First Total Synthesis of Grahamimycin A

Yuichi Kobayashi* and Michitaka Matsuumi

Department of Biomolecular Engineering, Tokyo Institute of Technology, Midori-ku, Yokohama 226-8501, Japan

ykobayas@bio.titech.ac.jp

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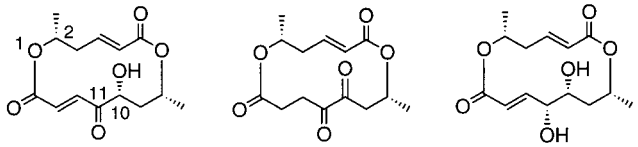
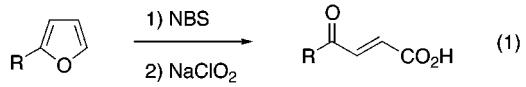
Introduction

Grahamimycin A and grahamimycin A_1 are 14-membered bislactones isolated from medium used for the aerobic fermentation of cultures of *Cytospora* sp. ATCC 20502.[1] Although their structures are similar, the former exhibits stronger antibacterial and antifungal activity toward pathogenic microorganisms. Interestingly, grahamimycin A was shown to be identical to colletoketol,[2] which had been isolated[3] from the pathogenic plant fungus *Colletotrichum capsici* along with other similar bislactones such as colletodiol, colletoallol, and colletol.



Grahamimycin A (**1**) Grahamimycin A_1 (**2**) Colletodiol (**3**)

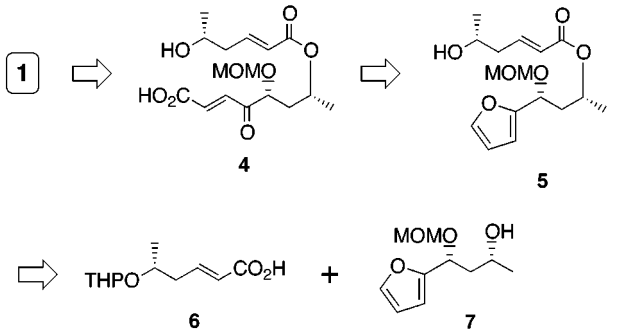
Among these natural products, grahamimycin A_1 and colletodiol are the only ones that have been target molecules for synthesis.[4,5] The synthetic strategies exploited for these compounds, however, seem to be only marginally applicable to construction of grahamimycin A. Recently we reported an oxidative conversion of 2-alkylfurans into *trans* 4-oxo-2-alkenoic acids (eq 1).[6]



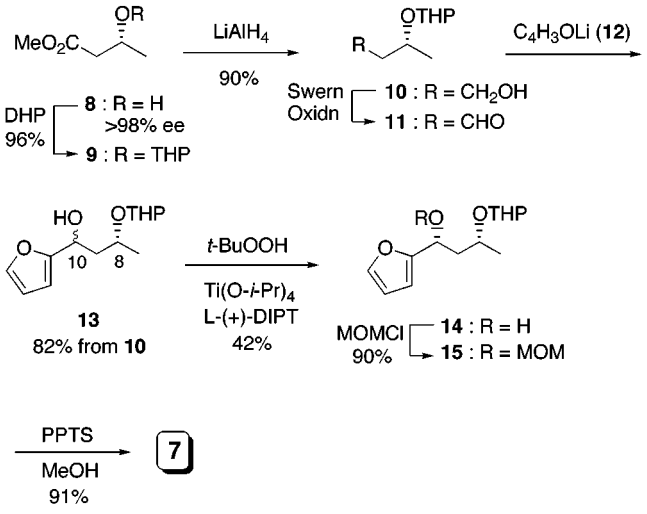
(1)

The conversion is convenient and compatible with the major functional groups commonly used in organic synthesis. Keeping the furan-ring oxidation in mind, grahamimycin A (**1**) was retrosynthesized through the seco acid **4** into the furan **5** and further into acid **6** and alcohol **7** as depicted in Scheme 1. Herein we report the first total synthesis of **1** based on this idea.

Scheme 1. Retrosynthesis of Grahamimycin A

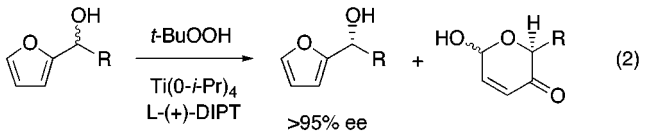


Scheme 2. Synthesis of Alcohol 7



Results and Discussion

First, we examined a route shown in Scheme 2 to synthesize the intermediate **7**. Enantiomerically enriched alcohol **8**[7] (>98% ee) was converted into aldehyde **11** by a conventional sequence of reactions through **9** in good yield. Reaction of **11** with 2-furyllithium (**12**) afforded a ca. 1:1 mixture of the diastereomers **13**, which appeared as a single spot on a TLC. To remove the unwanted diastereomer, the reaction shown in eq 2 was applied,



(2)

which was originally developed for the kinetic resolution of racemic furfuryl alcohols[8] by using the Sharpless reagent[9] (*t*-BuO_2H, $Ti(OPr)_4$, L-(+)- or D-(−)-DIPT). Reaction of **13** with L-(+)-DIPT proceeded without being

(1) Gurusiddaiah, S.; Ronald, R. C. *Antimicrob. Agents Chemother.* **1981**, *19*, 153−165.

(2) (a) O'Neill, J. A.; Simpson, T. J.; Willis, C. L. *J. Chem. Soc., Chem. Commun.* **1993**, 738−740. (b) Keck, G. E.; Boden, E. P.; Wiley: M. R. *J. Org. Chem.* **1989**, *54*, 896−906.

(3) MacMillan, J.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1487−1493.

(4) Synthesis of Grahamimycin A_1: (a) Seidel, W.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 159−162. (b) Ghiringhelli, D. *Tetrahedron Lett.* **1983**, *24*, 287−290. (c) Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50*, 470−473. (d) Bestmann, H.-J.; Schobert, R. *Tetrahedron Lett.* **1987**, *28*, 6587−6590. (e) Ohta, K.; Miyagawa, O.; Tsutsui, H.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 523−535.

(5) Synthesis of Colletodiol: (a) Tsutsui, H.; Mitsunobu, O. *Tetrahedron Lett.* **1984**, *25*, 2159−2162. (b) Tsutsui, H.; Mitsunobu, O. *Tetrahedron Lett.* **1984**, *25*, 2163−2166. (c) Schnurrenberger, P.; Hungerbühler, E.; Seebach, D. *Liebigs Ann. Chem.* **1987**, 733−744. (d) See ref 2b.

(6) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505−7515.

(7) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858.

(8) Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085−2091.

(9) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240. (b) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic Press: New York, 1985; Vol. 5, Chapter 8, p 247. (c) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic Press: New York, 1985; Vol. 5, Chapter 7, p 193.

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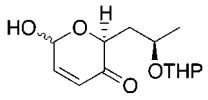
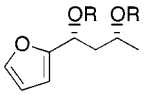
affected by the chiral center at the C(8) position (grahamimycin A numbering) and a mixture of 10*R*-alcohol **14**, pyranone **16**, and DIPT was successfully obtained. Sub-



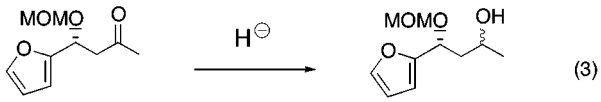
16

sequently, the mixture in Et_2O was stirred vigorously with aqueous NaOH to accomplish decomposition of **16** and hydrolysis of DIPT, thus facilitating chromatographic isolation of **14** (41% yield). The high diastereomeric purity of >95% at the C(10) position was determined by ^{1}H NMR spectroscopy of the crude diol **17** derived from **14** (PPTS, MeOH).[10] In addition, the relative stereochemistry of **14** was independently confirmed by ^{13}C NMR spectroscopy of the acetonide **18** prepared from diol **17** ($Me_2C(OMe)_2$, PPTS, CH_2Cl_2).[11a] Finally, protection of **14** as the MOM ether followed by selective hydrolysis of the THP group afforded **7** in 82% yield.



17 : R = H
18 : R = C(Me)$_2$

Because enantiomerically enriched furfuryl alcohols of >95% ee are conveniently prepared by the reaction of eq 2, reduction of ketone **19** seems to be a better way to prepare the alcohol **7** (eq 3). However, chromatographic

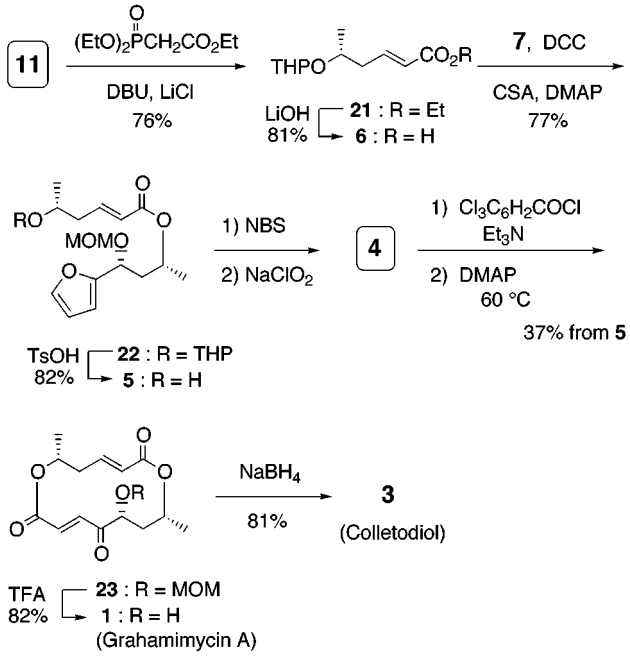


19 **7** (α–OH) **20** (β–OH) (3)

separation of diastereomeric alcohols **7** and **20** (1:1), prepared by reduction with $NaBH_4$ in 79% yield, was not successful as a result of the close R_f values. Consequently, further investigation to find a reagent suitable for stereoselective reduction of **19** was not continued.

Another fragment **6** proposed in Scheme 1 was prepared from aldehyde **11**, the intermediate used in Scheme 2, according to a modification of Simpson's[12] procedure. Thus, the Wittig reaction of **11** with $(EtO)_2P(=O)CH_2CO_2Et$ under the conditions developed by Masamune[13] (DBU, LiCl, MeCN) afforded ester **21**, which was not contaminated with the *cis* isomer (geometric isomer purity >95% by ^{1}H NMR spectroscopy), and hydrolysis then gave **6** in 62% yield (Scheme 3). Condensation[14] of acid **6** and alcohol **7** afforded **22**, and deprotection of the THP group with *p*-TsOH in MeOH produced the key intermediate **5** in good yield. The furan ring of **5** was transformed into the 4-oxo-2-enoic acid moiety by the protocol of eq 1, and the resulting seco acid **4**, without purification, was subjected to Yamaguchi macrocyclization[15] ($Cl_3C_6H_2COCl$, 60 °C) to afford the MOM ether **23**, which upon deprotection of the MOM group with CF_3CO_2H furnished (−)-grahamimycin A (**1**) ($[\alpha]^{25}_D = -34.2$ (*c* 0.052, $CHCl_3$); lit.[1,3] −33 to −34) in 30% overall yield from **5**. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra of synthetic **1** were in agreement with those previously reported.[1,3]

Scheme 3. Synthesis of Grahamimycin A (1)



In addition, we reinvestigated the reduction of **1** with $NaBH_4$ to produce colletodiol (**3**). This was reported by both Simpson[2a] and Ronald,[1] but neither gave detailed information about the procedure. Reduction was carried out at −15 °C in MeOH to furnish **3** in 81% yield with a high stereoselectivity of >95%: $[\alpha]^{27}_D = +35.8$ (*c* 0.118, $CHCl_3$) (lit.[16] $[\alpha]_D = +36$ (*c* 1.0, $CHCl_3$)). The ^{1}H NMR, ^{13}C NMR, and IR spectra of **3** thus synthesized were in accord with the reported data.[2b,3]

In conclusion, we have succeeded, for the first time, in the synthesis of grahamimycin A (**1**) (= colletoketol). We also confirmed high stereoselectivity in the reduction of **1** to colletodiol (**2**). We believe that the synthesis provides a good tool for investigation of the biochemical aspects

(10) Diagnostic signals in the ^{1}H NMR spectra of the *syn* alcohol **17** and the *anti* alcohol are 4.94 (dd, J = 9, 4 Hz, 1 H) and 5.03 (dd, J = 8, 3.5 Hz, 1 H), respectively. Data for **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J = 6 Hz, 1 H), 1.82−2.06 (m, 2 H), 3.09 (br s, 1 H), 3.46 (br s, 1 H), 4.02−4.15 (m, 1 H), 4.94 (dd, J = 9, 4 Hz, 1 H), 6.23 (dm, J = 3 Hz, 1 H), 6.32 (dd, J = 3, 1 Hz, 1 H), 7.36 (dd, J = 2, 1 Hz, 1 H); ^{13}C NMR δ 156.2, 141.9, 110.2, 105.7, 68.4, 68.3, 43.3, 24.2.

(11) (a) Resonances for the acetonide methyl groups of **18** are observed at δ 30.4 and 19.9 ppm, which are the characteristic values for the *syn* acetonide.[11b,c] Spectral data of **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, J = 6 Hz, 3 H), 1.46 (s, 3 H), 1.56 (s, 3 H), 1.69−1.77 (m, 2 H), 4.04−4.19 (m, 1 H), 4.89−5.02 (m, 1 H), 6.28 (d, J = 3 Hz, 1 H), 6.33 (dd, J = 3, 2 Hz, 1 H), 7.38 (d, J = 2 Hz, 1 H); ^{13}C NMR δ 154.3, 142.2, 110.1, 106.7, 99.1, 65.3, 65.1, 36.7, 30.4, 22.3, 19.9. (b) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−948. (c) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100.

(12) O'Neill, J. A.; Lindell, S. D.; Simpson, T. J.; Willis, C. L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 637−644.

(13) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

(14) (a) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394−2395. (b) Sunazuka, T.; Hirose, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Am. Chem. Soc.* **1997**, *119*, 10247−10248.

(15) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(16) Powell, J. W.; Whalley, W. B. *J. Chem. Soc. C* **1969**, 911−912.

of grahamimycin A as well as colletodiol by using analogues thereof.

Experimental Section

General Methods. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}). Unless otherwise noted, ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ ($\delta = 0$ ppm) and the center line of $CDCl_3$ triplet ($\delta = 77.1$ ppm) as internal standards, respectively. Methyl (*R*)-3-hydroxybutanoate (**8**) (98% ee) was kindly offered by Takasago International Corporation, Japan. Routinely, organic extracts were dried over $MgSO_4$ and concentrated using a rotary evaporator to afford residues, which were purified by chromatography on silica gel.

Methyl (*R*)-3-Tetrahydropyranyloxybutanoate (9). A solution of **8** (7.50 g, 63.5 mmol, >98% ee), DHP (7.5 mL, 83 mmol), and *p*-TsOH·H_2O (120 mg, 0.63 mmol) in CH_2Cl_2 (130 mL) was stirred at 0 °C for 2 h, and saturated $NaHCO_3$ was added into the solution. After 10 min of vigorous stirring, the resulting mixture was extracted with EtOAc twice, and the combined extracts were washed with brine, dried, and concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to afford THP ether **9** (12.35 g, 96%): IR (neat) 1741, 1199, 1022 cm^{-1}; ^1H NMR δ 1.18 and 1.28 (2d, $J = 6$ and 6 Hz, 3 H), 1.41−1.86 (m, 6 H), 2.33−2.74 (m, 2 H), 3.42−3.53 (m, 1 H), 3.66 and 3.67 (2s, 3 H), 3.77−3.94 (m, 1 H), 4.10−4.31 (m, 1 H), 4.62−4.78 (m, 1 H). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H 8.97. Found: C, 59.47; H, 8.98.

(*R*)-3-Tetrahydropyranyloxy-1-butanol (10). To an ice-cold suspension of $LiAlH_4$ (2.32 g, 61.1 mmol) in THF (90 mL) was added a solution of **9** (12.35 g, 61.1 mmol) dissolved in THF (10 mL × 3), and the mixture was stirred at 0 °C for 30 min and at room temperature for 60 min. The mixture was cooled to 0 °C again, and EtOAc (27 mL, 0.31 mol), H_2O (22 mL, 1.22 mol) in THF (44 mL), and NaF (25.7 g, 0.612 mol) were added to the mixture. The resulting mixture was stirred vigorously at room temperature for 1 h and filtered through a pad of Celite with EtOAc. The filtrate was concentrated, and the residue was purified by chromatography (hexane/EtOAc) to afford alcohol **10** (9.61 g, 90%). The ^1H NMR spectrum of **10** was identical with that reported.[17]

(1*R*,3*R*)- and (1*S*,3*R*)-1-(2-Furyl)-3-tetrahydropyranyloxy-1-butanol (13). To a solution of $(COCl)_2$ (3.8 mL, 43.6 mmol) in CH_2Cl_2 (90 mL) was injected DMSO (6.14 mL, 86.5 mmol) at −60 °C. The solution was stirred at the same temperature for 15 min, and a solution of alcohol **10** (5.05 g, 29.0 mmol) dissolved in CH_2Cl_2 (10 mL × 3) was added. After 1 h of stirring at −60 °C, Et_3N (28.3 mL, 204 mmol) was added, and the resulting mixture was warmed gradually to 0 °C over 2 h. Brine was added to the mixture, and the product was extracted with Et_2O three times. The combined ethereal solutions were washed with brine, dried, and concentrated to give aldehyde **11**, which was used for the next reaction without further purification.

To an ice-cold solution of furan (7.5 mL, 104 mmol) and bipyridine (ca. 10 mg) in THF (110 mL) was added *n*-BuLi (34 mL, 2.53 M in hexane, 86 mmol), and the solution was stirred at 0 °C for 80 min to prepare 2-furyllithium (**12**). The solution was cooled to −70 °C, and the above crude aldehyde **11** dissolved in THF (10 mL × 3) was added slowly. Stirring was continued at −70 °C for 2 h, and the solution was poured into a mixture of Et_2O and saturated NH_4Cl with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with Et_2O twice. The combined ethereal solutions were dried and concentrated to leave an oil, which was purified by chromatography (hexane/EtOAc) to afford alcohol **13** as a mixture of the diastereoisomers (5.69 g, 82% from alcohol **10**): IR (neat) 3418, 1023 cm^{-1}; ^1H NMR δ 1.20, 1.22, 1.32, and 1.33 (4d, $J = 6$, 6, 6, and 6 Hz, total 3 H), 1.46−2.19 (m, 8 H), 3.11−3.17 (m, 1 H), 3.44−3.59 (m, 1 H), 3.84−4.24 (m, 2 H), 4.51−5.10 (m, 2 H), 6.22−6.26 (m, 1 H), 6.31−6.35 (m, 1 H), 7.35−7.38 (m, 1 H). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.19; H, 8.45.

(1*R*,3*R*)-1-(2-Furyl)-3-tetrahydropyranyloxy-1-butanol (14). To a solution of Ti(O-*i*-Pr)$_4$ (0.29 mL, 0.99 mmol) in CH_2Cl_2 (3 mL) was added L-(+)-DIPT (0.25 mL, 1.2 mmol) at −20 °C. After 10 min of stirring, alcohol **13** (239 mg, 0.993 mmol) dissolved in CH_2Cl_2 (2 mL) and a solution of *t*-BuOOH in CH_2Cl_2 (0.24 mL, 2.5 M, 0.60 mmol) were added, and the resulting solution was kept in a freezer (−20 °C) for 30 h. To the solution were added Me_2S (0.044 mL, 0.60 mmol) and, after 30 min at −20 °C, 10% tartaric acid solution (0.20 mL) and NaF (0.25 g, 5.95 mmol). The mixture was stirred vigorously at room temperature for 60 min and filtered through a pad of Celite with Et_2O. The filtrate was concentrated, and the residue was diluted in Et_2O (16 mL). The solution was cooled to 0 °C, and 3 N NaOH (8 mL, 24 mmol) was added to it. The resulting mixture was stirred at room temperature for 1 h vigorously, and the product was extracted with Et_2O three times. The combined extracts were dried and concentrated to afford an oil, which was purified by chromatography (hexane/EtOAc) to afford **14** (98 mg, 41%). The diastereomeric purity at the C(10) position of **14** was determined to be >95% ds by ^1H NMR specroscopy of the diol **17**[10] prepared by deprotection of the THP group (PPTS (0.1 equiv), MeOH, rt, 12 h). Data for **14**: IR (neat) 3421, 1023 cm^{-1}; ^1H NMR δ 1.20 and 1.32 (2d, $J = 6$ and 6 Hz, total 3 H), 1.46−2.19 (m, 8 H), 3.06−4.26 (m, 4 H), 4.63−5.05 (m, 2 H), 6.22−6.26 (m, 1 H), 6.31−6.35 (m, 1 H), 7.35−7.38 (m, 1 H). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.00; H, 8.48.

(1*R*,3*R*)-1-(2-Furyl)-1-methoxymethyloxy-3-tetrahydropyranyloxybutane (15). A solution of **14** (2.05 g, 8.53 mmol), MOMCl (1.48 mL, 19.1 mmol), and *i*-Pr_2NEt (4.5 mL, 25.7 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature overnight and diluted with EtOAc and saturated $NaHCO_3$. The resulting mixture was stirred vigorously at room temperature for 1 h. The phases were separated, and the aqueous phase was extracted with EtOAc twice. The combined extracts were dried and concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to furnish MOM ether **15** (2.19 g, 90%): IR (neat) 1029, 921 cm^{-1}; ^1H NMR δ 1.15 and 1.27 (2d, $J = 6$ and 6 Hz, total 3 H), 1.42−2.08 (m, 7 H), 2.15−2.33 (m, 1 H), 3.347 and 3.353 (2s, total 3 H), 3.33−3.97 (m, 3 H), 4.45−4.90 (m, 4 H), 6.26−6.38 (m, 2 H), 7.37−7.43 (m, 1 H). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.41; H, 8.55.

(2*R*,4*R*)-4-(2-Furyl)-4-methoxymethyloxy-2-butanol (7). A solution of **15** (2.24 g, 7.88 mmol) and *p*-TsOH·H_2O (74 mg, 0.39 mmol) in MeOH (80 mL) was stirred at room temperature for 4 h and diluted with saturated $NaHCO_3$. Most of the MeOH was removed by evaporation, and the resulting mixture was extracted with EtOAc twice. The combined extracts were dried and concentrated. Chromatography (hexane/EtOAc) of the crude product afforded alcohol **7** (1.43 g, 91%): $[\alpha]^{28}_D = +177$ (*c* 1.07, $CHCl_3$); IR (neat) 3432, 1025, 922 cm^{-1};^1H NMR δ 1.22 (d, $J = 6$ Hz, 3 H), 1.89 (ddd, $J = 14$, 5, 3 Hz, 1 H), 2.15 (dt, $J = 14$, 9 Hz, 1 H), 2.87 (s, 1 H), 3.39 (s, 3 H), 3.38−4.00 (m, 1 H), 4.52 (d, $J = 7$ Hz, 1 H), 4.62 (d, $J = 7$ Hz, 1 H), 4.87 (dd, $J = 9$, 5 Hz, 1 H), 6.29−6.35 (m, 2 H), 7.39 (s, 1 H); ^{13}C NMR δ 152.9, 142.6, 110.1, 108.6, 93.8, 70.5, 66.9, 55.9, 42.9, 23.7. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H 8.05. Found: C, 59.59; H, 8.04.

Ethyl (5*R*,2*E*)-5-Tetrahydropyranyloxy-2-hexenoate (21). According to the procedure described above, alcohol **10** (8.72 g, 50.0 mmol) dissolved in CH_2Cl_2 (30 mL) was converted into aldehyde **11** by using $(COCl)_2$ (5.64 mL, 64.7 mmol), DMSO (9.10 mL, 129 mmol), Et_3N (42 mL, 302 mmol), and CH_2Cl_2 (120 mL). Crude **11** was used for the next reaction without further purification.

To an ice-cold suspension of LiCl (2.65 g, 62.5 mmol) in MeCN (120 mL) were added sequentially $(EtO)_2P(=O)CH_2CO_2Et$ (12.5 mL, 62.4 mmol), DBU (11.6 mL, 77.9 mmol), and crude aldehyde **11** dissolved in MeCN (10 mL × 3). The mixture was stirred at 0 °C for 30 min and then at room temperature for 60 min. Saturated NH_4Cl was added to the mixture, and most of the MeCN was removed by evaporation. The product was extracted with Et_2O three times, and the combined extracts were dried and concentrated. The residual oil was purified by chromatography (hexane/EtOAc) to afford ester **21** (9.16 g, 76%). The ^1H NMR spectrum of **21** was in good agreement with that reported.[12]

(5*R*,2*E*)-5-Tetrahydropyranyloxy-2-hexenoic Acid (6). To an ice-cold solution of ester **21** (9.16 g, 37.8 mmol) in THF (175

(17) Quinkert, G.; Döller, U.; Eichhorn, M.; Küber, F.; Nestler, H. P.; Becker, H.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta* **1990**, *73*, 1999−2047.

mL) were added H_2O (120 mL) and 2 N LiOH (57 mL). The mixture was stirred vigorously at room temperature for 20 h, and most of the THF was removed by evaporation. The residue was diluted with EtOAc and slightly acidified (pH = ca. 4) with 1 N HCl. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined EtOAc phases were dried and concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to afford acid **6** (5.87 g, 81%). The ^{1}H NMR spectrum of **6** was in good agreement with that reported.[12]

(1′*R*,3′*R*)-3′-(2-Furyl)-3′-methoxymethyloxy-1′-methylpropyl (5*R*,2*E*)-5-Tetrahydropyranyloxy-2-hexenoate (22). To an ice-cold solution of alcohol **7** (1.42 g, 7.09 mmol), acid **6** (1.97 g, 9.19 mmol), DMAP (171 mg, 1.40 mmol), and CSA (165 mg, 0.71 mmol) in CH_2Cl_2 (50 mL) was added DCC (2.20 g, 10.7 mmol) in CH_2Cl_2 (20 mL). The resulting solution was stirred at room temperature for 20 h and filtered through a pad of Celite with Et_2O. The filtrate was concentrated and the residual oil was purified by chromatography (hexane/EtOAc) to afford ester **22** (2.16 g, 77%): IR (neat) 1717, 1655, 1023 cm^{-1}; ^{1}H NMR δ 1.12−1.30 (m, 6 H), 1.41−1.89 (m, 6 H), 1.98−2.16 (m, 1 H), 2.20−2.58 (m, 3 H), 3.36 (s, 3 H), 3.42−3.54 (m, 1 H), 3.79−4.00 (m, 2 H), 4.50 (d, J = 7 Hz, 1 H), 4.58 (d, J = 7 Hz, 1 H), 4.63−4.76 (m, 2 H), 4.80−4.94 (m, 1 H), 5.83 and 5.85 (2d, J = 16 and 16 Hz, total 1 H), 6.24−6.34 (m, 2 H), 6.83−7.06 (m, 1 H), 7.38 (s, 1 H). Anal. Calcd for $C_{21}H_{32}O_7$: C, 63.62; H, 8.14. Found: C, 63.44; H, 8.09.

(1′*R*,3′*R*)-3′-(2-Furyl)-3′-methoxymethyloxy-1′-methylpropyl (5*R*,2*E*)-5-Hydroxy-2-hexenoate (5). A solution of THP ether **22** (2.16 g, 5.45 mmol) and *p*-TsOH·H_2O (52 mg, 0.27 mmol) in MeOH (55 mL) was stirred at room temperature for 3 h and diluted with saturated $NaHCO_3$. Most of the MeOH was removed by evaporation, and the resulting mixture was extracted with EtOAc three times. The combined extracts were dried and concentrated to leave a residue, which was purified by chromatography (hexane/EtOAc) to afford alcohol **5** (1.40 g, 82%): $[\alpha]^{31}_D$ = +55.9 (*c* 1.02, $CHCl_3$); IR (neat) 3448, 1716, 1032 cm^{-1}; ^{1}H NMR δ 1.24 (d, J = 6 Hz, 3 H), 1.27 (d, J = 6 Hz, 3 H), 1.67 (br s, 1 H), 2.09 (ddd, J = 14, 8, 5 Hz, 1 H), 2.23−2.40 (m, 3 H), 3.36 (s, 1 H), 3.89−4.01 (m, 1 H), 4.51 (d, J = 7 Hz, 1 H), 4.58 (d, J = 7 Hz, 1 H), 4.69 (dd, J = 8, 7 Hz, 1 H), 4.82−4.95 (m, 1 H), 5.87 (dt, J = 16, 2 Hz, 1 H), 6.26 (dd, J = 3, 1 Hz, 1 H), 6.31 (dd, J = 3, 2 Hz, 1 H), 6.93 (dt, J = 16, 8 Hz, 1 H), 7.38 (d, J = 2 Hz, 1 H); ^{13}C NMR δ 165.5, 152.7, 144.9, 142.6, 124.1, 110.1, 108.9, 93.9, 68.2, 68.1, 66.8, 55.7, 42.0, 40.3, 23.4, 20.2. Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.21;H, 7.61.

(3*E*,6*R*,8*R*,11*E*,14*R*)-8,14-Dimethyl-6-methoxymethyloxy-1,9-dioxacyclotetradeca-3,11-diene-2,5,10-trione (23). To a mixture of **5** (350 mg, 1.12 mmol) and $NaHCO_3$ (188 mg, 2.24 mmol) in acetone/H_2O (10:1, 6 mL) was added NBS (240 mg, 1.35 mmol) dissolved in acetone/H_2O (10:1, 2 mL) at −15 °C. The mixture was stirred for 2.5 h, and furan (0.16 mL, 2.2 mmol) was added to destroy excess NBS. After 60 min at −15 °C, pyridine (0.09 mL, 1.1 mmol) was added, and the mixture was stirred at room temperature for 21 h. Brine and EtOAc were added, and the resulting mixture was acidified with 1 N HCl to pH ca. 4. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined extracts were dried and concentrated to give an oil, which was passed through a short silica gel column with hexane/EtOAc to furnish the corresponding aldehyde: IR (neat) 3455, 1712, 1655 cm^{-1}; ^{1}H NMR δ 1.24 (d, J = 6 Hz, 3 H), 1.30 (d, J = 6 Hz, 3 H), 2.02 (ddd, J = 15, 6, 4.5 Hz, 1 H), 2.23 (ddd, J = 15, 9, 5 Hz, 1 H), 2.25−2.41 (m, 3 H), 3.37 (s, 3 H), 3.89−4.01 (m, 1 H), 4.32 (t, J = 6 Hz, 1 H), 4.68 (d, J = 7 Hz, 1 H), 4.72 (d, J = 7 Hz, 1 H), 5.10−5.24 (m, 1 H), 5.75 (d, J = 16 Hz, 1 H), 6.58−7.10 (m, 2 H), 7.28 (d, J = 16 Hz, 1 H), 9.73 (d, J = 8 Hz, 1 H); ^{13}C NMR δ 199.5, 193.6, 165.6, 146.3, 140.8, 138.2, 123.8, 96.6, 79.0, 67.0, 66.7, 56.4, 41.8, 38.3, 23.3, 20.0.

To a solution of the aldehyde obtained above and 2-methyl-2-butene (1.2 mL, 11 mmol) in *t*-BuOH (15 mL) and the phosphate buffer (pH 3.6, 7 mL) was added $NaClO_2$ (151 mg, purity 80%, 1.33 mmol) dissolved in H_2O (7 mL). The resulting mixture was stirred at room temperature for 3 h and slightly acidified by addition of 1 N HCl (pH ca. 4). Most of the *t*-BuOH was removed by using a vacuum pump. After addition of brine, the mixture was extracted with EtOAc three times. The combined extracts were dried and concentrated to leave crude **4**, which was used for the next reaction without further purification. Analytically pure sample was obtained by chromatography: IR (neat) 3161, 1712, 1178 cm^{-1}; ^{1}H NMR δ 1.25 (d, J = 6 Hz, 3 H), 1.28 (d, J = 6 Hz, 3 H), 2.03 (ddd, J = 15, 6, 4 Hz, 1 H), 2.21 (ddd, J = 15, 9, 5 Hz, 1 H), 2.28−2.46 (m, 2 H), 3.36 (s, 3 H), 3.90−4.08 (m, 1 H), 4.29 (dd, J = 6, 5 Hz, 1 H), 4.63 (d, J = 7 Hz, 1 H), 4.70 (d, J = 7 Hz, 1 H), 5.07−5.26 (m, 1 H), 5.75 (d, J = 16 Hz, 1 H), 5.58−6.07 (m, 2 H), 6.75 (d, J = 16 Hz, 1 H), 6.80−7.02 (m, 1 H), 7.41 (d, J = 16 Hz, 1 H); ^{13}C NMR δ 199.1, 168.3, 165.4, 145.8, 136.5, 130.8, 123.7, 96.5, 78.9, 67.1, 56.5, 41.9, 38.5, 23.3, 20.2.

To a solution of the above acid **4** and NEt_3 (0.72 mL, 5.18 mmol) in THF (10 mL) was added 2,4,6-trichlorobenzoyl chloride (0.25 mL, 1.55 mmol). The solution was stirred at room temperature for 4 h, and the resulting white precipitate (Et_3N·HCl) was removed by dilution with toluene (ca. 20 mL) followed by filtration through a pad of Celite with additional toluene (20 mL). The filtrate, after further dilution with toluene (100 mL), was divided into two equal portions, while two solutions of DMAP (each 85 mg, 0.70 mmol) in toluene (each 25 mL) were prepared. Each toluene solution containing the mixed anhydride was added to each solution of DMAP in toluene at 60 °C over 7 h. After the addition, the solutions were stirred further for 1 h and cooled to room temperature. The combined solutions were concentrated to afford a residue, which was purified by chromatography (hexane/EtOAc) to afford lactone **23** (128 mg, 37%) from furan **5**: $[\alpha]^{29}_D$ = −11.3 (*c* 0.558, $CHCl_3$); IR (neat) 1728, 1701, 1173, 1054 cm^{-1}; ^{1}H NMR δ 1.23 (d, J = 6 Hz, 3 H), 1.40 (d, J = 6 Hz, 3 H), 2.06−2.25 (m, 3 H), 2.41−2.50 (m, 1 H), 3.37 (s, 3 H), 4.25 (t, J = 4 Hz, 1 H), 4.66 (d, J = 7 Hz, 1 H), 4.72 (d, J = 7 Hz, 1 H), 5.20−5.35 (m, 2 H), 5.58 (d, J = 16 Hz, 1 H), 6.70 (ddd, J = 16, 11, 6 Hz, 1 H), 6.79 (d, J = 16 Hz, 1 H), 7.21 (d, J = 16 Hz, 1 H); ^{13}C NMR δ 200.1, 166.9, 165.2, 143.1, 134.0, 132.3, 127.2, 96.4, 79.1, 70.6, 66.2, 56.4, 40.9, 39.7, 20.5, 20.4. Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.79. Found: C, 58.68; H, 7.21.

Grahamimycin A (1). To an ice-cold solution of **23** (9.3 mg, 0.028 mmol) in CH_2Cl_2 (0.44 mL) was added CF_3CO_2H (0.44 mL, 5.7 mmol). The solution was allowed to stand in a refrigerator (at ca. 3 °C) for 17 h and concentrated to leave an oil, which was purified by chromatography (hexane/EtOAc) to afford **1** (7.0 mg, 87%): $[\alpha]^{25}_D$ = −34.2 (*c* 0.052, $CHCl_3$) [lit.[3] $[\alpha]^{21}_D$ = −33 (*c* 1.48, $CHCl_3$), lit.[1] $[\alpha]^{22}_D$ = −34 (*c* 1.47, $CHCl_3$)]; mp 138−140 °C (recrystallized from hexane/CH_2Cl_2) [lit.[3] mp 138−139 °C; lit.[1] mp 147.5−150 °C]. Spectral data of **1** updated: IR ($CHCl_3$) 1725, 1706, 1655, 1362, 1175 cm^{-1}; ^{1}H NMR δ 1.39 (d, J = 7 Hz, 3 H), 1.43 (d, J = 6 Hz, 3 H), 1.80 (ddd, J = 16, 5, 4 Hz, 1 H), 2.13 (ddd, J = 16, 5, 3 Hz, 1 H), 2.37 (dt, J = 13, 11 Hz, 1 H), 2.56 (dddd, J = 13, 5, 3, 2 Hz, 1 H), 3.14 (d, J = 5 Hz, 1 H), 4.54 (dt, J = 4, 5 Hz, 1 H), 5.00−5.14 (m, 1 H), 5.30−5.42 (m, 1 H), 5.90 (d, J = 16 Hz, 1 H), 6.71 (d, J = 16 Hz, 1 H), 6.75 (ddd, J = 16, 11, 5 Hz, 1 H), 7.09 (d, J = 16 Hz, 1 H); ^{13}C NMR δ 200.7, 165.3, 165.2, 143.9, 134.3, 132.6, 126.8, 72.9, 70.8, 67.1, 40.5, 40.3, 20.7, 18.6.

Reduction of Grahamimycin (1) to Colletodiol (3). To a solution of **1** (16 mg, 0.057 mmol) in MeOH (0.8 mL) at −15 °C was added $NaBH_4$ (4.3 mg, 0.11 mmol) portionwise. After 30 min at −15 °C, the solution was diluted with saturated NH_4Cl and EtOAc. The resulting mixture was extracted with EtOAc three times, and the combined extracts were dried and concentrated. The residue was purified by chromatography to furnish **3** (13 mg, 81%): $[\alpha]^{27}_D$ = +35.8 (*c* 0.118, $CHCl_3$) (lit.[16] $[\alpha]_D$ = +36 (*c* 1.0, $CHCl_3$)); mp 163−165 °C (recrystallized from hexane/Et_2O) (lit.[16] 164−167 °C; lit.[2b] 165 °C; lit.[18] 159−161 °C). The ^{1}H NMR, ^{13}C NMR, and IR spectra of **3** thus synthesized were in accord with the reported data.[2b,3]

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(18) Fujimoto, H.; Nagano, J.; Yamaguchi, K.; Yamazaki, M. *Chem. Pharm. Bull.* **1998**, *46*, 423−429.