Absolute Configuration and Total Synthesis of (+)-Curacin A, an Antiproliferative Agent from the Cyanobacterium *Lyngbya majuscula*

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Abstract: The absolute configuration of curacin A was determined as (2*R*,13*R*,19*R*,21*S*)-**1** by comparison of degradation products **2** and **3** with the same materials prepared by asymmetric synthesis. The total synthesis of **1** was completed from (1*R*,2*S*)-2-methylcyclopropanecarboxylic acid (**8**) and the amino alcohol derivative **46**. The latter was prepared from 4-pentynal (**14**) and the Garner aldehyde (**43**). Asymmetric allylation of **14** followed by methylation of the derived alcohol **16** gave **17**, which was subjected to zirconation−iodination to yield **18**. The latter was coupled to the vinyl boronate **21**, prepared from 4-pentynyl acetate (**20**), in the presence of Pd(0), and the resultant trienol **22** was converted to phosphonium iodide **24**. Wittig reaction of the ylide from **24** with **43** afforded tetraene **44** which produced **45** upon methanolysis. The mesylate **46** was advanced to thioester **48** either by direct coupling with potassium thiolate **47** obtained from (−)-**8** or indirectly via **49**. The amino thioester liberated from **48** underwent thermal cyclization to give (+)-curacin A.

The cyanobacterium *Lyngbya majuscula* is the source of a wide variety of biologically active marine metabolites, including the majusculamides,[1] malyngolide,[2] malyngamide A,[3] the pukeleimides,[4] lyngbyatoxin,[5] and debromoaplysiatoxin.[6] The well-known toxicity of *L. majuscula* is attributed principally to the latter two substances, which are also powerful tumor promoters.[7] In 1994, Gerwick reported the isolation of a potent antimitotic agent, curacin A (**1**) from *L. majuscula* collected

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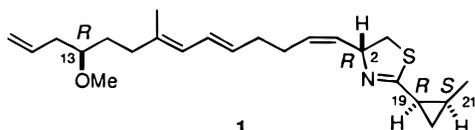
off the coast of Curaçao.[8] Curacin A was found to be cytotoxic against a Vero cell line (ATCCCCL81) and was highly toxic to brine shrimp (IC$_{50}$ 3 ng/mL). It also exhibited mammalian cell antiproliferative activity (IC$_{50}$ 6.8 ng/mL) in the Chinese hamster AuX B1 cell line. Further studies with **1** established that it binds with high affinity to the colchicine site (one of two distinct drug-binding locations) of tubulin and consequently inhibits the binding of colchicine.[9] This result is surprising and

therefore noteworthy in the context of new drug development, because curacin A and colchicine, as well as other tubulin-binding drugs such as podophyllotoxin, show little obvious structural homology.

The gross structure of **1** was deduced by Gerwick using extensive NMR studies including ^{1}H−^{1}H COSY, ^{1}H−^{13}C HETCOR, and HMBC.[8] However, the initial structural assignment was devoid of stereochemistry except for the allocation of *(E,E)* geometry to the conjugated diene, *(Z)* configuration to the double bond adjacent to the thiazoline ring, and *cis* relative configuration at the cyclopropane. In particular, the absolute configuration of curacin A could not be determined from the available data.

With a view to establishing an understanding of the interaction of curacin A with the colchicine-binding site of tubulin, we foresaw the need for an asymmetric synthesis of **1**. Prior to a synthesis, however, a complete determination of the stereochemistry of **1**, including its absolute configuration, was required. We envisioned that this could be accomplished by comparison of products obtained from chemical synthesis with those acquired by degradation of the natural material.

Determination of the Absolute Configuration of Curacin A

During degradative studies of **1**, Gerwick et al. found that ozonolysis, followed by oxidative workup with hydrogen peroxide and subsequent treatment with diazomethane, furnished sulfonate **2**.[8] On the other hand, selective hydrogenation of the vinyl group of **1** in the presence of Wilkinson's catalyst, followed by ozonolysis and reductive workup, afforded the methoxy ketone **3**. A full stereochemical definition of **2** was our first objective, which was achieved by asymmetric syntheses of two of its stereoisomers. Partial hydrogenation of 2-butyn-1-ol (**4**) in the presence of Lindlar's catalyst afforded *cis*-crotyl alcohol (**5**) in excellent yield and was more reproducible than Bergman's preparation of this substance by reduction of **4** with

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(3) Cardellina, J. H., II; Marner, F.-J.; Moore, R. E. *J. Am. Chem. Soc.* **1979**, *101*, 240.
(4) (a) Simmons, C. J.; Marner, F.-J.; Cardellina, J. H., II; Moore, R. E.; Seff, K. *Tetrahedron Lett.* **1979**, 2003. (b) Cardellina, J. H., II; Moore, R. E. *Tetrahedron Lett.* **1979**, 2007.
(5) Cardellina, J. H., II; Marner, F.-J.; Moore, R. E. *Science* **1979**, *204*, 193.
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(7) (a) Fujiki, H.; Suganuma, M.; Nakayasu, M.; Hoshino, H.; Moore, R. E.; Sugimura, T. *Gann* **1982**, *73*, 495. (b) Moore, R. E. *Pure Appl. Chem.* **1982**, *54*, 1919.
(8) Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243.

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1. O₃, H₂O₂
2. CH₂N₂ → **2**

1. H₂, (Ph₃P)₃RhCl
2. O₃, Me₂S → **3**

1

(-)-8 → (via (**10**) HCl·NH₂ / CO₂Me, DCC, HOBT, NaHCO₃, DMF, 46 %) → **11** → (1. O₃, MeOH CH₂Cl₂; 2. CH₂N₂ Et₂O, 43%) → **2**

(+)-8 → (via (**10**) HCl·NH₂ / CO₂Me, DCC, HOBT, NaHCO₃, DMF) → **12** → (1. O₃, MeOH CH₂Cl₂; 2. CH₂N₂ Et₂O) → **9**
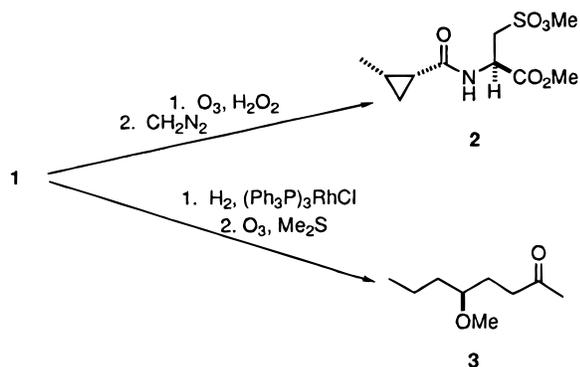
Zn−Cu couple.[10]   The alcohol **5** was subjected to Charette's asymmetric Simmons-Smith reaction with diethylzinc and diiodomethane in the presence of the complex **6** derived from *n*-butylboronic acid and (*S,S*)-(−)-*N,N,N′,N′*-tetramethyltartaramide.[11]   Cyclopropanation of **5** under these conditions afforded **7** with >95% ee as measured by the ¹H NMR spectrum of its Mosher ester derivative.[12]   Assignment of (1*R*,2*S*) configuration to this enantiomer is based on the close similarity of **7** to similar cyclopropanes prepared enantioselectively by Charette.   The (2*S*,3*R*) antipode of **7** was obtained using the tartaramide complex enantiomeric with **6**.   Each enantiomer was converted to the corresponding 2-methylcyclopropanecarboxylic acid, (+)- and (−)-**8**, by oxidation, first to the aldehyde with tetrapropy-

4 (with OH, terminal alkyne) → H₂, Pd/CaCO₃-PbO, MeOH, 83% → **5** (cis-allylic alcohol, OH)

5 → (*n*-BuB, O—O, CO₂NMe₂, CO₂NMe₂ (**6**); Et₂Zn, CH₂I₂, CH₂Cl₂, 75 %) → **7 (>95% ee)** (cyclopropane, OH)

7 → (1. TPAP, NMO, 4Å sieves; 2. NaClO₂, Me₂C=CHMe, NaH₂PO₄, *t*-BuOH-H₂O, 64 %) → **(-)-8** (cyclopropane, COOH)
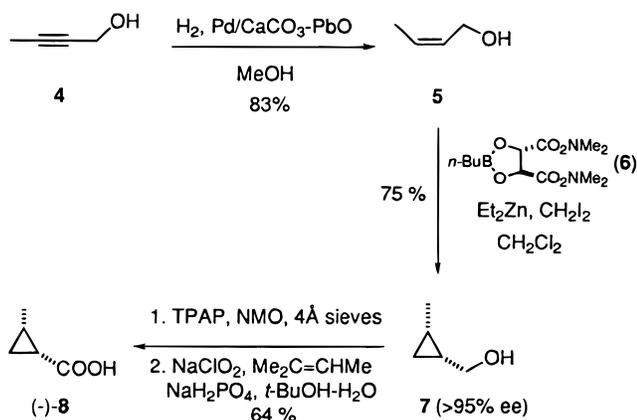
lammonium perruthenate (TPAP)[13] and then with buffered sodium chlorite.[14]   Comparison of data for (+)- and (−)-**8** with those reported by Bergman[10] confirmed our stereochemical assignments.

With both enantiomers of *cis*-2-methylcyclopropanecarboxylic acid available in high optical purity, the synthesis of **2** and its diastereomer **9** was initiated from (*R*)-(−)-cystine dimethyl ester dihydrochloride (**10**).   The use of this disulfide as starting material avoided protection and subsequent deprotection of the sulfur atom.   The cystine derivative **10** was coupled with (2*R*,3*S*)-**8** and its enantiomer using DCC and HOBT,[15] and the resulting amides **11** and **12** were ozonized[16] and then treated with diazomethane to give **2** and **9**, respectively.   Synthetic **2** was identical in all respects, including optical rotation, IR and
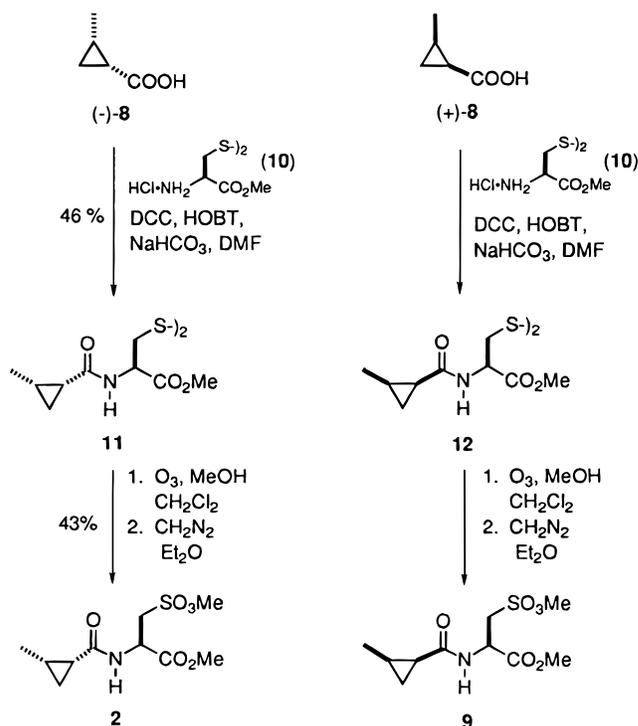
¹H and ¹³C NMR spectra, and GC−MS and MS data with the corresponding substance previously obtained from degradation of curacin A.   On the other hand, the stereoisomer **9** was easily distinguishable from **2** by ¹H NMR and ¹³C NMR spectral comparison and by comparison of GC−MS data.   By this means, three of the four stereogenic centers of curacin A are established as (2*R*,19*R*,21*S*).

The assignment of absolute configuration to **3** was also made by asymmetric synthesis of this material.   Swern oxidation of 4-pentyn-1-ol (**13**) to the known aldehyde **14**,[17] followed by treatment with the salt-free allylborane **15** derived from (−)-B-methoxydiisopinylcampheylborane,[18] afforded **16** in 95% ee as determined from the ¹H and ¹⁹F NMR spectra of its Mosher ester.   This alcohol was converted to its methyl ether **17** with sodium hydride and methyl iodide, and the latter was subjected to zirconation−iodination[19] to give the (*E*)-iodooctadiene **18**.   Reduction of the vinyl group of **18** with diimide, prepared from dipotassium azodicarboxylate and acetic acid in pyridine,[20] afforded the octene **19** which was ozonized to give (+)-**3** in good yield.   A parallel sequence from **14** employing the allylborane prepared from (+)-B-methoxydiisopinylcampheylborane yielded (−)-**3**.   The properties of synthesized (*S*)-(+)-**3** were in excellent agreement with those of **3** obtained by degradation of curacin A.   These results completely define the absolute configuration of the natural product as

(10) Bergman, R. G. *J. Am. Chem. Soc.* **1969**, *91*, 7405.

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

(19) Negishi, E.-I.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, 501.

(20) Hamersma, J. W.; Snyder, E. I. *J. Org. Chem.* **1965**, *30*, 3985.

(21) Preliminary account: 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. A partial solution to the absolute stereostructure of curacin A was reported by Iwasaki (Onoda, T.; Shirai, R.; Koiso, Y.; Iwasaki, S. *Tetrahedron Lett.* **1995, 36**, 5765).

(22) Preliminary account: White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1995, 117**, 5612. Subsequent to this report, syntheses of curacin A have been described by Aubé (Hoemann, M. Z.; Agrios, K. A.; Aubé, J. *Tetrahedron Lett.* **1996**, *37*, 953), by Kobayashi (Ito, H.; Imai, N.; Takao, K.-I.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37,* 1799), by Iwasaki (Onoda, T.; Shirai, R.; Koiso, Y.; Iwasaki, S. *Tetrahedron Lett.* **1996**, *37*, 4397), by Wipf (Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556), and by Falck (Lai, J.-Y.; Yu, J.; Mekonnen, B.; Falck, J. R. *Tetrahedron Lett.* **1996**, *37*, 7167).

$(2R,13R,19R,21S)$.[21] The finding that **1** possesses (R) configuration at C-2 is in accord with the proposal that the thiazoline portion of curacin A originates from L-cysteine.[8]

Synthesis of Curacin A

Fragments prepared in the course of studies designed to reveal the absolute configuration of curacin A were also used as intermediates for the total synthesis of the natural substance.[22] These include the cyclopropanecarboxylic acid (−)-**8** and the diene **18**. It was initially intended that curacin A would be constructed from two subunits, a lipid component **24** in the form of a phosphorane derived from **18** and a thiazoline carboxaldehyde that incorporated the structural features of **8**. Connection between these two subunits was envisioned via a Wittig reaction. For the reasons described below, it became necessary to modify this plan.

The synthesis of **24** departed from 4-pentynyl acetate (**20**) which was reacted with catecholborane to yield the vinylboronate **21**. The latter was not isolated but was subjected to *in situ* Suzuki coupling[23] with the iodoalkene **18** in the presence of tetrakis(triphenylphosphine)palladium as catalyst. This afforded **22** in which the conjugated diene unit was produced with clean (E,E) geometry. The alcohol **22** was converted first to its mesylate and then to the corresponding iodo derivative **23**, which was advanced to the phosphonium iodide **24** upon treatment with triphenylphosphine in acetonitrile.

Synthesis of the thiazolinecarboxaldehyde required for a Wittig reaction with **24** proved to be more problematic. Our initial approach to the Δ^2-thiazoline followed a strategy employed by Heathcock in his synthesis of mirabazole C,[24] where four β-mercaptoamide functions were cyclized simultaneously to thiazolines. However, although the diastereomeric mercaptoamides **25** and **26** were easily prepared by coupling (R)-S-benzylcysteinol (**27**) as its silyl ether **28** with (±)-**8** to give amides **29** and **30**, the thiols **25** and **26** produced by debenzylation with sodium−ammonia failed to yield a Δ^2-thiazoline under a variety of conditions. The susceptibility of the cyclopropyl moiety toward ring opening in the presence of
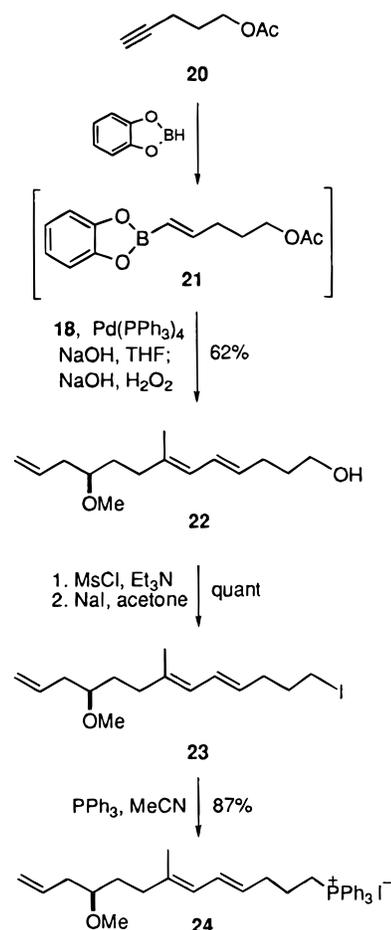
acidic reagents employed with **25** and **26** probably explains this outcome.
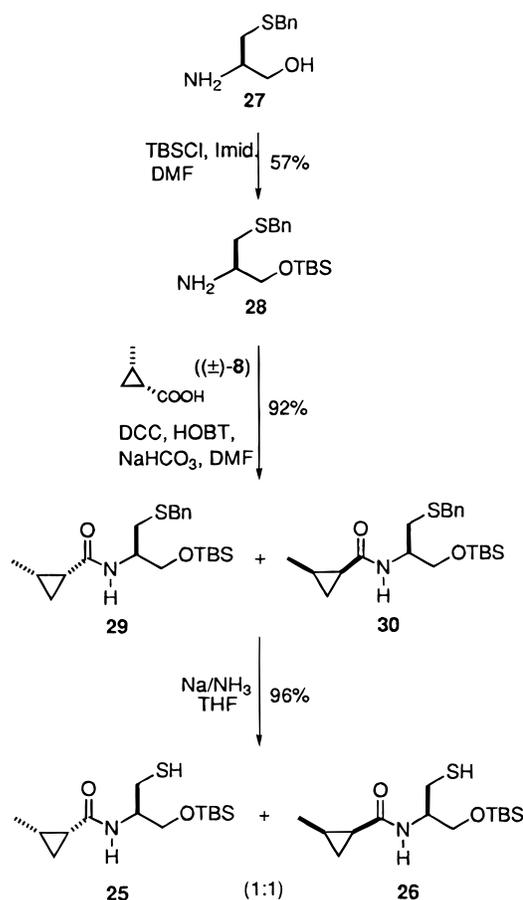
(23) (a) Miyaura, N.; Suzuki, A. *Org. Synth.* **1990**, *68*, 130. (b) Cassani, G.; Massardo, P.; Piccardi, P. *Tetrahedron Lett.* **1983**, *24*, 2513.
(24) Walker, M. A.; Heathcock, C. H., *J. Org. Chem.* **1992**, *57*, 5566.
(25) Ehrler, J.; Farooq, S. *Synlett* **1994**, 702.

The sensitivity of the cyclopropane in **25** and **26** toward acid forced us to turn to methods for the preparation of a thiazoline that avoided acidic conditions. One such approach involves the condensation of nitriles with 2-aminoethanethiols, a tactic that was recently employed by Ehrler in the synthesis of thiangazole.[25] Unfortunately, 2-methylcyclopropanecarbonitrile (**31**), prepared as a mixture of *cis* and *trans* isomers from (±)-1-chloro-3-cyano-2-methylpropane,[26] failed to react satisfactorily with cysteine methyl ester hydrochloride in methanol at reflux. Only an unidentified compound which was found to contain no cyclopropane was obtained. A more promising approach from **31** appeared to lie through the imidate hydrochloride **32** along lines developed by Pattenden in his approach to didehydromirabazole A.[27] Exposure of **31** to gaseous hydrogen chloride in methanol afforded **32**, which was reacted *in situ* with cysteine methyl ester hydrochloride in the presence of triethylamine to give a mixture of **33** and **34.** To our surprise, the reaction of **33** and **34** or the derived Weinreb amides **35** and **36** with diisobutylaluminum hydride gave neither the desired aldehyde nor the corresponding alcohol. Analysis of the reaction mixture in each case indicated that reduction of the thiazoline had occurred instead.
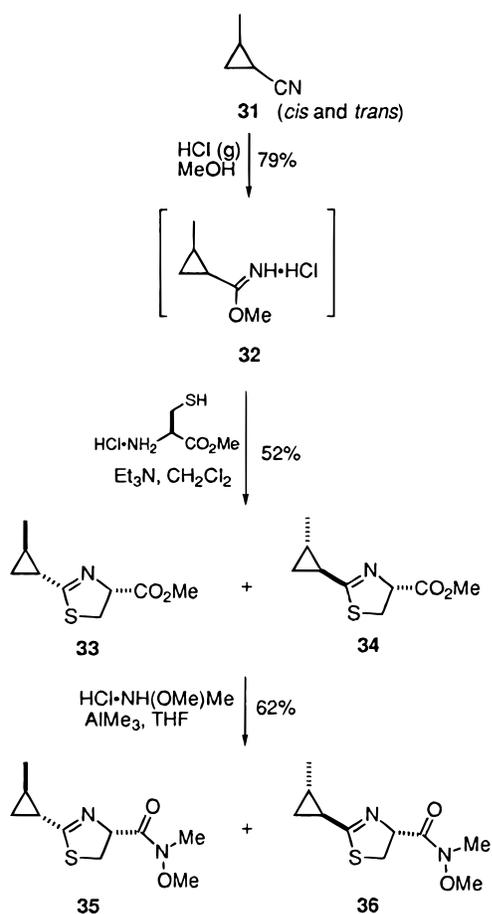
In light of the foregoing results, it was decided to postpone construction of the thiazoline moiety of curacin A to the final stages of the synthesis. In this revised plan, **1** would be fashioned directly from condensation of the aminothiol **37** with the imidate **38**. To this end, the *N*-Boc-protected thiazolidine **39** was prepared from cysteine via alcohol **40** following a route employed for the methyl carbamate analog of **39**.[28] The unstable aldehyde **39** was used directly in a Wittig reaction with the

(26) Applequist, D. E.; Peterson, A. H. *J. Am. Chem. Soc.* **1960**, *82*, 2372.

(27) Pattenden, G.; Thom, S. T., *J. Chem. Soc., Perkin Trans. 1* **1993**, 1629.
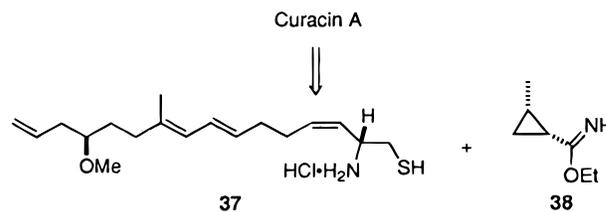
phosphorane derived from **24** by treatment with lithium hexamethyldisilazide to furnish the tetraene **41**. No trace of the *trans* $\Delta^{3,4}$ olefin isomer was observed in this coupling.
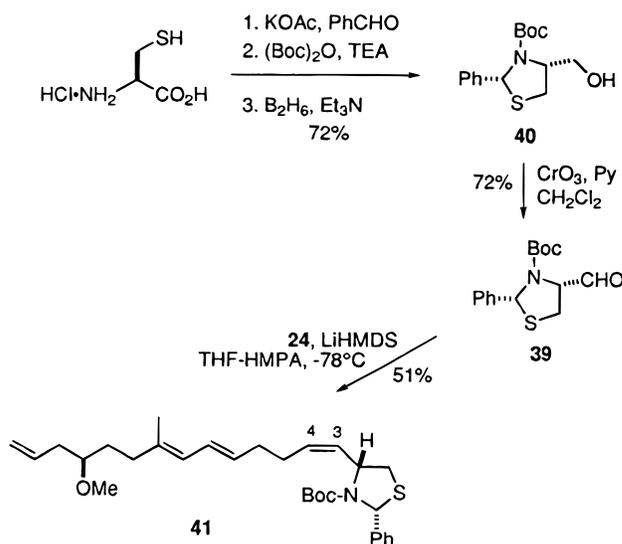
The imidate **38** was prepared from (−)-**8** via the known amide (2*R*,3*S*)-**42**.[10] Exposure of the amide to triethyloxonium hexafluorophosphate[29] gave **38**, which was unstable and therefore was used in coupling attempts with **37** without isolation. The thiazolidine **41** was unmasked, first by treatment with mercuric chloride in the presence of calcium carbonate to release the benzylidene protection, and then with hydrogen chloride generated *in situ* from methanol and acetyl chloride to remove the Boc group. Rigorous exclusion of air was essential for successful isolation of the hydrochloride salt of **37** due to its facile oxidative dimerization to a disulfide. The unpurified salt **37** was treated with **38** in the expectation that curacin A would result, but this reaction yielded no trace of **1**. Surmising that
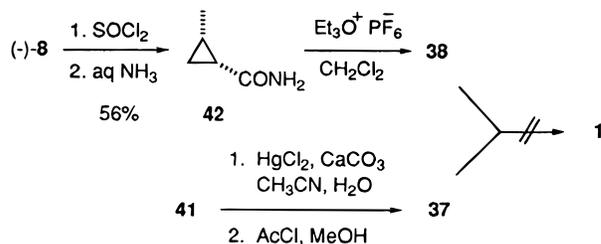
HCl released from **37** destroyed the imidate **38** before it had an opportunity to undergo coupling, an attempt was made to purify the free base of **37** by chromatography under an inert atmosphere. However, this resulted only in formation of the dimeric disulfide from **37** and unidentified byproducts.

Although the attempted coupling of **37** with **38** failed, a strategy that deferred construction of the thiazoline to the final stage of the synthesis nevertheless seemed the most feasible pathway to **1**. The propensity of the free thiol of **37** toward

(28) Confalone, P. N.; Pizzolato, G.; Baggiolini, E. G.; Lollar, D.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1977**, *99*, 7020.

(29) Baganz, H.; Domaschke, L. *Chem. Ber.* **1962**, *95*, 1842.

disulfide formation clearly encouraged masking of this function and persuaded us to explore its alternative presentation as a thioester. Thermal cyclization of thiol esters derived from vicinal amino thiols has been shown to afford a facile synthesis of Δ^2-thiazolines,[30] and a new approach was therefore devised that utilized this concept for fabricating the thiazoline portion of **1**. An advantage that was foreseen in this plan was introduction of the sulfur atom as a more compliant thiolate via a displacement process, a tactic which allowed construction of the thiazoline moiety to begin from a serine rather than a cysteine derivative.

The Garner aldehyde **43**,[31] prepared from Boc-protected methyl (*S*)-serinate, was reacted with the phosphorane acquired from **24** to give tetraene **44** as a single (*Z*) olefin isomer. Methanolysis of **44** in the presence of a catalytic amount of *p*-toluenesulfonic acid selectively removed the isopropylidene group[32] to furnish **45** in excellent yield, and treatment of this alcohol with methanesulfonyl chloride afforded the corresponding mesylate **46**. The latter was reacted with the potassium thiolate **47** prepared from **8** via displacement of the acyl chloride with potassium sulfide[33] to give the thioester **48** in moderate yield. Subsequently, an alternative and more efficient route to
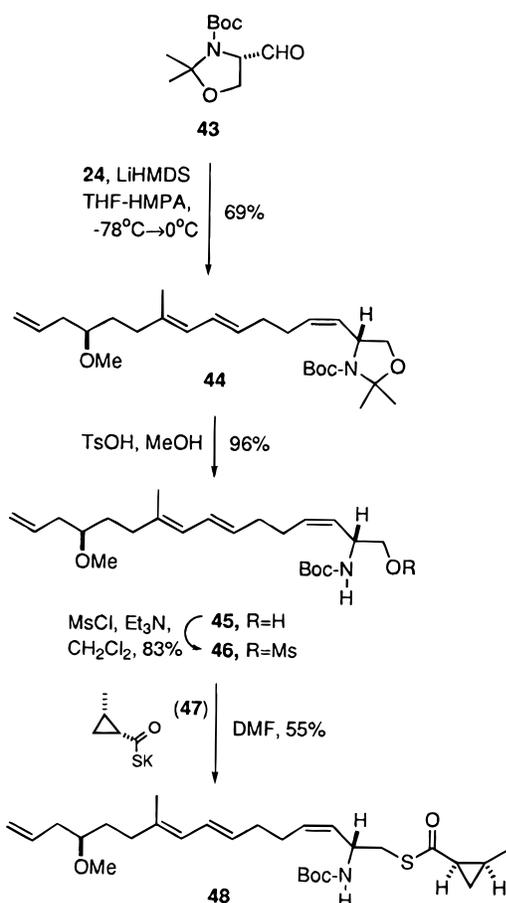
48 was devised, in which the mesylate **46** was treated with potassium thioacetate and the resultant thioester was converted to thiol **49** with sodium methoxide in methanol. Coupling of **49** with (2*R*,3*S*)-**8** in the presence of DCC and DMAP[34] afforded **48** in an overall 73% yield from **46**. The final cyclization of **48** to curacin A (**1**) was effected by cleavage of the Boc group with trifluoroacetic acid to furnish the corresponding ammonium

(30) Fukuyama, T.; Xu, L. *J Am. Chem. Soc.* **1993**, *115*, 8449.
(31) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
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(34) Grunwell, J. R.; Foerst, D. L. *Synth. Commun.* **1976**, *6*, 453.

trifluoroacetate salt, which was subjected to refluxing benzene without isolation. The resultant (+)-curacin A was indistin-

guishable from a sample of natural **1** by comparison of HPLC and other characteristic data including ^{1}H NMR, GC−MS, and circular dichroism spectra. In the course of this work, it was found that all of the synthetic intermediates in which the lipophilic portion of **1** is attached to a cysteine or a serine derivative, as well as curacin A itself, are unstable even below −20 °C. These substances are best preserved as a frozen solution in benzene.
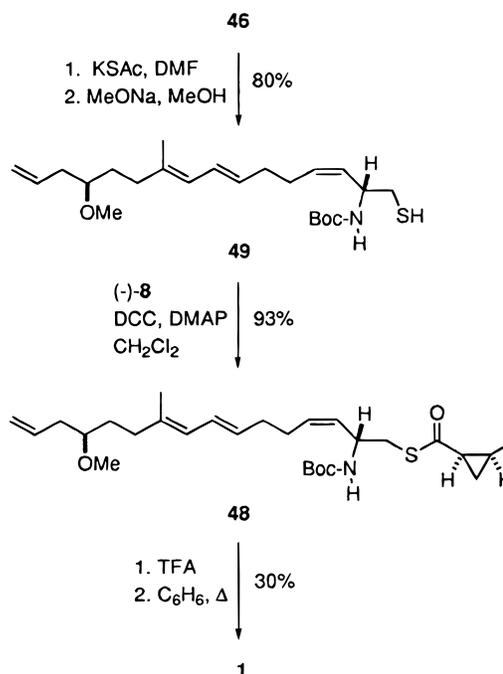
Experimental Section

***cis*-2-Butenol (5).** A solution of 2-butyn-1-ol (5.0 g, 71 mmol) and Lindlar's catalyst (50 mg) in MeOH (100 mL) was stirred under H$_2$ at 1 atm for 20 h. The solution was filtered through Celite, and the solvent was removed by distillation. Further distillation gave **5** (4.28 g, 83%) as a pale yellow oil: bp 70 °C (65 Torr).

(2*R*,3*S*)-2-Methylcyclopropanemethanol (7). A solution of (*S*,*S*)-(−)-*N*,*N*,*N*′,*N*′-tetramethyltartaramide (1.23 g, 6 mmol) and *n*-butylboric acid (615 mg, 6.0 mmol) in dry toluene (50 mL) was refluxed under a Dean-Stark trap for 14 h. The solvent was removed in vacuo, leaving the complex **6** (1.59 g, 5.9 mmol) as a clear oil. Diiodomethane (1.75 mL, 22 mmol) was added slowly to diethylzinc (1.36 g, 11 mmol) in CH$_2$Cl$_2$ (20 mL) at 0 °C, and the white slurry that was formed was stirred for 10 min. A solution of **5** (356 mg, 4.9 mmol) and **6** (1.47 g, 5.4 mmol) in CH$_2$Cl$_2$ (6 mL) was added, and the solution was warmed to room temperature and stirred for 1.5 h. The progress of the reaction was monitored by TLC using silver nitrate impregnated silica. The solution was cooled to 0 °C and quenched by addition of aqueous NH$_4$-Cl solution (3 mL). The resultant white precipitate was filtered, and the filtrate was washed with water (3 × 20 mL) and brine (1 × 20 mL) and dried over sodium sulfate. The solution was then concentrated by fractional distillation at 1 atm, and the residual oil was purified by chromatography on silica (pentane−ether, 1:1 to 2:1) to give **7** (297 mg, 70%) as a colorless oil: $[\alpha]^{23}_D$ +43.4 (*c* 0.90, CH$_2$Cl$_2$).

(2*R*,3*S*)-Methylcyclopropanecarboxylic Acid (8). A mixture of **7** (150 mg, 1.74 mmol), *N*-methylmorpholine oxide (306 mg, 2.61 mmol), and powdered 4 Å molecular sieves in CH$_2$Cl$_2$ (17.5 mL) was stirred for 10 min at room temperature under argon, and tetra-*n*-propylammonium perruthenate (31 mg, 87 μmol) was added in one portion. After 1 h, the mixture was diluted with CH$_2$Cl$_2$ (30 mL), filtered over a short pad of silica, and concentrated by distillation. The residue was diluted with 2-methyl-2-propanol (43.6 mL) and 2-methyl-2-butene (10.4 mL). To the solution was added a solution of sodium chlorite (1.74 g, 19.4

mmol) and monosodium phosphoric acid (1.74 g, 14.5 mmol) in water (17.4 mL) dropwise. The resulting yellow mixture was stirred for 4 h, concentrated, diluted with water, acidified with 2 N hydrochloric acid, and extracted with ether. The ethereal solution was dried over magnesium sulfate and concentrated, and the residual oil was purified by chromatography on silica (hexanes−ethyl acetate, 3:1) to give **8** (96 mg, 64%) as a colorless oil: $[\alpha]^{25}_D$ −25.0 (*c* 1.4, EtOH); IR (neat) 3583, 2998, 1729 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.94 (1H, m), 1.08 (1H, m), 1.23 (3H, d, *J* = 6 Hz), 1.39 (1H, m), 1.69 (1H, m); ^{13}C NMR (CDCl$_3$) δ 12.0, 15.3, 17.1, 18.4, 179.6.

Disulfide 11. To a stirred mixture of L-cystine dimethyl ester **10** (15.3 mg, 44.9 mmol), 1,3-dicyclohexylcarbodiimide (20.3 mg, 99.0 mmol), 1-hydroxybenzotriazole (12.1 mg, 89.9 mmol), and NaHCO$_3$ (21.5 mg, 256 mmol) was added (−)-**8** (9.0 mg, 89.9 mmol) in dry DMF (1.5 mL) at room temperature under argon. After 3 days, the mixture was poured into water and extracted with ether. The extract was dried over sodium sulfate and concentrated, and the residual oil was purified by chromatography on silica (hexanes−ethyl acetate, 1:1) to give **11** (9.0 mg, 46%) as a pale yellow oil: $[\alpha]^{25}_D$ +83.0 (*c* 0.10, CHCl$_3$); IR (neat) 3320, 2930, 1746, 1652, 1522, 1222 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.93 (2H, m); 1.13 (6H, d, *J* = 6 Hz), 1.26 (2H, m), 1.58 (2H, m), 3.21 (4H, m), 3.76 (6H, s), 4.80 (2H, m), 6.57 (2H, d, *J* = 7 Hz); ^{13}C NMR (CDCl$_3$) δ 12.0, 12.7, 15.3, 20.3, 41.1, 51.6, 52.6, 171.1, 171.3; MS (CI) *m/z* 433 (M$^+$ + 1), 401, 373, 351, 216, 184, 100, 83; HRMS (CI) *m/z* 433.1468 (M$^+$ + 1) (calcd for C$_{18}$H$_{29}$N$_2$O$_6$S$_2$ 433.1467).

Disulfide 12. This compound was prepared from (+)-**8** following the procedure described above: $[\alpha]^{25}_D$ +136.5 (*c* 0.30, CHCl$_3$); IR (neat) 3330, 2933, 1747, 1653, 1540 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.93 (2H, m); 1.13 (6H, d, *J* = 6 Hz), 1.26 (2H, m), 1.58 (2H, m), 3.23 (4H, m), 3.77 (6H, s), 4.90 (2H, m), 6.58 (2H, d, *J* = 7 Hz); ^{13}C NMR (CDCl$_3$) δ 12.0, 12.7, 15.3, 20.3, 40.8, 51.6, 52.6, 171.1, 171.4; MS (CI) *m/z* 433 (M$^+$ + 1), 401, 373, 351, 216, 184, 100, 83.

Methyl Sulfonate 2. Ozone was passed through a stirred solution of **11** (8.0 mg, 0.0185 mmol) in MeOH (0.4 mL) and CH$_2$Cl$_2$ (2.0 mL) at −78 °C. The solution was stirred for 15 min at −78 °C, warmed to room temperature, and stirred for a further 30 min. The mixture was concentrated and added to a solution of diazomethane in ether. The resulting yellow solution was stirred for 1 h and concentrated, and the residual oil was chromatographed on silica (hexanes−ethyl acetate, 2:1) to give **2** (4.4 mg, 43%) as a colorless oil: $[\alpha]^{23}_D$ −20 (*c* 0.2, MeOH); IR (neat) 3333, 2964, 1735, 1637, 1540, 1164 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.95 (2H, m), 1.15 (3H, d, *J* = 6 Hz), 1.53 (1H, m), 1.58 (1H, m), 3.79 (2H, d, *J* = 5 Hz), 3.81 (3H, s), 3.88 (3H, s), 4.90 (1H, m), 6.65 (1H, d, *J* = 7 Hz); ^{13}C NMR (CDCl$_3$) δ 11.9, 12.9, 15.6, 20.2, 48.7, 50.0, 53.1, 55.9, 169.1, 171.7; MS *m/z* 279 (M$^+$), 248, 220, 198, 138, 83, 55; HRMS *m/z* 279.0775 (calcd for C$_{10}$H$_{17}$NO$_6$S 279.0777).

Methyl Sulfonate 9. This compound was prepared following the procedure described for **2**: $[\alpha]^{25}_D$ −21 (*c* 0.2, MeOH); ^{1}H NMR (CDCl$_3$) δ 0.95 (2H, m), 1.15 (3H, d, *J* = 6 Hz), 1.53 (1H, m), 1.58 (1H, m), 3.79 (2H, d, *J* = 5 Hz), 3.82 (3H, s), 3.89 (3H, s), 4.94 (1H, m), 6.65 (1H, d, *J* = 7 Hz); ^{13}C NMR (CDCl$_3$) δ 12.0, 12.9, 15.6, 20.2, 48.7, 50.0, 53.3, 56.2, 169.1, 171.7; MS *m/z* 279 (M$^+$), 248, 220, 198, 138, 83, 55.

(5R)-(+)-1-Octyn-7-en-5-ol (16). To (−)-B-methoxydiisopinocampheylborane (7.0 g, 22 mmol) in dry ether (30 mL) at 0 °C was added allylmagnesium bromide (22 mL, 1 M in ether) dropwise. The resulting white slurry was stirred for 1.5 h at room temperature, centrifuged to remove magnesium salts, and concentrated in vacuo for 1 h at 5 Torr. The residue was taken up in pentane (40 mL), and the solution was centrifuged again to remove the remaining magnesium salts and was concentrated in vacuo for 10 min at 10 Torr followed by 1 h at 2 Torr. The residual oil was taken up in ether (20 mL), and a solution of **14** (1.53 g, 18.4 mmol) in ether (20 mL) at −100 °C was added dropwise along the sides of the flask. After 45 min, MeOH (1 mL) was added, and the solution was warmed to room temperature over 30 min, diluted with aqueous 3 N sodium hydroxide solution (12 mL) and hydrogen peroxide (24 mL, 30% aqueous solution), and stirred for 2.5 h under reflux. The mixture was cooled to 5 °C, and the organic layer was washed with water (2 × 30 mL) and brine (1 × 30 mL). The aqueous washes were combined and extracted again with ether (3 × 20 mL), and the ether extract was washed with brine (1 × 20 mL), then combined with the original ether fraction. The ethereal extract was concentrated by fractional distillation, and the residual oil was purified

by chromatography on silica (pentane−ether, 2:1) to give **16** (1.50 g, 66%) as a colorless oil: $[\alpha]^{23}_D$ +35.4 (*c* 2.36, CHCl$_3$); IR (neat) 3391, 3203, 2924, 1737, 1642, 1436, 1081, 1067, 988, 919, 635 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.68 (2H, m), 1.74 (1H, d, *J* = 4 Hz), 1.97 (1H, t, *J* = 3 Hz), 2.19 (1H, m), 2.31 (1H, m), 2.35 (2H, dt, *J* = 7, 3 Hz), 3.81 (1H, m), 5.14 (1H, m), 5.17 (1H, m), 5.82 (1H, m); ^{13}C NMR (CDCl$_3$) δ 14.8, 34.9, 41.7, 68.6, 69.3, 84.0, 118.0, 134.3; MS (CI) *m/z* 125 (M$^+$ + 1), 107, 99, 83, 71. Anal. Calcd for C$_8$H$_{12}$O: C, 77.38; H, 9.74. Found: C, 77.07; H, 9.84.

(5R)-(+)-5-Methoxy-1-octyn-7-ene (17). To NaH (330 mg, 13.8 mmol) in dry ether (7 mL) was added a solution of **16** (1.10 g, 8.86 mmol) in dry ether (1.25 mL) dropwise. The solution was refluxed for 1 h during which there was visible evolution of H$_2$. The solution was cooled to room temperature, and methyl iodide (1.2 mL, 19.30 mmol) was added dropwise. The solution was refluxed under argon for 18 h, cooled to 0 °C, diluted with water, and extracted with ether. The ethereal extract was washed with water and brine, dried over magnesium sulfate, and concentrated by fractional distillation. The residual oil was chromatographed on silica (pentane−CH$_2$Cl$_2$, 1:2) to give **17** (1.07 g, 88%) as a pale yellow oil: bp 50 °C (6 Torr); $[\alpha]^{23}_D$ +46.6 (*c* 1.61, CHCl$_3$); IR (neat) 2930, 2160, 1630, 1096, 915 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.68 (2H, m), 1.94 (1H, t, *J* = 3 Hz), 2.28 (4H, m), 3.35 (1H, p, *J* = 6 Jz), 3.37 (3H, s), 5.06 (1H, m), 5.11 (1H, m), 5.81 (1H, m); ^{13}C NMR (CDCl$_3$) δ 14.5, 32.4, 37.5, 56.8, 68.3, 78.8, 84.2, 117.2, 134.3; MS *m/z* 97 (M$^+$ − 41), 85, 67, 55.

(1E,5R)-(+)-5-Methoxy-1-iodo-2-methyl-1,7-octadiene (18). To zirconocene dichloride (1.42 g, 4.8 mmol) in dry dichloromethane (12 mL) was added trimethylaluminum (5.0 mL, 2.0 M in hexanes) at room temperature. The solution was stirred for 10 min under Ar, and **17** (584 mg, 4.2 mmol) was added dropwise. After stirring for 20 h, the solution was cooled to 0 °C and iodine (1.30 g, 5.1 mmol) in dry THF (10 mL) was added. After 10 min, the solution was diluted with water and THF, the solids were filtered off, and the filtrate was diluted with ether (20 mL). The ethereal solution was washed with aqueous Na$_2$SO$_3$ solution (10 mL), water (3 × 15 mL), and brine (1 × 15 mL), dried over magnesium sulfate, and concentrated. The residual oil was purified by chromatography on silica (pentane−ether, 4:1), followed by Kugelrohr distillation to give **18** (812 mg, 69%) as a colorless oil: $[\alpha]^{23}_D$ +10.8 (*c* 2.69, CHCl$_3$); IR (neat) 2929, 1640, 1438, 1376, 1271, 1096, 915, 758 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.61 (2H, m), 1.83 (3H, d, *J* = 1 Hz), 2.27 (4H, m), 3.18 (1H, tt, *J* = 5, 5 Hz), 3.33 (3H, s), 5.05 (1H, dd, *J* = 1, 1 Hz), 5.10 (1H, m), 5.79 (1H, m), 5.90 (1H, m); ^{13}C NMR (CDCl$_3$) δ 23.9, 31.5, 35.2, 37.5, 56.6, 74.7, 79.4, 117.2, 134.4, 147.8; MS (CI) *m/z* 281 (M$^+$ + 1), 248, 239, 207, 181, 153, 121, 111; HRMS (CI) *m/z* 281.0402 (M$^+$ + 1) (calcd for C$_{10}$H$_{18}$OI 281.0402).

(1E,5S)-(+)-5-Methoxy-1-iodo-2-methyl-1-octene (19). To a stirred solution of **18** (40 mg, 143 μmol) and dipotassium azodicarboxylate (277 mg, 1.43 mmol) in pyridine (2 mL) was slowly added acetic acid (14 mL) over 7 h. The mixture was cooled to 0 °C, diluted with water, and extracted with ether. The ethereal extract was washed with aqueous 1 N HCl solution and water, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica (pentane−ether, 9:1) to give **19** (40 mg, 99%) as a colorless oil: $[\alpha]^{23}_D$ +6.0 (*c* 0.1, ether); IR (neat) 2930, 1454, 1376, 1270, 1143, 1095, 772 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.91 (3H, t, *J* = 7 Hz), 1.40 (4H, m), 1.60 (2H, dt, *J* = 8, 2 Hz), 1.84 (3H, d, *J* = 1 Hz), 2.25 (2H, dt, *J* = 12, 6 Hz), 3.12 (1H, tt, *J* = 6, 6 Hz), 3.32 (3H, s), 5.90 (1H, s); ^{13}C NMR (CDCl$_3$) δ 14.2, 18.4, 23.9, 31.6, 35.2, 35.5, 56.4, 74.5, 79.8, 148.0; MS (CI) *m/z* 282 (M$^+$), 250, 194, 181, 155, 123, 87; HRMS *m/z* 282.0483 (M$^+$) (calcd for C$_{10}$H$_{19}$OI 282.0480).

(5S)-(+)-5-Methoxy-2-octanone (3). Ozone was passed through a solution of **19** (14 mg, 50 μmol) in MeOH (3 mL) at −78 °C for 1 min. The resulting brown solution was stirred for 5 min, excess dimethyl sulfide was added, and the solution was warmed to room temperature and stirred for 5 h. The solution was diluted with CH$_2$Cl$_2$ (25 mL), washed with aqueous sodium sulfite solution, water, and brine, dried over magnesium sulfate, and concentrated by distillation to leave **3** (5.0 mg, 64%) pure as a colorless oil: $[\alpha]^{23}_D$ +15.0 (*c* 0.36, CDCl$_3$); IR (neat) 2958, 1709, 1265, 1224 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.92 (3H, t, *J* = 7 Hz), 1.35 (3H, m), 1.50 (1H, m), 1.68 (1H, m), 1.83 (1H, m), 2.15 (3H, s), 2.50 (2H, dt, *J* = 7, 2 Hz), 3.17 (1H, m), 3.29 (3H, s); ^{13}C NMR (CDCl$_3$) δ 4.2, 18.5, 27.3, 30.0, 35.6, 39.3, 56.4, 79.7, 209.0; GC EIMS *m/z* 143 (M − 15), 126, 115, 100, 87, 83, 72, 71, 55.

4-Pentynyl Acetate (20). To a solution of **13** (1.80 g, 21.4 mmol) in dry pyridine (6 mL) was added acetic anhydride (2.4 mL, 25.4 mmol). The solution was stirred for 20 h, diluted with water, and extracted with pentane (40 mL). The pentane extract was washed with cold 5% HCl solution (2 × 10 mL), water, and brine, dried over magnesium sulfate, and concentrated. The residual oil was purified by fractional distillation to give **20** (2.20 g, 82%) as a colorless oil: bp 50 °C (2 Torr); IR (neat) 3298, 2964, 2118, 1740, 1435, 1389, 1369, 1246, 1043, 966, 877, 640, 608 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.86 (2H, tt, $J = 7$, 7 Hz), 1.97 (1H, dt, $J = 2$, 1 Hz), 2.06 (3H, s), 2.30 (2H, dt, $J = 3$, 7 Hz), 4.17 (2H, t, $J = 6$ Hz); ^{13}C NMR (CDCl$_3$) δ 15.0, 20.6, 27.3, 62.7, 68.9, 82.8, 170.7; MS (CI) m/z 127 (M$^+$ + 1), 111, 95, 85, 67, 61; HRMS (CI) m/z 127.0759 (M$^+$ + 1) (calcd for C$_7$H$_{11}$O$_2$ 127.0759).

(4R,7E,9E)-(−)-4-Methoxy-7-methyltrideca-1,7,9-trienol (22). To **20** (60 mg, 476 μmol) was added catecholborane (70 μL, 657 μmol). The mixture was heated at 70−80 °C for 2 h in a sealed tube under Ar. The resulting catecholboronate was diluted with degassed THF (3.3 mL) and added to a mixture of degassed 1 N NaOH (600 μL, 600 μmol), tetrakis(triphenylphosphine)palladium (3 mg, 2 μmol), and **18** (15 mg, 53 μmol). The mixture was stirred at 70 °C for 5 h, cooled to room temperature, and diluted with ether (30 mL). The solution was washed with water (3 × 20 mL) and brine (1 × 20 mL), dried over magnesium sulfate, and concentrated. The residual oil was purified by chromatography on silica (pentane−ether, 3:2) to give **22** (70 mg, 62%) as a pale yellow oil: [α]$^{23}_D$ −1.4 (c 2.90, CDCl$_3$); IR (neat) 3,360, 2934, 1643, 1443, 1095, 996, 964 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.56−1.72 (4H, m), 1.73 (3H, s), 2.09 (2H, m), 2.19 (2H, dt, $J = 7$, 7 Hz), 2.27 (2H, m), 3.20 (1H, tt, $J = 6$, 6 Hz), 3.34 (3H, s), 3.66 (2H, t, $J = 6$ Hz), 5.07 (2H, m), 5.58 (1H, m), 5.81 (2H, m), 6.27 (1H, m); ^{13}C NMR (CDCl$_3$) δ 16.5, 29.2, 31.6, 32.4, 35.3, 37.6, 56.5, 62.4, 79.9, 116.9, 124.6, 127.2, 131.3, 134.7, 136.6; MS (CI) m/z 238 (M$^+$), 206, 197, 179, 166, 147, 121, 105, 93; HRMS (CI) m/z 238.1934 (M$^+$) (calcd for C$_{15}$H$_{26}$O$_2$ 238.1933). Anal. Calcd for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 10.99. Found: C, 75.21; H, 10.79.

(4R,7E,9E)-(+)-4-Methoxy-7-methyl-13-iodotrideca-1,7,9-triene (23). To a solution of **22** (17 mg, 71 μmol) in dry CH$_2$Cl$_2$ (3 mL) was added dry triethylamine (20 μL, 143 μmol) followed by methanesulfonyl chloride (8 μL, 103 μmol) at −30 °C. After stirring at −20 to −10 °C for 1 h, the solution was allowed to warm to room temperature, concentrated under reduced pressure, and diluted with dry acetone (3 mL). To the solution was added sodium iodide (50 mg, 333 μmol), and the mixture was stirred for 15 h at room temperature and concentrated. The residue was taken up in hexane and concentrated again under reduced pressure. The residual oil was purified by chromatography on silica (hexanes−ethyl acetate, 4:1) to give **23** (24 mg, 100%) as a pale yellow oil: [α]$^{23}_D$ −0.9 (c 4.35, CHCl$_3$); IR (neat) 2928, 1639, 1442, 1357, 1217, 1097, 963, 914 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.59 (2H, dt, $J = 8$, 6 Hz), 1.74 (3H, s), 1.91 (2H, tt, $J = 7$ Hz), 2.09 (2H, m), 2.19 (2H, m), 2.27 (2H, m), 3.19 (3H, t, $J = 7$ Hz), 3.34 (3H, s), 5.07 (2H, m), 5.49 (1H, dt, $J = 16$, 8 Hz), 5.81 (2H, m), 6.30 (1H, dd, $J = 15$, 11 Hz); ^{13}C NMR (CDCl$_3$) δ 6.5, 16.6, 31.5, 33.0, 33.4, 35.3, 37.6, 56.5, 79.8, 116.9, 124.4, 128.1, 129.4, 134.7, 137.0; MS (CI) m/z 348 (M$^+$), 317, 307, 275, 249, 147, 93, 85; HRMS m/z 348.0963 (M$^+$) (calcd for C$_{15}$H$_{25}$OI 348.0950).

[(4R,7E,9E)-(+)-4-Methoxy-7-methyltrideca-1,7,9-trien-13-yl]-triphenylphosphonium Iodide (24). A solution of **23** (40 mg, 115 μmol) and triphenylphosphine (50 mg, 191 μmol) in dry acetonitrile (2 mL) was refluxed under argon for 16 h. The solution was concentrated, and the residue was purified by chromatography on silica (CH$_2$Cl$_2$ to CH$_2$Cl$_2$−MeOH, 4:1) to give **24** (61 mg, 87%) as a white foam: [α]$^{23}_D$ 0.0 (c 7.0, CHCl$_3$); IR (neat) 2930, 2891, 1438, 1112, 996, 968, 916, 723, 691 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.58 (2H, dt, $J = 8$, 7 Hz), 1.71 (3H, s), 1.72 (2H, m), 2.07 (2H, m), 2.26 (2H, m), 2.49 (2H, dt, $J = 7$, 7 Hz), 3.18 (1H, tt, $J = 6$, 6 Hz), 3.33 (3H, s), 3.75 (2H, m), 5.07 (2H, m), 5.41 (1H, dt, $J = 14$, 7 Hz), 5.80 (2H, m), 6.31 (1H, dd, $J = 15$, 11 Hz); ^{13}C NMR (CDCl$_3$) δ 16.5, 21.7, 22.4, 31.3, 32.9 (d, $J = 16$ Hz), 35.0, 37.3, 56.2, 79.5, 116.7, 117.1, 118.2, 124.0, 128.8 (d, $J = 14$ Hz), 130.3 (d, $J = 12$ Hz), 133.4 (d, $J = 10$ Hz), 134.4, 134.9, 137.6.

(R)-S-Benzylcysteinyl tert-Butyldimethylsilyl Ether (28). To a stirred solution of (R)-S-benzylcysteinyl alcohol (**27**; 1.0 g, 5.07 mmol) and imidazole (0.41 g, 6.08 mmol) in DMF (5 mL) was added *tert*-butyldimethylsilyl chloride (0.916 g, 6.08 mmol). The solution was

stirred for 20 h under argon and poured into water. The mixture was extracted with ether, and the extract was dried over magnesium sulfate and concentrated. The residue was purified by chromatography on silica (hexanes−ethyl acetate, 2:3) to give **28** (0.9 g, 57%) as a yellow oil: [α]$^{25}_D$ −31.3 (c 1.63, CHCl$_3$); IR (neat) 2928, 1471, 1252, 1098, 837 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.04 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 2.34 (1H, dd, $J = 3$, 4 Hz), 2.59 (1H, dd, $J = 1$, 4 Hz), 2.94 (1H, m), 3.48 (1H, dd, $J = 6$, 10 Hz), 3.56 (1H, $J = 4$, 10 Hz), 3.71 (3H, s); ^{13}C NMR δ −5.5, 18.2, 25.8, 36.0, 36.5, 51.8, 66.8, 126.9, 128.4, 128.8, 138.3; MS m/z 311 (M$^+$), 296, 254, 174, 137, 91; HRMS (CI) m/z 312.1816 (M$^+$ + 1) (calcd for C$_{16}$H$_{30}$NOSSi 312.1817).

Amides 29 and 30. To a mixture of **28** (150 mg, 0.48 mmol), 1,3-dicyclohexylcarbodiimide (108 mg, 0.52 mmol), sodium bicarbonate (100 mg, 1.19 mmol), and 1-hydroxybenzotriazole (64 mg, 0.48 mmol) was added (+)-**8** (48 mg, 0.48 mmol) in DMF (6 mL) at room temperature under argon. After 3 days, the mixture was diluted with water, and extracted with ether. The ethereal extract was dried over magnesium sulfate and concentrated under reduced pressure, and the residue was chromatographed on silica (hexanes−ethyl acetate, 9:1) to give a 1:1 mixture of **29** and **30** (174 mg, 92%) as a colorless oil: IR (neat) 3735, 2929, 1652, 1646, 1111, 836 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 1.09 (1H, m), 1.1−1.7 (6H, m), 2.58 (2H, m), 3.61 (2H, m), 3.74 (2H, d, $J = 4$ Hz), 3.85 (1H, m), 4.13 (1H, m), 5.91 (1H, m), 7.31 (5H, m); ^{13}C NMR (CDCl$_3$) δ −5.5, 12.0, 12.2, 14.6, 14.7, 18.2, 20.6, 24.6, 25.4, 25.7, 25.8, 32.1, 32.3, 34.8, 36.0, 36.3, 49.3, 49.4, 55.6, 62.7, 62.9, 126.8, 128.3, 128.4, 128.9, 128.9, 138.2, 170.7, 170.8; MS (CI) m/z 394 (M$^+$ + 1), 336, 307, 272, 247, 225, 207, 153, 125; HRMS (CI) m/z 394.2238 (M$^+$ + 1) (calcd for C$_{21}$H$_{36}$NO$_2$SiS 394.2236).

Thiols 25 and 26. To a dark blue solution of sodium−ammonia prepared from excess sodium and liquid ammonia (3 mL) was added a solution of **29** and **30** (57 mg, 0.145 mmol) in THF (0.8 mL) at −60 °C. The cold bath was removed, and after all ammonia had evaporated, the mixture was diluted with water and extracted with ether. The ethereal extract was washed with brine, dried over magnesium sulfate, and concentrated to leave a 1:1 mixture of **25** and **26** (42 mg, 96%) as a pale yellow oil: IR (neat) 3296, 2928, 1652, 1558, 837 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.94 (1H) and 6.02 (1H) (NHCO of each diastereomer); ^{13}C NMR δ 12.3 and 12.4 (methyl of each diastereomer); MS (CI) m/z 304 (M$^+$ + 1), 246, 225, 172, 147; HRMS m/z 304.1764 (M$^+$ + 1) (calcd for C$_{14}$H$_{30}$NO$_2$SSi 304.1766).

Methyl Esters 33 and 34. Into a stirred solution of a racemic *cis−trans* mixture of **31** (156 mg, 1.92 mmol) in methanol (3 mL) was introduced gaseous HCl for 3 h at 0 °C. The mixture was stirred for 1 h at 0 °C and then sealed and stored for 3 days at 0 °C. The resultant precipitate was washed with petroleum ether to give the imidate **32** as a white salt (226 mg, 79%): IR (neat) 3395, 2946, 1635, 1476, 1403, 1098, 872 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.75 (1H, m, *trans* isomer (87%)), 0.95 (1H, m, *cis* isomer (13%)); ^{13}C NMR (CDCl$_3$) δ 60.1 (OMe, *trans* isomer), 60.4 (OMe, *cis* isomer).

To **32** (47 mg, 0.314 mmol) and cysteine methyl ester hydrochloride (54 mg, 0.314 mmol) in CH$_2$Cl$_2$ (1 mL) was slowly added triethylamine (38 μL, 0.272 mmol). The resulting suspension was stirred for 24 h and diluted with water, and the solution was extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extract was dried over magnesium sulfate and concentrated, and the residue was chromatographed on silica (hexanes−ethyl acetate, 4:1) to give a 1:1 mixture of **33** and **34** (32 mg, 52%) as a colorless oil: IR (neat) 2954, 1744, 1613, 1437, 1272, 1200, 1080 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.79 (1H, m), 1.13 (3H, d, $J = 6$ Hz), 1.16 (1H, m), 1.39 (1H, m), 1.68 (1H, m), 3.51 (2H, m), 3.79 (3H, s), 5.01 (1H, m); ^{13}C NMR (CDCl$_3$) δ 17.7, 18.1, 18.2, 23.6, 35.1, 52.6, 77.7, 171.5, 176.6; MS (CI) m/z 200 (M$^+$ + 1), 182, 169, 147, 140, 119; HRMS (CI) m/z 200.0745 (calcd for C$_9$H$_{14}$NO$_2$S (M$^+$ + 1) 200.0745).

(2R,4R)-3-(tert-Butoxycarbonyl)-4-(hydroxymethyl)-2-phenyl-thiazolidine (40). To a solution of (2R,4R)-4-carboxy-2-phenylthiazolidine (2.36 g, 11.48 mmol), prepared from cysteine following a literature procedure,[26] in triethylamine (6.6 mL) and MeOH (66 mL) was added di-*tert*-butyl dicarbonate (5.0 g, 22.96 mmol) in one portion. The mixture was stirred for 30 min at 50 °C and concentrated, and the residue was taken up in 0.4 N hydrochloric acid (40 mL). The solution was extracted with CH$_2$Cl$_2$, and the extract was dried over magnesium sulfate and concentrated to leave a white solid (3.2 g, 90%). This was used for the next step without purification.

To a solution of the white solid obtained above (2.0 g, 6.47 mmol) in THF (10 mL) was added borane (8.6 mL, 8.6 mmol, 1.0 M in THF) dropwise at room temperature. The mixture was stirred for 30 min, and 10% aqueous sodium bicarbonate solution was added. The resulting turbid solution was extracted with CH_2Cl_2, and the extract was dried over sodium sulfate and concentrated to leave pure **40** (1.52 g, 80%) as a viscous oil: $[\alpha]^{25}_D$ +115.0 (*c* 1.02, CHCl₃); IR (neat) 3443, 2973, 1705, 1675, 1373, 1164, 1052 cm⁻¹; ¹H NMR (CDCl₃) δ 1.26 (9H, s), 2.85 (1H, m), 3.25 (1H, dd, *J* = 2, 4 Hz), 3.8−4.0 (2H, m), 4.57 (1H, m), 6.03 (1H, s), 7.34 (5H, m); ¹³C NMR (CDCl₃) δ 27.9, 32.7, 64.0, 66.3, 67.6, 81.5, 125.9, 127.7, 128.3, 141.2, 155.9; MS (CI) *m/z* 296 (M⁺ + 1), 268, 240, 196, 162, 134, 84; HRMS (CI) *m/z* 296.1321 (M⁺ + 1) (calcd for $C_{15}H_{22}NO_3S$ 296.1320).

Tetraene 41. To a solution of pyridine (0.31 mL, 3.88 mmol) in CH_2Cl_2 (6 mL) was added anhydrous chromium trioxide (194 mg, 1.94 mmol) in one portion. The solution was stirred for 15 min, and a solution of **40** (89 mg, 0.323 mmol) in CH_2Cl_2 (1 mL) was added in one portion. The resulting suspension was stirred for 15 min and extracted with CH_2Cl_2. The extract was concentrated, and the residue was taken up into ether. The ethereal solution was washed with water and dilute hydrochloric acid (3 × 10 mL), dried over sodium sulfate, and concentrated to leave aldehyde **39** (65 mg, 72%) as a colorless oil. This was used in the next step without purification.

To a solution of 1,1,1,3,3,3-hexamethyldisilazane (32.2 μL, 0.153 mmol) in THF (1.15 mL) and HMPA (0.25 mL) was added *n*-butyllithium (0.10 mL, 0.139 mmol, 1.6 M in hexane) at −78 °C. The resulting solution was warmed to 0 °C for 3 min and then cooled to −78 °C, and a solution of **24** (200 mg, 0.327 mmol) in THF (0.5 mL) at −78 °C was added. The resulting orange solution was stirred for 30 min, and a solution of **39** (65 mg, 0.222 mmol) in THF (0.5 mL) was added at −78 °C. The mixture was stirred for 10 min at −78 °C, warmed to 0 °C, and stirred for a further 10 min. The reaction was quenched with water at 0 °C, and the mixture was extracted with ether. The ethereal extract was dried over magnesium sulfate and concentrated under reduced pressure, and the residual oil was purified by chromatography on silica (hexanes−ethyl acetate, 15:1) to give **41** (35.2 mg, 32%) as a colorless oil: $[\alpha]^{25}_D$ +148.0 (*c* 0.98, CHCl₃); IR (neat) 2977, 1736, 1697, 1455, 1163, 1120 cm⁻¹; ¹H NMR (CDCl₃) δ 1.34 (9H, s), 1.58 (2H, m), 1.73 (3H, s), 2.0−2.4 (8H, m), 2.72 (1H, dd, *J* = 6, 12 Hz), 3.20 (2H, m), 3.34 (3H, s), 5.05 (3H, s), 5.50−5.75 (3H, m), 5.82 (2H, m), 6.14 (1H, s), 6.26 (1H, dd, *J* = 11, 15 Hz), 7.34 (5H, m); ¹³C NMR (CDCl₃) δ 16.5, 27.6, 28.2, 31.5, 32.7, 35.3, 36.7, 37.6, 56.5, 59.1, 66.1, 79.8, 80.5, 116.8, 124.6, 126.0 (2C), 127.3 (2C), 128.1 (2C), 130.2, 131.1 (2C), 134.6, 136.6, 141.9, 153.6; MS *m/z* 497 (M⁺), 442, 426, 410, 398, 366, 261, 206, 150, 106; HRMS *m/z* 497.2966 (calcd for $C_{30}H_{43}NO_3S$ 497.2963).

Tetraene 44. To a solution of 1,1,1,3,3,3-hexamethyldisilazane (76.0 μL, 0.359 mmol) in THF (2.3 mL) and HMPA (0.25 mL) was added *n*-butyllithium (0.20 mL, 0.327 mmol, 1.6 M in hexane) at −78 °C. The resulting solution was warmed to 0 °C for 3 min and then cooled to −78 °C, and a solution of **24** (200 mg, 0.327 mmol) in THF (1 mL) at −78 °C was added. The resulting orange solution was stirred for 30 min, and a solution of **43**[31] (70 mg, 0.305 mmol) in THF (0.5 mL) was added at −78 °C. The mixture was stirred for 10 min at −78 °C, warmed to 0 °C, and stirred for a further 10 min. The reaction was quenched with water at 0 °C, and the mixture was extracted with ether. The ethereal extract was dried over magnesium sulfate and concentrated under reduced pressure, and the residual oil was purified by chromatography on silica (hexanes−ethyl acetate, 15:1) to give **44** (88.4 mg, 69%) as a colorless oil: $[\alpha]^{25}_D$ +80.9 (*c* 1.1, CHCl₃); IR (neat) 2982, 1697, 1385, 1095 cm⁻¹; ¹H NMR (CDCl₃) δ 1.43 (9H, s), 1.45−1.57 (8H, m), 1.72 (3H, s), 1.9−2.4 (8H, m), 3.19 (1H, m), 3.33 (3H, s), 3.61 (1H, dd, *J* = 3, 9 Hz), 4.02 (1H, dd, 6, 9 Hz), 4.57 (1H, m), 5.07 (2H, m), 5.50 (3H, m), 5.82 (2H, m), 6.23 (1H, dd, *J* = 10, 15 Hz); ¹³C NMR (CDCl₃) δ 16.4, 24.0, 26.4, 27.4, 28.4 (3C), 31.5, 32.8, 35.2, 37.5, 54.4, 56.4, 68.9, 79.8 (2C), 93.8, 116.8, 124.5, 127.3, 129.7, 130.9 (2C), 134.6, 136.7, 151.9; MS *m/z* 433 (M⁺), 378, 362, 346, 334, 227, 109, 83; HRMS *m/z* 433.3193 (calcd for $C_{26}H_{43}NO_4$ 433.3192).

Alcohol 45. To a solution of **44** (5.5 mg, 12.7 μmol) in MeOH (1 mL) was added a crystal of *p*-toluenesulfonic acid, and the mixture was stirred for 1.25 h at 40−50 °C. Sodium bicarbonate (10 mg) was added, and the suspension was concentrated under reduced pressure. The residue was taken up into ether, and the ethereal solution was washed with aqueous sodium bicarbonate solution, dried over magnesium sulfate, and concentrated to give **45** (4.8 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ +24.8 (*c* 0.87, CHCl₃); IR (neat) 3357, 2975, 2931, 1702, 1692, 1503, 1366, 1169, 1090, 1052 cm⁻¹; ¹H NMR (CDCl₃) δ 1.42 (9H, s), 1.58 (2H, m), 1.71 (3H, s), 1.9−2.4 (8H, m), 3.17 (1H, m), 3.32 (3H, s), 3.57 (2H, m), 4.43 (1H, m), 4.81 (1H, d, *J* = 6 Hz), 5.05 (2H, m), 5.28 (1H, dd, *J* = 9, 11 Hz), 5.55 (2H, m), 5.77 (2H, m), 6.23 (1H, dd, *J* = 11, 15 Hz); ¹³C NMR (CDCl₃) δ 16.4, 27.8, 28.3 (3C), 31.5, 32.6, 35.3, 37.5, 50.5, 56.4, 66.1, 79.7, 79.8, 116.8, 124.5, 126.7, 127.3, 130.8, 133,4, 134.6, 136.6, 156.1; MS *m/z* 394 (M⁺ + 1), 382, 378, 366, 352, 326, 310, 278, 214, 179, 121, 85; HRMS *m/z* 394.2957 (M⁺ + 1) (calcd for $C_{23}H_{40}NO_4$ 394.2957).

Thioester 48. A. From Potassium Thiolate 47. To a solution of **45** (14 mg, 0.356 mmol) in CH_2Cl_2 (1 mL) at −45 °C were added triethylamine (15 μL, 0.107 mmol) and methanesulfonyl chloride (5.5 μL, 0.0712 mmol). The mixture was warmed slowly to room temperature, stirred for 1.5 h, and diluted with CH_2Cl_2 (4 mL). The solution was washed with water twice and with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give mesylate **46** (16 mg, 96%). This was used in the next step without purification.

To (−)-**8** (36 mg, 0.36 mmol) was added thionyl chloride (29 μL, 0.40 mmol), and the mixture was stirred for 16 h. This was added to a solution of potassium sulfide, prepared by bubbling H_2S gas into a solution of potassium hydroxide (40 mg, 0.73 mmol) in ethanol (1.5 mL) until the pH reached 8. After 1 h, the suspension was filtered through Celite, and the filtrate was concentrated under reduced pressure. The potassium thiolate **47**, obtained as a solid, was used for the next reaction without further purification.

To a solution of **46** (8 mg, 0.017 mmol) in DMF (0.5 mL) was added a solution of **47** (5.2 mg, 0.034 mmol) in DMF (0.5 mL) at room temperature under argon. The mixture was stirred for 20 h and concentrated under reduced pressure, and the residual oil was purified by chromatography on silica (hexanes−ethyl acetate, 6:1 to 2:1) to give **48** (3.3 mg, 55% based on recovered **46**) as a colorless oil: $[\alpha]^{23}_D$ −12.5 (*c* 0.32, CHCl₃); IR (neat) 3343, 2919, 1724, 1685, 1509, 1363, 1153, 1017 cm⁻¹; ¹H NMR (CDCl₃) δ 0.87 (1H, m), 1.14 (3H, d, *J* = 6.2 Hz), 1.15−1.40 (3H, m), 1.41 (9H, brs), 1.59 (2H, m), 1.72 (3H, s), 2.0−2.4 (8H, m), 2.94 (1H, dd, *J* = 6, 14 Hz), 3.17 (1H, m), 3.19 (1H, m), 3.34 (3H, s), 4.47 (1H, m), 4.69 (1H, m), 5.08 (2H, m), 5.25 (1H, m), 5.53 (2H, m), 5.82 (2H, m), 6.25 (1H, m); ¹³C NMR (CDCl₃) δ 7.3, 11.9, 15.9, 16.5, 19.2, 27.7, 28.3 (3C), 31.5, 32.6, 35.3, 37.6, 44.9, 28.5, 56.5, 78.9, 79.8, 116.8, 124.6, 127.2, 128.3, 131.1, 132.4, 136.4, 154.9, 196.5; MS *m/z* 491 (M⁺), 435, 420, 392, 227, 153, 117; HRMS *m/z* 491.3067 (calcd for $C_{28}H_{45}NO_4S$ 491.3069).

B. From Thiol 49. To a solution of **49** (5.0 mg, 0.012 mmol), 4-(dimethylamino)pyridine (0.1 mg, 1.2 μmol), and (−)-**8** (1.4 mg, 0.0144 mmol) in CH_2Cl_2 (1 mL) was added a solution of 1,3-dicyclohexylcarbodiimide (3.2 mg, 0.0159 mmol) in CH_2Cl_2 (0.5 mL) dropwise at 0 °C. After 20 h, the reaction mixture was filtered through Celite, the filtrate was concentrated, and the residue was purified by chromatography on silica (hexanes−ethyl acetate, 8:1) to give **48** (5.5 mg, 93%) as a colorless oil.

Thiol 49. To potassium thioacetate (4.7 mg, 41.4 μmol) under argon was added a solution of **46** (6.0 mg, 12.7 μmol) in DMF (1 mL). The resulting solution was stirred for 24 h and concentrated under reduced pressure. The residue was dissolved in MeOH (0.8 mL) and added to a solution of sodium methoxide (0.28 mL, 25.4 μmol, 0.092 N in MeOH). After 30 min, the mixture was poured into water and extracted with ether. The ethereal extract was washed with brine, dried over magnesium sulfate, and concentrated. The residual oil was purified by chromatography on silica (hexanes−ethyl acetate, 12:1) to give **49** (4.0 mg, 80%) as a colorless oil: $[\alpha]^{25}_D$ +19.5 (*c* 0.08, benzene); IR (neat) 3325, 2979, 1702, 1504, 1367, 1163, 1092 cm⁻¹; ¹H NMR (C₆D₆) δ 1.43 (9H, s), 1.5−1.7 (2H, m), 1.68 (3H, s), 2.0−2.5 (8H, m), 3.06 (1H, m), 3.14 (3H, s), 4.35 (1H, m), 4.60 (1H, m), 4.9−5.2 (3H, m), 5.39 (1H, m), 5.51 (1H, m), 5.83 (1H, m), 5.99 (1H, d, *J* = 11 Hz), 6.36 (1H, dd, *J* = 11, 15 Hz); ¹³C NMR (C₆D₆) δ 16.9, 28.7, 28.8 (3C), 30.4, 32.5, 33.4, 36.2, 38.4, 50.1, 56.7, 79.4, 80.3, 117.2, 125.9, 128.9, 129.1, 131.8, 133.5, 135.7, 136.8, 155.3; MS *m/z* 409 (M⁺), 354, 336, 322, 308, 276, 262, 193, 161, 119, 105; HRMS *m/z* 409.2651 (M⁺) (calcd for $C_{23}H_{39}NO_3S$ 409.2651).

Curacin A (1). To **48** (5.5 mg, 11.2 μmol) was added trifluoroacetic acid (1.0 mL) at room temperature. After 40 min, the mixture was concentrated under reduced pressure and diluted with benzene (5 mL). The solution was heated for 2 h at 80 °C under argon, cooled to room temperature, and concentrated. The residue was taken up into ether, and the ethereal solution was filtered over a short pad of silica gel. The filtrate was concentrated, and the residual oil was purified by HPLC (2 × 30 cm Versa-pack silica, 10 μm, hexanes−ethyl acetate, 25:1, UV detector) to give curacin A (1.4 mg, 30%) as a colorless oil: $[\alpha]^{23}_D$ +64.6 (*c* 0.02, CHCl$_3$);[35] IR (neat) 2938, 1608, 1438, 1065, 961 cm^{-1}; ^{1}H NMR (C$_6$D$_6$) δ 0.75 (1H, m), 0.98 (1H, m), 1.20 (1H, m), 1.21 (3H, d, *J* = 6 Hz), 1.5−1.7 (3H, m), 1.70 (3H, s), 2.0−2.4 (8H, m), 2.79 (1H, dd, *J* = 10, 11 Hz), 3.09 (2H, m), 3.18 (3H, s), 5.11 (2H, m), 5.45 (1H, m), 5.58 (1H, m), 5.69 (1H, dd, *J* = 11, 8 Hz), 5.87 (1H, m), 6.02 (1H, d, *J* = 11 Hz), 6.38 (1H, dd, *J* = 11, 15 Hz); ^{13}C NMR (C$_6$D$_6$) δ 12.6, 13.9, 15.3, 16.5, 19.8, 27.9, 31.6, 33.0, 35.2, 37.6, 39.5, 56.7, 73.5, 80.0, 117.1, 124.6, 127.5, 130.0, 131.1, 131.6, 134.8, 137.1, 170.1; CD (MeOH) θ_{max} 229 nm, θ_{min} 251 nm; GC−MS

(35) The specific rotation initially reported for curacin A (ref 8) is in error. It should be noted that curacin A is unstable in CHCl$_3$ solution, resulting in decreasing optical rotation with time in this solvent.

(retention time 17.1−17.3 min, cross-linked methyl silicone gum column (12 m × 0.2 mm × 0.33 mm (film width), 70−240 °C) 358 (M$^+$ − Me), 332, 300, 274, 180, 166. This substance was identical with a sample of natural curacin A by comparison of IR, ^{1}H NMR, GC−MS, and circular dichroism spectra.