Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 833–839

TETRAHEDRON

Synthesis of 5-(7-hydroxyhept-3-enyl)-1,2-dithiolan-3-one 1-oxide, a core functionality of antibiotic leinamycin

Alex H. F. Lee,[a,b] Albert S. C. Chan[a,b] and Tianhu Li[a,b,*]

[a]*Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis,*[†] *The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, People's Republic of China*

[b]*Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, People's Republic of China*

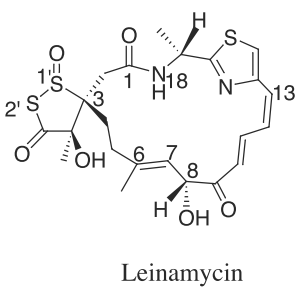
Received 7 October 2002; revised 19 November 2002; accepted 5 December 2002

Abstract—5-(7-Hydroxyhept-3-enyl)-1,2-dithiolan-3-one 1-oxide **1** possessing both the 1,2-dithiolan-3-one 1-oxide five-membered ring and the double bond at the gamma position of the heterocycle, characteristic of the antibiotic leinamycin, was synthesized. In addition, the activated ester form of **1** was prepared that may be useful for coupling **1** to certain DNA-binding agents. © 2003 Elsevier Science Ltd. All rights reserved.

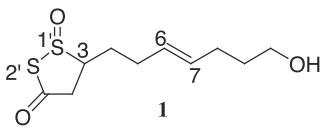
1. Introduction

The antibiotic leinamycin was isolated from *Streptomyces* sp. by Hara et al. at Kyowa Hakko Kogyo Ltd in 1989. Subsequent spectroscopic analysis and X-ray crystallography[1–4] resolved its exact molecular structure as that shown in Figure 1. Further bioassays demonstrated that this natural product exhibited potent activity against murine experimental tumor leukemia P388 and sarcoma 180 as well as against Gram-positive bacteria.[5] In addition, leinamycin is capable of causing single stranded DNA cleavage in vitro in the presence of thiols as activating reagents, a mechanism that may underlie the cytotoxic properties of this antibiotic.[6–13] Based on these promising biological properties, certain pharmaceutical companies have expressed their interest in pursuing leinamycin as an anticancer drug candidate.[14]

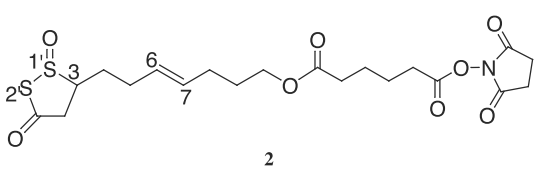
From the viewpoint of chemistry, one of the distinctive characteristics of leinamycin in structure is its possession of an unusual 1,3-dioxo-1,2-dithiolane moiety connected to an 18-membered lactam ring.[15,16] In addition, certain mechanistic investigations demonstrate that the double bond at the gamma position of the heterocycle plays a significant role in the DNA-cleaving process induced by leinamycin.[5,7–9,17] With the aim of further exploring the chemical and biological properties of this antibiotic, we have recently designed and synthesized 5-(7-hydroxyhept-3-enyl)-1,2-



Leinamycin



1



2

Figure 1.

Keywords: antibiotic leinamycin; heterocycle; DNA-cleaving agent; activated ester; antisense oligonucleotide; 1,2-dithiolan-3-one 1-oxide.

* Corresponding author. Address: Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China. Tel.: +852-2766-7778; fax: +852-2364-9932; e-mail: bctli@polyu.edu.hk

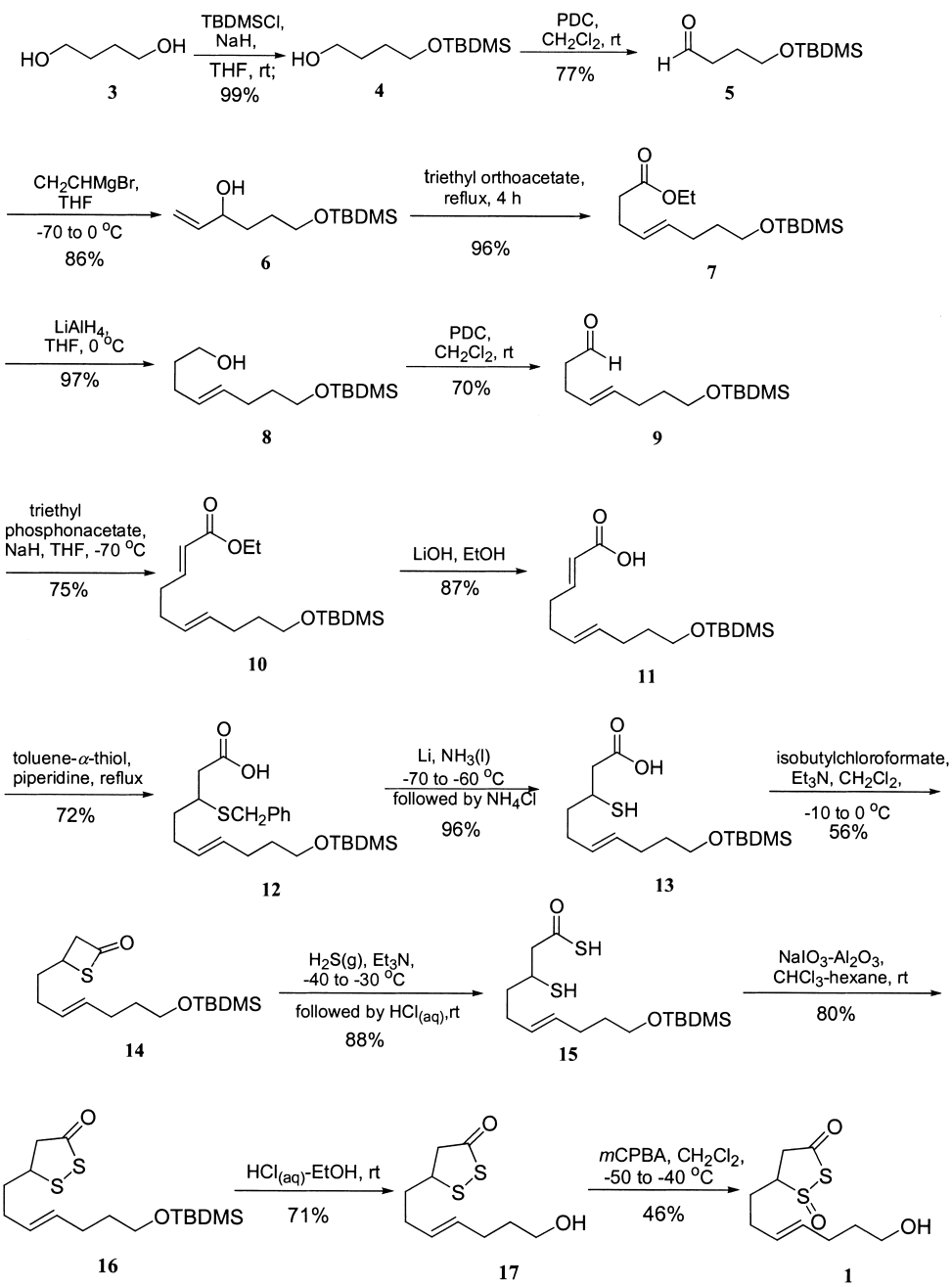
† A University Grants Committee Area of Excellence Scheme in Hong Kong.

PII: S0040-4020(02)01600-9

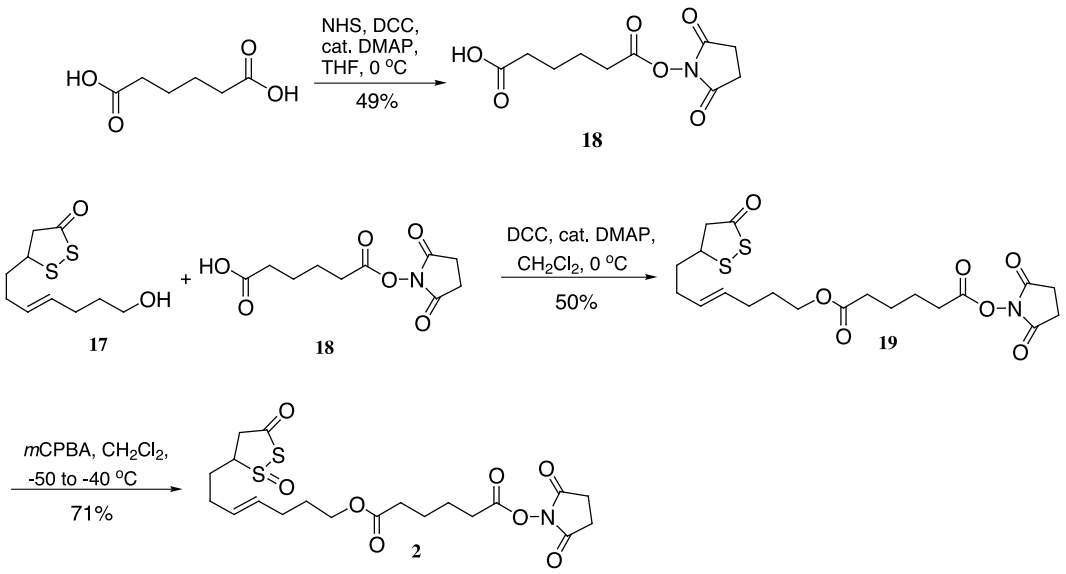
dithiolan-3-one 1-oxide **1** as well as its corresponding activated ester **2** that possess both the 1,3-dioxo-1,2-dithiolane heterocycle and a double bond at the gamma position of the heterocycle. It is anticipated that **2** could be readily linked to a DNA binding reagent such as antisense oligonucleotide or peptides.[18–20] We now report the synthesis of 5-(7-hydroxyhept-3-enyl)-1,2-dithiolan-3-one 1-oxide **1** and its corresponding activated ester **2** in detail.

2. Results and discussion

Our synthesis of **1** began with the monosilylation of 1,4-butanediol followed by an oxidation reaction using PDC to afford the corresponding aldehyde **5**. The reaction of vinylmagnesium bromide with **5** gave rise to allylic alcohol **6**. The ethyl ester **7** was obtained through the reaction of **6** with triethyl orthoacetate in the presence of a catalytic amount of propanoic acid. Compound **8** was produced through the reduction reaction of **7** with $LiAlH_4$ in THF, which was re-oxidized using PDC in CH_2Cl_2 to afford aldehyde **9**. The synthesis of **10** was carried out by means of the Horner–Emmons reaction[21] of **9** with phosphonate carbanions in an aprotic polar solvent. Hydrolysis of **10** was achieved by utilizing lithium hydroxide/ethanol. Production of benzyl thioether **12** was accomplished by the reaction of prop-2-enoic acid **11** with toluene-α-thiol in piperidine.[22] Li/liquid ammonia was employed to carry out this debenzylation reaction because the mercapto acid **13** is too unstable to survive in many purification processes.



Scheme 1.



Scheme 2.

Cyclization of **13** in a solution of isobutyl chloroformate and triethylamine gave rise to the corresponding thiolactone **14**. The mercapto thioic acid **15** was obtained through a ring opening reaction[17] of **14**. Oxidative ring closure of mercapto-thiolic acid **15** generated dithiolane **16** through exposure of the reaction mixture to sodium iodate supported on neutral alumina.[23] Desilylation of **16** in hydrochloric acid/ethanol was utilized to produce the corresponding alcohol **17**. Finally, *m*-CPBA was used to accomplish the *S*-oxidation of 1,2-dithiolan-3-one moiety to produce the 1,2-dithiolan-3-one 1-oxide **1** (Scheme 1).

With the intention of covalently linking the core functionality of leinamycin to certain DNA-binding agents for the future use, **2** was also synthesized. Compound **18** was prepared from the reaction of adipic acid and *N*-hydroxysuccinimide, and this was condensed with compound **17** to afford **19**. Subsequently oxidation of **19** by *m*-CPBA provided the activated ester **2** (Scheme 2).

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were obtained on a Bruker Advance DPX 400 FT-NMR Spectrometer or Varian Unity INOVA 500 FT-NMR Spectrometer as solutions in $CDCl_3$ unless otherwise indicated, and the chemical shifts are reported in parts per million (ppm, δ). Coupling constants are reported in hertz (Hz). Low resolution mass spectra were obtained on Fisons VG Platform Mass Spectrometer, or Hewlett Packard G1800C GCD Series II GCMS. High resolution mass spectra (HRMS) were measured by Finnigan MAT95 and Thermo Finnigan MAT95XL Mass Spectrometers. IR spectra were recorded on Nicolet Avatar 360 FT-IR Spectrometer as a thin film on the polished NaCl plates and the characteristic bands were reported in reciprocal centimeters (cm^{-1}). All reactions were monitored by thin layer chromatography (TLC) performed on Merck precoated silica gel 60 F_{254} plates. Flash chromatography was carried out on columns of NA or Merck silica gel 60 (230–400 mesh). THF was distilled from Na/benzophenone and dichloromethane was distilled from CaH_2 respectively prior to use. Unless otherwise noted, materials and solvents were obtained from commercial suppliers and used without further purification.

3.1.1. 4-*tert*-Butyldimethylsiloxy-*n*-butan-1-ol (4). A solution of **3** (23.0 mL, 0.25 mol) in THF (40 mL) was added to a suspension of sodium hydride (11.20 g, 0.28 mol) in THF (600 mL), and the mixture was stirred at room temperature for 2.5 h. *tert*-Butyldimethylsilyl chloride (42.2 g, 0.28 mol) in THF (60 mL) was added and the mixture was stirred at room temperature overnight followed by the addition of saturated aqueous K_2CO_3 (300 mL). The mixture was extracted with diethyl ether (3×250 mL) and the combined organic extracts were washed with brine (150 mL), dried (Na_2SO_4) and concentrated in vacuo to yield the known compound,[24] **4** (57.42 g, 99%) as a colorless syrup: IR (film) 3682, 3611, 3339, 3017, 2930, 2858, 1424, 1265, 1219, 1091, 1025, 784, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.65 (m, 4H), 1.64 (m, 4H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 63.3, 62.8, 30.2, 29.9, 25.9, 18.3, −5.5; ESIMS *m/z* (%): 205 ($[M+1]^+$, 100).

3.1.2. 4-*tert*-Butyldimethylsiloxy-1-butyraldehyde (5). A solution of **4** (31.5 g, 0.15 mol) in distilled CH_2Cl_2 (80 mL) was added to a mixture of PDC (84.6 g, 0.23 mol) and activated molecular sieves (type 5A powder, 25 g) in distilled CH_2Cl_2 (200 mL), and the mixture was stirred for 8 h. Diethyl ether (50 mL) was added, and the ethereal mixture was suction-filtered and the filter-cake was washed with diethyl ether and EtOAc. The organics were concentrated in vacuo and the residue was purified by flash chromatography (hexane/EtOAc 20:1) to afford **5**[25] (29.6 g, 77%) as a colorless oil: IR (film) 3058, 2991, 2955, 2924, 2853, 1716, 1424, 1271, 1096, 892, 840, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.79 (s, 1H), 3.65 (t, 2H,

J=6.0 Hz), 2.50 (td, 2H, J=7.0, 1.5 Hz), 1.86 (quintet, 2H, J=6.5 Hz), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.6, 62.0, 40.7, 25.8, 25.4, 18.2, −5.5; ESIMS m/z (%): 203 ($[M+1]^+$, 8), 187 (100); HREIMS calcd for $C_{10}H_{21}O_2Si$ $[M-H]^+$ 201.1305; found: 201.1305.

3.1.3. 6-*tert*-Butyldimethylsiloxy-hex-1-en-3-ol (6). A few drops of iodomethane were added to a mixture of magnesium turnings (2.8 g, 0.106 mol) and distilled THF (10 mL) followed by the addition of 1 M of vinyl bromide in THF (92.0 mL). After reflux for 1 h, the resultant Grignard reagent was cooled to room temperature, filtered and transferred to a different flask by cannula. A solution of **5** (15.6 g, 76.7 mmol) in distilled THF (35.0 mL) at −70°C was added to this filtered Grignard reagent, and the mixture was stirred at the same temperature for 1 h. The mixture was further stirred overnight while the solution was allowed to warm up to room temperature. Saturated aqueous NH_4Cl (50 mL) was added into the white turbid solution chilled in an ice bath. The aqueous phase was extracted with EtOAc (3×100 mL) and the combined organic extracts were washed with water (50 mL) and brine (2×50 mL), dried (Na_2SO_4) and concentrated in vacuo to give a yellow syrup. Purification with flash column chromatography (hexane/EtOAc 15:1) to afford **6** (15.3 g, 86%) as a slightly yellow oil: IR (film) 3442, 3345, 3017, 2960, 2925, 2847, 1465, 1255, 1209, 1096, 927, 835, 753, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.87 (m, 1H), 5.23 (d, 1H, J=17.5 Hz), 5.09 (d, 1H, J=10.5 Hz), 4.12 (m, 1H), 3.66 (t, 2H, J=6.0 Hz), 1.63 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.2, 114.3, 72.6, 63.4, 34.4, 28.7, 25.9, 18.3, −5.4; ESIMS m/z (%): 231 ($[M+1]^+$, 100), 213 (24), 205 (31), 195 (20), 187 (12); HRESIMS calcd for $C_{12}H_{27}O_2Si$ $[M+H]^+$ 231.1773; found: 231.1775.

3.1.4. 8-*tert*-Butyldimethylsiloxy-oct-4-enoic acid ethyl ester (7). A mixture of **6** (12.7 g, 55.1 mmol), triethyl orthoacetate (80 mL, 0.496 mol) and catalytic amount of propanoic acid (0.41 mL, 5.50 mmol) was refluxed for 4 h followed by the removal of triethyl orthoacetate. The residues were dissolved in EtOAc (80 mL), and the mixture was extracted with brine (2×30 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 25:1) to afford **7** (15.9 g, 96%) as a yellow syrup: IR (film) 3012, 2955, 2925, 2848, 1721, 1521, 1470, 1255, 1214, 1086, 1040, 835, 748, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.43 (m, 2H), 4.12 (q, 2H, J=7.0 Hz), 3.58 (t, 2H, J=6.4 Hz), 2.32 (m, 4H), 2.02 (q, 2H, J=6.3 Hz), 1.55 (quintet, 2H, J=6.6 Hz), 1.26 (t, 3H, J=11.0 Hz), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 131.1, 128.3, 62.5, 60.2, 34.4, 32.5, 28.7, 27.9, 25.9, 18.3, 14.2, −5.3; ESIMS m/z (%): 301 ($[M+1]^+$, 100), 169 (25); HRCIMS calcd for $C_{16}H_{31}O_3Si$ $[M-H]^-$ 299.2034; found: 299.2048.

3.1.5. 8-*tert*-Butyldimethylsiloxy-oct-4-en-1-ol (8). $LiAlH_4$ (2.34 g, 58.8 mmol) was added to a solution of **7** (16.08 g, 53.5 mmol) in distilled THF (150 mL) at 0°C, and the solution was stirred at room temperature for 1.5 h. EtOAc (20 mL) and 10% aqueous HCl were added and the mixture was extracted with EtOAc (3×90 mL). The combined extracts were washed with water (40 mL) and brine (40 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 4:1) to give **8** (13.41 g, 97%) as a colorless oil: IR (film) 3621, 3452, 3350, 3017, 2935, 2848, 1255, 1209, 1091, 835, 739, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.44 (m, 2H), 3.65 (t, 2H, J=6.5 Hz), 3.60 (t, 2H, J=6.5 Hz), 2.05 (m, 4H), 1.63 (quintet, 2H, J=6.5 Hz), 1.55 (quintet, 2H, J=6.5 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.6, 129.8, 62.6, 32.6, 32.4, 28.9, 28.8, 25.9, 18.3, −5.3; ESIMS m/z (%): 258 (M^+, 18), 209 (14), 187 (29), 177 (11), 145 (59), 127 (100); HRFABMS calcd for $C_{14}H_{31}O_2Si$ $[M+H]^+$ 259.2088; found: 259.2086.

3.1.6. 8-*tert*-Butyldimethysiloxy-oct-4-en-1-al (9). A solution of **8** (8.99 g, 34.80 mmol) in distilled CH_2Cl_2 (120 mL) was added to a mixture of PDC (19.64 g, 52.20 mmol) and activated molecular sieves (type 5A powder, 7.2 g) in distilled CH_2Cl_2 (250 mL) at room temperature, and the mixture was stirred at the same temperature for 3 h. Diethyl ether (90 mL) was added, and the ethereal phase was suction-filtered. The combined organics were concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EtOAc 20:1) to yield **9** (6.25 g, 70%) as a colorless oil: IR (film) 3360, 3022, 2929, 2853, 1726, 1470, 1260, 1209, 1096, 835, 758, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.76 (s, 1H), 5.44 (m, 2H), 3.58 (t, 2H, J=6.5 Hz), 2.49 (td, 2H, J=7.0, 1.5 Hz), 2.32 (q, 2H, J=7.0 Hz), 2.03 (q, 2H, J=7.5 Hz), 1.55 (quintet, 2H, J=7.5 Hz), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.4, 131.4, 127.9, 62.5, 43.5, 43.4, 32.4, 28.7, 25.9, 25.2, 18.3, −5.3; ESIMS m/z (%): 257 ($[M+1]^+$, 100), 228 (20), 125 (12); HRESIMS calcd for $C_{14}H_{29}O_2Si$ $[M+H]^+$ 257.1929; found: 257.1917.

3.1.7. Ethyl (*E*)-10-*tert*-butyldimethylsiloxy-dec-2-enoate (10). Triethyl phosphonoacetate (7.2 mL, 36.32 mmol) was added to NaH (2.61 g, 32.40 mmol) in THF (100 mL), and the solution was stirred at room temperature for 1 h followed by the addition of **9** (7.76 g, 30.27 mmol) in THF (60 mL). The mixture was heated at reflux for 1 h and allowed to cool down to room temperature. After the removal of the solvents, the residue was dissolved in CH_2Cl_2, and the mixture was washed with water (30 mL) and brine (40 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 60:1) to afford **10** (7.41 g, 75%) as a slightly yellow syrup: IR (film) 3017, 2930, 2853, 1711, 1655, 1470, 1368, 1250, 1209, 1096, 1035, 840, 743, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.95 (s, 1H), 5.81 (dd, 1H, J=15.5, 1.5 Hz), 5.42 (m, 2H), 4.18 (q, 2H, J=7.0 Hz), 3.59 (t, 2H, J=7.0 Hz), 2.25 (q, 2H, J=7.0 Hz), 2.14 (q, 2H, J=6.0 Hz), 2.03 (q, 2H, J=6.5 Hz), 1.56 (quintet, 2H, J=7.0 Hz), 1.28 (t, 3H, J=6.5 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 148.6, 131.1, 128.7, 121.5, 62.5, 60.1, 32.5, 32.2, 32.2, 30.9, 28.7, 25.9, 18.3, 18.3, 14.3, −5.3; ESIMS m/z (%): 327 ($[M+1]^+$, 13), 277 (10), 255 (12), 235 (13), 214 (9), 213 (100), 167 (22); HRCIMS calcd for $C_{18}H_{33}O_3Si$ $[M-H]^-$ 325.2204; found: 325.2204.

3.1.8. (*E*)-10-*tert*-Butyldimethylsiloxy-dec-2-enoic acid (11). LiOH (25.52 g, 0.340 mol) was added to a solution of **10** (18.64 g, 56.74 mmol) in ethanol (120 mL) and water

(5 mL), and the mixture was stirred at room temperature for 22 h. The mixture was filtered and the filter-cake was washed with EtOAc. The combined organics were concentrated in vacuo and the residue was dissolved in water (30 mL). The aqueous solution was acidified to pH 4–5 by adding 10% aqueous HCl. The mixture was extracted with CH_2Cl_2 (3×90 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc 10:1) to afford **11** (14.83 g, 87%) as a white solid: mp 35.0–36.8°C; IR (film) 3611, 3442, 3349, 3017, 2925, 2848, 1695, 1655, 1429, 1214, 1096, 1045, 835, 753, 656 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.06 (m, 1H), 5.83 (dt, 1H, J=15.5, 2.0 Hz), 5.43 (m, 2H), 3.60 (t, 2H, J=6.5 Hz), 2.28 (q, 2H, J=6.5 Hz), 2.16 (q, 2H, J=7.0 Hz), 2.04 (q, 2H, J=7.0 Hz), 1.56 (quintet, 2H, J=6.5 Hz), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 151.6, 131.3, 128.5, 120.9, 62.6, 32.5, 32.3, 30.8, 28.7, 25.9, 18.3, −5.3; ESIMS *m/z* (%): 298 ([M+1]$^+$, 24), 227 (11), 213 (31), 186 (8), 185 (100), 167 (40); HRESIMS calcd for $C_{16}H_{30}O_3Si$ [M+H]$^+$ 298.1956; found: 298.1951.

3.1.9. 3-Benzylsulfanyl-10-*tert*-butyldimethylsiloxy-dec-6-enoic acid (12). A mixture of **11** (12.12 g, 40.33 mmol), toluene-α-thiol (5.51 mL, 44.36 mmol) and freshly distilled piperidine (30 mL) was refluxed under nitrogen overnight. The mixture was chilled in an ice bath followed by the addition of 10% aqueous HCl to allow the pH of the aqueous solution to reach 2–3. The suspension was extracted with diethyl ether (3×100 mL) and the combined extracts were washed with brine (3×40 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 10:1 initially and 3:1 subsequently) to afford **12** (12.21 g, 72%) as a yellow oil: IR (film) 3683, 3339, 3017, 2935, 2848, 1706, 1521, 1419, 1209, 1096, 968, 922, 748, 661 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (m, 4H), 7.22 (m, 1H), 5.33 (m, 2H), 3.75 (s, 2H), 3.59 (t, 2H, J=6.5 Hz), 2.97 (quintet, 1H, J=6.0 Hz), 2.60 (dd, 2H, J=7.0, 2.5 Hz), 2.05 (m, 4H), 1.60 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7, 138.5, 130.8, 130.5, 129.6, 129.1, 128.9, 128.5, 127.0, 62.6, 40.6, 35.5, 34.6, 32.5, 29.6, 28.8, 25.9, 25.6, 18.3, −5.3; ESIMS *m/z* (%): 423 ([M+1]$^+$,29), 422 (M$^+$, 29), 377 (12), 376 (80), 310 (14), 309 (100), 252 (83), 227 (30), 219 (40), 213 (39), 190 (44), 167 (14); HRCIMS calcd for $C_{23}H_{37}O_3SSi$ [M−H]$^-$ 421.2238; found: 421.2246.

3.1.10. 10-*tert*-Butyldimethylsiloxy-3-mercapto-dec-6-enoic acid (13). A flask equipped with a stirrer, calcium chloride drying tube, nitrogen inlet, dry ice condenser and ammonia inlet was flushed thoroughly with a stream of nitrogen. A solution of **12** (0.791 g, 1.878 mmol) in distilled THF (8 mL) was added to the flask chilled at −78°C. Gaseous ammonia (ca. 25 mL) was passed through and condensed into the flask at the same temperature. Finely divided metal lithium was added and a deep blue color of the solution persisted. The mixture was stirred at −78°C for 30 min followed by the addition of solid NH_4Cl. After removal of remaining ammonia by a stream of nitrogen, the residue was dissolved in water (20 mL) and the mixture was acidified by the addition of 15% aqueous HCl to allow the pH of the aqueous solution to reach 2–3. The mixture was extracted with CH_2Cl_2 (3×50 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated in vacuo to afford **13** (0.596 g, 96%) as a colorless syrup: IR (film) 3395, 3012, 2924, 2585, 1711, 1516, 1465, 1409, 1209, 1045, 840, 758, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.42 (m, 2H), 3.60 (t, 2H, J=6.5 Hz), 3.18 (m, 1H), 2.73 (dd, 1H, J=16.5, 5.5 Hz), 2.57 (dd, 1H, J=16, 8.5 Hz), 2.11 (m, 4H), 1.70 (d, 1H, J=8.0 Hz), 1.57 (m, 4H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8, 131.2, 128.7, 62.6, 44.0, 37.9, 35.5, 32.5, 29.9, 28.8, 25.9, 25.6, 18.3, −5.3; ESIMS *m/z* (%): 332 (M$^+$, 12), 330 (22), 286 (8), 285 (14), 284 (78), 227 (100), 217 (41), 146 (20), 139 (18), 129 (8); HRESIMS calcd for $C_{16}H_{34}O_3SSi$ [M+2]$^+$ 334.1989; found: 334.2010.

3.1.11. 4-(7-*tert*-Butyldimethysiloxyhept-3-enyl)thietan-2-one (14). Freshly distilled isobutyl chloroformate (1.40 mL, 10.76 mmol) was added to a solution of **13** (3.23 g, 9.786 mmol) and Et_3N (1.27 mL, 11.74 mmol) in CH_2Cl_2 (25 mL) at −10°C. The mixture was stirred for 15 min while its temperature was allowed to warm up to 0°C. The mixture was diluted with CH_2Cl_2 (25 mL) and washed with cold 15% aqueous HCl (3×15 mL), water (20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The resultant residue was purified by flash column chromatography (hexane/EtOAc 15:1) to yield **14** (1.378 g, 56%) as a slightly yellow oil: IR (film) 3053, 2980, 2925, 2853, 1747, 1655, 1419, 1265, 1096, 979, 886, 840, 753, 702 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 5.28 (m, 1H), 5.17 (m, 1H), 3.54 (t, 2H, J=6.5 Hz), 3.24 (q, 1H, J=7.0 Hz), 2.81 (q, 1H, J=4 Hz), 2.77 (m, 1H), 2.06 (q, 2H, J=7.0 Hz), 1.70 (m, 2H), 1.56 (quintet, 2H, J=6.5 Hz), 1.32 (q, 2H, J=8.0 Hz), 0.99 (s, 9H), 0.07 (s, 6H); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.46 (m, 1H), 5.39 (m, 1H), 4.01 (q, 1H, J=10 Hz), 3.60 (t, 2H, J=6.5 Hz), 3.52 (m, 2H), 2.06 (m, 5H), 1.90 (m, 1H), 1.57 (quintet, 2H, J=6.5 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.9, 131.8, 128.1, 62.5, 60.6, 37.6, 32.7, 32.6, 32.5, 31.7, 28.8, 25.9, 18.3, −5.3; ESIMS *m/z* (%): 315 ([M+1]$^+$, 100), 273 (71), 257 (89), 183 (46), 149 (14), 141 (39); HRCIMS calcd for $C_{16}H_{29}O_2SSi$ [M−H]$^-$ 313.1663; found: 313.1657.

3.1.12. 10-*tert*-Butyldimethylsiloxy-3-mercapto-dec-6-enethioic acid (15). A stirred solution of the thiolactone **14** (1.021 g, 3.247 mmol) in CCl_4 (20 mL) at ca −35°C was saturated with hydrogen sulfide gas, and the mixture was stirred at the same temperature for 20 min. Freshly distilled Et_3N (0.55 mL, 4.871 mmol) was added to the reaction mixture through a hypodermic syringe. The solution was further saturated with H_2S gas for 8 h at the same temperature. The resultant mixture was diluted with $CHCl_3$ (20 mL) and washed with 10% aqueous HCl (2×10 mL), water (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo to give **15** (0.996 g, 88%) as a yellow oil which was subjected to the oxidative reaction in the next step without further purification.

3.2. Preparation of sodium iodate supported on neutral alumina

Sodium iodate (0.4 g, 2 mmol) was added to 5 mL of distilled water in a 50 mL round-bottom flask, and the mixture was warmed up to allow the solution to become

transparent. 1.0 g of alumina was added to the mixture, and the mixture was shaken for 30 min followed by the removal of solvents in vacuo.

3.2.1. 5-(7-*tert*-Butyldimethysiloxyhept-3-enyl)-1,2-dithiolan-3-one (16). Excess $NaIO_3/Al_2O_3-NaIO_3$ (8.1 g) was added to **15** (0.996 g, 2.854 mmol) in a mixture of hexane and $CHCl_3$ (16 mL: 2 mL), and the mixture was stirred at room temperature for 40 min followed by suction filtration. The filter-cake was washed with CH_2Cl_2 (50 mL). The combined organics were concentrated in vacuo, and the residue was purified by flash column chromatography (hexane/EtOAc 15:1) to afford **16** (0.791 g, 80%) as a slightly yellow oil: IR (film) 3012, 2935, 2858, 1705, 1470, 1429, 1388, 1255, 1214, 1096, 968, 840, 763, 661, 615 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.50 (m, 1H), 5.39 (m, 1H), 3.70 (quintet d, 1H, J=7.3, 2.5 Hz), 3.60 (t, 2H, J=6.5 Hz), 3.00 (dd, 1H, J=16, 5.5 Hz), 2.67 (dd, 1H, J=16.5, 8.5 Hz), 2.17 (quintet, 2H, J=6.5 Hz), 2.03 (q, 2H, J=6.5 Hz), 1.82 (m, 2H), 1.57 (quintet, 2H, J=7.0 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.5, 132.1, 127.9, 62.5, 49.2, 48.3, 32.5, 32.4, 30.6, 28.8, 25.9, 19.1, 18.3, −5.3; ESIMS m/z (%): 350 (20), 347 ([M+1]$^+$, 14), 339 (38), 307 (68), 275 (84), 257 (100), 233 (54), 199 (63), 193 (40), 161 (49); HRCIMS calcd for $C_{16}H_{30}O_2S_2Si$ [M]$^-$ 346.1462; found: 346.1460.

3.2.2. 5-(7-Hydroxyhept-3-enyl)-1,2-dithiolan-3-one (17). 15% Aqueous HCl was added to a solution of **16** (0.439 g, 1.267 mmol) in absolute EtOH (15 mL), and the mixture was stirred at room temperature for 30 min followed by the addition of Et_3N (0.5 mL). The neutralized solution was extracted with CH_2Cl_2 (20 mL) and washed with water (10 mL) and brine (10 mL). The extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 5:1) to afford **17** (0.207 g, 71%) as a yellow syrup: IR (film) 3688, 3606, 3447, 3345, 3022, 2919, 2858, 1721, 1404, 1214, 1091, 1045, 835, 758, 677 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 5.26 (m, 1H), 5.10 (m, 1H), 3.38 (t, 2H, J=6.0 Hz), 2.92 (m, 1H), 2.28 (dd, 1H, J=15.5, 5.0 Hz), 1.97 (m, 3H), 1.73 (m, 2H), 1.44 (quintet, 2H, J=7.0 Hz), 1.33 (m, 1H), 1.12 (m, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 204.5, 131.6, 128.5, 61.9, 48.6, 48.2, 32.6, 32.3, 30.6, 29.1; ESIMS m/z (%): 234 ([M+2]$^+$, 31), 232 (M$^+$, 43), 223 (23), 217 (12), 203 (25), 201 (43), 199 (100), 185 (22), 171 (47); HRESIMS calcd for $C_{10}H_{16}O_2S_2$ [M]$^+$ 232.0683; found: 232.0687.

3.2.3. 5-(7-Hydroxyhept-3-enyl)-1,2-dithiolan-3-one 1-oxide (1). A solution of 70–75% *m*-CPBA (0.480 g, 1.902 mmol) in distilled CH_2Cl_2 (6 mL) was added to a solution of 1,2-dithiolan-3-one **17** (0.178 g, 0.761 mmol) in distilled CH_2Cl_2 (10 mL), and the mixture was stirred at −40 to −50°C for 30 min and warmed up to 0°C. Saturated sodium sulfite solution was added, and the aqueous suspension was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with saturated sodium sulfite solution (20 mL), water (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. The resultant residue was purified by flash column chromatography (hexane/EtOAc 3:1 initially and 2:1 subsequently) to afford **1** (0.087 g, 46%) as a slightly yellow oil: IR (film) 3339, 3012, 2925, 2853, 1721, 1440, 1209, 1040, 758, 661 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 5.25 (m, 1H), 5.06 (m, 1H), 3.32 (t, 2H, J=6.5 Hz), 2.69 (dd, 1H, J=17.0, 12.5 Hz), 2.33 (m, 1H), 2.16 (dd, 1H, J=17.0, 5.5 Hz), 1.95 (q, 2H, J=7.0 Hz), 1.69 (m, 2H), 1.53 (m, 1H), 1.42 (q, 2H, J=6.5 Hz), 1.21 (m, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 200.1, 132.2, 63.6, 61.8, 41.7, 32.4, 29.6, 29.1, 27.7; ESIMS m/z (%): 249 ([M+1]$^+$,100), 217 (10); HRCIMS calcd for $C_{10}H_{16}O_3S_2$ [M]$^-$ 248.0546; found 248.0539.

3.2.4. Hexanedioic acid mono-(2,5-dioxo-pyrrolidin-1-yl)ester (18). To a solution of adipic acid (5.02 g, 34.1 mmol) and *N*-hydroxysuccinimide (4.05 g, 40.9 mmol) in distilled THF (60 mL) at 0°C was added *N*,*N*′-dicyclohexylcarbodiimide (7.22 g, 34.9 mmol) in distilled THF (20 mL). The mixture was stirred at the same temperature for 15 min followed by the addition of catalytic amount of DMAP (~30 mg) and further stirred overnight during which time period the mixture was allowed to warm up to room temperature. The resultant DCU was filtered off and the filtrate was concentrated in vacuo. The resultant residue was redissolved in CH_2Cl_2 (50 mL). The organics were washed with water (2×20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. The resultant residue was purified by flash column chromatography (hexane/ EtOAc/CH_2Cl_2 10:1:1) to afford **18** (3.83 g, 49%) as white crystals: IR (film) 3017, 1742, 1521, 1424, 1214, 1060, 758, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.84 (brd, 4H, J=4.5 Hz), 2.65 (t, 2H, J=7.0 Hz), 2.42 (t, 2H, J=7.0 Hz), 1.79 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.2, 169.5, 168.5, 33.6, 30.8, 25.8, 24.1, 23.9; ESIMS m/z (%): 244 ([M+1]$^+$, 38), 226 (11), 225 (100), 111 (9), 91 (14); HRESIMS calcd for $C_{10}H_{13}NO_6$ [M]$^+$ 243.1029; found: 243.1018.

3.2.5. Hexanedioic acid 2,5-dioxo-pyrrolidin-1-yl ester 7-hept-3-enyl-[5-(1,2-dithiolan-3-one)] ester (19). *N*,*N*′-dicyclohexylcarbodiimide (0.110 g, 0.506 mmol) in distilled CH_2Cl_2 (2 mL) was added to a solution of **17** (0.108 g, 0.456 mmol) and **18** (0.125 g, 0.506 mmol) in CH_2Cl_2 (4 mL) at 0°C, and the mixture was stirred at the same temperature for 5 min. A catalytic amount of DMAP (~10 mg) was added, and the mixture was stirred at room temperature for 3 h. The resultant DCU was filtered off and the filter-cake was washed with CH_2Cl_2. The combined organics were concentrated in vacuo and the resultant residue was purified by flash column chromatography (hexane/EtOAc 5:1) to afford **19** (0.104 g, 50%) as a white semi solid: IR (film) 3048, 2981, 1819, 1783, 1741, 1419, 1363, 1260, 1204, 1060, 892, 733, 702 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 5.19 (m, 1H), 5.09 (m, 1H), 3.99 (t, 2H, J=6.5 Hz), 2.95 (m, 1H), 2.30 (dd, 1H, J=13.5, 8.0 Hz), 2.07 (t, 2H, J=6.5 Hz), 1.99 (dd overlap with t, 3H, J=17.0, 7.0 Hz), 1.89 (q, 2H, J=7.5 Hz), 1.78 (m, 1H), 1.70 (m, 3H), 1.50 (m, 4H), 1.42 (m, 5H), 1.16 (m, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 205.0, 172.3, 168.7, 168.7, 13.1, 129.1, 63.4, 48.6, 48.1, 33.5, 32.2, 30.6, 30.5, 28.9, 28.5, 25.1, 24.1, 24.0; ESIMS m/z (%): 457 (M$^+$, 33), 344 (13), 343 (100), 317 (49), 225 (21), 217 (30), 215 (38), 212 (24), 149 (21), 135 (35), 91 (52); HRCIMS calcd for $C_{20}H_{27}NO_7S_2$ [M]$^-$ 457.1234; found: 457.1225.

3.2.6. Hexanedioic acid 2,5-dioxo-pyrrolidin-1-yl ester 7-hept-3-enyl-[5-(1,2-dithiolan-3-one 1-oxo)] ester (2). A

solution of 70–75% *m*-CPBA (0.110 g, 0.434 mmol) in CH_2Cl_2 (3 mL) was added to a solution of 1,2-dithiolan-3-one **19** (0.080 g, 0.170 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at −40 to −50°C for 30 min. After warming the mixture up to 0°C, saturated sodium sulfite aqueous solution was added, followed by the extraction of the aqueous suspension with CH_2Cl_2 (2×15 mL). The combined organic extracts were washed with saturated sodium sulfite aqueous solution (3×10 mL), water (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 8:1 initially and 3:1 subsequently) to afford **2** (0.058 g, 71%) as a colorless oil consisting of two inseparable diastereomers* due to the chiral centers at 1' and 3 positions of the molecule: IR (film) 3017, 2955, 1818, 1782, 1736, 1516, 1419, 1214, 1060, 922, 748, 666 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 5.13 (m, 1H), 4.96 (m, 1H), 3.98 (m, 2H), 3.24 (dd, 0.5H, J=17.0, 6.0 Hz)*, 2.84 (q, 0.5H, J=6.5 Hz)*, 2.74 (dd, 0.5H, J=17.0, 13.0)*, 2.44 (m, 0.5H)*, 2.25 (m, 1H), 2.08 (t, 2H, J=7.0 Hz), 1.99 (m, 2H), 1.88 (quintet, 2H, J=7.0 Hz), 1.69 (m, 3H), 1.49 (m, 9H), 1.30 (m, 1H), 1.12 (m, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 172.4, 168.8, 168.7, 131.4, 131.15, 128.9, 128.4, 65.9, 63.6, 63.3, 42.2, 41.7, 33.5, 30.5, 29.8, 29.5, 28.9, 28.9, 28.5, 28.4, 28.2, 27.7, 25.2, 24.1, 24.0; ESIMS *m*/*z* (%): 474 ($[M+1]^+$, 22), 360 (8), 359 (51), 317 (23), 231 (16), 225 (100), 213 (23), 135 (21), 91 (26); HRCIMS calcd for $C_{20}H_{27}NO_8S_2[M]^-$ 473.1184; found: 473.1191.

Acknowledgements

We thank the Hong Kong Polytechnic University Area of Strategic Development Fund, the University Grants Committee of Hong Kong (Areas of Excellence Scheme, AoEP/10-01) and The Hong Kong Research Grant Council research grant (B-Q534) for the financial support and to Dr Jinyou Xu for helpful discussions.

References

1. Hara, M.; Takahashi, I.; Yoshida, M.; Asano, K.; Kawamoto, I.; Morimoto, M.; Nakano, H. *J. Antibiot.* **1989**, *42*, 333–335.
2. Hara, M.; Asano, K.; Kawamoto, I.; Takiguchi, T.; Katsumata, S.; Takahashi, K.; Nakano, H. *J. Antibiot.* **1989**, *42*, 1768–1774.
3. Hirayama, N.; Matsuzawa, E. S. *Chem. Lett.* **1993**, *11*, 1957–1958.
4. Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451–8452.
5. Hara, M.; Saitoh, Y.; Nakano, H. *Biochemistry* **1990**, *29*, 5678–5681.
6. Behroozi, S. J.; Kim, W.; Gates, K. S. *J. Org. Chem.* **1995**, *60*, 3964–3966.
7. Behroozi, S. J.; Kim, W.; Dannaldson, J.; Gates, K. S. *Biochemistry* **1996**, *35*, 1768–1774.
8. Asai, A.; Hara, M.; Kakita, S.; Kanda, Y.; Yoshida, M.; Saito, H.; Saitoh, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6802–6803.
9. Mitra, K.; Kim, W.; Daniels, J. S.; Gates, K. S. *J. Am. Chem. Soc.* **1997**, *119*, 11691–11692.
10. Asai, A.; Saito, H.; Saitoh, Y. *Bioorg. Med. Chem.* **1997**, *5*, 723–729.
11. Kanda, Y.; Ashizawa, T.; Saitoh, Y.; Saito, H.; Gomi, K.; Okabe, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 909–912.
12. Kanda, Y.; Ashizawa, T.; Kakita, S.; Takahashi, Y.; Kono, M.; Yoshida, M.; Saitoh, Y.; Okabe, M. *J. Med. Chem.* **1999**, *42*, 1330–1332.
13. Gates, K. S. *Chem. Res. Toxicol.* **2000**, *13*, 953–956.
14. Borman, S. *C&EN* **1996**, 38. Feb. 26.
15. Pattenden, G.; Shuker, A. J. *Tetrahedron Lett.* **1991**, *32*, 6625–6628.
16. Kanda, Y.; Saito, H.; Fukuyama, T. *Tetrahedron Lett.* **1992**, *33*, 5701–5704.
17. Pattenden, G.; Shuker, A. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1215–1221.
18. Li, T.; Rokita, S. E. *J. Am. Chem. Soc.* **1991**, *113*, 7771–7773.
19. Li, T.; Nicolaou, K. C. *Nature* **1994**, *369*, 218–221.
20. Nicolaou, K. C.; Ajito, K.; Komatsu, H.; Smith, B. M.; Li, T.; Egan, M. G.; Gomez, P. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 576–578.
21. Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624–2626.
22. Sweetman, B. J.; Vestling, M. M.; Ticaric, S. T.; Kelly, P. L.; Field, L.; Merryman, P.; Jaffe, I. A. *J. Med. Chem.* **1971**, *14*, 868–872.
23. Hirano, M.; Yakabe, S.; Ando, K.; Morimoto, T. *J. Chem. Res.* **1998**, 816–817.
24. McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388–3390.
25. Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865–3866.