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Total Synthesis of (+)-Curacin A, a Marine Cytotoxic Agent†

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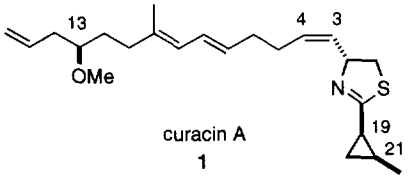
Abstract: The total synthesis of curacin A, a cytotoxic agent that interacts with the colchicine binding site on tubulin, is described. The convergent synthesis utilizes natural product and chiral pool starting materials (geraniol, serine) and asymmetric synthesis (chiral allylborane addition, Charette cyclopropanation) to procure the various chiral fragments in enantiomerically pure form. The assembly of the natural product involves carbon-carbon bond formation (Julia coupling) and heterocycle preparation (Wipf thiazoline synthesis). © 1997 Elsevier Science Ltd.

The discovery of the novel cytotoxic agent curacin A (**1**) by Gerwick et al. has generated significant interest in the scientific community.[1] Curacin A was isolated from the marine cyanobacterium *Lyngbya majuscula*. The basic attachments, olefin geometries, and some of the relative stereochemistry of the molecule were established in the original report by ^{1}H NMR, but determining the absolute configurations of all of the stereocenters required combined degradative and synthetic studies.[2] Curacin A was found to be a potent cytotoxic agent that acted by inhibition of tubulin polymerization. It exerts this action by competitively binding to the colchicine binding site of tubulin and not that of the vinca alkaloids, displaying a biological profile similar to podophyllotoxin. A later report by Hamel indicated that curacin A affected the morphology of those microtubules which managed to form in its presence.[3]



curacin A
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We were drawn to curacin A as a synthetic target because of its encouraging biological activity – it is equipotent to other agents that competitively bind to the colchicine binding site of tubulin – but also because its structure clearly represents a new departure in the previously established structure/activity regime[4] of this target (Figure 1). Although the reported instability of curacin A renders it useless as a drug candidate, it is an exciting new lead for the development of synthetic cytotoxic agents. For this to occur, a facile and readily adaptable route to the synthesis of curacin A and its congeners is an essential first step.

These concerns have motivated a significant world-wide effort toward the total synthesis of curacin A in a remarkably short time. Ultimately, the proposed structure was confirmed by the first enantioselective total synthesis of curacin A by White and coworkers at the University of Oregon.[5] Our own preliminary report[6] was quickly followed by subsequent total syntheses by the groups of Kobayashi,[7] Iwasaki,[8] Wipf,[9] and Falck.[10] An additional synthetic effort that includes analogue preparation has also appeared.[2b] We wish to disclose the

† This paper is respectfully dedicated to Professor Samuel Danishefsky in honor of his many contributions to the science of organic chemistry.

full details of our synthetic efforts toward curacin A, which have positioned us for a program of pharmacophore identification of the natural product. Where appropriate, comparisons between the salient features of our synthesis and other approaches will be made.

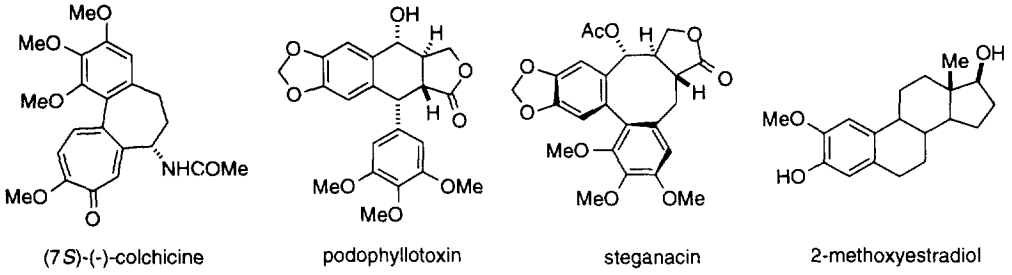


Figure 1. Structures of some agents that interact with the colchicine binding site of tubulin.

The relative isolation of the stereochemical elements of curacin A immediately suggested a convergent synthesis that would readily be adapted for analogue synthesis. We decided to forestall sulfur introduction until late in the synthesis and settled on a Julia coupling to form the trans-7,8 double bond (Figure 2). Three pieces (**A**–**C**) were needed to implement this plan. The sulphone **A** would be prepared from geraniol through ozonolysis/asymmetric allylation at one end and functional group manipulation at the other, thus allowing the purchase of the *E*-9,10 olefin. In this report, we provide a streamlined solution to a surprisingly sticky issue of our first synthesis, namely the methylation of the C(13) alcohol. Compound **B** was foreseen to arise from L-serine, with the cis olefin coming from an unstabilized Wittig reaction. And the interesting *cis*-methylcyclopropanecarboxylic acid unit in **C** would readily be formed via an asymmetric Simmons-Smith reaction on a cis olefin derived from 2-butyn-1-ol.

The asymmetric allylation rendering C(13) is common to all of the published syntheses; the use of this reaction is practically irresistible due to the isolation of this stereocenter and the opportunity to use the resulting homoallylic alcohol "as is". Our route to the cyclopropane mirrors that of three syntheses,[5,9,10] whereas Iwasaki[8] used a diastereoselective cyclopropanation and Kobayashi[7] an enzyme-provoked hydrolysis.

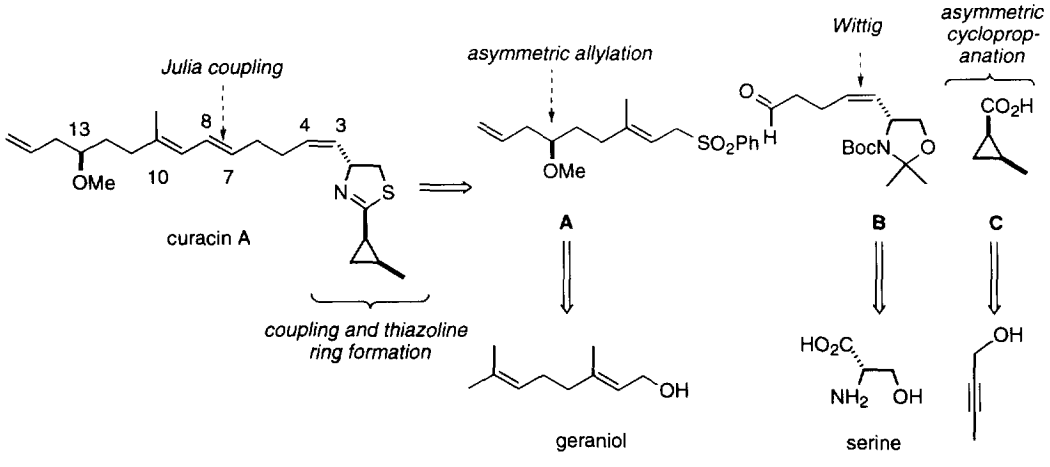
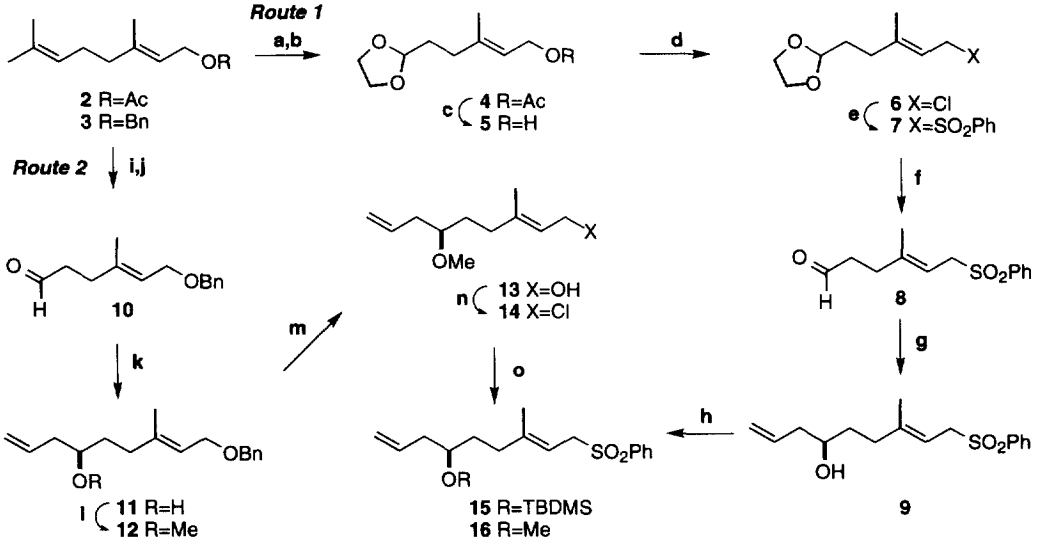


Figure 2. Retrosynthetic analysis of curacin A.

Results and Discussion

In our original communication, the synthesis of the C(8-16) segment started with geranyl acetate (**2**) (Scheme 1, Route 1). Regioselective ozonolysis[11] followed by protection of the aldehyde as the acetal gave **4**. This protection step was undertaken reluctantly because, although allylation of the aldehyde corresponding to **4** went smoothly, acetate migration interfered with all attempts to directly methylate the resulting homoallylic alcohol. This problem was presumably encountered in Kobayashi's[7] and Iwasaki's[8] syntheses, both of which also used geraniol as a starting material. These groups also resorted to protection/deprotection schemes to circumvent acetate migration.

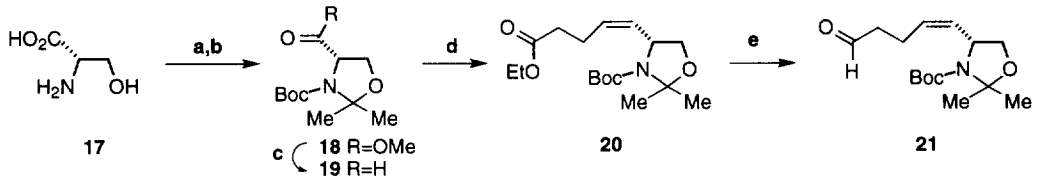
Removal of the acetate from **4** was followed by conversion of the resulting alcohol to known allylic sulphone **7**.[12] The acetal was then removed with 10% HCl in THF to give aldehyde **8**. This sequence was amenable to scale up and required minimal purification (chromatography was employed after the ozonolysis and of compounds **7** and **8**). Aldehyde **8** was treated with Brown's asymmetric allylborane,[13] derived from (–)-*B*-methoxydiisopinocampheylborane under salt-free conditions,[14] to set the absolute stereochemistry of the C(13) homoallylic alcohol **9** in 62% yield. The enantioselectivity of this reaction was determined to be 86% ee by preparation of the Mosher's ester and evaluation of the ^{1}H and ^{19}F-NMR spectra.[15] Once again, attempts to methylate the C(13) alcohol under both acidic and basic conditions were thwarted, this time by the presence of the allylic sulphone. All we obtained were bad mixtures of mono- and dimethylated products. Interestingly, although only the hydroxyl group of alcohol **9** reacted when treated with cesium carbonate and methyl iodide, we isolated the methyl carbonate rather than the methyl ether as the sole product in 45% yield. Accordingly, we protected the alcohol as the *tert*-butyldimethylsilyl ether to give one partner **15** for the upcoming Julia coupling.



Scheme 1. (a) i. O_3, MeOH, CH_2Cl_2, -78 °C; ii. Me_2S, -78-25 °C (88%); (b) $HOCH_2CH_2OH$, PPTS, PhH, Δ (96%); (c) K_2CO_3, MeOH, 20 °C (91%); (d) NCS-DMS, CH_2Cl_2, -10 °C (89%); (e) $PhSO_2Na$, DMF, 20 °C (68%); (f) 10% HCl, THF, 20 °C (72%); (g) $(ipc)_2BCH_2CH{=}CH_2$, Et_2O, -100 °C (62%, 86% ee); (h) TBDMSOTf, NEt_3, CH_2Cl_2, 20 °C (97%); (i) Sharpless AD (68%); (j) $NaIO_4$, CH_2Cl_2, 20 °C (84%); (k) $(ipc)_2BCH_2CH{=}CH_2$, Et_2O, -78 °C (60%, 80% ee); (l) i. NaH, THF, 20°C; ii. MeI, THF, 20 °C (76%); (m) Li, NH_3/THF, -78 °C (62%); (n) NCS-DMS, CH_2Cl_2, -10 °C; (o) $PhSO_2Na$, DMF, 20 °C (81%, 2 steps).

An improved route begins with *O*-benzyl geraniol (Scheme 1, Route 2). Regioselective cleavage of the 6,7-olefin was accomplished using a Sharpless asymmetric dihydroxylation[16] followed by cleavage of the resulting diol with sodium periodate, delivering **10** in 57% yield. This aldehyde was subjected to asymmetric allylboration as before to give alcohol **11** in 60% yield, which was readily methylated using NaH/MeI (76% yield). Again, the enantioselectivity of the allylation was determined by preparation of the Mosher's ester, and found to be 80% ee. The benzyl group was then removed with lithium in ammonia in 62% yield and functional group transformation gave the sulphone **16** in 81% yield over the last two steps. *This maneuver avoids the whole issue of transient protection of the alcohol. The synthesis of aldehyde* ***10****, as facilitated by the Sharpless AD process, should expand the use of geraniol as an educt in natural product synthesis.*

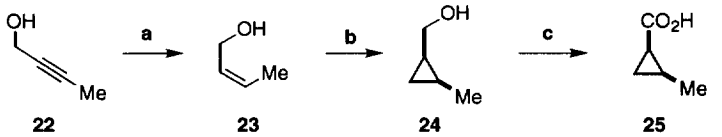
The construction of the C(1-7) segment began with Garner's aldehyde **19**,[17] prepared in large quantities from commercially available L-serine (Scheme 2). The aldehyde was reacted with the Wittig salt derived from ethyl 4-bromobutyrate[18] to give the *Z*-isomer of **20** as the major product (10:1 *Z*/*E* ratio) in 85% yield as determined by ^{1}H-NMR. The ester was then selectively reduced with diisobutylaluminum hydride at low temperature to afford the aldehyde **21** as the other partner for the Julia reaction.



Scheme 2. (a) i. Boc_2O, NaOH, dioxane; ii. CH_2N_2, Et_2O (70%); (b) DMP, PPTS, PhH, Δ (93%); (c) DIBAL-H, $PhCH_3$, -78 °C (90%); (d) $EtO_2C(CH_2)_3PPh_3Br$, NaHMDS, THF, -78 °C (83%); (e) DIBAL-H, $PhCH_3$, -78 °C (86%).

We chose serine as a progenitor of the C(1-3) portion of the target for several reasons. Mainly, we wished to have access to oxo analogs of curacin A for our proposed structure/activity work. In addition, we do admit to a prejudice for installing the sulfur atom of the thiazoline portion of the target as late as possible in the synthesis; had we foreseen the difficulty of converting the amido alcohol **30** to the natural product, we may well have chosen another course of action (see Scheme 5 and the accompanying text). For the record, White's,[5] Wipf's,[9] and Falck's[10] syntheses also used serine for this purpose, whereas the Kobayashi[7] and Iwasaki[8] groups went right in with cysteine. Incidentally, the Gerwick/White team used cystine dimethyl ester to prepare the analogous segment in their absolute configuration study of the right-hand portion of curacin A,[2a] and another useful approach to this segment was recently published.[19]

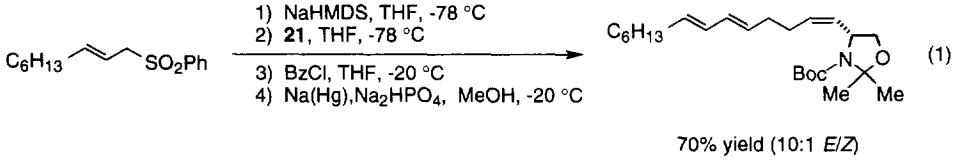
The C(18-22) cyclopropane portion was prepared using an asymmetric Simmons-Smith reaction of *Z*-2-butenol, developed by Charette, in 50% yield (Scheme 3).[20] Again, preparation of the derived Mosher's ester and evaluation of its ^{1}H NMR spectrum indicated a 96% ee for the cyclopropanation reaction. The alcohol was then sequentially oxidized, first with tetrapropylammonium perruthenate and then by sodium chlorite, to afford carboxylic acid **25**[5,9] in 78% yield.



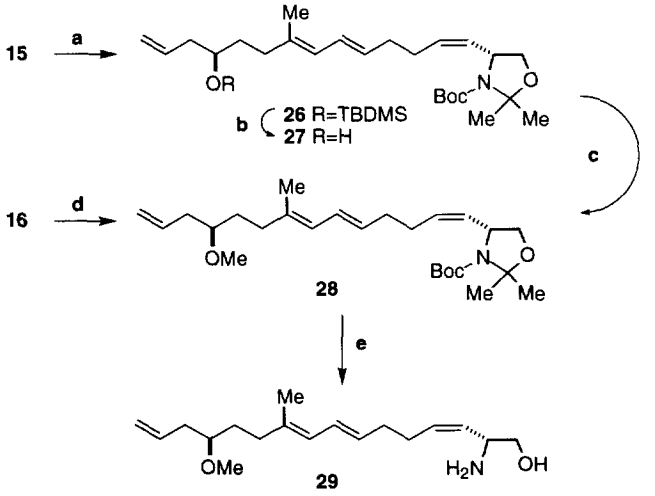
Scheme 3. (a) Zn(Cu), EtOH (60%); (b) Et_2Zn–DME (50%); (c) i. TPAP, NMO; ii. $NaClO_2$ (78%).

The Julia coupling was carried out using standard conditions (Scheme 4).[21] Deprotonation of either allylic sulphone, **15** or **16**, followed by addition of the aldehyde **21** gave intermediates that were quenched with

benzoyl chloride. The resulting crude α-benzoyl sulphones were immediately treated with 5% sodium amalgam in the presence of a buffer to give dienes **26** or **28** as ca. 3:1 inseparable mixtures of *E/Z* diastereomers in 71% and 70% yields, respectively. These ratios could not be improved with the use of samarium diiodide for the reductive elimination.[22] Should the C-17 carbon prove nonessential for biological activity, the straightforward Julia approach should be effective for analog synthesis (eq 1). A 5:1 ratio was reported[7b] for a related Julia coupling whereas two different Horner–Emmons approaches gave 8.5:1[8] or 23.5:1[10] ratios of E/Z isomers, respectively. Novel organometallic-based approaches were used by White[5] and Wipf,[9] each of whom achieved essentially complete diastereoselection for the diene segment.



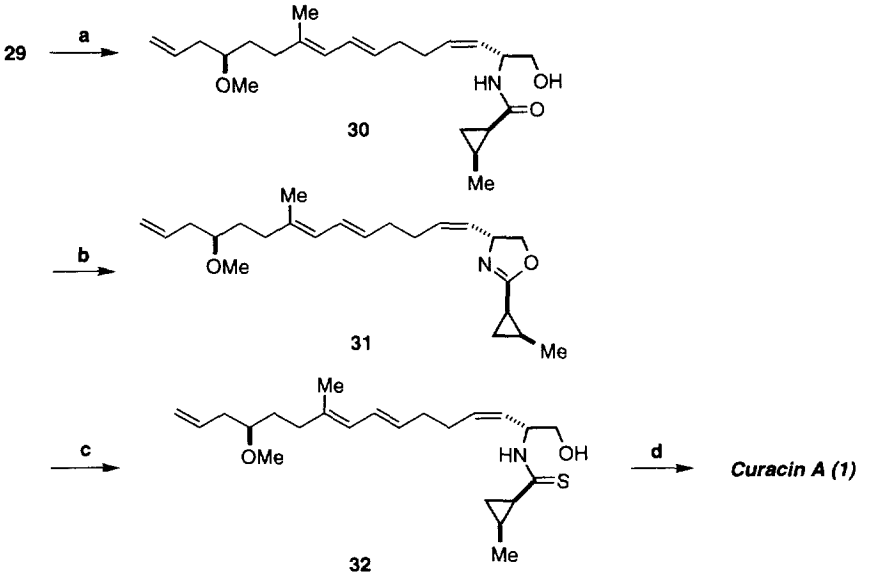
We decided to carry on the mixture of diastereomers in hopes that they could be separated at a later point in the synthesis. The C(13) *tert*-butyldimethylsilyl ether **26** was converted to the methyl ether **28** using standard chemistry, bringing the two routes to convergency not only with one another, but also with an intermediate in the White synthesis, thus constituting a formal synthesis at this point. We wished to evaluate alternative approaches to the thiazoline portion of the molecule and thus completed the synthesis in our own manner. Concomitant deprotection of the *tert*-butoxycarbonyl and aminal groups with 10% HCl gave a crude amino alcohol **29** in 84% yield that was ready for coupling with the C(18-22) segment.



Scheme 4. (a) i. NaHMDS, THF, -78 C; ii. **21**, THF, -78 °C; iii. BzCl, THF, -78-20 °C; iv. 5% Na(Hg), Na_2HPO_4, MeOH, -20 °C (71%, 3:1 *E/Z*); (b) TBAF, THF, 20 °C (71%); (c) i. NaH, THF, 20 °C; ii. MeI, THF, 20 °C (93%); (d) NaHMDS, THF, -78 °C; ii. **21**, THF, -78 °C; iii. BzCl, THF, -78-20 °C; iv. 5% Na(Hg), Na_2HPO_4, MeOH, -20 °C (70%, 3:1 *E/Z*); (e) 10% HCl, THF, 20 °C (84%).

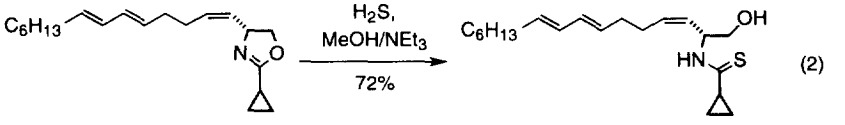
The crude amino alcohol was reacted with the cyclopropanecarboxylic acid **25** using DCC as a coupling reagent to afford amide **30** in 50% yield (Scheme 5). It was our intention at this point to convert the amide directly to the thioamide. However, treatment of the amide with Lawesson's reagent and derivatives thereof led

to decomposition of the starting material. Therefore, an alternative two-step procedure was employed.[23] Dehydrative cyclization in 55% yield with Burgess reagent followed by treatment of the resulting oxazoline with hydrogen sulfide in a methanol and triethylamine solvent system gave the desired thioamide in a low but acceptable 38% yield (along with 41% of recovered starting material). Finally, dehydrative cyclization with Burgess reagent gave curacin A in 50% yield as only one isomer after careful chromatography. The synthetic curacin A was found to be identical to an authentic sample by comparison of their ^{1}H NMR, ^{13}C NMR, and IR. The specific rotation of synthetic curacin A prepared herein ($[\alpha]_D^{20}$ +56.3 (*c* 0.40, $CHCl_3$)) matched that of an authentic sample provided by Professor Gerwick ($[\alpha]_D^{20}$ +57.9 (*c* 0.47, $CHCl_3$)). The originally reported value, obtained from a small sample of the naturally isolated material, was $[\alpha]_D^{20}$ +86.0 (*c* 0.64, $CHCl_3$) but this value has been revised using a larger sample of newly-isolated curacin A to $[\alpha]_D^{20}$ +62.0 (*c* 1.10, $CHCl_3$).[24]



Scheme 5. (a) **25**, DCC, $PhCH_3$, Δ (50%); (b) Burgess reagent, THF, 20 °C (55%); (c) H_2S, 2:1 MeOH/Et_3N, 25 °C, 48 h (38%; 64% based on recovered starting material); (d) Burgess Reagent, THF, 20 °C (50%).

The relatively low yield of the conversion of **31**→**32** (Scheme 5) may well be due to steric interference from the cyclopropyl methyl substituent as evidenced by the model reaction shown in eq 2. Since the completion of our synthesis, the sequence of compound **30** to curacin A has been optimized by Wipf to proceed in 29.5% yield.[9]



In conclusion, the enantioselective total synthesis of curacin A was achieved in a general convergent manner, affording an overall yield of about 0.8% for two different approaches of 13 and 15 steps, respectively. Current efforts are underway in our lab to adapt this for the preparation of analogs for biological evaluation.

Experimental Section

General Methods. ^1H and ^{13}C NMR were recorded on a Varian XL-300, GE QE-300 (300 and 74.5 MHz, respectively), or a Brucker AM-500 (500 and 125.7 MHz) instrument. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane with either TMS or residual solvent as an internal reference. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. Mass spectra were obtained using a Varian MAT CH5 instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at ambient temperature; concentrations are reported in g/100 mL. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed in-house. Column chromatography was carried out with 230-400 mesh silica gel. Except where noted, all starting materials were purchased from Aldrich or Sigma Chemical Co. and used as received.

1-Benzyloxy-3,7-dimethyl-2,6-octadiene (3). To a suspension of sodium hydride (285 mg, 7.13 mmol, 60% mineral oil dispersion) in THF (30 mL) at 20 °C was added geraniol (1.12 mL, 6.48 mmol). The reaction mixture was stirred for 1 h and then benzyl bromide (0.85 mL, 7.13 mmol) was added. The reaction mixture was stirred for 16 h at 20 °C and then quenched with saturated NH_4Cl (50 mL). The mixture was extracted with ether (50 mL), washed with saturated $NaHCO_3$ (50 mL), saturated NaCl (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (hexanes/CH_2Cl_2 2:1) to give **3** (1.42 g, 90% yield) as a colorless oil: R_f 0.50 (hexane/EtOAc 10:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.42 (t, J = 6.7 Hz, 1H), 5.12 (t, J = 5.4 Hz, 1H), 4.52 (s, 2H), 4.04 (d, J = 6.8 Hz, 2H), 2.12 (m, 4H), 1.70 (s, 3H), 1.66 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 138.6, 131.7, 128.4, 127.9, 127.5, 124.0, 120.9, 72.0, 66.6, 39.6, 26.4, 25.7, 17.7, 16.5; IR (neat) cm^{-1} 2920 (s) 2840 (s) 1435 (s) 1060 (s) 735 (s) 699 (s).

(4*E*)-4-Methyl-6-phenylsulfonyl-4-hexenal (8). To a solution of acetal **7**[12] (19.3 g, 65.0 mmol) in THF (100 mL) was added 10% HCl (75 mL). The reaction mixture was heated to 40 °C for 24 h and then cooled to 25 °C. The reaction mixture was quenched with saturated $NaHCO_3$ (100 mL) and extracted with ether (150 mL). The organic layer was washed with saturated $NaHCO_3$ (200 mL), saturated NaCl (200 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was resubjected to the reaction conditions an additional 24 h and worked up again. The crude material was purified by chromatography (hexanes/EtOAc 3:1) to give **8** (11.8 g, 72% yield) as a colorless oil: R_f 0.35 (hexanes/EtOAc 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (t, J = 1.6 Hz, 1H), 7.81 (d, J = 7.8 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 5.18 (t, J = 8.0 Hz, 1H), 3.77 (d, J = 7.9 Hz, 2H), 2.46 (t, J = 7.5 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 144.4, 138.5, 133.7, 129.1, 128.4, 111.3, 55.9, 41.5, 31.5, 16.3.

(4*R*,7*E*)-7-Methyl-9-phenylsulfonyl-1,7-nonadiene-4-ol (9). To a solution of (-)-*B*-methoxydiisopinocampheylborane (10.3 g, 32.6 mmol) in ether (150 mL) at 0 °C was added allylmagnesium bromide (32.6 mL, 32.6 mmol, 1.0 M in ether). The reaction mixture was stirred at 25 °C for 1 h. The solvent was removed under vacuum and the residue suspended in pentane. The slurry was filtered through Celite under a stream of argon. The filtrate was concentrated under vacuum and the salt-free allylborane was dissolved in ether (150 mL) and cooled to -100 °C. Aldehyde **8** (5.0 g, 19.8 mmol) in ether (50 mL) was added slowly dropwise and the reaction mixture was stirred at -100 °C for 1 h. The reaction mixture was quenched with methanol (2 mL) and warmed to 25 °C. Then 3 N NaOH (12 mL) and 30% hydrogen peroxide (24 mL) were added and the mixture was heated to reflux for 1 h. The mixture was extracted with ether (150 mL) and the organic layer dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by chromatography (hexanes/EtOAc 1:1) to give homoallylic **9** (3.97 g, 62% yield) as a colorless oil: R_f 0.30 (hexanes/EtOAc 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.9 Hz, 2H), 5.80 (m, 1H), 5.22 (t, J = 6.8 Hz, 1H), 5.16 (s, 1H), 5.11 (d, J = 4.4 Hz, 1H), 3.79 (d, J = 8.0 Hz, 2H), 3.57 (m, 1H), 2.35-2.00 (m, 4H), 1.72 (br s, 1H), 1.50 (m, 2H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 138.6, 134.5, 133.6, 129.0, 128.5, 118.3, 110.5, 70.0, 56.1, 42.0, 35.8, 34.5, 16.2; IR (neat) 3505 (b) 2940 (m) 1635 (w) 1305 (s) 1145 (s) 915 (s) 735 (s) cm^{-1}; MS (FAB positive) m/z 295 $[MH]^+$ (45) 277 (10) 253 (8) 235 (7) 209 (5) 143 (23) 135 (100); HRMS calc'd 295.1368 found 295.1371; Anal. Calc'd for $C_{16}H_{22}O_3S$: C, 65.28; H, 7.53, found C, 65.19; H, 7.71; $[\alpha]_D^{20}$ +5.49 (*c* 1.62, $CHCl_3$).

Mosher's ester analysis of **9**[15] showed a ratio of 93:7 by integration of the following pairs of signals: δ 5.72 vs. 5.60, 3.55 vs. 3.51, and 2.00 vs. 1.84.

(2*E*,6*R*)-1-Benzyloxy-3,7-dimethyl-2-octene-6,7-diol. To a solution of *O*-benzyl geraniol **3** (1.00 g, 4.09 mmol) in *tert*-butyl alcohol (20 mL) and water (20 mL) was added potassium ferricyanide (4.04 g, 12.3 mmol), potassium carbonate (1.70 g, 12.3 mmol), methane sulfonamide (389 mg, 4.09 mmol), and $(DHQD)_2PHAL$ (159 mg, 0.20 mmol). The reaction mixture was cooled to 0 °C and potassium osmate(IV)

dihydrate (15 mg, 0.04 mmol) was added. The reaction was stirred for 24 h at 0 °C. The reaction mixture was quenched with solid Na_2SO_3 (4.0 g) and stirred for 30 min at 0 °C. The mixture was extracted with dichloromethane (3x50 mL). The organic layer was washed with 3 N NaOH (100 mL), saturated NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by chromatography (EtOAc) to give the title compound (785 mg, 68% yield) as a colorless oil: R_f 0.50 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.45 (t, J = 6.7 Hz, 1H), 4.50 (s, 2H), 4.02 (d, J = 6.8 Hz, 2H), 3.32 (d, J = 10.2 Hz, 1H), 2.30 (m, 1H), 2.10 (m, 1H), 1.66 (s, 3H), 1.58 (m, 1H), 1.45 (m, 1H), 1.18 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.4, 128.4, 127.8, 127.6, 121.2, 78.1, 73.0, 72.2, 66.6, 36.6, 29.5, 26.5, 23.2, 16.5; IR (neat) cm^{-1} 3410 (br s) 2980 (s) 2920 (s) 2860 (s) 1450 (m) 1380 (s) 1070 (s) 735 (s) 699 (s); MS (FAB positive) *m/z* 277 [M-H]$^+$ (2) 171 (17) 153 (100) 143(20); HRMS calc'd 277.1804 found 277.1806; Anal. Calc'd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41, found C, 72.98; H, 9.41.

(4*E*)-6-Benzyloxy-4-methyl-4-hexenal (10). To a solution of the above diol (940 mg, 3.38 mmol) in dichloromethane (16 mL) at 20 °C was added saturated $NaHCO_3$ (1 mL), and sodium periodate (2.17 g, 10.1 mmol). The reaction mixture was stirred for 48 h at 20 °C. The reaction was diluted with water (50 mL) and extracted with dichloromethane (2x50 mL). The organic was dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (hexanes/EtOAc 3:1) to give **10** (620 mg, 84% yield) as a colorless oil: R_f 0.50 (hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, J = 1.7 Hz, 1H), 7.35 (m, 5H), 5.42 (t, J = 6.6 Hz, 1H), 4.50 (s, 2H), 4.02 (d, J = 6.9 Hz, 2H), 2.58 (t, J = 7.7 Hz, 2H), 2.37 (t, J = 7.3 Hz, 2H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 138.4, 138.2, 128.4, 127.8, 127.6, 121.9, 72.2, 66.4, 64.9, 41.8, 31.5, 16.7; IR (neat) cm^{-1} 2920 (s) 2860 (s) 1715 (s) 1450 (m) 1070 (s) 735 (s) 699 (s); MS (FAB positive) *m/z* 217 [M-H]$^+$ (23) 181 (13) 171 (10) 155 (23) 111 (100); HRMS calc'd 217.1228 found 217.1239.

(4*R*,7*E*)-9-Benzyloxy-7-methyl-1,7-nonadiene-4-ol (11). To a solution of (-)-*B*-methoxydiisopinocampheylborane (4.30 g, 13.6 mmol) in ether (100 mL) at 0 °C was added allylmagnesium chloride (13.6 mL, 13.6 mmol, 1.0 M in Et_2O) slowly dropwise. The reaction mixture was stirred for 1 h at 0 °C and then cooled to -78 °C. The aldehyde **10** (2.48 g, 11.3 mmol) in ether (50 mL) was added dropwise and the reaction mixture was stirred for 1 h at -78 °C. The reaction mixture was warmed to 0 °C and stirred for an additional hour. The reaction was quenched with methanol (1.4 mL) and then 3 N NaOH (9.0 mL) was added followed by 30% hydrogen peroxide (18 mL). The reaction was heated to reflux for 1 h and then cooled. The mixture was extracted with ether and the organic layer dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (CH_2Cl_2 /MeOH 20:1) to give **11** (1.71 g, 60% yield) as a colorless oil: R_f 0.30 (CH_2Cl_2 /MeOH 20:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.81 (m, 1H), 5.45 (t, J = 6.8 Hz, 1H), 5.10 (m, 2H), 4.51 (s, 2H), 4.03 (d, J = 6.8 Hz, 2H), 3.64 (quintet, J = 4.5 Hz, 1H), 2.40-2.20 (m, 4H), 1.79 (br s, 1H), 1.66 (s, 3H), 1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 138.5, 134.7, 128.4, 127.8, 127.6, 121.1, 118.1, 81.0, 72.1, 70.4, 66.6, 42.0, 35.7, 34.7, 16.5; IR (neat) cm^{-1} 3400 (br s) 2960 (s) 2840 (s) 1640 (w) 1445 (m) 1070 (s) 915 (m) 735 (m) 699 (m); MS (FAB positive) *m/z* 259 [MH]$^+$ (20) 153 (100) 135 (52) 111(50); HRMS calc'd 259.1698 found 259.1721; $[\alpha]_D^{20}$ +3.24 (*c* 0.62, $CHCl_3$).

(4*R*,7*E*)-9-Benzyloxy-4-methoxy-7-methyl-1,7-nonadiene (12). To a solution of **11** (311 mg, 1.20 mmol) in THF (10 mL) was added sodium hydride (72 mg, 1.81 mmol, 60% mineral oil dispersion). The reaction mixture was heated to reflux and stirred for 15 min and then methyl iodide (150 mL, 2.41 mmol) was added. The reaction mixture was cooled to 20 °C and stirred for 16 h. The reaction was quenched with saturated NH_4Cl (50 mL) and extracted with ether (50 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL), saturated NaCl (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (hexanes/EtOAc 5:1) to give **12** (250 mg, 76% yield) as a colorless oil: R_f 0.50 (hexanes/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.82 (m, 1H), 5.43 (t, J = 6.8 Hz, 1H), 5.10 (m, 2H0, 4.52 (s, 2H), 4.04 (d, J = 6.8 Hz, 2H), 3.35 (s, 3H), 3.22 (quintet, J = 5.8 Hz, 1H), 2.30 (m, 2H), 2.14 (m, 2H), 1.66 (s, 3H), 1.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.6, 134.7, 128.4, 127.8, 127.5, 120.9, 117.0, 79.9, 72.0, 66.6, 56.6, 37.7, 35.2, 31.5, 16.6; IR (neat) cm^{-1} 2960 (s) 2840 (s) 1640 (w) 1445 (m) 1090 (s) 915 (m) 735 (m) 699 (m); MS (FAB positive) *m/z* 273 [M-H]$^+$ (20) 167 (90) 135 (100); HRMS calc'd 273.1833 found 273.1854; $[\alpha]_D^{20}$ +3.48 (*c* 0.55, $CHCl_3$).

(4*R*,7*E*)-4-Methoxy-7-methyl-1,7-nonadiene-9-ol (13). To a solution of lithium metal (20 mg, 2.83 mmol) in liquid ammonia (50 mL) at -78 °C was added **12** (705 mg, 2.57 mmol) in THF (5 mL). The reaction mixture was stirred for 15 min at -78 °C and then warmed to 20 °C. The reaction mixture was quenched with solid NH_4Cl (10 g) and the ammonia was allowed to evaporate by permitting the reaction to warm to room temperature. The residue was extracted with CH_2Cl_2 (50 mL) and the organic layer washed with water (50 mL),

dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (hexanes/EtOAc 1:1) to give **13** (292 mg, 62% yield) as a colorless oil: R_f 0.50 (hexanes/EtOAc 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.37 (t, J = 6.7 Hz, 1H), 5.05 (m, 2H), 4.09 (d, J = 6.7 Hz, 2H), 3.30 (s, 3H), 3.17 (quintet, J = 5.8 Hz, 1H), 2.22 (m, 2H), 2.02 (m, 2H), 1.62 (s, 3H), 1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 134.6, 123.6, 117.0, 79.9, 59.1, 56.4, 37.6, 35.0, 31.4, 16.2; IR (neat) cm^{-1} 3370 (br s) 2920 (s) 1640 (w) 1435 (m) 1080 (s); MS (FAB positive) *m/z* 185 $[MH]^+$ (60) 167 (100) 135 (85); HRMS calc'd 183.1380 found 183.1385; $[\alpha]_D^{20}$ +7.06 (*c* 0.54, $CHCl_3$).

(4*R*,7*E*)-9-Chloro-4-methoxy-7-methyl-1,7-nonadiene (14). To a suspension of *N*-chlorosuccinimide (148 mg, 1.11 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added dimethyl sulfide (108 mL, 1.48 mmol). The reaction mixture was stirred for 15 min and then cooled to -20 °C. Alcohol **13** (136 mg, 0.74 mmol) in CH_2Cl_2 (2 mL) was added, the reaction warmed to 0 °C, stirred for 2.5 h, and then quenched with water (10 mL) and extracted with CH_2Cl_2 (15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude material was used immediately without purification or characterization.

(4*R*,7*E*)-4-*tert*-Butyldimethylsilyloxy-7-methyl-9-phenylsulfonyl-1,7-nonadiene (15). To a solution of alcohol **9** (7.93 g, 26.9 mmol) in dichloromethane (50 mL) at 0 °C was added triethylamine (4.13 mL, 29.6 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (6.80 mL, 29.6 mmol). The reaction mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was quenched with saturated $NaHCO_3$ (50 mL) and extracted with dichloromethane (50 mL). The organic layer was washed with saturated NaCl (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by chromatography (hexanes/EtOAc 3:1) to give **15** (10.7 g, 97% yield) as a colorless oil: R_f 0.50 (hexanes/EtOAc 3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 5.77 (m, 1H), 5.17 (t, J = 8.0, 1H), 5.05 (br s, 1H), 5.00 (br s, 1H), 3.77 (d, J = 7.9 Hz, 2H), 3.64 (quintet, J = 5.1 Hz, 1H), 2.18 (t, J = 5.9 Hz, 2H), 2.00 (m, 2H), 1.40 (m, 2H), 1.26 (s, 3H), 0.87 (m, 9H), 0.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 138.5, 134.9, 133.5, 128.9, 128.5, 116.9, 110.0, 71.4, 56.0, 41.7, 35.4, 34.7, 25.8, 18.0, 16.2, -4.4, -4.6; IR (neat) 2980 (s) 2960 (s) 2850 (s) 1640 (w) 1310 (s) 1145 (s) 1080 (s) 835 (s) 770 (s) cm^{-1}; MS (FAB positive) *m/z* 409 $[MH]^+$ (24) 351 (20) 257 (40) 217 (30) 199 (50) 135 (100) 93 (100); HRMS calc'd 409.2233 found 409.2234; Anal. Calc'd for $C_{22}H_{36}O_3SSi$: C, 64.66; H, 8.88, found C, 64.48; H, 8.79; $[\alpha]_D^{20}$ +10.2 (*c* 0.925, $CHCl_3$).

(4*R*,7*E*)-4-Methoxy-7-methyl-9-phenylsulfonyl-1,7-nonadiene (16). To a solution of **14** (0.74 mmol) in DMF (10 mL) at 20 °C was added sodium benzenesulfinate (133 mg, 0.81 mmol). The reaction mixture was stirred for 24 h and then quenched with water (25 mL). The mixture was extracted with ether (25 mL) and the organic layer washed with saturated NaCl (25 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (hexanes/EtOAc 1:1) to give **16** (184 mg, 81% yield over two steps) as a colorless oil: R_f 0.70 (hexanes/EtOAc 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 5.75 (m, 1H), 4.20 (t, J = 7.0 Hz, 1H), 5.05 (m, 2H), 3.79 (d, J = 7.0 Hz, 2H), 3.31 (s, 3H), 3.14 (quintet, J = 5.9 Hz, 1H), 2.22 (m, 2H), 2.03 (m, 2H), 1.47 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 138.7, 134.5, 133.6, 129.0, 128.5, 117.2, 110.4, 79.6, 56.6, 56.0, 37.5, 35.3, 31.4, 16.2; IR (neat) cm^{-1} 3040 (w) 2980 (s) 2910 (s) 1640 (w) 1435 (m) 1305 (s) 1145 (s) 1080 (s) 735 (m); MS (FAB positive) *m/z* 309 $[MH]^+$ (26) 243 (20) 143 (28) 135 (100); HRMS calc'd 309.1541 found 309.1524; $[\alpha]_D^{20}$ +6.55 (*c* 0.58, $CHCl_3$).

Ester 20. To a suspension of ethyl 1-(triphenylphosphonium bromide)-4-butyrate[18] (3.34 g, 7.30 mmol) in THF (40 mL) at -78 °C was added sodium bis(trimethylsilyl)amide (8.76 mL, 8.76 mmol, 1.0 M in THF). The bright orange suspension was stirred for 15 min at -78 °C and then aldehyde **19**[17] (1.22 g, 5.33 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm to 20 °C and stirred overnight. The reaction mixture was quenched with 10% $KHSO_4$ (10 mL) and extracted with ether (100 mL). The organic layer was washed with 10% $KHSO_4$ (100 mL), saturated NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by chromatography (hexanes/EtOAc 3:1) to give olefin (1.45 g, 83% yield, 10:1 *Z/E*) as a colorless oil: R_f 0.47 (hexanes/EtOAc 3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (m, 2H), 4.62 (m, 1H), 4.04 (m, 3H), 3.60 (dd, J = 8.4, 2.3 Hz, 1H), 2.52-2.20 (m, 4H), 1.52 (s, 3H), 1.47 (s, 3H), 1.41 (s, 9 H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 69.3, 60.7, 54.8, 34.5, 28.9, 23.3, 14.6; IR (neat) 2960 (s) 2920 (m) 2850 (m) 1725 (s) 1685 (s) 1370 (s) 1245 (s) 1160 (s) 1080 (s) 1040 (s) 840 (m) cm^{-1}; MS (FAB positive) *m/z* 328 $[MH]^+$ (60) 272 (25) 228 (78) 212 (65) 196 (18) 170 (20), 57 (100); HRMS calc'd 328.2124 found 328.2112; Anal. Calc'd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28, found C, 62.26; H, 8.90; N, 4.18; $[\alpha]_D^{20}$ +51.0 (*c* 1.51, $CHCl_3$).

Aldehyde 21. To a solution of **20** (1.45g, 4.43 mmol) in toluene (50 mL) at -78 °C was added diisobutylaluminum hydride (3.54 mL, 5.31 mmol, 1.5 M in toluene). The reaction mixture was stirred for 1 h at -78 °C and then quenched with methanol (4 mL). The mixture was poured onto 10% HCl (100 mL) at 0 °C and stirred for 15 min. The mixture was extracted with EtOAc (100 mL). The organic layer was dried (Na_2SO_4), filtered through silica gel, and concentrated. The crude material was purified by chromatography (hexanes/EtOAc 3:1) to give **21** (1.08 g, 86% yield) as a colorless oil: *Rf* 0.33 (hexanes/EtOAc 3:1); ^{1}H NMR(300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 5.37 (m, 2H), 4.60 (b, 1H), 4.00 (m, 1H), 3.53 (m, 1H), 2.48-2.18 (m, 4H), 1.50 (s, 3H), 1.43 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 131.8, 130.4, 129.4, 127.9, 94.4, 94.0, 79.9, 79.7, 68.8, 68.4, 54.2, 43.5, 28.4, 27.4, 26.5, 24.9, 23.9, 20.0; IR (neat) 2960 (s) 2920 (m) 2850 (m) 1715 (s) 1680 (s) 1380 (s) 1240 (s) 1165 (s) 1080 (s) 840 (s) cm^{-1}; MS (FAB positive) *m/z* 284 $[MH]^+$ (18) 228 (50) 184 (30) 168 (25) 136 (25), 57 (100); HRMS calc'd 284.1862 found 284.1871.

Julia Coupling of Sulphone 15. Synthesis of 26. To a solution of sulphone **15** (5.17 g, 12.6 mmol) in THF (100 mL) at -78 °C was added sodium bistrimethylsilylamide (13.9 mL, 13.9 mmol, 1.0 M in THF). The orange solution was stirred for 25 min and aldehyde **21** (3.59 g, 12.6 mmol) in THF (50 mL) was added. The reaction mixture was stirred for 15 min at -78 °C and then benzoyl chloride (2.20 mL, 19.0 mmol) was added. The reaction mixture was allowed to warm to 25 °C and stirred overnight. The reaction was quenched with saturated $NaHCO_3$ (250 mL) and extracted with ether (150 mL). The organic layer was washed with saturated $NaHCO_3$ (250 mL), saturated NaCl (250 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was used immediately as a 1:1 mixture of diastereomers. To a solution of sulphone (12.6 mmol) in methanol (40 mL) at -20 °C was added Na_2HPO_4 (10.8 g, 75.9 mmol) and sodium amalgam (19.4 g, 50.6 mmol, 5% w/w). The reaction mixture was stirred vigorously for 2 h at -20 °C. The reaction mixture was decanted and the flask rinsed with ether (100 mL). The organic layer was washed with H_2O (2x100 mL), dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by chromatography (hexanes/EtOAc 10:1) to give **26** (4.78 g, 71% yield overall) as a ~3:1 mixture of *E/Z* diastereomers: *Rf* 0.40 (hexanes/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 15.0, 10.8 Hz, 1H), 5.80 (m, 2H), 5.50, (m, 3H), 5.04 (d, *J* = 9.6 Hz, 1H), 5.00 (s, 1H), 4.60 (m, 1H), 4.03 (dd, *J* = 8.7, 6.3 Hz, 1H), 3.64 (t, *J* = 5.9 Hz, 1H), 3.62 (dd, *J* = 8.7, 3.2 Hz, 1H), 2.30-1.90 (m, 10H), 1.71 (s, 3H), 1.58 (s, 3H), 1.51 (s, 3H), 1.44 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 138.6, 135.1, 127.3, 124.3, 116.7, 94.0, 79.9, 71.7, 69.0, 54.5, 41.8, 35.5, 35.0, 32.9, 28.5, 27.4, 25.9, 18.0, 16.6, -4.4, -4.6; IR (neat) 2960 (s), 2930 (s), 1690 (s), 1645 (w), 1630 (w), 1370 (s), 1240 (s), 1170 (s), 1080 (s), 835 (s), 735 (s), cm^{-1}; MS (FAB positive) *m/z* 534$[MH]^+$ (1) 533 (2) 478 (5) 434 (24) 418 (20) 185 (80) 144 (90) 119 (83) 105 (100); HRMS calc'd 534.3978 found 534.3964; Anal. Calc'd for $C_{31}H_{55}NO_4Si$: C, 69.74; H, 10.38; N, 2.62, found C, 69.49; H, 9.99; N, 2.38; $[\alpha]_D^{20}$ +49.0 (*c* 1.10, $CHCl_3$).

Alcohol 27. To a solution of silyl ether **26** (1.12 g, 2.10 mmol) in THF (50 mL) at 20 °C was added tetrabutylammonium fluoride (2.30 mL, 2.30 mmol, 1.0 M in THF). The reaction mixture was stirred for 24 h at 20 °C. The reaction was quenched with saturated $NaHCO_3$ (50 mL) and extracted with ether (100 mL), washed with saturated NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (hexane/EtOAc 3:1) to give **27** (634 mg, 71% yield) as a colorless oil: *Rf* 0.35 (hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 15.0, 10.7 Hz, 1H), 5.80 (m, 2H), 5.45, (m, 3H), 5.14 (d, *J* = 3.0 Hz, 2H), 5.09 (s, 1H), 4.60, (m, 1H), 4.02 (dd, *J* = 8.6, 6.1 Hz, 1H), 3.63, (dd, *J* = 8.6, 3.4 Hz, 1H), 2.40-2.00 (m, 8H), 1.73 (s, 3H), 1.58 (m, 5H), 1.50 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 134.8, 131.2, 130.9, 130.7, 129.6, 127.3, 124.8, 118.1, 70.3, 69.0, 54.5, 42.0, 36.0, 34.8, 32.9, 28.5, 27.5, 16.5; IR (neat) 3400 (br s) 2960 (s) 2910 (s) 2840 (s) 1680 (s) 1370 (s) 1240 (s) 1170 (s) 1080 (s) cm^{-1}; MS (FAB positive) *m/z* 420 $[MH]^+$ (20) 364 (10) 320 (100) 304 (25); HRMS calc'd 420.3114 found 420.3139; Anal. Calc'd for $C_{25}H_{41}NO_4$: C, 71.56; H, 9.85; N, 3.34, found C, 71.15; H, 10.00; N, 3.10; $[\alpha]_D^{20}$ +63.4 (*c* 0.93, $CHCl_3$).

Oxazolidine 28. Method A. To a suspension of sodium hydride (295 mg, 7.37 mmol, 60% mineral oil dispersion) in THF (90 mL) at 20 °C was added alcohol **27** (2.06 g, 4.92 mmol) in THF (10 mL). The reaction mixture was allowed to reflux for 1 h and then methyl iodide (918 µL, 14.7 mmol) was added. The reaction mixture was cooled and stirred for 16 h at 20 °C. The reaction mixture was quenched with saturated NH_4Cl (100 mL) and extracted with ether (100 mL). The organic layer was washed with saturated NaCl (200 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (hexane/EtOAc 5:1) to give **28** (1.99 g, 93% yield) as a colorless oil.

Method B: To a solution of sulphone **16** (155 mg, 0.50 mmol) in THF (7 mL) at -78 °C was added sodium bistrimethylsilylamide (0.55 mL, 0.55 mmol, 1.0 M in THF). The reaction mixture was stirred for 15

min and then aldehyde **21** (142 mg, 0.50 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 15 min at -78 °C and then benzoyl chloride (88 mL, 0.75 mmol) was added. The reaction was warmed to 20 °C and stirred for 16 h. The reaction mixture was quenched with saturated $NaHCO_3$ (10 mL) and extracted with ether (25 mL). The organic layer was washed with saturated $NaHCO_3$ (25 mL), saturated NH_4Cl (25 mL), saturated NaCl (25 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was dissolved in MeOH (20 mL) and cooled to -20 °C. To this solution was added Na_2HPO_4 (428 mg, 3.02 mmol) and 5% sodium amalgam (925 mg, 2.00 mmol). The reaction mixture was stirred for 2 h at -20 °C and the solvent was decanted and the flask rinsed with ether (25 mL). The organic layer was washed with H_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (hexanes/EtOAc 5:1) to give **28** (153 mg, 70% yield) as a 3:1 mixture of *E/Z* diastereomers: R_f 0.62 (hexane/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 14.8, 10.8 Hz, 1H), 5.79 (m, 2H), 5.50 (m, 3H), 5.07 (dd, *J* = 10.9, 2.0 Hz, 1H), 5.03 (d, *J* = 2.0 Hz, 1H), 4.60 (m, 1H), 4.02 (dd, *J* = 8.7, 6.2 Hz, 1H), 3.62 (dd, *J* = 8.6, 3.3 Hz, 1H), 3.33 (s, 3H), 3.18 (quintet, *J* = 5.9 Hz, 1H), 2.30-2.00 (m, 8H), 1.72, (s, 3H), 1.58 (m, 5H), 1.50 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 134.7, 131.0, 130.9, 130.8, 129.7, 127.4, 124.6, 117.0, 80.9, 79.8, 69.0, 56.6, 54.5, 37.6, 35.9, 35.4, 32.9, 31.7, 28.5, 27.5, 16.6; IR (neat) 2980 (s) 2920 (s) 2850 (m) 1685 (s) 1370 (s) 1080 (s) cm^{-1}; MS (FAB positive) *m/z* 434 [MH]$^+$ (18) 378 (42) 334 (100) 318 (40) 154 (50), 144 (75); HRMS calc'd 434.3270 found 434.3292; Anal. Calc'd for $C_{26}H_{43}NO_4$: C, 72.02; H, 9.99; N, 3.23, found C, 71.94; H, 10.18; N, 3.00; $[\alpha]_D^{20}$ +59.2 (*c* 0.75, $CHCl_3$).

Amino Alcohol 29. A solution of oxazolidine **28** (113 mg, 0.26 mmol) in methanol (12 mL) and 10% HCl (6 mL) was heated to 45 °C for 8 h. The reaction mixture was diluted with dichloromethane (25 mL), and washed with saturated $NaHCO_3$ (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The amino alcohol (64 mg, 84% yield) was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 14.6, 10.7 Hz, 1H), 5.80 (m, 2H), 5.51 (m, 2H), 5.27 (m, 1H), 5.07 (m, 2H), 3.34 (m, 2H), 3.33 (m, 4H), 3.19 (m, 1H), 2.30-2.20 (m, 8H), 1.73 (s, 3H), 1.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 134.7, 131.6, 130.9, 127.5, 124.6, 117.0, 79.9, 66.3, 56.6, 50.2, 37.7, 35.4, 32.9, 31.6, 27.8, 16.6; IR (neat) 3350 (br s) 2960 (s) cm^{-1}. MS (FAB positive) *m/z* 294[MH]$^+$ (28) 154 (30) 136 (30) 119 (35) 85 (75) 57 (100); HRMS calc'd 294.2433 found 294.2429.

Amide 30. A solution of amino alcohol **29** (78 mg, 0.27 mmol), acid **25**[5] (40 mg, 0.40 mmol), and DCC (82 mg, 0.40 mmol) in toluene (1.5 mL) was stirred at 20 °C for 18 h and then concentrated. The residue was taken up in EtOAc (25 mL) and filtered through Celite. The organic layer was washed with saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by chromatography (hexane/EtOAc 1:1) to give **30** (50 mg, 50% yield) as a white solid. R_f 0.20 (hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 14.7, 10.8 Hz, 1H), 6.10 (m, 1H), 5.80 (m, 2H), 5.59 (m, 2H), 5.35 (t, *J* = 9.4 Hz, 1H), 5.07 (m, 2H), 4.74 (m, 1H), 3.63 (m, 2H), 3.34 (s, 3H), 3.21 (m, 1H), 2.30-2.00 (m, 8H), 1.73 (s, 3H), 1.59 (m, 2H), 1.43 (m, 1H), 1.25 (m, 1H), 1.16 (s, 3H), 0.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 136.7, 134.7, 133.9, 130.9, 127.5, 126.3, 124.6, 117.0, 79.9, 66.7, 56.5, 50.2, 37.6, 35.4, 32.6, 31.6, 27.9, 20.6, 16.6, 15.0, 12.5, 12.0; IR (neat) 3300 (br s) 2960 (s) 1638 (s) 1540 (s) 1435 (s) 1090 (s) cm^{-1}; MS (FAB positive) *m/z* 376 [MH]$^+$ (23) 344 (18) 225 (20) 154 (20) 83 (100); HRMS calc'd 376.2852 found 376.2858.

Oxazoline 31. To a solution of amide **30** (99 mg, 0.26 mmol) in THF (6 mL) at 25 °C was added Burgess reagent (69 mg, 0.29 mmol). The reaction mixture was stirred for 24 h and concentrated. The crude residue was purified by chromatography (hexane/EtOAc 1:1) to give **31** (52 mg, 55% yield) and unreacted starting material (34 mg, 34 % recovery). R_f 0.55 (hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, CDCl3) δ 6.22 (dd, *J* = 14.9, 10.7 Hz, 1H), 5.79 (m, 2H), 5.53 (m, 2H), 5.34 (t, *J* = 9.3 Hz, 1H), 5.06 (m, 2H), 4.84 (q, *J* = 9.2 Hz, 1H), 4.34 (dd, *J* = 9.5, 8.2 Hz, 1H), 3.72 (t, *J* = 8.7 Hz, 1H), 3.32 (s, 3H), 3.17 (quintet, *J* = 5.9 Hz, 1H), 2.40-2.00 (m, 8H), 1.70 (s, 3H), 1.65-1.45 (m, 3H), 1.18 (m, 1H), 1.11 (s, 3H), 0.98 (m, 1 H), 0.82 (m, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 168.0, 136.7, 134.7, 131.7, 131.0, 130.8, 127.3, 124.6, 116.9, 79.9, 72.5, 62.8, 56.5, 37.6, 35.4, 32.8, 31.6, 27.8, 16.5, 14.2, 14.0, 12.7; IR (neat) 2920 (s) 1725 (m) 1650 (s) 1435 (m) 1170 (s) 1090 (s) cm^{-1}; MS (FAB positive) *m/z* 358 [MH]$^+$ (70) 278 (25) 165 (68) 117 (83) 105 (100); HRMS calc'd 358.2746 found 358.2758.

Thioamide 32. A solution of oxazolidine (41 mg, 0.11 mmol) in methanol (1.2 mL) and triethylamine (0.8 mL) at 25 °C was saturated with hydrogen sulfide for 10 min. The reaction mixture was stirred for 12 h and then concentrated. The crude residue was purified by chromatography (hexane/EtOAc 1:1) to give **32** (17 mg, 38% yield) as a pale yellow oil plus recovery of starting material (17 mg, 41% recovery). R_f 0.38 (hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 6.23 (dd, 1H), 5.80-5.30 (m, 5 H), 5.09

(m, 2H), 3.78 (m, 2H), 3.38 (s, 3H), 3.35 (m, 1H), 3.20 (m, 1H), 2.40-2.00 (m, 8H), 1.73 (s, 3H), 1.60 (m, 2H), 1.25 (m, 2H), 1.18 (s, 3H), 0.82 (m, 2H).

Curacin A (1). To a solution of **32** (8.5 mg, 0.022 mmol) in THF (0.5 mL) at 25 °C was added Burgess reagent (15.5 mg, 0.065 mmol). The reaction mixture was stirred for 24 h and then concentrated. The crude residue was purified by chromatography (hexane/EtOAc 2:1) to give curacin A (4.0 mg, 50% yield) as a colorless oil. The ^{1}H NMR, ^{13}C NMR, and IR spectra matched an authentic sample graciously provided by Dr. William H. Gerwick. The optical rotation was found to match the authentic sample as well [synthetic material, $[\alpha]_D^{20}$ +56.3 (*c* 0.40, $CHCl_3$); authentic sample, $[\alpha]_D^{20}$ +57.9 (*c* 0.47, $CHCl_3$)].

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