JOC*Note*

Ring-Closing Metathesis-Based Synthesis of (3*R*,4*R*,5*S*)-4-Acetylamino-5-amino-3-hydroxy-cyclohex-1-ene-carboxylic Acid Ethyl Ester: A Functionalized Cycloalkene Skeleton of GS4104

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(3*R*,4*R*,5*S*)-4-Acetylamino-5-amino-3-hydroxy-cyclohex-1-ene-carboxylic acid ethyl ester, a functionalized cyclohexene skeleton of GS4104, was diastereoselectively synthesized. A major advantage of this synthesis is the use of readily available L-serine to replace frequently used (−)-shikimic acid or (−)-quinic acid as the starting material. Ring-closing metathesis and diastereoselective Grignard reactions successfully served as the key steps. Absolute configurations of the key intermediates were confirmed by corresponding two-dimensional NMR studies.

Periodically developed new strains of influenza continue threatening the public health and can result in pandemics leading to the death of millions of people.[1] Influenza neuraminidase (NA) is an important antiviral target of high pharmaceutical interest because of its essential role in cleaving sialic acid residues from cell surface glycoproteins and facilitating release of virions from infected cells.[2] During the past decade, drug design and development studies on the NA inhibitors led to the discovery of two famous anti-influenza drugs, GG167 (**1**, zanamivir) and GS4104 (**2**, oseltamivir).[3] Both of the NA inhibitors have currently emerged as the promising therapeutics for the treatment of avian flu H5N1 infection. Because of the oral bioavailability and good toleration,[4] Roche's GS4104 (commercially known as Tamiflu) is recommended as the best choice among the currently available anti-influenza drugs[5] and could be used for prophylaxis influenza. To the best of our knowledge, all industrially used and most literature syntheses toward GS4104[6] and its analogue[7] pass through similar intermediates and commonly start from (−)-shikimic acid **3** or (−)-quinic acid **4** (Figure 1). Major differences in these routes lie in the preparations of corresponding key vicinal *anti*-amino alcohols and/or vicinal *anti*-diamines by different small-ring openings from epoxide or aziridine precursors, respectively. However, short supply of (−)-shikimic acid, the major industrial starting material for GS4101, has been becoming a bottleneck of increasing demand for Tamiflu, especially in today's global battle against bird flu. New efficient routes for GS4104 starting from other readily available materials are, therefore, required.

In recent years, a ring-closing metathesis (RCM)-based synthetic strategy was developed by us to construct some biologically interesting carbocylic sugar-like compounds including 4,5-diamino-cyclohexane-1,2,3-triol and 5,6-diamino-cyclohex-2-enol with diverse stereochemistries.[8] The vicinal *trans*-diamino functionalities and carbocylic features of these compounds are somewhat similar to GS4104. Thus, novel syntheses of GS4104 as well as GS4104-like molecules using a similar RCM-based strategy would be possible. Herein, we report a diastereoselective synthesis of (3*R*,4*R*,5*S*)-4-acetylamino-5-amino-3-hydroxy-cyclohex-1-enecarboxylic acid ethyl ester (**5**), a functionalized cyclohexene skeleton of GS4104. In this synthesis, the inexpensive and readily available L-serine replaced (−)-shikimic acid or (−)-quinic acid as the starting material. Diastereoselective Grignard additions to the corresponding aldehyde and nitrone derived from different sides of L-serine and an efficient catalytic RCM[9] successfully served as the key steps (Figure 2).

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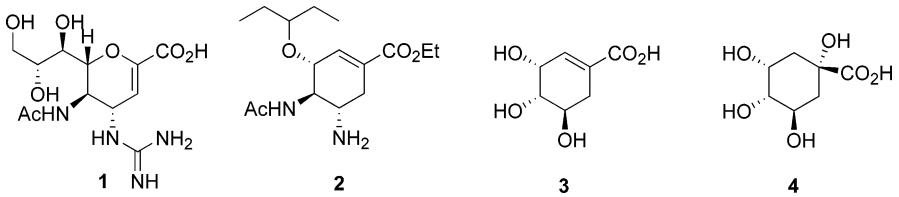

FIGURE 1. GG167 (**1**), GS4104 (**2**), (−)-shikimic acid (**3**), and (−)-quinic acid (**4**).

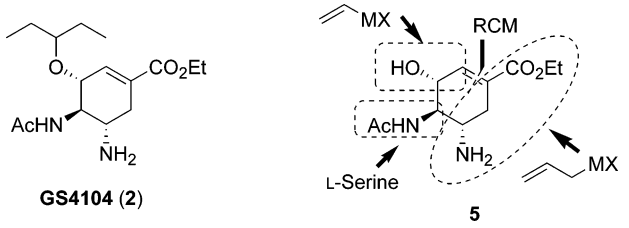

FIGURE 2. Retrosynthetic perspective of **5** and an outline of the key operations.

At first, L-serine was efficiently converted to the known alkene **6** according to the literature methods[8,10] (Scheme 1). The terminal olefin **6** was dihydroxylated by NMO and a catalytic amount of OsO_4 in acetone−H_2O to give diol **7** in 89% yield. Both *N*-PMB and *N*-Cbz groups of **7** were deprotected by hydrogenolysis in methanol using 20% $Pd(OH)_2/C$ as the catalyst, and the resulting primary amine was then protected by CbzCl immediately to give **8**. It is noteworthy here that the initial efforts all failed in the selective deprotection of *N*-PMB of **7** in the presence of *N*-Cbz using a variety of conditions. The primary hydroxyl of diol **8** was selectively protected by TBDPS. A Swern oxidation of alcohol **9**, followed by Wittig olefination,[11] afforded olefin **10** in 86% yield in two steps.

Selective deprotection of the *N*,*O*-acetal in **10** was accomplished in acetonitrile with a catalytic amount of $BiBr_3$.[12] Swern oxidation of primary alcohol **11**, followed by addition of vinylmagnesium bromide (3.0 equiv) in the presence of anhydrous $ZnCl_2$ (1.0 equiv)[13] at −30 °C in THF, predominantly gave the *anti*-adduct **12** in 56% yield, along with the minor *syn*-adduct **13** in 19% yield. In the presence of Grubbs catalyst **16**, RCM reactions of the linear compounds **12** and **13** in anhydrous CH_2Cl_2 afforded cyclohexene derivatives **14** and **15**, respectively. Relative configurations of **12** and **13** were indirectly confirmed by the NOESY studies of cyclohexenes **14** and **15** (Scheme 2). These results showed that the major product **14** coincidently matched the functionalities and corresponding absolute stereochemistries of the cyclohexene ring of GS4104.

For further elaboration of the cyclohexene skeleton, protecting groups of the RCM substrate were optimized. The exposed hydroxyl of **12** was protected by MOMCl first to give a fully protected linear precursor **17**. Diolefin **17** was treated with the 2nd generation Grubbs catalyst **23** in CH_2Cl_2 to afford the corresponding cyclohexene **18** in almost quantitative yield. Much lower yields were observed under the similar RCM conditions using the 1st generation Grubbs catalyst **16** (Scheme 3). Deprotection of *O*-TBDPS of **18** by TBAF gave the corresponding alcohol **19**. PCC oxidation of **19**, followed by treatment with $NaClO_2$ combined with K_2HPO_4 and 2,3-dimethylbuta-1,3-diene in *t*-BuOH−THF−H_2O (v/v/v 4:1:1),[14] afforded acid **20** in 88% yield. EDCI-based esterification of **20** afforded its ethyl ester **21**. Both the *O*-MOM and *N*-Boc groups of **21** were deprotected using a 5% HCl alcoholic solution, and the resultant free amine was immediately converted to the corresponding acetamide **22** by treatment with acetic anhydride. Finally, selective deprotection of the *N*-Cbz group of **22** in the presence of a double bond was carried out under $Pd(OAc)_2$-catalyzed reductive conditions[15] to give (3*R*,4*R*,5*S*)-4-acetylamino-5-amino-3-hydroxy-cyclohex-1-ene-carboxylic acid ethyl ester (**5**) in 92% yield.

In summary, a novel synthesis of a functionalized cycloalkene skeleton of GS4104, (3*R*,4*R*,5*S*)-4-acetylamino-5-amino-3-hydroxy-cyclohex-1-ene-carboxylic acid ethyl ester was achieved in 13 operations and 19% overall yield from known intermediate **6**. Diastereoselective Grignard additions to an aldehyde and a nitrone, respectively, served as the key steps. Its cyclohexene ring was efficiently constructed by an RCM reaction. The advantage of this approach also includes the use of inexpensive and readily available starting material L-serine. This new synthesis potentially provides an economic alternative entrance to GS4104 and the GS4104-like molecules with biologically interesting properties.

Experimental Section

[(1*R*,2*S*)-2-Benzyloxycarbonylamino-4-(*tert*-butyl-diphenyl-silanyloxymethyl)-1-((*R*)-1-methoxymethoxy-allyl)-pent-4-enyl]-carbamic Acid *tert*-Butyl Ester (17). To a solution of alcohol **12** (1.27 g, 1.93 mmol) in anhydrous CH_2Cl_2 (20 mL) was added *N*,*N*-diisopropylethylamine (DIPEA, 1.3 mL, 7.72 mmol, 4.0 equiv) and MOMCl (0.29 mL, 3.86 mmol, 2.0 eq.) dropwise at 0 °C under N_2. The reaction mixture was stirred at room temperature for 24 h. After the starting material disappeared, saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give **17** (1.35 g, 98%) as a colorless oil. $[\alpha]^{25}_D$ −34.5 (*c* 1.51 $CHCl_3$). IR (neat): 3362, 3072, 2959, 2931, 2858, 1699, 1589, 1517, 1429, 1245, 1167, 1112, 1029, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.38−1.43 (m, 9H), 2.12−2.20 (m, 1H), 2.32−2.46 (m, 1H), 3.29 (s, 3H), 3.52−3.59 (m, 1H), 4.01−4.12 (m, 4H), 4.47 (d, J = 6.9 Hz, 1H), 4.63 (d, J = 6.9 Hz, 1H), 4.95 (br s, 1H), 4.99−5.10 (m, 3H), 5.17−5.30 (m, 4H), 5.67−5.78 (m, 1H), 7.25−7.68 (m, 15H) ppm. ESI-MS (*m*/*z*, %): 725.4 ($M + Na^+$, 100%). Anal. Calcd for

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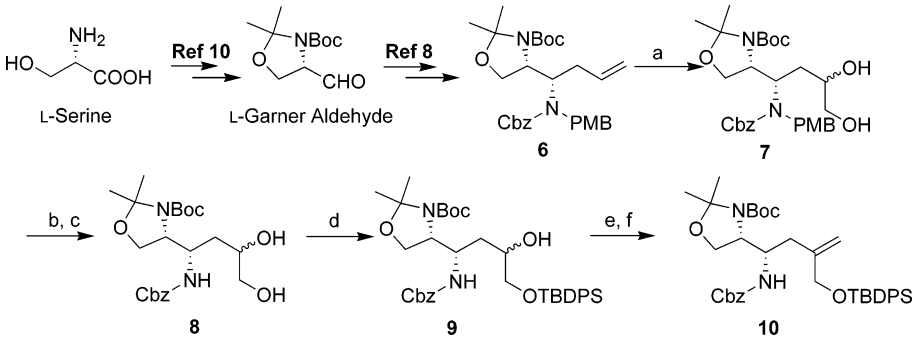
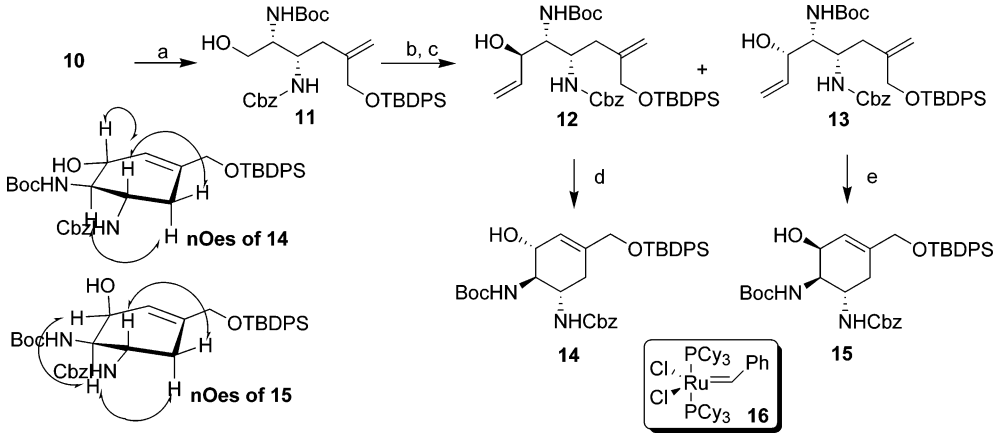
SCHEME 1 [a]



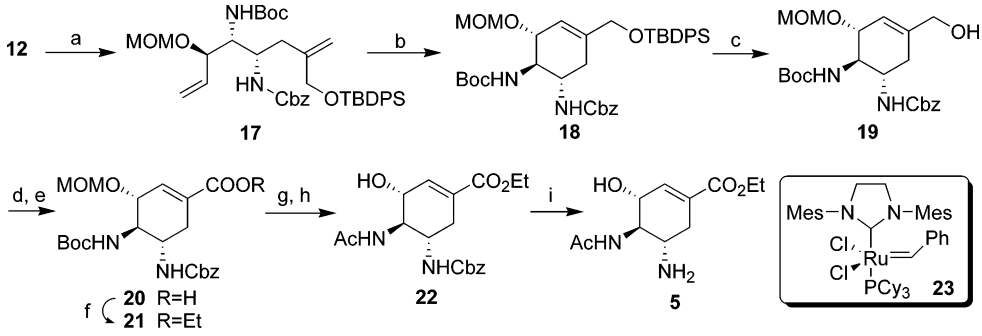
[a] Reagents and conditions: (a) OsO_4, NMO, acetone/H_2O 5:1, 89%; (b) $Pd(OH)_2/H_2/CH_3OH$, 35 °C; (c) CbzCl, $NaHCO_3$, H_2O/EtOAc v/v = 1:1, 86% (for 2 steps); (d) TBDPSCl, imid., CH_2Cl_2, rt, 96%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C; (f) Ph_3PCH_3Br, *n*-BuLi, THF, −78 °C to room temperature, 86% (for 2 steps).

SCHEME 2 [a]



[a] Reagents and conditions: (a) $BiBr_3$ (20% mol), MeCN, rt, 89%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C; (c) vinylMgBr (3.0 equiv), $ZnBr_2$ (1.0 equiv), THF, −78°C to −30°C, **12** (56%), **13** (19%); (d) **16** (10 mol %), CH_2Cl_2, rt, 77%; (e) **16** (10 mol %), CH_2Cl_2, rt, 70%.

SCHEME 3 [a]



[a] Reagents and conditions: (a) MOMCl, DIPEA, CH_2Cl_2, rt, 98%; (b) **23** (10 mol %), CH_2Cl_2, rt, 98%; (c) TBAF, THF, rt, 96%; (d) PCC, 4 Å sieve, CH_2Cl_2, rt; (e) $NaClO_2$, K_2HPO_4, 2,3-dimethylbuta-1,3-diene, *t*-BuOH/THF/H_2O (v/v/v 4:1:1), 10 °C to room temperature, 88% (for 2 steps); (f) EtOH, HOBt, EDCI, DIPEA, CH_2Cl_2, rt, 85%; (g) 5% HCl/EtOH, 0 °C to room temperature; (h) AcCl, Na_2CO_3, EtOH, 0 °C to room temperature, 83% (for 2 steps); (i) $Pd(OAc)_2$, Et_3SiH, Et_3N, CH_2Cl_2, 0 °C to room temperature, 92%.

$C_{40}H_{54}N_2O_7Si$ (%): C, 68.34; H, 7.74; N, 3.99. Found: C, 68.63; H, 7.75; N, 3.61.

[(1*R*,2*R*,6*S*)-6-Benzyloxycarbonylamino-4-(*tert*-butyl-diphenyl-silanyloxymethyl)-2-methoxymethoxy-cyclohex-3-enyl]-carbamic Acid *tert*-Butyl Ester (18). To a solution of diene **17** (510 mg, 0.73 mmol) in anhydrous CH_2Cl_2 (75 mL) was added 2nd generation Grubbs catalyst **23** (62 mg, 0.073 mmol, 0.1 equiv) under N_2. The reaction mixture was stirred at room temperature for 24 h. After the starting material disappeared, water (10 mL) and DMSO (1 mL) was added, and the whole mixture was stirred vigorously at room temperature for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to give **18** (480 mg, 98%). $[\alpha]^{25}_D$ −27.2 (*c* 1.23, $CHCl_3$). IR (neat): 3326, 3071, 2959, 2932, 2857, 1693, 1589, 1539, 1282, 1113, 1045, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.41 (s, 9H), 1.96−2.04 (m, 1H), 2.30−2.36 (m, 1H), 3.39 (s, 3H), 3.76−3.78 (m, 2H), 4.04 (br s, 3H), 4.69−4.74

(m, 2H), 4.78 (d, J = 6.9 Hz, 1H), 5.08−5.13 (m, 2H), 5.72−5.76 (m, 2H), 7.28−7.66 (m, 15H) ppm. ESI-MS (*m*/*z*, %): 697.2 (M + Na^+, 100%). Anal. Calcd for $C_{38}H_{50}N_2O_7Si$ (%): C, 67.63; H, 7.47; N, 4.15. Found: C, 67.82; H, 7.40; N, 3.83.

((1*S*,5*R*,6*R*)-6-*tert*-Butoxycarbonylamino-3-hydroxymethyl-5-methoxymethoxy-cyclohex-3-enyl)-carbamic Acid Benzyl Ester (19). To a stirred solution of **18** (2.0 g, 2.97 mmol) in THF (30 mL) was added TBAF (1.0 M in THF, 3.0 mL, 3.0 mmol, 1.01 equiv) at 0 °C. The reaction was stirred at room temperature for 2 h, and then saturated aqueous NH_4Cl (20 mL) was added to quench the reaction. The layers were separated, and the aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 1:2) to give alcohol **19** (1.25 g, 96%) as a white wax. $[\alpha]^{25}_D$ −62.3 (*c* 0.95, $CHCl_3$). IR (neat): 3321, 3070, 2959, 2857, 1690, 1542, 1282, 1047 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 9H), 1.79 (br s, 1H, ex. D_2O), 2.10−2.19 (m, 1H), 2.41 (dd, J = 17.1, 4.8 Hz, 1H), 3.38 (s, 3H), 3.70−3.80 (m, 2H), 4.01 (br s, 2H), 4.06−4.08 (m, 1H), 4.67 (d, J = 7.2 Hz, 1H), 4.72 (d, J = 6.9 Hz, 1H), 4.93 (d, J = 8.4 Hz, 1H), 5.07 (br s, 2H), 5.66 (s, 1H), 6.02 (d, J = 8.1 Hz, 1H), 7.32 (br s, 5H) ppm. ESI-MS (*m*/*z*, %): 459.2 (M + Na^+, 100%). Anal. Calcd for $C_{22}H_{32}N_2O_7$ (%): C, 60.54; H, 7.39; N, 6.42. Found: C, 60.55; H, 7.47; N, 6.18.

(3*R*,4*R*,5*S*)-5-Benzyloxycarbonylamino-4-*tert*-butoxycarbonylamino-3-methoxymethoxy-cyclohex-1-enecarboxylic Acid Ethyl Ester (21). To a stirred suspension of alcohol **19** (377 mg, 0.86 mmol) and activated 4 Å molecular sieves (220 mg) in anhydrous CH_2Cl_2 (17 mL) was added PCC (186 mg, 1.03 mmol, 1.2 equiv). The whole mixture was stirred at room temperature for 2 h, diluted with Et_2O (50 mL), and filtered through a pad of Celite. The solution was washed successively with saturated aqueous NH_4Cl (30 mL × 3) and brine (30 mL × 3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) to afford the aldehyde as a white wax, which was used directly for the next steps without characterization.

To a stirred solution containing freshly prepared aldehyde (0.86 mmol) and 2,3-dimethylbuta-1,3-diene (0.92 mL, 8.64 mmol, 10.0 equiv) in *tert*-butyl alcohol/THF/H_2O (v/v/v 4:1:1, 25 mL) was added slowly sodium chlorite (294 mg, 2.59 mmol, 3.0 equiv) and sodium dihydrogen phosphate (353 mg, 2.59 mmol, 3.0 equiv) in water (4 mL) under 10 °C. The resultant suspension was stirred at room temperature for 6 h. Saturated aq $NaHSO_3$ (10 mL) was added to quench the reaction. The layers were separated, and the aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:10) to afford the acid **20** (342 mg, 88% for 2 steps). ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 9H), 2.23−2.31 (m, 1H), 2.80−2.87 (m, 1H), 3.40 (s, 3H), 3.72−3.78 (m, 1H), 3.81−3.86 (m, 1H), 4.20−4.23 (m, 1H), 4.68 (d, J = 6.9 Hz, 1H), 4.75 (d, J = 7.2 Hz, 1H), 5.08−5.12 (m, 3H), 6.04 (d, J = 8.7 Hz, 1H), 6.84 (s, 1H), 7.31 (br s, 5H) ppm. ESI-MS (*m*/*z*, %): 473.2 (M + Na^+, 100%).

To a stirred solution of acid **20** (1.0 g, 2.2 mmol) in anhydrous CH_2Cl_2 (66 mL) was added DIPEA (0.45 mL, 2.7 mmol, 1.2 equiv), HOBt·H_2O (413 mg, 2.7 mmol, 1.2 equiv), and EDCI (518 mg, 2.7 mmol, 1.2 equiv) at 0 °C under N_2. After stirring for 30 min at 0 °C, anhydrous EtOH (160 μL, 2.7 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with saturated aqueous NH_4Cl (50 mL × 3) and brine (50 mL × 3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to afford ester **21** (899 mg, 85%). $[\alpha]^{25}_D$ −49.2 (*c* 0.95, $CHCl_3$). IR (neat): 3330, 3070, 2980, 2825, 1717, 1690, 1540, 1284, 1239, 1046 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H), 1.39 (s, 9H), 2.25−2.30 (m, 1H), 2.41 (dd, J = 17.4, 4.5 Hz, 1H), 3.41 (s, 3H), 3.73−3.81 (m, 2H), 4.15−4.24 (m, 3H), 4.69 (d, J = 7.2 Hz, 1H), 4.76 (d, J = 7.2 Hz, 1H), 4.85 (d, J = 6.9 Hz, 1H), 5.09 (br s, 2H), 5.67 (d, J = 7.5 Hz, 1H), 6.77 (s, 1H), 7.32 (br s, 5H) ppm. ESI-MS (*m*/*z*, %): 379.2 (M − Boc + H^+, 95%), 501.2 (M + Na^+, 100%). Anal. Calcd for $C_{24}H_{34}N_2O_8$ (%): C, 60.24; H, 7.16; N, 5.85. Found: C, 60.23; H, 7.22; N, 5.60.

(3*R*,4*R*,5*S*)-4-Acetylamino-5-benzyloxycarbonylamino-3-hydroxy-cyclohex-1-enecarboxylic Acid Ethyl Ester (22). The ester **21** (405 mg, 0.84 mmol) was treated with 5% HCl solution in EtOH (50 mL) at 0 °C and then stirred at room temperature overnight. EtOH was removed in vacuo, and the residue was again diluted with EtOH (10 mL). After treatment with saturated aqueous Na_2CO_3 (10 mL), AcCl (1 mL) was added dropwise at 0 °C under vigorous stirring. The reaction mixture was stirred for 30 min at room temperature. EtOH was removed in vacuo, and the residue was diluted with EtOAc (50 mL) and H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:10) to afford **22** (262 mg, 83% for 2 steps). $[\alpha]^{22}_D$ 5.56 (*c* 0.97, $CHCl_3$). IR (neat): 3287, 3082, 2926, 2854, 1720, 1689, 1657, 1630, 1550, 1374, 1289, 1251, 1046 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, J = 7.5 Hz, 3H), 1.86 (s, 3H), 2.16−2.26 (m, 1H), 2.86 (dd, J = 17.1, 4.2 Hz, 1H), 3.74−3.80 (m, 1H), 3.84−3.90 (m, 1H), 4.20 (q, J = 7.5 Hz, 2H), 4.30 (br s, 1H), 4.84 (s, 1H), 5.06 (d, J = 12.6 Hz, 1H), 5.10 (d, J = 7.5 Hz, 1H), 5.19 (d, J = 11.7 Hz, 1H), 6.78 (s, 1H), 6.95 (d, J = 5.7 Hz, 1H), 7.36 (br s, 5H) ppm. ESI-MS (*m*/*z*, %): 377.1 (M + H^+, 100%). Anal. Calcd for $C_{19}H_{24}N_2O_5$ (%): C, 60.63; H, 6.43; N, 7.44. Found: C, 60.69; H, 6.64; N, 7.19.

(3*R*,4*R*,5*S*)-4-Acetylamino-5-amino-3-hydroxy-cyclohex-1-enecarboxylic Acid Ethyl Ester (5). To a stirred suspention of Pd(OAc)$_2$ (4 mg, 0.02 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (4 mL) was added Et_3N (7 μL, 0.05 mmol, 0.3 equiv) and Et_3SiH (55 μL, 0.34 mmol, 2.0 equiv) dropwise at 0 °C under N_2. After stirring at room temperature for 15 min, a solution of **22** (64 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise at room temperature under N_2. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (chloroform/methanol = 8:1) to afford **5** (38 mg, 92%) as a pale-brown wax. $[\alpha]^{24}_D$ −13.8 (*c* 1.01, CH_3OH). IR (neat): 3252, 3074, 2930, 1713, 1658, 1556, 1445, 1374, 1245, 1125 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.31 (t, J = 7.2 Hz, 3H), 2.05 (s, 3H), 2.15−2.27 (m, 1H), 2.82 (dd, J = 17.7, 4.5 Hz, 1H), 2.92−2.97 (m, 1H), 3.72 (dd, J = 10.5, 9.3 Hz, 1H), 4.16−4.26 (m, 3H), 6.77 (s, 1H) ppm. ^{13}C NMR (300 MHz, CD_3OD): δ 15.0, 23.6, 33.9, 51.4, 59.9, 62.5, 71.6, 130.5, 141.3, 168.1, 175.4 ppm. ESI-MS (*m*/*z*, %): 243.2 (M + H^+, 100%). HR-MALDI-MS calcd for $C_{11}H_{19}N_2O_4$ (M + H^+), 243.1346; found, 243.1339.

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Supporting Information Available: General experimental methods, experimental details, and characterizations for compounds **7**−**15**, ^1H NMR spectra of compounds **5**, **7**−**15**, **17**−**19**, **21**, and **22**, ^{13}C NMR spectrum of compound **5**, and ^1H−^1H COSY and NOESY spectra of compounds **14** and **15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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