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Synthesis of *N*-Bz-Protected D-Daunosamine and D-Ristosamine by Silica Gel Promoted Intramolecular Conjugate Addition of Trichloroacetimidates obtained from Osmundalactone and Its Epimer

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Trichloroacetimidates prepared from osmundalactone and its epimer unexpectedly undergo intramolecular conjugate addition during silica gel chromatography to produce oxazolines in excellent yields. The novel, simple synthesis of *N*-Bz-protected D-daunosamine and D-ristosamine from these oxazolines is described in this paper.

Introduction

Amino sugars, especially deoxyamino sugars, are found in clinically important antibiotics such as antimicrobial macrolides and anthracycline antitumor antibiotics.[1] In most instances, the sugar components of these antibiotics are essential for biological activity; however, the functions of the sugar moieties have not been investigated thus far.[2] We envisaged that modification of the sugar moieties of these antibiotics may serve as a tool for investigating the significance of amino sugars and the structure–activity relationship and for elucidating the biosynthetic route of antibiotics.[3,4] For this purpose, a versatile and synthetic route for deoxyamino sugars is highly desirable. We were especially interested in developing a new synthetic route to deoxyamino sugars from nonsugar materials.[5–7]

Similar to deoxyamino sugars, 1,2- and 1,3-amino alcohol moieties are often found in natural products and potent drugs. These moieties have also been used as synthetic intermediates. An effective method for the introduction of functionality into acyclic olefinic systems is required. While a variety of stereoselective synthetic methods have been developed for 1,2-amino alcohol moieties,[8] there are relatively few methods for 1,3-amino alcohols.[9] We observed the intramolecular conjugate addition of γ-trichloroacetimidoyloxy-α,β-unsaturated esters during the course of developing a simple synthetic strategy for deoxyamino sugars.[6,10] We investigated the potential of trichloroacetimidate-mediated functionalization for the introduction of nitrogen functionality[11] into the β-carbon of γ- and δ-hydroxy-α,β-unsaturated esters, a new method to synthesize 1,2- or 1,3-amino alcohol moieties in an acyclic system.[7]

Recently, we reported the application of trichloroacetimidate-mediated functionalization for providing a simple and useful method for the stereoselective synthesis of polyfunctionalized carbocycles such as 3-hydroxy-substituted 2-aminocycloalkanecarboxylates.[12]

The purpose of this study was to utilize trichloroacetimidate-mediated functionalization for the introduction of nitrogen functionality in the stereoselective synthesis of polyfunctionalized heterocycles such as deoxyamino sugars. This paper describes a methodology applicable for the construction of polyfunctionalized carbocyclic systems, a novel route to 3-amino-2,3,6-trideoxy sugars, especially for daunosamine and ristosamine, which are the amino sugar constituents of daunomycin and other antibiotics.[13]

Results and Discussion

For the synthesis of polyfunctionalized heterocyclic compounds such as deoxyamino sugars, we prepared amino alcohol moieties with lactones by employing the intramolecular conjugate addition of trichloroacetimidates to α,β-unsaturated lactones. We assumed that osmundalactone and its epimer would be suitable substrates for deoxyamino sugars having a 3,4-*cis*-amino alcohol moiety, especially daunosamine and ristosamine.

From the retrosynthetic analysis of *N*-Bz-D-daunosamine (**1**) and *N*-Bz-D-ristosamine (**2**), as shown in Scheme 1, we found that **1** and **2** could be obtained from preceding lactones **3** and **4** with the oxazoline moiety, respectively. In fact, racemic oxazoline **2** was reported as the precursor of **1**.[14] Oxazoline intermediates **3** and **4** in turn could be obtained from 4-*epi*-osmundalactone (**5**) and osmundalactone (**6**) by the key intramolecular conjugate addition of the corresponding trichloroacetimidates.[6,10,11] 4-*epi*-Osmundalactone (**5**) and osmundalactone (**6**) individually could be prepared from chiral starting materials **7** and **8** by lactone formation, accompanied by geometrical isomerization

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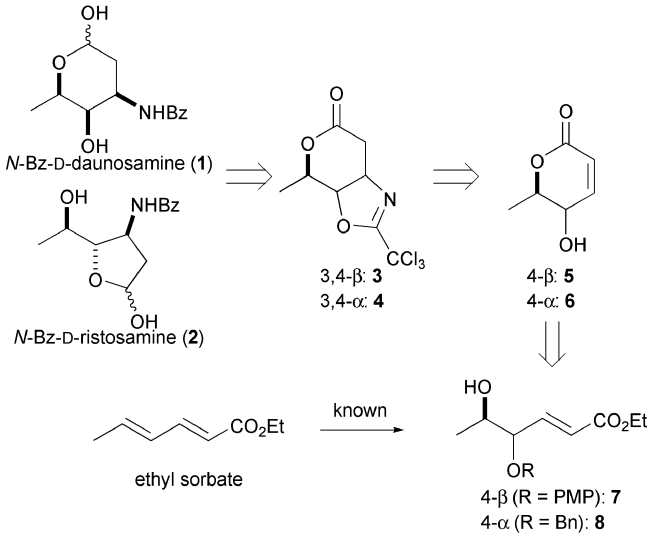
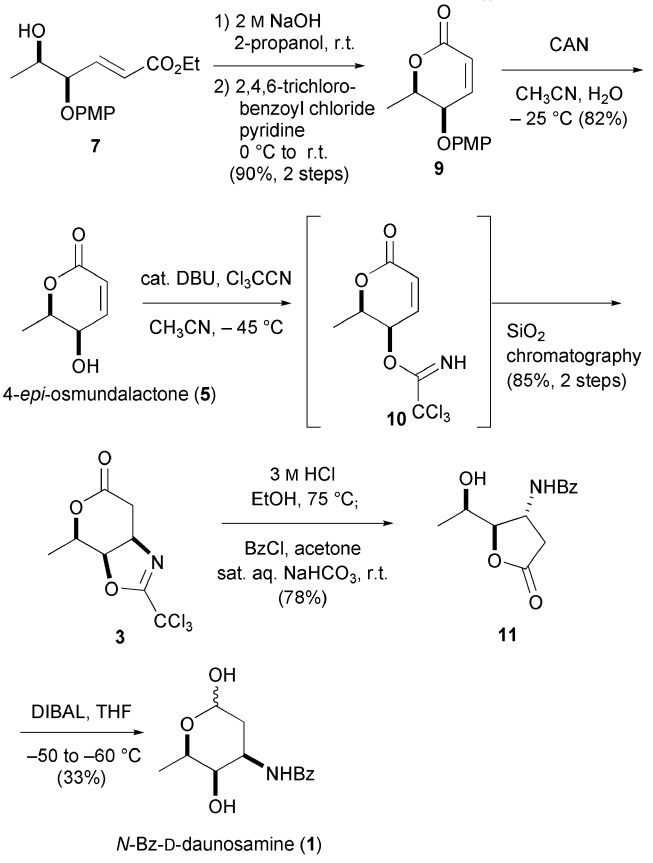
(*trans* to *cis*) of the double bond.[15] Compound **7** was known to be obtained from the commercially available ethyl sorbate by Sharpless asymmetric dihydroxylation, following Pd-catalyzed etheration, as previously reported,[7] whereas chiral starting material **8** was also known to be derived from ethyl sorbate by Shi's asymmetric epoxidation[16] and epoxide ring opening,[17] as reported in the literature.



Scheme 1. Retrosynthetic analysis of *N*-Bz-D-daunosamine (**1**) and *N*-Bz-D-ristosamine (**2**).



Scheme 2. Synthesis of *N*-Bz-D-daunosamine (**1**) from chiral alcohol **7**.

The first stage of our study was the synthesis of the intermediary 4-*epi*-osmundalactone (**5**) from the chiral starting material, δ-hydroxy-α,β-unsaturated ester **7** (Scheme 2).[7] Ester **7** was hydrolyzed with 2 M sodium hydroxide in 2-propanol, and the resulting crude carboxylic acid was successively subjected to δ-lactonization in the presence of 2,4,6-trichlorobenzoyl chloride and pyridine to give the α,β-unsaturated-δ-lactone congener **9** (90% yield in 2 steps), accompanied by successful *trans*/*cis* isomerization.[15] The *p*-methoxyphenyl (PMP) group was oxidatively cleaved by ceric ammonium nitrate (CAN) to give **5**, which was obtained in 82% yield.[18] The spectroscopic data (^{1}H and ^{13}C NMR, IR) and optical rotation of **5** were identical to those reported in the literature.[19]

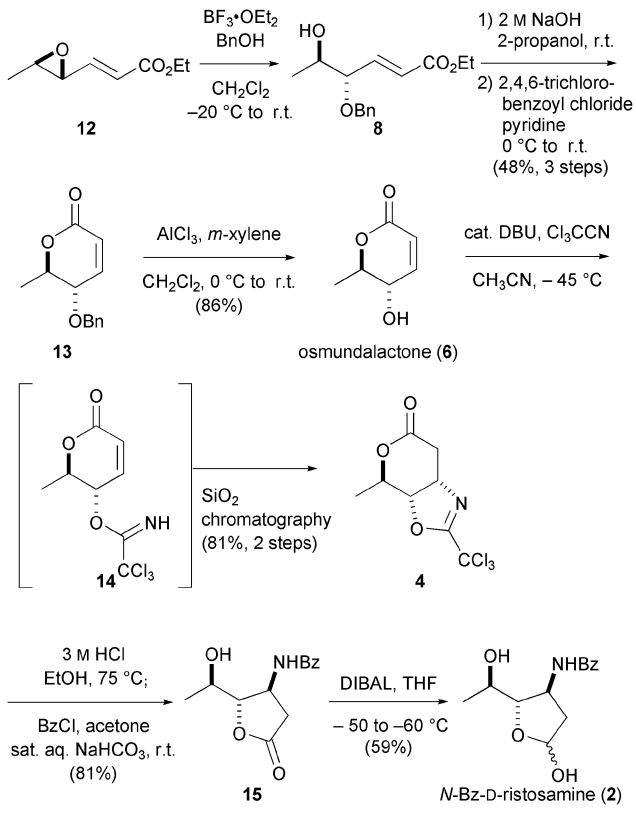
For the intramolecular conjugate addition, **5** was transformed into the corresponding trichloroacetimidate **10** by treating it with a catalytic amount of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and an excess amount of trichloroacetonitrile in acetonitrile. Resulting crude **10**, whose structure was confirmed by ^{1}H NMR spectroscopy, was subjected to silica gel chromatography for purification, as reported previously. However, **10** was not practically obtained in the expected fractions. Fortunately, desired oxazoline **3** (73% in 2 steps) was found after close analysis of the more polar fractions. During chromatography, a silica gel promoted intramolecular conjugate addition unexpectedly occurred and, consequently, **10** was directly transformed into desired oxazoline **3**. Further investigation showed that regulation of the retention period of the eluent after charging crude **10** on the silica gel column improved the yield of oxazoline **3** up to 85% in this transformation.

To the best of our knowledge, trichloroacetimidates are rarely affected by silica gel. Therefore, their isolated yields are seldom affected by the deprotection of the trichloroacetimidate group during chromatography. In addition, conjugate addition has never been observed during silica gel chromatography thus far. This might be attributed to the conformational regulation of the trichloroacetimidate being close to the reaction site, because the reactant lactone itself is cyclic and besides the methyl group is substituted on the opposite site. From the viewpoint of green chemistry, our finding that silica gel promotes intramolecular conjugate addition could be very important, because conjugate additions are inherently atom economic, and the use of silica promotes conjugate additions. However, only few studies on heteroconjugate additions promoted by silica gel have been reported thus far.[20]

With objective intermediary oxazoline **3** in hand, the semifinal manipulation of our work was the transformation into *N*-Bz-γ-lactone **11**; the known exact precursor[21] of 3-amino-2,3,6-trideoxyhexose, namely, daunosamine. Thus far,[14] the hydrolysis of the oxazoline ring of compound **3** and the spontaneous formation of the γ-lactone were realized by heating the compound with 3 M hydrochloric acid in ethanol, followed by evaporation to afford the corresponding γ-lactone hydrochloride. This was immediately

suspended in acetone and treated with a saturated aqueous solution of sodium hydrogen carbonate and benzoyl chloride to produce desired *N*-Bz-γ-lactone **11** in 78% yield in 2 steps. Finally, the half reduction of lactone **11** was achieved by using diisobutylaluminium hydride (DIBAL) in tetrahydrofuran (THF)/hexane at –60 °C to produce *N*-Bz-protected D-daunosamine (**1**, 33% yield). The spectroscopic data (^{1}H and ^{13}C NMR, IR) and the optical rotation of resulting compound **1** were identical to those reported in the literature.[21,22]

For another type of 3-amino-2,3,6-trideoxyhexose, ristosamine, we first synthesized intermediary osmundalactone **6** from the chiral starting material δ-hydroxy-α,β-unsaturated ester (**8**), which was prepared from ethyl sorbate as reported in the literature (Scheme 3).[16,17] Ester **8** was hydrolyzed, and the obtained crude carboxylic acid was successively transformed into α,β-unsaturated-δ-lactone **13** by treating it with 2,4,6-trichlorobenzoyl chloride in pyridine (48% in 3 steps) along with *trans*/*cis* isomerization.[15] The benzyl group of lactone **13** was cleaved by aluminium chloride to give **6** in 86% yield. The spectroscopic data (^{1}H and ^{13}C NMR, IR) and optical rotation of obtained **6** were identical to those reported in the literature.[19,23]



Scheme 3. Synthesis of *N*-Bz-D-ristosamine (**2**) from chiral epoxide **12**.

Next, for the key intramolecular conjugate addition, **6** was transformed into the corresponding trichloroacetimidate **14** by treating it with a catalytic amount of DBU and an excess amount of trichloroacetonitrile in acetonitrile. Thus obtained crude **14** was charged onto a silica gel column for the intramolecular conjugate addition to occur in the same manner as that described above. As a result, **14** was also successfully transformed into desired oxazoline **4** (81% in 2 steps).

Finally, a three-step process was used, which was the same at that used in the case of *N*-Bz-D-daunosamine, to afford *N*-Bz-protected D-ristosamine (**2**). Acidic hydrolysis of compound **9** along with its transformation into γ-lactone was achieved by heating the compound with 3 M hydrochloric acid in ethanol. The obtained crude γ-lactone hydrochloride was benzoylated to give *N*-Bz-γ-lactone **15** in 81% yield in 2 steps. Finally, half reduction of lactone **15** was achieved by using DIBAL in THF/hexane at –60 °C to give **2** (59% yield). The spectroscopic data (^{1}H and ^{13}C NMR, IR) and optical rotation of resulting **2** were identical to those reported in the literature.[21,24]

Conclusions

In conclusion, we have succeeded in developing a very concise route for the synthesis of *N*-Bz-protected D-daunosamine and D-ristosamine by silica gel promoted intramolecular conjugate addition of γ-trichloroacetimidates obtained from osmundalactone and its epimer. This shows that our synthetic strategy is applicable for the synthesis of 3-amino-2,4,6-trideoxysugars from nonsugar chiral starting materials. Further synthetic studies using this type of intramolecular conjugate addition, especially from the viewpoint of green chemistry, are in progress and will be reported in due course.

Experimental Section

General Information: NMR spectra were recorded with a JEOL GSX-270 spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in δ values based on internal tetramethylsilane (δ_H = 0 ppm) or solvent signal ($CDCl_3$ δ_C = 77.0 ppm; C_6D_6 δ_H = 7.15 ppm; [D_6]DMSO δ_C = 39.5 ppm) as reference. IR spectra were recorded with a HORIBA FT-720 Fourier-transform infrared spectrometer. Optical rotations were measured with a Rudolph Research Analytical AUTOPOL V polarimeter. Mass spectra were measured with a Shimadzu LCMS-IT-TOF mass spectrometer. Flash silica gel column chromatography was carried out on Kanto Chemical Co., Inc., Silica Gel 60 N (spherical, neutral, 40–50 mm).

(4*R*,5*R*)-4-(*p*-Methoxyphenoxy)-5-methyl-2-hexen-5-olide (9): To a solution of **7**[7] (206.9 mg, 0.738 mmol) in 2-propanol (2.0 mL) was added 2 M NaOH (1.0 mL, 2.0 mmol), and the reaction mixture was stirred for 2.5 h at room temperature. The reaction mixture was concentrated in vacuo. To the residue was added 2 M HCl, and the mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. To an ice-cold solution of the thus obtained crude carboxylic acid in dry pyridine (1.5 mL) was added dropwise 2,4,6-trichlorobenzoyl chloride (135 μL, 0.864 mmol), and the mixture was stirred for 1.5 h under a dry atmosphere (calcium chloride tube). The reaction mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give lactone **9** (155.4 mg,

90% yield, 2 steps) as a colorless solid. An analytical sample (colorless rod) was obtained by recrystallization from EtOAc/hexane; m.p. 62.0–63.5 °C. $[\alpha]_D^{24.7}$ = –369 (*c* = 0.630, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2954, 1736, 1718, 1508, 1242, 1225, 1107, 1059, 1030, 982, 958, 822, 771 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 6.98 (dd, *J* = 4.9, 9.8 Hz, 1 H, 3-H), 6.93–6.81 (m, 4 H, Ar), 6.18 (d, *J* = 9. 8 Hz, 1 H, 2-H), 4.73 (dq, *J* = 3.4, 6.6 Hz, 1 H, 5-H), 4.62 (dd, *J* = 3.4, 4.7 Hz, 1 H, 4-H), 3.78 (s, 3 H, OMe), 1.56 (d, *J* = 6.6 Hz, 3 H, 5-Me) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 162.9, 155.0, 151.0, 142.0, 123.7, 117.5, 114.9, 76.1, 69.3, 55.8, 15.8 ppm. $C_{13}H_{14}O_4$ (234.25): calcd. C 66.66, H 6.02; found C 66.51, H 6.12.

(4*R*,5*R*)-4-Hydroxy-5-methyl-2-hexen-5-olide (4-*epi*-Osmundalactone) (5): To a cooled (bath temp. –25 °C) solution of **9** (69.2 mg, 0.295 mmol) in acetonitrile (3.0 mL) and water (0.75 mL) was added ceric ammonium nitrate (416 mg, 0.759 mmol), and the mixture was stirred for 15 min. The mixture was filtered through a pad of silica gel and eluted with hexane/EtOAc (1:5), and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 1:3) to give **5** (31.0 mg, 82%) as a colorless solid. An analytical sample (colorless powder) was obtained by recrystallization from Et_2O; m.p. 49.5–53.5 °C {ref.[19] (+)-**5**, m.p. 48–53 °C}. $[\alpha]_D^{26.6}$ = –230 (*c* = 0.550, H_2O) {ref.[19] (+)-**5**, $[\alpha]_D^{33}$ = +230.6 (*c* = 0.51, H_2O)}. IR (KBr): $\tilde{\nu}$ = 3448, 1711, 1387, 1263, 1115, 1061, 989, 958, 833 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.02 (dd, *J* = 5.8, 9.6 Hz, 1 H, 3-H), 6.11 (d, *J* = 9. 8 Hz, 1 H, 2-H), 4.54 (dq, *J* = 2.7, 6.7 Hz, 1 H, 5-H), 4.03 (ddd, *J* = 2.8, 5.8, 9.4 Hz, 1 H, 4-H), 2.21 (d, *J* = 9.4 Hz, 1 H, OH), 1.51 (d, *J* = 6.8 Hz, 3 H, 5-Me) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 163.8, 144.5, 122.8, 77.1, 63.0, 15.7 ppm. $C_6H_8O_3$ (128.13): calcd. C 56.24, H 6.29; found C 56.20, H 6.33.

(3a*R*,4*R*,7a*R*)-2-Trichloromethyl-3a,4,7,7a-tetrahydro-4-methylpyrano[4,3-*d*]oxazol-6-one (3): To a cooled (bath temp. – 45 °C) solution of **5** (160.9 mg, 1.26 mmol) and trichloroacetonitrile (1.26 mL, 12.6 mmol) in dry acetonitrile (4.8 mL) was added dropwise DBU (95.0 µL, 0.635 mmol), and the mixture was stirred for 15 min under a dry atmosphere (calcium chloride tube). The reaction mixture was poured into a cold saturated aqueous solution of NH_4Cl and extracted with EtOAc. The extract was washed successively with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$), and concentrated in vacuo. Thus obtained crude **10** [(4*R*,5*R*)-4-trichloroacetimidoyloxy-5-methyl-2-hexen-5-olide] was subjected to flash column chromatography: ^1H NMR (270 MHz, $CDCl_3$): δ = 8.50 (br. s, 1 H, NH), 7.13 (dd, *J* = 5.6, 9.6 Hz, 1 H, 3-H), 6.27 (d, *J* = 9. 8 Hz, 1 H, 2-H), 5.31 (dd, *J* = 2.9, 5.4 Hz, 1 H, 4-H), 4.78 (dq, *J* = 2.9, 6.6 Hz, 1 H, 5-H), 1.56 (d, *J* = 6.6 Hz, 3 H, 5-Me)] ppm. The conditions for chromatography were as follows: SiO_2: 80 g, solvents: hexane/EtOAc = 1:1 to 1:3. Elution with polar solvents (hexane/EtOAc, 1:3) was started ca. 30 min after charging the column with crude **10**. Oxazoline **3** (291.7 mg, 85% yield, 2 steps) was obtained as a colorless solid through an intramolecular conjugate addition. An analytical sample (colorless rod) was obtained by recrystallization from EtOAc/hexane; m.p. 197.5–199.3 °C {ref.[14] (±)-**3**, 178–181 °C}. $[\alpha]_D^{25.7}$ = +88.7 (*c* = 0.565, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2991, 1743, 1660, 1348, 1284, 1254, 1107, 1036, 999, 804, 793, 673 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 5.07 (dd, *J* = 1.7, 10.0 Hz, 1 H, 3a-H), 4.94 (ddd, *J* = 1.9, 5.6, 10.0 Hz, 1 H, 7a-H), 4.49 (dq, *J* = 1.7, 6.6 Hz, 1 H, 4-H), 3.08 (dd, *J* = 1.9, 16.0 Hz, 1 H, one of 7-H), 2.72 (dd, *J* = 5.7, 16.1 Hz, 1 H, one of 7-H), 1.56 (d, *J* = 6.6 Hz, 3 H, 4-Me) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 168.7, 163.8, 85.7, 81.7, 74.1, 63.4, 32.6, 15.9 ppm. $C_8H_8Cl_3NO_3$ (272.51): calcd. C 35.26, H 2.96, N 5.14; found C 35.05, H 2.99, N 5.07.

(3*R*,4*R*,5*R*)-3-Benzamido-5-hydroxy-4-hexanolide (11): To a solution of oxazoline **3** (276.4 mg, 1.01 mmol) in EtOH (19 mL) was added 3 M HCl (19 mL, 57 mmol), and the reaction mixture was heated (bath temp 75 °C) for 12 h. The reaction mixture was concentrated in vacuo. To the suspension of the residue in acetone (6.5 mL) and saturated aqueous $NaHCO_3$ (16 mL) was added dropwise benzoyl chloride (390 µL, 3.35 mmol), and the mixture was stirred for 4 h at room temperature. The mixture was acidified with 2 M HCl and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 1:2) to give **11** (197.7 mg, 78%) as a colorless solid. An analytical sample (colorless needle) was obtained by recrystallization from EtOAc/hexane; m.p. 143.0–146.5 °C {ref.[22a] m.p. 147 °C; ref.[20b] m.p. 143–144 °C; ref.[22e] m.p. 148–149 °C; cf. ref.[14] (±)-**11**, 137–139 °C}. $[\alpha]_D^{28.7}$ = +18.9 (*c* = 1.01, EtOH) {ref.[22b] $[\alpha]_D^{26}$ = –19.4 (*c* = 1.0, EtOH); ref.[22e] $[\alpha]_D^{18}$ = –19.7 (*c* = 1.02, EtOH)}. IR (KBr): $\tilde{\nu}$ = 3465, 3338, 2937, 1774, 1641, 1537, 1269, 1203, 1151, 1039, 694, 663, 633 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.83–7.75 (m, 2 H, Ar), 7.60–7.41 (m, 3 H, Ar), 6.63 (br. d, *J* = 6.2 Hz, 1 H, NH), 4.82 (dddd, *J* = 3.6, 4.4, 7.0, 8.9 Hz, 1 H, 3-H), 4.37 (dd, *J* = 2.8, 3.4 Hz, 1 H, 4-H), 4.16 (ddq, *J* = 2.7, 6.4, 6.4 Hz, 1 H, 5-H), 3.18 (dd, *J* = 9.0, 18.2 Hz, 1 H, one of 2-H), 2.59 (dd, *J* = 4.3, 18.2 Hz, 1 H, one of 2-H), 2.18 (d, *J* = 6.2 Hz, 1 H, OH), 1.35 (d, *J* = 6.6 Hz, 3 H, Me) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 175.2, 167.7, 133.0, 132.3, 128.8, 127.0, 88.9, 67.9, 49.0, 35.1, 19.3 ppm. $C_{13}H_{15}NO_4$ (249.26): calcd. C 62.64, H 6.07, N 5.62; found C 62.48, H 6.12, N 5.58.

3-Benzamido-2,3,6-trideoxy-D-*lyxo*-hexopyranose (*N*-Bz-D-Daunosamine) (1): To a solution of lactone **11** (64.5 mg, 0.259 mmol) in dry THF (10 mL) was added dropwise DIBAL (0.98 M in hexane, 1.32 mL, 1.29 mmol) under an argon atmosphere at –60 °C, and the reaction mixture was stirred for 1 h at –60 to –50 °C. The reaction was quenched by the dropwise addition of acetone/MeOH (1:1, 2.5 mL), and the mixture was warmed gradually to room temperature with stirring for ca. 1 h. The mixture was filtered through a pad of Celite. The filter cake was washed with acetone/MeOH (1:1), and then the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc) to give **1** (21.7 mg, 33%). An analytical sample (colorless rod) was obtained by recrystallization from EtOAc/hexane; m.p. 151.0–154.0 °C {ref.[22a] m.p. 151.5–153 °C; ref.[22c] m.p. 152–154 °C; ref.[22d] m.p. 153–155 °C; ref.[22e] m.p. 154–156 °C; ref.[22f] m.p. 146–149 °C; cf. ref.[14] (±)-**1**, 137–139 °C}. $[\alpha]_D^{26.9}$ = +128 (immediately after preparation), $[\alpha]_D^{23.0}$ = +93.5 (after 3 h, constant) (*c* = 0.149, EtOH) {ref.[22a] $[\alpha]_D^{26}$ = –106 (EtOH); ref.[22c] $[\alpha]_D^{22}$ = –106.7 (*c* = 0.22, EtOH); ref.[22d] $[\alpha]_D^{20}$ = –109 (*c* = 0.08, EtOH); ref.[22e] $[\alpha]_D^{20}$ = –108 (*c* = 0.093, EtOH); ref.[22f] $[\alpha]_D^{25}$ = –87.8 to –61.8 (*c* = 0.50, EtOH, 3 h)}. IR (KBr): $\tilde{\nu}$ = 3442, 3330, 2974, 1637, 1577, 1525, 1489, 1350, 1279, 1248, 1192, 1165, 1082, 1016, 982, 930, 692 cm^{-1}. ^1H and ^{13}C NMR spectra of this material were identical with those reported in the literature.[21] $C_{13}H_{17}NO_4$ (251.28): calcd. C 62.14, H 6.82, N 5.57; found C 61.81, H 6.85, N 5.49.

(4*S*,5*R*)-4-Benzyloxy-5-methyl-2-hexen-5-olide (13): To a cooled (bath temp. –20 °C) solution of epoxide **12**[16] (756.6 mg, 4.84 mmol) and benzyl alcohol (1.25 mL, 12.1 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise $BF_3{\cdot}OEt_2$ (1.20 mL, 9.72 mmol), and the mixture was stirred for 1 h at room temperature. To the mixture was added water, and the mixture was extracted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 5:1) to give **8** contaminated with benzyl alcohol. [A small amount of pure **8** (ethyl (2*E*,4*S*,5*R*)-4-benzyloxy-5-hy-

droxyhex-2-enoate)(colorless oil) obtained during flash column chromatography was used for several analyses: $[\alpha]_D^{25.7}$ = +64.1 (*c* = 0.605, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3464, 2979, 1718, 1657, 1454, 1369, 1300, 1275, 1178, 1095, 1041, 698 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.41–7.26 (m, 5 H, Ar), 6.91 (dd, *J* = 6.7, 15.9 Hz, 1 H, 3-H), 6.07 (dd, *J* = 1.1, 15.8 Hz, 1 H, 2-H), 4.65 (d, *J* = 11.8 Hz, 1 H, one of benzyl), 4.42 (d, *J* = 11.8 Hz, 1 H, one of benzyl), 4.23 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.03–3.89 (m, 1 H, 5-H), 3.91 (ddd, *J* = 1.2, 3.7, 6.7 Hz, 1 H, 4-H), 2.19 (br. d, *J* = 4.9 Hz, 1 H, OH), 1.31 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.16 (d, *J* = 6.4 Hz, 3 H, $CH(OH)CH_3$) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$) δ = 165.7, 143.9, 137.6, 128.5, 127.9, 127.8, 124.8, 81.9, 71.3, 69.2, 60.6, 17.9, 14.2 ppm. HRMS (ESI-TOF): calcd. for $C_{15}H_{21}O_4$ $[M+H]^+$ 265.1440; found 265.1474.] To a solution of thus obtained crude product in 2-propanol (10 mL) was added 2 M NaOH (5.0 mL, 10 mmol), and the reaction mixture was stirred for 2.5 h at room temperature. After an additional amount of 2 M NaOH (3.0 mL, 6.0 mmol), the reaction mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo. The residue was washed with $CHCl_3$ for removal of benzyl alcohol. After acidification (pH ca. 1) with 2 M HCl, the mixture was extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. To an ice-cold solution of thus obtained crude carboxylic acid (650.3 mg, mmol) in dry pyridine (6.0 mL) was added dropwise 2,4,6-trichlorobenzoyl chloride (480 µL, 3.07 mmol), and the mixture was stirred for 1.5 h under a dry atmosphere (calcium chloride tube). The reaction mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give **13** (506.1 mg, 48% yield, 3 steps) as a colorless oil. $[\alpha]_D^{25.6}$ = +95.0 (*c* = 1.03, $CHCl_3$) {ref.[15] (+)-**13**, $[\alpha]^{25}$ = +97.4 (*c* = 0.35, $CHCl_3$); ref.[15] (–)-**13**, $[\alpha]^{25-}$ = 97.8 (*c* = 0.32, $CHCl_3$)}. IR (neat): $\tilde{\nu}$ = 2983, 1738, 1726, 1454, 1387, 1236, 1113, 1076, 1030, 737, 700 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.44–7.30 (m, 5 H, Ar), 6.87 (dd, *J* = 2.1, 10.0 Hz, 1 H, 3-H), 6.00 (dd, *J* = 1.8, 9.9 Hz, 1 H, 2-H), 4.71 (d, *J* = 11.8 Hz, 1 H, one of benzyl), 4.63 (d, *J* = 11.8 Hz, 1 H, one of benzyl), 4.47 (dq, *J* = 6.4, 8.5 Hz, 1 H, 5-H), 3.99 (ddd, *J* = 2.0, 2.0, 8.6 Hz, 1 H, 4-H), 1.45 (d, *J* = 6.4 Hz, 3 H, 5-Me) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 162.9, 145.9, 136.8, 128.7, 128.3, 128.0, 121.0, 77.2, 73.9, 72.1, 18.3 ppm. HRMS (ESI-TOF): calcd. for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1021; found 219.1037.

(4*S*,5*R*)-4-Hydroxy-5-methyl-2-hexen-5-olide (6): To an ice-cooled suspension of $AlCl_3$ (756 mg, 5.67 mmol) in dry CH_2Cl_2 (11 mL) was added a solution of **13** (495.1 mg, 2.27 mmol) in *m*-xylene (2.0 mL), and the mixture was stirred for 1 h. The reaction mixture was poured into cold saturated aqueous NH_4Cl and extracted successively with EtOAc and $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 1:2) to give **6** (248.7 mg, 86%) as a colorless solid. An analytical sample (colorless plate) was obtained by recrystallization from Et_2O; m.p. 75.0–78.5 °C {ref.[23c] (+)-**6**, m.p. 80 °C; ref.[23a] (–)-**6**, m.p. 82–82.5 °C; ref.[23b] m.p. 82.5 °C; ref.[23d] m.p. 77–80 °C}. $[\alpha]_D^{25.9}$ = +73.0 (*c* = 1.13, H_2O) {ref.[23c] (+)-**6**, $[\alpha]_D^{22}$ = +65.8 (*c* = 0.16, H_2O); ref.[23a] (–)-**6** $[\alpha]_D^{22}$ = –70.6 (*c* = 2.0, H_2O); ref.[23b] $[\alpha]_D^{20}$ = –70.3 (*c* = 0.56, H_2O); ref.[23d] $[\alpha]_D^{30}$ = –47.9 (*c* = 1.01, H_2O)}. IR (KBr): $\tilde{\nu}$ = 3386, 2987, 1705, 1618, 1390, 1365, 1304, 1282, 1246, 1171, 1107, 1061, 1022, 964, 850, 808, 744, 469 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 6.84 (dd, *J* = 2.2, 9.9 Hz, 1 H, 3-H), 5.99 (dd, *J* = 1.9, 9.8 Hz, 1 H, 2-H), 4.38 (dq, *J* = 6.3, 8.9 Hz, 1 H, 5-H), 4.26 (dddd, *J* = 2.0, 2.0, 6.9, 8.9 Hz, 1 H, 4-H), 2.35 (br. d, *J* = 6.8 Hz, 1 H, OH), 1.49 (d, *J* = 6.2 Hz, 3 H, 5-Me) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 163.2, 148.6, 120.7, 79.0, 67.7, 18.1 ppm. $C_6H_8O_3$ (128.13): calcd. C 56.24, H 6.29; found C 56.21, H 6.33.

(3a*S*,4*R*,7a*S*)-2-Trichloromethyl-3a,4,7,7a-tetrahydro-4-methylpyrano[4,3-*d*]oxazol-6-one (4): To a cooled (bath temp. –45 °C) solution of **6** (209.8 mg, 1.64 mmol) and trichloroacetonitrile (1.70 mL, 17.0 mmol) in dry acetonitrile (7.5 mL) was added dropwise DBU (123 µL, 0.822 mmol), and the mixture was stirred for 20 min under a dry atmosphere (calcium chloride tube). The reaction mixture was poured into cold saturated aqueous NH_4Cl and extracted with EtOAc. The extract was washed successively with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$), and concentrated in vacuo. Thus obtained crude **14** [(4*S*,5*R*)-4-trichloroacetimidoyloxy-5-methyl-2-hexen-5-olide] was subjected to flash column chromatography. ^1H NMR (270 MHz, $CDCl_3$) δ 8.59 (br. s, 1 H, NH), 6.93 (dd, *J* = 2.9, 9.9 Hz, 1 H, 3-H), 6.14 (dd, *J* = 1.6, 9.9 Hz, 1 H, 2-H), 5.45 (ddd, *J* = 1.6, 2.9, 7.8 Hz, 1 H, 4-H), 4.74 (dq, *J* = 6.5, 7.7 Hz, 1 H, 5-H), 1.51 (d, *J* = 6.4 Hz, 3 H, 5-Me)] ppm. The conditions for chromatography were as follows: SiO_2: 80 g, solvents: hexane/EtOAc, 5:1 to 2:1. Elution with polar solvents (hexane/EtOAc, 2:1) was started ca. 1 h after charging the column with crude **14**. Oxazoline **4** (361.7 mg, 81% yield, 2 steps) was obtained as a colorless solid. An analytical sample (colorless rod) was obtained by recrystallization from EtOAc/hexane; m.p. 179.0–179.2 °C. $[\alpha]_D^{25.5}$ = +34.4 (*c* = 0.515, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1755, 1657, 1250, 1005, 989, 835, 802, 663 cm^{-1}. ^1H NMR (270 MHz, C_6D_6): δ = 3.68 (ddd, *J* = 6.8, 9.4, 9.4 Hz, 1 H, 7a-H), 3.55 (dd, *J* = 8.3, 9.4 Hz, 1 H, 3a-H), 3.42 (dq, *J* = 6.3, 8.3 Hz, 1 H, 4-H), 2.50 (dd, *J* = 6.9, 15.5 Hz, 1 H, one of 7-H), 1.85 (dd, *J* = 9.3, 15.5 Hz, 1 H, one of 7-H), 0.87 (d, *J* = 6.2 Hz, 3 H, 4-Me) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 168.7, 162.8, 85.7, 82.7, 73.3, 62.9, 33.3, 18.0 ppm. $C_8H_8Cl_3NO_3$ (272.51): calcd. C 35.26, H 2.96, N 5.14; found C 34.97, H 3.09, N 5.08.

(3*S*,4*S*,5*R*)-3-Benzamido-5-hydroxy-4-hexanolide (15): To a solution of **4** (280.2 mg, 1.03 mmol) in EtOH (19 mL) was added 3 M HCl (19 mL, 57 mmol), and the reaction mixture was heated (bath temp 75 °C) for 12 h. The reaction mixture was concentrated in vacuo. To the suspension of the residue in acetone (6.5 mL) and saturated aqueous $NaHCO_3$ (16 mL) was added dropwise benzoyl chloride (400 µL, 3.45 mmol), and the mixture was stirred for 4.5 h at room temperature. The mixture was acidified with 2 M HCl and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 1:2) to give **15** (207.7 mg, 81%) as a colorless solid. An analytical sample (colorless powder) was obtained by recrystallization from EtOAc/hexane; m.p. 153.0–154.0 °C (ref.[24a] m.p. 152–154 °C; ref.[24b] m.p. 149 °C). $[\alpha]_D^{28.7}$ = –41.4 (*c* = 1.12, EtOH) (ref.[24b] $[\alpha]_D^{20}$ = +42 (*c* = 0.41, EtOH). IR (KBr): $\tilde{\nu}$ = 3334, 2912, 1757, 1724, 1645, 1545, 1319, 1186, 1144, 1007, 714, 690 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.83–7.74 (m, 2 H, Ar), 7.60–7.41 (m, 3 H, Ar), 6.62 (br. d, *J* = 7.1 Hz, 1 H, NH), 4.84 (dddd, *J* = 3.8, 4.6, 7.2, 9.0 Hz, 1 H, 3-H), 4.30 (dd, *J* = 3.7, 4.8 Hz, 1 H, 4-H), 4.07 (ddq, *J* = 4.6, 4.6, 6.4 Hz, 1 H, 5-H), 3.17 (dd, *J* = 9.1, 18.3 Hz, 1 H, one of 2-H), 2.76 (d, *J* = 4.3 Hz, 1 H, OH), 2.61 (d, *J* = 4.7, 18.4 Hz, 1 H, one of 2-H), 1.38 (d, *J* = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 174.8, 167.7, 133.0, 132.3, 128.8, 127.0, 89.2, 68.2, 47.9, 35.5, 19.1 ppm. $C_{13}H_{15}NO_4$ (249.26): calcd. C 62.64, H 6.07, N 5.62; found C 62.44, H 5.93, N 5.59.

3-Benzamido-2,3,6-trideoxy-D-*ribo*-hexofuranose (*N*-Bz-D-Ristosamine) (2): To a solution of **15** (63.7 mg, 0.256 mmol) in dry THF (10 mL) was added dropwise DIBAL (0.98 M in hexane, 1.30 mL, 1.28 mmol) under an argon atmosphere at –60 °C, and the reaction

mixture was stirred for 1 h at –60 to –50 °C. The reaction was quenched by the dropwise addition of acetone/MeOH (1:1, 2 mL), and the mixture was warmed gradually to room temperature with stirring for ca. 1 h. The mixture was filtered through a pad of Celite. The filter cake was washed with acetone/MeOH (1:1), and then the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 1:5 to EtOAc) to **2** (37.6 mg, 59%). An analytical sample (colorless needle) was obtained by recrystallization from acetone; m.p. 136.8–137.8 °C {ref.[24a] m.p. 132–134 °C; ref.[24b] m.p. 131–133 °C}. $[\alpha]_D^{23.0}$ = –11.3 (after 10 min), + 25.8° (after 4 d, constant) (*c* = 0.257, EtOH) {ref.[24a] $[\alpha]_D^{23.0}$ = –10 (after 10 min), –24° (after 3 h, constant) (*c* = 0.20, EtOH); ref.[24b] $[\alpha]_D^{25}$ = +28.0 (*c* = 0.23, EtOH)}. IR (KBr): $\tilde{\nu}$ = 3354, 3280, 2974, 1635, 1579, 1541, 1489, 1448, 1406, 1375, 1294, 1074, 1020, 964, 696 cm^{-1}. ^1H and ^{13}C NMR spectra of this material were identical with those reported in the literature.[21] $C_{13}H_{17}NO_4$ (251.28): calcd. C 62.14, H 6.82, N 5.57; found C 61.81, H 6.85, N 5.49.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra.

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