Total Synthesis of (–)-Grahamimycin A_1[1]

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A total synthesis of the novel antibiotic (–)-grahamimycin A_1 (1) is described. The macrocycle 1 was prepared from the convergence of 5(*R*)-hydroxy-2(*E*)-hexenoate 2 and (*R*)-7-octynoic acid 3, both of which were readily attainable from (*R*)-methyloxirane. The final steps of the sequence center upon a procedure for oxidizing an alkyne to an α-diketone in the presence of a conjugated carbonyl system.

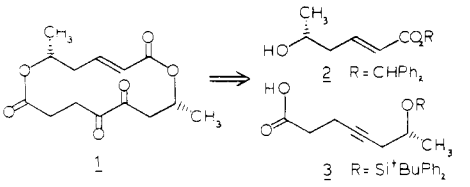
(–)-Grahamimycin A_1 (1) is a macrolide antibiotic recently isolated from the fungus *Cytospora*.[2] Bioassay studies of this highly novel antibiotic have shown antibacterial activity against a variety of pathogenic microorganisms. At the onset of the synthesis of 1, preliminary chemical degradation and X-ray crystallographic studies[3] of the similarly structured family of grahamimycins (A and B)[4] indicated that the absolute configuration was most probably *R,R*. This stereochemistry has recently been confirmed by the synthesis of (*S,S*)-(+)-grahamimycin A_1, the unnatural, inactive enantiomer of 1.[5] We have previously described an efficient synthesis of enantiomerically pure (*R*)-methyloxirane, 4,[6] and now report the application of this optically pure starting material in the first synthesis of the natural product, (–)-grahamimycin A_1.

The synthetic approach to 1 (Scheme I) involved disjuncture of the unsymmetrical 14-membered ring into two functionalized hydroxy acids, the C_6 hydroxy ester 2 and C_8 acetylenic acid 3. The triple bond of 3 served as a latent α-diketone which would be generated following condensation and cyclization of the two fragments.

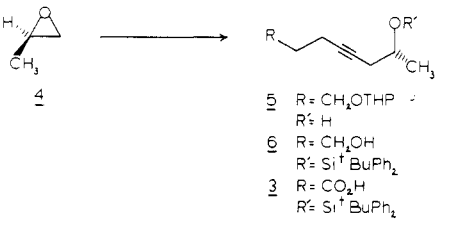
The bottom half of the molecule, 3, was accessible through initial ring opening of (*R*)-methyloxirane 4 with the lithio derivative of 1-(2-tetrahydropyranyloxy)-4-pentyne[7] (Scheme II). Addition of 4 to a 13% HMPA/THF solution of the pentynyllithium afforded the homopropargylic alcohol 5 (69%). Silylation (*tert*-butylchlorodiphenylsilane/imidazole)[8] followed by tetrahydropyranyl ether cleavage (pyridinium *p*-toluenesulfonate/EtOH)[9] gave the primary alcohol 6 (86%). Jones oxidation (0 °C, 30 min, 82%) yielded the (+)-octynoic acid 3 (49% from 4).

The top half of the molecule, 2, was approached by the addition of 4 (Scheme III) to a 1,3-bis(methylthio)allyllithium solution (THF/–78 °C/12 h).[10] This gave 7 as an isomeric mixture of alcohols (91%). Acetylation and hydrolysis (CH_3CN/H_2O, $HgCl_2$) afforded the (+)-acetoxy aldehyde 8 in 75% yield. Oxidation of this sensitive aldehyde was achieved by a $NaClO_2/NaH_2PO_4$/2-methyl-2-butene solution[11] to give the (+)-α,β-unsaturated acid

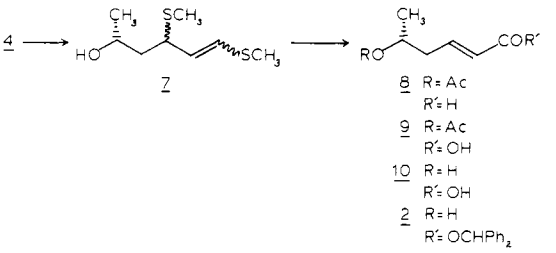
Scheme I



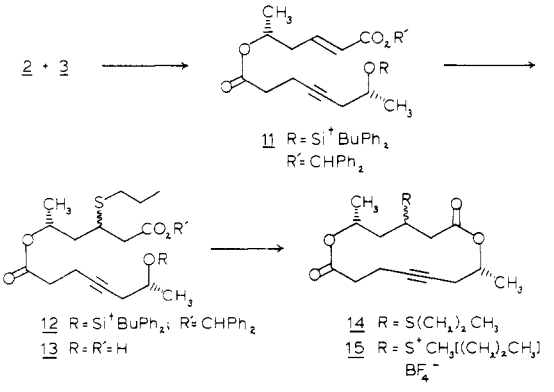
Scheme II



Scheme III



Scheme IV



9 (92%). Treatment of 9 with NaOH (0 °C → room temperature) followed by acidification yielded the crystalline (–)-hydroxy acid 10 (85%): mp 75–76 °C; $[\alpha]^{20}_D$ –10.7° (*c* 1.0, EtOH) [lit. $[\alpha]^{20}_D$ –10.0° (*c* 1.0, EtOH),[12b] $[\alpha]^{20}_D$ –11°

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(c 0.99, EtOH)[13]]. The (−)-5-hydroxy-2(*E*)-hexenoic acid (**10**) gave the same spectral data as material previously isolated by degradation of authentic grahamimycin A[3] and colletodiol.[12] The melting point and IR spectrum, however, were not in agreement with that previously reported by Doleźal[14] for synthetic (±)-**10**. Since (−)-**10** had IR[12] and ^{1}H and NMR[3] spectra identical with the degradation product, we concluded that Doleźal's assignment was erroneous. Esterification (Ph_2CN_2/EtOAc) of (−)-acid **10** gave the acid labile (−)-ester **2** (43% from **4**).

Coupling (DCC/DMAP/Et_2O)[15] of **2** and **3** (Scheme IV) produced the (+)-diester **11** (83%). At this point, we introduced 1-propanethiol, via a 1,4-addition, to the α,β-unsaturated ester of **11** to facilitate two future events in the synthesis, cyclization, and alkyne oxidation. First, we believed this would enhance intramolecular cyclization by increasing the flexibility of the molecule. Second, protection of the α,β-unsaturated system was found to be paramount to oxidation of the triple bond. Of the various methods available for this conversion (OsO_4,[16] $KMnO_4$,[17] NBS/DMSO,[18] $Tl(NO_3)_3$,[19] $(Ph_3P)_3RuCl_2$/PhIO[20]), none were specific enough to produce a α-diketone in the presence of an α,β-unsaturated ester.[21] Utilizing the thiol Michael adduct to protect the conjugated carbonyl system, the triple bond would be oxidized. Following oxidation, elimination of the sulfide (via the sulfonium salt) would recreate the α,β-unsaturated moiety.

Following this strategy, Michael addition ($CH_3(CH_2)_2SH/Na_2B_4O_7/THF/H_2O$)[22] to **11** gave a diastereomeric mixture of sulfide **12** (91%). Cleavage of the diphenylmethyl ester and silyl ether groups of **12** (HF/CH_3NO_2/AcOH, (12:2:1), 4 h) afforded the diastereomeric hydroxy acid **13** (91%). The diastereomeric ratio, following characterization with diazomethane, was determined (200 MHz NMR) to be 50:50. Lactonization (2-pyridyl thiochloroformate[23]/C_6H_6/80 °C) of **13** went smoothly to yield a separable diastereomeric mixture of macrodiolide **14** (83%).

With the acetylenic macrocycle **14** in hand, final adjustments of the aforementioned oxidation/elimination scheme were performed. Alkylation ($AgBF_4/CH_3I$) of diastereomeric **14** gave the methyl sulfonium tetrafluoroborate **15** (97% yield as a hygroscopic salt). However, attempted catalytic oxidation (OsO_4 or $(Ph_3P)_3RuCl_2$) of the triple bond of **14** followed by elimination of the sulfonium salt (aqueous $NaHCO_3$) yielded primarily the elimination product, without alkyne oxidation. From these results, it appeared that the macrolide ring was functioning in a nonproductive association with the catalytic oxidants.

To overcome this effect, a stoichiometric oxidation was investigated. Combining **15** with 2.5 equiv of osmium tetraoxide (THF/dry C_5H_5N) gave an immediate precipitate (oxo osmium(VI) ester) which was collected and introduced into an aqueous sodium sulfite (pH 7.4)–ethanol solution.[24] Extractive workup of this heterogeneous mixture gave the synthetic natural product, **1**, in 10% yield. The synthetic (−)-grahamimycin A_1 obtained was identical in all respects with an authentic sample of the natural product.

Experimental Section

Melting points wre obtained on a Thomas-Hoover Unimelt apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Beckmann Acculab 1 spectrophotometer, and nuclear magnetic resonance (NMR) spectra were recorded at either 200 MHz (Nicolet NT-200), 90 MHz (Jeol FX90Q), or 60 MHz (Varian EM-360). Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ 0.0) as an internal standard. Mass spectra were measured on a Hewlett-Packard 5985 mass spectrometer. Rotations were performed on a Jasco DIP-181 digital polarimeter. Microanalyses were performed by either Galbraith Laboratories, Inc., Knoxville, TN, or MicAnal, Organic Microanalysis, Tuscon, AZ.

Reagents were used as received from commercial sources unless indicated otherwise. Tetrahydrofuran and diethyl ether were distilled from sodium–benzophenone. Benzene and toluene were distilled from sodium. Pyridine, hexamethylphosphoric triamide, dimethylformamide, triethylamine, and diisopropylamine were distilled from calcium hydride. Petroleum ether used was of bp 35–60 °C. Analytical thin-layer chromatography (TLC) was carried out on Merck glass plates precoated with silica gel 60 F-254 (0.25 mm). Preparative TLC was performed on 20 × 20 cm plates coated with Merck silica gel 60 PF-254 (1.5 mm). Column chromatography was performed in glass columns utilizing J.T. Baker 60–200 mesh silica gel.

(2*R*)-8-(2-Tetrahydropyranyloxy)-4-octyn-2-ol (5). To a solution of 1-(2-tetrahydropyranyloxy)-4-pentyne[7] (10.01 g, 59.58 mmol) in 100 mL of tetrahydrofuran at 0 °C under argon was added *n*-butyllithium (1.37 M in hexane, 45.7 mL, 62.60 mmol). After 1 h at 0 °C, the reaction mixture was cooled to −50 °C (dry ice/acetone) followed by rapid addition of 15.0 mL of HMPA and (*R*)-methyloxirane **4**[6] (4.6 mL, 65.82 mmol). The dry ice bath was replaced with an ice bath and the reaction was allowed to come to room temperature. After stirring at room temperature for 10 h, the light brown solution was diluted with 5 M aqueous ammonium chloride and extracted with two 50-mL portions of ether. The combined organic extracts were washed (water and brine, dried ($MgSO_4$), and concentrated at reduced pressure to yield a yellow oil. Distillation (98–99 °C (0.1 mm)) gave **5** (9.31 g, 69.1%) as a colorless liquid: $[\alpha]^{22}_D$ −10.0 (*c* 0.9, $CHCl_3$); IR (neat) 3650–3100, 2940, 1450, 1350, 1190, 1110, 1055, 1025, 980, 930, 860, 805 cm^{-1}; NMR (60 MHz, CCl_4) δ 1.17 (d, 3 H, J = 6 Hz), 1.29–2.03 (m, 8 H), 2.22 (m, 4 H), 2.45 (s, 1 H), 3.13–4.06 (m, 5 H), 4.48 (br s, 1 H). Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.03; H, 9.73. Found: C, 68.87; H, 9.93.

(*R*)-7-(*tert*-Butyldiphenylsiloxy)-4-octyn-1-ol (6). A solution of alcohol **5** (9.11 g, 40.33 mmol) in 40 mL of dimethylformamide was treated under an argon atmosphere with *tert*-butylchlorodiphenylsilane (11.6 mL, 44.60 mmol) and imidazole (6.03 g, 88.67 mmol).[8] The reaction was stirred at 35 °C for 12 h, then diluted with water, and extracted with two 75-mL portions of ether. The combined organic extracts were washed with 5% hydrochloride acid, water, and brine, dried over anhydrous magnesium sulfate, and concentrated at reduced pressure to yield (7R)-7-(*tert*-butyldiphenylsiloxy)-1-(2-tetrahydropyranyloxy)-4-octyne as a pale yellow oil (18.46 g). This material was used directly in the following procedure.

Purification of a small sample from an earlier run with silica gel chromatography (20% ethyl acetate–petroleum ether) yielded a colorless oil: $[\alpha]^{22}_D$ +15.9° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3060, 2990, 2940, 1585, 1420, 1370, 1100, 990, 895, 860, 810 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.90 (s, 9 H), 1.16 (d, 3 H, J = 6.1 Hz), 1.36–1.89 (m, 8 H), 2.09–2.33 (m, 4 H), 3.28–4.05 (m, 5 H), 4.55 (br s, 1 H), 7.30–7.47 (m, 5 H), 7.57–7.76 (m, 5 H). Anal. Calcd for $C_{29}H_{40}O_3Si$: C, 75.00; H, 8.62. Found: C, 75.13; H, 8.79.

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To a 200-mL solution of the above tetrahydropyranyl ether (18.46 g) in absolute ethanol stirred at room temperature was added pyridinium *p*-toluenesulfonate (1.08 g, 4.29 mmol).[9] After 20 h, the solvent was removed at aspirator pressure and residue was chromatographed on 275 g of silica gel. Elution with 20% ethyl acetate–petroleum ether gave 13.16 g (85.9% from **5**) of **6** as an oil: $[\alpha]^{22}_D$ +19.6° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3610, 3600–3250, 3060, 2920, 2840, 1580, 1460, 1365, 1100, 1000, 820 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.13 (d, 3 H, *J* = 6 Hz), 1.42–1.97 (m, 3 H), 2.02–2.40 (m, 4 H), 3.68 (t, 2 H, *J* = 6 Hz), 3.85 (m, 1 H, *J* = 6 Hz), 7.17–7.48 (m, 5 H), 7.48–7.79 (m, 5 H). Anal. Calcd for $C_{24}H_{32}O_2Si$: C, 75.79; H, 8.92. Found: C, 75.79; H, 8.74.

(*R*)-7-(*tert*-Butyldiphenylsiloxy)-4-octynoic Acid (3). To a solution of alcohol **6** (2.62 g, 6.89 mmol) in 100 mL of acetone at 0 °C was added Jones' reagent (2.2 M) until an orange color persisted (3.4 mL). After stirring an additional 15 min, the reaction was quenched with isopropyl alcohol (0.8 mL, 10.5 mmol). Dilution with 200 mL of water dissolved the chromium salts and the acetone was removed at reduced pressure. The resulting blue-green solution was extracted with three 100-mL portions of ether. Combining the ether extracts, washing with brine, drying over anhydrous magnesium sulfate, and concentrating at reduced pressure gave an oily residue which was subjected to chromatography on 150 g of silica gel. Elution with 2% methanol–23% ethyl acetate–petroleum ether gave 2.32 g (82.1%) of **3** as an oil: $[\alpha]^{19}_D$ +15.5° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3600–2500, 3080, 2940, 2860, 1710, 1425, 1380, 1110, 820 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 1.16 (d, 3 H, *J* = 5.9 Hz), 2.18–2.54 (m, 6 H), 3.91 (m, 1 H), 7.28–7.49 (m, 5 H), 7.57–7.76 (m, 5 H), 10.82 (br s, 1 H). Anal. Calcd for $C_{24}H_{30}O_3Si$: C, 73.10; H, 7.61. Found: C, 72.96; H, 7.90.

(*R*)-5-Acetoxy-2(*E*)-hexenal (8). In accordance with the procedure of Corey,[10] into a solution of 1,3-bis(methylthio)allyllithium (12.51 mmol) in 38 mL of tetrahydrofuran under argon at −78 °C was added (*R*)-methyloxirane **4**[6] (0.96 mL, 13.74 mmol). The reaction was stirred at −78 °C for 12 h then quenched (5 M NH_4Cl) and extracted with ether. Combining the organic extracts, washing (brine), drying (Na_2SO_4), and concentration gave a brown residue that was applied to 150 g of silica gel. Elution with 10% ether–dichloromethane yielded 2.189 g (91.1%) of isomeric **7**: $[\alpha]^{22}_D$ +23.2° (*c* 2.4, $CHCl_3$); IR (neat) 3700–3100, 2920, 1600, 1430, 1370, 1310, 1120, 935, 740 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.20 (d, 3 H, *J* = 6.1 Hz), 1.69 (m, 2 H), 1.99–2.11 (m, 2 H), 2.27 (s, 3 H), 2.42 (br s, 1 H), 3.38 (m, 1 H), 3.91 (m, 1 H), 5.00–5.71 (m, 1 H), 5.99–6.22 (m, 1 H). Anal. Calcd for $C_8H_{16}OS_2$: C, 50.00; H, 8.33. Found: C, 50.30; H, 8.55.

A solution of 20.26 g (0.105 M) of the above alcohol **7** in acetic anhydride (100 mL) and dry pyridine (135 mL) was stirred at room temperature for 4 h. Concentration at reduced pressure followed by evaporative distillation (95–98 °C (2.75 mm)) yielded 24.122 g (98.2%) of the isomeric (2*R*)-4,6-bis(methylthio)-5-hexen-2-yl acetate as a colorless liquid: $[\alpha]^{22}_D$ +3.4° (*c* 3.7, $CHCl_3$); IR (neat) 2980, 2925, 1720, 1595, 1360, 1235, 1145, 935 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.22 (isomeric d, 3 H), 1.49–2.15 (m, 8 H), 2.25 (isomeric s, 3 H), 3.15–3.89 (m, 1 H), 4.73–5.55 (m, 2 H), 5.96–6.15 (m, 1 H). Anal. Calcd for $C_{10}H_{18}O_2S_2$: C, 51.28; H, 7.69. Found: C, 50.93; H, 7.82.

A solution of the above acetate (24.122 g, 0.103 M) in 1036 mL of acetonitrile containing water (263 mL), calcium carbonate (66.0 g), and mercuric chloride (123.9 g) was stirred at 45 °C. After 1 h, the reaction was filtered (Celite), diluted with brine, and extracted with three 250-mL portions of ether. Combining the ether extracts, drying ($MgSO_4$), concentration, and evaporative distillation (80–81 °C (0.1 mm)) gave 12.326 g (76.6%) of **8** as a colorless liquid: $[\alpha]^{23}_D$ +54.9° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3020, 2980, 2825, 1725, 1690, 1375, 1245, 1060, 975 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.28 (d, 3 H, *J* = 6.4 Hz), 2.04 (s, 3 H), 2.60 (complex 7-line system, 2 H), 5.09 (m, 1 H), 6.15 (dd with further fine splitting, 1 H, *J* = 1.2, 7.8, and 15.6 Hz), 6.79 (dt, 1 H, *J* = 4.1 and 15.6 Hz), 9.53 (d, 1 H, *J* = 7.8 Hz). Anal. Calcd for $C_8H_{12}O_3$: C, 61.54; H, 7.69. Found: C, 61.33; H, 7.79.

(*R*)-5-Acetoxy-2(*E*)-hexenoic Acid (9). To a solution of aldehyde **8** (12.110 g, 77.63 mmol) in 100 mL of *tert*-butyl alcohol was added 55 mL of 2-methyl-2-butene. To this was added a solution containing sodium chlorite (11.40 g, 1.3 equiv of 80% $NaClO_2$) and sodium dihydrogen phosphate monohydrate (13.85 g, 100.4 mmol) in 80 mL of H_2O dropwise (slightly exothermic).[11] The resulting pale yellow solution was stirred at room temperature overnight, concentrated in vacuo, diluted with 200 mL of water, and extracted with two 75-mL portions of hexane. The aqueous phase was acidified to pH 2 (5% HCl), saturated with sodium chloride, and extracted with three 100-mL portions of ether. Combining the ether layers, drying ($MgSO_4$), and concentration under reduced pressure gave 12.276 g (91.9%) of pure **9** as an oil: $[\alpha]^{21}_D$ +35.7° (*c* 1.6); IR (neat) 3600–2400, 2980, 2940, 1720, 1690, 1645, 1415, 1365, 1235, 1125, 1055, 970 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.24 (d, 3 H, *J* = 6.4 Hz), 2.02 (s, 3 H), 2.47 (seven-line system, 2 H), 5.01 (m, 1 H), 5.86 (br d, 1 H, *J* = 16 Hz), 6.99 (dt, 1 H, *J* = 7.3 and 16 Hz), 10.05 (br s, 1 H). Anal. calcd for $C_8H_{12}O_4$: C, 55.81; H, 6.98. Found: C, 55.74; H, 6.95.

(*R*)-5-Hydroxy-2(*E*)-hexenoic Acid (10). To a 5 M aqueous sodium hydroxide solution (20 mL) at 0 °C was added acetoxy acid **9** (7.822 g, 45.48 mmol). The reaction was stirred at 0 °C for 0.5 h, then at room temperature for 3.5 h. The solution was acidified to pH 1 with 98% sulfuric acid, saturated with sodium chloride, and extracted with chloroform. Combination of the organic extracts, drying over anhydrous magnesium sulfate, and concentration in vacuo yielded a light yellow crystal. Recrystallization (dichloromethane–hexane) afforded 5.013 g (84.8%) of **10** as feathery white crystals: mp 75–76 °C; $[\alpha]^{20}_D$ −10.7° (*c* 1.0 EtOH) [lit. $[\alpha]^{20}_D$ −10.0° (*c* 1.0, EtOH),[12] $[\alpha]_D$ −11° (*c* 0.99, EtOH)[13]]; IR ($CHCl_3$) 3650–2300, 2980, 2940, 1698, 1660, 1425, 1290, 985, 930 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.24 (d, 3 H, *J* = 6.1 Hz), 2.39 (seven-line system, 2 H), 3.99 (m, 1 H), 5.30 (br s, 2 H), 5.91 (dt, 1 H, *J* = 1.5 and 15.6 Hz), 7.08 (dt, 1 H, *J* = 7.3 and 15.6 Hz). Anal. Calcd for $C_6H_{10}O_3$: C, 55.38; H, 7.69. Found: C, 55.24; H, 7.78.

Diphenylmethyl (*R*)-5-Hydroxy-2(*E*)-hexenoate (2). The acid **10** (1.952 g, 15.02 mmol) and diphenyldiazomethane (2.732 g, 14.08 mmol) were dissolved in 50 mL of ethyl acetate and stirred at room temperature. After 24 h, the wine-red solution was diluted with ether, washed (5% $NaHCO_3$, H_2O, brine), dried ($MgSO_4$), and concentrated at reduced pressure to yield an oily residue which was chromatographed on 100 g of silica gel. Elution with 10% ethyl acetate–hexane (to remove unreacted diphenyldiazomethane) followed by 50% ethyl acetate–hexane yielded 3.336 (80.1%) of **2** as an oil: $[\alpha]^{24}_D$ −7.7° (*c* 1.3, $CHCl_3$); IR (neat) 3600–3150, 3060, 3025, 2970, 2930, 1700, 1645, 1595, 1580, 1485, 1445, 1250, 1160, 1020, 980, 740, 690 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.16 (d, 3 H, *J* = 6.2 Hz), 2.30 (overlapping m, 3 H), 3.87 (m, 1 H), 5.98 (dt, 1 H, *J* = 1.4 and 15.7 Hz), 6.91 (s, 1 H), 7.01 (dt, 1 H, *J* = 7.4 and 15.7 Hz), 7.29 (m, 10 H). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.03; H, 6.76. Found: C, 77.13; H, 7.00.

Diphenylmethyl (2*E*,5*R*,13*R*)-13-(*tert*-Butyldiphenylsiloxy)-5-methyl-6-oxa-7-oxotetradec-2-en-10-ynoate (11). The alcohol **2** (0.175 g, 0.59 mmol), acid **3** (0.250 g, 0.63 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.260 g, 1.26 mmol), and 4-(dimethylamino)pyridine (0.040 g, 0.33 mmol) were combined in 7 mL of dry ether under argon and stirred at room temperature.[15] After 48 h, the mixture was diluted with ether (20 mL) and filtered through 2 cm of silica gel. The filtrate was washed (5% HCl, 5% $NaHCO_3$, H_2O, brine) and dried ($MgSO_4$), and the solvent was removed at aspirator pressure to yield a residue containing a small amount of white precipitate. This material was purified by preparative thin-layer chromatography (30% ethyl acetate–petroleum ether) to afford 0.328 g (82.6%) of **11** as a pale yellow viscous oil (R_f 0.68–0.75): $[\alpha]^{27}_D$ +14.5° (*c* 1.4, $CHCl_3$); IR (neat) 3070, 3030, 2960, 2930, 2860, 1725, 1655, 1590, 1425, 1375, 1255, 1160, 1100, 990, 820, 780, 695 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.14 (d, 3 H, *J* = 6.1 Hz), 1.21 (d, 3 H, *J* = 6.3 Hz), 2.15–2.53 (m, 8 H), 3.86 (m, 1 H), 4.93 (m, 1 H), 5.89 (dt, 1 H, *J* = 1.4 and 15.8 Hz), 6.84 (dt, 1 H, *J* = 7.4 and 15.8 Hz), 6.88 (s, 1 H), 7.16–7.69 (m, 20 H). Anal. Calcd for $C_{43}H_{48}O_5Si$: C, 76.79; H, 7.14. Found: C, 76.71; H, 7.34.

Diphenylmethyl (5*R*,13*R*)-13-(*tert*-Butyldiphenylsiloxy)-5-methyl-6-oxa-7-oxo-3-(1-propylthio)tetradec-10-ynoate (12). To a solution of 1-propanethiol (0.75 mL, 0.631 g, 8.30 mmol), water (3 mL), and sodium tetraborate decahydrate (0.200 g, 0.52 mmol) in 20 mL of tetrahydrofuran under nitrogen was added diester **11** (0.202 g, 0.30 mmol).[22] The mixture was stirred at room temperature for 18 h, and then the volatile components were removed via evaporative distillation. Dissolving the residue

in 35 mL of ether, washing (brine), drying ($MgSO_4$), and concentrating at reduced pressure yielded a crude product which was subjected to preparative thin-layer chromatography (10% ether–hexane). The UV active band at R_f 0.35–0.48 afforded 0.205 g (91.4%) of sulfide **12** as an oil: $[\alpha]^{25}_D$ +8.5° (*c* 1.4, $CHCl_3$); IR (neat) 3070, 2960, 2930, 2860, 1730, 1585, 1450, 1425, 1375, 1230, 1105, 990, 820, 740, 690 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.89 (m, 3 H), 1.01–1.22 (m, 12 H), 1.16 (d, 3 H, *J* = 6.1 Hz), 1.31–2.80 (m, 14 H), 3.03 (m, 1 H), 3.92 (m, 1 H), 5.11 (m, 1 H), 6.91 (s, 1 H), 7.19–7.48 (m, 15 H), 7.52–7.81 (m, 5 H). Anal. Calcd for $C_{46}H_{56}O_5SSi$: C, 73.80; H, 7.49. Found: C, 73.60; H, 7.65.

(5*R*,13*R*)-13-Hydroxy-5-methyl-6-oxa-7-oxo-3-(1-propylthio)tetradec-10-ynoic Acid (13) and Methyl Ester. In a 250-mL Nalgene bottle were placed sulfide **12** (2.462 g, 3.29 mmol), nitromethane (60 mL), 49% hydrofluoric acid (10 mL), and acetic acid (5 mL). The solution was stirred at room temperature for 4 h, diluted with brine, and extracted with three 50-mL portions of chloroform. Combining the organic phases, washing (brine), drying ($MgSO_4$), and concentrating in vacuo afforded a viscous residue. This material was further purified by dissolving in 30 mL of ether and extracting with three 30-mL portions of 5% aqueous bicarbonate. The combined aqueous phases were washed (ether), acidified to pH 2 (HCl), and extracted with three 30-mL portions of chloroform. The chloroform extracts were washed (brine) and dried ($MgSO_4$), and the solvent was removed at aspirator pressure to yield 0.915 g (80.8%) of pure **13** as an oil. By analytical TLC (10% acetic acid–20% ethyl acetate–hexane), the acid was a single spot at R_f 0.18. A 32-mg sample of **13** was characterized via derivatization with diazomethane to afford 32 mg (96.1%) of the methyl ester: $[\alpha]^{23}_D$ −8.4° (*c* 0.3, $CHCl_3$); IR (neat) 3700–3150, 2980, 2940, 2890, 1720, 1430, 1370, 1160, 1125, 1115, 980, 935 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.98 (diastereomeric t, 3 H), 1.25 (diastereomeric d, 6 H), 1.35–2.67 (m, 15 H), 3.04 (m, 1 H), 3.60 (diastereomeric s, 3 H), 3.89 (m, 1 H), 5.15 (m, 1 H). Anal. Calcd for $C_{18}H_{30}O_5S$: C, 60.34; H, 8.38. Found: C, 60.55; H, 8.57.

(6*R*,14*R*)-6,14-Dimethyl-1,7-dioxa-4-(1-propylthio)cyclotetradec-11-yne-2,8-dione (14). To a solution of hydroxy acid **13** (0.915 g, 2.66 mmol) and triethylamine (0.40 mL, 2.88 mmol) in 10 mL of dichloromethane under nitrogen at 0 °C was added 2-pyridyl thiochloroformate[23] (2.70 mmol) in dichloromethane (15 mL). The mixture was stirred 0.5 h, diluted with 25 mL of dichloromethane, washed (cold 10% $NaHCO_3$, 5% HCl, and brine), dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. The oil was combined with toluene and concentrated in vacuo (three times), diluted with 1 L of oxygen-free benzene, and heated at gentle reflux. After 48 h, the golden yellow solution was concentrated at aspirator pressure and the residue was chromatographed on 150 g of silica gel. Elution with 50% ether–hexane afforded 0.718 g (82.8%) of diastereomeric **14** as a colorless oil. The diastereomeric dilactones were chromatographically separable, analytical TLC (45% hexane–ether): lactone A, R_f 0.55; lactone B, R_f 0.44.

Lactone A: $[\alpha]^{24}_D$ +12.7° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 2980, 2930, 1720, 1450, 1425, 1260, 1220, 1155, 1125, 1070, 1000 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.00 (t, 3 H, *J* = 7.1 Hz), 1.27 (d, 3 H, *J* = 6.6 Hz), 1.34 (d, 3 H, *J* = 6.6 Hz), 1.63 (m, 2 H), 1.83–2.87 (m, 12 H), 3.19 (m, 1 H), 4.96 (m, 1 H), 5.44 (m, 1 H); MS, *m/e* (intensity) 326 (M^+, 70), 283 (21), 265 (24), 189 (64), 139 (60), 129 (64), 127 (81), 113 (100), 79 (75), 77 (91), 67 (52).

Lactone B: $[\alpha]^{23}_D$ +18.3° (*c* 0.40, $CHCl_3$); IR (neat) 2980, 2940, 1725, 1450, 1425, 1370, 1290, 1255, 1220, 1160, 1125, 1075, 1045 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.01 (t, 3 H, *J* = 6.8 Hz), 1.27 (d, 3 H, *J* = 6.1 Hz), 1.30 (d, 3 H, *J* = 6.3 Hz), 1.39–2.88 (m, 12 H), 3.21 (m, 1 H), 4.79–5.32 (m, 2 H); MS, *m/e* (intensity) 326 (M^+, 54), 283 (16), 265 (16), 189 (74), 139 (59), 129 (61), 127 (64), 113 (100), 79 (62), 77 (81), 67 (46).

An analytical sample was prepared from a mixture of the two diastereomers: Anal. Calcd for $C_{17}H_{26}O_4S$: C, 62.58; H, 7.98. Found: C, 62.64; H, 8.07.

(6*R*,14*R*)-6,14-Dimethyl-4-(methylpropylsulfonio)-1,7-dioxacyclotetradec-11-yne-2,8-dione Tetrafluoroborate (15). To a vigorously stirred solution of diastereomeric sulfide **14** (0.554 g, 1.70 mmol), iodomethane (1.1 mL), toluene (5 mL), and dichloromethane (20 mL) under nitrogen was added silver tetrafluoroborate (0.331 g, 1.70 mmol) in toluene (15 mL). After stirring for 2 h, the precipitated silver iodide was filtered (suction) and the solvent removed in vacuo to yield 0.707 g (97.2%) of synthetically pure **15** as an oil. Characterization was performed by dissolving an analytical sample in 15 mL of water and extracting with three 10-mL portions of ether. The aqueous phase was lyophilized to yield the diastereomeric sulfonium salt as a highly hygroscopic white crystal: mp 53–60 °C; IR (CH_2Cl_2) 3600–3100 (br), 3070, 2980, 2940, 1735, 1455, 1425, 1380, 1350, 1230, 1160, 1150–1000 (br) cm^{-1}; NMR (90 MHz, CD_2Cl_2) V 0.97–1.43 (m, 9 H), 1.51–3.49 (m, 20 H), 3.86 (m, 1 H), 4.98 (m, 2 H). Combustion analysis corresponds to the sesquihydrate, $C_{18}H_{29}O_4SBF_4 \cdot {}^3/_2H_2O$: Found: C, 47.65; H, 6.71. Calcd: C, 47.49; H, 7.03.

(−)-Grahamimycin A_1 (1). To a tetrahydrofuran solution (15 mL) containing **15** (0.254 g, 0.59 mmol) and dry pyridine (0.5 mL) was added osmium tetraoxide (0.367 g, 1.47 mmol).[24] A brown precipitate formed immediately. After stirring 15 min, the precipitate was collected and washed repeatedly with ether. Drying in vacuo afforded 0.677 g of the osmium(VI) adduct as a fine brown powder: IR (KBr) 3650–3200, 2980, 2930, 1725, 1605, 1450 (sp), 1150–1000 (br), 835 (OsO_2, vs), 765, 595 (Os–O, s) cm^{-1}. The osmium(VI) ester was added to an ethanol (10 mL)–aqueous sodium sulfite (0.75 M, 25 mL) solution acidified to pH 7.4 with hydrochloric acid. After 0.5 h, the mixture was neutralized, the precipitate filtered, and the filtrate extracted with three 50-mL portions of dichloromethane. The residue was recombined with another portion of sodium sulfite (pH 7.4)–ethanol solution and stirred an additional 2 h. Repeating the workup, combining the organic phases, drying ($MgSO_4$), and concentrating are reduced pressure yielded a yellow oil. This material was subjected to preparative thin-layer chromatography (10% ether–dichloromethane) to afford (−)-grahamimycin A_1 (**1**) (17 mg, 10.2%) as an intensely yellow band at R_f 0.51–0.60: mp 90.5–91 °C (diisopropyl ether); $[\alpha]^{23}_D$ −14.3° (*c* 0.1, $CHCl_3$) [lit.[3] mp 91–92 °C; $[\alpha]^{22}_D$ −14.7° (*c* 0.76, $CHCl_3$)]; an admixture with the natural product gave mp 90–91 °C. The synthetic product proved identical with authentic (−)-grahamimycin A_1 by comparison (IR, ^1H NMR, UV, mass) of spectra and TLC mobility on silica gel in several solvent systems. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.38. Found: C, 59.60; H, 6.36.

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Registry No. 1, 74838-13-4; **2**, 94138-51-9; **3**, 94138-52-0; **4**, 15448-47-2; **5**, 94138-53-1; **6**, 94138-54-2; **7**, 94138-55-3; **8**, 94233-56-4; **9**, 94138-56-4; **10**, 91603-57-5; **11**, 94138-57-5; **12** isomer 1, 94138-58-6; **12** isomer 2, 94233-57-5; **13** isomer 1, 94138-59-7; **13** isomer 2, 94233-58-6; **13** methyl ester isomer 1, 94138-60-0; **13** methyl ester isomer 2, 94233-59-7; **14** isomer 1, 94138-61-1; **14** isomer 2, 94233-60-0; **15** isomer 1, 94233-97-3; **15** isomer 2, 94138-63-3; 1-(2-tetrahydropyranyloxy)-4-pentyne, 62992-46-5; (7*R*)-7-(*tert*-butyldiphenylsiloxy)-1-(2-tetrahydropyranyloxy)-4-octyne, 94138-64-4; 4,6-bis(methylthio)-5-hexen-2-yl acetate, 94138-65-5.