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The first enantioselective synthesis of imino-deoxydigitoxose and protected imino-digitoxose by using L-threonine aldolase-catalyzed aldol condensation

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ABSTRACT

The first enantioselective synthesis of protected imino-digitoxose (−)-**16** was attained starting with a synthetic intermediate of polyoxin C prepared by the L-threonine aldolase-catalyzed aldol condensation of (2*S*,3*S*)-2,3-*O*-isopropyriden-4-penten-1-al **8** and glycine. The strategy took advantage of an intramolecular nucleophilic attack by a Cbz-protected amino group on the hemiacetal carbon, a side reaction in the synthesis of natural products, for the formation of the piperidine ring of the imino-sugar. Imino-deoxydigitoxose (+)-**18** was also synthesized from (−)-**16** by reduction and acid hydrolysis.

1. Introduction

Digitoxin **1**, a cardiac active glycoside isolated from *Digitalis purpurea* L. (Scrophraliaceae), acts as a potent inhibitor of Na^+/K^+-ATPase, and has widely been prescribed to patients with congestive heart failure and cardiac arrhythmia.[1] Recently, Repke and his colleagues suggested that digitoxin **1** binds to a cavity formed by two extracellular-exposed peptide moieties of the catalytic α subunit, which penetrates the cell membrane eight times, in the diprotomeric Na^+/K^+-ATPase.[2] Digitoxin **1** is composed of a featured steroid carrying a γ-lactone, digitoxigenin **2**,[3] and the trisaccharide of digitoxose **3** (Fig. 1).[4,5] Although it has no resemblance to ATP, the substrate of Na^+/K^+-ATPase, digitoxin **1** behaved as a non-competitive and heterotropically acting allosteric inhibitor, its activity leading to increased intracellular calcium ion concentrations and strengthened heart contractions. Interestingly, studies on the biotransformation of **1** found that the trisaccharide chain prolongs its half-life time in animal bodies.[6,7]

2. Results and discussion

Therefore, digitoxin **1** should be modified by replacing one of three digitoxoses **3** in the trisaccharide moiety with artificial sugar analogues to design novel active glycosides having a longer half-life time in vivo. Imino-digitoxose **4** seemed to be the most promising analogue of **3** in terms of a prolonged half-life time among a huge number of analogues imaginable because imino-sugars, for example, nojirimycin and galactostatin, and imino-sugar-containing oligosaccharides, such as acarbose[8] and validamycin,[9] could markedly inhibit glycosidic bond-cleaving enzymes.[10] However, the synthesis of imino-digitoxose **4** has not been reported to date.

Recently, we found that the key intermediate **5** in our chemoenzymatic synthesis of polyoxin C[11] could be converted to **4** via the Cbz-protected imino-sugar **6** as shown in Eq. 1 (Scheme 1). Dondoni and his colleagues encountered a similar reaction in the total synthesis of polyoxin J (Scheme 1, Eq. 2), but did not scrutinize the reaction any further.[12]

Thus, we attempted the synthesis of **4** starting from **9a**, which is produced by L-threonine aldolase, having so far been developed by ourselves toward biologically active glycoconjugates (Scheme 2).

First, the protected amino acid **9b**,[11] produced during the synthesis of polyoxin C by the L-threonine aldolase-catalyzed reaction of (2*S*,3*S*)-2,3-*O*-isopropyriden-4-penten-1-al **8** and glycine followed by the protection of amino and carboxyl groups (three steps, overall yield, 46%), was reduced with lithium borohydride to afford the primary alcohol **10**. The primary hydroxyl group of **10** was converted to tosylate **11** by treatment with *p*-toluenesulfonyl chloride. Herein, the remaining hydroxyl group and the Cbz-protected amino group were further protected with an acetonide group by a conventional method to provide **12**, since direct reduction of the tosylate group of **11** into a methyl group with hydride reagents was retarded by the hetero atom-binding protons, that is, CbzN*H* and O*H*. In our first attempts, treatment of **12** with lithium triethylborohydride only resulted in the decomposition (Table 1, entries 1 and 2), and reaction with sodium borohydride provided the desired compound **13** in low to moderate yields (Table 1, entries 3 and 4). The reduction with lithium borohydride in dimethyl sulfoxide at 100 °C, however, gave the product **13** in satisfactory yield (Table 1, entries 5 and 6).

Selective deprotection of acetonide group in **13** with Dowex resin (H^+-form) followed by acetylation by a conventional method afforded triacetate **14**. Next, deoxygenation at the allylic position

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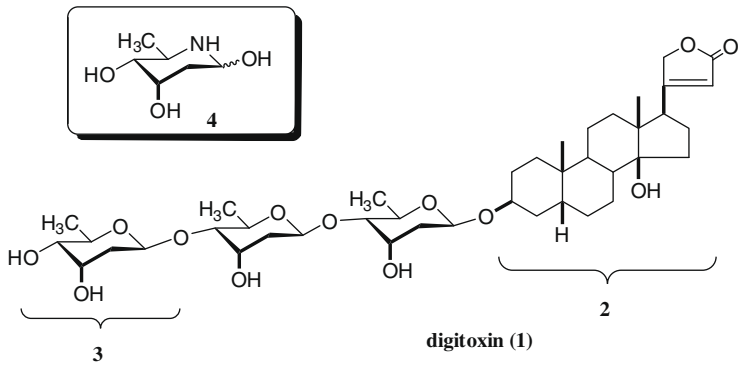
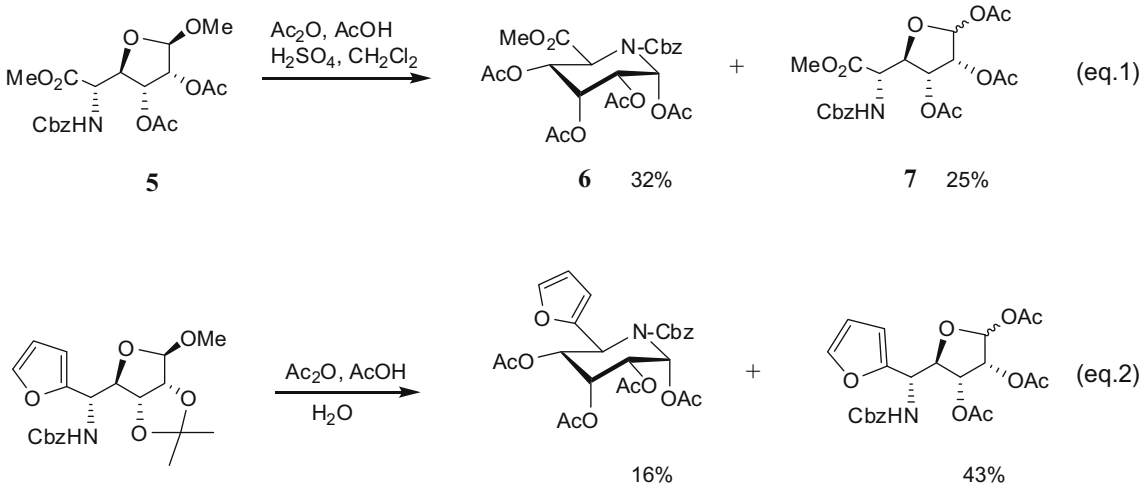
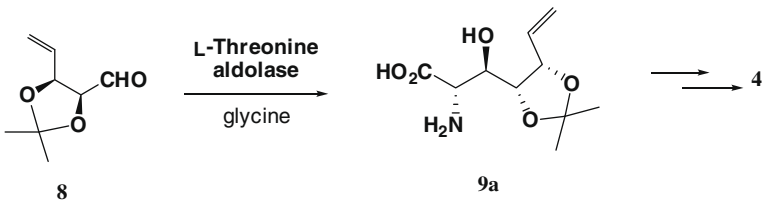


Figure 1. The structure of digitoxin **1**.

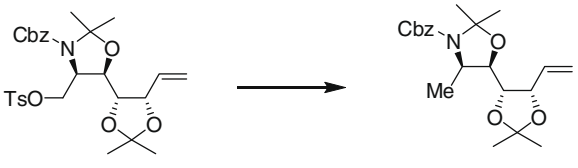


Scheme 1. Conversion of **5** into the derivative of imino-pyranose **6**.



Scheme 2. Synthetic strategy to imino-digitoxose **4**.

Table 1
Reducing conditions for the conversion of **12** to **13**



Entry	Reagents	Eq.	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	$LiEt_3BH$	6.0	THF	4	50	[a]
2	$LiEt_3BH$	6.0	DMSO	15	100	[a]
3	$NaBH_4$	2.0	DMSO	15	150	28
4	$NaBH_4$	4.0	DMSO	15	120	50
5	$LiBH_4$	6.0	DMSO	16	100	61
6	$LiBH_4$	6.0 + 2.0	DMSO	15 + 1	100	67

[a] Too many compounds were produced whilst no starting material **12** remained.

of **14** with Pd (0) in the presence of ammonium formate yielded **15**.[13] Ozonolysis of **15** provided the annulated imino-hemiacetal (−)-**16**, a protected form of imino-digitoxose **4**, in high yield via an intramolecular nucleophilic attack by the Cbz-protecting amino group on the aldehyde carbonyl group. Evans and his colleagues observed similar reactivity of the Cbz-protected amino group during the synthesis of L-calliperitose.[14] The reactivity of the Cbz-protected amino group explains why the reaction shown in Scheme 1 afforded the imino-sugar derivative **6** in only low yield, accompanied by the furanose derivative **7** (Scheme 1). Namely, acetic acid and a small amount of contaminated water would have reacted with the oxonium intermediate generated from **5** in the presence of strong acid to afford the hemiacetal acetate **7** and hemiacetal, respectively. While the former was stable and remained intact under the reaction conditions, the latter was reannelated to yield the imino-sugar derivative **6** as a result of a nucleophilic attack by the Cbz-protected amino group on the hemiacetal carbon.

Finally, the reduction of (−)-**16** with triethylsilyl hydride in the presence of boron trifluoride etherate complex and successive acid hydrolysis yielded imino-deoxydigitoxose (+)-**18** via a fully protected imino-deoxydigitoxose (−)-**17** (Scheme 3).

3. Conclusion

In conclusion, we have succeeded in the first enantioselective synthesis of a protected imino-digitoxose (−)-**16** from the key synthetic intermediate (+)-**9a**, which was prepared by taking advantage of the L-threonine aldolase-catalyzed reaction. Our method should advance the study of digitoxin **1** and related natural cardiotonic products, such as ouabain and bufalin.

Attempts to synthesize novel analogues of digitoxin **1**, which incorporate imino-digitoxose **4** instead of one of three digitoxoses **3**, and investigations of their biological activities are underway.

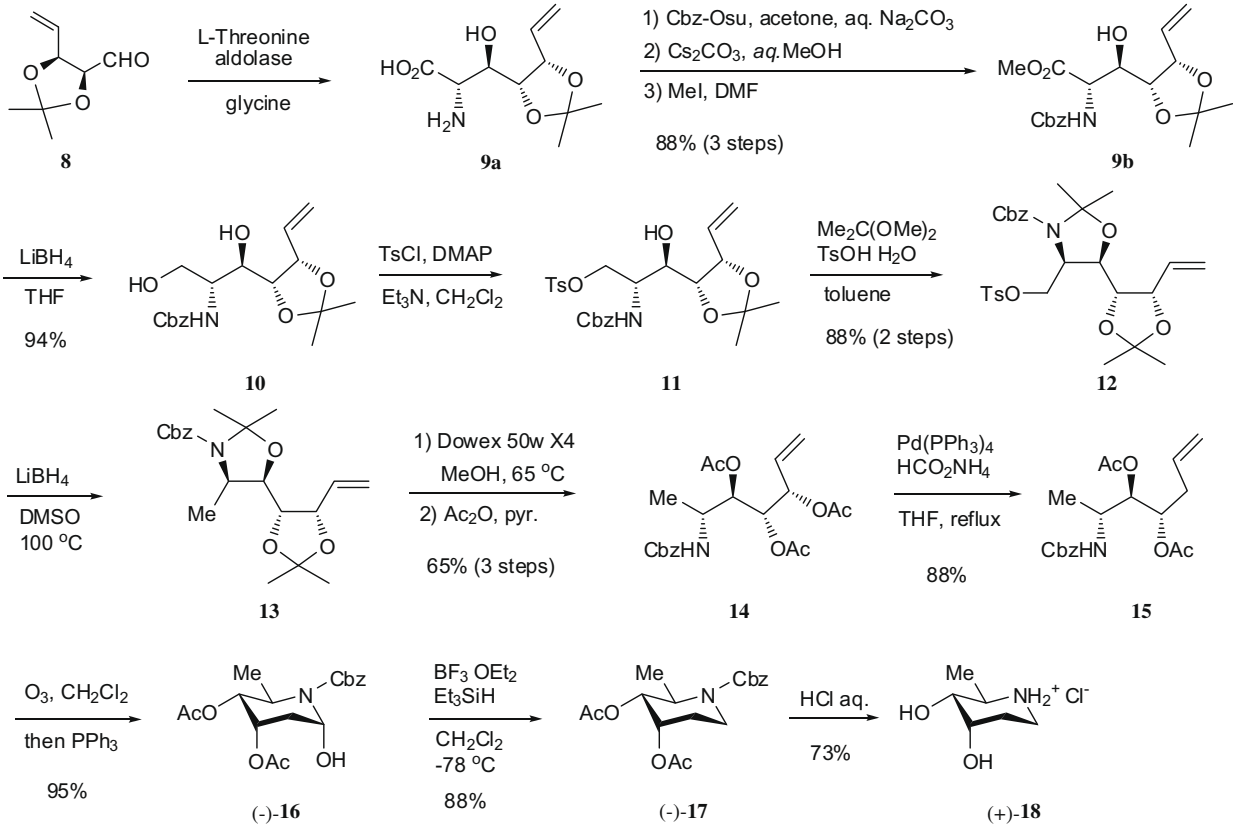
4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer. ^{1}H NMR spectra were obtained on a JEOL JNM-AL400 spectrometer with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. If the sample was not soluble in $CDCl_3$, D_2O was used as a solvent and HOD as an internal standard. ^{13}C NMR spectra were obtained on a JEOL JNM-AL400 spectrometer with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Unless the sample was soluble in $CDCl_3$, D_2O was used as a solvent and CH_3CN as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC–mate mass spectrometer. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Kieselgel (70–230 mesh, Merk Art. 07734) was used for open column chromatography. Kieselgel 60 F-254 plates (Merck) were used for thin layer chromatography (TLC). Preparative TLC (PTLC) was conducted with Kieselgel 60 F-254 plates (0.25 mm, Merck) or Silica gel 60 F-254 plates (0.5 mm, Merk). Unless the compound was pure enough, it was subjected to recycle HPLC (JAI LC-908) on a GPC column (JAIGEL 1H and 2H). If possible, diastereomeric mixtures were also separated by recycle HPLC (JAI LC-908) on a silica gel column (Kusano Si-10) after purification.

4.2. Methyl (2*S*,3*R*,4*S*,5*S*)-2-*N*-carboxybenzylamido-3-hydroxy-4,5-*O*-isopropyriden-6-hepten-1-ol 10

A solution of 2.0 M of lithium borohydride in tetrahydrofuran (21.9 mL, 43.8 mmol) was added to a solution of (+)-**9** (1.85 g, 4.87 mmol) in a mixed solvent of tetrahydrofuran (30.0 mL) and methanol (9.5 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. The mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 1:2) to afford **10** (1.61 g, 94%) as colorless needles. Mp 121–122 °C (hexane/ethyl acetate); $[\alpha]_D^{24} = +6.8$ (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz,$CDCl_3$): δ 1.37, 1.50 (each s, 3H), 2.77 (br dd, *J* = 8.4, 3.2 Hz, 1H, O*H*), 3.26 (br d, *J* = 6.4 Hz, 1H, O*H*), 3.78–3.86 (m, 2H), 3.96–4.04 (m, 2H), 4.13 (dd, *J* = 9.6, 6.0 Hz, 1H), 4.74 (t, *J* = 6.0 Hz, 1H), 5.12 (s, 2H, –*CH*$_2$Ph), 5.31 (d, *J* = 10.4 Hz, 1H, CH*H*=CH), 5.46 (d, *J* = 17.2 Hz, 1H, CH*H*=CH), 5.71 (brd, *J* = 6.4 Hz, 1H, N*H*), 6.01 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H, CH$_2$=C*H*), 7.37–7.31



Scheme 3. Synthesis of the protected form of imino-digitoxose (−)-**16** and imino-deoxydigitoxose (+)-**18**.

(m, 5H, –Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 27.8, 53.6, 62.6, 67.1, 72.7, 77.3, 78.8, 109.3, 118.4, 128.1(2C), 128.3, 128.6(2C), 133.5, 136.1, 157.1; IR ($CHCl_3$): 3435, 3028, 3018, 2991, 2939, 2412, 1716, 1602, 1506, 1456, 1429, 1375, 1319, 1261, 1244, 1228, 1213, 1201 cm^{-1}; MS FAB(+) *m/z*: 352 (M^++H); HRMS calcd for $C_{18}H_{26}NO_6$ (M^++H): 352.1760, found: 352.1755. Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.51; H, 7.24; N, 3.97.

4.3. (2*S*,3*R*,4*S*,5*S*)-2-*N*-Carboxybenzylamido-3-hydroxy-2,3/4,5-*O*,*N*-diisopropyriden-6-heptenyl 1-*O*-*p*-toluenesulfonylate 12

Triethylamine (86 μL), *p*-toluenesulfonyl chloride (58.7 mg, 0.31 mmol), and *N*,*N*-dimethyl-*p*-aminopyridine were added to a solution of **10** (43.3 mg, 0.123 mmol) in dichloromethane (3.0 mL), and the mixture was stirred for 14 h at room temperature. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 2:1) to afford **11** (78.7 mg) as a colorless oil. Next, without further purification, 2,2-dimethoxypropane (46 μL, 0.37 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate were added to a solution of **11** (78.7 mg) in toluene (3.0 mL), and the reaction mixture was stirred for 45 min at 50 °C and for another 20 min at 80 °C. The mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane: ethyl acetate = 5:1) to afford **12** (59.3 mg, 88% overall yield in two steps) as a colorless oil. $[\alpha]_D^{26} = -2.6$ (*c* 0.94, $CHCl_3$); ^{1}H NMR (400 MHz,$CDCl_3$, major conformer): δ 1.28, 1.41 (each s, 3H), 1.47 (s, 3H, –O–C(CH_3)$_2$–N–), 1.55 (s, 3H, –O–C(CH_3)$_2$–N–), 2.42 (s, 3H), 4.00 (dd, *J* = 9.8, 5.6 Hz, 1H), 4.08 (m, 1H), 4.17–4.24 (m, 2H), 4.28 (dd, *J* = 9.8, 4.4 Hz, 1H), 4.68 (t, *J* = 6.0 Hz, 1H), 4.90 (d, A part of AB, *J* = 12.0 Hz, 1H, –CH*H*Ph), 5.04 (d, B part of AB, *J* = 12.0 Hz, 1H, –C*H*HPh), 5.23 (dt, *J* = 10.8, 1.6 Hz, 1H, CH*H*=CH), 5.40 (dt, *J* = 17.2, 1.6 Hz, 1H, C*H*H=CH), 5.87 (ddd, *J* = 17.2, 10.8, 6.0 Hz, 1H, CH_2=C*H*), 7.24–7.38 (m, 7H), 7.72 (d, *J* = 8.0 Hz, 2H.); ^{13}C NMR (100 MHz, $CDCl_3$, maj. conf.): δ 21.6, 23.2, 25.1, 25.6, 27.6, 57.2, 66.5, 67.0, 73.3, 74.6, 78.3, 95.0, 109.2, 117.5, 127.9, 128.1(2C), 128.2(2C), 128.5(2C), 129.8(2C), 132.6, 132.8, 136.0, 144.8, 151.7; IR ($CHCl_3$): 3022, 3010, 1705, 1599, 1410, 1381, 1352, 1236, 1222 cm^{-1}; MS FAB(+) *m/z*: 568 (M^++Na); HRMS calcd for $C_{28}H_{35}NO_8SNa$ (M^++Na): 568.1981, found: 568.1984.

4.4. (2*S*,3*R*,4*S*,5*S*)-2-*N*-Carboxybenzylamido-3,4,5-triacetoxy-6-heptene 14

A solution of 2.0 M of lithium borohydride in tetrahydrofuran (0.12 mL, 0.24 mmol) was added to a solution of **12** (22.0 mg, 0.04 mmol) in dimethyl sulfoxide (2.0 mL), and the mixture was stirred for 17 h at 100 °C. After another solution of lithium borohydride in tetrahydrofuran (0.06 mL, 0.12 mmol) was added and stirred for another 1 h at the same temperature as above, the reaction mixture was poured into ice water and extracted with diethyl ether. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and condensed in vacuo. The residue was purified by preparative silica gel thin layer chromatography (*n*-hexane/ethyl acetate = 2:1) to afford **13** (10.2 mg, 67%). Next, Dowex 50 W (X4, H^+-form) was added to a solution of **13** (537 mg, 1.43 mmol) in methanol (20.0 mL), and the mixture was stirred for 14 h at 65 °C. The reaction mixture was filtered, and the filtrate was condensed in vacuo. The residue was used for further reactions without any purification. Pyridine (5.0 mL), acetic anhydride (2.5 mL), and a catalytic amount of *N*,*N*-dimethyl-*p*-aminopyridine were added to a solution of a partial moiety of the residue (420 mg), and the mixture was stirred at room temperature for 25 min. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with a saturated solution of sodium chloride, dried over sodium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 2:1) to afford **14** (587 mg, 97%) as a colorless oil. $[\alpha]_D^{27} = +22.6$ (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz,$CDCl_3$): δ 1.12 (d, *J* = 7.2 Hz, 3H), 2.07, 2.08, 2.10 (each s, 3H), 4.05 (m, 1H), 5.05–5.13 (m, 2H), 5.08, 5.12 (each d, AB type, *J* = 12.0 Hz, 1H, CH_2-Ph), 5.25 (dd, *J* = 7.6, 3.8 Hz, 1H), 5.30 (d, *J* = 16.8 Hz, 1H, CH*H*=CH-), 5.31 (d, *J* = 11.0 Hz, 1H, CH*H*=CH-), 5.43 (dd, *J* = 6.8, 3.8 Hz, 1H, CH*H*=CH), 5.84 (ddd, *J* = 16.8, 11.0, 6.8 Hz, 1H, C*H*=CH_2), 7.29–7.38 (m, 5H, –Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 20.8(2C), 20.9, 47.1, 66.7, 71.3, 73.1, 73.2, 120, 128.1(3C), 128.5(2C), 131.0, 136.4, 155.4, 169.9, 170.0, 170.1; IR ($CHCl_3$): 3026, 3014, 1744, 1602, 1510, 1456, 1429, 1371, 1240 cm^{-1}; MS FAB(+) *m/z*: 444 (M^++Na); HRMS calcd for $C_{21}H_{27}NO_8Na$ (M^++Na): 444.1634, found: 444.1638.

4.5. (2*S*,3*R*,4*S*,5*S*)-2-*N*-Carboxybenzylamido-3,4-diacetoxy-6-heptene 15

Ammonium formate (7.4 mg, 0.12 mmol) and tetrakis(triphenylphosphine) palladium (20.4 mg, 0.02 mmol) were added to a solution of **14** (24.8 mg, 0.059 mmol) in tetrahydrofuran (2.0 mL), and the mixture was stirred for 15 h at reflux. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 2:1) to afford **15** (105 mg, 88%) as a pale yellow oil. $[\alpha]_D^{25} = +24.0$ (*c* 1.17, $CHCl_3$); ^{1}H NMR (400 MHz,$CDCl_3$): δ 1.14 (d, *J* = 6.8 Hz, 3H), 2.04, 2.09 (each s, 3H), 2.31 (m, 1H), 2.47 (m, 1H), 4.04 (m, 1H), 4.96 (br d, 8.8 Hz, 1H, –NH), 5.00–5.14 (m, 6H), 5.70 (ddt, *J* = 16.8, 10.0, 7.0 Hz, 1H, –C*H*=CH_2) 7.29–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 20.8, 20.9, 34.4, 46.7, 66.8, 71.3, 75.5, 118.2, 128.0(2C), 128.1, 128.5(2C), 132.9, 136.3, 155.5, 170.4(2C); IR ($CHCl_3$): 3431, 3039, 3022, 3012, 1732, 1645, 1603, 1510, 1456, 1435, 1371, 1238, 1228, 1215, 1207 cm^{-1}; MS FAB(+) *m/z*: 386 (M^++Na); HRMS calcd for $C_{19}H_{25}NO_6Na$ (M^++Na): 386.1580, found: 386.1576.

4.6. 5-*N*-Carboxybenzylamido-5,6-dideoxy-3,4-diacetoxy-D-*allo*-iminopyranoside (−)-16

Ozone gas was bubbled into a solution of compound **15** (109 mg, 0.30 mmol) in dichloromethane (35 ml) at −78 °C until a pale purple color was maintained in the solution. After the excess ozone was removed from the reaction mixture by bubbling nitrogen gas, triphenylphosphine (158 mg, 0.60 mmol) was added, and the mixture was stirred overnight at room temperature. The organic solvent was evaporated off, and the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 2:1) to afford (−)-**16** (105 mg, 95%) as a colorless oil. $[\alpha]_D^{21} = -26.4$ (*c* 1.24, $CHCl_3$); ^{1}H NMR (400 MHz,$CDCl_3$): δ 1.42 (d, *J* = 7.2 Hz, 3H), 2.02, 2.06 (each s, 3H), 1.97–2.04 (br, 1H), 2.15 (td, *J* = 12.8, 4.4 Hz, 1H), 3.15 (br, 1H, O*H*), 4.34 (br, 1H), 5.12–5.26 (m, 3H), 5.53 (ddd, *J* = 12.8, 4.8, 2.8 Hz, 1H), 5.99 (br s, 1H), 7.29–7.39 (m, 5H, –Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 20.9, 21.0, 30.1, 52.5, 63.9, 67.7, 70.2, 76.3, 127.9, 128.3(2C), 128.6(2C), 136.0, 152.3, 170.2(2C); IR ($CHCl_3$): 3678, 3595, 3017, 1740, 1693, 1602, 1499, 1417, 1369, 1334, 1242, 1220, 1203 cm^{-1}; MS FAB(+) *m/z*: 388

(M^++Na); HRMS calcd for $C_{18}H_{23}NO_7Na$ (M^++Na): 388.1372, found *m/z*: 388.1378.

4.7. 5-*N*-Carboxybenzylamido-1,5,6-trideoxy-3,4-diacetoxy-D-*allo*-iminopyranoside (−)-17

Triethylsilane (0.033 ml, 0.21 mmol) and boron trifluoride etherate complex (0.027 mL, 0.23 mmol) were added to a solution of (−)-**16** (19.0 mg, 0.052 mmol) in dichloromethane (2.0 mL), and the mixture was stirred at −78 °C for 45 min. The reaction was quenched by adding a saturated aqueous solution of sodium bicarbonate, and the mixture was diluted with distilled water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and condensed in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 2:1) to afford (−)-**17** (16.0 mg, 88%) as a colorless oil. $[\alpha]_D^{25} = -56.9$ (*c* 0.690, $CHCl_3$); ^{1}H NMR (400 MHz,$CDCl_3$): δ 1.67 (d, *J* = 7.2 Hz, 3H), 1.73 (br d, *J* = 11.2 Hz, 1H), 1.92–2.02 (m, 1H), 1.98, 2.01 (each s, 3H), 3.06 (td, *J* = 14.0, 2.8 Hz, 1H), 4.25 (br, 1H), 4.57 (br, 1H), 5.04 (br s, 1H), 5.10–5.19 (m, 3H), 7.30–7.38 (m, 5H, –Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 20.8, 21.0, 25.5, 37.4, 51.3, 67.2, 67.4, 70.6, 127.8(2C), 128.0, 128.5(2C), 136.6, 155.5, 170.2(2C); IR ($CHCl_3$): 3030, 3017, 2360, 1737, 1693, 1602, 1497, 1429, 1365, 1332, 1311, 1251, 1236, 1213, 1207 cm^{-1}; MS FAB(+) *m/z*: 372 (M^++Na); HRMS calcd for $C_{18}H_{23}NO_6Na$ (M^++Na): 372.1423, found: 372.1430.

4.8. 5-*N*-Carboxybenzylamido-1,5,6-trideoxy-3,4-dihydro-D-*allo*-iminopyranoside hydrochloride (+)-18

A solution of (−)-**17** (76.6 mg, 0.22 mmol) in 5 M hydrochloric acid (5.0 mL) was stirred for 2 h at reflux. The reaction mixture was condensed in vacuo and further lyophilized after a small amount of distilled water was added. The residue was purified by recrystallization from a mixed solvent of *n*-hexane and ethanol to afford **(+)-18** (26.8 mg, 73%) as colorless needles. Mp 192–193 °C (*n*-hexane/ethanol); $[\alpha]_D^{25} = +46.75$ (*c* 0.86, MeOH); ^{1}H NMR (400 MHz, D_2O): δ 1.38 (d, *J* = 6.8 Hz, 3H), 1.91–2.00 (m, 1H), 2.02–2.09 (dq, *J* = 15.2, 4.8 Hz, 1H), 3.22 (m, 2H), 3.43 (dq, *J* = 9.6, 6.8 Hz, 1H), 3.64 (dd, *J* = 9.6, 2.5 Hz, 1H), 4.14 (dt, *J* = 4.8, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, D_2O): δ 14.9, 27.7, 38.6, 51.7, 65.8, 71.3; IR (KBr): 3863, 3841, 3822, 3805, 3786, 3737, 3710, 3670, 3645, 3627, 3614, 3600, 3400, 3251, 3209, 1614, 1431, 1207 cm^{-1}; MS FAB(+): 132 (M^++H); HRMS calcd for $C_6H_{14}NO_2$ (M^++H): 132.1025, found: 132.1021: Anal. Calcd for $C_6H_{14}ClNO_2$: C, 42.99; H, 8.42; N, 8.36. Found: C, 42.89; H, 8.27; N, 8.14.

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