EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300804

Total Syntheses of (+)-Valiolamine and (–)-1-*epi*-Valiolamine from Naturally Abundant (–)-Shikimic Acid

Na Quan,[a] Liang-Deng Nie,[a] Rui-Heng Zhu,[a] Xiao-Xin Shi,*[a] Wei Ding,[a] and Xia Lu[a]

Keywords: Total synthesis / Drug design / Natural products / Carbohydrates / Inhibitors

Total syntheses of (+)-valiolamine (**1**) and (–)-1-*epi*-valiolamine (**2**) from the naturally abundant (–)-shikimic acid are described. Ethyl 3-*epi*-5-*O*-methylsulfonyl-shikimate (**3**), as the key common intermediate, was first synthesized in five steps in 74 % overall yield, and then converted into the targets **1** and **2** in seven steps in 48 and 41 % overall yield, respectively.

Introduction

Glycosidases are pivotal enzymes that are responsible for cleavage of glycosidic bonds, glycoprotein processing on the surface of cell walls, and digestion of carbohydrates in animals. Inhibition of glycosidases has significant implications for chemotherapy of some diseases,[1] especially for the therapy of diabetes mellitus.[2] Inhibition of intestinal α-glucosidases has been suggested as a possible means of controlling diabetes mellitus and obesity. (+)-Valiolamine (**1**; see Figure 1) has shown very strong α-glucosidase inhibitory activity against porcine intestinal sucrase, maltase and isomaltase.[3] Its diastereomer (–)-1-*epi*-valiolamine (**2**; see Figure 1) has also shown medium α-glucosidase inhibitory activity.[4] Moreover, *N*-[2-hydroxy-1-(hydroxymethyl)ethyl] valiolamine (Voglibose[5a] or coded as AO-128,[5b] see Figure 1) has displayed higher activities than the parent **1** and was used in clinical trials for the treatment of diabetes.[5]

(+)-Valiolamine (**1**) was first isolated from the fermentation broth of *Streptomyces hygroscopicus subsp. limoneus IFO12703*,[3] and could also be obtained from stereoselective transformation of valienamine or validamine,[6] and chemical total syntheses. Compound **1** has aroused much interest from synthetic chemists, and some total syntheses of **1** have been reported.[7–11] These total syntheses have started from natural materials such as D-glucose,[5b,7] L-quinic acid,[8] D-arabinose,[9] *myo*-inositol [or (–)-*vibo*-quercitol],[4,10] and D-tartaric acid.[11] (–)-1-*epi*-Valiolamine (**2**) could not be obtained from a natural source, but has been obtained from chemical total syntheses.[3,7a]

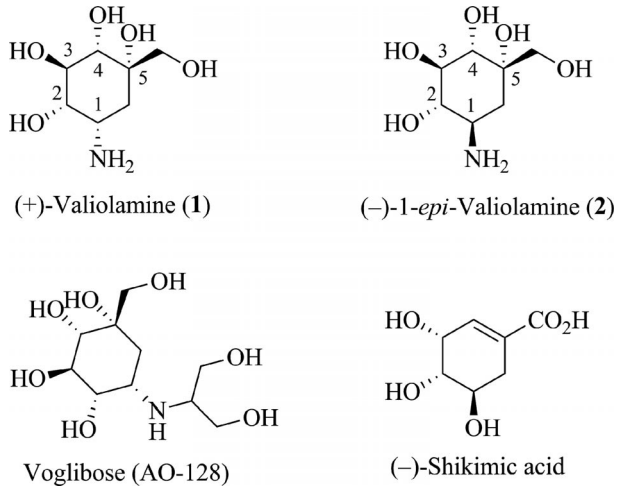


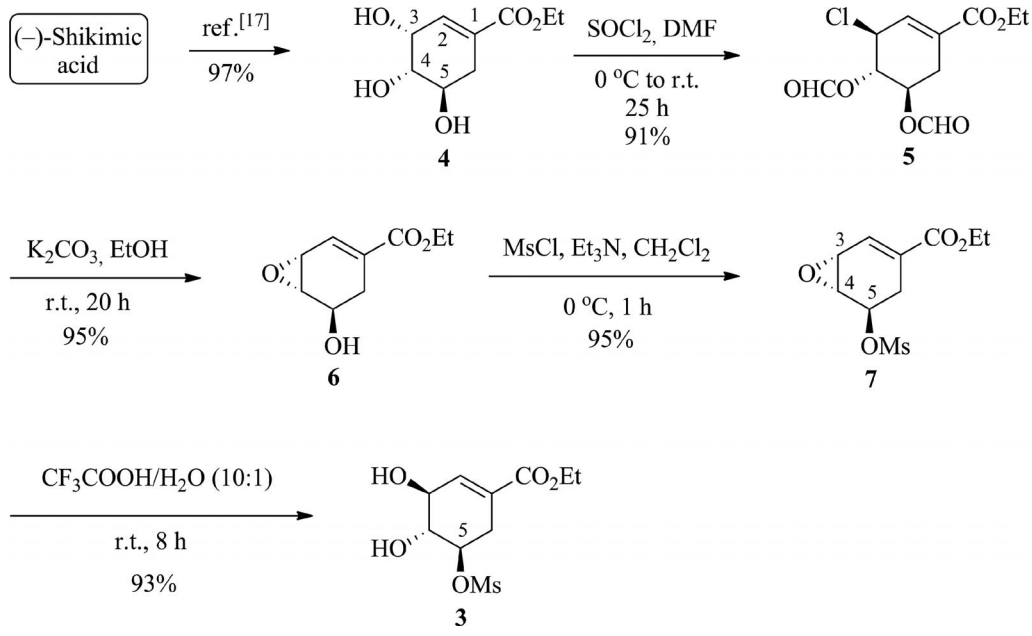
Figure 1. Structure of some related compounds.

(–)-Shikimic acid (see Figure 1) is the key biogenetic precursor of a variety of naturally occurring aromatic compounds in the biosynthesis through the shikimate pathway in plants and microorganisms.[12] (–)-Shikimic acid can be readily obtained in large quantity by extraction from Chinese star anise or other natural plants,[13] or by fermentation using genetically modified *E. coli*.[14] Recently, (–)-shikimic acid has been used as a starting material for the syntheses of osetalmivir phosphate (Tamiflu)[15] and some chiral building blocks for natural products.[16]

Because of the wide availability of (–)-shikimic acid, and the structural resemblance between (–)-shikimic acid and the two target molecules, (–)-shikimic acid could be used as an appropriate starting material for the total syntheses of the two target compounds. Herein, we report the total syntheses of **1** and **2** from the naturally abundant (–)-shikimic acid.

[a] Department of Pharmaceutical Engineering, School of Pharmacy, East China University of Science and Technology, 130 Mei-Long Road, Shanghai 200237, P. R. China
E-mail: xxshi@ecust.edu.cn
Homepage: http://www.ecust.edu.cn/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300804.



Scheme 1. Synthesis of the key intermediate **3** from (–)-shikimic acid.

Results and Discussion

Our synthetic efforts began with synthesis of a key intermediate, ethyl 3-*epi*-5-*O*-methylsulfonyl shikimate (**3**), starting from (–)-shikimic acid according to the route shown in Scheme 1.

Ethyl shikimate **4** was first prepared in 97% yield according to a known procedure,[17] and then treated with 5.0 equiv. thionyl chloride in *N*,*N*-dimethylformamide (DMF) at 0 °C to room temperature. The hydroxyl group at the allylic (C-3) position is much more reactive than the other two hydroxyl groups at C-4 and C-5, hence, highly regioselective chlorination of the C-3 hydroxyl by Vilsmeier reagent ($Cl^-Me_2N^+$=CHCl)[18] took place smoothly, while the hydroxyl groups at C-4 and C-5 were masked by formyl groups. As a result, compound **5** was obtained in 91% yield. Compound **5** was treated with 2.0 equiv. of powdered K_2CO_3 in anhydrous ethanol at room temperature to induce alcoholysis of both ester groups; subsequent intramolecular S_N2-type substitution took place smoothly to afford epoxide **6** in 95% yield. Compound **6** was exposed to 1.5 equiv. triethylamine and 1.2 equiv. methanesulfonyl chloride (MsCl) at 0 °C in dichloromethane to afford methanesulfonate **7** in 95% yield. The stereochemistry of **7** was unequivocally confirmed by X-ray crystallographic analysis of its single crystal, as shown in Figure 2.

Subsequently, **7** was treated with aqueous trifluoroacetic acid (TFA/H_2O, 10:1 v/v) at room temperature, during which water preferentially attacks the much more reactive allylic (C-3) position on the opposite side of the epoxide, thus, highly regio- and stereoselective epoxide-opening took place to furnish the expected ethyl 3-*epi*-5-*O*-methylsulfonyl-shikimate **3** in 93% yield.

Compound **3** is the common key intermediate for the syntheses of **1** and **2**. It was converted into the two target

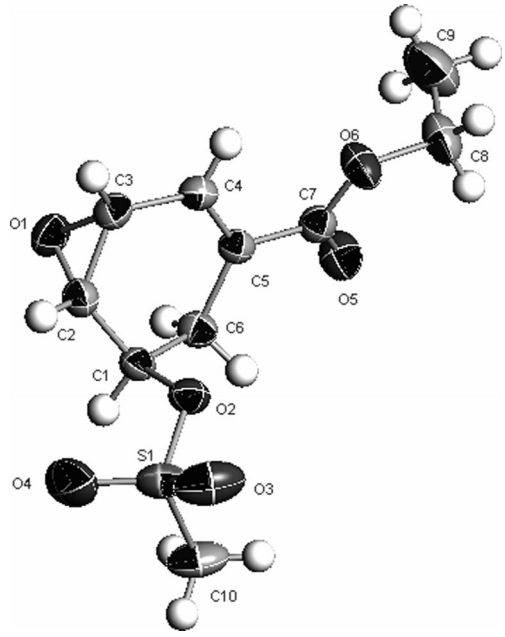
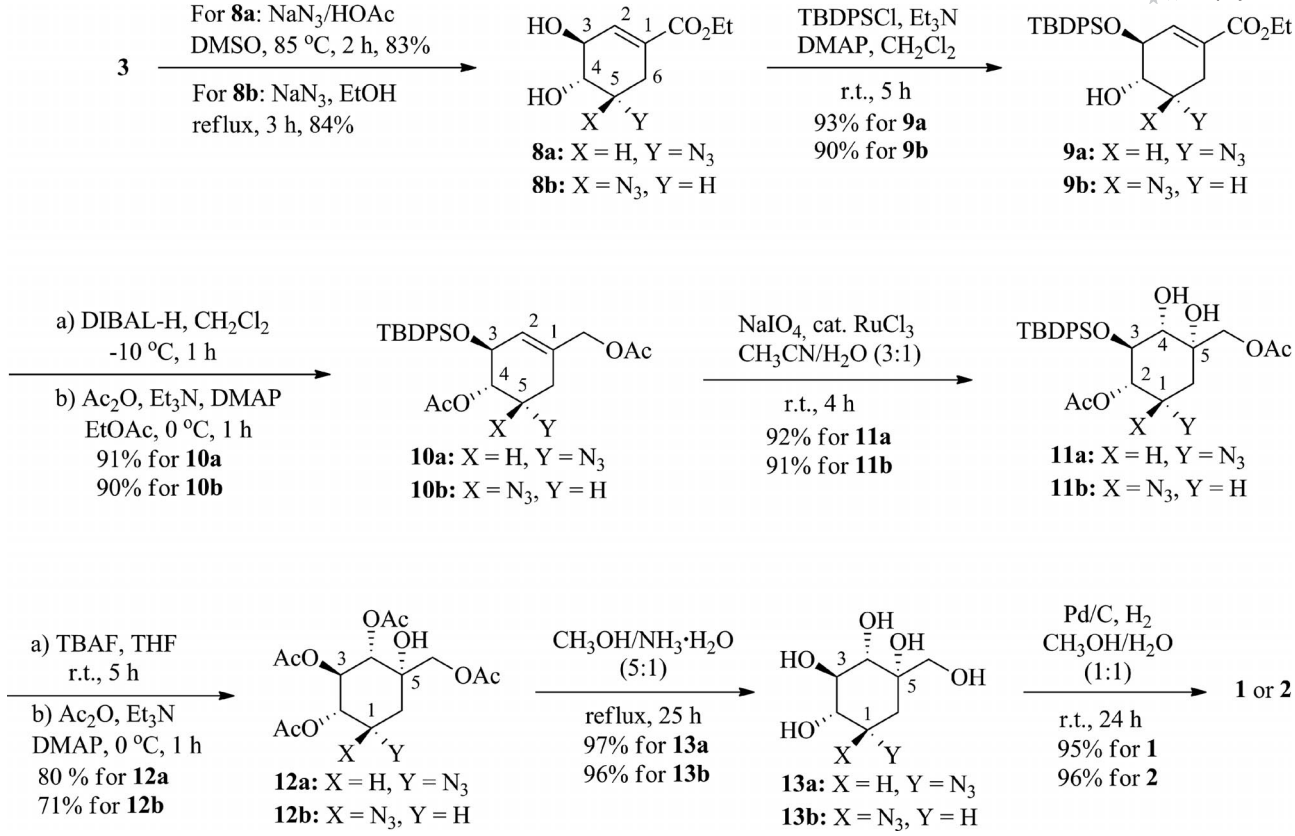


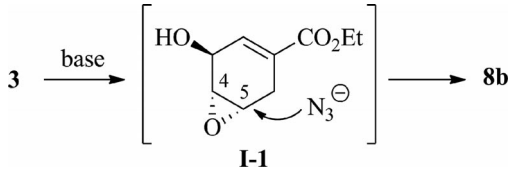
Figure 2. ORTEP drawing of methanesulfonate **7**.

compounds according to the synthetic route shown in Scheme 2. Thus, compound **3** was treated with 2.0 equiv. sodium azide at 85 °C in the presence of 0.5 equiv. AcOH in dimethyl sulfoxide (DMSO) as solvent, leading to a typical S_N2-type nucleophilic substitution to afford **8a** in 83% yield; the (*R*) configuration of C-5 was inverted to the (*S*) configuration through a Walden type inversion. In contrast, when **3** was treated with 2.0 equiv. sodium azide at reflux by using ethanol as the solvent, compound **8b** was obtained in 84% yield; the (*R*) configuration of C-5 was retained during the substitution.



Scheme 2. Syntheses of **1** and **2** from key intermediate compound **3**.

A reasonable explanation for the formation of **8b** from **3** in ethanol is summarized in Scheme 3. Compound **3** may first undergo intramolecular substitution under basic conditions to form epoxide intermediate **I-1**, then the azide anion (N_3^-) may attack C-5 on the opposite side of the epoxide, thus the (*R*) configuration of C-5 of compound **8b** remains intact after double inversion. The presence of acetic acid was helpful for the formation of **8a** through direct S_N2 nucleophilic substitution in DMSO, but the solvent effect seemed more decisive herein because the reaction of **3** with 2.0 equiv. sodium azide at reflux in ethanol in the presence of 0.5 equiv. acetic acid also produced **8b** as the major product in 80% yield, and only a trace amount of **8a** (<5%) was detected.



Scheme 3. Mechanism for conversion of **3** into **8b**.

It is worth pointing out that 2D ^{1}H NMR analyses support the stereochemistry of compounds **8a** and **8b** as drawn in Figure 3. In the ^{1}H-^{1}H NOESY spectra of **8a**, 4-H correlates with 6-H_β, with the correlation spot between 5-H and 6-H_β being clearly greater than the correlation spot between 5-H and 6-H_α, which suggests that 4-H, 6-H_β, and 5-H are on the same face of the hexenoid ring, thus C-5 should possess (*S*)-configuration. In the ^{1}H-^{1}H NOESY spectra of compound **8b**, 4-H correlates with 6-H_β, with the correlation spot between 5-H and 6-H_α being clearly greater than the correlation spot between 5-H and 6-H_β; moreover, 5-H also correlates with 3-H, which suggests that 4-H, 6-H_α, and 3-H are on the same face of the hexenoid ring, thus C-5 should possess (*R*)-configuration.

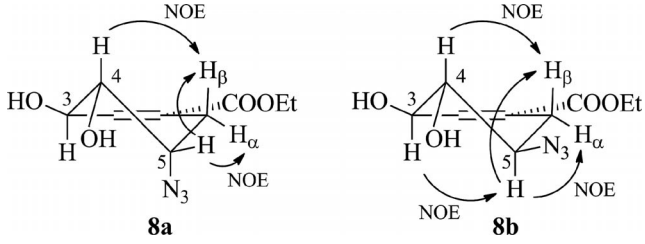


Figure 3. Stereochemistry and NOE of **8a** and **8b**.

When compounds **8a** and **8b** were exposed to 1.5 equiv. *tert*-butyldiphenylsilyl chloride (TBDPSCl), 5.0 equiv. triethylamine, and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at room temperature in CH_2Cl_2, selective protection of the less hindered hydroxyl group at C-3 took place smoothly to afford **9a** and **9b** in 93 and 90% yield, respectively. When **9a** and **9b** were treated with 2.5 equiv. diisobutylaluminum hydride (DIBAL-H) at –10 °C in CH_2Cl_2, the ester groups of **9a** and **9b** were clearly reduced, leaving the azido groups intact. The crude re-

duction products were used as such in the next step, and were exposed to 3.0 equiv. acetic anhydride, 4.0 equiv. triethylamine, and a catalytic amount of DMAP at 0 °C in dichloromethane, thus, **10a** and **10b** were obtained in 91 and 90% yield, respectively.

When **10a** and **10b** were treated with 2.0 equiv. sodium periodate ($NaIO_4$) and 0.1 equiv. ruthenium trichloride at room temperature in a mixed solvent of acetonitrile and deionized water (CH_3CN/H_2O, 3:1), Rh-catalyzed asymmetric dihydroxylation[19] took place smoothly to afford **11a** and **11b** in 92 and 91% yield, respectively. The steric bulk of the *tert*-butyldiphenylsilyloxy (TBDPSO) group directed the ruthenium catalyst to approach the double bond from the opposite side during the asymmetric dihydroxylation, thus each of the two hydroxyl groups at C-4 and C-5 of **11a** and **11b** had the desired opposite orientation to the TBDPSO group at C-3.

When **11a** and **11b** were treated first with 4.5 equiv. tetrabutylammonium fluoride (TBAF) at room temperature for 5 h in tetrahydrofuran, and then with 5.0 equiv. acetic anhydride, 5.0 equiv. triethylamine, and a catalytic amount of DMAP at 0 °C for 1 h in tetrahydrofuran, removal of the protecting group (TBDPS) and subsequent acetylation of the two hydroxyl groups at C-3 and C-4 occurred smoothly to produce **12a** and **12b** in 80 and 71% yields, respectively.

The stereochemistry of **12b** was unequivocally confirmed by X-ray crystallographic analysis of its single crystal as shown in Figure 4. As can be seen from the X-ray crystallographic structure of **12b**, the two acetoxyl (AcO) groups at C-3 and C-4 have a *trans* relationship, whereas the acetoxyl group at C-4 and the hydroxyl group at C-5 have a *cis* relationship, which are coincident with the stereochemistry of target compounds **1** and **2**. Moreover, 1-H and 3-H have a *cis* relationship, which are coincident with the aforementioned 2D ^{1}H NMR analysis of **8b**.

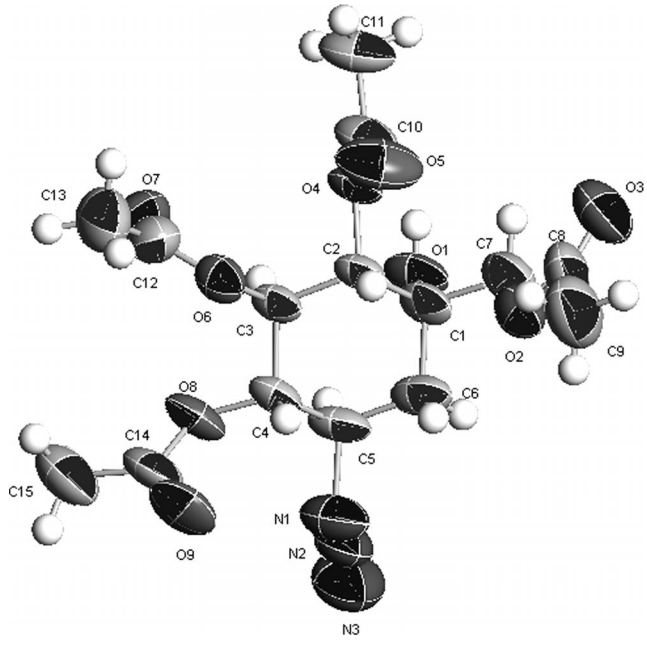


Figure 4. ORTEP drawing of **12b**.

All four acetyl groups of **12a** or **12b** could be cleanly removed in one step. When a solution of **12a** or **12b** was heated to reflux for approximately 25 h in a mixed solvent of methanol and ammonia hydrate ($CH_3OH/NH_3{\cdot}H_2O$, 5:1), compounds **13a** and **13b** were obtained in 97 and 96% yield, respectively.

The azido group of **13a** or **13b** could be cleanly reduced by Pd/C-catalyzed hydrogenation. When a solution of **13a** or **13b** in aqueous methanol (CH_3OH/H_2O, 1:1) was exposed to a H_2 atmosphere at room temperature for 24 h in the presence of palladium on charcoal (Pd/C), (+)-valiolamine (**1**) and (–)-1-*epi*-valiolamine (**2**) were obtained in 95 and 96% yield, respectively.

Conclusions

We have successfully developed novel asymmetric total syntheses of (+)-valiolamine (**1**) and (–)-1-*epi*-valiolamine (**2**). By using naturally abundant (–)-shikimic acid as the starting material, the first target compound **1** was synthesized in 12 steps in 35% overall yield, and the second target compound **2** was also synthesized in 12 steps in 30% overall yield. The intermediate compounds **7**, **8a**, **8b**, and **12b** were extensively analyzed by X-ray crystallographic or 2D ^{1}H NMR techniques, which confirmed that the two target compounds **1** and **2** have correct stereochemical structures.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were acquired with a Bruker AM-400 or AM-500 instrument. Chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded with a Nicolet Magna IR-550 spectrometer. MS spectra were recorded with Shimadzu GC–MS 2010 (EI) or Mariner Mass Spectrum (ESI) equipment. Optical rotations of chiral compounds were measured with a WZZ-1S polarimeter at room temperature. Melting points were determined with a Mel-TEMP II melting point apparatus. Column chromatography was performed on silica gel (Qingdao Chemical Factory). All reagents and solvents were analytically pure, and were used as received from the chemical suppliers. (–)-Shikimic acid was purchased from Shanxi Huachang Biotech. Ltd. (–)-Ethyl shikimate **4** was prepared in 97% yield according to a known method.[17]

(3*S*,4*S*,5*R*)-Ethyl 3-Chloro-4,5-bis(formyloxy)cyclohex-1-ene-1-carboxylate (5): Thionyl chloride (14.70 g, 123.6 mmol) was slowly added into a round-bottomed flask containing DMF (25 mL) at room temperature over 30 min, and the resulting solution was cooled to 0 °C in an ice bath. Powdered crystals of (–)-ethyl shikimate **4** (5.000 g, 24.73 mmol) were added in portions over 10 min, and the reaction mixture was then warmed to room temperature. The viscous solution was further stirred at room temperature for 25 h, then toluene (200 mL) and water (150 mL) were added. While the mixture was vigorously stirred, powdered potassium carbonate was added in portions until pH 8–9. The phases were separated and the aqueous solution was extracted with toluene (2 × 50 mL). The organic extracts were combined, washed with brine (30 mL), and dried with anhydrous $MgSO_4$. Removal of solvent by vacuum distillation gave a pale-yellow oil that could be directly used in the

next step or purified by flash chromatography (EtOAc/hexane, 1:5) to furnish **5** (6.230 g, 22.52 mmol, 91%). $[\alpha]_D^{20}$ = +36.1 (*c* = 5.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H, CH_3 in COOEt), 2.45–2.56 (m, 1 H, 6-H), 3.04 (dd, *J* = 17.9, 5.8 Hz, 1 H, 6-H), 4.22 (q, *J* = 7.1 Hz, 2 H, CH_2 in COOEt), 4.65–4.72 (m, 1 H, 5-H), 5.18–5.25 (m, 1 H, 4-H), 5.48 (dd, *J* = 9.6, 7.9 Hz, 1 H, 3-H), 6.76–6.81 (m, 1 H, 2-H), 8.04 (s, 1 H, OC*H*O), 8.14 (s, 1 H, OC*H*O) ppm. ^{13}C NMR ($CDCl_3$): δ = 164.69 (*C*OOEt), 159.69 (O*C*HO), 159.43 (O*C*HO), 134.87 (C-2), 129.11 (C-1), 73.31 (C-3), 67.99 (C-4), 61.57 (C-5), 55.62 (O*C*H_2CH$_3$), 29.13 (C-6), 14.18 (OCH$_2$*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{11}H_{13}O_6ClK$ [M + K]$^+$ 315.0038; found 315.0042. IR (neat): $\tilde{\nu}$ = 2981, 1726 (br., three C=O), 1374, 1253, 1168, 1074 cm^{-1}.

(3*R*,4*S*,5*R*)-Ethyl 3,4-Epoxy-5-hydroxycyclohex-1-ene-1-carboxylate (6): Compound **5** (10.00 g, 36.14 mmol) was dissolved in ethanol (100 mL) and potassium carbonate (9.990 g, 72.28 mmol) was added. The reaction mixture was stirred at room temperature for 20 h, and the progress of the reaction was monitored by TLC. Upon completion, the potassium salt was filtered under suction, and the filtrate was concentrated under vacuum to give an oily residue, which was partitioned between ethyl acetate (200 mL) and water (50 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (50 mL). Organic extracts were combined, washed with brine (20 mL), and dried with anhydrous $MgSO_4$. Removal of the solvent by vacuum distillation gave a pale-yellow oil that could be directly used for the next step or purified by flash chromatography (EtOAc/hexane, 1:4) to furnish **6** (6.320 g, 34.31 mmol, 95%). $[\alpha]_D^{20}$ = +91.7 (*c* = 3.60, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H, CH_3 in COOEt), 2.22–2.31 (m, 1 H, 6-H), 2.47 (d, *J* = 6.5 Hz, 1 H, O*H*), 2.70–2.80 (m, 1 H, 6-H), 3.45 (dd, *J* = 4.1, 4.0 Hz, 1 H, 4-H), 3.50–3.56 (m, 1 H, 5-H), 4.17 (q, *J* = 7.1 Hz, 2 H, CH_2 in COOEt), 4.48–4.55 (m, 1 H, 3-H), 7.08–7.12 (m, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.26 (*C*OOEt), 133.18 (C-2), 131.03 (C-1), 63.31 (C-3), 61.09 (C-5), 56.05 (O*C*H$_2$CH$_3$), 46.33 (C-4), 29.19 (C-6), 14.13 (OCH$_2$*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_9H_{13}O_4$ [M + H]$^+$ 185.0814; found 185.0816. IR (neat): $\tilde{\nu}$ = 3438 (O–H), 2981, 1716 (C=O), 1648, 1369, 1267, 1099, 1001 cm^{-1}.

(3*R*,4*R*,5*R*)-Ethyl 3,4-Epoxy-5-(methylsulfonyloxy)cyclohex-1-ene-1-carboxylate (7): Compound **6** (5.000 g, 27.15 mmol) was dissolved in dichloromethane (100 mL) and triethylamine (4.120 g, 40.72 mmol) was added. The resulting solution was cooled to 0 °C in an ice bath and methanesulfonyl chloride (3.730 g, 32.56 mmol) was then added dropwise over 30 min. When the addition was finished, the reaction mixture was further stirred at 0 °C for 30 min. The reaction was quenched by adding a dilute potassium carbonate aqueous solution until pH 8–9. The organic and aqueous phases were separated and the aqueous phase was extracted with dichloromethane (80 mL). The organic extracts were combined and dried with anhydrous $MgSO_4$. Evaporation of the solvent under vacuum gave a pale-yellow solid product that could be directly used for the next step or purified by flash chromatography (EtOAc/hexane, 1:6) to furnish **7** (6.760 g, 25.77 mmol, 95%), m.p. 72.8–73.1 °C. $[\alpha]_D^{20}$ = +220 (*c* = 2.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3 in COOEt), 2.37–2.45 (m, 1 H, 6-H), 2.98–3.07 (m, 1 H, 6-H), 3.03 (s, 3 H, CH_3 in OMs), 3.56 (dd, *J* = 4.0, 3.9 Hz, 1 H, 4-H), 3.75 (dd, *J* = 4.0, 5.6 Hz, 1 H, 3-H), 4.20 (q, *J* = 7.1 Hz, 2 H, CH_2 in COOEt), 5.42–5.48 (m, 1 H, 5-H), 7.11–7.15 (m, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 165.34 (*C*OOEt), 132.89 (C-2), 130.15 (C-1), 72.91 (C-5), 61.26 (C-3), 53.83 (*C*H$_2$ in COOEt), 46.67 (C-4), 38.69 (*C*H$_3$ in OMs), 26.86 (C-6), 14.16 (*C*H$_3$ in COOEt) ppm. HRMS (ESI): calcd. for $C_{10}H_{14}O_6SNa$ [M + Na]$^+$ 285.0409; found 285.0403. IR (KBr film): $\tilde{\nu}$ = 2990, 1710 (C=O), 1347, 1275, 1173, 1099, 933, 881 cm^{-1}.

(3*S*,4*R*,5*R*)-Ethyl 5-*O*-(Methylsulfonyl)shikimate (3): Compound **7** (5.000 g, 19.06 mmol) was dissolved in a mixed solvent of TFA (50 mL) and H_2O (5 mL). The resulting solution was stirred at room temperature for ca. 8 h, until the reaction was complete. The solution was then concentrated under vacuum to give a crude solid product that was triturated with a mixed solvent of ethyl acetate and hexane (1:2) to give pure **3** (4.970 g, 17.73 mmol, 93%), m.p. 125.5–125.8 °C. $[\alpha]_D^{20}$ = –34.1 (*c* = 1.00, CH_3OH). ^1H NMR ([D$_6$]DMSO): δ = 1.22 (t, *J* = 7.1 Hz, 3 H, CH_3 in COOEt), 2.36–2.46 (m, 1 H, 6-H), 2.83 (dd, *J* = 17.1, 5.8 Hz, 1 H, 6-H), 3.18 (s, 3 H, CH_3 in Ms), 3.50 (dd, *J* = 9.9, 7.6 Hz, 1 H, 4-H), 4.12–4.22 (m, 3 H, CH_2 in COOEt, and 3-H), 4.54–4.64 (m, 1 H, 5-H), 5.52 (br. s, 1 H, O*H*), 5.67 (br. s, 1 H, O*H*), 6.56–6.61 (m, 1 H, 2-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 165.08 (*C*OOEt), 140.61 (C-2), 125.53 (C-1), 79.54 (C-3), 73.12 (C-5), 70.86 (*C*H$_2$ in COOEt), 60.52 (C-4), 37.71 (*C*H$_3$ in Ms), 30.84 (C-6), 14.00 (*C*H$_3$ in COOEt) ppm. HRMS (ESI): calcd. for $C_{10}H_{17}O_7S$ [M + H]$^+$ 281.0695; found 281.0695. IR (KBr film): $\tilde{\nu}$ = 3435 (O–H), 3242 (O–H), 1697 (C=O), 1350, 1294, 1266, 1174, 1096, 954, 841, 793, 744, 522 cm^{-1}.

(3*S*,4*S*,5*S*)-Ethyl 5-Azido-3,4-dihydroxycyclohex-1-ene-1-carboxylate (8a): To a solution of **3** (2.000 g, 7.135 mmol) in DMSO (20 mL), sodium azide (930.0 mg, 14.30 mmol) and acetic acid (215.0 mg, 3.580 mmol) were added. The mixture was heated and stirred at 85 °C for approximate 2 h. When TLC showed the reaction was complete, ethyl acetate (100 mL) and H_2O (80 mL) were added and the mixture was vigorously stirred for 15 min. The phases were separated and the aqueous phase was extracted with ethyl acetate (2× 50 mL). The organic extracts were combined, washed with brine (20 mL), and dried with anhydrous $MgSO_4$. The organic solution was concentrated under vacuum to give the crude product, which was purified by flash chromatography (EtOAc/hexane, 1:3) to afford **8a** (1.346 g, 5.924 mmol, 83%) as off-white crystals, m.p. 65.2–66.5 °C. $[\alpha]_D^{20}$ = +60.1 (*c* = 1.00, $CHCl_3$). ^1H NMR ([D$_6$]acetone): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3 in COOEt), 2.52 (dd, *J* = 18.0, 5.5 Hz, 1 H, 6-H$_\alpha$), 2.62 (dd, *J* = 18.0, 4.6 Hz, 1 H, 6-H$_\beta$), 3.89 (dd, *J* = 6.1, 4.5 Hz, 1 H, 4-H), 3.94–4.00 (m, 1 H, 5-H), 4.20 (q, *J* = 7.1 Hz, 2 H, CH_2 in COOEt), 4.33 (dd, *J* = 2.1, 4.7 Hz, 1 H, 3-H), 6.75–6.79 (m, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.28 (*C*OOEt), 138.03 (C-2), 127.97 (C-1), 73.57 (C-3), 69.36 (*C*H$_2$ in COOEt), 61.31 (C-5), 60.29 (C-4), 29.03 (C-6), 14.13 (*C*H$_3$ in COOEt) ppm. HRMS (ESI): calcd. for $C_9H_{13}N_3O_4Na$ [M + Na]$^+$ 250.0804; found 250.0808. IR (KBr film): $\tilde{\nu}$ = 3425 (O–H), 3354 (O–H), 2134 (N$_3$), 1688 (C=O), 1654, 1294, 1261, 1085, 1040, 907, 740 cm^{-1}.

(3*S*,4*S*,5*R*)-Ethyl 5-Azido-3,4-dihydroxycyclohex-1-ene-1-carboxylate (8b): To a solution of **3** (2.000 g, 7.135 mmol) in ethanol (20 mL), sodium azide (930.0 mg, 14.30 mmol) was added, and the mixture was heated and stirred at reflux for approximate 3 h. When TLC showed the reaction was complete, ethanol was removed by vacuum distillation to give a residue, which was then partitioned between ethyl acetate (50 mL) and water (20 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (30 mL). The organic extracts were combined, washed with brine (20 mL), and dried with anhydrous $MgSO_4$. Evaporation of the solvent under vacuum gave the crude product, which was purified by flash chromatography (EtOAc/hexane, 1:3) to afford **8b** (1.362 g, 5.994 mmol, 84%) as pale-yellow crystals, m.p. 102.3–103.2 °C. $[\alpha]_D^{20}$ = –23.5 (*c* = 1.00, $CHCl_3$). ^1H NMR ([D$_6$]acetone): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3 in COOEt), 2.06–2.15 (m, 1 H, 6-H$_\beta$), 2.77 (dd, *J* = 17.6, 5.6 Hz, 1 H, 6-H$_\alpha$), 3.55 (dd, *J* = 10.2, 7.9 Hz,

1 H, 4-H), 3.67–3.75 (m, 1 H, 5-H), 4.19 (q, J = 7.1 Hz, 2 H, CH_2 in COOEt), 4.25–4.31 (m, 1 H, 3-H), 6.68–6.72 (m, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 165.87 (*C*OOEt), 138.47 (C-2), 128.30 (C-1), 75.95 (C-3), 72.04 (*C*H$_2$ in COOEt), 61.36 (C-5), 60.57 (C-4), 30.11 (C-6), 14.10 (*C*H$_3$ in COOEt) ppm. HRMS (ESI): calcd. for $C_9H_{13}N_3O_4Na$ [M + Na]$^+$ 250.0804; found 250.0806. IR (KBr film): $\tilde{\nu}$ = 3420 (O–H), 2984, 2105 (N_3), 1713 (C=O), 1657, 1370, 1254, 1095, 1040, 960, 877, 738 cm^{-1}.

(3*S*,4*S*,5*S*)-Ethyl 5-Azido-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxycyclohex-1-ene-carboxylate (9a): To a solution of **8a** (1.000 g, 4.401 mmol) in dichloromethane (10 mL), TBDPSCl (1.814 g, 6.600 mmol), DMAP (54 mg, 0.44 mmol) and triethylamine (2.227 g, 22.01 mmol) were added in turn. The resulting solution was then stirred at room temperature for approximate 5 h. The reaction was concentrated under vacuum to dryness, and then ethyl acetate (80 mL) and dilute aqueous hydrochloric acid (2 M, 30 mL) were added. After the mixture was vigorously stirred for 10 min, the organic phase was separated and washed successively with potassium carbonate aqueous solution (10% w/v, 30 mL) and brine (20 mL). The organic solution was dried with anhydrous $MgSO_4$ and then concentrated under vacuum to give a pale-yellow oily residue, which was purified by flash chromatography (EtOAc/hexane, 1:6) to give **9a** (1.906 g, 4.095 mmol, 93%). $[\alpha]_D^{20}$ = +73.7 (c = 1.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.08 [s, 9 H, C(CH_3)$_3$], 1.25 (t, J = 7.1 Hz, 3 H, CH_3 in COOEt), 2.48 (dd, J = 18.1, 6.6 Hz, 1 H, 6-H), 2.66 (dd, J = 18.1, 4.4 Hz, 1 H, another 6-H), 3.89–3.99 (m, 2 H, 4-H and 5-H), 4.15 (q, J = 7.1 Hz, 2 H, CH_2 in COOEt), 4.38 (dd, J = 5.1, 5.6 Hz, 1 H, 3-H), 6.57–6.61 (m, 1 H, 2-H), 7.35–7.47 (m, 6 H, Ph-H), 7.64–7.72 (m, 4 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 165.99 (*C*OOEt), 136.77 (C-2), 135.88 (Ar), 135.70 (Ar), 133.12 (Ar), 133.05 (Ar), 130.20 (Ar), 130.14 (Ar), 128.55 (Ar), 128.03 (C-1), 127.88 (Ar), 73.10 (C-3), 70.63 (*C*H$_2$ in COOEt), 60.92 (C-4), 58.44 (C-5), 27.07 (C-6), 26.95 [*C*(CH$_3$)$_3$], 19.24 [C(*C*H$_3$)$_3$], 14.18 (*C*H$_3$ in COOEt) ppm. HRMS (ESI): calcd. for $C_{25}H_{31}N_3O_4SiNa$ [M + Na]$^+$ 488.1892; found 488.1982. IR (neat): $\tilde{\nu}$ = 3479 (O–H), 2932, 2100 (N_3), 1715 (C=O), 1471, 1428, 1249, 1110, 824, 705, 610, 506 cm^{-1}.

(3*S*,4*S*,5*R*)-Ethyl 5-Azido-3-(*tert*-butyldiphenylsilyloxy)-4-hydroxycyclohex-1-ene-carboxylate (9b): The same procedure described for the preparation of **9a** was followed, and compound **9b** was obtained from **8b** in 90% yield. $[\alpha]_D^{20}$ = +28.6 (c = 1.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.09 [s, 9 H, C(CH_3)$_3$], 1.23 (t, J = 7.1 Hz, 3 H, CH_3 in COOEt), 2.15–2.24 (m, 1 H, 6-H), 2.77 (dd, J = 17.6, 5.6 Hz, 1 H, 6-H), 3.42–3.51 (m, 1 H, 5-H), 3.74 (dd, J = 10.5, 7.6 Hz, 1 H, 4-H), 4.15 (q, J = 7.1 Hz, 2 H, CH_2 in COOEt), 4.35 (dd, J = 2.5, 7.6 Hz, 1 H, 3-H), 6.52–6.56 (m, 1 H, 2-H), 7.36–7.48 (m, 6 H, Ph-H), 7.68–7.75 (m, 4 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 165.63 (*C*OOEt), 138.89 (C-2), 136.01 (Ar), 135.76 (Ar), 133.22 (Ar), 133.04 (Ar), 130.11 (Ar), 128.01 (C-1), 127.88 (Ar), 127.80 (Ar), 127.66 (Ar), 76.68 (C-3), 74.34 (*C*H$_2$ in COOEt), 60.98 (C-4), 60.23 (C-5), 29.96 (C-6), 26.96 [*C*(CH$_3$)$_3$], 19.33 [C(*C*H$_3$)$_3$], 14.16 (*C*H$_3$ in COOEt) ppm. HRMS (ESI): calcd. for $C_{25}H_{31}N_3O_4SiK$ [M + K]$^+$ 504.1721; found 504.1719. IR (neat): $\tilde{\nu}$ = 3500 (O–H), 2958, 2107 (N_3), 1715 (C=O), 1472, 1427, 1366, 1250, 1109, 976, 823, 705, 610, 506 cm^{-1}.

(3*S*,4*S*,5*S*)-4-Acetoxy-5-azido-3-(*tert*-butyldiphenylsilyloxy)cyclohex-1-enyl Methyl Acetate (10a): A solution of **9a** (1.500 g, 3.222 mmol) in dichloromethane (15 mL) was cooled to –10 °C in a salt-ice bath, and a solution of DIBAL-H (1.0 M in hexane, 8.1 mL, 8.1 mmol) was slowly added by using a syringe. When the addition was finished, the mixture was further stirred at –10 °C for 1 h. Ethyl acetate (60 mL) and dilute aqueous hydrochloric acid (2 M, 20 mL) were added. The mixture was vigorously stirred for 15 min, the phases were separated, and the aqueous phase was extracted with ethyl acetate (20 mL). The organic extracts were combined, washed with brine (15 mL), and dried with anhydrous $MgSO_4$. The organic solution was concentrated under vacuum to dryness. The residue was dissolved in anhydrous ethyl acetate (20 mL), and the resulting solution was cooled to 0 °C by an ice bath. Triethylamine (1.304 g, 12.89 mmol), acetic anhydride (1.000 g, 9.795 mmol) and a catalytic amount of DMAP (39.1 mg, 0.320 mmol) were then added in turn. After the addition, the mixture was further stirred at 0 °C for 1 h. The reaction was quenched by adding dilute aqueous hydrochloric acid (2 M, 10 mL), then the mixture was vigorously stirred for 15 min. The phases were separated and the aqueous phase was extracted with ethyl acetate (30 mL). The organic extracts were combined, washed successively with potassium carbonate aqueous solution (10% w/v, 10 mL) and brine (10 mL), and dried with anhydrous $MgSO_4$. Evaporation of solvent under vacuum gave a residue, which was purified by flash chromatography (EtOAc/hexane, 1:8) to afford **10a** (1.490 g, 2.935 mmol, 91%) as a colorless oil. $[\alpha]_D^{20}$ = +59.7 (c = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.06 [s, 9 H, C(CH_3)$_3$], 1.86 (s, 3 H, CH_3COO), 2.04 (s, 3 H, CH_3COO), 2.23 (dd, J = 17.6, 6.0 Hz, 1 H, 6-H), 2.43 (dd, J = 17.6, 4.5 Hz, 1 H), 4.03–4.08 (m, 5-H), 4.40 (s, 2 H, CH_2OAc), 4.42–4.47 (m, 1 H, 4-H), 5.15 (dd, J = 5.9, 2.4 Hz, 1 H, 3-H), 5.40–5.44 (m, 1 H, 2-H), 7.37–7.45 (m, 6 H, Ph-H), 7.63–7.70 (m, 4 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.56 (CH$_3$*C*OO), 170.32 (CH$_3$*C*OO), 135.97 (C-2), 135.74 (Ar), 133.33 (Ar), 133.31 (Ar), 131.65 (Ar), 129.96 (Ar), 129.87 (Ar), 127.74 (C-1), 127.73 (Ar), 125.56 (Ar), 75.17 (C-3), 68.07 (*C*H$_2$OAc), 66.39 (C-4), 56.64 (C-5), 29.02 (C-6), 26.85 (*C*H$_3$COO), 20.84 (*C*H$_3$COO), 20.76 [*C*(CH$_3$)$_3$], 19.22 [C(*C*H$_3$)$_3$] ppm. HRMS (ESI): calcd. for $C_{27}H_{33}N_3O_5SiK$ [M + K]$^+$ 546.1827; found 546.1828. IR (neat): $\tilde{\nu}$ = 2932, 2858, 2119 (N_3), 1746 (C=O), 1428, 1370, 1228, 1110, 1049, 824, 742, 705, 610, 508 cm^{-1}.

(3*S*,4*S*,5*R*)-4-Acetoxy-5-azido-3-(*tert*-butyldiphenylsilyloxy)cyclohex-1-enyl Methyl Acetate (10b): The same procedure described for the preparation of **10a** was followed, and compound **10b** was obtained from **9b** in 90% yield. $[\alpha]_D^{20}$ = +41.4 (c = 1.20, $CHCl_3$). ^{1}H NMR($CDCl_3$): δ = 1.03 [s, 9 H, C(CH_3)$_3$], 1.95 (s, 3 H, CH_3COO), 1.99 (s, 3 H, CH_3COO), 2.14–2.24 (m, 1 H, 6-H), 2.36 (dd, J = 17.1, 5.8 Hz, 1 H, 6-H), 3.45–3.55 (m, 1 H, 5-H), 4.34 (s, 2 H, CH_2OAc), 4.38–4.43 (m, 1 H, 4-H), 5.21 (dd, J = 10.8, 7.7 Hz, 1 H, 3-H), 5.37–5.40 (m, 1 H, 2-H), 7.35–7.47 (m, 6 H, Ph-H), 7.60–7.70 (m, 4 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.41 (CH$_3$*C*OO), 170.21 (CH$_3$*C*OO), 136.03 (C-2), 135.83 (Ar), 133.43 (Ar), 133.14 (Ar), 130.83 (Ar), 129.94 (Ar), 129.87 (Ar), 127.74 (C-1), 127.73 (Ar), 126.91 (Ar), 76.50 (C-3), 71.63 (*C*H$_2$OAc), 65.85 (C-4), 58.52 (C-5), 31.16 (C-6), 26.75 (*C*H$_3$COO), 20.91 (*C*H$_3$COO), 20.73 [*C*(CH$_3$)$_3$], 19.19 [C(*C*H$_3$)$_3$] ppm. HRMS (ESI): calcd. for $C_{27}H_{34}N_3O_5Si$ [M + H]$^+$ 508.2268; found 508.2267. IR (neat): $\tilde{\nu}$ = 2933, 2858, 2102 (N_3), 1749 (C=O), 1429, 1368, 1224, 1110, 1049, 823, 705, 505 cm^{-1}.

(1*S*,2*S*,3*S*,4*S*,5*S*)-2-Acetoxy-1-azido-3-(*tert*-butyldiphenylsilyloxy)-4,5-dihydroxycyclohex-5-yl Methyl Acetate (11a): Compound **10a** (1.500 g, 2.955 mmol) was dissolved in CH_3CN (15 mL), and an aqueous solution of $RuCl_3$ (60.0 mg, 0.289 mmol) and $NaIO_4$ (1.265 g, 5.914 mmol) in deionized water (5 mL) was added. The two-phase mixture was then vigorously stirred at room temperature for 4 h, then the reaction was quenched by adding saturated aqueous $Na_2S_2O_3$ solution (15 mL). Ethyl acetate (60 mL) was added and the mixture was vigorously stirred for 10 min. The phases were separated, the aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the combined organic extracts were dried with $MgSO_4$

and filtered. Concentration of the filtrate followed by flash chromatography (EtOAc/hexane, 1:4) afforded **11a** (1.473 g, 2.719 mmol, 92%) as a colorless oil. $[\alpha]_D^{20}$ = –39.7 (*c* = 1.00, $CHCl_3$). ^1H NMR($CDCl_3$): δ = 1.08 [s, 9 H, C(CH_3)$_3$], 1.43 (s, 3 H, CH_3COO), 1.80 (dd, *J* = 15.5, 3.6 Hz, 1 H, 6-H), 1.93 (dd, *J* = 15.5, 3.2 Hz, 1 H, 6-H), 2.10 (s, 3 H, CH_3COO), 2.35 (br. s, 1 H, O*H*), 3.02 (br. s, 1 H, O*H*), 3.50–3.58 (m, 1 H, 1-H), 3.89 (d, *J* = 11.1 Hz, 1 H, C*H*HOAc), 4.03 (d, *J* = 11.1 Hz, 1 H, CH*H*OAc), 4.06–4.18 (m, 2 H, 3-H and 4-H), 4.89 (dd, *J* = 9.9, 3.5 Hz, 1 H, 2-H), 7.35–7.50 (m, 6 H, Ph-H), 7.60–7.65 (m, 2 H, Ph-H), 7.77–7.84 (m, 2 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.64 (CH$_3$*C*OO), 170.59 (CH$_3$*C*OO), 136.15 (Ar), 135.52 (Ar), 134.50 (Ar), 132.18 (Ar), 130.17 (Ar), 129.56 (Ar), 127.88 (Ar), 127.63 (Ar), 76.09 (C-5), 74.35 (C-2), 73.27 (C-4), 71.66 (C-3), 66.38 (*C*H$_2$OAc), 58.37 (C-1), 32.36 (C-6), 27.01 (*C*H$_3$COO), 20.96 (*C*H$_3$COO), 20.02 [*C*(CH$_3$)$_3$], 19.73 [C(*C*H$_3$)$_3$] ppm. HRMS (ESI): calcd. for $C_{27}H_{35}N_3O_7SiNa$ [M + Na]$^+$ 564.2142; found 564.2144. IR (neat): $\tilde{\nu}$ = 3496 (O–H), 2933, 2858, 2117 (N_3), 1735 (CH$_3$*C*OO), 1429, 1374, 1231, 1113, 1043, 978, 887, 823, 743, 706, 609, 514 cm^{-1}.

(1*R*,2*S*,3*S*,4*S*,5*S*)-2-Acetoxy-1-azido-3-(*tert*-butyldiphenylsilyloxy)-4,5-dihydroxycyclohex-5-yl Methyl Acetate (11b): The same procedure described for the preparation of **11a** was followed, and compound **11b** was obtained from **10b** in 91% yield as a colorless oil. $[\alpha]_D^{20}$ = –26.2 (*c* = 1.10, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.02 [s, 9 H, C(CH_3)$_3$], 1.59 (dd, *J* = 13.8, 12.0 Hz, 1 H, 6-H), 1.81 (s, 3 H, CH_3COO), 2.04 (dd, *J* = 13.8, 8.9 Hz, 1 H, C-6), 2.10 (s, 3 H, CH_3COO), 2.33 (br. s, 1 H, OH), 2.43 (br. s, 1 H, O*H*), 3.49 (d, *J* = 8.8 Hz, 1 H, 4-H), 3.53–3.62 (m, 1 H, 1-H), 3.83 (d, *J* = 11.2 Hz, 1 H, C*H*HOAc), 3.91 (dd, *J* = 8.8, 9.2 Hz, 1 H, 3-H), 4.01 (d, *J* = 11.2 Hz, 1 H, CH*H*OAc), 5.02 (dd, *J* = 9.2, 9.6 Hz, 1 H, 2-H), 7.36–7.49 (m, 6 H, Ph-H), 7.65–7.72 (m, 4 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.14 (CH$_3$*C*OO), 170.46 (CH$_3$*C*OO), 135.90 (Ar), 135.61 (Ar), 133.39 (Ar), 132.83 (Ar), 130.11 (Ar), 129.90 (Ar), 128.04 (Ar), 127.77 (Ar), 75.66 (C-5), 74.36 (C-2), 73.67 (C-4), 72.03 (C-3), 66.91 (*C*H$_2$OAc), 57.91 (C-1), 34.20 (C-6), 26.94 (*C*H$_3$COO), 20.91 (*C*H$_3$COO), 20.88 [*C*(CH$_3$)$_3$], 19.55 [C(*C*H$_3$)$_3$] ppm. HRMS (ESI): calcd. for $C_{27}H_{35}N_3O_7SiK$ [M + K]$^+$ 580.1881; found 580.1877. IR (neat): $\tilde{\nu}$ = 3483 (O–H), 2957, 2103 (N_3), 1742 (C=O), 1428, 1374, 1238, 1112, 1041, 742, 706, 609, 514 cm^{-1}.

(1*S*,2*S*,3*R*,4*S*,5*S*)-5-Acetoxymethyl-1-azido-5-hydroxy-2,3,4-triacetoxycyclohexane (12a): Compound **11a** (1.300 g, 2.400 mmol) was dissolved in tetrahydrofuran (15 mL), and TBAF (2.820 g, 10.79 mmol) was added. After stirring was continued at room temperature for approximate 5 h, the mixture was cooled to 0 °C. Triethylamine (1.215 g, 12.01 mmol), acetic anhydride (1.225 g, 12.00 mmol) and DMAP (30.0 mg, 0.245 mmol) were added in turn, then the mixture was further stirred at 0 °C for 1 h. The reaction solution was concentrated under vacuum and the residue was partitioned between ethyl acetate (50 mL) and aqueous HCl (2 M, 20 mL). The phases were separated, the aqueous phase was extracted with ethyl acetate (2× 25 mL), and the organic extracts were combined, washed successively with potassium carbonate aqueous solution (10% w/w, 10 mL), water (10 mL) and brine (10 mL), and dried with anhydrous $MgSO_4$. Evaporation of the solvent under vacuum gave a crude product, which was purified by flash chromatography (EtOAc/hexane, 1:6) to afford **12a** (745.5 mg, 1.925 mmol, 80%) as off-white crystals, m.p. 122.8–124.2 °C. $[\alpha]_D^{20}$ = –13.2 (*c* = 2.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.97 (dd, *J* = 16.0, 3.6 Hz, 1 H, 6-H), 2.00 (s, 3 H, CH_3 in Ac), 2.05 (s, 3 H, CH_3 in Ac), 2.06 (s, 3 H, CH_3 in Ac), 2.10 (s, 3 H, CH_3 in Ac), 2.11 (dd, *J* = 16.0, 3.0 Hz, 1 H, 6-H), 3.40 (s, 1 H, O*H*), 3.70 (d, *J* = 11.4 Hz, 1 H, C*H*HOAc), 4.00 (d, *J* = 11.4 Hz, 1 H, CH*H*OAc), 4.24–4.29 (m, 1 H, 1-H), 5.06 (d, *J* = 10.2 Hz, 4-H), 5.08 (dd, *J* = 10.3, 3.8 Hz, 1 H, 2-H), 5.69 (dd, *J* = 10.3, 10.2 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.22 (CH$_3$*C*OO), 169.97 (CH$_3$*C*OO), 169.85 (CH$_3$*C*OO), 169.70 (CH$_3$*C*OO), 73.36 (C-5), 73.14 (C-4), 71.83 (C-3), 68.51 (C-2), 65.55 (*C*H$_2$OAc), 58.35 (C-1), 33.30 (C-6), 20.77 (*C*H$_3$COO), 20.58 (*C*H$_3$COO), 20.54 (*C*H$_3$COO), 20.42 (*C*H$_3$COO) ppm. HRMS (ESI): calcd. for $C_{15}H_{21}N_3O_9Na$ [M + Na]$^+$ 410.1175; found 410.1174. IR (neat): $\tilde{\nu}$ = 3349 (O–H), 2926, 2111 (N_3), 1743 (C=O), 1425, 1375, 1236, 1038, 917, 814, 745, 627, 602, 531 cm^{-1}.

(1*R*,2*S*,3*R*,4*S*,5*S*)-5-Acetoxymethyl-1-azido-5-hydroxy-2,3,4-triacetoxycyclohexane (12b): The same procedure described for the preparation of **12a** was followed, and compound **12b** was obtained from **11b** in 71% yield as off-white crystals, m.p. 113.1–114.5 °C. $[\alpha]_D^{20}$ = –11.0 (*c* = 1.00, $CHCl_3$). ^1H NMR($CDCl_3$): δ = 1.68 (dd, *J* = 14.0, 12.7 Hz, 1 H, 6-H), 1.99 (s, 3 H, CH_3COO), 2.08 (s, 3 H, CH_3COO), 2.10 (s, 3 H, CH_3COO), 2.10 (s, 3 H, CH_3COO), 2.19 (dd, *J* = 14.0, 4.8 Hz, 1 H, 6-H), 2.68 (br. s, 1 H, O*H*), 3.88 (d, *J* = 11.4 Hz, 1 H, C*H*HOAc), 3.93–4.05 (m, 2 H, 1-H and CH*H*OAc), 5.07 (dd, *J* = 10.0, 9.8 Hz, 1 H, 2-H), 5.11 (d, *J* = 10.1 Hz, 1 H, 4-H), 5.40 (dd, *J* = 10.1, 10.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.58 (CH$_3$*C*OO), 170.11 (CH$_3$*C*OO), 169.88 (CH$_3$*C*OO), 169.26 (CH$_3$*C*OO), 73.97 (C-5), 72.15 (C-4), 72.12 (C-3), 71.22 (C-2), 66.23 (*C*H$_2$OAc), 57.22 (C-1), 35.09 (C-6), 20.71 (*C*H$_3$COO), 20.65 (*C*H$_3$COO), 20.55 (*C*H$_3$COO), 20.49 (*C*H$_3$COO) ppm. HRMS (ESI): calcd. for $C_{15}H_{21}N_3O_9Na$ [M + Na]$^+$ 410.1175; found 410.1176. IR (neat): $\tilde{\nu}$ = 3409 (O–H), 2926, 2106 (N_3), 1748 (C=O), 1381, 1238, 1048, 915, 829, 606 cm^{-1}.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1-Azido-5-hydroxymethyl-2,3,4,5-tetrahydroxycyclohexane (13a): Compound **12a** (500.0 mg, 1.291 mmol) was dissolved in a mixed solvent of methanol (10 mL) and ammonia hydrate (25% w/w, 2 mL), and the mixture was heated to reflux for approximately 25 h. The solution was then concentrated under vacuum to give an oily residue, which was dissolved in pure water (0.5 mL). The aqueous solution was washed with diethyl ether (2× 10 mL), and the ether phase was decanted each time. The aqueous solution was concentrated under vacuum to remove water. Compound **13a** (274.5 mg, 1.252 mmol, 97%) was thus obtained as a colorless oil. $[\alpha]_D^{20}$ = +6.5 (*c* = 0.9, CH_3OH). ^1H NMR ($CDCl_3$): δ = 1.71 (dd, *J* = 15.7, 3.0 Hz, 1 H, 6-H), 1.92 (dd, *J* = 15.7, 2.6 Hz, 1 H, 6-H), 3.26 (d, *J* = 10.0 Hz, 1 H, C*H*HOAc), 3.28 (d, *J* = 10.0 Hz, 1 H, CH*H*OAc), 3.40 (d, *J* = 10.3 Hz, 1 H, 4-H), 3.53 (dd, *J* = 9.8, 3.4 Hz, 1 H, 2-H), 3.66 (dd, *J* = 10.3, 9.8 Hz, 1 H, 3-H), 3.95–4.02 (m, 1 H, 1-H) ppm. ^{13}C NMR (D_2O): δ = 74.52 (C-5), 73.16 (C-4), 72.76 (C-3), 70.77 (C-2), 65.16 (C-1), 60.97 (*C*H$_2$OH), 31.57 (C-6) ppm. HRMS (ESI): calcd. for $C_7H_{13}N_3O_5Na$ [M + Na]$^+$ 242.0753; found 242.0753. IR (neat): $\tilde{\nu}$ = 3302 (O–H), 2924, 2113 (N_3), 1662, 1401, 1347, 1096, 1045 cm^{-1}.

(1*R*,2*S*,3*R*,4*S*,5*S*)-1-Azido-5-hydroxymethyl-2,3,4,5-tetrahydroxycyclohexane (13b): The same procedure described for the preparation of **13a** was followed, and compound **13b** was obtained from **12b** in 96% yield as a colorless oil. $[\alpha]_D^{20}$ = –9.3 (*c* = 1.5, CH_3OH). ^1H NMR ($CDCl_3$): δ = 1.39 (dd, *J* = 14.0, 12.0 Hz, 1 H, 6-H), 1.89 (dd, *J* = 14.0, 4.4 Hz, 1 H, 6-H), 3.22 (dd, *J* = 10.0, 9.8 Hz, 1 H, 2-H), 3.28 (d, *J* = 9.6 Hz, 1 H, 4-H), 3.35 (d, *J* = 11.5 Hz, C*H*HOH), 3.44 (d, *J* = 11.5 Hz, 1 H, CH*H*OH), 3.45–3.52 (m, 2 H, 1-H and 3-H) ppm. ^{13}C NMR (D_2O): δ = 75.90 (C-5), 73.65 (C-4), 73.51 (C-3), 72.49 (C-2), 65.23 (C-1), 59.99 (*C*H$_2$OH), 33.87 (C-6) ppm. HRMS (ESI): calcd. for $C_7H_{13}N_3O_5Na$ [M + Na]$^+$ 242.0753; found 242.0753. IR (neat): $\tilde{\nu}$ = 3377 (O–H), 2938, 2105 (N_3), 1663, 1430, 1258, 1087, 824, 623 cm^{-1}.

(+)-Valiolamine (1): A solution of **13a** (300.0 mg, 1.369 mmol) in a mixed solvent of methanol (10 mL) and water (10 mL) was placed into a flask, which was equipped with a magnetic stirring bar, an inlet and an outlet of H_2. Palladium on charcoal Pd/C (10% w/w, 50 mg) was added. After the flask was purged with H_2 several times, the black suspension was well-stirred at room temperature for 24 h under an atmosphere of H_2. The mixture was then filtered through a thin layer of Celite to remove the Pd/C catalyst. The solvent was concentrated under vacuum to give **1** (251.2 mg, 1.300 mmol, 95%) as a colorless syrup. $[a]_D^{20}$ = +18.6 (*c* = 1.05, H_2O) [ref.[4] $[a]_D^{23}$ = +18.5 (*c* = 1.00, H_2O)]. ^1H NMR (D_2O): δ = 1.64 (dd, *J* = 15.4, 3.8 Hz, 1 H, 6-H), 1.80 (dd, *J* = 15.4, 2.4 Hz, 1 H, 6-H), 3.32 (d, *J* = 11.0 Hz, 1 H, C*H*HOH), 3.33–3.39 (m, 2 H, 1-H and 4-H), 3.42 (d, *J* = 11.0 Hz, 1 H, CH*H*OH), 3.54 (dd, *J* = 9.8, 4.3 Hz, 1 H, 2-H), 3.70 (dd, *J* = 9.8, 9.3 Hz, 1 H, 3-H) ppm. ^{13}C NMR (D_2O): δ = 76.47 (C-5), 74.07 (C-4), 73.04 (C-3), 71.71 (C-2), 65.98 (*C*H_2OH), 51.22 (C-1), 32.17 (C-6) ppm. HRMS (ESI): calcd. for $C_7H_{16}NO_5$ $[M + H]^+$ 194.1028; found 194.1030. IR (neat): $\tilde{\nu}$ = 3360 (OH and NH_2), 2925, 1666, 1568, 1407, 1096, 1050, 813, 652 cm^{-1}.

(–)-1-*epi*-Valiolamine (2): The same procedure described for the preparation of **1** was followed, and compound **2** was obtained from **13b** in 96% yield as a colorless syrup. $[a]_D^{20}$ = –18.0 (*c* = 1.00, H_2O). [ref.[4] $[a]_D^{20}$ = –17 (*c* = 0.42, H_2O)]. ^1H NMR (D_2O): δ = 1.43 (dd, *J* = 14.0, 6.5 Hz, 1 H, 6-H), 1.89 (dd, *J* = 14.0, 4.3 Hz, 1 H, 6-H), 2.93–3.01 (m, 1 H, 1-H), 3.14 (dd, *J* = 9.8, 9.6 Hz, 1 H, 2-H), 3.38 (d, *J* = 11.2 Hz, 1 H, C*H*HOH), 3.43 (d, *J* = 11.2 Hz, 1 H, CH*H*OH), 3.49–3.58 (m, 2 H, 3-H and 4-H) ppm. ^{13}C NMR (D_2O): δ = 76.44 (C-5), 73.85 (C-4), 73.62 (C-3), 72.76 (C-2), 65.30 (*C*H_2OH), 48.75 (C-1), 35.07 (C-6) ppm. HRMS (ESI): calcd. for $C_7H_{15}NO_5Na$ $[M + Na]^+$ 216.0848; found 216.0849. IR (neat): $\tilde{\nu}$ = 3415 (OH and NH_2), 2924, 1656, 1598, 1206, 1097, 1041 cm^{-1}.

CCDC-894838 (for **7**) and -934069 (for **12b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Crystal data and structure refinement for **7** and **12b**; ^1H and ^{13}C NMR spectra of **1**–**3** and **5**–**13**; ^1H-^1H NOESY spectra of **8a** and **8b**.

Acknowledgments

The authors thank the National Natural Science Foundation of China (NSFC) (grant number 20972048) for financial support of this work.

[1] For reviews, see: a) T. M. Gloster, G. J. Davies, *Org. Biomol. Chem.* **2010**, *8*, 305–320; b) X. Chen, Y. Fan, Y. Zheng, Y. Shen, *Chem. Rev.* **2003**, *103*, 1955–1977; c) N. Asano, *Glycobiology* **2003**, *13*, 93R–104R; d) V. H. Lillelund, H. H. Jensen, X. Liang, M. Bols, *Chem. Rev.* **2002**, *102*, 515–553; e) A. A. Waston, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265–295; f) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; g) B. Winchester, G. W. J. Fleet, *Glycobiology* **1992**, *2*, 199–210; h) J. E. Groopman, *Rev. Infect. Dis.* **1990**, *12*, 908–911.

[2] For reviews, see: a) A. J. Krentz, C. J. Bailey, *Drugs* **2005**, *65*, 385–411; b) J. L. Treadway, P. Mendys, D. J. Hoover, *Expert Opin. Invest. Drugs* **2001**, *10*, 439–454; c) B. Goke, C. Herrmann-Rinke, *Diabetes Metab. Rev.* **1998**, *14*, S31–S38; d) E. Truscheit, I. Hillebrand, B. Junge, L. Muller, W. Puls, D. Schmidt, *Prog. Clin. Biochem. Med.* **1988**, *7*, 17–99.

[3] Y. Kameda, N. Asano, M. Yoshikawa, M. Takeuchi, T. Yamaguchi, K. Matsui, S. Horii, H. Fukase, *J. Antibiot.* **1984**, *37*, 1301–1307.

[4] S. Ogawa, Y. Ohishi, M. Asada, A. Tomoda, A. Takahashi, Y. Ooki, M. Mori, M. Itoh, T. Korenaga, *Org. Biomol. Chem.* **2004**, *2*, 884–889.

[5] a) R. Kawamori, N. Tajima, Y. Iwamoto, A. Kashiwagi, K. Shimamoto, K. Kaku, *Lancet* **2009**, *373*, 1607–1614; b) H. Fukase, S. Horii, *J. Org. Chem.* **1992**, *57*, 3642–3650; c) S. Horii, H. Fukase, T. Matsuo, Y. Kameda, N. Asano, K. Matsui, *J. Med. Chem.* **1986**, *29*, 1038–1046.

[6] S. Horii, H. Fukase, Y. Kameda, *Carbohydr. Res.* **1985**, *140*, 185–200.

[7] a) H. Fukase, S. Horii, *J. Org. Chem.* **1992**, *57*, 3651–3658; b) M. Hayashida, N. Sakairi, H. Kuzuhara, *J. Carbohydr. Chem.* **1988**, *7*, 83–94; c) T. K. M. Shing, H. M. Cheng, *Org. Lett.* **2008**, *10*, 4137–4139.

[8] a) T. K. M. Shing, L. H. Wan, *Angew. Chem.* **1995**, *107*, 1742; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1643–1645; b) T. K. M. Shing, L. H. Wan, *J. Org. Chem.* **1996**, *61*, 8468–8479.

[9] O. Sellier, P. Van de Weghe, D. Le Nouen, C. Strehler, J. Eustache, *Tetrahedron Lett.* **1999**, *40*, 853–856.

[10] S. Ogawa, M. Kanto, *J. Nat. Prod.* **2007**, *70*, 493–497.

[11] H.-J. Lo, C.-Y. Chen, W.-L. Zheng, S.-M. Yeh, T.-H. Yan, *Eur. J. Org. Chem.* **2012**, 2780–2785.

[12] a) N. Yoshida, K. Ogasawara, *Org. Lett.* **2000**, *2*, 1461–1463; b) P. M. Dewick, *Nat. Prod. Rep.* **1998**, *15*, 17–58.

[13] a) X.-H. He, L. Liu, X.-G. Liu, Z.-P. Liu, G.-M. Zhao, H.-Y. Li, *Nat. Prod. Res. Dev. (in Chinese)* **2008**, *20*, 914–917; b) L. B. Enrich, M. L. Scheuermann, A. Mohadjer, K. R. Matthias, C. F. Eller, M. S. Newman, M. Fujinaka, T. Poon, *Tetrahedron Lett.* **2008**, *49*, 2503–2505; c) H. Ohira, N. Torii, T. M. Aida, M. Watanabe, R. L. Smith Jr., *Sep. Purif. Technol.* **2009**, *69*, 102–108; d) S. Ghosh, Y. Chisti, U. C. Banerjee, *Biotechnol. Adv.* **2012**, *30*, 1425–1431.

[14] a) K. M. Draths, D. R. Knop, J. W. Frost, *J. Am. Chem. Soc.* **1999**, *121*, 1603–1604; b) R. Sui, *Chem. Eng. Technol.* **2008**, *31*, 469–473; c) S. S. Chandran, J. Yi, K. M. Draths, R. von Daeniken, W. Weber, J. W. Frost, *Biotechnol. Prog.* **2003**, *19*, 808–814.

[15] a) L.-D. Nie, X.-X. Shi, K. H. Ko, W.-D. Lu, *J. Org. Chem.* **2009**, *74*, 3970–3973; b) L.-D. Nie, X.-X. Shi, *Tetrahedron: Asymmetry* **2009**, *20*, 124–129; c) L.-D. Nie, X.-X. Shi, N. Quan, F.-F. Wang, X. Lu, *Tetrahedron: Asymmetry* **2011**, *22*, 1692–1699; d) L.-D. Nie, W. Ding, X.-X. Shi, N. Quan, X. Lu, *Tetrahedron: Asymmetry* **2012**, *23*, 742–747; e) M. Karpf, R. Trussardi, *Angew. Chem.* **2009**, *121*, 5871; *Angew. Chem. Int. Ed.* **2009**, *48*, 5760–5762; f) H.-K. Kim, K.-J. J. Park, *Tetrahedron Lett.* **2012**, *53*, 1561–1563.

[16] N. Quan, L. Nie, X. Shi, R. Zhu, L. Xia, *Chin. J. Chem.* **2012**, *30*, 2759–2766.

[17] M. Federspiel, R. Fischer, M. Hennig, H.-J. Mair, T. Oberhauser, G. Rimmler, T. Albiez, J. Bruhin, H. Estermann, C. Gandert, V. Gockel, S. Gotzo, U. Hoffmann, G. Huber, G. Janatsch, S. Lauper, O. Rockel-Stabler, R. Trussardi, A. G. Zwahlen, *Org. Process Res. Dev.* **1999**, *3*, 266–274.

[18] P. G. M. Wuts, J. M. Northuis, T. A. Kwan, *J. Org. Chem.* **2000**, *65*, 9223–9225.

[19] T. K. M. Shing, C. S. K. Kwong, A. W. C. Cheung, S. H.-L. Kok, Z. Yu, J. Li, C. H. K. Cheng, *J. Am. Chem. Soc.* **2004**, *126*, 15990–15992.

Received: May 30, 2013
Published Online: August 15, 2013

