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Synthesis of Urea-Tethered Disaccharides in Water

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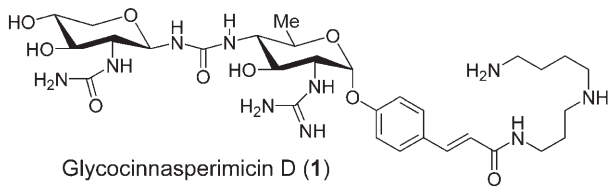
Abstract: A new method for the synthesis of urea-linked disaccharides in aqueous media has been developed. The key feature of our approach is two strained Steyermark-type gluco- and galactopyranosyl oxazolidinones. Each oxazolidinone is attached to a pyranose ring in a di-equatorial *trans*-annulation framework. Reaction of these oxazolidinones with 4-aminohexopyranose in water proceeded smoothly to afford the urea-tethered cellobiose and lactose analogues. The galactose-type oxazolidinone proved to be more reactive than the glucose-type, which is explained by the presence of an axial hydroxy group at C4 in the former.

Keywords: carbohydrates · disaccharides · glycosylation · oxazolidinone · urea

Introduction

Over the last few years, we carried out synthetic studies of the amino sugar antibiotic glycocinnasperimicin D (**1**), which was isolated from the fermentation broth of the *Nocardia* strain by Umezawa and co-workers.[1] Its unique structural feature is found by the urea glycoside linkage, which connects two unusual amino sugars, 2-ureidopentose and 2-guanidino-4-ureido-6-deoxy-α-D-glucopyranose.



Glycocinnasperimicin D (**1**)

While exploring the synthesis of this target molecule, we established a new method for the stereoselective synthesis of α- and β-urea glycosides, which involves the reaction of glycopyranosyl isocyanates with amines.[2] The heart of our method is the oxidation of glycopyranosyl isonitriles to access the highly reactive glycopyranosyl isocyanates. Currently, our method successfully bore fruit in the first total synthesis of **1** (Scheme 1).[3] Oxidation of pyranosyl isonitrile **2** with pyridine *N*-oxide in the presence of a catalytic amount of iodine gave rise to the glycopyranosyl isocyanate **3**, which was immediately treated in situ with amino sugar **4** to furnish the urea-linked disaccharide **5** in 85% yield. Importantly, the reaction was carried out in the presence of a water scavenger (MS3A = 3-Å molecular sieves) with organic solvent (CH_3CN) to avoid the hydrolysis of **3**. In parallel with our endeavors to synthesize the natural product, we also explored the development of a biomimetic approach for the synthesis of urea-linked disaccharides. The word "biomimetic" herein means that construction of the urea glycosyl linkage can be performed by using unprotected sugars in water without enzymes.

In 1962, Steyermark reported the reaction of β-D-glucopyranosylamine **6** with phosgene to synthesize the known *N*,*N*′-di-β,β-D-glucopyranosyl urea **7** (Scheme 2); however, only cyclic carbamate **8** was isolated in poor yields (6–30%).[4] Interestingly, oxazolidinone **8** showed anomalous reactivity: acetylation of the nitrogen atom occurred under mild conditions (Ac_2O, pyridine, room temperature) to afford tetraacetate **9**. This surprising reactivity is in sharp contrast with that of the mannose-type compound (Scheme 3), that is, acetylation of **10** (Ac_2O, pyridine, room

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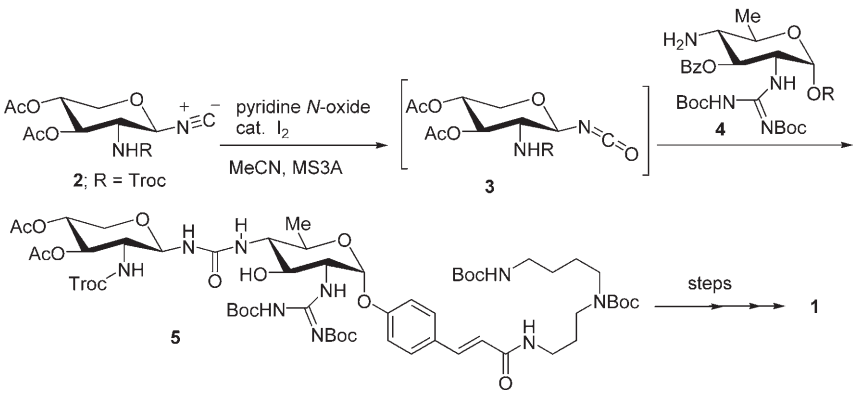
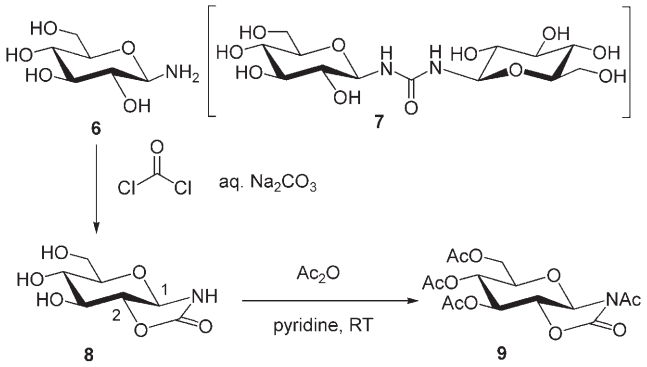
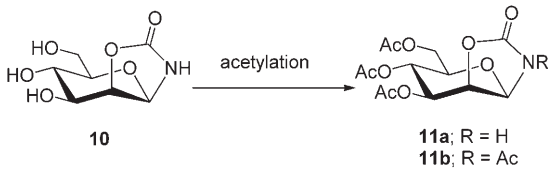


Scheme 1. Total synthesis of glycocinnasperimicin D (**1**). Boc = *tert*-butoxycarbonyl, Bz = benzoyl, Troc = 2,2,2-trichloroethoxycarbonyl.



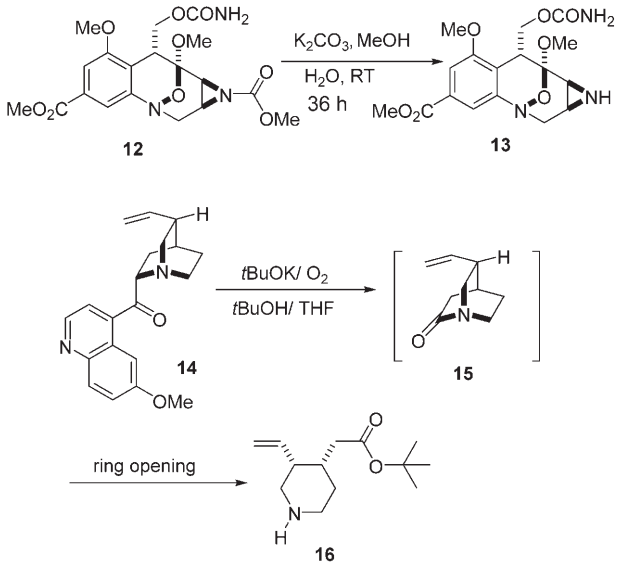
Scheme 2. Unexpected results from the reaction of β-D-glucopyranosylamine **6** with phosgene.[4]



Scheme 3. Acetylation of mannose-type oxazolidinone **10**.[5]

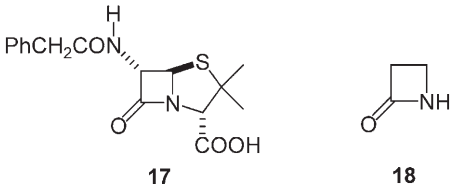
temperature) produced triacetate **11a**, whereas *N*-acetylation of the oxazolidinone in **10** took place under more-forcing conditions (Ac_2O, AcONa, reflux) to afford tetraacetate **11b**.[5] These experimental results clearly indicate that lone-pair electrons on nitrogen in **8** did not conjugate with the carbonyl group owing to its exceptional structural motif. In fact, the twisted structure of **8** was suggested by Pinter and co-workers, who determined the correct stereochemistry of **8** at the anomeric position based on the large coupling constant between 1-H and 2-H ($J_{1\text{-H},2\text{-H}} = 9.2$ Hz).[6]

It is well-known that carbonyl groups attached to nitrogen have increased kinetic reactivity towards nucleophilic attack/hydrolysis when delocalization of the lone-pair electrons on nitrogen into the carbonyl group is disturbed. For example, McClure and Danishefsky observed that methyl carbamate **12** underwent smooth hydrolysis without affecting the methyl ester moiety to afford **13** (Scheme 4).[7] This facile hydrolysis of methyl carbamate may be explained by presuming that delocalization of the nitrogen lone-pair electrons increases the angle strain in the aziridine ring. On the other hand, Doering and Chanley found that, during degradation studies of quininone **14**, the amide carbonyl group in **15** behaves chemically as an acylating agent to give the *tert*-butyl ester **16**.[8] In this case, Wood-



Scheme 4. Representative examples of strained carbamates and amides.

ward rationalized that the bicyclic structure in **15** prevented overlap of the lone-pair electrons on the bridgehead nitrogen atom with the carbonyl group.[8] The most-prominent example of strained amides is the β-lactam antibiotic penicillin, which acylates a serine hydroxy group in the catalytic center of bacterial transpeptidase nicely in water. Imming et al. examined the kinetics and estimated that benzylpenicillin **17** was hydrolyzed approximately 3000 times faster than unsubstituted β-propiolactam **18**.[9] This remarkable difference in reactivity between **17** and **18** was attributed to the geometrical constraints brought about by the butterfly



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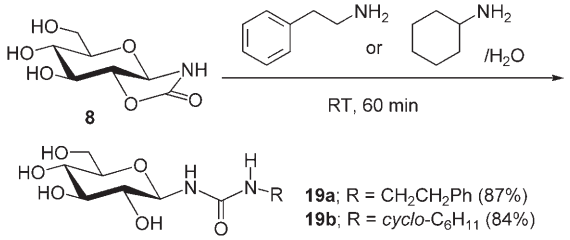
shape of **17**, which prevents the normal planar arrangement assumed necessary for delocalization of the nitrogen lone-pair electrons and reduces amide resonance. Penicillins, by fusing the β-lactam to the thiazolidine ring, increase their reactivity by approximately 3000-fold compared with monocyclic β-lactams.

By analogy of these unusual molecules (methyl carbamate **12**, bicyclic amides **15** and **17**), it was anticipated that the carbonyl group in the bicyclic oxazolidinone **8**, which is situated in the diequatorial *trans*-annulation framework, should exhibit facile ring-opening with nucleophiles. This was indeed found to be the case, and we established that Steyermark's oxazolidinone **8** derived from glucose reacted with



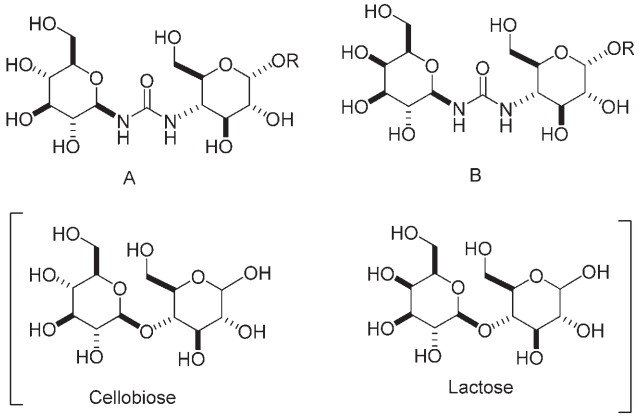
Scheme 5. Reaction of Steyermark oxazolidinone **8** with amines in water.

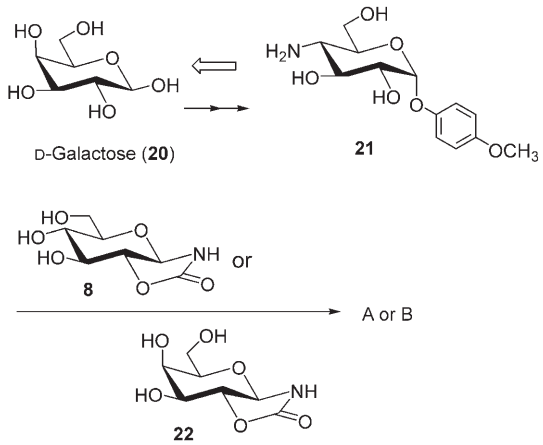
amines in water under mild conditions (room temperature, 60 min) to furnish the urea glucosides **19** in good yields (Scheme 5).[10]

Herein, we report further developments of our approach for the synthesis of urea-tethered pseudodisaccharides in aqueous media by utilizing Steyermark-type oxazolidinones.

Results and Discussion

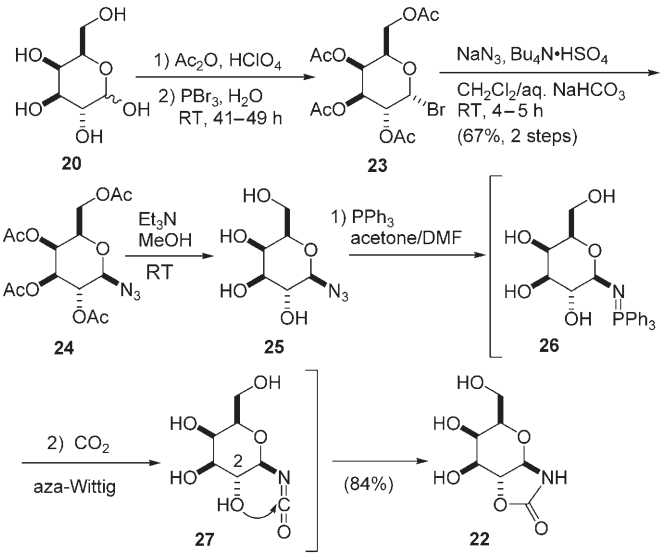
We planned to synthesize two urea-linked pseudodisaccharides A and B, which are mimics of cellobiose and lactose, respectively. These two urea-linked pseudodisaccharides were thought to be derived from the reaction of amino sugar **21** with Steyermark-type oxazolidinones **8** and **22**, respectively (Scheme 6). Amino sugar **21**, which bears a reactive site for the reaction with Steyermark-type oxazolidinones, was planned to be prepared from D-galactose (**20**). As a protecting group at the anomeric position of **21**, we selected the *p*-methoxyphenyl group, which was expected to facilitate purification with reversed-phase chromatography.





Scheme 6. Retrosynthetic analysis of the urea-linked disaccharides A and B.

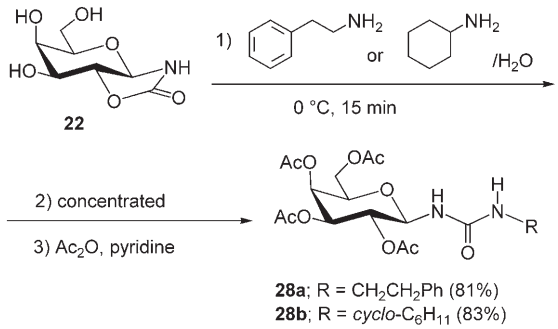
Initial studies focused on the preparation of **22** to investigate its unknown reactivity towards amines (Scheme 7). Acetylation of **20** followed by bromination was carried out in a simple one-pot process to afford α-bromo-tetra-*O*-acetylgalactopyranose **23**.[11] Displacement of bromide **23** with sodium azide under phase-transfer conditions (NaN_3, $Bu_4N{\cdot}HSO_4$, CH_2Cl_2/aq. $NaHCO_3$) gave galactopyranosyl azide **24** in 67% yield from D-galactose.[12] Removal of the acetyl groups in **24** (Et_3N, MeOH) followed by the Staudinger reaction of **25** with triphenylphosphine in a mixture of acetone and DMF (3:1) provided phosphinimine **26**.[13] Subsequent treatment of **26** with carbon dioxide furnished **22** in



Scheme 7. Synthesis of galactose-type oxazolidinone **22**. DMF = *N*,*N*-dimethylformamide.

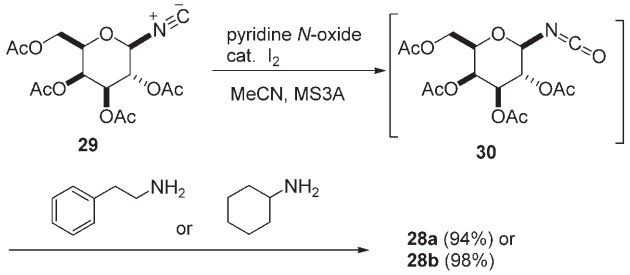
84% yield from **25**. The mechanism of this reaction sequence may involve the aza-Wittig reaction of **26** with carbon dioxide to furnish isocyanate **27**, which spontaneously undergoes cyclization by intramolecular attack of the 2-OH group on the neighboring isocyanate group to result in the product **22**.[14]

The reaction of **22** with amines was then examined (Scheme 8). To our delight, **22** underwent ring opening with 2-phenylethylamine more rapidly than **8** derived from glucose. In fact, the reaction was completed at 0°C within 15 min, and concentration of the reaction mixture followed by acetylation gave urea galactoside **28a** in 81% yield. Cyclohexylamine, a model compound of amino sugar **21**, also reacted smoothly with **22** to afford the urea galactoside **28b** in good yield (83% after acetylation). The higher reactivity of galactose-type compound **22** compared with glucose-type **8** may be explained by the presence of the axial hydroxy group at C4, which could destabilize the ground state of **22**.



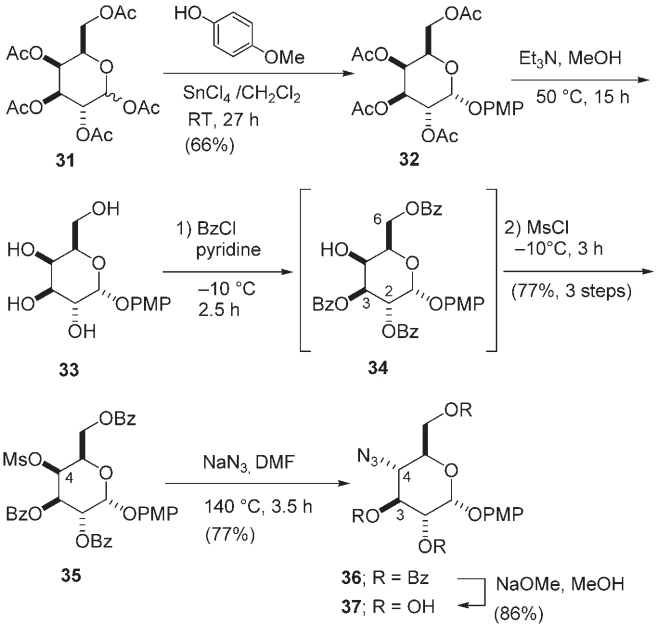
Scheme 8. Reaction of galactose-type oxazolidinone **22** with amines in water.

Authentic samples of **28** were prepared by oxidation of isonitrile **29** followed by reaction of the resultant galactopyranosyl isocyanate **30** with amines in organic solvent under anhydrous conditions (CH_3CN, MS3A) to yield **28a** and **28b** (Scheme 9), which proved to be identical to those prepared from **22**.[15]



Scheme 9. Synthesis of urea galactosides **28** from isonitrile **29**.

The synthesis of 4-aminohexopyranose **21** began with Lewis acid catalyzed glycosylation of *p*-methoxyphenol with pentaacetyl-D-galactose **31** under thermodynamically controlled conditions ($SnCl_4$, CH_2Cl_2, room temperature, 27 h) to furnish *p*-methoxyphenyl-α-galactoside **32** in 66% yield after recrystallization (Scheme 10).[16] Methanolysis of the acetyl groups in **32** (Et_3N, MeOH) gave the tetraol **33**, which was further transformed into **35** by selective benzoylation of three hydroxy groups at C2, C3, and C6 (BzCl, pyridine, −10°C) followed by mesylation of the hydroxy group at C4 (subsequent addition of MsCl, −10°C) in a one-pot process; **35** was obtained in 77% yield from **32**.[17] Nucleophilic S_N2 displacement of mesylate **35** with sodium azide in DMF proceeded smoothly (140°C, 3.5 h) to afford the azide **36** in 77% yield. ^1H NMR spectroscopic analysis of **36** showed a large vicinal coupling constant of 10 Hz between 3-H and 4-H ($J_{3\text{-H},4\text{-H}}$), which indicates the inverted stereochemistry at C4. Finally, the three benzoyl groups in **36** were removed with sodium methoxide in methanol to furnish the triol **37**, which is a precursor of **21**.



Scheme 10. Synthesis of 4-azidohexopyranose **37** from pentaacetyl-D-galactose **31**. Ms = methanesulfonyl, PMP = *p*-methoxyphenyl.

The synthesis of urea-tethered pseudodisaccharides began with catalytic hydrogenation of azide **37** (Scheme 11). The resulting 4-aminohexopyranose **21** was subsequently dissolved in water and then treated with **8** at 40°C. Surprisingly, the reaction of **8** with **21** proceeded much more slowly than with the simple model compound, cyclohexylamine (Scheme 5), and a considerable amount of hydrolysis of **8** was observed. To solve this problem, stepwise addition of **8** (total 3.6 equiv) was carried out. After the consumption of **21** was checked by TLC, the resultant reaction mixture was subjected directly to reversed-phase chromatography to give the urea-tethered disaccharide **38** in 78% yield. In the case of galactose-type oxazolidinone **22**, we were delighted to find that urea glycosylation was completed after 12 h at 40°C by employing two equivalents of **22**, which reflected

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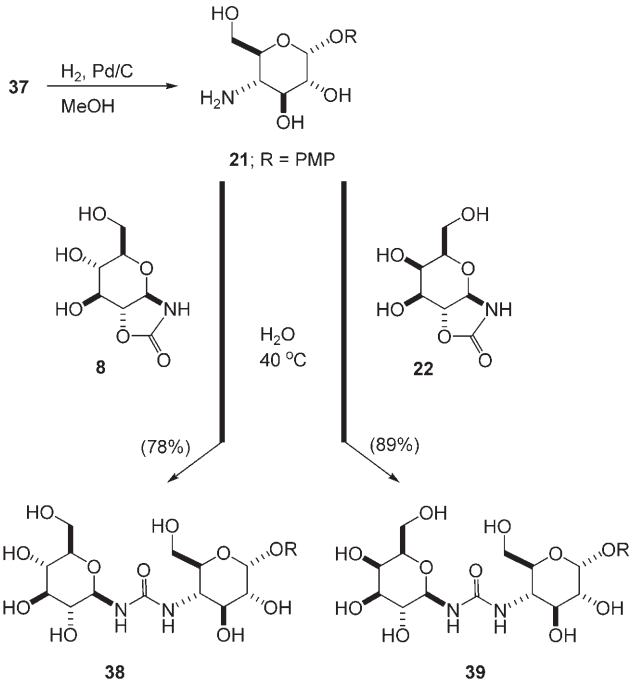


Scheme 11. Synthesis of urea-tethered pseudodisaccharides **38** and **39** in water.

the higher reactivity of galactose-type **22** relative to glucose-type **8**. As a result, urea-linked lactose analogue **39** was isolated in 89% yield.

Although most of the ^{1}H NMR signals of **38** and **39** measured in D_2O overlapped, ^{13}C NMR spectroscopic data for the urea carbonyl carbon nuclei ($\delta = 155.3$ ppm for **38** and **39**) and anomeric carbon nuclei linked to ureido nitrogen atoms ($\delta = 81.8$ ppm for **38** and 82.2 ppm for **39**) confirmed the β stereochemistry.[18] Acetylation of **38** and **39** (Ac_2O, pyridine) gave the heptaacetates **40** and **41**, which showed well-separated ^{1}H NMR spectra (Table 1).

Conclusions

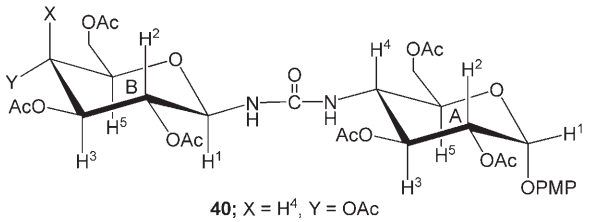
A new approach for the synthesis of urea-linked analogues of cellobiose and lactose has been established. The key feature in the present synthesis is the use of strained bicyclic oxazolidinones **8** and **22**. Although galactose-type **22** was much more reactive than glucose-type **8** owing to the presence of an axial hydroxy group at C4, it is fortunate that Steyermark-type oxazolidinone **22** is not so labile as to become hydrolyzed on its way toward the amines.

Experimental Section

Materials and Methods

Melting points were recorded on a micro-melting-point apparatus and are not corrected. Optical rotations were measured at the sodium D line with a cell of path length 100 mm and are reported as follows: $[\alpha]_D^T$, concentration (g per 100 mL), solvent. IR spectra are reported in cm^{-1}. ^{1}H NMR chemical shifts (δ) are reported in ppm relative to tetramethylsilane ($\delta = 0.00$ ppm in $CDCl_3$) and *t*BuOH ($\delta = 1.24$ ppm in D_2O) as internal standards. Coupling constants (J) are given in Hz. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad), coupling constant, integration. ^{13}C NMR chemical shifts (δ) are reported in ppm relative to $CDCl_3$ ($\delta = 77.0$ ppm) and *t*BuOH ($\delta = 30.29$ ppm in D_2O) as internal standards. Reactions that are sensitive to moisture or oxygen were run under argon atmosphere. Dichloromethane was dried over MS3A. Pyridine and triethylamine were stocked over anhydrous KOH. All other commercially available reagents were used as received.

Table 1. ^{1}H NMR chemical shifts (ppm), multiplicities, and coupling constants (Hz) of selected protons of **40** and **41**.[a]



40; X = H^4, Y = OAc

41; X = OAc, Y = H^4

	40		41	
	A	B	A	B
H^1	5.62, d	5.05, t	5.63, d	
	$J = 3.5$	$J = 9.5$	$J = 3.5$	
H^2	5.01, dd	4.86, t	5.02, dd	5.03, t
	$J = 10.0, 3.5$	$J = 9.5$	$J = 10.0, 3.5$	$J = 10.0$
H^3	5.49, t	5.29, t	5.50, t	5.12, dd
	$J = 10.0$	$J = 9.5$	$J = 10.0$	$J = 10.0, 3.5$
H^4	4.01, t	5.03, t		5.43, d
	$J = 10.0$	$J = 9.5$		$J = 3.5$
H^5	4.00, dt	3.80, ddd		
	$J = 10.0, 3.5$	$J = 9.5, 4.0, 2.0$		

[a] Measured in $CDCl_3$.

Syntheses

22: A solution of triphenylphosphine (1.54 g, 5.88 mmol) in acetone (5.0 mL) was added to a solution of **25** (1.09 g, 5.35 mmol) in acetone (15.0 mL) and DMF (5.0 mL) saturated with CO_2. CO_2 was bubbled through the solution for 3 h, and the mixture was then poured into CH_2Cl_2 (50 mL). The resulting precipitate was collected and washed with EtOAc (15 mL) to give **22** as a white amorphous solid (0.93 g, 84%). M.p.: 187 °C (decomp.); $[\alpha]_D^{19} = +70.9$ ($c = 1.00$, H_2O); IR (KBr): $\tilde{\nu}_{max} =$ 3400, 3263, 1769 cm^{-1}; ^{1}H NMR (D_2O, 400 MHz): $\delta = 3.81$ (dd, $J = 12.0$, 4.5 Hz, 1H), 3.86 (dd, $J = 12.0$, 7.0 Hz, 1H), 3.92 (ddd, $J = 7.0$, 4.5, 1.5 Hz, 1H), 4.10 (dd, $J = 3.5$, 1.5 Hz, 1H), 4.20 (dd, $J = 11.0$, 3.0 Hz, 1H), 4.26 (dd, $J = 11.0$, 8.5 Hz, 1H), 4.89 ppm (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (D_2O, 100 MHz): $\delta = 61.5$, 70.2, 70.5, 80.5, 81.5, 86.7, 160.7 ppm; elemental analysis: calcd (%) for $C_7H_{11}NO_6$: C 40.98, H 5.40, N 6.83; found: C 41.10, H 5.11, N 6.90.

28a: Phenylethylamine (28 μl, 0.20 mmol) was added to a solution of **22** (20 mg, 0.10 mmol) in water (1.0 mL) cooled to 0 °C. After being stirred at 0 °C for 15 min, the reaction mixture was concentrated under reduced pressure to afford urea glycoside, which was dissolved in pyridine (0.30 mL). Acetic anhydride (50 μl, 0.53 mmol) and 4-dimethylaminopyridine (DMAP; 12 mg, 0.10 mmol) were added, and the mixture was stirred at room temperature for 1 h. Concentration of the reaction mixture under reduced pressure gave the residue, which was purified by silica-gel chromatography (EtOAc/hexane = 1:1) to give **28a** (40 mg, 81%) as a white solid. M.p.: 55–56 °C; $[\alpha]_D^{19} = +19.3$ ($c = 0.60$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3355$, 1751, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.99$ (s, 3H), 2.02 (s, 3H) 2.05 (s, 3H), 2.14 (s, 3H), 2.80 (t, $J = 7.0$ Hz, 2H), 3.44 (q, $J = 7.0$ Hz, 2H), 4.00 (td, $J = 6.5$, 1.0 Hz, 1H), 4.07 (dd, $J = 11.0$, 6.5 Hz, 1H), 4.13 (dd, $J = 11.0$, 7.0 Hz, 1H), 4.65 (br s, 1H), 5.07 (t, $J =$

9.0 Hz, 1H), 5.11 (dd, J=12.0, 9.0 Hz, 1H), 5.12 (dd, J=12.0, 3.0 Hz, 1H), 5.29 (d, J=9.0 Hz, 1H), 5.43 (dd, J=3.0, 1.0 Hz, 1H), 7.17–7.32 ppm (5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=20.5, 20.6, 20.7, 23.2., 35.9, 41.5, 61.2, 67.1, 68.1, 71.0, 71.9, 80.3, 126.4, 128.5, 128.6, 128.7, 138.8, 156.4, 169.7, 170.0, 170.3, 171.1 ppm; elemental analysis: calcd (%) for $C_{23}H_{30}N_2O_{10}$: C 55.86, H 6.12, N 5.67; found: C 55.70, H 6.12, N 5.45.

32: Tin(IV) chloride (1.50 mL, 1.0 mmol) was added to a solution of **31** (5.17 g, 13.3 mmol) and *p*-methoxyphenol (4.94 g, 39.8 mmol) in CH_2Cl_2 (40 mL) cooled to 0°C, and the cooling bath was removed. After being stirred at room temperature for 44 h, the reaction mixture was poured into cold aqueous K_2CO_3 (5%, 200 mL). The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with NaOH (1M, 2 times), HCl (1M), aqueous $NaHCO_3$, and brine, and dried (Na_2SO_4). Concentration under reduced pressure and purification by column chromatography on silica gel (EtOAc/hexane=1:3) provided **32** as a colorless oil (3.93 g, 66%): $[\alpha]_D^{24}$=+156.1 (c=0.94, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$=2962, 2836, 1230 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz): δ= 1.97 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.09 (s, 3H), 2.17 (s, 3H), 3.77 (s, 3H), 1.97 (s, 3H), 4.08 (dd, J=11.2, 7.0 Hz, 1H), 4.14 (dd, J=11.2, 6.0 Hz, 1H), 4.40 (ddd, J=7.0, 6.0,1.2 Hz, 1H), 5.53 (dd, J=3.4, 1.2 Hz, 1H), 5.56 (dd, J=10.5, 3.4 Hz, 1H), 5.26 (dd, J=10.5, 3.6 Hz, 1H), 5.66 (d, J=3.6 Hz, 1H), 6.80–7.00 ppm (4H); ^{13}C NMR (CD_3OD, 100 MHz): δ=20.6, 20.6, 20.7, 20.7, 55.6, 61.5, 67.0, 67.5, 67.9, 67.9, 95.8, 114.6, 118.1, 150.3, 155.4, 170.0, 170.2, 170.3, 170.4 ppm; elemental analysis: calcd (%) for $C_{21}H_{26}O_{11}$: C 55.50, H 5.77; found: C 55.51, H 5.89.

35: A solution of **32** (265 mg, 0.58 mmol) in methanol (2.7 mL) and triethylamine (0.27 mL) was heated at 50°C for 15 h. Concentration of the reaction mixture gave a crude triol, which was dissolved in pyridine (2.0 mL). The solution was cooled to 0°C and then treated with benzoyl chloride (0.21 mL, 1.81 mmol). The cooling bath was removed. After being stirred at room temperature for 2.5 h, the reaction mixture was cooled to −10°C, then methanesulfonyl chloride (0.10 mL, 1.94 mmol) was added. The solution was warmed to room temperature, and the stirring was continued for 7.5 h. Concentration of the reaction mixture under reduced pressure and purification by column chromatography on silica gel (EtOAc/hexane=1:4) provided **35** as a white foam (297 mg, 77%). M.p.: 62–63°C; $[\alpha]_D^{16}$=+113.4 (c=1.01, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$= 3063, 2957, 2835 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz): δ=3.10 (s, 3H), 3.70 (s, 3H), 4.48 (dd, J=11.5, 5.5 Hz, 1H), 4.65 (dd, J=11.5, 7.5 Hz, 1H), 4.76 (br t, J=7.5, 5.5 Hz, 1H), 5.56 (d, J=3.0 Hz, 1H), 5.78 (dd, J= 11.0, 3.5 Hz, 1H), 5.84 (d, J=3.5 Hz, 1H), 6.05 (dd, J=11.0, 3.0 Hz, 1H), 6.65–6.75 (2H), 6.97–7.03 (2H), 7.37–7.58 (9H), 7.96–8.04 ppm (6H); ^{13}C NMR (CD_3OD, 100 MHz): δ=38.6, 55.2, 62.4, 67.2, 67.9, 68.1, 76.0, 76.7, 77.0, 77.3, 96.1, 114.4, 118.3, 128.2, 128.3, 128.3, 128.7, 129.2, 129.6, 129.7, 133.0, 133.4, 150.0, 155.3, 165.6, 165.6, 165.6 ppm; elemental analysis: calcd (%) for $C_{35}H_{32}O_{12}S$: C 62.12, H 4.77; found: C 62.19, H 4.59.

36: A suspension of **35** (1.63 g, 2.47 mmol) and sodium azide (0.48 g, 7.41 mmol) in DMF (30.0 mL) was heated at reflux for 3.5 h. The reaction mixture was diluted with EtOAc, then washed with water and brine and dried (Na_2SO_4). Concentration under reduced pressure gave a residue, which was purified by silica-gel chromatography (EtOAc/hexane= 1:2) to afford **36** as a white foam (1.19 g, 77%). M.p.: 46–47°C; $[\alpha]_D^{16}$= +145.2 (c=1.01, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$=2110, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=3.73 (s, 3H), 3.93 (t, J=10.0 Hz, 1H), 4.27 (ddd, J=10.0, 5.0, 2.5 Hz, 1H), 4.60 (dd, J=12.5, 5.0 Hz, 1H), 4.68 (dd, J= 12.5, 2.5 Hz, 1H), 5.35 (dd, J=10.5, 3.5 Hz, 1H), 5.81 (d, J=3.5 Hz, 1H), 6.20 (t, J=10.0 Hz, 1H), 6.70–6.75 (2H), 7.00–7.05 (2H), 7.36–7.63 (10H), 7.97–8.04 ppm (6H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ=55.5, 60.9, 63.3, 68.7, 71.0, 71.4, 95.6, 114.6, 118.2, 128.4, 128.5, 128.7, 128.9, 129.5, 129.8, 129.8, 129.0, 133.3, 133.5, 150.1, 155.4, 165.6, 165.8, 166.1 ppm; elemental analysis: calcd (%) for $C_{34}H_{29}N_3O_9$: C 65.48, H 4.69, N 6.74; found: C 65.40, H 4.55, N 6.68.

37: Sodium methoxide (prepared from 14 mg of NaH and 1.0 mL of MeOH) was added to a suspension of **36** (290 mg, 0.93 mmol) in methanol (15.0 mL). The mixture was stirred at room temperature for 16 h, and the reaction was quenched by the addition of AcOH. Concentration of the mixture afforded a residue, which was purified by silica-gel chromatography (EtOAc/hexane=2:1) to give **37** (125 mg, 86%) as a white solid. M.p.: 158–159°C; $[\alpha]_D^{16}$=+244.0 (c=0.53, MeOH); IR (KBr): $\tilde{\nu}_{max}$=3433, 3341, 2108 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz): δ=1.84 (br s, 1H), 2.31 (br d, 1H), 2.94 (s, 1H), 3.63 (dd, 1H), 3.72 (dt, 1H), 3.77 (s, 3H), 4.03 (t, J=9.5 Hz, 1H), 5.46 (d, J=4.0 Hz, 1H), 6.82–6.85 (2H, aromatic), 7.00–7.01 ppm (2H, aromatic); ^{13}C NMR (CD_3OD, 400 MHz): 56.0, 62.2, 63.5, 72.6, 73.3, 74.0, 100.3, 115.5, 119.5, 152.4, 156.7 ppm; elemental analysis: calcd (%) for $C_{13}H_{17}N_3O_6$: C 50.16, H 5.50, N 13.50; found: C 50.27, H 5.64, N 13.38.

38: A solution of **37** (30 mg, 0.096 mmol) and palladium on carbon (10%, 3 mg) in methanol (3.0 mL) was stirred vigorously under hydrogen atmosphere overnight. The mixture was filtered through a pad of celite and concentrated under reduced pressure. The resulting **21**, without further purification, was dissolved in water (2.0 mL), and **8** (39 mg, 0.19 mmol) in water (1.0 mL) was added at 40°C. After the mixture was stirred at 40°C for 30 h, more **8** (10 mg, 0.048 mmol) was added. Two further portions of **8** (10 mg, 0.048 mmol; 12 mg, 0.059 mmol) were added at 13-hr and 30-hr intervals. The reaction mixture was stirred at 40°C for 15 h after the final addition of **8** and then loaded directly onto a column of ODS (Cosmosil 75 C_{18}-OPN, H_2O followed by H_2O/MeOH=20:1) to afford **38** as a white solid (74 mg, 78%). M.p.: 220°C (decomp.); $[\alpha]_D^{16}$= +82.3 (c=0.82, DMF); IR (KBr): $\tilde{\nu}_{max}$=3290–3485, 1650, 1568 cm^{-1}; ^{1}H NMR (D_2O, 400 MHz): δ=3.35 (d, J=9.3 Hz, 1H), 3.40 (d, J= 9.8 Hz, 1H), 3.49–3.54 (m, 2H) 3.65 (t, J=11.5 Hz, 1H), 3.71 (dd, J= 12.2, 5.4 Hz, 1H), 3.77 (dd, J=9.8, 3.7 Hz, 1H), 3.80 (s, 3H), 3.88 (dd, J=12.0, 2.0 Hz, 1H), 3.92 (dd, J=7.43, 3.6 Hz, 1H), 3.99 (t, J=9.8 Hz, 1H), 5.55 (d, J=3.7 Hz, 1H), 6.96–7.00 (2H), 7.11–7.16 (2H) ppm; ^{13}C NMR (D_2O, 100 MHz): δ=52.8, 56.5, 61.3, 70.1, 70.5, 71.7, 72.2, 72.5, 72.6, 77.2, 77.8, 81.8 ppm.

39: Compound **21** was prepared from **37** (30 mg, 0.096 mmol), palladium on carbon (10%, 3 mg), and methanol (3.0 mL) with procedures similar to those described above and was dissolved without further purification in water (1.0 mL). Compound **22** (40 mg, 0.19 mmol, dissolved in 1.0 mL of H_2O) was then added. After being stirred at room temperature for 12 h, the reaction mixture was passed directly through a column of ODS (Cosmosil 75 C_{18}-OPN, H_2O) to afford **39** as a white solid (84 mg, 89%). M.p.: 190°C (decomp.); $[\alpha]_D^{15}$=+74.0 (c=0.24, DMF); IR (KBr): $\tilde{\nu}_{max}$= 3357, 1653, 1570 1226 cm^{-1}; ^{1}H NMR (D_2O, 400 MHz): δ=3.35 (d, J= 9.3 Hz, 1H), 3.80 (s, 3H, OMe), 3.59 (t, J=9.5 Hz, 1H), 3.66–3.73 (12H), 3.91 (dt, J=11.0, 3.5 Hz, 1H), 3.95 (d, J=4.0 Hz, 1H), 4.00 (t, J= 10.0 Hz, 1H), 5.55 (d, J=3.5 Hz, 1H), 6.98–7.00 (2H), 7.12–7.15 ppm (2H); ^{13}C NMR (D_2O, 100 MHz): δ=52.8, 56.5, 61.4, 61.7, 70.2, 71.7, 72.2, 72.5, 74.1, 77.0, 72.2, 98.7, 115.8, 119.5, 150.9, 155.3, 150.1 ppm.

40: A solution of **38** (20 mg, 0.040 mmol) in a mixture of pyridine (0.50 mL) and acetic anhydride (0.27 mL) was stirred at room temperature for 5 h. The mixture was concentrated under reduced pressure, and the crude residue was purified by silica-gel chromatography (EtOAC/ hexane=3:1) to give **40** (31 mg, 99%) as a white solid. M.p.: 144–145°C; $[\alpha]_D^{21}$=+90.4 (c=1.10, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$=3363, 1749, 1557, 1229 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.99 (3H, Ac), 2.03 (3H), 2.05 (3H), 2.07 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 3.77 (s, 3H), 3.80 (ddd, J=9.5, 4.0, 2.0 Hz, 1H), 4.00 (dt, J=10.0, 3.5 Hz, 1H), 4.01 (t, J=10.0 Hz, 1H), 4.08 (dd, J=12.0, 2.0 Hz, 1H), 4.19 (d, J= 3.5 Hz, 2H), 4.25 (dd, J=12.5, 3.5 Hz, 1H), 4.86 (t, J=9.5 Hz, 1H), 5.01 (dd, J=10.0, 3.5 Hz, 1H), 5.03 (t, J=9.5 Hz, 1H), 5.05 (t, J=9.5 Hz, 1H), 5.10 (d, 1H, NH), 5.29 (t, J=9.5 Hz, 1H), 5.47 (d, 1H, NH), 5.49 (t, J=10.0 Hz, 1H), 5.62 (d, J=3.5 Hz, 1H), 6.80–6.84 (2H), 6.97–7.01 ppm (2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=20.53, 20.58, 20.7, 20.7, 51.44, 55.6, 61.9, 62.6, 68.31, 69.8, 70.1, 70.5, 70.7, 72.8, 73.2, 80.1, 95.3, 114.6, 118.0, 150.2, 155.4, 155.7, 169.6, 169.9, 170.1, 170.6, 170.6, 171.3, 171,7 ppm; elemental analysis: calcd (%) for $C_{34}H_{44}N_2O_{16}$: C 52.04, H 5.65, N 3.57; found: C 51.96, H 5.81, N 3.48.

41: Compound **39** (20 mg, 0.040 mmol) was dissolved in pyridine (0.50 mL) and then treated with acetic anhydride (0.27 mL). After being stirred at room temperature for 5 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica-gel chromatography (EtOAc/hexane=3:1) to afford **41** (26 mg, 81%) as a white solid. M.p.: 97–98°C; $[\alpha]_D^{18}$=+116.4 (c=1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$=2920, 1749, 1557, 1226 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.99

(3H), 2.03 (3H), 2.05 (3H), 2.07 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 2.15 (s, 3H), 3.77 (s, 3H), 3.98–4.20 (overlapped, 6H), 4.21 (dd, $J=12.0$, 5.0 Hz, 1H), 4,94 (d, 1H, NH), 5.02 (dd, $J=10.0$, 3.5 Hz, 1H), 5.03 (t, $J=10.0$ Hz, 1H), 5.12 (dd, $J=10.0$, 3.5 Hz, 1H), 5.43 (d, $J=$ 3.5 Hz, 1H), 5.45 (overlapped, 1H, NH), 5.50 (t, $J=10.0$ Hz, 1H), 5.63 (d, $J=3.5$ Hz, 1H), 6.80–6.83 (2H), 6.97–7.01 ppm (2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=20.5$, 20.6, 20.6, 20.7, 20.7, 51.4, 55.6, 61.3, 62.6, 67.2, 68.1, 69.8, 70.1, 70.7, 70.9, 70.9, 80.4, 95.4, 114.6, 118.0, 150.2, 155.4, 155.7, 169.8, 170.1, 170.3, 170.6, 171.6, 1718 ppm; elemental analysis: calcd (%) for $C_{34}H_{44}N_2O_{16}$: C 52.04, H 5.65, N 3.57; found: C 51.96, H 5.81, N 3.48.

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