# Total Synthesis of the Antimitotic Marine Natural Product (+)-Curacin A

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The structurally novel antimitotic agent curacin A was prepared in 15 steps and in 2.6% yield for the longest linear sequence. Key steps in our synthesis are the use of a hydrozirconation−transmetalation protocol for the preparation of divinyl alcohol **8**, the stereoselective formation of the acyclic triene segment **11** via enol triflate chemistry, and a second hydrozirconation of the conjugated triene followed by an isocyanide insertion. For the preparation of the heterocyclic moiety of curacin A, the oxazoline → thiazoline conversion offered an efficient access to the sensitive marine natural product.

Since the disclosure of the structure of the *Lyngbya majuscula* metabolite curacin A (**1**) by Gerwick and coworkers in 1994,[2] considerable synthetic activity has been directed toward this unusual natural product.[3] White's group published the first total synthesis and thus achieved an unambiguous assignment of the stereochemistry of curacin A in 1995.[3a] More recently, the research teams of Aubé and Kobayashi have also reported versatile synthetic routes toward curacin A.[3d−f] The vivid interest in this marine natural product is due to the exciting combination of unique structural features and potent biological activity. Curacin A demonstrated promising antiproliferative effects, possibly due to a potent inhibition of tubulin polymerization at the colchicin site.[4] Maybe the most striking structural feature of curacin A is the cyclopropylated vinylthiazoline moiety that contains three of the four stereocenters of the molecule and is responsible for its lack of stability. Curacin A is especially sensitive toward oxidation and acid- as well as base-treatments and has to be stored under an inert gas atmosphere at or below −80 °C. Among other natural products containing thiazoline rings,[5] the presence of alkenyl and cyclopropyl substituents at C(4) and C(2) of the heterocycle is unprecedented.

Curacin A offered unique opportunities for us to demonstrate the synthetic scope of our oxazoline → thiazoline conversion[6] and zirconocene[7] methodologies (Figure 1 and 2). Retrosynthetically, we envisioned a

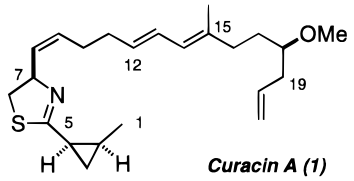


**Figure 1.** Curacin A, an antimitotic metabolite of the blue-green alga *L. majuscula*.

formation of carbon−carbon bonds C(13),C(14) and C(17),C(18) via *in situ* zirconium → zinc transmetalation/aldehyde addition[7a] of **5** and **6** and cationic zirconocene-mediated epoxide rearrangement[7c] reactions between **3** and **4**, respectively. The preparation of the heterocyclic moiety from acylated serine would involve the oxazoline intermediate **2** en route to a final *cis*-selective Wittig segment condensation. Oxazolines are considerably easier to prepare than thiazolines and are much less sensitive toward epimerization of endocyclic and adjacent exocyclic stereocenters.[6] Scrambling of stereochemistry at C(4) is a considerable concern for curacin A, since the *cis*-cyclopropane is readily converted to the thermodynamically much more stable *trans*-cyclopropane ring.

**Synthesis of the C(9)−C(21) Segment of Curacin A.** Hydrozirconation[8] of *tert*-butyldiphenylsilyl-protected alkyne **7** with zirconocene hydrochloride (Schwartz reagent) in $CH_2Cl_2$ provided the alkenylzirconocene **5**, which was readily transmetalated to the corresponding alkenylzinc reagent by addition of stoichiometric amounts of diethylzinc to the reaction mixture (Scheme 1).[7a] Subsequent treatment with aldehyde **6** led to the sensitive divinyl alcohol **8**, which was immediately oxidized with activated manganese dioxide to give ketone **9**. In the aldehyde addition reaction, the conversion of the alkenylzirconocene to a more reactive organometallic is necessary since zirconocenes are sterically quite hindered and their uncatalyzed addition to carbonyl compounds is extremely sluggish. The *in situ* Zr → Zn transmetalation protocol simplifies the more traditional two-step procedure for this reaction sequence, e.g., the conversion of the alkenylzirconocene to the alkenyl bromide or iodide, followed by a halogen−metal exchange.[9]

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(1) Alfred P. Sloan Research Fellow, 1994−1996; NSF Presidential Faculty Fellow, 1994−1999; Camille Dreyfus Teacher−Scholar, 1995−1997.

(2) Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. *J. Org. Chem.* **1994**, *59*, 1243.

(3) (a) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1995**, *117*, 5612. (b) Nagle, D. G.; Geralds, R. S.; Yoo, H.-D.; Gerwick, W. H.; Kim, T.-S.; Nambu, M.; White, J. D. *Tetrahedron Lett.* **1995**, *36*, 1189. (c) Onoda, T.; Shirai, R.; Koiso, Y.; Iwasaki, S. *Tetrahedron Lett.* **1995**, *36*, 5765. (d) Hoemann, M. Z.; Agrios, K. A.; Aubé, J. *Tetrahedron Lett.* **1996**, *37*, 953. (e) Ito, H.; Imai, N.; Tanikawa, S.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 1795. (f) Ito, H.; Imai, N.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 1799.

(4) Blokhin, A. V.; Yoo, H. D.; Geralds, R. S.; Nagle, D. G.; Gerwick, W. H.; Hamel, E. *Mol. Pharm.* **1995**, *48*, 523.

(5) For representative structures, see: (a) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771. (b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75 and references cited therein.

(6) (a) Wipf, P.; Miller, C. P.; Venkatraman, S.; Fritch, P. C. *Tetrahedron Lett.* **1995**, *36*, 6395. (b) Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397. (c) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1995**, *60*, 7224.

(7) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P. *Synthesis* **1993**, 537. (c) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825.

(8) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.

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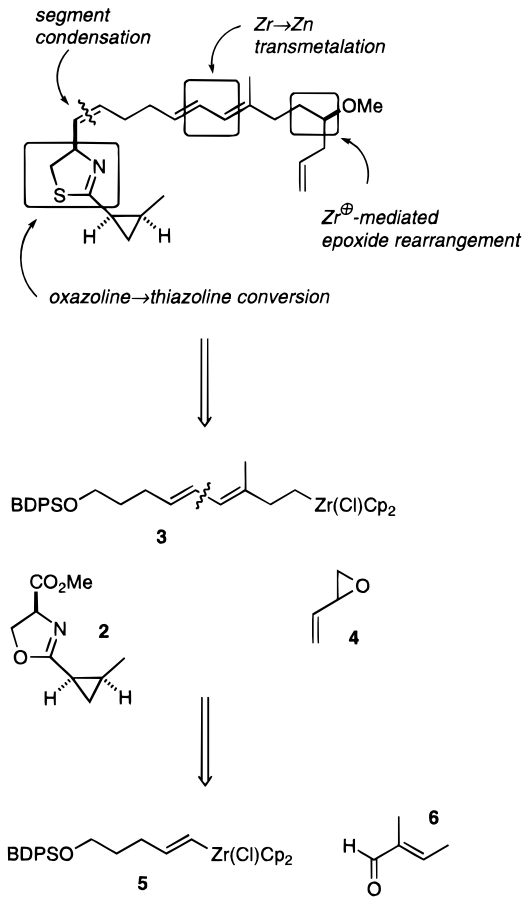
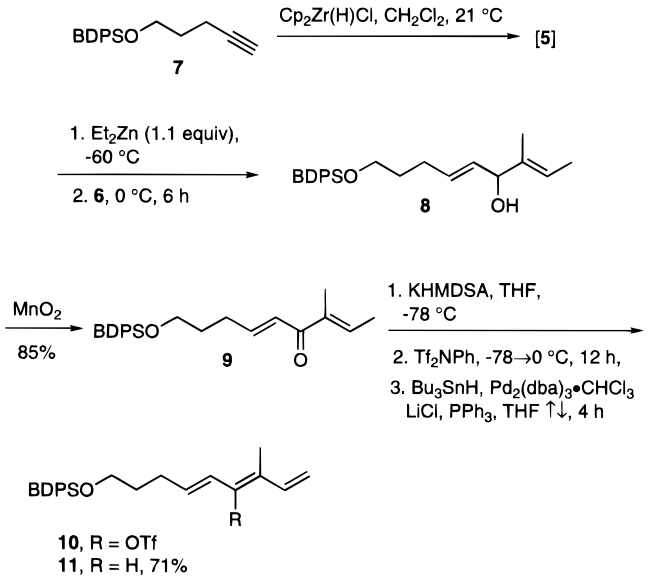


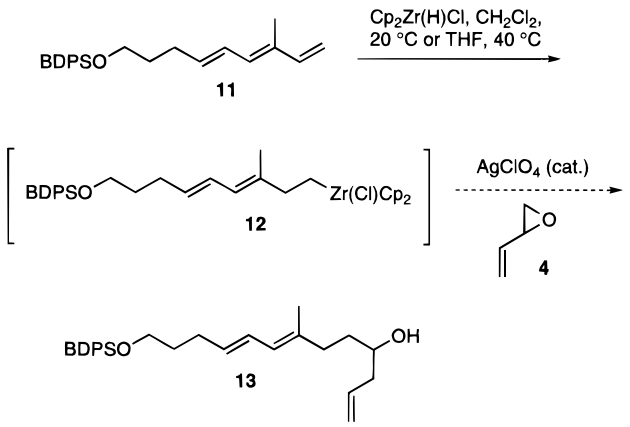

**Figure 2.** Retrosynthetic analysis of curacin A.

**Scheme 1**




For the conversion of the divinyl ketone **9** to the triene **11**, the starting material for our next hydrozirconation–C,C-bond formation sequence, we selected a palladium-catalyzed reduction of the enol triflate intermediate **10**.[10] A regio- and stereoselective enolization at the terminal methyl group of ketone **9** was achieved by treatment with 1 equiv of KHMDSA in THF at −78 °C. Subsequent trapping with *N*-phenyltriflimide provided the desired enol triflate **10** as a single diastereomer in the *all-trans* configuration. Enol triflates of this type are extremely useful synthetic intermediates since they are readily converted to branched alkenes by Pd-catalyzed couplings or cuprate displacements.[11] In our case, Pd(0)-catalyzed reduction of **10** with $Bu_3SnH$ gave triene **11** in an overall yield of 71%. To the best of our knowledge, this reaction sequence represents the first application of this methodology for the stereoselective synthesis of highly substituted acyclic triene moieties.[11]

**Scheme 2**




Hydrozirconation of triene **11** at the terminal vinyl group was rather sluggish and was best accomplished in $CH_2Cl_2$ at room temperature or in THF at 40 °C overnight (Scheme 2). The resulting alkylzirconocene **12** was treated with 5 mol % $AgClO_4$ in the presence of an excess of vinyl oxirane **4** to effect an *in situ* epoxide rearrangement–carbonyl addition cascade.[7c] However, due to an unexpected neighboring group participation of the diene moiety in **12**, the reactivity of the cationic zirconocene derived from chloride abstraction from **12** was too low for the desired pathway to compete with the concomitant polymerization of the sensitive oxirane **4**. Accordingly, only traces of the desired homoallylic alcohol **13** were detected in the reaction mixture. In spite of an extensive variation of reaction parameters, we were unable to improve this transformation. We were, however, able to solve the impasse by treatment of alkylzirconocene intermediate **12** with *n*-butyl isocyanide and subsequent hydrolysis of the resulting iminoylzirconocene[12] with aqueous hydrochloric acid to give the aldehyde **14** in 54% yield (Scheme 3). After this one-carbon homologation of alkene **11**, allylation[3a,13] with borane **15** derived from (−)-*B*-methoxydiisopinocampheylborane gave alcohol **13** in 63% yield.[14] In a straightforward sequence of high-yielding transformations, **13** was subsequently converted to the phosphonium salt **16**.

**Synthesis of the C(1)–C(8) Segment of Curacin A.** For the preparation of the heterocyclic moiety of curacin A, *cis*-cyclopropanoic acid **18**, obtained by an

(9) (a) Labinger, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 667–702. (b) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.

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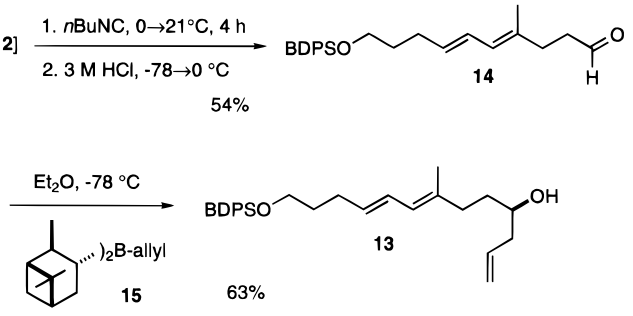
(11) (a) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313. (b) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47. (c) Ritter, K. *Synthesis* **1993**, 735. (d) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

(12) Negishi, E.; Swanson, D. R.; Miller, S. R. *Tetrahedron Lett.* **1988**, *29*, 1631.

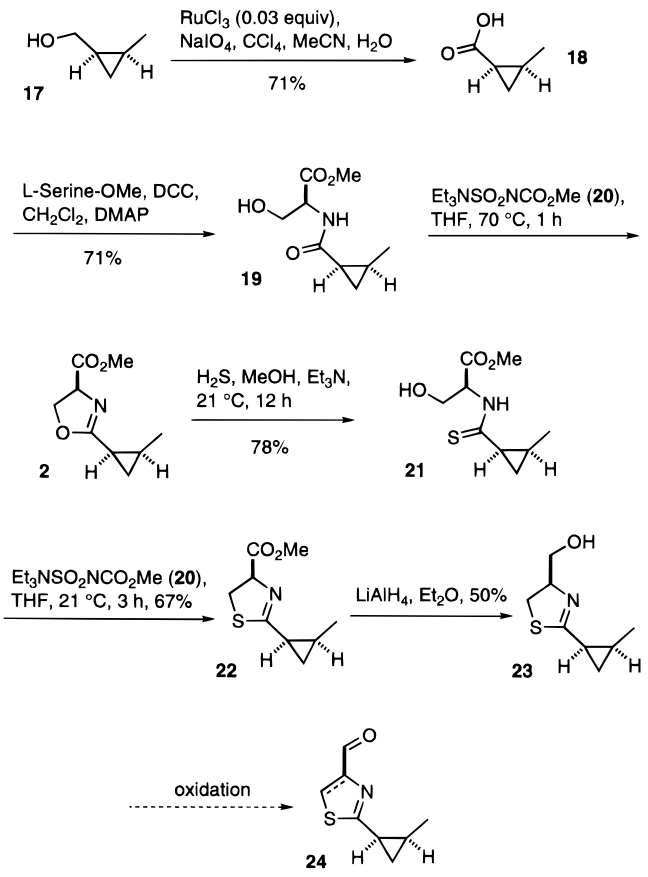
(13) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(14) The enantiomeric excess of the homoallylic alcohol **13** was determined as 93% by Mosher ester analysis.

**Scheme 3**

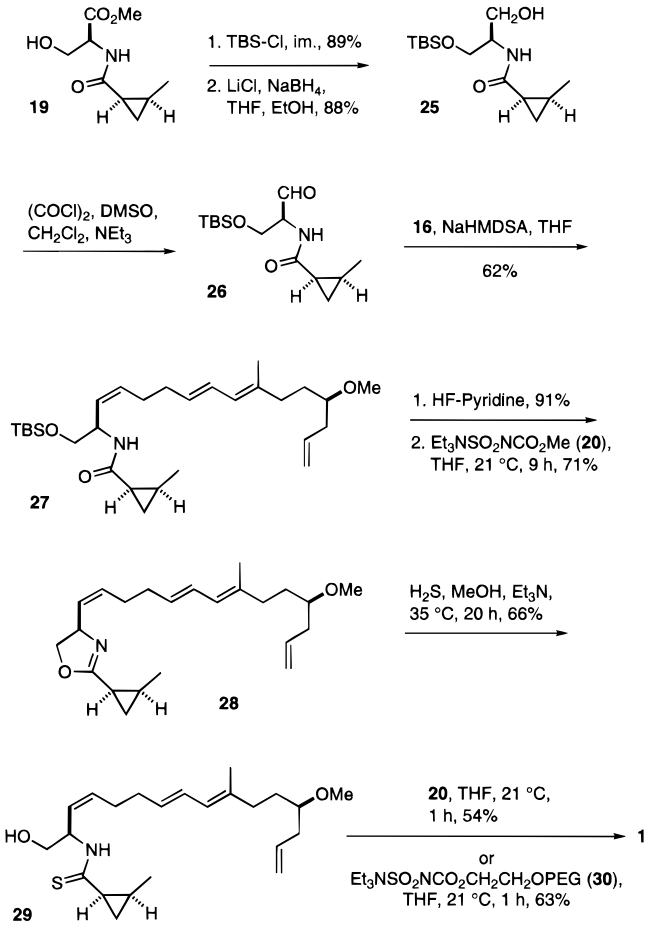



**Scheme 4**




asymmetric Charette cyclopropanation of *cis*-crotyl alcohol[15] and ruthenium-catalyzed oxidation of the resulting **17**, was condensed with serine methyl ester (Scheme 4). Cyclodehydration of **19** with Burgess reagent,[16] followed by thiolysis of oxazoline **2**, provided thioamide **21** in 78% overall yield. A second cyclodehydration step with Burgess reagent cleanly converted the thioamide to the desired thiazoline **22**.[6] In spite of the success of our

**Scheme 5**




oxazoline → thiazoline conversion protocol for the preparation of the sensitive heterocyclic moiety in curacin A, we were unable to apply this synthetic sequence for our total synthesis since all attempts to obtain the aldehyde **24** by oxidation of the thiazoline alcohol **23** failed or led to large amounts of aromatized product. We were also unable to control the partial reduction of ester **22** to give aldehyde **24** directly.[17] Therefore, the sensitivity of the thiazoline residue forced us to postpone the formation of this heterocycle to the very end of the planned synthesis.

**Segment Condensation.** Side-chain hydroxyl group protection of serine **19**, ester reduction, and Swern oxidation provided aldehyde **26**, which was immediately subjected to Wittig condensation with the phosphorane derived from deprotonation of **16** with NaHMDSA (Scheme 5). Particulary on a small scale, this reaction required carefully degassed solvents. Under optimal conditions, 62% of the tetraene **27** was isolated. With the complete carbon-skeleton of the target molecule assembled, the final steps of our synthesis focused on the construction of the heterocycle. Our biggest concern was the thiolysis step of the planned oxazoline → thiazoline conversion, since the harsher conditions that would be necessary for the ring-opening of the unactivated oxazoline **28** might lead to side reactions at the cyclopropane or alkene moieties.[18]

As expected, deprotection of the silyl ether **27** and cyclodehydration with Burgess reagent (**20**)[16] led to

(15) (a) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081. (b) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.

(16) (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (b) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267. (c) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744.

(17) For a related, successful partial reduction of a thiazolyl ester, see: Rinehart, K. L.; Staley, A. L.; Wilson, S. R.; Ankenbauer, R. G.; Cox, C. D. *J. Org. Chem.* **1995**, *60*, 2786.

oxazoline **28** in high yield. The experimental conditions for the thiolysis of **28** indeed required some optimization, and satisfactory results were obtained at 35 °C. After exposure for 20 h, 66% of the desired thioamide **29** was isolated. The subsequent cyclodehydration of **29** with reagent **20** provided curacin A (**1**) in 54%. The synthetic compound was purified by chromatography on Florisil and proved to be identical in all regards (spectroscopic data, HPLC retention time) to a sample of the natural product.[19] Less than 5% of the thermodynamically favored *trans*-cyclopropyl isomer (the C(4)-epimer of **1**) was detected. In an alternative protocol, our recently developed poly(ethylene glycol)-linked reagent **30**[20] was used for the cyclodehydration of thioamide **29**. With many sensitive substrates, this readily separable polymeric version of Burgess reagent provides superior yields.[20] Indeed, compound **1** was isolated in excellent purity and in 63% yield under these conditions.

In summary, a remarkable overall yield of 42% was obtained for the oxazoline → thiazoline conversion of the oxazoline analog **28** to air- and base-labile curacin A. In terms of yield and stereoselectivity, our method compares favorably to other protocols for the formation of the sensitive thiazoline heterocycle.[3,21]

**Conclusion.** We have developed an efficient strategy for the preparation of the structurally novel antitumor agent curacin A. The highly convergent approach that we had originally envisioned via aldehyde **24** was thwarted by the instability of the thiazoline moiety. Nonetheless, the present route provides the natural product in an overall yield of 2.6% from alkyne **7**, which is obtained in a quantitative fashion by silylation of commercially available alcohol. Highlights of our approach to curacin A are the use of two hydrozirconation sequences and a stereoselective triene preparation in the formation of the C(9)−C(21) carbon chain and the successful completion of the total synthesis by a stereoselective oxazoline → thiazoline conversion. This route provides a straightforward access to interesting structural analogs for exploration of the pharmacological potential of the natural product.

## Experimental Section

**General Methods.** All glassware was dried in an oven at 150 °C prior to use. THF and dioxane were dried by distillation over Na/benzophenone under a nitrogen atmosphere. Dry $CH_2Cl_2$, DMF, and $CH_3CN$ were obtained by distillation from $CaH_2$. Other solvents or reagents were used as acquired except when otherwise noted. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F-254 plates available from Merck. Column chromatography was performed using silica gel 60 (particle size 0.040−0.055 mm, 230−400 mesh). Visualization was accomplished with UV light or by staining with a basic $KMnO_4$ solution or Vaughn's reagent. NMR spectra were recorded in $CDCl_3$ unless otherwise noted at either 300 MHz ($^1$H NMR) or 75 MHz ($^{13}$C NMR).

**(2*E*,5*E*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-3-methylnona-2,5-dien-4-ol (8).** A solution of 12.9 g (40.0 mmol) of *tert*-butyl(pent-4-ynyloxy)diphenylsilane (**7**) in 80 mL of $CH_2Cl_2$ was portionwise treated at 22 °C with 11.3 g (44.0 mmol, 1.1 equiv) of $Cp_2Zr(H)Cl$. The mixture was stirred at 22 °C until a homogenous solution formed. After another 20 min, it was cooled to −60 °C, and 44.0 mL (44.0 mmol, 1.1 equiv) of $Et_2Zn$ (1.0 M solution in hexanes) was added over 1.5 h. The solution was immersed in an ice bath, and 4.2 mL (44.0 mmol, 1.1 equiv) of *trans*-2-methyl-2-butenal (**6**) was added dropwise. The reaction mixture was stirred at 0 °C for 6 h, poured into an ice-cold 5% aqueous $NaHCO_3$ solution, and stirred vigorously until bubbling had ceased. The solution was then filtered through a pad of Celite and extracted with $Et_2O$ (4×). The combined ether layers were washed with brine, dried ($Na_2SO_4$), filtered through a pad of Florisil, and concentrated *in vacuo* to give 15.3 g (94%) of **8** as a colorless oil: IR (neat) 3370 cm$^{-1}$; $^1$H NMR $\delta$ 7.72−7.69 (m, 4 H), 7.48−7.38 (m, 6 H), 5.72−5.64 (m, 1 H), 5.60−5.47 (m, 2 H), 4.46 (d, 1 H, $J$ = 6.2 Hz), 3.70 (t, 2 H, $J$ = 6.3 Hz), 2.22−2.11 (m, 2 H), 1.77−1.53 (m, 3 H), 1.65 (d, 3 H, $J$ = 6.8 Hz), 1.61 (s, 3 H), 1.09 (s, 9 H); $^{13}$C NMR $\delta$ 137.2, 135.6, 134.0, 131.7, 131.3, 129.6, 127.6, 120.3, 78.1, 63.2, 32.0, 28.5, 26.9, 19.2, 13.2, 11.9; MS (EI) *m*/*z* (relative intensity) 351 ([M − $C_4H_9$]$^+$); HRMS (EI) *m*/*z* calcd for $C_{22}H_{27}O_2Si$ (M − $C_4H_9$) 351.1780, found 351.1778.

**(2*E*,5*E*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-3-methylnona-2,5-dien-4-one (9).** To a solution of 15.3 g (37.5 mmol) of **8** in 150 mL of hexanes was added 60 g of activated $MnO_2$. The reaction mixture was stirred at 22 °C overnight and filtered, and the solid residue was washed with 30% EtOAc in hexanes solution. The combined filtrates were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:10) to give 13.7 g (90%) of **9** as a colorless oil: IR (neat) 1659 cm$^{-1}$; $^1$H NMR $\delta$ 7.67−7.64 (m, 4 H), 7.45−7.35 (m, 6 H), 6.83 (dt, 1 H, $J$ = 15.3, 6.8 Hz), 6.69−6.61 (m, 2 H), 3.68 (t, 2 H, $J$ = 6.1 Hz), 2.34 (q, 2 H, $J$ = 7.1 Hz), 1.85 (d, 3 H, $J$ = 6.8 Hz), 1.83 (s, 3 H), 1.72 (p, 2 H, $J$ = 6.6 Hz), 1.05 (s, 9 H); $^{13}$C NMR $\delta$ 192.2, 146.6, 138.9, 137.3, 135.6, 133.9, 129.7, 127.7, 125.5, 63.0, 31.2, 29.1, 26.9, 19.3, 14.8, 11.5; MS (EI) *m*/*z* (relative intensity) 349 ([M − $C_4H_9$]$^+$); HRMS (EI) *m*/*z* calcd for $C_{22}H_{25}O_2Si$ (M − $C_4H_9$) 349.1624, found 349.1623.

**Trifluoromethanesulfonic acid (1*Z*)-1-[(1*E*)-5-[(*tert*-Butyldiphenylsilyl)oxy]pent-1-enyl]-2-methylbuta-1,3-dienyl Ester (10).** A mixture of 27.8 mL (27.8 mmol, 1.1 equiv) of potassium bis(trimethylsilylamide) (1.0 M solution in THF) in 60 mL of THF was cooled to −78 °C, and 10.3 g (25.3 mmol) of **9** in 25 mL of THF was added dropwise. The reaction mixture was stirred at −78 °C for an additional 2 h, and 9.9 g (27.8 mmol, 1.1 equiv) of *N*-phenyltrifluoromethanesulfonimide in 55 mL of THF was then added dropwise. The solution was stirred at 0 °C overnight, brine was added, and the mixture was extracted with $Et_2O$ (4×). The combined ether layers were washed with water (2×) and brine and dried ($Na_2SO_4$). The solution was concentrated *in vacuo*, and the crude product (**10**, 13.7 g, quantitative) was used without further purification: IR (neat) 1428, 1139, 1083 cm$^{-1}$; $^1$H NMR $\delta$ 7.70−7.66 (m, 4 H), 7.43−7.36 (m, 6 H), 6.69 (dd, 1 H, $J$ = 17.1, 10.9 Hz), 6.38 (d, 1 H, $J$ = 15.4 Hz), 6.07 (dt, 1 H, $J$ = 15.4, 7.1 Hz), 5.47 (d, 1 H, $J$ = 17.0 Hz), 5.33 (d, 1 H, $J$ = 10.9 Hz), 3.70 (t, 2 H, $J$ = 6.1 Hz), 2.33 (q, 2 H, $J$ = 7.3 Hz), 1.98 (s, 3 H), 1.71 (p, 2 H, $J$ = 6.8 Hz), 1.07 (s, 9 H); $^{13}$C NMR $\delta$ 144.5, 135.9, 135.6, 133.9, 132.0, 129.7, 127.7, 126.6, 119.8, 118.4, 62.9, 31.7, 29.4, 26.9, 19.3, 12.9; MS (EI) *m*/*z* (relative intensity) 481 ([M − $C_4H_9$]$^+$); HRMS (EI) *m*/*z* calcd for $C_{23}H_{24}O_4SiF_3S$ (M − $C_4H_9$) 481.1117, found 481.1091.

**(4*E*,6*E*)-*tert*-Butyl[(7-methylnona-4,6,8-trienyl)oxy]-diphenylsilane (11).** To a slurry of 2.5 g (59.7 mmol, 3.0 equiv) of LiCl, 400 mg (0.40 mmol, 0.02 equiv) of tris-(dibenzylideneacetone)dipalladium(0)−chloroform adduct, and 500 mg (1.99 mmol, 0.10 equiv) of triphenylphosphine in 100 mL of THF was added a solution of 10.7 g (19.9 mmol) of **10** in 40 mL of THF followed by an additional 40 mL of THF. After addition of 6.4 mL (23.8 mmol, 1.2 equiv) of tributyltin hydride, the reaction mixture was heated at reflux for 4 h, cooled, and diluted with $Et_2O$. The solution was washed with 5% aqueous $NH_4OH$ (3×) and brine, dried ($Na_2SO_4$), and chromatographed on $SiO_2$ (EtOAc/hexanes, 1:20) to give 5.54 g (71%) of **11** as a colorless oil: IR (neat) 1428, 1111, 823, 701

(18) The rate of thiolysis of oxazolines correlates roughly with the electron-withdrawing effect of the substituent α to the nitrogen atom. Acceptor, e.g., ester-substituted, oxazolines are generally thiolyzed more readily than unsubstituted or donor-substituted heterocycles: Wipf, P.; Venkatraman, S. *Synlett*, in press.

(19) We would like to thank Professor Gerwick for a generous sample of natural curacin A.

(20) Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659.

(21) Aubé and co-workers[3d] have also successfully applied the oxazoline → thiazoline strategy in their synthesis of curacin A.

cm$^{-1}$; $^1$H NMR $\delta$ 7.69−7.66 (m, 4 H), 7.45−7.35 (m, 6 H), 6.44 (d, 1 H, $J$ = 17.2 Hz), 6.37 (d, 1 H, $J$ = 10.9 Hz), 6.03 (d, 1 H, $J$ = 11.1 Hz), 5.73 (dt, 1 H, $J$ = 15.0, 7.1 Hz), 5.18 (d, 1 H, $J$ = 17.2 Hz), 5.00 (d, 1 H, $J$ = 10.6 Hz), 3.68 (t, 2 H, $J$ = 6.3 Hz), 2.27 (q, 2 H, $J$ = 7.3 Hz), 1.85 (s, 3 H), 1.68 (p, 2 H, $J$ = 6.8 Hz), 1.06 (s, 9 H); $^{13}$C NMR $\delta$ 141.5, 135.7, 134.1, 133.3, 131.6, 129.6, 127.7, 127.1, 111.9, 63.2, 32.3, 29.5, 26.9, 19.3, 12.0; MS (EI) *m*/*z* (relative intensity) 333 ([M − $C_4H_9$]$^+$); HRMS (EI) *m*/*z* calcd for $C_{22}H_{25}OSi$ (M − $C_4H_9$) 333.1674, found 333.1670.

**(4*E*,6*E*)-10-[(*tert*-Butyldiphenylsilyl)oxy]-4-methyldeca-4,6-dienal (14).** A solution of 1.0 g (2.56 mmol) of **11** in 10 mL of THF was treated at 22 °C with 0.66 g (2.56 mmol, 1.0 equiv) of $Cp_2Zr(H)Cl$. The reaction mixture was stirred at 40 °C overnight. Butyl isocyanide (0.29 mL, 2.81 mmol) was added dropwise at 0 °C, and the solution was stirred at 22 °C for 4 h. After addition of $Et_2O$ (10 mL), the solution was cooled to −78 °C, and 3 M HCl (2 mL) was added with vigorous stirring. The reaction mixture was warmed to 0 °C, and the organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution and brine, and dried ($Na_2SO_4$). The solvent was removed, and the product was purified by chromatography on Florisil (EtOAc/hexanes, 1:30) to give 0.58 g (54%) of **14** as a colorless oil: IR (neat) 1724, 1111, 822, 701 cm$^{-1}$; $^1$H NMR $\delta$ 9.78 (t, 1 H, $J$ = 1.6 Hz), 7.69−7.66 (m, 4 H), 7.45−7.35 (m, 6 H), 6.23 (dd, 1 H, $J$ = 15.0, 10.8 Hz), 5.80 (d, 1 H, $J$ = 10.6 Hz), 5.59 (dt, 1 H, $J$ = 15.0, 7.1 Hz), 3.68 (t, 2 H, $J$ = 6.3 Hz), 2.56 (t, 2 H, $J$ = 7.5 Hz), 2.38 (t, 2 H, $J$ = 7.5 Hz), 2.22 (q, 2 H, $J$ = 7.3 Hz), 1.74 (s, 3 H), 1.64 (p, 2 H, $J$ = 6.7 Hz), 1.05 (s, 9 H); $^{13}$C NMR $\delta$ 202.3, 135.6, 134.1, 133.8, 133.1, 129.6, 127.7, 126.6, 125.7, 63.3, 42.1, 32.4, 32.0, 29.3, 26.9, 19.3, 16.7; MS (EI) *m*/*z* (relative intensity) 363 ([M − $C_4H_9$]$^+$); HRMS (EI) *m*/*z* calcd for $C_{23}H_{27}O_2Si$ (M − $C_4H_9$) 363.1780, found 363.1776.

**(4*R*,7*E*,9*E*)-13-[(*tert*-Butyldiphenylsilyl)oxy]-7-methyltrideca-1,7,9-trien-4-ol (13).** A solution of (−)-*B*-methoxydiisopinocampheylborane (300 mg, 0.95 mmol) in 1.0 mL of dry $Et_2O$ was cooled to 0 °C, and allylmagnesium bromide (0.95 mL, 0.95 mmol) (1.0 M solution in $Et_2O$) was added dropwise. The reaction mixture was vigorously stirred at 22 °C for 1 h and cooled to −78 °C, and a solution of **14** (400 mg, 0.95 mmol) in 1.0 mL of $Et_2O$ was added dropwise. The mixture was stirred at −78 °C for 4 h, 60 $\mu$L (0.95 mmol) of ethanolamine was added, and stirring was continued at 22 °C for 2 h. After addition of $Et_2O$, the organic layer was washed with brine, dried ($Na_2SO_4$), and chromatographed on $SiO_2$ (EtOAc/hexanes, 1:10) to give 277 mg (63%) of **13** as a colorless oil: $[\alpha]_D$ −7.2° (*c* 0.6, $CHCl_3$); IR (neat) 3360, 1111, 702 cm$^{-1}$; $^1$H NMR $\delta$ 7.69−7.66 (m, 4 H), 7.45−7.35 (m, 6 H), 6.24 (dd, 1 H, $J$ = 15.0, 10.8 Hz), 5.85−5.79 (m, 2 H), 5.56 (dt, 1 H, $J$ = 15.0, 7.0 Hz), 5.17−5.12 (m, 2 H), 3.67 (t, 2 H, $J$ = 6.4 Hz), 3.69−3.65 (m, 1 H), 2.31−2.05 (m, 6 H), 1.74 (s, 3 H), 1.70−1.58 (m, 5 H), 1.05 (s, 9 H); $^{13}$C NMR $\delta$ 136.0, 135.6, 134.8, 134.1, 132.3, 129.6, 127.7, 126.9, 125.1, 118.3, 70.5, 63.3, 42.0, 36.0, 34.9, 32.5, 29.2, 26.9, 19.3, 16.6; MS (EI) *m*/*z* (relative intensity) 462 (M$^+$); HRMS (EI) *m*/*z* calcd for $C_{30}H_{42}O_2Si$ 462.2954, found 462.2965.

***tert*-Butyl-(4*E*,6*E*,10*R*)-[(10-methoxy-7-methyltrideca-4,6,12-trienyl)oxy]diphenylsilane.** To a suspension of NaH (83 mg, 60%, 2.08 mmol) in 1.0 mL of THF was added dropwise 480 mg (1.04 mmol) of **13** in 2 mL of THF. The mixture was stirred at 22 °C for 2 h, treated dropwise with 0.13 mL (2.08 mmol) of methyl iodide, and stirred at 22 °C for 4 h. Water was added slowly, and the reaction mixture was extracted with $Et_2O$ (3×). The combined ether layers were dried ($Na_2SO_4$) and purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:30) to give 445 mg (90%) of *tert*-butyl-(4*E*,6*E*,10*R*)-[(10-methoxy-7-methyltrideca-4,6,12-trienyl)oxy]diphenylsilane as a colorless oil: $[\alpha]_D$ −1.1° (*c* 0.35, $CHCl_3$); IR (neat) 1111, 1095, 823, 702 cm$^{-1}$; $^1$H NMR $\delta$ 7.69−7.66 (m, 4 H), 7.45−7.34 (m, 6 H), 6.25 (dd, 1 H, $J$ = 15.0, 10.7 Hz), 5.86−5.77 (m, 2 H), 5.56 (dt, 1 H, $J$ = 15.0, 6.9 Hz), 5.12−5.05 (m, 2 H), 3.67 (t, 2 H, $J$ = 6.4 Hz), 3.35 (s, 3 H), 3.17 (p, 1 H, $J$ = 5.9 Hz), 2.31−2.03 (m, 6 H), 1.73 (s, 3 H), 1.68−1.56 (m, 4 H), 1.05 (s, 9 H); $^{13}$C NMR $\delta$ 136.3, 135.7, 134.8, 134.1, 132.0, 129.6, 127.7, 127.0, 124.9, 117.1, 80.0, 63.3, 56.7, 37.7, 35.4, 32.5, 31.7, 29.3, 26.9, 19.3, 16.6; MS (EI) *m*/*z* (relative intensity) 476 (M$^+$); HRMS (EI) *m*/*z* calcd for $C_{31}H_{44}O_2Si$ 476.3111, found: 476.3138.

**(4*E*,6*E*,10*R*)-10-Methoxy-7-methyltrideca-4,6,12-trien-1-ol.** To a solution of 380 mg (0.80 mmol) of *tert*-butyl-(4*E*,6*E*,-10*R*)-[(10-methoxy-7-methyltrideca-4,6,12-trienyl)oxy]diphenylsilane in 8 mL of THF was added dropwise 0.96 mL (0.96 mmol, 1.2 equiv) of tetrabutylammonium fluoride (1.0 M solution in THF). The reaction mixture was stirred at 22 °C for 3 h, diluted with EtOAc, washed with brine, dried ($Na_2SO_4$), and purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:4) to give 170 mg (89%) of (4*E*,6*E*,10*R*)-10-methoxy-7-methyltrideca-4,6,12-trien-1-ol as a colorless oil: $[\alpha]_D$ −1.8° (*c* 1.0, $CHCl_3$); IR (neat) 3392, 1095, 1060 cm$^{-1}$; $^1$H NMR $\delta$ 6.26 (dd, 1 H, $J$ = 15.0, 10.7 Hz), 5.84−5.73 (m, 2 H), 5.57 (dt, 1 H, $J$ = 15.0, 7.0 Hz), 5.10−5.03 (m, 2 H), 3.65 (t, 2 H, $J$ = 6.4 Hz), 3.33 (s, 3 H), 3.17 (p, 1 H, $J$ = 5.8 Hz), 2.28−2.00 (m, 6 H), 1.78 (s, 3 H), 1.68−1.55 (m, 5 H); $^{13}$C NMR $\delta$ 136.7, 134.8, 131.5, 127.3, 124.7, 117.1, 80.0, 62.5, 56.6, 37.7, 35.4, 32.5, 31.6, 29.3, 16.6; MS (EI) *m*/*z* (relative intensity) 238 (M$^+$); HRMS (EI) *m*/*z* calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1944.

**Methanesulfonic Acid (4*E*,6*E*,10*R*)-10-Methoxy-7-methyltrideca-4,6,12-trienyl Ester.** To a solution of 120 mg (0.50 mmol) of (4*E*,6*E*,10*R*)-10-methoxy-7-methyltrideca-4,6,-12-trien-1-ol in 1 mL of $CH_2Cl_2$ was added triethylamine (84 $\mu$L, 0.6 mmol) followed by methanesulfonyl chloride (42 $\mu$L, 0.55 mmol). The reaction mixture was stirred at 22 °C overnight and concentrated *in vacuo*, and the residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:4) to give 150 mg (95%) of methanesulfonic acid (4*E*,6*E*,10*R*)-10-methoxy-7-methyltrideca-4,6,12-trienyl ester as a colorless oil: $[\alpha]_D$ −1.0° (*c* 0.9, $CHCl_3$); IR (neat) 1356, 1176, 1094, 966 cm$^{-1}$; $^1$H NMR $\delta$ 6.26 (dd, 1 H, $J$ = 15.0, 10.9 Hz), 5.82−5.73 (m, 2 H), 5.48 (dt, 1 H, $J$ = 15.0, 7.0 Hz), 5.08−5.01 (m, 2 H), 4.20 (t, 2 H, $J$ = 6.4 Hz), 3.31 (s, 3 H), 3.20−3.13 (m, 1 H), 2.97 (s, 3 H), 2.26−1.97 (m, 6 H), 1.82 (p, 2 H, $J$ = 6.9 Hz), 1.70 (s, 3 H), 1.61−1.52 (m, 2 H); $^{13}$C NMR $\delta$ 137.4, 134.7, 129.4, 128.2, 124.3, 117.0, 79.8, 69.4, 56.5, 37.6, 37.3, 35.3, 31.6, 28.9, 28.6, 16.6; MS (EI) *m*/*z* (relative intensity) 316 (M$^+$); HRMS (EI) *m*/*z* calcd for $C_{16}H_{28}O_4S$ 316.1708, found 316.1694.

**(4*R*,7*E*,9*E*)-13-Iodo-4-methoxy-7-methyltrideca-1,7,9-triene.** To a solution of 56 mg (0.17 mmol) of methanesulfonic acid (4*E*,6*E*,10*R*)-10-methoxy-7-methyltrideca-4,6,12-trienyl ester in 1 mL of acetone was added 80 mg (0.51 mmol, 3.0 equiv) of NaI. The reaction mixture was heated at reflux for 2 h, and acetone was removed *in vacuo*. The residue was diluted with $CH_2Cl_2$ (2 mL) and water (1 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3×), and the combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:20) to give 59 mg (99%) of (4*R*,7*E*,9*E*)-13-iodo-4-methoxy-7-methyltrideca-1,7,9-triene as a colorless oil: $[\alpha]_D$ −1.5° (*c* 1.0, $CHCl_3$); IR (neat) 1440, 1096, 964 cm$^{-1}$; $^1$H NMR $\delta$ 6.28 (dd, 1 H, $J$ = 15.0, 10.9 Hz), 5.84−5.73 (m, 2 H), 5.48 (dt, 1 H, $J$ = 15.0, 7.0 Hz), 5.09−5.04 (m, 2 H), 3.33 (s, 3 H), 3.27−3.15 (m, 3 H), 2.28−2.01 (m, 6 H), 1.94−1.87 (m, 2 H), 1.72 (s, 3 H), 1.62−1.49 (m, 2 H); $^{13}$C NMR $\delta$ 137.1, 134.8, 129.5, 128.2, 124.5, 117.0, 79.9, 56.6, 37.7, 35.4, 33.5, 33.1, 31.6, 16.6, 6.6; MS (EI) *m*/*z* (relative intensity) 348 (M$^+$); HRMS (EI) *m*/*z* calcd for $C_{15}H_{25}OI$ 348.0950, found 348.0929.

**[(4*R*,7*E*,9*E*)-4-Methoxy-7-methyltrideca-1,7,9-trien-13-yl]triphenylphosphonium Iodide (16).** A solution of 120 mg (0.35 mmol) of (4*R*,7*E*,9*E*)-13-iodo-4-methoxy-7-methyltrideca-1,7,9-triene and 90 mg (0.35 mmol) of triphenylphosphine in 2 mL of degassed acetonitrile was transferred into an ampule, sealed, and heated at 90 °C for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue (220 mg, quantitative) was used without further purification: $^1$H NMR $\delta$ 7.78−7.65 (m, 15 H), 6.24 (dd, 1 H, $J$ = 15.0, 10.9 Hz), 5.77−5.68 (m, 2 H), 5.36 (dt, 1 H, $J$ = 14.9, 7.3 Hz), 5.02−4.96 (m, 2 H), 3.62−3.52 (m, 2 H), 3.27 (s, 3 H), 3.14−3.10 (m, 1 H), 2.45−1.96 (m, 6 H), 1.66 (s, 3 H), 1.66−1.18 (m, 4 H).

**(1*R*,2*S*)-2-Methylcyclopropanecarboxylic Acid (18).** To a solution of 1.8 g (21.0 mmol) of alcohol **17** and 18.0 g (84 mmol) of $NaIO_4$ in 42 mL of $CCl_4$, 42 mL of $CH_3CN$, and 63 mL of $H_2O$ was added 130 mg (0.63 mmol) of $RuCl_3 \cdot H_2O$. The reaction mixture was vigorously stirred at 22 °C for 6 h, $Et_2O$

and brine were added, and the aqueous layer was saturated with NaCl and extracted with $Et_2O$ (3×). The combined ether layers were dried ($Na_2SO_4$) and filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. Bulb-to-bulb distillation (bp 60 °C/11 mmHg) gave 1.49 g (71%) of **18** as a colorless oil that was immediately used for the next reaction: $[\alpha]_D$ −27.5° (*c* 1.0, 95% EtOH); $^1$H NMR $\delta$ 1.71−1.63 (m, 1 H), 1.41−1.33 (m, 1 H), 1.23 (d, 3 H, $J$ = 6.1 Hz), 1.12−1.05 (m, 1 H), 0.96−0.90 (m, 1 H); $^{13}$C NMR $\delta$ 179.6, 18.6, 17.2, 15.4, 12.2.

**(2*S*)-3-Hydroxy-2-[(1*R*,2*S*)-(2-methylcyclopropanecarbonyl)amino]propionic Acid Methyl Ester (19).** A solution of 0.7 g (7.0 mmol) of **18** in 70 mL of $CH_2Cl_2$ was treated at 22 °C with 1.22 mL (7.0 mmol) of diisopropylethylamine, 1.09 g (7.0 mmol) of L-serine methyl ester hydrochloride, and 80 mg (0.7 mmol) of 4-(dimethylamino)pyridine. After 30 min, 1,3-dicyclohexylcarbodiimide (1.44 g, 7.0 mmol) was added. The reaction mixture was stirred at 22 °C overnight. The white precipitate was filtered through a pad of Celite, the solvent was evaporated, and the residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:1) to give 1.0 g (71%) of **19** as a colorless wax: $[\alpha]_D$ +41.3° (*c* 1.0, $CHCl_3$); IR (neat) 3360, 1743, 1649, 1210, 1175 cm$^{-1}$; $^1$H NMR $\delta$ 6.73 (d, 1 H, $J$ = 6.8 Hz), 4.67 (p, 1 H, $J$ = 3.8 Hz), 3.94 (dd, 1 H, $J$ = 11.1, 4.1 Hz), 3.86 (dd, 1 H, $J$ = 11.1, 3.4 Hz), 3.77 (s, 3 H), 3.20 (b, 1 H), 1.61−1.53 (m, 1 H), 1.25−1.16 (m, 1 H), 1.13 (d, 3 H, $J$ = 5.7 Hz), 0.96−0.89 (m, 2 H); $^{13}$C NMR $\delta$ 172.4, 171.3, 64.0, 55.0, 52.8, 20.5, 15.4, 12.9, 12.1; MS (EI) *m*/*z* (relative intensity) 201 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_9H_{15}NO_4$ 201.1001, found 201.1015.

**(2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[(1*R*,2*S*)-(2-methylcyclopropanecarbonyl)amino]propionic Acid Methyl Ester.** A solution of 1.0 g (5.0 mmol) of **19** in 15 mL of $CH_2Cl_2$ was treated with 0.75 g (5.0 mmol) of *tert*-butyldimethylchlorosilane, 0.48 g (7.0 mmol) of imidazole, and 60 mg (0.5 mmol) of 4-(dimethylamino)pyridine. The reaction mixture was stirred at 22 °C overnight, diluted with $Et_2O$, washed with 1 M HCl, $H_2O$, and dried ($Na_2SO_4$). The solvent was removed, and the product was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:4) to give 1.40 g (89%) of (2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-[(1*R*, 2*S*)-(2-methylcyclopropanecarbonyl)amino]propionic acid methyl ester as a colorless oil: $[\alpha]_D$ +64.9° (*c* 1.3, $CHCl_3$); IR (neat) 3300, 1747, 1660 cm$^{-1}$; $^1$H NMR $\delta$ 6.40 (d, 1 H, $J$ = 7.5 Hz), 4.70 (dt, 1 H, $J$ = 8.1, 2.8 Hz), 4.03 (dd, 1 H, $J$ = 10.2, 2.7 Hz), 3.79 (dd, 1 H, $J$ = 10.1, 2.9 Hz), 3.74 (s, 3 H), 1.59−1.52 (m, 1 H), 1.25−1.18 (m, 1 H), 1.14 (d, 3 H, $J$ = 5.4 Hz), 0.98−0.93 (m, 2 H), 0.86 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); $^{13}$C NMR $\delta$ 171.3, 64.0, 54.4, 52.4, 25.8, 20.6, 18.3, 15.0, 12.6, 12.1, −5.5; MS (EI) *m*/*z* (relative intensity) 258 ([M − $C_4H_9$]$^+$); HRMS (EI) *m*/*z* calcd for $C_{11}H_{20}NO_4Si$ (M − $C_4H_9$): 258.1162, found 258.1164.

**(1*R*,2*S*)-2-Methylcyclopropanecarboxylic Acid [(1*R*)-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-hydroxyethyl]-amide (25).** A solution of 500 mg (1.58 mmol) of (2*S*)-3-[(*tert*-butyldimethylsilanyloxy)-2-[(1*R*,2*S*)-(2-methylcyclopropanecarbonyl)amino]propionic acid methyl ester in 3 mL of THF was treated with anhydrous LiCl (134 mg, 3.16 mmol), $NaBH_4$ (120 mg, 3.16 mmol), and 6 mL of EtOH. The reaction mixture was stirred at 22 °C overnight, cooled with ice−water, adjusted to pH 4 by gradual addition of 10% aqueous citric acid solution, and concentrated *in vacuo*. Water (6 mL) was added to the residue, and the solution was extracted with $CH_2Cl_2$ (3×). The combined organic layers were washed with saturated $NaHCO_3$ solution, dried ($Na_2SO_4$), and chromatographed on $SiO_2$ (EtOAc/hexanes, 1:1) to give 390 mg (88%) of **25** as a colorless oil: $[\alpha]_D$ +40.2° (*c* 1.6, $CHCl_3$); IR (neat) 3328, 3316, 1650, 1644, 1254, 1103 cm$^{-1}$; $^1$H NMR $\delta$ 6.31 (d, 1 H, $J$ = 7.3 Hz), 3.96−3.92 (m, 1 H), 3.80−3.59 (m, 4 H), 3.52−3.48 (m, 1 H), 1.48−1.43 (m, 1 H), 1.21−1.15 (m, 1 H), 1.11 (s, 3 H), 0.94−0.92 (m, 2 H), 0.86 (s, 9 H), 0.03 (s, 6 H); $^{13}$C NMR $\delta$ 172.0, 63.7, 63.5, 52.1, 25.8, 20.6, 18.2, 14.8, 12.4, 12.1, −5.5; MS (EI) *m*/*z* (relative intensity) 230 ([M − $C_4H_9$]$^+$); HRMS (EI) *m*/*z* calcd for $C_{10}H_{20}NO_3Si$ (M − $C_4H_9$) 230.1212, found 230.1215.

**(1*R*,2*S*)-2-Methylcyclopropanecarboxylic Acid [(1*S*)-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-oxoethyl]-amide (26).** A solution of oxalyl chloride (68 $\mu$L, 0.78 mmol, 1.5 equiv) in $CH_2Cl_2$ (0.6 mL) under Ar was cooled to −60 °C, and dry DMSO (74 $\mu$L, 1.04 mmol, 2.0 equiv) followed by a solution of **25** (150 mg, 0.52 mmol) in 2 mL of $CH_2Cl_2$ were added dropwise. After the solution was stirred at −60 °C for 15 min, $Et_3N$ (0.29 mL, 2.08 mmol, 4.0 equiv) was added dropwise. The reaction was quenched after 20 min by addition of $H_2O$ (1.5 mL/mmol of alcohol). The resulting slurry was immediately poured into hexanes and washed with 20% aqueous $KHSO_4$ solution (prepared by diluting saturated $KHSO_4$ solution 5:1 with $H_2O$). The aqueous layer was extracted with $Et_2O$ (3×), and the combined organic layers were washed with saturated $NaHCO_3$ solution, $H_2O$, and brine and dried ($Na_2SO_4$). The solvent was removed by evaporation (bath temperature < 30 °C), and the crude product (150 mg, quantitative) was used immediately without further purification: $[\alpha]_D$ +72.5° (*c* 1.2, $CHCl_3$); IR (neat) 3321, 1652, 1254, 1111 cm$^{-1}$; $^1$H NMR $\delta$ 9.64 (s, 1 H), 6.45−6.35 (m, 1 H), 4.60−4.55 (m, 1 H), 4.21 (dd, 1 H, $J$ = 10.5, 3.0 Hz), 3.85 (dd, 1 H, $J$ = 10.5, 4.2 Hz), 1.57−1.55 (m, 1 H), 1.25−1.22 (m, 1 H), 1.15 (d, 3 H, $J$ = 5.7 Hz), 0.97−0.88 (m, 2 H), 0.83 (s, 9 H), 0.04 (s, 6 H); $^{13}$C NMR $\delta$ 199.2, 171.8, 61.5, 60.7, 25.8, 20.5, 18.3, 15.3, 12.8, 12.1, −5.5; MS (EI) *m*/*z* (relative intensity) 256 ([M − CHO]$^+$, 5), 228 ([M − $C_4H_9$]$^+$); HRMS (EI) *m*/*z* calcd for $C_{10}H_{18}NO_3Si$ (M − $C_4H_9$) 228.1056, found 228.1040.

**(1*R*,2*S*)-2-Methylcyclopropanecarboxylic Acid [(1*R*,2*Z*,6*E*,8*E*,12*R*)-1-[[(tert-butyldimethylsilyl)oxy]-methyl]-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]amide (27).** A solution of 110 mg (0.18 mmol) of phosphonium salt **16** in 1 mL of THF was degassed, cooled to −78 °C, and treated dropwise with 0.21 mL (0.21 mmol, 1.2 equiv) of sodium bis(trimethylsilylamide) (1.0 M solution in THF). The resulting red-orange solution was stirred at −78 °C for 1 h, and a solution of 61 mg (0.21 mmol, 1.2 equiv) of aldehyde **26** in 1 mL of THF was added slowly. The reaction mixture was slowly warmed to 0 °C, treated with 1 mL of $H_2O$, and extracted with $Et_2O$ (3×). The combined ether layers were dried ($Na_2SO_4$), concentrated, and purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:5) to give 55 mg (62%) of **27** as a colorless oil: $[\alpha]_D$ +26.7° (*c* 0.7, $CHCl_3$); IR (neat) 3300, 1637, 1628, 1246, 1097, 833 cm$^{-1}$; $^1$H NMR $\delta$ 6.21 (dd, 1 H, $J$ = 14.9, 10.4 Hz), 5.90−5.87 (m, 1 H), 5.84−5.72 (m, 2 H), 5.56−5.40 (m, 3 H), 5.09−5.03 (m, 2 H), 4.78−4.74 (m, 1 H), 3.65 (dd, 1 H, $J$ = 9.8, 4.2 Hz), 3.55 (dd, 1 H, $J$ = 9.9, 3.7 Hz), 3.33 (s, 3 H), 3.20−3.16 (m, 1 H), 2.25−2.03 (m, 8 H), 1.76 (s, 3 H), 1.62−1.54 (m, 2 H), 1.43−1.37 (m, 1 H), 1.24−1.14 (m, 1 H), 1.17 (s, 3 H), 1.01−0.95 (m, 2 H), 0.89 (s, 9 H), 0.04 (s, 6 H); $^{13}$C NMR $\delta$ 170.5, 136.5, 134.8, 133.7, 132.3, 128.5, 127.3, 124.8, 117.0, 79.9, 65.9, 56.6, 48.2, 37.7, 35.4, 32.9, 31.6, 27.9, 26.0, 20.8, 18.4, 16.6, 14.7, 12.2, −5.3; MS (EI) *m*/*z* (relative intensity) 489 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{29}H_{51}NO_3Si$ 489.3638, found 489.3637.

**(1*R*,2*S*)-2-Methylcyclopropanecarboxylic Acid [(1*R*,2*Z*,6*E*,8*E*,12*R*)-1-(Hydroxymethyl)-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]amide.** A solution of 46 mg (0.094 mmol) of **27** in 9 mL of THF was cooled to 0 °C, and hydrogen fluoride−pyridine complex (0.28 mL, 3 mL/mmol of silyl ether) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and then warmed to 22 °C. After 3 h, the solution was cooled to 0 °C, treated with $Et_2O$ (10 mL), and poured into ice-cold saturated $NaHCO_3$ solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (5×). The combined organic layers were dried ($Na_2SO_4$) and purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:1) to give 32 mg (91%) of (1*R*,2*S*)-2-methylcyclopropanecarboxylic acid [(1*R*,2*Z*,6*E*,8*E*,12*R*)-1-(hydroxymethyl)-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]-amide as a colorless oil: $[\alpha]_D$ +46.8° (*c* 1.1, $CHCl_3$); IR (neat) 3328, 1640, 1536, 1095, 1070 cm$^{-1}$; $^1$H NMR $\delta$ 6.23 (dd, 1 H, $J$ = 14.9, 10.1 Hz), 5.88−5.73 (m, 3 H), 5.65−5.53 (m, 2 H), 5.37−5.30 (m, 1 H), 5.10−5.03 (m, 2 H), 4.88−4.75 (m, 1 H), 3.72−3.58 (m, 2 H), 3.33 (s, 3 H), 3.20−3.13 (m, 1 H), 2.26−2.03 (m, 8 H), 1.72 (s, 3 H), 1.59 (p, 2 H, $J$ = 6.5 Hz), 1.48−1.38 (m, 2 H), 1.33−1.21 (m, 1 H), 1.16 (s, 3 H), 0.94−0.87 (m, 2 H); $^{13}$C NMR $\delta$ 172.6, 136.9, 134.8, 134.3, 130.9, 127.6, 126.1, 124.6, 117.1, 79.9, 67.3, 56.6, 50.5, 37.7, 35.4, 32.6, 31.6, 28.0, 20.7, 16.6, 15.1, 12.6, 12.0; MS (EI) *m*/*z* (relative intensity) 357

([M − $H_2O$]$^+$); HRMS (EI) *m*/*z* calcd for $C_{23}H_{35}NO_2$ (M − $H_2O$) 357.2668, found 357.2663.

**4-[(1*Z*,5*E*,7*E*,11*R*)-11-Methoxy-8-methyltetradeca-1,5,7,13-tetraenyl]-2-[(1*R*,2*S*)-2-methylcyclopropyl]-4,5-dihydrooxazole (28).** A solution of 15 mg (0.04 mmol) of (1*R*,2*S*)-2-methylcyclopropanecarboxylic acid [(1*R*,2*Z*,6*E*,8*E*,-12*R*)-1-(hydroxymethyl)-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]amide in 0.6 mL of THF was degassed, and 11 mg (0.048 mmol, 1.2 equiv) of Burgess reagent **20** was added. The reaction mixture was stirred at 21 °C for 9 h, and the solvent was removed by passing an Ar stream over the surface. The residue was purified by chromatography on Florisil (EtOAc/hexanes, 1:9) to yield 10 mg (71%) of **28** as a colorless oil: $[\alpha]_D$ +32.0° (*c* 0.85, $CHCl_3$); IR (neat) 1731, 1441, 1364, 1096, 1075 cm$^{-1}$; $^1$H NMR $\delta$ 6.23 (dd, 1 H, *J* = 14.9, 10.4 Hz), 5.85−5.73 (m, 2 H), 5.6−5.5 (m, 2 H), 5.4−5.3 (m, 1 H), 5.10-5.04 (m, 2 H), 4.90−4.81 (m, 1 H), 4.39−4.33 (m, 1 H), 3.76−3.70 (m, 1 H), 3.34 (s, 3 H), 3.21−3.14 (m, 1 H), 2.3−2.0 (m, 8 H), 1.72 (s, 3 H), 1.65−1.55 (m, 2 H), 1.48−1.21 (m, 2 H), 1.13 (d, 3 H, *J* = 5.7 Hz), 1.01−0.94 (m, 1 H), 0.89−0.83 (m, 1 H); $^{13}$C NMR $\delta$ 168.0, 134.8, 131.8, 130.8, 127.4, 124.6, 117.1, 79.9, 72.6, 62.9, 56.6, 37.7, 35.4, 32.9, 31.6, 29.8, 27.9, 16.6, 14.3, 14.1, 12.8; MS (EI) *m*/*z* (relative intensity) 357 (M$^+$); HRMS (EI) *m*/*z* calcd for $C_{23}H_{35}NO_2$ 357.2668, found 357.2683.

**(1*R*,2*S*)-2-Methylcyclopropanecarbothioic Acid [(1*R*,2*Z*,6*E*,8*E*,12*R*)-1-(Hydroxymethyl)-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]amide (29).** A solution of 18 mg (0.050 mmol) of **28** in 0.5 mL of 1:1 MeOH/$Et_3N$ was saturated with $H_2S$ gas and stirred at 35 °C for 20 h. The solvent was removed by passing an Ar stream over the surface, and the residue was purified by chromatography on Florisil (EtOAc/hexanes, 1:2) to give 13 mg (66%) of **29** as a slightly yellow oil: $[\alpha]_D$ +46.8° (*c* 1.10, $CHCl_3$); IR (neat) 3260, 1653, 1635, 1226, 1088 cm$^{-1}$; $^1$H NMR $\delta$ 7.30 (br s, 1 H), 6.23 (dd, 1 H, *J* = 14.9, 10.4 Hz), 5.85−5.76 (m, 1 H), 5.73−5.67 (m, 1 H), 5.57−5.51 (m, 2 H), 5.49−5.40 (m, 2 H), 5.10−5.04 (m, 2 H), 3.88−3.78 (m, 1 H), 3.78−3.70 (m, 1 H), 3.34 (s, 3 H), 3.2−3.1 (m, 2 H), 2.26−2.04 (m, 8 H), 1.72 (s, 3 H), 1.64−1.55 (m, 2 H), 1.44−1.23 (m, 2 H), 1.13 (d, 3 H, *J* = 6.1 Hz), 1.09−1.03 (m, 1 H), 0.90−0.82 (m, 1 H); $^{13}$C NMR $\delta$ 203.4, 136.9, 134.8, 131.6, 131.2, 130.2, 127.4, 124.7, 117.1, 79.9, 62.7, 56.7, 50.5, 39.7, 37.7, 35.4, 32.9, 28.0, 19.9, 16.7, 15.4, 13.9, 12.5; MS (EI) *m*/*z* (relative intensity) 391 (M$^+$); HRMS (EI) *m*/*z* calcd for $C_{23}H_{37}NO_2S$ 391.2545, found 391.2532.

**Curacin A (1). Method A.** A solution of 8 mg (0.02 mmol) of thioamide **29** in 0.3 mL of THF was degassed, and Burgess reagent **20** (5 mg, 0.022 mmol) was added. The reaction mixture was stirred at 21 °C for 1 h. The solvent was removed by passing an Ar stream over the surface, and the residue was purified by chromatography on Florisil (EtOAc/hexanes, 1:9) to give 4 mg (54%) of curacin A as a slightly yellow oil: $[\alpha]_D$ +64.3° (*c* 0.32, $CHCl_3$);[22] IR (neat) 2924, 1616, 1094, 1073, 1002, 963 cm$^{-1}$; $^1$H NMR ($C_6D_6$) $\delta$ 6.34 (dd, 1 H, *J* = 14.9, 10.8 Hz), 5.98 (d, 1 H, *J* = 10.7 Hz), 5.88−5.76 (m, 1 H), 5.66 (dd, 1 H, *J* = 10.5, 9.1 Hz), 5.55−5.49 (m, 1 H), 5.44−5.36 (m, 1 H), 5.10−5.01 (m, 3 H), 3.14 (s, 3 H), 3.08−3.01 (m, 1 H), 3.04 (dd, 1 H, *J* = 10.6, 8.3 Hz), 2.75 (t, 1 H, *J* = 10.2 Hz), 2.24−2.04 (m, 8 H), 1.68 (s, 3 H), 1.66−1.58 (m, 3 H), 1.22−1.17 (m, 1 H), 1.18 (d, 3 H, *J* = 6.1 Hz), 0.98−0.90 (m, 1 H), 0.74−0.70 (m, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.2, 136.9, 134.8, 131.6, 131.2, 130.2, 127.4, 124.7, 117.1, 79.9, 73.6, 56.7, 39.7, 37.7, 35.4, 32.9, 31.6, 28.0, 19.9, 16.7, 15.4, 13.9, 12.5; MS (EI) *m*/*z* (relative intensity) 373 (M$^+$, 20), 342 (50), 332 (40), 274 (40), 180 (100), 166 (40), 79 (90), 41 (60); HRMS (EI) *m*/*z* calcd for $C_{23}H_{35}NOS$ 373.2439, found 373.2442.

**Method B.** A solution of 21 mg (0.054 mmol) of thioamide **29** in 0.3 mL of THF was degassed, and poly(ethylene glycol)-linked reagent **30**[20] (60 mg) was added. The reaction mixture was stirred at 21 °C for 1 h. The solvent was removed by passing an Ar stream over the surface, and the residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:20) to give 12 mg (63%) of curacin A.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra for curacin A and synthetic intermediates (41 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(22) The originally reported $[\alpha]_D$ for the natural product has been corrected to $[\alpha]_D$ +62.0 (*c* 1.10, $CHCl_3$).[3d]