Formal Total Synthesis of (+)-Trehazolin. Application of an Asymmetric Aldol−Olefin Metathesis Approach to the Synthesis of Functionalized Cyclopentenes

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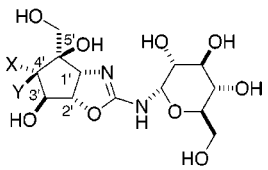
An asymmetric synthesis of the aminocyclopentitol pseudosugar of trehazolin has been completed. The synthesis hinges on an asymmetric aldol-ring closing metathesis strategy to construct the five-membered ring with control of both the relative and absolute stereochemistry.

Glycosyl transferases and glycosidases control the biosynthesis of various glycoconjugates such as glycolipids, glycoproteins, and oligosaccharides. As such, these enzymes have a profound effect on a variety of biological functions including signal transduction and cell recognition.[1] Glycosidases are enzymes that catalyze the hydrolysis of glycosidic bonds; thus, glycosidase inhibitors can be of importance in the study of processes controlled by glycoconjugates and as potential clinical agents to control disease caused by malfunction of glycoconjugates. A diverse collection of naturally occurring glycosidase inhibitors is known, many of which contain an aminocyclopentitol unit. Included in the aminocyclopentitol glycosidases are trehazolin,[2] the mannostatins,[3] and the allosamidins.[4] The biological activity and synthetic approaches to these aminocyclopentitol glycosidases have been extensively studied.[5]

Trehalase is a glycosidase that catalyzes the breakdown of α,α-trehalose to glucose. As a result, specific and potent inhibitors of trehalase might be used as insecticides because trehalose is the principal blood sugar found in insects and is used to support various energy-requiring functions.[6] Trehazolin **1** and trehalostatin **2** (Figure 1), isolated by Ando and co-workers[2] in 1991 and Nakayama and co-workers[7] in 1991, respectively, fit the above criteria and thus have attracted much interest from the synthetic community. Trehazolin was isolated from a culture broth of *Micromonospora strain* SANK 62390, while trehalostatin from *Amycolatopsis trehalostatica*. The absolute configuration of trehazolin was established through the synthetic efforts of Shiozaki and co-workers.[8a] It was also determined through the synthetic studies of Ogawa and co-workers that the structure of trehalostatin was incorrect and that in fact trehazolin and trehalostatin are the same compound.[8b]



1, trehazolin X = OH, Y = H
2, trehalostatin, X = H, Y = OH

Figure 1. Trehalase inhibitors.

Several total syntheses of trehazolin[8] have been reported since the seminal work of Shiozaki and Ogawa. All the syntheses rely on the coupling of trehazolamine or a protected form of trehazolamine with a glucose derivative near the end of the synthesis. As such, any synthesis of trehazolamine constitutes a formal synthesis of the natural product, trehazolin. For comparison, the efficiency to trehazolamine or a protected form are discussed below. The most recent synthesis of trehazolamine, by Al-Abed,[8I] utilizes a ring-closing metathesis of a diene derived from arabinose to construct the five-membered carbocycle in nine steps from 2′,3′,5′-tri-*O*-benzyl-D-arabinose. The syntheses by Chiara[8g,h] and Giese[8f] rely on a pinacol coupling of a hydroxylamine derived from either mannose or glucose to prepare the five-membered ring. The Chiara and Giese approaches produce trehazolamine in 12 and 11 steps, respectively, from the appropriate natural carbohydrate. Knapp's[8c] 15-step approach to trehazolamine utilized ribonolactone as the starting point for preparation of the carbocyclic sugar.

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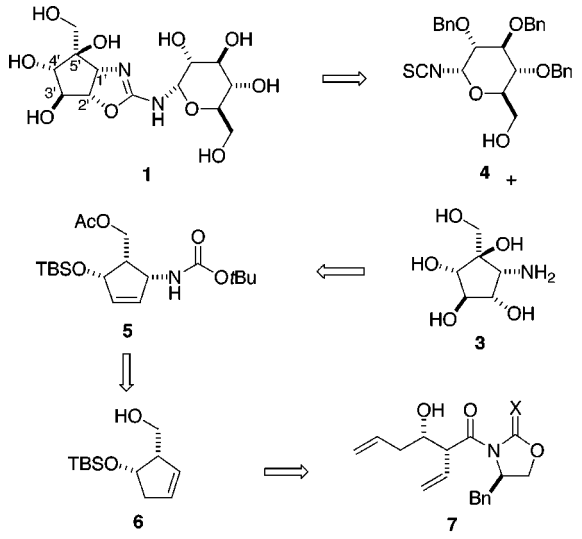
Scheme 1



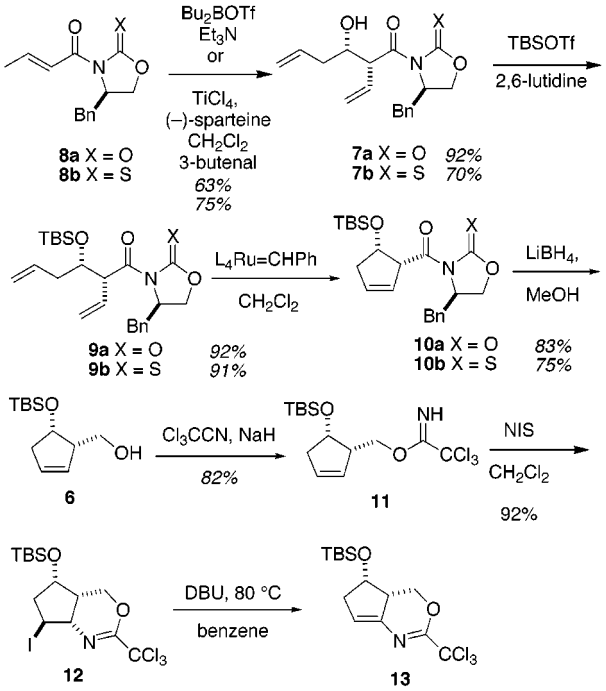
The Ganem[8e] and Carreira[8d] approaches began with cyclopentadiene as the synthon for the carbocycle and produced a trehazolamine derivative in 12 and 14 steps, respectively.

After our initial total synthesis of the carbocyclic nucleosides carbovir and abacavir using an asymmetric aldol-metathesis strategy[9] to access a functionalized cyclopentene derivative, it was decided to apply this strategy to the total synthesis of trehazolin, which contains a heavily functionalized cyclopentane ring.

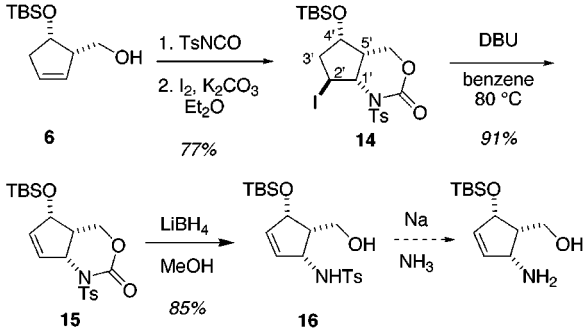
Retrosynthetically, trehazolin can arise from the coupling of aminocyclopentitol **3** and the α-D-glucosyl isothiocyanate **4**[8d] following precedented work of others (Scheme 1).[8] The aminocyclitol can arise from cyclopentene **5** through a series of functional group manipulations. An electrophilic cyclization−elimination sequence could provide the aminocyclopentene **5** from cyclopentenol derivative **6**, which is the product of a ring-closing metathesis of diene **7**. Diene **7** is the obvious product of an asymmetric aldol addition reaction.

The acylated oxazolidinone **8a** was subjected to the Evans dialkyl boron triflate[10] protocol using 3-butenal[11] to yield the syn aldol product **7a** in 63% yield as shown in Scheme 2. Similarly, but in slightly higher yield (75%), the *N*-acyloxazolidinethione **8b** delivered the aldol adduct **7b** when enolized with $TiCl_4$-(−)-sparteine[12] and then treated with 3-butenal. To our knowledge, this is the first example of an asymmetric crotonyl aldol addition through the use of a chlorotitanium enolate. Attempted ring closing metathesis[13] on diene **7a** or **7b** led to incomplete conversion to the desired cyclopentene (56:44 ratio of starting material to product) presumably due to the coordination of the homoallylic alcohol to the metal center in the intermediate alkylidine. As a result, the secondary alcohol was protected to circumvent the problem. Protection of the alcohol as the *tert*-butyldimethylsilyl ether provided **9a** or **9b** in high yield and exposure of the diene **9a** and **9b** to the Grubbs catalyst[14] generated cyclopentene **10a** or **10b** in 85% yield over two steps. Reductive removal of the chiral auxiliary followed by treatment of the resultant alcohol with trichloroacetonitrile gave imidate **11**. It was anticipated that an electrophilic cyclization of the imidate on the cyclopentene olefin would be used to introduce the amine at C1′ stereoselectively. Treatment of imidate **11** with phenylselenyl chloride or *N*-(phenylseleno)phthalimide[15] gave no reaction; however, *N*-iodosuccinimide-promoted cyclization smoothly produced the iodide **12**. Unfortunately, elimination using DBU resulted in the undesired cyclopentene regioisomer **13**.

Scheme 2



Scheme 3



The electrophilic cyclization developed by Hirama and Ito[16] was next investigated in an attempt to generate the desired cyclopentene after elimination of the halide (Scheme 3). Treatment of the alcohol **6** with *p*-toluenesulfonyl isocyanate followed by cyclization with iodine

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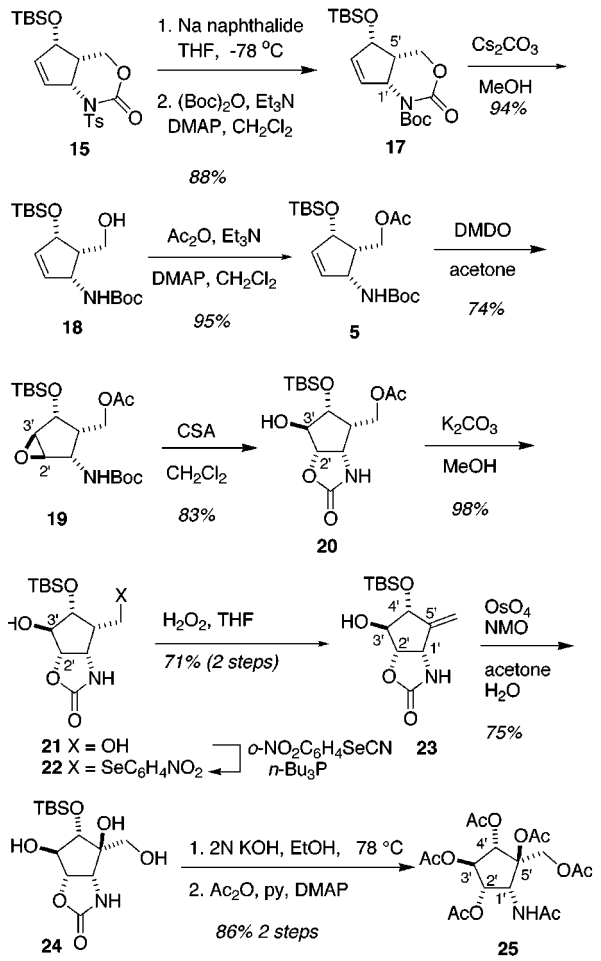
Scheme 4



generated iodide **14** in 77% overall yield. Elimination of the halide with DBU yielded 91% of the cyclopentene **15**.

With the successful introduction of the stereocenter at C1′, efforts were next directed toward the incorporation of the C2′ and C3′ centers, which effectively required a selective anti dihydroxylation of the alkene. A neighboring group directed nucleophilic opening of the cyclopentene β-epoxide was envisioned as a possible solution. Reduction of the cyclic carbamate **15** with $LiBH_4$-generated alcohol **16**. Reductive removal of the sulfonamide with sodium and ammonia led to scrambling of the *tert*-butyldimethylsilyl ether. Consequently, a new strategy, as shown in Scheme 4, was investigated to circumvent the silyl transfer.

Hydrolysis of the cyclic carbamate was next attempted using the protocol developed by Kunieda.[17] Reductive removal of the sulfonamide of alkene **15** using sodium naphthalide[18] followed by acylation of the nitrogen with di-*tert*-butyl dicarbonate generated cyclic carbamate **17** in 88% yield. Attempted epoxidation of cyclopentene **17** led to formation of the epoxide in only 26% yield due to the formation of an enone as a side product. Thus, epoxidation was attempted after hydrolysis of the carbamate. Cesium carbonate mediated hydrolysis of the carbamate, and protection of the alcohol with acetic anhydride gave ester **5** in 95% overall yield. Epoxidation of the less hindered face of the alkene using dimethyldioxirane[19] gave 74% of epoxide **19** as the only detectable isomer. Acid-promoted nucleophilic opening of the epoxide by the neighboring carbamate carbonyl oxygen generated oxazolidinone **20** in 83% yield. Finally, introduction of the stereocenter at C5′ was accomplished. Deprotection of the acetate under basic conditions provided the primary alcohol which was converted to the primary selenide using the protocol developed by Grieco (70% overall).[20] Thus, treatment of alcohol **21** with 2-nitrophenylselenocyanate[21] and tributylphosphine gave the intermediate selenide **22** which was immediately oxidized with hydrogen peroxide to give the exocyclic olefin **23**. Osmylation of the alkene gave 75% of triol **24** as a single observable diastereomer. Exposure of oxazolidinone **24** to aqueous base followed by peracetylation with acetic anhydride gave ester **25** which was spectroscopically identical (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$) to that previously reported. Ester **25** has been taken on to trehazolin as described by Shiozaki.[8a]

An asymmetric aldol ring closing metathesis approach has been applied to the synthesis of the carbocyclic sugar trehazolamine. The synthesis was completed in 18 steps form the *N*-acyloxazolidinethione **8b**. While the synthesis is not as efficient as some previous approaches, it demonstrates the power and flexibility of the general strategy of combining reactions which control acyclic stereochemistry with the ring-closing metathesis reaction.

Experimental Section

Materials and Methods. General Procedures. Infrared (IR) spectra were obtained using a Perkin-Elmer 283 infrared spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on the following instrument: Bruker Model Avance 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz). Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Thin-layer chromatography (TLC) was conducted on silica gel F_{254} TLC plates purchased from Scientific Adsorbents, Inc. Flash chromatography was carried out using silica gel (32−63 μm) purchased from Scientific Adsorbents, Inc. Diethyl ether, tetrahydrofuran (THF), and dichloromethane were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines, and benzene were distilled from calcium hydride immediately prior to use. 1,2-dimethoxyethane was distilled from sodium immediately prior to use. All air and water sensitive reactions were performed in flasks flame dried under a positive flow of argon and conducted under an argon atmosphere.

(4*R*)-Benzyl-3-((3*S*)-hydroxy-(2*R*)-vinylhex-5-enoyl)oxazolidin-2-one (7a). A solution of the acyloxazolidinone **8a**[10] (13.17 g, 54 mmol) in 280 mL of CH_2Cl_2 was cooled to −78 °C. Bu_2BOTf (14.7 mL, 59 mmol) was diluted in 15 mL of CH_2Cl_2 and then added dropwise slowly. The mixture was stirred for 5 min at −78 °C. Et_3N (10.5 mL, 75 mmol) was diluted with 10 mL of CH_2Cl_2 and then added dropwise slowly. After complete addition, the mixture was stirred at −78 °C for 1 h. The mixture was gradually warmed to 0 °C, stirred for 15 min, and then recooled to −78 °C. A solution of 3-butenal (277 mmol) in 100 mL of CH_2Cl_2 was cooled to −78 °C and added to the enolate solution via cannula. The reaction was stirred for 1 h at −78 °C, gradually warmed to 0 °C, and stirred for 1

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h. The reaction was quenched with 1 M $NaHSO_4$ and warmed to 25 °C. The layers were separated, and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were washed with brine and concentrated in vacuo. The residue was dissolved in 360 mL of Et_2O and cooled to 0 °C. A solution of pH 7 buffer (53 mL) was added followed by dropwise addition of H_2O_2 (53 mL of a 30% solution in H_2O) while the temperature was maintained around 0 °C. The mixture was stirred for 1 h. Water was added, and the layers were separated. The aqueous layer was extracted twice with ether. The combined extracts were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 3.58 g of acyloxazolidinone and 10.7 g of alcohol **7a** (63%; 90% based on recovered starting material): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.25 (m, 3H), 7.19−7.16 (m, 2H), 6.00 (ddd, J = 17.6, 9.6, 9.2 Hz, 1H), 5.81 (dddd, J = 16.8, 10.4, 6.8, 6.8 Hz, 1H), 5.43−5.39 (m, 2H), 5.14−5.09 (m, 2H), 4.70 (dddd, J = 9.2, 7.6, 3.2, 3.2 Hz, 1H), 4.58 (dd, J = 9.2, 3.6 Hz, 1H), 4.17 (AB portion of ABX, J_{AB} = 8.8 Hz, J_{AX} = 21.2 Hz, J_{BX} = 7.6 Hz, $\Delta\nu_{AB}$ = 9 Hz, 2H), 4.09−4.04 (m, 1H), 3.22 (dd, J = 13.2, 3.2 Hz, 1H), 2.97 (d, J = 2 Hz, 1H), 2.73 (dd, J = 13.6, 9.6 Hz, 1H), 2.35−2.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.8, 152.8, 134.8, 134.2, 131.0, 129.4, 128.9, 127.3, 121.7, 117.9, 70.9, 65.9, 55.0, 51.5, 38.6, 37.5; IR (film) 3500 (br), 3080, 1775, 1685 cm^{-1}; $[\alpha]^{24}_D$ = −22.8 (*c* 1.47, CH_2Cl_2). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.42; H, 6.69; N, 4.29.

(4*R*)-Benzyl-3-[(3*S*)-(*tert*-butyldimethylsilanyloxy)-(2*R*)-vinylhex-5-enoyl]oxazolidin-2-one (9a). To a cooled solution (0 °C) of alcohol **7a** (12.1 g, 38 mmol) in 300 mL of CH_2Cl_2 was added 2,6-lutidine (17.9 mL, 150 mmol) followed by dropwise addition of TBSOTf (15.4 mL, 67 mmol) diluted in 15 mL of CH_2Cl_2. The reaction was stirred for 2 h and quenched with saturated $NaHCO_3$. The layers were separated, and the organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 15.02 g of diene **9a** (92%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.23 (m, 3H), 7.19−7.17 (m, 2H), 6.01 (ddd, J = 17.4, 10.4, 9.2 Hz, 1H), 5.81 (dddd, J = 17.0, 10.4, 7.2, 7.2 Hz, 1H), 5.30−5.22 (m, 2H), 5.04−4.97 (m, 2H), 4.60 (dddd, J = 9.6, 6.8, 3.2, 3.2 Hz, 1H), 4.50 (dd, J = 9.2, 5.6 Hz, 1H), 4.16−4.10 (m, 3H), 3.24 (dd, J = 13.2, 3.2 Hz, 1H), 2.73 (dd, J = 13.6, 9.6 Hz, 1H), 2.35−2.29 (m, 2H), 0.87 (s, 9H), 0.03 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4, 152.8, 135.2, 134.4, 133.4, 129.5, 128.9, 127.3, 119.6, 117.3, 72.4, 65.9, 55.5, 53.2, 40.6, 37.5, 25.8, 18.0, −4.2, −4.8; IR (film) 3080, 1780, 1695, 1640 cm^{-1}; $[\alpha]^{24}_D$ = −45.1 (*c* 0.88, CH_2Cl_2). Anal. Calcd for $C_{24}H_{35}NO_4Si$: C, 67.10; H, 8.21; N, 3.26. Found: C, 67.16; H, 8.22; N, 3.31.

(4*R*)-Benzyl-3-[(1*R*,5*S*)-5-(*tert*-butyldimethylsilanyloxy)-cyclopent-2-enecarbonyl]oxazolidin-2-one (10a). A solution of diene **9a** (14.56 g, 34 mmol) in 300 mL of CH_2Cl_2 was heated to reflux. Grubbs' metathesis catalyst [$Cl_2(Cy_3P)_2Ru$=CHPh; 1.39 g, 1.7 mmol] was added in one portion and the reaction was stirred for 2 h at reflux. After cooling to 25 °C, the mixture was stirred open to air overnight and concentrated in vacuo. Purification by flash chromatography gave 12.56 g of alkene **10a** (92%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.20 (m, 5H), 5.92 (dddd, J = 6.4, 2.4, 2.2, 2.0 Hz, 1H), 5.72 (dddd, J = 6.0, 2.0, 2.0, 2.0 Hz, 1H), 4.92 (ddd, J = 7.0, 7.0, 2.8 Hz, 1H), 4.82 (dddd, J = 7.2, 4.0, 2.0, 2.0 Hz, 1H), 4.61 (dddd, J = 10.0, 7.6, 3.2, 3.2 Hz, 1H), 4.14 (AB portion of ABX, J_{AB} = 2.8 Hz, J_{AX} = 9.2 Hz, J_{BX} = 9.2 Hz, $\Delta\nu_{AB}$ = 14 Hz, 2H), 3.34 (dd, J = 13.6, 3.2 Hz, 1H), 2.74 (dd, J = 13.2, 9.6 Hz, 1H), 2.67−2.60 (m, 1H), 2.38−2.32 (m, 1H), 0.80 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 153.3, 135.5, 131.6, 129.4, 128.9, 127.2, 127.0, 73.0, 65.9, 56.0, 55.4, 42.5, 38.1, 25.5, 17.6, −4.5, −5.4; IR (film) 1785, 1705 cm^{-1}; $[\alpha]^{24}_D$ = −47.2 (*c* 0.90, CH_2Cl_2). Anal. Calcd for $C_{22}H_{31}NO_4Si$: C, 65.80; H, 7.78; N, 3.49. Found: C, 65.52; H, 7.96; N, 3.47.

[(1*S*,5*S*)-5-(*tert*-Butyldimethylsilanyloxy)cyclopent-2-enyl]methanol (6). A solution of alkene **10a** (12.85 g, 32 mmol) in anhydrous methanol (1.94 mL, 48 mmol) and 300 mL of ether was cooled to 0 °C. Lithium borohydride (24 mL of a 2.0 M solution in THF, 48 mmol) was added dropwise, and the reaction was stirred for 2 h at 0 °C and 1 h at 25 °C. The mixture was recooled to 0 °C and quenched with the dropwise addition of 1 M NaOH. The mixture was warmed to 25 °C, and the layers were separated. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 6.1 g of alcohol **6** (83.4%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74 (dddd, J = 6.0, 2.4, 2.4, 2.4 Hz, 1H), 5.57 (dddd, J = 6.0, 2.0, 2.0, 2.0 Hz, 1H), 4.67 (ddd, J = 7.4, 7.4, 5.6 Hz, 1H), 3.74 (d, J = 4.8 Hz, 1H), 3.72 (d, J = 4.8 Hz, 1H), 2.91 (dd, J = 6.4, 6.4 Hz, 1H), 2.81−2.77 (m, 1H), 2.58−2.51 (m, 1H), 2.34−2.27 (m, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.2, 129.9, 75.3, 62.2, 50.6, 41.4, 25.8, 17.9, −4.6, −5.2; IR (film) 3420 (br) cm^{-1}; $[\alpha]^{24}_D$ = −17.7 (*c* 0.81, CH_2Cl_2). Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 63.16; H, 10.59.

1-[(4R)-4-Benzyl-2-thioxooxazolidin-3-yl]but-2-en-1-one (8b). To a cooled solution (−78 °C) of (*R*)-4-benzyl-2-oxazolidinethione (2.05 g, 10.6 mmol) and Et_3N (1.92 mL, 14.0 mmol) in 75 mL of CH_2Cl_2 was added dropwise *trans*-crotonyl chloride (1.22 mL, 12.7 mmol). The mixture was stirred for 30 min and quenched with H_2O. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 2.33 g of acylated thione **8b** (84%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dq, J = 15.2, 1.6 Hz, 1H), 7.34−7.09 (m, 6H), 4.90 (dddd, J = 13.6, 6.4, 3.6, 2.8 Hz, 1H), 4.33−4.27 (m, 2H), 3.34 (dd, J = 13.2, 3.2 Hz, 1H), 2.78 (dd, J = 13.2, 10.0 Hz, 1H), 1.99 (dd, J = 6.8, 1.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.5, 166.0, 146.4, 135.2, 129.3, 128.9, 127.2, 123.2, 70.4, 60.0, 37.4, 18.5; IR (film) 1680, 1640 cm^{-1}; $[\alpha]^{24}_D$ = −109.3 (*c* 0.91, CH_2Cl_2). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.44; H, 5.68; N, 5.38.

(2*R*,3*S*)-1-[(4*R*)-4-Benzyl-2-thioxooxazolidin-3-yl]-3-hydroxy-2-vinylhex-5-en-1-one (7b). A solution of the acyloxazolidinethione **8b** (1.16 g, 4.46 mmol) in 30 mL of CH_2Cl_2 was cooled to −78 °C. Titanium tetrachloride (0.51 mL, 4.68 mmol) was added dropwise slowly. The mixture was stirred for 5 min at −78 °C. (−)-Sparteine (2.56 mL, 11 mmol) was then added dropwise slowly. After complete addition, the mixture was stirred at −78 °C for 2 h. A solution of 3-butenal (31 mmol) in 14 mL of CH_2Cl_2 was cooled to −78 °C and added to the enolate solution via cannula. The reaction was stirred for 1 h at −78 °C, gradually warmed to 0 °C, and stirred for 1 h. The reaction was quenched with half-saturated NH_4Cl and warmed to 25 °C. The layers were filtered through Celite, separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 1.10 g of alcohol **7b** (75%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.24 (m, 3H), 7.20−7.18 (m, 2H), 6.03 (ddd, J = 17.2, 10.4, 8.8 Hz, 1H), 5.81 (dddd, J = 16.8, 10.0, 7.2, 7.2 Hz, 1H), 5.58 (dd, J = 8.8, 4.0 Hz, 1H), 5.44−5.38 (m, 2H), 5.15−5.10 (m, 2H), 4.95 (dddd, J = 13.6, 3.6, 3.4, 3.2 Hz, 1H), 4.32−4.25 (m, 2H), 4.13−4.08 (m, 1H), 3.23 (dd, J = 13.2, 3.2 Hz, 1H), 2.74 (d, J = 2.8 Hz, 1H), 2.72 (dd, J = 13.2, 10.0 Hz, 1H), 2.32−2.27 (m, 2H),; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.9, 174.5, 134.9, 134.0, 130.9, 129.3, 129.0, 127.4, 121.5, 118.1, 71.2, 70.1, 59.9, 51.1, 38.8, 37.3; IR (film) 3480 (br), 1685 cm^{-1}; $[\alpha]^{24}_D$ = −64.2 (*c* 1.3, CH_2Cl_2). Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.27; H, 6.25; N, 4.22.

(2*R*,3*S*)-1-[(4*R*)-4-Benzyl-2-thioxooxazolidin-3-yl]-3-(*tert*-butyldimethylsilanyloxy)-2-vinylhex-5-en-1-one (9b). To a cooled solution (0 °C) of alcohol **7b** (440 mg, 1.33 mmol) in 10 mL of CH_2Cl_2 was added 2,6-lutidine (0.62 mL, 5.3 mmol) followed by TBSOTf (0.46 mL, 2.00 mmol). The reaction was stirred for 1.5 h and quenched with saturated $NaHCO_3$. The layers were separated, and the organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 414 mg of diene **9b** (70%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.19 (m, 5H), 6.06 (ddd, J = 17.4,

10.4, 8.8 Hz, 1H), 5.81 (dddd, J = 16.8, 10.0, 7.2, 7.2 Hz, 1H), 5.40 (dd, J = 8.8, 5.2 Hz, 1H), 5.32 (dd, J = 10.4, 1.6 Hz, 1H), 5.27−5.23 (m, 1H), 5.04−4.98 (m, 2H), 4.85−4.79 (m, 1H), 4.28 (dd, J = 9.6, 2.0 Hz, 1H), 4.26−4.16 (m, 2H), 3.27 (dd, J = 13.6, 3.2 Hz, 1H), 2.71 (dd, J = 13.2, 10.4 Hz, 1H), 2.39−2.26 (m, 2H), 0.86 (s, 9H), 0.03 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.6, 173.2, 135.3, 134.3, 133.1, 129.4, 129.0, 127.4, 119.7, 117.5, 72.9, 69.8, 60.6, 52.9, 40.7, 37.2, 25.7, 18.0, −4.1, −4.7; IR (film) 1695 cm^{-1}; $[\alpha]^{24}_D$ = −62.2 (*c* 2.6, CH_2Cl_2). Anal. Calcd for $C_{24}H_{35}NO_3SSi$: C, 64.68; H, 7.92; N, 3.14. Found: C, 64.55; H, 8.03; N, 3.21.

[(4*R*)-4-Benzyl-2-thioxooxazolidin-3-yl]-[(1*R*,5*S*)-5-(*tert*-butyldimethylsilanyloxy)cyclopent-2-enyl]methanone (10b). A solution of diene **9b** (105 mg, 0.24 mmol) in 5 mL of CH_2Cl_2 was heated to reflux. Grubbs' metathesis catalyst (10 mg, 0.01 mmol) was added in one portion, and the reaction was stirred for 2.5 h at reflux. After being cooled to 25 °C, the mixture was stirred open to air overnight and concentrated in vacuo. Purification by flash chromatography gave 90 mg of alkene **10b** (91%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.21 (m, 5H), 5.91 (dddd, J = 6.0, 2.4, 2.4, 2.4 Hz, 1H), 5.86−5.82 (m, 1H), 5.73 (dddd, J = 6.0, 2.4, 2.2, 2.0 Hz, 1H), 5.05 (ddd, J = 7.2, 7.0, 2.8 Hz, 1H), 4.88−4.83 (m, 1H), 4.30 (dd, J = 9.2, 2.0 Hz, 1H), 4.20−4.16 (m, 1H), 3.33 (dd, J = 13.2, 3.2 Hz, 1H), 2.74 (dd, J = 13.2, 10.4 Hz, 1H), 2.71−2.64 (m, 1H), 2.40−2.34 (m, 1H), 0.78 (s, 9H), 0.03 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.3, 171.8, 135.5, 131.2, 129.4, 129.0, 127.3, 127.2, 73.1, 69.8, 60.4, 56.2, 42.8, 37.8, 25.6, 17.7, −4.4, −4.9; IR (film) 1700 cm^{-1}; $[\alpha]^{24}_D$ = +15.9 (*c* 0.75, CH_2Cl_2). Anal. Calcd for $C_{22}H_{31}NO_3SSi$: C, 63.27; H, 7.48; N, 3.35. Found: C, 63.60; H, 7.43; N, 3.30.

[(1*S*,5*S*)-5-(*tert*-Butyldimethylsilanyloxy)cyclopent-2-enyl]methanol (6). A solution of alkene **10b** (86 mg, 0.21 mmol) in anhydrous methanol (0.02 mL, 0.4 mmol) and 3 mL of ether was cooled to 0 °C. Lithium borohydride (0.20 mL of a 2.0 M solution in THF, 0.4 mmol) was added dropwise, and the reaction was stirred for 1.5 h 0 °C. The mixture was quenched with the dropwise addition of 1 M NaOH. The mixture was warmed to 25 °C, and the layers were separated. The aqueous layer was extracted once with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 35 mg (75%) of alcohol **6** identical to that prepared above.

[8*S*,9*S*]-(5*S*)-(*tert*-Butyldimethylsilanyloxy)-(7*S*)-iodo-1-(toluene-4-sulfonyl)hexahydrocyclopenta[*d*][1,3]oxazin-2-one (14). To a stirred solution of alcohol **6** (6.1 g, 27 mmol) in 200 mL of THF was added *p*-toluenesulfonyl isocyanate (4.47 mL, 29 mmol). The mixture was stirred for 12 h and concentrated in vacuo. Purification by flash chromatography afforded 10.7 g of alkene (94.5%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (ddd, J = 8.4, 2.0, 2.0 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.31 (br s, 1H), 5.72 (dddd, J = 6.0, 2.4, 2.2, 2.0 Hz, 1H), 5.48 (dddd, J = 6.0, 2.0, 2.0, 2.0 Hz, 1H), 4.46 (ddd, J = 6.8, 6.8, 4.4 Hz, 1H), 4.30 (dd, J = 10.8, 6.4 Hz, 1H), 4.08 (dd, J = 10.4, 7.2 Hz, 1H), 2.83−2.76 (m, 1H), 2.52−2.45 (m, 1H), 2.42 (s, 3H), 2.24−2.19 (m, 1H), 0.80 (s, 9H), −0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.5, 144.9, 135.5,,130.4, 129.5, 129.2, 128.3, 72.3, 66.4, 48.3, 41.8, 25.7, 21.6, 17.9, −4.8, −5.2; IR (film) 3240, 1730, 1600 cm^{-1}; $[\alpha]^{24}_D$ = −39.3 (*c* 0.77, CH_2Cl_2). Anal. Calcd for $C_{20}H_{31}NO_5SSi$: C, 56.44; H, 7.34; N, 3.29. Found: C, 56.67; H, 7.26; N, 3.29.

To a solution of alkene (11.37 g, 27 mmol) in 220 mL of ether was added K_2CO_3 (9.23 g, 67 mmol). The mixture was cooled to 0 °C, and iodine (13.56 g, 53 mmol) was added. The mixture was warmed to 25 °C and stirred for 36 h. The reaction was quenched with 10% Na_2SO_3, and the mixture was stirred until both layers were colorless. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were separately washed with saturated Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 12.08 g of iodide **14** (82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (ddd, J = 8.4, 2.0, 2.0 Hz, 2H), 7.34 (ddd, J = 8.6, 2.4, 2.0 Hz, 2H), 5.31 (dd, J = 9.6, 0.8 Hz, 1H), 4.76 (ddd, J = 9.6, 8.6, 6.0 Hz, 1H), 4.55 (dd, J = 11.2, 1.2 Hz, 1H), 4.12 (d, J = 6.0 Hz, 1H), 4.01 (dd, J = 11.2, 4.4 Hz, 1H), 2.95 (ddd, J = 9.0, 9.0, 3.2 Hz, 1H), 2.43 (s, 3H), 2.18 (dd, J = 14.8, 6.0 Hz, 1H), 1.84 (ddd, J = 14.6, 10.0, 6.0 Hz, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.6, 145.6, 135.0, 129.6, 129.3, 72.4, 67.6, 64.8, 44.8, 40.6, 25.6, 24.8, 21.7, 17.9, −4.7, −5.1; IR (film) 1740 cm^{-1}; $[\alpha]^{24}_D$ = −22.4 (*c* 1.9, CH_2Cl_2). Anal. Calcd for $C_{20}H_{30}INO_5SSi$: C, 43.56; H, 5.48; N, 2.54. Found: C, 43.93; H, 5.57; N, 2.59.

[8*R*,9*S*]-(5*S*)-(*tert*-Butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-4,4a,5,7a-tetrahydro-1*H*-cyclopenta[*d*][1,3]-oxazin-2-one (15). To a solution of iodide **14** (12.19 g, 22 mmol) in 200 mL of benzene was added DBU (6.6 mL, 44 mmol). The mixture was heated at reflux for 1 h, cooled to 25 °C, and filtered. Purification by flash chromatography afforded 8.5 g of alkene **15** (91%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (ddd, J = 8.4, 2.0, 2.0 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 6.01 (ddd, J = 6.0, 1.6, 1.6 Hz, 1H), 5.85 (ddd, J = 5.6, 1.6, 1.6 Hz, 1H), 5.10 (dddd, J = 7.6, 2.0, 1.8, 1.6 Hz, 1H), 4.90 (dddd, J = 6.8, 1.6, 1.6, 1.6 Hz, 1H), 4.22 (dd, J = 11.6, 8.4 Hz, 1H), 4.14 (dd, J = 11.2, 5.2 Hz, 1H), 3.03−2.96 (m, 1H), 2.42 (s, 3H), 0.86 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.4, 145.1, 136.8, 135.2, 131.6, 129.4, 129.1, 75.0, 65.5, 62.4, 41.2, 25.6, 21.6, 18.0, −4.8, −5.1; IR (film) 1740 cm^{-1}; $[\alpha]^{24}_D$ = −77.1 (*c* 1.37, CH_2Cl_2). Anal. Calcd for $C_{20}H_{29}NO_5SSi$: C, 56.71; H, 6.90; N, 3.31. Found: C, 56.65; H, 6.94; N, 3.26.

[8*R*,9*S*]-(5*S*)-(*tert*-Butyldimethylsilanyloxy)-2-oxo-4,-4a,5,7a-tetrahydrocyclopenta[*d*][1,3]oxazine-1-carboxylic Acid *tert*-Butyl Ester (17). To a solution of naphthalene (13.1 g, 102 mmol) in 88 mL of 1,2-dimethoxyethane was added sodium (2.07 g, 90 mmol). The mixture was sonicated for 2 h to give a dark green solution.[22]

A solution of alkene **15** (8.87 g, 20.9 mmol) in 180 mL of THF was cooled to −78 °C. Sodium naphthalenide (68 mL of a 1 M solution, 68 mmol) was added dropwise, and the mixture was stirred for 15 min. The reaction was quenched with saturated NH_4Cl and warmed to 25 °C. The layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 5.21 g of oxazolidinone (92.4%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.58 (s, 1H), 5.75 (ddd, J = 6.0, 1.2, 1.2 Hz, 1H), 5.72 (ddd, J = 5.6, 1.6, 1.6 Hz, 1H), 4.96 (dddd, J = 6.8, 1.6, 1.6, 1.6 Hz, 1H), 4.27 (dddd, J = 6.8, 1.6, 1.4, 1.2 Hz, 1H), 4.19 (dd, J = 11.6, 5.6 Hz, 1H), 4.05 (dd, J = 11.6, 11.6 Hz, 1H), 2.93−2.86 (m, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.5, 134.7, 132.2, 76.3, 65.4, 56.9, 39.0, 25.7, 18.0, −4.9, −5.1; IR (film) 3320, 1670 cm^{-1}; $[\alpha]^{24}_D$ = −6.5 (*c* 0.53, CH_2Cl_2). Anal. Calcd for $C_{13}H_{23}NO_3Si$: C, 57.96; H, 8.60; N, 5.20. Found: C, 57.98; H, 8.64; N, 5.38.

To a cooled solution (0 °C) of oxazolidinone (5.21 g, 19 mmol) in 160 mL of THF were added Et_3N (2.7 mL, 19 mmol), di-*tert*-butyl dicarbonate (8.89 mL, 39 mmol), and 4-(dimethylamino)pyridine (0.473 g, 3.9 mmol). The reaction was warmed to 25 °C, stirred for 12 h, and concentrated in vacuo. Purification by column chromatography afforded 6.85 g of alkene **17** (96%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.86 (ddd, J = 5.6, 1.6, 1.6 Hz, 1H), 5.83 (ddd, J = 6.0, 1.2, 1.2 Hz, 1H), 4.94−4.89 (m, 2H), 4.23 (dd, J = 10.8, 6.8 Hz, 1H), 4.10 (dd, J = 11.2, 5.2 Hz, 1H), 2.96 (dddd, J = 8.0, 7.2, 7.2, 4.8 Hz, 1H), 1.52 (s, 9H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.6, 152.0, 136.8, 130.5, 83.6, 75.6, 64.8, 60.9, 41.0, 27.9, 25.7, 18.1, −4.7, −5.0; IR (film) 1740 cm^{-1}; $[\alpha]^{24}_D$ = −97.4 (*c* 0.65, CH_2Cl_2). Anal. Calcd for $C_{18}H_{31}NO_5Si$: C, 58.51; H, 8.46; N, 3.79. Found: C, 58.64; H, 8.51; N, 3.94.

[(1*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilanyloxy)-5-hydroxymethylcyclopent-2-enyl]carbamic Acid *tert*-Butyl Ester (18). To a cooled solution (0 °C) of alkene **17** (3.24 g, 8.8 mmol) in 80 mL of MeOH was added Cs_2CO_3 (0.571 g, 1.8 mmol).

(22) Azuma, T.; Yanagida, S.; Sakurai, H. *Synth. Commun.* **1982**, *12*, 137−140.

The reaction was warmed to 25 °C and stirred for 48 h. The reaction was quenched with saturated NH_4Cl, and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 2.82 g of alcohol **18** (93.6%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.91 (dd, J = 6.0, 2.0 Hz, 1H), 5.86 (ddd, J = 5.6, 1.6, 1.6 Hz, 1H), 5.17 (d, J = 10 Hz, 1H), 4.77−4.75 (m, 1H), 4.72−4.68 (m, 1H), 3.86 (ddd, J = 12.2, 5.2, 2.4 Hz, 1H), 3.66 (ddd, J = 11.6, 11.6, 3.2 Hz, 1H), 2.89 (dd, J = 11.2, 2.8 Hz, 1H), 2.54−2.48 (m, 1H), 1.43 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3, 135.5, 135.1, 79.5, 76.9, 60.2, 55.8, 47.1, 28.3, 25.7, 17.9, −4.5, −5.1; IR (film) 3420 (br, 1700 cm^{-1}; $[\alpha]^{24}_D$ = +50.3 (*c* 1.05, CH_2Cl_2). Anal. Calcd for $C_{17}H_{33}NO_4Si$: C, 59.44; H, 9.68; N, 4.08. Found: C, 59.55; H, 9.69; N, 4.03.

Acetic Acid (1*S*,2*R*,5*S*)-2-*tert*-Butoxycarbonylamino-5-(*tert*-butyldimethylsilanyloxy)cyclopent-3-enylmethyl Ester (5). To a cooled solution (0 °C) of alcohol **18** (2.82 g, 8.2 mmol) in 75 mL of CH_2Cl_2 were added Et_3N (3.43 mL, 25 mmol), Ac_2O (1.16 mL, 12 mmol), and 4-(dimethylamino)-pyridine (0.05 g, 0.41 mmol). The reaction was warmed to 25 °C and stirred for 6 h. The reaction was quenched with 1 M HCl. The layers were separated, and the aqueous layer was washed with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 3.02 g of ester **5** (95.3%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.98 (dd, J = 5.6, 2.4 Hz, 1H), 5.96 (dd, J = 5.6, 2.4 Hz, 1H), 4.67 (ddd, J = 10.4, 6.8, 2.0 Hz, 1H), 4.55 (dd, J = 5.6, 2.0 Hz, 1H), 4.37 (d, J = 10.4 Hz, 1H), 4.21 (dd, J = 11.2, 6.8 Hz, 1H), 4.16 (dd, J = 11.2, 8.0 Hz, 1H), 2.44−2.37 (m, 1H), 2.02 (s, 3H), 1.41 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 154.9, 135.9, 135.1, 79.2, 74.5, 61.0, 54.8, 44.9, 28.2, 25.7, 20.9, 17.9, −4.4, −5.2; IR (film) 3450, 3360, 1720 cm^{-1}; $[\alpha]^{24}_D$ = +32.6 (*c* 1.48, CH_2Cl_2). Anal. Calcd for $C_{19}H_{35}NO_5Si$: C, 59.19; H, 9.15; N, 3.63. Found: C, 59.45; H, 9.14; N, 3.61.

Acetic Acid (1*R*,2*S*,3*S*,4*R*,5*R*)-2-*tert*-Butoxycarbonylamino-4-(*tert*-butyldimethylsilanyloxy)-6-oxabicyclo[3.1.0]-hex-3-ylmethyl Ester (19). Ester **5** (3.02 g, 7.8 mmol) was dissolved in dimethyldioxirane (218 mL of a 0.05 M solution in acetone, 10.9 mmol). The reaction was stirred for 5 h and concentrated in vacuo. Purification by flash chromatography afforded 2.34 g of epoxide **19** (74.3%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.74 (d, J = 10.4 Hz, 1H), 4.33 (dd, J = 10.4, 6.0 Hz, 1H), 4.25 (d, J = 4.0 Hz, 1H), 4.17 (dd, J = 10.8, 6.8 Hz, 1H), 4.06 (dd, J = 10.8, 8.8 Hz, 1H), 3.48 (d, J = 2.0 Hz, 1H), 3.37 (d, J = 2.4 Hz, 1H), 2.20−2.16 (m, 1H), 2.02 (s, 3H), 1.40 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 155.0, 79.5, 71.2, 59.4, 56.7, 56.3, 50.6, 40.8, 28.1, 25.6, 20.8, 17.7, −4.6, −5.5; IR (film) 3440, 1725 cm^{-1}; $[\alpha]^{24}_D$ = +17.1 (*c* 1.37, CH_2Cl_2). Anal. Calcd for $C_{19}H_{35}NO_6Si$: C, 56.83; H, 8.78; N, 3.49. Found: C, 57.06; H, 8.83; N, 3.52.

Acetic acid (4*S*,5*R*,6*R*,7*S*,8*S*)-5-(*tert*-Butyldimethylsilanyloxy)-6-hydroxy-2-oxohexahydrocyclopentaoxazol-4-ylmethyl Ester (20). To a solution of epoxide **19** (2.34 g, 5.8 mmol) in 60 mL of CH_2Cl_2 was added (1*S*)-(+)-10-camphorsulfonic acid (0.136 g, 0.58 mmol). The reaction was stirred for 12 h. The reaction was quenched with saturated $NaHCO_3$, and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 1.67 g of alcohol **20** (83%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.58 (s, 1H), 4.80 (dd, J = 7.6, 1.2 Hz, 1H), 4.43 (dd, J = 11.2, 9.2 Hz, 1H), 4.29 (dd, J = 6.8, 6.8 Hz, 1H), 4.24−4.20 (m,2H), 4.11 (d, J = 3.6 Hz, 1H), 2.50−2.43 (m, 2H), 2.05 (s, 3H), 0.85 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 158.6, 85.9, 79.4, 78.6, 60.7, 56.7, 45.7, 25.5, 20.9, 17.9, −4.8, −5.5; IR (KBr) 3410, 1740, 1720 cm^{-1}; $[\alpha]^{24}_D$ = −11.5 (*c* 0.96, MeOH); mp 196−198 °C. Anal. Calcd for $C_{15}H_{27}NO_6Si$: C, 52.15; H, 7.88; N, 4.05. Found: C, 52.19; H, 7.82; N, 3.91.

(4*S*,5*R*,6*R*,7*S*,8*S*)-5-(*tert*-Butyldimethylsilanyloxy)-6-hydroxy-4-hydroxymethylhexahydrocyclopentaoxazol-2-one (21). To a solution of alcohol **20** (1.47 g, 4.24 mmol) in 40 mL of MeOH was added K_2CO_3 (0.59 g, 4.24 mmol). The reaction was stirred for 2 h. The reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted five times with ethyl acetate, and the combined organic layers were washed with brine and concentrated in vacuo. Purification by flash chromatography afforded 1.26 g of diol **21** (98%): ^{1}H NMR (CD_3CN, 400 MHz) δ 5.70 (s, 1H), 4.66 (dd, J = 8.0, 1.2 Hz, 1H), 4.29 (dd, J = 7.2, 7.2 Hz, 1H), 4.02 (d, J = 3.6 Hz, 2H), 3.77−3.69 (m, 2H), 3.35 (d, J = 3.6 Hz, 1H), 2.61 (t, J = 4.8, 4.8 Hz, 1H), 2.25 (dddd, J = 7.5, 7.5, 5.0, 4.0 Hz, 1H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (CD_3CN, 100 MHz) δ 159.7, 86.7, 81.2, 79.6, 58.9, 57.8, 49.8, 26.4, 19.0, −4.3, −4.9; IR (KBr) 3350 (br), 1710 cm^{-1}; $[\alpha]^{24}_D$ = −7.5 (*c* 0.86, MeOH); mp 201−203 °C. Anal. Calcd for $C_{13}H_{25}NO_5Si$: C, 51.46; H, 8.30; N, 4.62. Found: C, 51.23; H, 8.45; N, 4.59.

(5*R*,6*R*,7*S*,8*S*)-5-(*tert*-Butyldimethylsilanyloxy)-6-hydroxy-4-methylenehexahydrocyclopentaoxazol-2-one (23). To a solution containing diol **21** (1.26 g, 4.16 mmol) and 2-nitrophenyl selenocyanate (2.36 g, 10.4 mmol) in 40 mL of THF was added freshly distilled tri-*n*-butylphosphine (3.11 mL, 12.0 mmol) dropwise. The reaction was stirred for 12 h and quenched with saturated $NaHCO_3$. The aqueous layer was extracted four times with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 1.8 g of selenide, which was used immediately in the next reaction.

To a cooled solution (0 °C) of the selenide (1.8 g) in 50 mL of THF was added H_2O_2 (4.8 mL of a 30% solution in H_2O) dropwise. The reaction was warmed to 25 °C and stirred for 12 h. The reaction was quenched with H_2O and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with saturated Na_2SO_3 and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 0.94 g of alkene **23** (79% over two steps): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88 (s, 1H), 5.34 (dd, J = 2.0, 2.0 Hz, 1H), 5.24 (dd, J = 1.6, 1.6 Hz, 1H), 4.76 (ddd, J = 8.6, 3.6, 0.8 Hz, 1H), 4.53−4.50 (m, 1H), 4.26 (ddd, J = 6.0, 1.6, 1.2 Hz, 1H), 4.06 (ddd, J = 6.0, 4.0, 4.0 Hz, 1H), 2.42 (d, J = 4.4 Hz, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 149.0, 113.2, 83.7, 81.1, 77.7, 55.2, 25.7, 18.1, −4.7, −4.8; IR (film) 3370, 1745 cm^{-1}; $[\alpha]^{24}_D$ = −33.6 (*c* 1.8, MeOH). Anal. Calcd for $C_{13}H_{23}NO_4Si$: C, 54.71; H, 8.12; N, 4.91. Found: C, 54.34; H, 8.04; N, 4.79.

(4*R*,5*R*,6*R*,7*S*,8*R*)-5-(*tert*-Butyldimethylsilanyloxy)-4,6-dihydroxy-4-hydroxymethylhexahydrocyclopentaoxazol-2-one (24). To a solution of alkene **23** (0.63 g, 2.21 mmol) and *n*-methylmorpholine *n*-oxide (0.60 g of NMO·H_2O, 4.4 mmol) in 30 mL of acetone and 10 mL of H_2O was added OsO_4 (1.4 mL of a 0.01 g/mL solution, 0.06 mmol). The mixture was stirred for 12 h. The reaction was quenched with saturated Na_2SO_3 and stirred for 1 h, and the aqueous layer was extracted five times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 0.53 g of triol **24** (75%): ^{1}H NMR (CD_3CN, 400 MHz) δ 5.95 (s, 1H), 4.86 (d, J = 8.8 Hz, 1H), 4.10 (d, J = 8.0 Hz, 1H), 4.02 (d, J = 6.0 Hz, 1H), 3.87 (d, J = 1.6 Hz, 1H), 3.75−3.66 (m, 4H), 2.93 (s, 1H), 0.86 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (CD_3CN, 100 MHz) δ 159.2, 86.9, 85.9, 82.6, 82.3, 64.6, 62.9, 26.3, 18.9, −4.3, −4.8; IR (KBr) 1735 cm^{-1}; $[\alpha]^{24}_D$ = +13.5 (*c* 0.34, MeOH); mp 215−216 °C. Anal. Calcd for $C_{13}H_{25}NO_6Si$: C, 48.88; H, 7.89; N, 4.38. Found: C, 48.63; H, 7.88; N, 4.29.

[1*R*-(1α,2*β*,3α,4*β*,5*β*)]-5-Acetamido-1,2,3,4-tetracetoxy-1-(acetoxymethyl)cyclopentane (25). Triol **24** (30.5 mg, 0.095 mmol) in 5 mL of ethanol and 2 mL of 2 N KOH was heated at reflux for 12 h. The mixture was concentrated in vacuo by azeotroping with several aliquots of methanol. To the mixture was added 2 mL of pyridine, 3 mL of acetic anhydride, and 15 mg of 4-(dimethylamino)pyridine. The mixture was

stirred for 12 h, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 33 mg of ester **25**[8a] (80% over two steps): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (d, J = 9.6 Hz, 1H), 5.77 (d, J = 5.6 Hz, 1H), 5.34 (dd, J = 7.6, 4.8 Hz, 1H), 5.29 (dd, J = 9.2, 8.2 Hz, 1H), 5.21 (t, J = 5.2, 5.2 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 169.9, 169.7, 169.5, 168.93, 168.90, 86.6, 78.9, 76.4, 73.3, 59.5, 52.7, 23.1, 21.6, 20.9, 20.7, 20.6, 20.5; IR (film) 3320, 3000, 1750, 1670, 1530, 1435, 1375, 1225, 1045, 895 cm^{-1}; $[\alpha]^{24}_D$ = +4.1 (*c* 1.57, $CHCl_3$).

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