394 g, 1.94 mmol) and 2,6-lutidine (0.26 mL, 2.23 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added *tert*-butyldimethylsilyltrifluoromethanesulfonate (TBSOTf) (0.47 mL, 2.04 mmol) dropwise. The reaction mixture was stirred for 30 min at 0 °C before it was diluted with CH_2Cl_2 (10 mL) and 10 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). All the organic layers were combined and dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexane) to give the desired product **7** (0.560 g, 91%) as a colorless oil: R_f 0.63 (50% EtOAc/hexane); $[\alpha]_D^{20}$ +1.9 (*c* 1.07, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 2960, 2881, 2857, 1667, 1462, 1411, 1383, 1254; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.84 (d, 3H, *J* 6.6 Hz), 0.88 (t, 3H, *J* 7.1 Hz), 0.92 (s, 9H), 1.16 (d, 3H, *J* 6.9 Hz), 1.19 (m, 1H), 1.32 (m, 1H), 1.46 (m, 1H), 3.10 (m, 1H), 3.17 (s, 3H), 3.70 (s, 3H), 3.88 (dd, 1H, *J* 8.8, 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.6, −3.5, 12.4, 13.5, 15.9, 18.5, 26.2, 26.8, 26.9, 39.0, 40.0, 61.0, 76.0, 177.0; HRMS calcd for $C_{16}H_{35}NO_3Si$ [M^+] 317.2386, found 317.2378.

(4*R*,5*R*,6*S*,*E*)-Methyl 5-(*tert*-Butyldimethylsilyloxy)-4,6-dimethyloct-2-enoate (30). Amide **7** (2.03 g, 6.41 mmol) was dissolved in freshly distilled toluene (40 mL) under an N_2 atmosphere. The solution was cooled to 0 °C, and DIBAL-H (1.0 M in toluene, 12.8 mL) was added. The solution was stirred for 30 min at 0 °C before the reaction was quenched with MeOH (1 mL). The mixture was allowed to warm to

ambient temperature before an aqueous solution of Rochelle's salt was added (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography on silica gel (20% EtOAc/hexane) gave an aldehyde as a colorless oil. ^{1}H NMR spectroscopy of the unpurified aldehyde was very clean. To a stirred suspension of NaH (0.198 g, 8.28 mmol) in THF (10 mL) at 0 °C under argon was added methyl diethylphosphonoacetate (1.7 mL, 9.31 mmol). The reaction mixture was allowed to warm to ambient temperature, and then a solution of the previously prepared aldehyde in 5 mL of THF was added dropwise. After the mixture was stirred for 12 h, the reaction was diluted with 15 mL of Et_2O, and the reaction was quenched by the slow addition of 6 mL of H_2O. The layers were separated, and the aqueous phase was extracted with two 15 mL portions of Et_2O. The combined organic extracts were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (20% EtOAc/hexane) to give unsaturated ester **30** (1.80 g, 90% over two steps, ds >95:5) as a colorless oil: R_f 0.73 (50% EtOAc/hexane); $[\alpha]_D^{20}$ +6.4 (*c* 0.97, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 2959, 2932, 2858, 1728, 1657, 1462, 1256; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.82 (d, 3H, *J* 6.6 Hz), 0.87 (t, 3H, *J* 7.5 Hz), 0.91 (s, 9H), 1.05 (d, 3H, *J* 6.6 Hz), 1.26 (m, 1H), 1.40 (m, 2H), 2.52 (m, 1H), 3.49 (dd, 1H, *J* 3.2, 6.2 Hz), 3.70 (s, 3H), 5.78 (dd, 1H, *J* 7.7, 15.7 Hz), 6.99 (dd, 1H, *J* 8.0, 15.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.7, −3.6, 12.2, 14.0, 16.0, 18.5, 26.2, 27.2, 38.9, 41.4, 51.4, 78.5, 119.5, 152.8, 167.0; HRMS calcd for $C_{17}H_{34}O_3Si$ [M$^+$] 314.2277, found 314.2271.

(4*R*,5*R*,6*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)-4,6-dimethyloct-2-en-1-ol (6). Unsaturated ester **30** (0.689 g, 2.19 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 mL) under an N_2 atmosphere. The solution was cooled to −23 °C, and DIBAL-H (4.55 mmol, 0.82 mL) was added. The solution was stirred for 2 h at −23 °C before the reaction was quenched with EtOAc (5 mL). The mixture was allowed to warm to ambient temperature before an aqueous solution of Rochelle's salt was added (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography on silica gel (20% EtOAc/hexane) gave allylic alcohol **6** (0.565 g, 90%) as a colorless oil: R_f 0.61 (50% EtOAc/hexane); $[\alpha]_D^{20}$ +6.0 (*c* 1.23, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3349, 2959, 2930, 1667, 1462, 1380, 1254; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.82 (d, 3H, *J* 6.6 Hz), 0.87 (t, 3H, *J* 7.5 Hz), 0.97 (s, 9H), 1.00 (d, 3H, *J* 6.6 Hz), 1.18 (m, 1H), 1.45 (m, 2H), 2.36 (sext, 1H, *J* 6.6 Hz), 3.39 (dd, 1H, *J* 2.9, 6.2 Hz), 4.10 (d, 2H, *J* 5.2 Hz), 5.57 (dt, 1H, *J* 5.2, 15.3 Hz), 5.67 (dd, 1H, *J* 6.9, 15.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.6, −3.5, 12.3, 14.1, 16.9, 18.5, 26.2, 27.3, 38.6, 40.9, 65.9, 79.1, 127.5, 136.8; HRMS calcd for $C_{16}H_{34}O_2Si$ [M$^+$] 286.2328, found 286.2388.

((2*S*,3*S*)-3-((2*R*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-methylhexan-2-yl)oxiran-2-yl)methanol (31). To a stirred solution of allylic alcohol **6** (0.217 g, 0.76 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added *m*-CPBA (0.261 g, 1.51 mmol, 77% pure), and the resulting white suspension was stirred for 1 h. The reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (2 mL) and stirred for 15 min at ambient temperature. After addition of 5% $NaHCO_3$ aqueous solution (15 mL), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with H_2O and brine and then dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (20% EtOAc/hexane) to give epoxide **31** (0.220 g, 96%, ds > 95:5) as a colorless oil: R_f 0.61 (50% EtOAc/hexane); $[\alpha]_D^{20}$ −3.7 (*c* 1.15, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3427, 2959, 2857, 1463, 1381, 1254, 1108; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.87 (d, 3H, *J* 6.6 Hz), 0.88 (t, 3H, *J* 7.3 Hz), 0.92 (d, 3H, *J* 7.3 Hz), 0.93 (s, 9H), 1.12 (m, 1H), 1.52 (m, 3H), 1.80 (br s, 1H), 2.90 (dd, 1H, *J* 2.5, 8.0 Hz), 2.95 (dt, 1H, *J* 4.4, 2.2 Hz), 3.61 (dd, 1H, *J* 4.4, 8.0 Hz), 3.65 (t, 1H, *J* 4.4 Hz), 3.92 (dd, 1H, *J* 2.5, 9.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.9, −3.6, 11.7, 12.2, 15.0, 18.5, 26.2, 26.4, 39.3, 39.4, 58.4, 58.5, 61.8, 76.7; HRMS calcd for $C_{16}H_{34}O_3Si$ [M$^+$] 302.2277, found 302.2273.

(2*R*,3*R*,4*R*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethyloctane-1,3-diol (32).[4g] To a suspension of copper(I) cyanide (0.50 g, 5.58 mmol) in THF (2 mL) at −78 °C was added a 1.37 M solution of MeLi in Et_2O (7.7 mL, 10.6 mmol) dropwise. After the solution was stirred at −78 °C for 30 min, a solution of epoxide **31** (0.187 g, 0.62 mmol) in THF (3 mL) was added. The reaction mixture was stirred at −20 °C for 20 h, and a 2:1 (3 mL) mixture of saturated aqueous NH_4Cl and 28% aqueous NH_3 was added. The resulting mixture was stirred at room temperature for 1.5 h, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O and brine (5 mL of each), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (10% EtOAc/hexane) to give diol **32** (0.177 g, 90%) as a colorless oil: R_f 0.38 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +4.2 (*c* 0.95, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3389, 2059, 2881, 2857, 1462, 1385, 1254, 1062; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.15 (s, 3H), 0.83 (d, 3H, *J* 6.9 Hz), 0.90 (t, 3H, *J* 7.3 Hz), 0.91 (s, 9H), 0.97 (d, 3H, *J* 6.6 Hz), 1.12 (d, 1H, *J* 7.2 Hz), 1.23 (m, 1H), 1.40 (m, 1H), 1.59 (m, 1H), 1.72 (m, 1H), 2.06 (m, 1H), 3.37 (br s, 1H), 3.58 (m, 1H), 3.72 (dd, 1H, *J* 9.3, 2.7 Hz), 3.83 (ap t, 1H, *J* 2.7 Hz), 3.94 (dd, 1H, *J* 10.8, 2.7 Hz), 4.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.3, −4.1, 12.3, 13.9, 15.3, 15.6, 18.1, 25.9, 28.5, 35.8, 36.6, 40.2, 64.6, 79.6, 80.2; HRMS calcd for $C_{13}H_{29}O_3Si$ [(M − C_4H_9)$^+$] 261.1886, found 261.1895.

***tert*-Butyl((2*R*,3*R*,4*S*)-2-((2*R*,4*R*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methylhexan-3-yloxy)dimethylsilane (33).** To a solution of diol **32** (0.029 g, 0.09 mmol) in CH_2Cl_2 (5 mL) at ambient temperature were added *p*-methoxybenzaldehyde dimethyl acetal (0.065, 0.36 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 0.005 g). The reaction mixture was stirred at ambient temperature for 6 h before it was concentrated in vacuo. The remaining organic residue was purified by flash chromatography on silica gel (3% EtOAc/hexane) to provide the desired product **33** (0.038 g, 96%) as a colorless oil: R_f 0.71 (40% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.13 (s, 3H), 0.80 (d, 3H, *J* 6.5 Hz), 0.85 (s, 9H), 0.86 (d, 3H, *J* 6.9 Hz), 0.90 (t, 3H, *J* 6.9 Hz), 1.16 (m, 1H), 1.38−1.57 (m, 2H), 1.96 (m, 2H), 3.33 (dd, 1H, *J* 3.4, 9.8 Hz), 3.44 (t, 1H, *J* 11,3 Hz), 3.80 (s, 3H), 3.93 (dd, 1H, *J* 4.2, 3.2 Hz), 4.08 (dd, 1H, *J* 4.7, 11.3 Hz), 5.40 (s, 1H), 6.80 (dt, 2H, *J* 6.2, 2.2 Hz), 7.30 (dt, 2H, *J* 6.2, 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.3, −3.8, 12.4, 13.3, 13.8, 14.4, 26.2, 26.4, 31.5, 39.3, 42.0, 55.3, 73.3, 86.5, 101.4, 113.2, 127.4.

(2*R*,3*R*,4*S*,5*R*,6*S*)-1-(*tert*-Butyldiphenylsilyloxy)-2,4,6-trimethyloctane-3,5-diol (34). To a solution of diol **32** (0.221 g, 0.69 mmol) in 5 mL of THF at ambient temperature was added 1.39 mL (1.39 mmol) of a 1.0 M solution of TBAF in THF. The reaction mixture was stirred at ambient temperature for 16 h and then concentrated in vacuo. The crude product was purified by flash chromatography (80% EtOAc/hexane) to give the desired triol (0.140 g, 98%) as a viscous oil. R_f 0.42 (80% EtOAc/hexane). To a stirred solution of this triol (0.140 g, 0.69 mmol) in DMF (4 mL) at ambient temperature were added imidazole (0.059 g, 0.9 mmol) and *tert*-butyldiphenylsilyl chloride (0.2 g, 0.77 mmol), and stirring was continued for 1 h. The reaction mixture was partitioned between EtOAc and H_2O, and then the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification of the crude product on silica gel (15% EtOAc/hexane) gave the silyl ether **34** (0.279 g, 92%) as a viscous oil: R_f 0.62 (50% EtOAc/hexane); IR ν_{max} (film, cm^{-1}) 3390, 2065, 2887, 1462, 1385; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (d, 3H, *J* 6.9 Hz), 0.91 (d, 3H, *J* 5.5 Hz), 1.02 (d, 3H, *J* 7.6 Hz), 1.04 (s, 9H), 1.05 (t, 3H, *J* 6.9 Hz), 1.42 (m, 1H), 1.54 (m, 1H), 1.60 (br s, 1H), 1.88 (m, 1H), 2.12 (m, 1H), 3.60−3.74

(m, 3H), 3.77 (dd, 1H, *J* 4.3, 10.3 Hz), 7.38−7.48 (m, 6H), 7.64−7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 11.3, 13.1, 15.5, 19.0, 25.1, 26.8, 34.7, 37.0, 37.5, 70.5, 74.9, 83.5, 114.9, 127.7, 129.9, 135.3; HRMS calcd for $C_{27}H_{42}O_3Si$ [M^+] 442.2903, found 442.2891.

***tert*-Butyl((*R*)-2-((4*R*,5*S*,6*R*)-6-((*S*)-*sec*-butyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propoxy)diphenylsilane (35).** To a solution of diol **34** (0.013 g, 0.03 mmol) in 2,2-dimethoxypropane (3 mL) at ambient temperature was added pyridinium *p*-toluenesulfonate (PPTS, 0.005 g). The reaction mixture was stirred at ambient temperature for 2 h before it was concentrated in vacuo. The remaining organic residue was purified by flash chromatography on silica gel (5% EtOAc/hexane) to provide the desired product **35** (0.013 g, 92%) as a colorless oil: R_f 0.52 (5% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, 3H, *J* 6.5 Hz), 0.88 (d, 3H, *J* 6.5 Hz), 1.02 (d, 3H, *J* 7.6 Hz), 1.05 (s, 9H), 1.07 (t, 3H, *J* 6.9 Hz), 1.26 (s, 3H), 1.30 (s, 3H), 1.36−1.48 (m, 2H), 1.58 (br s, 1H), 1.83 (m, 2H), 3.28 (dd, 1H, *J* 3.8, 10.4 Hz), 3.32 (t, 1H, *J* 6.5 Hz), 3.65 (dd, 1H, *J* 5.8, 9.8 Hz), 3.67 (dd, 1H, *J* 5.1, 9.8 Hz), 7.33−7.44 (m, 6H), 7.65−7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 12.8, 13.7, 15.6, 19.3, 23.6, 24.4, 25.3, 26.9, 34.1, 35.0, 40.3, 65.2, 73.5, 76.0, 100.2, 127.4, 129.3, 133.8, 135.4.

(2*S*,3*S*,4*R*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-2,4,6-trimethyloctanal.[4f] In an oven-dried flask under an N_2 atmosphere, DMSO (0.08 mL, 1.0 mmol) was dissolved in freshly distilled CH_2Cl_2 (1 mL). The solution was cooled to −78 °C, and $(COCl)_2$ (0.05 mL, 0.5 mmol) was added dropwise. After 5 min, diol **32** (0.126 g, 0.4 mmol) was added via cannula as a solution in CH_2Cl_2 (1.5 mL). The white slurry was stirred for 10 min at −78 °C before Et_3N (0.3 mL, 2.0 mmol) was added dropwise. The solution was allowed to warm to ambient temperature before being diluted in Et_2O (30 mL) and washed with saturated aq NH_4Cl (20 mL), $NaHCO_3$ (30 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The remaining organic residue was purified by flash chromatography on silica gel (5% EtOAc/hexane) to provide the desired hydroxy aldehyde (0.115 g, 0.36 mmol) as a clear oil: R_f 0.27 (10% EtOAc/hexane); $[\alpha]^{20}_D$ +17.8 (*c* 2.10, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3470, 2975, 2930, 1720, 1107; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.82 (d, 3H, *J* 6.7 Hz), 0.88 (t, 3H, *J* 7.1 Hz), 0.90 (s, 9H), 0.98 (d, 3H, *J* 6.5 Hz), 1.23 (d, 3H, *J* 7.2 Hz), 1.17−1.53 (m, 2H), 1.59 (m, 1H), 1.99 (m, 1H), 2.45 (m, 1H), 3.75 (m, 1H), 3.88 (m, 1H), 4.3 (m, 1H), 9.81 (d, 1H, *J* 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.4, 11.3, 12.3, 13.9, 15.6, 18.1, 25.8, 28.8, 36.1, 41.1, 49.1, 76.3, 79.9, 206.2.

(4*R*,5*R*,6*R*,7*R*,8*S*,*E*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2,4,6,8-tetramethyldec-2-enoate (37).[4f,g] The previously prepared aldehyde (0.115 g, 0.36 mmol) and (1-ethoxycarbonylethylidene)triphenylphosphorane **36** (0.492 g, 1.44 mmol) were combined in freshly distilled 1,2-dichloroethane (5 mL). The solution was heated to reflux and stirred for 15 h. The reaction mixture was concentrated, and the resulting residue was purified by flash chromatography (5% EtOAc/hexane) to give unsaturated ester **37** (0.141 g, 89% over two steps): R_f 0.26 (10% EtOAc/hexane); $[\alpha]^{20}_D$ +29.5 (*c* 0.95, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3482, 2975, 2860, 1712, 1465, 1100; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.11 (s, 3H), 0.70 (d, 3H, *J* 6.8 Hz), 0.89 (t, 3H, *J* 7.3 Hz), 0.92 (s, 9H), 1.00 (d, 3H, *J* 6.8 Hz), 1.10 (d, 3H, *J* 6.9 Hz), 1.20−1.40 (m, 2H), 1.28 (t, 3H, *J* 7.1 Hz), 1.54−1.62 (m, 1H), 1.66−1.72 (m, 1H), 1.85 (d, 3H, *J* 1.4 Hz), 2.58 (m, 1H), 3.66−3.80 (m, 2H), 4.16 (dq, 2H, *J* 6.9, 3.2), 4.49 (br s, 1H), 6.97 (dd, 1H, *J* 10.2, 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.0, 12.2, 12.6, 14.1, 14.4, 15.4, 16.9, 18.1, 25.9, 29.7, 35.5, 36.4, 41.7, 60.3, 77.4, 80.8, 127.4, 142.3, 168.0; HRMS calcd for $C_{18}H_{35}O_4Si$ [$(M - C_4H_9)^+$] 343.2305, found 343.2321.

(4*R*,5*R*,6*R*,7*R*,8*S*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-2,4,6,8-tetramethyldec-2-ene-1,5-diol.[4f] Unsaturated ester **37** (0.137 g, 0.34 mmol) was dissolved in freshly distilled CH_2Cl_2 (5 mL) under an N_2 atmosphere. The solution was cooled to −23 °C, and DIBAL-H (1.12 mmol, 0.2 mL) was slowly added. The solution was stirred for 2 h at −23 °C before the reaction was quenched with EtOAc (5 mL). The mixture was allowed to warm to ambient temperature before an aqueous solution of Rochelle's salt was added (30 mL) and stirred for 1 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography on silica gel (10% EtOAc/hexane) gave the desired allylic alcohol (0.101 g, 82%) as a pale oil: R_f 0.40 (35% EtOAc/hexane); $[\alpha]^{20}_D$ +17.5 (*c* 1.6, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3430, 2978, 2935; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.10 (s, 3H), 0.73 (d, 3H, *J* 6.9 Hz), 0.90 (t, 3H, *J* 7.3 Hz), 0.91 (s, 9H), 0.99 (d, 3H, *J* 6.9 Hz), 1.05 (d, 3H, *J* 6.9 Hz), 1.20−1.40 (m, 2H), 1.6 (m, 1H), 1.70 (d, 3H, *J* 1.1 Hz), 1.70−1.78 (m, 1H), 2.42−2.70 (m, 3H), 3.61 (dd, 1H, *J* 10.2, 2.2 Hz), 3.70 (t, 1H, *J* 2.9 Hz), 4.01 (s, 2H), 5.55 (dd, 1H, *J* 9.5, 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, −3.9, 12.2, 13.8, 13.9, 15.5, 18.1, 18.2, 26.0, 28.9, 35.0, 36.1, 41.2, 69.3, 77.4, 80.3, 126.8, 134.7; HRMS calcd for $C_{16}H_{34}O_2Si$ [M^+] 358.2903, found 358.2901.

(4*R*,5*R*,6*R*,7*R*,8*S*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2,4,6,8-tetramethyldec-2-enal (38).[4f] To a solution of the previously prepared allylic alcohol (0.121 g, 0.34 mmol) in freshly distilled CH_2Cl_2 (5 mL) was added manganese(IV) oxide (0.148 g), and the heterogeneous mixture was stirred at ambient temperature for 2 h. The mixture was then filtered through Celite and concentrated to give aldehyde **38** (0.101 g, 0.34 mmol): R_f 0.77 (30% EtOAc/hexane); $[\alpha]^{20}_D$ +10.2 (*c* 1.26, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3470, 2978, 2940, 1686, 1112; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.73 (d, 3H, *J* 7.0 Hz), 0.91 (t, 3H, *J* 7.3 Hz), 0.91 (s, 9H), 0.99 (d, 3H, *J* 6.8 Hz), 1.15 (d, 3H, *J* 6.9 Hz), 1.20−1.40 (m, 2H), 1.65 (m, 2H), 1.75 (d, 3H, *J* 1.0 Hz), 2.80 (m, 1H), 3.66 (t, 1H, *J* 2.9 Hz), 3.76 (d, 1H, *J* 10.6 Hz), 4.6 (br s, 1H), 6.8 (d, 1H, *J* 9.6 Hz), 9.5 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, −4.1, 9.5, 12.1, 14.1, 15.4, 13.1, 16.9, 18.1, 25.9, 29.1, 35.5, 36.5, 41.9, 77.4, 80.7, 139.0; 155.5, 196.0. HRMS calcd for $C_{20}H_{40}O_3Si$ [M^+] 356.2747, found 356.2735.

(4*R*,5*R*,6*S*,7*R*,8*S*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-2,4,6,8-tetramethyl-5-(trimethylsilyloxy)dec-2-enal.[4f] To a stirred solution of aldehyde **38** in CH_2Cl_2 (4 mL) at 0 °C were added DMAP (0.043 g), triethylamine (0.3 mL, 2.11 mmol), and trimethylsilyl chloride (0.13 mL, 1.06 mmol), and stirring was continued for 2 h. The reaction mixture was partitioned between EtOAc and H_2O, and then the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated: R_f 0.77 (30% EtOAc/hexane); $[\alpha]^{20}_D$ −1.6 (*c* 3.0, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 2980, 2960, 1694, 1646; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.20 (s, 9H), 0.73 (d, 3H, *J* 7.0 Hz), 0.84 (d, 3H, *J* 6.5 Hz), 0.91 (s, 18H), 0.87 (ap t, 3H), 1.08 (d, 3H, *J* 6.9 Hz), 1.06 (m, 1H), 1.30−1.59 (m, 3H), 1.75 (d, 3H, *J* 1.1 Hz), 2.84 (m, 1H), 3.60 (m, 2H), 6.71 (d, 1H, *J* 9.7 Hz), 9.4 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.7, −3.2, 1.1, 9.2, 12.3, 12.5, 13.6, 18.4, 18.5, 25.9, 35.8, 41.9, 76.1, 78.7, 138.0; 156.5, 196.0. HRMS calcd for $C_{23}H_{48}O_3Si_2$ [M^+] 428.3142, found 428.3123.

(1*E*,3*E*,5*R*,6*R*,7*S*,8*R*,9*S*)-8-(*tert*-Butyldimethylsilyloxy)-1-iodo-3,5,7,9-tetramethyl-6-(trimethylsilyloxy)undeca-1,3-diene (3). To a stirred solution of anhydrous chromium(II) chloride (0.209 mg, 1.77 mmol, gently flame-dried under a vacuum (0.1 mmHg)) in dry THF (1 mL) at ambient temperature were added dropwise via cannula a solution of the C17-TMS-protected aldehyde prepared before and iodoform (0.223 g, 0.57 mmol) in THF (3 mL). The reaction mixture was stirred in the dark at ambient temperature for 1 h, during which time it turned brown. The reaction was quenched by the addition of H_2O (5 mL), and the phases were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with $Na_2S_2O_3$ solution (6 mL, 0.5 N aq) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo to give (*E*)-vinyl iodide **3** (0.095 g, *E*:*Z* > 95:5, 45%

over four steps) as a pale yellow oil: R_f 0.72 (5% EtOAc/hexane); IR ν_{max} (film, cm^{-1}) 3075, 2988, 2930, 1108; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.15 (s, 9H), 0.71 (d, 3H, *J* 6.9 Hz), 0.82 (t, 3H, *J* 6.9 Hz), 0.87 (d, 3H, *J* 7.3 Hz), 0.89 (s, 9H), 0.97 (d, 3H, *J* 6.9 Hz), 1.00−1.18 (m, 1H), 1.37 (m, 1H), 1.42−1.62 (m, 2H), 1.71 (s, 3H), 2.66−2.54 (m, 1H), 3.45 (dd, 1H, *J* 8.2, 2.2 Hz), 3.63 (ap t, 1H, *J* 3.4 Hz), 5.64 (d, 1H, *J* 9.5 Hz), 6.10 (d, 1H, *J* 14.6 Hz), 7.04 (d, 1H, *J* 14.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.4, −3.1, 1.3, 12.1, 12.3, 12.6, 13.8, 18.6, 19.3, 26.1, 26.2, 35.1, 41.5, 41.6, 72.5, 76.0, 79.4, 132.9, 136.0, 150.0; HRMS calcd for $C_{24}H_{49}IO_2Si_2$ [M$^+$] 552.2316, found 552.2308.

(1*E*,3*E*,5*R*,6*R*,7*R*,8*R*,9*S*)-8-(*tert*-Butyldimethylsilyloxy)-1-iodo-3,5,7,9-tetramethylundeca-1,3-dien-6-ol (39).[4f] To a solution of (*E*)-vinyl iodide **3** (0.187 g, 0.34 mmol) in anhydrous ethanol (3 mL) at ambient temperature was added camphor sulfonic acid (CSA, 0.015 g). The reaction mixture was stirred at ambient temperature for 12 h before it was concentrated in vacuo. The remaining organic residue was purified by flash chromatography on silica gel (5% EtOAc/hexane, deactivated with Et_3N) to provide the desired product **39** (0.156 g, 96%) as a viscous yellow oil: R_f 0.61 (15% EtOAc/hexane); $[\alpha]^{20}_D$ +41.2 (*c* 1.17, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3473, 3080, 2980, 1110; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.10 (s, 3H), 0.70 (d, 3H, *J* 6.8 Hz), 0.88 (t, 3H, *J* 7.2 Hz), 0.93 (s, 9H), 0.98 (d, 3H, *J* 6.8 Hz), 1.05 (d, 3H, *J* 6.8 Hz), 1.20−1.37 (m, 3H), 1.70 (m, 1H), 1.73 (d, 3H, *J* 1.1 Hz), 2.54 (m, 1H), 3.63 (m, 2H), 4.2 (br s, 1H), 5.7 (d, 1H, *J* 10.3 Hz), 6.14 (d, 1H, *J* 14.5 Hz), 7.00 (d, 1H, *J* 14.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, −4.2, 11.9, 12.1, 13.7, 15.4, 17.5, 18.0, 25.8, 26.0, 29.0, 35.6, 41.5, 72.8, 77.3, 80.4, 134.0, 135.2, 150.0; HRMS calcd for $C_{21}H_{41}IO_2Si$ [M$^+$] 480.1921, found 480.1916.

(2*R*,6*R*)-2-((1*E*,3*Z*,5*R*,7*E*,9*E*,11*R*,12*R*,13*S*,14*R*,15*S*)-14-(*tert*-Butyldimethylsilyloxy)-3-ethyl-5,9,11,13,15-pentamethyl-12-(trimethylsilyloxy)heptadeca-1,3,7,9-tetraenyl)-6-isopropoxy-3,6-dihydro-2*H*-pyran (40) and (3*S*,4*R*,5*R*,6*R*,7*R*,8*E*,10*E*,13*R*,14*Z*,16*E*)-4-(*tert*-Butyldimethylsilyloxy)-15-ethyl-17-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)-3,5,7,9,13-pentamethylheptadeca-8,10,14,16-tetraen-6-ol (41). To a solution of alkyl iodide **2** (0.055 g, 0.14 mmol) in anhydrous Et_2O (2 mL) at ambient temperature was added 9-MeO-9-BBN (0.37 mL, 1.0 M in hexanes). The mixture was cooled to −78 °C, and *t*-BuLi (0.19 mL, 1.7 M in pentane) was added rapidly. The resulting mixture was stirred for 10 min; THF (2.0 mL) was added, and the mixture was warmed to ambient temperature and stirred for an additional 1 h. In a separate flask, vinyl iodide **3** (0.051 g, 0.092 mmol) was dissolved in DMF (1.5 mL), and Pd(dppf)-Cl_2 (0.0034 g, 0.0046 mmol), $AsPh_3$ (0.0042 g, 0.014 mmol), $CsCO_3$ (0.12 g, 0.37 mmol), and water (0.040 mL, 2.2 mmol) were added. The ethereal solution of alkyl boronate prepared before was then cannulated into the DMF solution, and the resulting mixture was stirred for 15 h at ambient temperature. The reaction mixture was partitioned between Et_2O and H_2O, the organic layer extracted with Et_2O (3 × 10 mL), and then the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to give a 34:66 mixture of lactols **40** and **41**, respectively, together with α,β-unsaturated aldehyde **43**. This mixture was carried on without further purification, although an analytical sample of lactol **40** was obtained for purposes of comparison with that described by Lautens and Stammers.[4g] Lactol **40**: R_f 0.38 (5% EtOAc/hexane); $[\alpha]^{20}_D$ +55.3 (*c* 2.15, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 2965, 2930, 2880, 1465, 1182, 1100; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.15 (s, 9H), 0.72 (d, 3H, *J* 7.0 Hz), 0.83 (d, 3H, *J* 6.9 Hz), 0.85 (t, 3H, *J* 7.3 Hz), 0.89 (s, 9H), 0.96 (m, 6H), 1.04 (t, 3H, *J* 7.3 Hz), 1.05 (m, 1H), 1.16 (d, 3H, *J* 6.3 Hz), 1.25 (d, 3H, *J* 6.2 Hz), 1.37 (m, 1H), 1.65 (m, 1H), 1.70 (d, 3H *J* 0.8 Hz), 2.08 (m, 4H), 2.20 (m, 2H), 2.39 (m, 1H), 2.66 (m, 2H), 2.77 (m, 1H), 3.48 (dd, 1H, *J* 7.7, 2.1 Hz), 3.65 (t, 1H, *J* 3.6 Hz), 4.01 (hept, 1H, *J* 6.1 Hz), 4.50 (m, 1H), 5.12 (s, 1H), 5.21 (d, 1H, *J* 9.4 Hz), 5.47 (m, 2H), 5.73 (m, 2H), 6.04 (m, 2H), 6.58 (d, 1H, *J* 15.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −3.6, −3.3, 1.5, 12.4, 12.9, 13.7, 13.8, 18.7, 19.7, 20.9, 22.2, 24.0, 24.3, 24.5, 26.3, 26.5, 31.0, 32.4, 35.5, 41.2, 41.7, 41.9, 67.3, 69.9, 76.1, 80.3, 93.6, 125.2, 126.5, 127.6, 128.7, 128.8, 132.3, 132.4, 135.9, 136.1, 137.0. HRMS calcd for $C_{38}H_{69}O_4Si_2$ [(M − C_3H_7)$^+$] 645.4734, found 645.4722.

The same experimental procedure was used for the coupling of (*E*)-vinyl iodide **39** with alkyl iodide **2**, providing coupled product **41** in 67% isolated yield.

(2*R*,6*R*)-6-((1*E*,3*Z*,5*R*,7*E*,9*E*,11*R*,12*R*,13*R*,14*R*,15*S*)-14-(*tert*-Butyldimethylsilyloxy)-3-ethyl-12-hydroxy-5,9,11,-13,15-pentamethylheptadeca-1,3,7,9-tetraenyl)-5,6-dihydro-2*H*-pyran-2-ol (42). To the mixture containing lactols **40** and **41** as well as aldehyde **43** obtained before in anhydrous THF (1 mL) at ambient temperature was added water (0.17 mL) and glacial AcOH (0.17 mL), and the resulting solution was stirred for 4 days. The reaction was quenched by the slow addition of saturated aqueous $NaHCO_3$ (10 mL), and the phases were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried with $MgSO_4$, and concentrated in vacuo to give lactol **42** (0.020 g, 38%, over two steps) and α,β-unsaturated aldehyde **43** (0.013 g, 25%, over two steps) as colorless oils.

(*R*)-6-((1*E*,3*Z*,5*R*,7*E*,9*E*,11*R*,12*R*,13*R*,14*R*,15*S*)-14-(*tert*-Butyldimethylsilyloxy)-3-ethyl-12-hydroxy-5,9,11,13,15-pentamethylheptadeca-1,3,7,9-tetraenyl)-5,6-dihydropyran-2-one (44). To a solution of lactol **42** (0.011 g) in freshly distilled CH_2Cl_2 (3 mL) was added activated manganese(IV) oxide (0.024 g, 0.2 mmol). The resulting mixture was stirred at ambient temperature for 20 h, filtered through Celite, and concentrated in vacuo to give (C17)-hydroxy lactone **44** (0.0079 g, 72%) as a viscous oil: R_f 0.12 (30% EtOAc/hexanes); $[\alpha]^{20}_D$ +51.4 (*c* 0.27, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3485, 2975, 1725, 1468, 1250; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.08 (s, 3H), 0.71 (d, 3H, *J* 7.0 Hz), 0.90 (t, 3H, *J* 7.3 Hz), 0.91 (s, 9H), 0.95 (d, 3H, *J* 7.1 Hz), 0.98 (d, 3H, *J* 7.0 Hz), 1.03 (t, 3H, *J* 6.9 Hz), 1.07 (d, 3H, *J* 6.9 Hz), 1.20 (m, 1H), 1.35 (m, 1H), 1.57 (m, 1H), 1.72 (d, 3H, *J* 0.9 Hz), 1.75 (m, 1H), 2.10 (t, 2H, *J* 6.9 Hz), 2.18 (q, 1H, *J* 7.3 Hz), 2.20 (q, 1H, *J* 7.1 Hz), 2.46 (m, 2H), 2.57 (m, 1H), 2.64 (m, 1H), 3.63 (d, 1H, *J* 9.7 Hz), 3.67 (t, 1H, *J* 0.8 Hz), 4.08 (br s, 1H), 4.97 (q, 1H, *J* 7.1 Hz), 5.3 (d, 1H, *J* 9.3 Hz), 5.3 (dt, 1H, *J* 15.5, 7.5 Hz), 5.6 (d, 1H, *J* 9.9 Hz), 5.8 (dd, 1 H, *J* 15.7, 6.7 Hz), 6.00 (m, 2H), 6.67 (d, 1H, *J* 15.7 Hz), 6.87 (dt, 1H, *J* 9.9, 4.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −4.0, 12.1, 12.9, 13.6, 14.0, 15.7, 18.2, 20.7, 26.1, 26.5, 29.1, 30.1, 30.4, 32.7, 35.8, 36.1, 41.2, 41.5, 78.1, 79.2, 80.9, 122.1, 125.0, 125.2, 130.3, 131.4, 133.4, 135.5, 137.1, 137.6, 145.1, 164.5. HRMS calcd for $C_{36}H_{64}O_4Si$ [M$^+$] 588.4574, found 588.4563.

(*R*)-6-((1*E*,3*Z*,5*R*,7*E*,9*E*,11*R*,13*S*,14*R*,15*S*)-14-(*tert*-Butyldimethylsilyloxy)-3-ethyl-5,9,11,13,15-pentamethyl-12-oxoheptadeca-1,3,7,9-tetraenyl)-5,6-dihydropyran-2-one (45). To a solution of (C17)-hydroxy lactone **44** (0.0056 g, 0.010 mmol) in freshly distilled CH_2Cl_2 (1 mL) was added Dess−Martin periodinane (0.012 g, 0.02 mmol). The resulting mixture was stirred at ambient temperature for 1 h, filtered through Celite, and concentrated in vacuo. Purification by silica gel flash column chromatography (5% EtOAc/hexane) gave ketolactone **45** (C19-TBS callystatin A) (0.0044 g, 81%) as a colorless oil: R_f 0.32 (30% EtOAc/hexane); $[\alpha]^{20}_D$ −81.1 (*c* 0.045, CH_2Cl_2); IR ν_{max} (film, cm^{-1}) 3032, 2930, 2857, 1733, 1712, 1460; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.73 (d, 3H, *J* 6.6 Hz), 0.82 (t, 3H, *J* 7.2 Hz), 0.90 (s, 9H), 0.95 (d, 3H, *J* 6.5 Hz), 1.05 (t, 3H, *J* 7.3 Hz), 1.08 (d, 3H, *J* 7.1 Hz), 1.12 (d, 3H, *J* 7.0 Hz), 1.80 (d, 3H, *J* 1.1 Hz), 2.07 (m, 3H), 2.18 (m, 2H), 2.34 (m, 1H), 2.46 (m, 2H), 2.65 (m, 1H), 2.82 (m, 1H), 3.64 (m, 1H), 3.86 (dd, 1H, *J* 7.7, 1.9 Hz), 5.01 (m 1H), 5.18 (d, 1H, *J* 9.7 Hz), 5.25 (d, 1H, *J* 9.7 Hz), 5.7 (dt, 1H, *J* 15.6, 7.0 Hz), 5.8 (dd, 1H, *J* 15.9, 6.8 Hz), 6.02 (d, 1H, *J* 15.7 Hz), 6.04 (dt, 1H, *J* 9.9, 1.6 Hz), 6.62 (d, 1H, *J* 15.7 Hz), 6.91 (dt, 1H, *J* 9.4, 4.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$)

δ −4.2, −3.8, 12.5, 13.1, 13.3, 13.4, 15.4, 16.6, 18.5, 20.8, 26.3, 26.4, 27.1, 30.2, 32.1, 40.5, 40.8, 45.8, 49.2, 75.5, 78.8, 121.7, 124.9, 127.2, 129.1, 129.7, 135.5, 135.8, 137.4, 144.5, 164.2, 214.3. HRMS calcd for $C_{35}H_{58}IO_4Si$ [M^+] 570.4104, found 570.4089.

(*R*)-6-((1*E*,3*Z*,5*R*,7*E*,9*E*,11*R*,13*S*,14*R*,15*S*)-3-Ethyl-14-hydroxy-5,9,11,13,15-pentamethyl-12-oxoheptadeca-1,3,7,9-tetraenyl)-5,6-dihydropyran-2-one (1), (−)-Callystatin A. To a solution of ketolactone **45** (C19-TBS callystatin A) (0.0034 g, 0.0055 mmol) in freshly distilled THF (0.5 mL) in a plastic vial was added pyridine (0.3 mL). The reaction mixture was cooled to 0 °C, and HF·pyridine (70:30, 0.2 mL) was added dropwise. After the addition was complete, the reaction was let to warm to ambient temperature, stirred for 3 days, and then transferred directly to a pipet column loaded with silica gel. Elution (30% EtOAc/hexane) gave (−)-callystatin A (0.0021 mg, 77% yield) as a colorless oil: R_f 0.19 (30% EtOAc/hexane); $[\alpha]^{20}_D$ −81.7 (*c* 0.043, MeOH); IR ν_{max} (film, cm^{-1}) 3475, 2925, 2855, 1730, 1710, 1455, 1385, 1240; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* 7.4 Hz); 0.90 (d, 3H, *J* 6.7 Hz), 0.97 (d, 3H, *J* 6.6 Hz),1.05 (t, 3H, *J* 7.5 Hz), 1.11 (d, 3H, *J* 7.1 Hz), 1.14 (d, 3H, *J* 6.7 Hz), 1.37 (m, 3H), 1.82 (d, 3H, *J* 1.2 Hz), 2.10 (m, 2H), 2.18 (m, 2H), 2.46 (m, 2H), 2.67 (m, 1H), 2.87 (dq, 1H, *J* 7.2, 4.3 Hz), 3.56 (dd, 1H, *J* 6.8, 4.3 Hz), 3.65 (m, 1H), 4.98 (dt, 1H, *J* 14.1, 6.5 Hz), 5.14 (d, 1H, *J* 9.7 Hz), 5.25 (d, 1H, *J* 9.7 Hz), 5.61 (dt, 1H, *J* 15.6, 7.5 Hz), 5.78 (dd, 1H, *J* 15.8, 6.8 Hz), 6.02 (d, 1H, *J* 15.5 Hz), 6.06 (dq, 1H, *J* 9.8, 1.7 Hz), 6.62 (d, 1H, *J* 15.7 Hz), 6.91 (dt, 1H, *J* 9.6, 4.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 11.2, 13.0, 13.5, 14.2, 16.2, 20.7, 25.8, 26.4, 30.1, 32.2, 36.7, 40.7, 45.6, 45.8, 74.4, 78.8, 121.7, 124.8, 127.6, 128.4, 129.9, 135.3, 135.4, 136.2, 137.0, 144.6, 164.1, 216.4. HRMS calcd for $C_{29}H_{44}O_4$ [M^+] 456.3240, found 456.3229.

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Supporting Information Available: Experimental procedures and product characterization for compounds **9**, **10**, **11a**, **12a**, **12b**, **13**, **18**, **19a**, **19b**, **25**, and **25-TBS**. Selected IR, ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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