Approach Toward the Total Synthesis of Griseoviridin: Formation of Thioethynyl and Thiovinyl Ether-Containing Nine-Membered Lactones through a Thioalkynylation−Macrolactonization−Hydrostannylation Sequence

Carine Kuligowski,[†] Sophie Bezzenine-Lafollée,[†] Grégory Chaume,[†] Jacqueline Mahuteau,[‡] Jean-Claude Barrière,[§] Eric Bacqué,[§] Ange Pancrazi,*[,†] and Janick Ardisson*[,†]

"Laboratoire de Synthèse Organique Sélective et Chimie Organométallique", CNRS-UCP-ESCOM, FRE 2126, 13 Bd de l'Hautil, 95092 Cergy-Pontoise Cedex, France, Service de RMN, CNRS-BIOCIS, Université de Châtenay-Malabry, Faculté de Pharmacie, 92296 Châtenay-Malabry, France, and Aventis Pharma, Medicinal Chemistry, Bat Grignard 3A, 13 Quai Jules Guesde, 94403 Vitry sur Seine, France

a.pancrazi@escom.fr

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Synthesis of the lactone core **17** of 8-*epi*-griseoviridin is reported. Thioethynyl derivative **11** was easily prepared via an anionic coupling reaction between acetylenic compound **9** and sulfone **10**. After desilylation of **11**, saponification of the resulting hydroxy ester **12** followed by a Mitsunobu macrolactonization furnished the unusual triple-bond-containing nine-membered lactone **13** in 50% yield for the last two steps (39% after recrystallization). Stannylation under Magriotis conditions led to the pure regio- and stereocontrolled vinyltin **14** (80% yield). After a Sn/I exchange, palladium-catalyzed carbonylation delivered either the ester lactone **16** in 67% yield or the propargyl amide **17** in 65% yield. Synthesis of propargyl amide **17** of the lactone core of 8-*epi*-griseoviridin was achieved in 11.9% overall yield from commercial L-cystin dimethyl ester (nine steps).

Streptogramin antibiotics are made of two structurally different components: polyunsaturated macrolactones (group A) and cyclic hexadepsipeptides (group B). Streptogramin derivatives of group A and B are bacteriostatic separately but exhibit synergetic activities against gram-positive organisms when associated. Furthermore, little resistance among staphylococci has been observed over 30 years of clinical practice in Europe for this class of antibiotics.[1] The significant antibiotic activity of streptogramin derivatives has attracted considerable attention from synthetic organic chemists.[2]

Griseoviridin **1**, a representative member of group A molecules, was first isolated from *Streptomyces griseus*.[3] The cyclic structure of griseoviridin encompasses the unsaturated sulfur-containing nine-membered lactone subunit **2** built from non natural D-(*R*)-cysteine (Scheme 1). Several synthetic approaches to griseoviridin **1** have been reported by Meyers,[4] Helquist,[5] Miller,[6] and Marcantoni,[7] but the only total synthesis of **1** was very recently described by Meyers.[8]

Our synthesis of lactone **2** is based on a thioalkynylation−macrolactonization−hydrostannylation sequence as shown in Scheme 2. This approach relies on a regio- and stereoselective Magriotis hydrostannylation[9] of a thioethynyl ether, which should lead selectively to (*E*)-vinylstannane **3**. The regioselectivity in this reaction should be controlled by the sulfur atom. Transformation of **3** into the target **2** could be effected by Sn/I exchange, followed by a Heck carbonylation reaction.[10]

This route involves an initial Mitsunobu lactonization of thioethynyl ether **5** to form lactone **4**. This intermediate **5** would be made by coupling acetylide **6** with the S-activated cysteine derivative **7**.

In this preliminary study, we decided to use the natural, less expensive L-(*S*)-cysteine, in place of the (*R*)-enantiomer, and therefore undertook the construction of the lactone core of the 8-*epi*-griseoviridin.

* Corresponding Authors. Phone: (33) 1 30 75 61 86. Fax: (33) 1 30 75 60 15. E-mail (J.A.): j. ardisson@escom.fr.

† "Laboratoire de Synthèse Organique Sélective et Chimie Organométallique".

‡ Université de Châtenay-Malabry. Phone: (33) 1 46 83 56 52.

§ Aventis Pharma. Phone: (33) 1 55 71 88 14. Fax: (33) 1 55 71 80 14.

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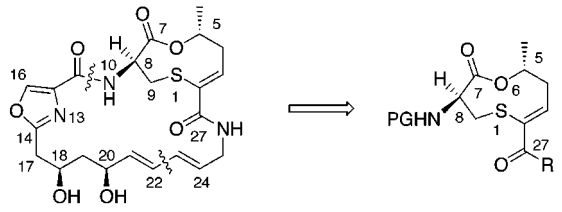
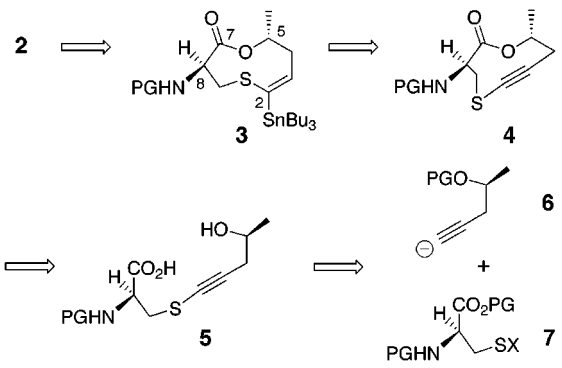
Scheme 1

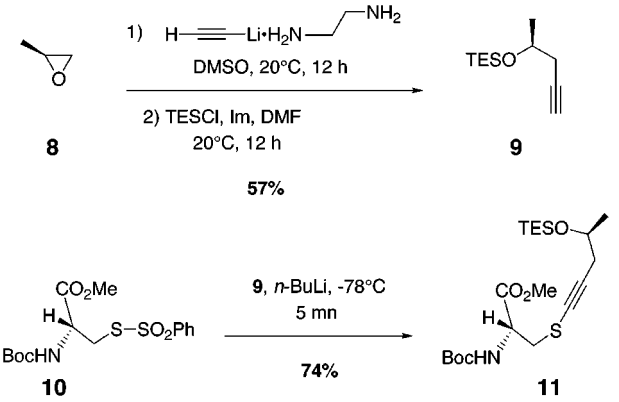


Griseoviridin 1 **2**

Scheme 2



Scheme 3

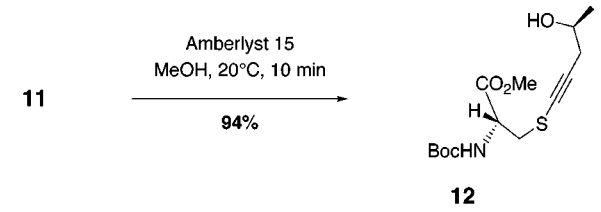


The required acetylenic compound **9** was prepared by opening (*S*)-propylene oxide **8** with lithium acetylide−ethylenediamine complex,[11] followed by protection of the secondary alcohol as a triethylsilyl ether (TES) in 57% yield for the two steps (Scheme 3).[12] Reaction of 2 equiv of the lithioacetylide derived from **9** (2 equiv of **9**, 2 equiv of *n*-BuLi, −78 °C, 45 min) with thiosulfonate **10**[13] at −78 °C for 5 min furnished the expected thioacetylenic derivative **11** in 74% yield.

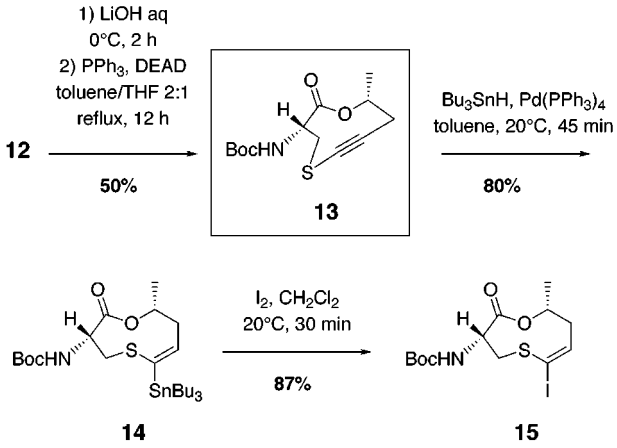
Deprotection of the triethylsilyl ether was effected under acidic conditions (Amberlyst 15/MeOH) to give hydroxy ester **12** in 94% yield (Scheme 4).

After saponification of **12** with LiOH in THF−H_2O (0 °C, 2 h), the crude hydroxy acid was directly subjected to Mitsunobu conditions,[14] previously used by Meyers, Helquist, and Miller (PPh_3/DEAD, 2:1 toluene/THF, 25 °C, 1.4×10^{-2} M), to furnish the expected

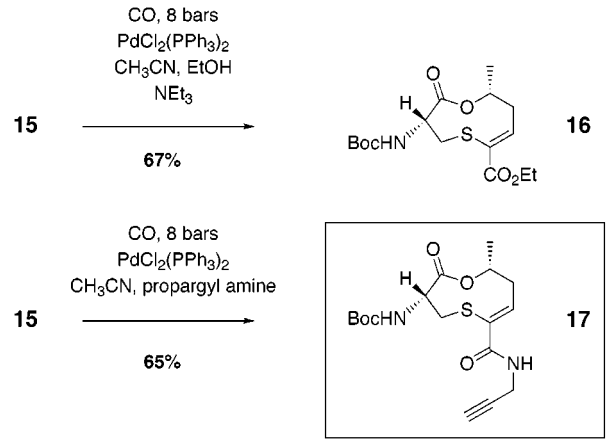
Scheme 4



Scheme 5



Scheme 6



unsaturated nine-membered lactone **13** as a white solid in 50% yield for the two steps (39% after recrystallization) (Scheme 5).

This cyclization step was followed by a Magriotis hydrostannylation of **13** [Bu_3SnH, $Pd(PPh_3)_4$, toluene, 20 °C, 45 min], which gave pure vinyltin lactone **14** in 80% yield. Formation of the corresponding iodo lactone **15** (I_2, CH_2Cl_2, 0 °C, 30 min) was then achieved in 87% yield by a Sn/I exchange.

The final carbonylation reaction step was first checked using CO (8 bar) and $PdCl_2(PPh_3)_2$ in CH_3CN/EtOH in the presence of NEt_3. Under these conditions, vinyl iodide **15** led to the ester **16** in 67% yield (Scheme 6). Since this reaction proceeded in good yield, we decided to use propargylamine in place of ethanol [CO, 8 bar, $PdCl_2(PPh_3)_2$, CH_3CN, propargylamine, Δ]. Thus, amide **17**, an advanced intermediate in the synthesis of 8-*epi*-griseoviridin, was obtained in 65% yield from **15**.

The synthesis of lactone core **17** of 8-*epi*-griseoviridin was achieved in 11.9% yield from commercial L-cystine dimethyl ester (nine steps) using a Mitsunobu macrolac-

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tonization−Magriotis hydrostannylation−Heck carbonylation sequence. The key step in this strategy is the formation of the novel thioethynyl−containing nine-membered lactone **13** in 50% yield (39% yield after recrystallization). The strategy developed here is being transposed to the synthesis of the natural lactone core **2** of griseoviridin from D-(*R*)-cysteine methyl ester. The synthesis of the remaining part of **1** is also in progress.

Experimental Section

Mass spectra were obtained via direct introduction by chemical ionization with ammonia (CI, NH_3). ^{1}H NMR spectra were recorded at 200 and 400 MHz and ^{13}C NMR at 50.3 and 100.6 MHz. Assignments were obtained using J-mod experiments and, when necessary, COSY, HMBC, HMQC, and NOESY experiments. Thin layer chromatography (TLC) was performed on a precoated plate of silica gel 60F 254 or aluminum oxide 60F 254. Flash chromatography was performed on silica gel 60, 230−400 mesh.

(4*S*)-4-[(Triethyl)silyloxy)]pent-1-yne (9). To a solution of commercial lithium acetylide−ethylenediamine complex (1.7 g, 18.6 mmol, 1.3 equiv) in DMSO (15 mL) at 5 °C was added commercial (*S*)-propylene oxide **8** (1 mL, 14.3 mmol). The reaction mixture was stirred at 20 °C for 12 h and poured into an aqueous NH_4Cl/diethyl ether mixture (20:50 mL) at 0 °C. The aqueous phase was extracted with diethyl ether (3 × 50 mL), and the combined organic phases were washed with 2 N HCl and brine. After the solution was dried over Na_2SO_4, the solvent was concentrated under reduced pressure. The crude residue was taken up in DMF (15 mL), and to this solution were added imidazole (1.96 g, 28.8 mmol, 2.02 equiv) and triethylsilyl chloride (3.6 mL, 21.4 mmol, 1.5 equiv). After stirring for 12 h at 20 °C, the reaction mixture was extracted with diethyl ether (3 × 50 mL) and washed with 2 N HCl and brine. After the solution was dried over Na_2SO_4, the solvent was concentrated under reduced pressure. Purification by flash chromatography of the crude residue on silica gel (cyclohexane) gave 1.62 g (57%) of **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.61 (q, 6 H, J = 7.9 Hz), 0.96 (t, 9 H, J = 7.9 Hz), 1. 26 (d, 3 H, J = 6.0 Hz), 1.98 (t, 1 H, J = 2.6 Hz), 2.27 (ddd, 1 H, J = 16.5, 5.3, 2.6 Hz), 2.39 (ddd, 1 H, J = 16.5, 5.3, 2.6 Hz), 3.97 (dqd, 2 H, J = 7.3, 6.0, 5.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 4.8 (3 CH_2), 6.7 (3 CH_3), 23.1 (CH_3), 29.4 (CH_2), 67.2 (CH), 69.7 (C), 81.6 (CH); IR (CCl_4) ν 3327, 2113 cm^{-1}; MS (CI, NH_3) m/z 216 ($M + NH_4^+$), 199 (MH^+), 186, 170, 159, 132, 119; $[\alpha]_D$ −2.5 (*c* 4.34, MeOH).

***N*-(*tert*-Butoxy)carbonyl-*S*-phenylsulfonyl-L-cysteine Methyl Ester (10).** To a solution of commercial dihydrochloride L-cystine dimethyl ester (0.94 g, 2.76 mmol) in dichloromethane (5 mL) was added a solution of di-*tert*-butyl dicarbonate (2.77 g, 12.7 mmol, 4.6 equiv) in dichloromethane (5 mL), followed by triethylamine (3 mL, 22 mmol, 8 equiv), and the reaction mixture was stirred at reflux for 2.5 h. After addition of water at 0 °C, the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed successively with 2 N aqueous HCl, water, and saturated aqueous NaCl and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography of the crude residue on silica gel (7:3 cyclohexane/ethyl acetate) delivered the *N*,*N*′-bis(*tert*-butoxy)carbonyl-L-cystine dimethyl ester (1.08 g, 83% yield) as a white solid: mp 96−97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 18 H), 3.16 (d, 4 H, J = 5.0 Hz), 3.76 (s, 6 H), 4.60 (dt, 2 H, J = 6.3, 5.0 Hz), 5.38 (d, 2 H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.3 (6 CH_3), 41.3 (2 CH_2), 52.6 (2 CH_3), 52.8 (2 CH), 80.2 (2 C), 155.0 (2 C), 171.1 (2 C); IR (CCl_4) ν 3458, 1753, 1722 cm^{-1}; MS (CI, NH_3) m/z 486 ($M + NH_4^+$), 469 (MH^+), 413, 369, 313, 269, 197, 179, 136, 102. Anal. Calcd for $C_{18}H_{32}O_8N_2S_2$: C, 46.14; H, 6.88; N, 5.98. Found: C, 46.03; H, 6.94; N, 5.89.

To a solution of the *N*,*N*′-bis(*tert*-butoxy)carbonyl-L-cystine dimethyl ester (vide supra, 994 mg, 2.12 mmol) and sodium phenylsulfonate (1.04 g, 6.36 mmol, 3 equiv) in dichloromethane (18 mL) at 0 °C was slowly added, under an argon atmosphere, a solution of bromine (160 mL, 3.2 mmol, 1.5 equiv) in dichloromethane (3.5 mL). A persistent red-orange color appeared during the addition. The mixture was then stirred for 20 h at 20 °C before filtration through a pad of Celite and the filtrate concentrated under reduced pressure. Chromatography of the crude product on silica gel (75:25 cylohexane/ethyl acetate) gave sulfone **10** (1.59 g, 100% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9 H), 3.41 (dd, 1 H, J = 13.9, 5.5 Hz), 3.54 (dd, 1 H, J = 13.9, 4.8 Hz), 3.73 (s, 3 H), 4.55 (ddd, 1 H, J = 6.4, 5.5, 4.8 Hz), 5.34 (d, 1 H, J = 6.4 Hz), 7.56 (t, 2 H, J = 7.7 Hz), 7.64 (t, 1 H, J = 7.7 Hz), 7.92 (d, 2 H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.8 (3 CH_3), 37.1 (CH_2), 52.4 (CH + CH_3), 79.8 (C), 126.5 (2 CH), 129.0 (2 CH), 133.6 (CH), 143.9 (C), 154.6 (C), 169.8 (C); IR (CCl_4) ν 3450, 3010, 2986, 2962, 2938, 1755, 1721, 1492, 1368, 1164, 1149 cm^{-1}; MS (CI, NH_3) m/z 393 ($M + NH_4^+$), 376 (MH^+), 337, 320, 276. Anal. Calcd for $C_{15}H_{21}O_6NS_2$: C, 47.98; H, 5.64; N, 3.73. Found: C, 47.82; H, 5.60; N, 3.65. $[\alpha]_D$ −47.6 (*c* 0.55, MeOH).

[2*R*(4*S*)]-2-[*N*-(*tert*-Butoxy)carbonyl]-3-{[4-(triethyl)silyloxy]pent-1-ynylsulfanyl}propionic Acid Methyl Ester (11). To a solution of hexyne **9** (1.67 g, 8.4 mmol, 2 equiv) in THF (9 mL) at −78 °C was added a solution of *n*-BuLi (1.5 M in hexanes, 5.5 mL, 8.25 mmol, 2.04 equiv). The resulting solution was stirred for 45 min at −78 °C. A cooled (−78 °C) solution of the sulfone **10** (1.58 g, 4.2 mmol, 1 equiv) in THF (9 mL) was then slowly added to the acetylide solution. After stirring for 5 min, the mixture was diluted with diethyl ether (50 mL) and water (20 mL). After extraction with diethyl ether (3 × 50 mL), the combined organic phases were washed successively with 2 N aqueous HCl, water, and saturated aqueous NaCl and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography on silica gel of the crude residue (cylohexane/ethyl acetate, 9:1) led to the title product **11** (1.35 g, 74% yield) as a pale yellow oil: bp 180 °C/0.6 mmHg: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.61 (q, 6 H, J = 7.9 Hz), 0.97 (t, 9 H, J = 7.9 Hz), 1.24 (d, 3 H, J = 6.0 Hz), 1.46 (s, 9 H), 2.35 (dd, 1 H, J = 16.7, 7.4 Hz), 2.48 (dd, 1 H, J = 16.7, 5.3 Hz), 3.15 (d, 2 H, J = 4.7 Hz), 3.78 (s, 3 H), 3.94 (ddd, 1 H, J = 7.4, 6.0, 5.3 Hz), 4.65 (dt, 1 H, J = 7.7, 4.7 Hz), 5.46 (d, 1 H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 4.7 (3 CH_2), 6.7 (3 CH_3), 23.4 (CH_3), 28.2 (3 CH_3), 31.0 (CH_2), 37.5 (CH_2), 52.4 (CH_3), 53.3 (CH), 67.3 (CH), 68.8 (C), 80.1 (C), 91.9 (C), 154.9 (C), 170.6 (C); IR (CCl_4) ν 3458, 1755, 1722, 1482, 1248, 1210, 1169, 1102 cm^{-1}; MS (CI, NH_3) m/z 432 (MH^+). Anal. Calcd for $C_{20}H_{37}O_5NSSi$: C, 55.64; H, 8.64; N, 3.26. Found: C, 55.64; H, 8.61; N, 3.28. $[\alpha]_D$ −49.3 (*c* 0.73, MeOH).

[2*R*(4*S*)]-2-[*N*-(*tert*-butoxy)carbonyl]-3-[(4-hydroxy)-pent-1-ynylsulfanyl]propionic Acid Methyl Ester (12). To a solution of **11** (706 mg, 1.64 mmol) in methanol (5 mL) was added Amberlyst 15 (50 mg). The mixture was stirred at 20 °C until the reaction was complete (120 min). Triethylamine was added to the mixture, which was filtered and concentrated under reduced pressure. Chromatography on silica gel (7:3 cylohexane/ethyl acetate) gave the hydroxy ester (490 mg, 94% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, 3 H, J = 6.3 Hz), 1.46 (s, 9 H), 2.37 (dd, 1 H, J = 16.8, 6.9 Hz), 2.52 (dd, 1 H, J = 16.8, 4.0 Hz), 2.76 (d, 1 H, J = 4.3 Hz), 2.98 (dd, 1 H, J = 13.5, 6.1 Hz), 3.16 (dd, 1 H, J = 13.5, 4.6 Hz), 3.79 (s, 3 H), 3.97 (dqdd, 1 H, J = 6.9, 6.3, 4.3, 4.0 Hz), 4.741 (ddd, 1 H, J = 8.2, 6.1, 4.6 Hz), 5.43 (d, 1 H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.2 (CH_3), 28.1 (3 CH_3), 30.5 (CH_2), 37.3 (CH_2), 52.6 (CH_3), 52.7 (CH), 66.1 (CH), 69.3 (C), 80.2 (C), 91.9 (C), 155.0 (C), 171.0 (C); IR (CCl_4) ν 3375, 1744, 1694, 1507, 1366, 1347, 1247, 1216, 1160 cm^{-1}; MS (CI, NH_3) m/z 318 (MH^+), 279, 262, 244, 218, 200, 117. Anal. Calcd for $C_{14}H_{23}O_5NS$: C, 52.98; H, 7.30; N, 4.41. Found: C, 52.78; H, 7.44; N, 4.26. $[\alpha]_D$ −79.1 (*c* 1.32, MeOH).

(5*R*,8*R*)-8-[*N*-(*tert*-Butoxy)carbonyl]-5-methyl-2,3,4,5,8,9-hexahydro-2-yne-7*H*-[1,6]-oxathionin-7-one (13). To a solution of **12** (926 mg, 2.92 mmol) in THF (30 mL) at 0 °C was added a 1 M aqueous LiOH solution (5.8 mL, 5.8 mmol, 2 equiv). The mixture was stirred at 0 °C for 2 h and diluted

with a mixture of diethyl ether and water (40/20 mL), and the etheral phase was washed with water (3 × 50 mL). The aqueous phases were acidified (pH 2) and extracted with ethyl acetate (3 × 80 mL). The ethyl acetate phases were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude [2*R*(4S)]-2-[*N*-(*tert*-butoxy)carbonyl]-3-[(4-hydroxy)pent-1-ynylsulfanyl]propionic acid (854 mg).

To a solution of triphenylphosphine (978 mg, 3.73 mmol, 1.50 equiv) in THF (255 mL) at reflux was added, over a period of 12 h, a solution of the crude hydroxy acid obtained above (765 mg, 2.49 mmol) and diethyl azodicarboxylate (590 mL, 3.73 mmol, 1.55 equiv) in THF (25 mL). The reflux was maintained for an additional 12 h and then the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel (9:1 cylohexane/ethyl acetate) to give lactone **13** (351 mg, 50% yield) as a white solid. Recrystallization in pentane−diethyl ether gave 274 mg of **13** as white crystals (39% yield): mp 117 °C; ^{1}H NMR (400 MHz) δ 1.45 (d, 3 H, J = 6.4 Hz), 1.49 (s, 9 H), 2.46 (dd, 1 H, J = 16.1, 6.5 Hz), 2.52 (dd, 1 H, J = 16.1, 8.95 Hz), 3.08 (dd, 1 H, J = 12.8, 5.9 Hz), 3.93 (dd, 1 H, J = 12.8, 1.7 Hz), 4.87 (ddd, 1 H, J = 7.3, 5.9, 1.7 Hz), 5.33 (ddq, 1 H, J = 8.9, 6.5, 6.4 Hz), 5.41(d, 1H, J = 7.3 Hz); ^{13}C NMR (100.6 MHz) δ 20.0 (CH_3), 28.3 (3 CH_3), 29.1 (CH_2), 40.3 (CH_2), 52.7 (CH), 70.0 (CH), 77.0 (C), 80,3 (C), 97.3 (C), 155.1 (C), 171.9 (C); IR (CCl_4) ν 3437, 2184, 1740, 1731, 1713, 1638, 1490, 1293, 1145, 1060 cm^{-1}; MS (CI, NH_3) m/z 303 (M + NH_4^+), 286 (MH^+), 247, 230, 212, 202, 186, 158. Anal. Calcd for $C_{13}H_{19}O_4NS$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.64; H, 6.70; N, 4.93. $[\alpha]_D$ +127.6 (*c* 1.76, MeOH).

(2*E*,5*R*,8*R*)-8-[*N*-(*tert*-Butoxy)carbonyl]-2-tributylstannyl-5-methyl-4,5,8,9-tetrahydro-7*H*-[1,6]-oxathionin-7-one (14). To a solution of lactone **13** (235 mg, 0.82 mmol) in toluene (1.5 mL) was added a suspension of $Pd(PPh_3)_4$ (190 mg, 0.17 mmol, 0.2 equiv) in toluene (5 mL) via cannula. Bu_3SnH (270 mL, 0.99 mmol, 1.2 equiv) was then slowly added to the reaction mixture. After the mixture was stirred for 45 min at 20 °C, the solvent was removed under vacuum at 20 °C. The crude residue was purified by chromatography on silica gel (92:8 cyclohexane/ethyl acetate) to give tin compound **14** (380 mg, 80% yield) as a colorless oil: ^{1}H NMR (400 MHz) δ 0.89 (t, 9 H, J = 7.3 Hz), 0.97 (t, 6 H, J = 8.2 Hz), 1.31 (sext, 6 H, J = 7.3 Hz), 1.37 (d, 3H, J = 6.4 Hz),1.45 (s, 9H), 1.49 (tt, 6H, J = 8.2, 7.3 Hz), 2.13 (ddd, 1 H, J = 11.7, 7.8, 6.1 Hz), 2.89 (dd, 1 H, J = 14.3, 3.5 Hz), 3.00 (ddd, 1 H, J = 11.7, 7.8, 6.1 Hz), 3.07 (dd, 1 H, J = 14.3, 1.9 Hz), 4.47 (ddd, 1 H, J = 7.9, 3.5, 1.9 Hz), 5.01 (qd, 1 H, J = 6.4, 6.1 Hz), 5.46 (d, 1 H, J = 7.9 Hz), 6.25 (t, 1 H, J = 7.8 Hz, $J^{117}_{Sn-H} = J^{119}_{Sn-H}$ = 45.1 Hz); ^{13}C NMR (100.6 MHz) δ 10.5 (3CH_2, J 119_{Sn-13C} = 333.6 Hz, J $^{117}_{Sn-13C}$ = 318.9 Hz), 13.6 (3 CH_3), 20.2 (CH_3), 27.3 (3 CH_2, $J^{119}_{Sn-13C} = J^{117}_{Sn-13C}$ = 58.6 Hz), 28.2 (3 CH_3), 28.9 (3 CH_2, $J^{119}_{Sn-13C} = J^{117}_{Sn-13C}$ = 13.7 Hz), 37.7 (CH_2 $J^{119}_{Sn-13C} = J^{117}_{Sn-13C}$ = 40.4 Hz), 42.4 (CH_2), 53.4 (CH), 69.9 (CH), 79.9 (C), 142.8 (C), 148.2 (CH), 154.8 (C), 169.0 (C); IR (CCl_4) ν 3462, 1743, 1716, 1491, 1457, 1391, 1366, 13308, 1166, 1056 cm^{-1}; MS (CI, NH_3) for the ^{120}Sn major isotope m/z 578 (MH^+), 478, 308, 291, 232, 188. Anal. Calcd for $C_{25}H_{47}O_4NSSn$: C, 52.10; H, 8.22; N, 2.43. Found: C, 52.54; H, 8.53; N, 2.19. $[\alpha]_D$ +33.3 (*c* 0.77, MeOH).

(2*E*,5*R*,8*R*)-8-[*N*-(*tert*-Butoxy)carbonyl]-2-iodo-5-methyl-4,5,8,9-tetrahydro-7*H*-[1,6]-oxathionin-7-one (15). To a solution of the stannyl compound **14** (530 mg, 0.92 mmol) in dichloromethane (5 mL) at 0 °C was slowly added a solution of iodine (245 mg, 0.97 mmol, 1.05 equiv) in dichloromethane (13 mL). The resulting brown solution was stirred at 0 °C for 30 min and concentrated under reduced pressure. The crude residue was taken up in diethyl ether (15 mL) and treated with an aqueous KF solution (2 g/10 mL). After 3 h at 20 °C, the mixture was filtered through a pad of Celite. The aqueous phase was extracted with diethyl ether, and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (9:1 cyclohexane/ethyl acetate) gave 332 mg (87%) of iodide **15**: ^{1}H NMR (400 MHz) δ 1.32 (d, 3 H, J = 6.4 Hz), 1.41 (s, 9 H), 1.91 (m, 1 H), 2.73 (m, 1 H), 3.12 (m, 1 H), 3.39 (dd, 1 H, J = 14.8, 3.6 Hz), 4.59 (ddd, 1 H, J = 14.8, 3.6, 2.8 Hz), 5.02 (m, 1H), 5.37 (d, 1 H, J = 7.6 Hz), 6.86 (t, 1H, J = 8.4 Hz); ^{13}C NMR (50.3 MHz) δ 19.9 (CH_3), 28.3 (3CH_3), 40.2 (CH_2), 43.2 (CH_2), 52.5 (CH), 68.8 (CH), 80.3 (C), 92.2 (C), 150.4 (CH), 154.7 (C), 168.5 (C); IR (CCl_4) ν 3450, 1743, 1710, 1490, 1210, 1162, 1046 cm^{-1}; MS (CI, NH_3) m/z 414 (MH^+). Anal. Calcd for $C_{13}H_{20}O_4NSI$: C, 37.78; H, 4.88; N, 3.39. Found: C, 38.03; H, 4.93; N, 3.19. $[\alpha]_D$ +121 (*c* 0.93, MeOH).

(2*E*,5*R*,8*R*)-8-[*N*-(*tert*-Butoxy)carbonyl]-2-ethoxycarbonyl-5-methyl-4,5,8,9-tetrahydro-7*H*-[1,6]-oxathionin-7-one (16). To a solution of **15** (100 mg, 0.24 mmol), ethanol (240 mL, 3.6 mmol), and triethylamine (510 mL, 3.6 mmol, 15 equiv), in acetonitrile (6 mL), was added $PdCl_2(PPh_3)_2$ (34 mg, 0.2 equiv). The reaction mixture was stirred at 50 °C for 3 h under 8 bar of pressure of carbon monoxide. The solution was then cooled and the solvent evaporated under reduced pressure. Purification by flash chromatography on silica gel of the crude residue (9:1 cyclohexane/ethyl acetate) gave 59 mg (67%) of lactone ester **16**: ^{1}H NMR (400 MHz) δ 1.30 (t, 3H, J = 7.1 Hz), 1.43 (d, 3H, J = 8.0 Hz), 1.45 (s, 9H), 2.38 (m, 1H), 3.00 (m, 1H), 3.04 (m, 1H), 3.36 (dd, 1H, J = 14.9, 3.8 Hz), 4.23 (q, 2H, J = 7.1 Hz), 4.48 (m, 1H), 5.10 (m, 1H), 5.42 (d, 1H, J = 8.1 Hz), 7.47 (t, 1H, J = 8.5 Hz); ^{1}H NMR (400 MHz, C_6D_6, 77 °C) δ 0.91 (d, 1H, J = 6.5 Hz), 1.0 (t, 3H, J = 7.1 Hz), 1.38 (s, 9H), 1.78 (dd, 1H, J = 12.5, 8.6 Hz), 2.60 (ddd, 1H, J = 12.5, 8.6, 8.0 Hz), 2.90 (dd, J = 14.9, 3.1 Hz, 1H), 3.37 (dd, J = 14.9, 4.0 Hz, 2H), 4.02, 4.0 (2q, 2H, J = 7.1 Hz), 4.52 (m, 1H), 4.74 (dq, 1H, J = 8.0, 6.5 Hz), 5.23 (m, 1H), 7.25 (t, 1H, J = 8.6 Hz); ^{13}C NMR (100.6 MHz) δ 14.1 (CH_3), 20.4 (CH_3), 28.2 (3CH_3), 37.7 (CH_2), 41.6 (CH_2), 53.2 (CH), 62.0 (CH_2), 68.8 (CH), 80.2 (C), 130.1 (C), 149.0 (CH), 154.8 (C), 164.8 (C), 169.4 (C); IR (CCl_4) ν 3455, 2984, 2937, 1750, 1710, 1611, 1494, 1370, 1259, 1162, 1067, 1042 cm^{-1}; MS (CI, NH_3) m/z 360 (MH^+). Anal. Calcd for $C_{16}H_{25}O_6NS$: C, 53.46; H, 7.01; N, 3.90. Found: C, 53.28; H, 7.24; N, 3.78. $[\alpha]_D$ +12.5 (*c* 0.72, MeOH).

(2*E*,5*R*,8*R*)-8-[*N*-(*tert*-Butoxy)carbonyl]-5-methyl-2-[(*N*-propargyl)carboxamide]-4,5,8,9-tetrahydro-7*H*-[1,6]-oxathionin-7-one (17). To a solution of **15** (100 mg, 0.24 mmol), in acetonitrile (6 mL), were added $PdCl_2(PPh_3)_2$ (38 mg, 0.054 mmol, 0.2 equiv) and propargylamine (249 mL, 3.6 mmol, 15 equiv). The reaction mixture was stirred at 50 °C for 3 h under 8 bar of pressure of carbon monoxide. The solution was then cooled and the solvent evaporated under reduced pressure. Purification by flash chromatography on silica gel of the crude residue (9:1 cyclohexane/ethyl acetate) gave 58 mg (65%) of **17** as a white crystalline solid:^{1}H NMR (400 MHz) δ 1.45 (m, 12H), 2.24 (t, 1H, J = 2.4 Hz), 2.50 (m, 1H), 2.90 (m, 1H), 3.08 (m, 2H), 4.10 (m, 2H), 4.50 (m, 1H), 5.05 (m, 1H), 5.33 (m, 1H), 7.28 (m, 1H), 7.51 (t, 1H, J = 8.6 Hz); ^{1}H NMR (400 MHz, C_6D_6, 77 °C) δ 0.93 (d, 1H, J = 6.5 Hz), 1.39 (s, 9H), 1.85 (t, 1H, J = 2.5 Hz), 1.94 (dd, 1H, J = 11.0, 8.5 Hz), 2.41 (ddd, 1H, J = 11.0, 8.5, 8.0 Hz), 2.63 (dd, 1H, J = 14.2, 3.1 Hz), 2.75 (dd, 1H, J = 14.2, 4.2 Hz), 3.86, 3.93 (2ddd, 2H, J = 17.5, 5.5, 2.5 Hz), 4.46 (m, 1H), 4.59 (dq, 1H, J = 8.0, 6.6 Hz), 5.15 (m, 1H), 6.90 (m, 1H), 7.39 (t, 1H, J = 8.5 Hz); ^{13}C NMR (100.6 MHz) δ 20.2 (CH_3), 28.2 (3CH_3), 29.8 (CH_2), 37.0 (CH_2), 41.8 (CH_2), 53.3 (CH), 69.5 (CH), 71.8 (C), 79.2 (CH), 80.3 (C), 131.0 (C), 146.0 (CH), 154.8 (C), 163.5 (C), 168.9 (C); IR (CCl_4)-ν 3450, 3308, 1744, 1709, 1666, 1611, 1493, 1262, 1162 cm^{-1}; MS (CI, NH_3) m/z 369 (MH^+). Anal. Calcd for $C_{17}H_{24}O_5N_2S$: C, 55.42; H, 6.57; N, 7.60. Found: C, 55.31; H, 6.56; N, 7.53. $[\alpha]_D$ + 23.8 (*c* 0.42, MeOH).

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