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Approaches toward the Total Synthesis of the Nine-Membered Thio-Lactone Core of Griseoviridin

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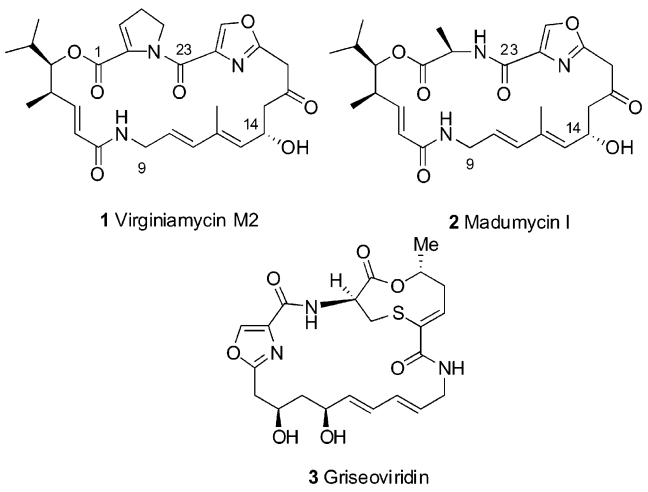
Three different approaches toward the synthesis of the macrocyclic thiolactone core of griseoviridin have been studied. Intramolecular palladium-catalyzed thiol coupling and esterification (carboxylate activation) have led to the formation of unexpected rearranged products. An intermolecular palladium-catalyzed thiol/vinyl iodide coupling followed by an esterification (alcohol activation) ultimately led to the nine-membered core of griseoviridin.

The streptogramin antibiotics are a family of natural products that have been isolated from strains of *Streptomyces* found in soil organisms. The streptogramin antibiotics can be divided in two groups (group A and group B). Group A consists of a series of 23-membered macrolactones each incorporating a 2,4-disubstituted oxazole, an (*E*,*E*)-dienylamine, and 1,3-dioxygen substitution such as in virginiamycin **1**,[1,2] madumycin **2**,[3] and griseoviridin **3**.[4−10] Group B streptogramin antibiotics, such as etamycin,[11] usually contain a series of amino acids in cyclic array. Group A and B streptogramin antibiotics used together exhibit a potent synergistic effect against Gram-positive bacteria and a combination of two semisynthetic group A and B streptogramin antibiotics, marketed under the name Synercid (Aventis), was recently approved for the treatment of vancomycin-resistant bacteria (Scheme 1).[12]

Several synthetic approaches toward the total synthesis of griseoviridin have been described by the groups of Meyers,[4] Helquist,[5] Miller,[6] Marcantoni,[7] and Ardisson/Pancrazi[8] culminating in one total synthesis reported by Meyers in 2000.[9] It is noteworthy that all reported strategies have used an intramolecular Mitsunobu lactonization to obtain the nine-membered thio-lactone core of griseoviridin. We would like to describe herein our different approaches to construct such a thio-lactone core.

SCHEME 1



Our synthetic plan is outlined in Scheme 2. It was envisaged to assemble the target from two building blocks **6** and **7** by means of a palladium-catalyzed thiol coupling and an esterification. Compound **6** could be easily obtained from the corresponding D-cysteine and vinyl iodide **7** could be prepared from either commercially available (*R*)- or (*S*)-ethyl hydroxy-3-butyrate **8**.

Since the palladium-catalyzed cross-coupling of thiols and (aryl)vinyl halides have received rather little attention in the literature,[13−15] we first decided to investigate this cross-coupling reaction from a methodological point of view.

Using the conditions developed by Ortar et al.,[14] the phenyl sulfide **9**[14] derived from Ac-Cys-OMe was obtained in 80% yield in either NMP at 60 °C or refluxing acetone.Gratifyingly, the same conditions could be applied on the model vinyl iodide **10** leading to the corresponding cysteinyl vinyl sulfide **11** in 68% yield (NMP at 60 °C). Starting from these results, we could then turn

* To whom correspondence should be addressed.

(1) Virginiamycin total syntheses: (a) Schlessinger, R. H.; Li, Y.-J. *J. Am. Chem. Soc.* **1996**, *118*, 3301. (b) Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 3149.

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(3) Madumycin total syntheses: (a) Tavares, F.; Lawson, J. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 3303. (b) Ghosh, A. K.; Liu, W. *J. Org. Chem.* **1997**, *62*, 7908.

(4) Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870.

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(11) Barrière, J.-C.; Bacqué, E.; Puchault, G.; Quenet, Y.; Molherat, C.; Cassayre, J.; Paris, J.-M. *Tetrahedron* **1998**, *54*, 12859.

(12) (a) Allington, D. R.; Rivey, M. P. *Clin. Ther.* **2001**, *23*, 24. (b) Delgado, G.; Neuhauser, M. M.; Bearden, D.; Danzinger, L. H. *Pharmacotherapy* **2000**, *20*, 1469.

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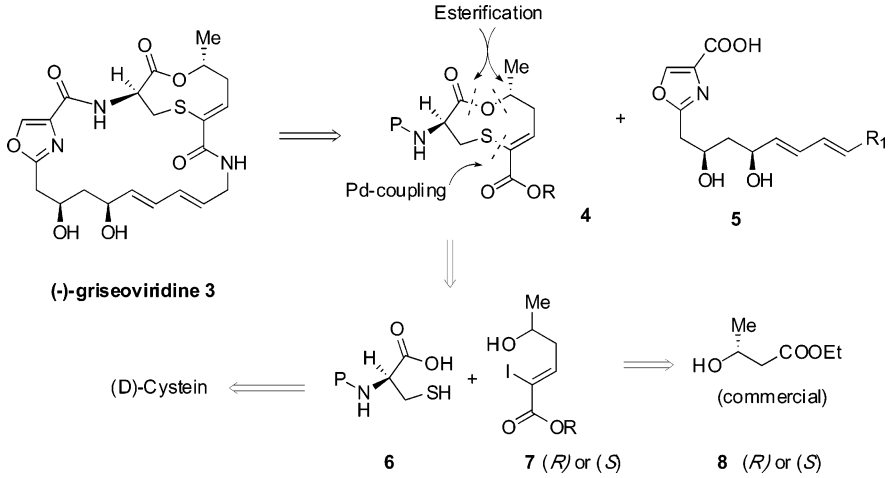
SCHEME 2



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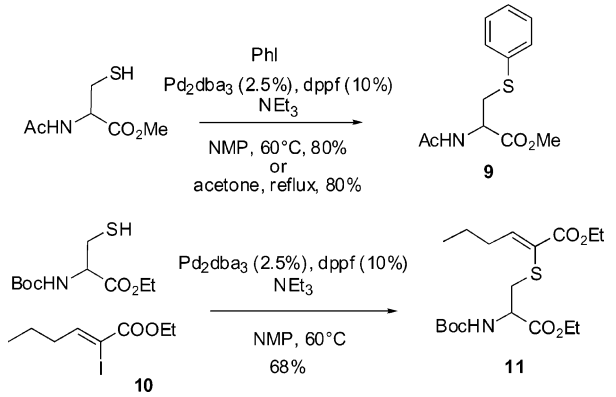
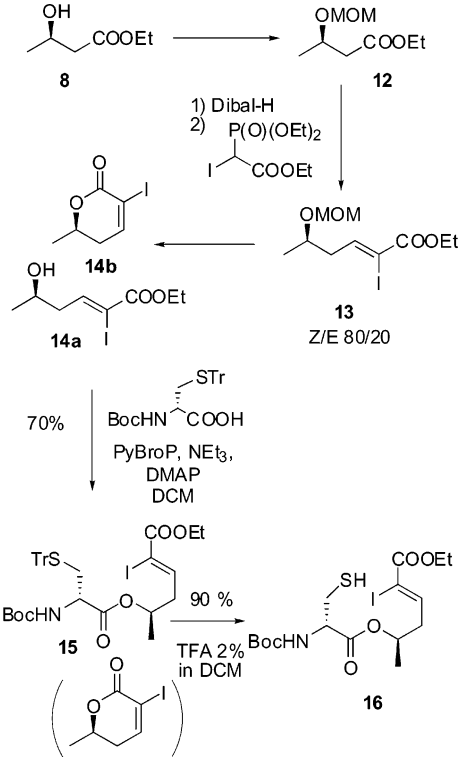


SCHEME 4



our attention to the total synthesis of the thiolactone core of griseoviridin.

Along the strategy described in Scheme 2, we first envisaged the tactic involving an intermolecular esterification followed by an intramolecular palladium-catalyzed thiol coupling. Enantiomerically pure ethyl (*R*)-3-hydroxybutyrate was first protected as the MOM-ether **12**[7] using a standard procedure. DIBALH-mediated ester reduction to the corresponding aldehyde, followed by a modified Horner−Wadsworth−Emmons[16a] reaction led to the expected vinyl iodide **13** in 60% yield (over three steps) as an inseparable 80/20 (*Z*)/(*E*) mixture. After MOM deprotection under acidic conditions, the expected (*Z*) isomer **14a** was obtained as an inseparable mixture with the lactone **14b** stemming from the undesired (*E*) isomer (Scheme 4).

The PyBroP[17] (bromotris(pyrrolidino)phosphonium hexafluorophosphate) mediated esterification with commercial Boc-D-Cys(Trt)-OH led to the formation of compound **15**, which could be separated from the nonreacted lactone **14b**. Final removal of the trityl protecting group under mild acidic conditions (2% TFA in DCM) led to **16**, the substrate for the palladium-catalyzed cyclization.

Unfortunately, under all the conditions tested, the palladium-catalyzed reaction on substrate **16** led predominantly to the dienic ester **17**,[18] formally resulting from an elimination of the cysteinyl carboxylate (Scheme 5).

This intriguing, and to the best of our knowledge unprecedented, result led us to change the tactic. Ac-

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(14) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133.

(15) Copper-catalyzed reactions: (a) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019. (b) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (c) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517.

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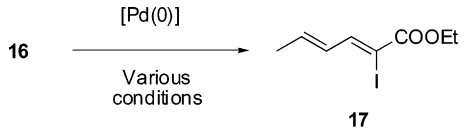
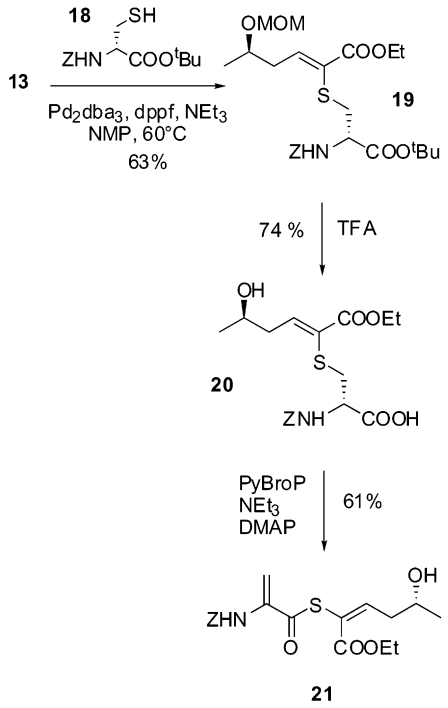
(17) Coste, J.; Frérot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967.

(18) Dienic ester **17** could not be isolated in pure form but its structure was determined by comparison with the dienic ester obtained from the modified Horner−Wadsworth−Emmons reaction[16a] on crotonaldehyde.

SCHEME 5



SCHEME 6

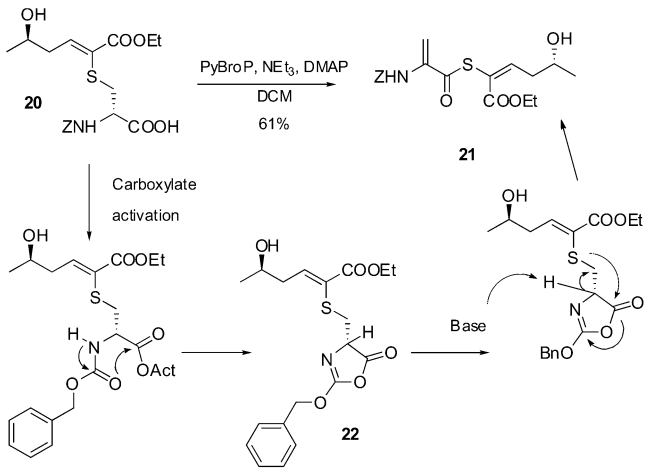


cordingly, with compound **13** in hand, an intermolecular palladium-catalyzed cross-coupling reaction followed by a lactonization was thus investigated.

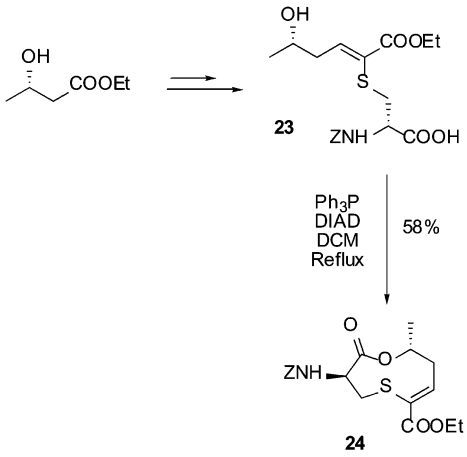
The intermolecular palladium catalyzed cross-coupling reaction between vinyl-iodide **13** and Z-D-Cys-O-*t*-Bu **18**, led to the expected vinyl sufide **19** in 63% yield, which was followed by an acidic treatment to remove both MOM-ether and *tert*-butyl ester in 74% yield. However the esterification, under the conditions developed for the intermolecular coupling, did not lead to the expected lactone but rather to the dehydroalanine thioester **21** obtained in 61% yield (Scheme 6).

The formation of this product could be explained through an intermediate oxazolone **22**: the deprotonation of the α proton could result in the formation of the dehydro derivative and the liberated thiolate anion could react onto the oxazolone, resulting in the formation of the dehydroalanine thioester **21** as illustrated in Scheme 7.[19,20] When the same lactonization was performed in the absence of DMAP, the formation of **21** was still observed, and using Trost's acid-catalyzed macrolactonization conditions,[21] no dehydro product **21** was observed but lactone yield could not be raised to useful synthetic levels (yield < 10%).[22]

SCHEME 7



SCHEME 8



This disappointing result led us to consider a third tactic involving a Mitsunobu lactonization. Exploiting the route developed for compound **20** (Scheme 3), the *seco*-acid **23** was thus obtained starting from the (*S*)-enantiomer of ethyl 3-hydroxybutyrate. Under classical Mitsunobu conditions, the nine-membered thiolactone **24** could ultimately be obtained in 58% yield (Scheme 8).

In conclusion, three different tactics (palladium-catalyzed intramolecular thiol/vinyl iodide coupling, PyBroP-mediated lactonization, and Mitsunobu lactonization) have been envisaged. The two first tactics led to the formation of unexpected rearrangement products. The third tactic, involving an intermolecular palladium thiol/vinyl iodide coupling and an intramolecular Mitsunobu lactonization, was successful leading to an efficient and convergent synthesis of the nine-membered core of griseoviridin.

Experimental Section

General Methods. Unless otherwise specified, the reactions were carried out in oven-dried glassware under an argon

(19) For similar results obtained in the formation of a dehydroalanine starting from various cysteine derivatives upon carboxylate activation, see: (a) Moroder, L.; Musiol, H.-J.; Schaschke, N.; Chen, L.; Hargittai, B.; Barany, G. *Houben-Weyl* **2002**, *Board E22a*, pp 384−393. (b) Threadgill, M. D.; Gledhill, A. P. *J. Org. Chem.* **1989**, *54*, 2940. (c) Ueki, M.; Ikeo, T.; Hokari, K.; Nakamura, K.; Saeki, A.; Komatsu, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 829.

(20) An alternative mechanism involving a direct attack of the sulfide on the PyBroP-activated carboxylate cannot be ruled out (thanks to a reviewer for pointing out this alternative mechanism to our attention).

(21) Trost, B. M.; Chisholm, J. D. *Org. Lett.* **2002**, *4*, 3743.

(22) Under Yamaguchi's conditions, only extensive decomposition was observed.

atmosphere. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, or at 250 and 63 MHz in $CDCl_3$ as solvent: chemical shifts are given in ppm. Column chromatography was performed on silica gel 230−400 mesh. THF was distilled from sodium/benzophenone. Dichloromethane, diisopropylamine, and chlorotrimethylsilane were distilled over CaH_2 prior to use. *N*-Methylpyrrolidine (NMP) was degassed using argon bubbling. Elemental analyses were carried out by Laboratoire de Micro-Analyze ICSN - Gif/Yvette. IR spectra were recorded with an FTIR spectrometer. Mass spectra were recorded by Navigator LC/MS (source AQA) for electrospray ionization. Optical rotations were determined operating at the sodium D line.

2-Iodohex-2-enoic Acid Ethyl Ester (10). To a solution of triethylphosphonoacetate (200 μL, 1 mmol) in anhydrous THF (4 mL) were successively added NaH (60% dispertion in mineral oil) (88 mg, 2.2 mmol) and *N*-iodosuccinimide (300 mg, 1.3 mmol). The solution was stirred for 1 h at room temperature, and butyraldehyde (88 μL, 1 mmol) was added dropwise. The stirring was maintained for an additional 15 min, and the solution was quenched with a saturated solution of ammonium chloride (1 mL). The mixture was filtered through silica gel (diethyl ether), the organic layer was washed with a saturated $Na_2S_2O_3$ solution and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography on silica gel (30/1 heptane/ethyl acetate) gave **10** (196 mg, 73% yield) as an inseparable *Z*/*E* mixture (80/20): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, J = 7.4 Hz, 0.6H), 1.00 (t, J = 7.3 Hz, 2.4H), 1.34 (t, J = 7.1 Hz, 3H), 1.48 (m, 0.4H), 1.56 (m, 1.6H), 2.30 (q, J = 7.2 Hz, 1.6H), 2.44 (q, J = 7.7 Hz, 0.4H), 4.26 (q, J = 7.1 Hz, 0.4H), 4.27 (q, J = 7.2 Hz, 1.6H), 6.90 (t, J = 7.7 Hz, 0.2H), 7.21 (t, J = 7.2 Hz, 0.8H); ^{13}C NMR ($CDCl_3$, 75 MHz) (Z isomer) δ 14.3, 14.6, 21.3, 39.4, 63.0, 95.7, 153.4, 163.3; (E isomer) δ 14.0, 14.5, 35.7, 62.5, 95.7, 156.3, 164.3; IR (KCl, cm^{-1}) ν 668, 757, 1034, 1216, 1253, 1613, 1711, 2930; MS (EI) *m*/*z* 268 ($M^{\bullet+}$), 198, 67, 55, 53, 43, 41. Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 36.01; H, 4.94.

2-((2*S*)-2-*tert*-Butoxycarbonylamino-2-methoxycarbonylethylsulfanyl)hex-2-enoic Acid Ethyl Ester (11). To a solution of **10** (30 mg, 0.12 mmol), Pd_2dba_3 (3.1 mg, 0.003 mmol), and dppf (6.7 mg, 0.012 mmol) in *N*-methylpyrrolidone (1 mL) was added triethylamine (33 μL, 0.24 mmol). The solution was stirred for 20 min at room temperature and then warmed to 60 °C. Boc-L-cysteine ethyl ester (42 mg, 0.17 mmol) in NMP (0.5 mL) was added over 30 min. The mixture was stirred for an additional 2 h 30, cooled to room temperature, and quenched with brine. After extraction with EtOAc, the organic layers were washed twice with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography on silica gel (4/1 heptane/ethyl acetate) gave **11** (33 mg, 68% yield) as an inseparable *Z*/*E* mixture (80/20): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 7.4 Hz, 0.6H), 0.95 (t, J = 7.3 Hz, 2.4H), 1.22−1.38 (m, 8H), 1.44 (bs, 9H), 2.41 (m, 0.4H), 2.45 (m, 1.6H), 3.11 (bd, J = 4.2 Hz, 0.4H), 3.21 (bd, J = 4.7 Hz, 1.6H), 4.07−4.30 (m, 4H), 4.45 (m, 1H), 5.41 (bd, J = 7.6 Hz, 1H, NH), 6.51 (t, J = 7.6 Hz, 0.2H), 7.21 (t, J = 7.4 Hz, 0.8H); ^{13}C NMR ($CDCl_3$,75 MHz) (*Z* isomer) δ 13.9, 14.0, 14.2, 21.6, 28.2, 32.9, 35.8, 53.6, 61.3, 61.6, 79.9, 126.5, 152.3, 155.0, 164.9, 170.6; (*E* isomer) δ 13.8, 14.1, 14.1, 22.2, 28.1, 33.1, 35.8, 53.3, 61.3, 61.6, 79.9, 126.5, 150.2, 155.0, 164.9, 170.7; IR (KCl, cm^{-1}) ν 756, 1165, 1369, 1499, 1712, 2360, 2981, 3400; ESI-MS *m*/*z* 412.2 ($M + Na^+$), 290.2. Anal. Calcd for $C_{18}H_{31}NO_6S$: C, 55.50; H, 8.02; N, 3.60. Found: C, 55.72; H, 8.24; N, 3.89.

(2*Z*,5*R*)-2-Iodo-5-methoxymethoxyhex-2-enoic Acid Ethyl Ester (13). To a solution of (*R*)-3-hydroxybutyric acid ethyl ester (500 μL, 3.78 mmol) in $CH_2(OCH_3)_2$ (10 mL) were added dropwise allyltrimethylsilane (720 μL, 4.54 mmol) and iodine (50 mg, 0.189 mmol). The mixture was stirred overnight at room temperature and poured into a saturated solution of $Na_2S_2O_3$. After extraction with diethyl ether, the organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude residue was taken up in CH_2Cl_2 (30 mL), and the solution was cooled to −78 °C. DIBALH (1 M in hexane) (4.6 mL) was added dropwise over 30 min. The mixture was stirred for 30 min, methanol (2 mL) was added dropwise, and the solution was poured into 1 N HCl. After the mixture was warmed for an additional 1 h to room temperature, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give crude aldehyde, which was used without further purification in the next step.

To a solution of triethylphosphonoacetate (750 μL, 3.78 mmol) in anhydrous THF (16 mL) were added NaH (60% dispersion in mineral oil) (335 mg, 7.56 mmol) and *N*-iodosuccinimide (1.1 g, 4.91 mmol). The solution was stirred for 1 h at room temperature, and crude aldehyde in CH_2Cl_2 (2 mL) was added dropwise. The stirring was maintained for an additional 15 min, and the solution was quenched with saturated solution of ammonium chloride (1 mL). The mixture was filtered over silica gel (diethyl ether), the organic layer was washed with a saturated solution of $Na_2S_2O_3$ and dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography on silica gel (4/1 heptane/ethyl acetate) gave **13** (750 mg, 60% yield over three steps) as an inseparable *Z*/*E* mixture (80/20): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (d, J = 6.2 Hz, 0.6H), 1.25 (d, J = 6.2 Hz, 2.4H), 1.33 (t, J = 7.1 Hz, 3H), 2.53 (∼t, J = 6.5 Hz, 1.6H), 2.69 (∼t, J = 6.8 Hz, 0.4H), 3.39 (s, 3H), 3.83 (∼sext, J = 6.0 Hz, 0.2H), 3.95 (∼sext, J = 6.1H Hz, 0.8H), 4.26 (q, J = 7.1 Hz, 0.4H), 4.28 (q, J = 7.1 Hz, 1.6H), 4.62 (d, J = 6.6 Hz, 0.2H), 4.64 (d, J = 7.0 Hz, 0.8H), 4.69 (d, J = 4.9 Hz, 0.2H), 4.71 (d, J = 7.0 Hz, 0.8H), 7.03 (t, J = 7.4 Hz, 0.2H), 7.30 (t, J = 6.8 Hz, 0.8H); ^{13}C NMR ($CDCl_3$,75 MHz) (*Z* isomer) δ 14.6, 20.8, 44.6, 55.8, 63.0, 71.6, 86.8, 95.2, 149.9, 163.0; (*E* isomer) δ 14.5, 20.6, 40.6, 55.8, 62.6, 72.2, 88.0, 97.3, 152.8, 164.0; IR (KCl, cm^{-1}) ν 741, 918, 1035, 1247, 1718, 2976; ESI-MS *m*/*z* 366.9 ($M + K^+$), 351 ($M + Na^+$), 329 ($M + H^+$), 253. Anal. Calcd for $C_{10}H_{17}IO_4$: C, 36.68; H, 5.28. Found: C, 36.60; H, 5.22.

(2*Z*,5*R*) 5-Hydroxy-2-iodohex-2-enoic Acid Ethyl Ester (14a). To a solution of **13** (1 g, 3 mmol) in methanol (5 mL) was added dropwise 2 M HCl (5 mL). The resulting mixture was refluxed for 2 h. The solution was then cooled and the solvent evaporated under reduced pressure. After addition of saturated aqueous $NaHCO_3$, the reaction mixture was extracted with diethyl ether. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was then filtered over silica gel to give an inseparable mixture of **14a** and **14b** (670 mg, 78% yield) in a proportion of 80/20, which was used for the next step without further purication.

(2*Z*,5*R*)-5-[(2*S*)2-*tert*-Butoxycarbonylamino-3-tritylsulfanylpropionyloxy]-2-iodohex-2-enoic Acid Ethyl Ester (15). To a solution of the mixture of **14a** and **14b** obtained above, in dichloromethane (20 mL), were added *N*-(Boc)-*S*-(Trt)-D-cysteine (630 mg, 2.2 mmol), PyBroP (1.3 g, 2.86 mmol), DIEA (1.15 mL, 6.6 mmol), and DMAP (30 mg, 0.22 mmol). The mixture was stirred for 2 h at room temperature. After addition of saturated aqueous $NaHCO_3$, the reaction mixture was extracted with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography on silica gel (3/1 heptane/ethyl acetate) gave **15** (1.1 g, 70% yield) as a colorless oil and unreacted lactone **14b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24−1.32 (m, 6H), 1.43 (bs, 9H), 2.47−2.66 (m, 4H), 4.15−4.28 (m, 3H), 5.03 (bd, J = 8.6 Hz, NH), 5.07−5.13 (m, 1H) 7.12−7.40 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) 14.4, 19.9, 28.6, 29.9, 43.3, 52.8, 63.0, 66.1, 70.6, 80.2, 98.5, 127.1, 128.3, 129.7, 144.5, 147.5, 155.2, 162.8, 170.4; IR (KCl, cm^{-1}) ν 700, 1165, 1249, 1492, 1715, 2925; ESI-MS *m*/*z* 768 ($M + K^+$), 752.2 ($M + Na^+$), 440.3, 398.2, 320.1. Anal. Calcd for $C_{35}H_{40}INO_6S$: C, 57.61; H, 5.53; N, 1.92. Found: C, 57.15; H, 5.69; N, 1.83.

(6*R*)-3-Iodo-6-methyl-5,6-dihydropyran-2-one (14b): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (d, J = 6.3 Hz, 3H), 2.41 (m, 2H), 4.68 (m, 1H), 7.53 (~dd, J = 3.5 Hz, J = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$,75 MHz) δ 20.8, 35.4, 75.5, 89.8, 154.0, 160.8; IR (KCl, cm^{-1}) ν 669, 756, 1215, 3020; MS (IE) m/z 238 ($M^{\bullet+}$), 194, 166, 68, 43, 41; mp 68−69 °C. Anal. Calcd for $C_6H_7IO_2$: C, 30.28; H, 2.96. Found: C, 30.44; H, 2.96.

(2*Z*,5*R*)-5-[(2*S*)2-*tert*-Butoxycarbonylamino-3-mercaptopropionyloxy]-2-iodohex-2-enoic Acid Ethyl Ester (16). To a solution of **15** (110 mg, 0.15 mmol) and triethylsilane (27 μL, 0.17 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (60 μL, 4% v/v). The mixture was stirred for 40 min and treated with saturated $NaHCO_3$ solution. After extraction with CH_2Cl_2, the organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography on silica gel (2/1 heptane/ethyl acetate) gave **16** (66 mg, 90% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23−1.32 (m, 6H), 1.39 (s, 9H), 2.56 (m, 2H), 2.91 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.51 (bs, 1H), 5.13 (~sext, J = 6.15 Hz, 1H), 5.35 (bs, 1H), 7.13 (~q, J = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$,75 MHz) 14.5, 20.3, 27.7, 28.5, 43.4, 55.3, 63.3, 71.2, 80.7, 98.8, 147.5, 155.4, 162.9, 170.1; IR (KCl, cm^{-1}) ν 756, 1165, 1250, 1367, 1499, 1715, 2980, 3429; ESI-MS m/z 526 (M + K^+), 510 (M + Na^+), 488.1 (M + H^+), 387.9, 130.3; HRMS ES+ calcd for $C_{16}H_{26}INO_6S$ 510.04233 (M + Na^+), found 510.04183.

Z-D-cysteine-O-*t*-Bu (18). To a solution of Z-D-cystine-O-*t*-Bu[23] (510 mg, 0.82 mmol) in THF/H_2O (10/1) (7 mL) was added tributyl phosphine (234 μL, 0.92 mmol). The mixture was stirred for 5 min at room temperature, and the solvent was removed under reduced pressure. Chromatography on silica gel (heptane/ethyl acetate 3/1) gave **18** (500 mg, 98% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9H), 2.97 (bdd, J = 3.4, 8.3 Hz, 2H), 4.54 (m, 1H), 5.11 (s, 2H), 5.76 (bd, J = 6.2 Hz, NH), 7.35 (bs, 5H); ^{13}C NMR ($CDCl_3$,75 MHz) 27.2, 27.8, 55.3, 66.8, 82.7, 127.9, 128.0, 128.4, 136.0, 155.5, 168.7; IR (KCl, cm^{-1}) ν 697, 1062, 1154, 1218, 1346, 1369, 1506, 1722, 3421; ESI-MS m/z 334.1 (M + Na^+), 278.0. Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50. Found: C, 58.03; H, 6.67; N, 4.21.

(2*Z*,5*R*)-2-((2*S*)2-Benzyloxycarbonylamino-2-*tert*-butoxycarbonylethylsulfanyl)-5-hydroxyhex-2-enoic Acid Ethyl Ester (19). To a solution of **13** (175 mg, 0.53 mmol), Pd_2dba_3 (13.7 mg, 0.013 mmol), and dppf (30 mg, 0.053 mmol) in *N*-methylpyrrolidone (9 mL) was added triethylamine (150 μL, 1.06 mmol). The solution was stirred for 30 min at room temperature and then warmed to 60 °C. Z-D-cysteine *tert*-butyl ester (**18**) (231 mg, 0.74 mmol) in NMP (2.5 mL) was added over 1 h 30. The mixture was stirred for an additional 2 h, cooled at room temperature, and quenched with brine. After extraction with EtOAc, the organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography on silica gel (7/1 pentane/acetone) gave **19** (170 mg, 63% yield) as an inseparable *Z*/*E* mixture (80/20) and 15 mg of starting material (8.5%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (bd, 6.3 Hz, 0.6H), 1.20 (bd, 2.4H), 1.23 (t, J = 7.1 Hz, 0.4H), 1.29 (t, J = 7.1 Hz, 1.6H), 1.46 (s, 9H), 2.47−2.64 (m, 1H), 2.73−2.84 (m, 1H), 3.02 (dd, J = 4.6, 13.2 Hz, 0.2H), 3.12 (dd, J = 4.8, 14.4 Hz, 0.8H), 3.27 (m, 0.2H), 3.32 (m, 0.8H), 3.31 (s, 2.4H), 3.36 (s, 0.6H), 3.79 (m, 0.2H), 3.85 (m, 0.8H), 4.22 (q, 7.1 Hz, 2H), 4.46 (m, 1H), 4.55 (bd, J = 6.7 Hz, 1H), 4.64 (bd, J = 6.7 Hz, 1H), 5.06 (bs, 2H), 5.64 (bd, J = 8 Hz, 0.2H), 5.8 (bd, J = 7.4 Hz, 0.8H), 6.54 (dt, J = 1.4, 7.4 Hz, 0.2H), 7.21 (bt, J = 7.2 Hz, 0.8H), 7.33 (bs, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) (*Z* isomer) 14.2, 20.3, 27.9, 35.6, 38.2, 55.1, 55.3, 61.6, 66.9, 71.7, 82.6, 94.6, 128.1, 128.3, 128.5, 136.3, 148.1, 155.6, 164.7, 169.2. (*E* isomer) 14.2, 20.4, 27.9, 35.7, 37.9, 55.1, 55.3, 61.4, 66.9, 72.6, 82.7, 95.0, 128.1, 128.3, 128.5, 136.3, 144.7, 155.6, 164.7, 169.2; IR (KCl, cm^{-1}) ν 1037, 1154, 1247, 1506, 1718, 2339, 2360, 2933, 2977; ESI-MS m/z 550.3 (M + K^+), 534.3 (M + Na^+), 478.4; HRMS ES+ calcd for $C_{25}H_{37}NO_8SNa$ 534.2137 (M + Na), found 534.2163.

(2*Z*,5*R*)-2-((2*S*)2-Benzyloxycarbonylamino-2-carboxythylsulfanyl)-5-hydroxyhex-2-enoic Acid Ethyl Ester (20). To a solution of **19** (98 mg, 0.19 mmol) in CH_2Cl_2 (1.2 mL) were added triethylsilane (34 μL, 0.21 mmol) and TFA (0.8 mL) dropwise. The mixture was stirred for 2 h at room temperature and treated with a saturated solution of $NaHCO_3$. After extraction with CH_2Cl_2, the aqueous layer was acidified with a few drops of concentrated HCl and extracted with CH_2Cl_2, The organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product (84 mg,74% yield) was directly used for the next step.

(2*Z*,5*R*)-2-((2*S*)2-Benzyloxycarbonylaminoacryloylsulfanyl)-5-hydroxyhex-2-enoic Acid Ethyl Ester (21). To a solution of crude material **20** (84 mg, 0.14 mmol) in CH_2Cl_2 (60 mL) were added triethylamine (51.5 μL, 0.36 mmol), PyBroP (80 mg, 0.17 mmol), and DMAP (1.5 mg, 0.0018 mmol). The mixture was stirred overnight at room temperature, and the solvent was evaporated under reduced pressure. The crude product was taken up in CH_2Cl_2 and treated with a saturated solution of $NaHCO_3$. After extraction with CH_2Cl_2, the organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography on silica gel (3/1 heptane/ethyl acetate) gave **21** (28 mg, 61% yield) as an colorless oil (this compound could not be separated from unidentified byproducts ~10%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, 6.2 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 2.54 (dd, J = 6.1, 7.5 Hz, 2H), 4.01 (sext, J = 6.1 Hz, 1H), 4.25 (q, J = 7.1 Hz), 5.16 (s, 2H), 5.95 (bt, J = 1.8 Hz), 6.51 (bd, J = 1.8 Hz), 7.22 (bs, 1H), 7.37 (bs, 5H), 7.64 (t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$,75 MHz) δ 14.1, 23.5, 40.5, 62.0, 66.7, 67.2, 106.9, 123.4, 128.2, 128.4, 128.6, 135.6, 137.4, 152.4, 158.1, 171.1, 187.3; ESI-MS m/z 432.1 (M + K^+), 416.2 (M + Na^+), 370.1, 130.4; HRMS ES+ calcd for $C_{19}H_{23}NO_6SNa$ 416.1144 (M + Na^+), found 416.1146.

(6*Z*,3*S*,9*R*)-3-Benzyloxycarbonylamino-9-methyl-2-oxo-3,4,8,9-tetrahydro-2*H*-[1,5]oxathionine-6-carboxylic Acid Ethyl Ester (24). To a solution of crude material **23** (29 mg, 0.07 mmol) in THF (35 mL) were added triphenylphosphine (55 mg, 0.21 mmol) and diisopropyl azodicarboxylate (43 μL, 0.21 mmol). The mixture was stirred overnight at reflux. The solvent was removed under reduced pressure. Chromatography on silica gel (3/1 heptane/ethyl acetate) gave **24** (16 mg, 58% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, J = 7.1 Hz, 3H), 1.36 (d, J = 6.7 Hz, 3H), 2.51 (m, 1H), 3.01 (m, 1H), 3.07 (dd, J = 5.3, 14.5 Hz, 1H), 3.33 (dd, J = 3.3, 14.2 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.65 (m, 1H), 5.11 (s, 2H), 5.26 (m, 1H), 5.69 (bd, J = 5.8 Hz), 7.36 (bs, 5H), 7.52 (dd, J = 7.2, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$,75 MHz) 14.3, 18.9, 34.8, 41.1, 54.2, 62.0, 67.1, 69.9, 128.2, 128.4, 128.7, 132.8, 136.2, 148.4, 155.5, 165.4, 171.1; IR (KCl, cm^{-1}) ν 1056, 1194, 1253, 1357, 1514, 1713, 1741, 2928, 2981, 3419; ESI-MS m/z 432.1 (M + K^+), 416.1 (M + Na^+). Anal. Calcd for $C_{19}H_{23}NO_6S$: C, 58.00; H, 5.89; N, 3.56. Found: C, 57.88; H, 5.94; N, 3.74. $[\alpha]_D$ = −41.8 (c = 0.77, $CHCl_3$).

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