for the rate constants k_1 and k_2 could be made. No attempt was made to evaluate the rate constants k_1 and k_2 for hydrolysis of 1 at pH 7.0. However, the product ratio for $CHCl_3$/4-nitrophenol of 98:2 indicates that k_2 remains approximately 49-fold greater than k_1 for hydrolysis of 1 at this pH. For hydrolysis of 1 at pH 4.9, k_2 was determined both by following production of $CHCl_3$ and by following formation of (4-nitrophenyl)phenylphosphonic acid, 3, at 307 nm.

The validity of these kinetic results and the final concentration values for reaction products from both pathways for the hydrolysis of 1 depends on the stability of the reaction products produced by both paths. Thus, phenyl(trichloromethyl)phosphinic acid (2), 3, and $CHCl_3$ must be stable under the reaction conditions and the time periods studied. We have found this to be true under the reaction conditions employed.

In summary, these studies represent the first example of an acid-mediated cleavage of the P–CCl_3 in an organophosphorus ester. Further, these studies represent the first report of kinetic rate studies for P–CCl_3 cleavage in any organophosphorus ester, and for cleavage of both P–O and P–CCl_3 in the same molecule. It is of interest to contrast these present results with the reported results for phenyl(trichloromethyl)phosphinyl chloride, where chloride replaces the 4-nitrophenoxy leaving group. Hydrolysis of that compound in dilute nitric acid gave 2,[1c] with no evidence for P–C bond cleavage. This result is in agreement with our finding that 2 is stable under the reaction conditions employed in the current work.

This novel bond scission could find utility in conventional synthetic organic chemistry and in transformations of sensitive compounds of biological importance. For example, in the preparation of nucleoside 3′,5′-cyclic phosphates. That k_2 remains greater than k_1, as reflected by the product ratios summarized in Table I, over the entire pH range examined is surprising. One would expect that general acid catalysis in pathway a would play a more significant role at the lower pH conditions.

Registry No. 1, 81344-26-5.

Synthesis of C(6)-Carboxylate Analogues of *N*-Acetylmuramic Acid

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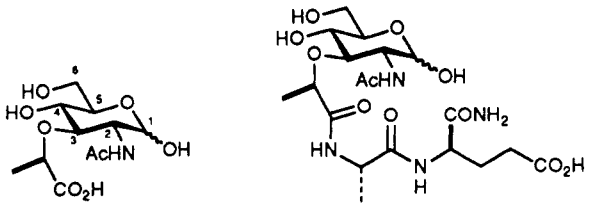
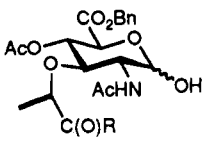
The *N*-acetylmuramic acid unit is an important structural component of the bacterial cell wall.[1] It is also a key structural element in an important class of immunomodulators, represented by muramyl dipeptide (MDP).[2] Our interest in the design and synthesis of agents that inhibit bacterial cell wall biosynthesis prompted our desire to prepare muramic acid cogeners **1a** and **1b**, in which carbon-6 is oxidized to a carboxylate. The preparation of C(6)-carboxylate analogues of *N*-acetylmuramic acid has been reported previously by only one group, that of Zemlyakov and co-workers.[3] We wish to report a new synthesis that utilizes a muramic acid 1′,4-lactone to directly protect the 4-hydroxyl group (Chart I).

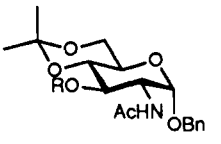
Chart I



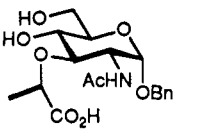
N-acetylmuramic acid MDP



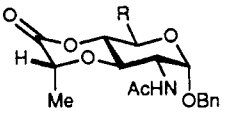
1a: R = NH_2
1b: R = OMe



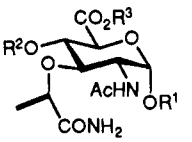
2: R = H
3: R = (*R*)-CH(Me)CO_2H



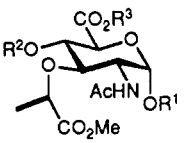
4



5: R = CH_2OH
6: R = CO_2H



7a: R^1 = CH_2Ph; R^2 = H; R^3 = H
8a: R^1 = CH_2Ph; R^2 = Ac; R^3 = H
9a: R^1 = CH_2Ph; R^2 = H; R^3 = CH_2Ph
10a: R^1 = CH_2Ph; R^2 = Ac; R^3 = CH_2Ph
11a: R^1 = H; R^2 = Ac; R^3 = H



7b: R^1 = CH_2Ph; R^2 = H; R^3 = H
9b: R^1 = CH_2Ph; R^2 = H; R^3 = CH_2Ph
10b: R^1 = CH_2Ph; R^2 = Ac; R^3 = CH_2Ph
11b: R^1 = H; R^2 = Ac; R^3 = H

Alkylation of *N*-acetylglucosamine derivative **2** with (*S*)-2-chloropropionic acid affords carboxylic acid **3**;[4] hydrolysis of the acetonide affords benzyl *N*-acetylmuramic acid (4).[5] In order to allow selective oxidation at C(6), the 4-hydroxyl group of 4 requires protection; this is conven-

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(4) Hasegawa, A.; Kaneda, Y.; Amano, M.; Kiso, M.; Azuma, I. *Agric. Biol. Chem.* **1978**, *42*, 2187.

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0022-3263/90/1955-6051$02.50/0

iently effected by cyclization to lactone **5**[6] using *p*-toluenesulfonic acid in acetonitrile.

Oxidation of the C(6) alcohol to either the carboxylic acid or aldehyde oxidation state was accomplished with considerable effort. After numerous unsuccessful attempts to effect this transformation ($KMnO_4$ in aqueous acetone;[7] CrO_3 in aqueous acetic acid;[7] PDC in DMF or dichloromethane;[8] PCC in dichloromethane;[9] oxalyl chloride/DMSO;[10] PtO_2/O_2[7]), we were gratified to find that ruthenium trichloride hydrate/sodium periodate[11] cleanly generates carboxylic acid **6**. Interestingly, use of anhydrous ruthenium trichloride under identical conditions gives much lower yields of the desired acid, even though water is present in the reaction mixture.

Having accomplished the desired oxidation, the next task was cleavage of the lactone and acetylation of the 4-hydroxyl group. Reaction of lactone **6** with ammonia in methanol provides carboxamide **7a**; alternatively, heating in methanol affords methyl ester **7b**. These reactions are known to proceed without racemization at the postion α to the carboxyl group.[6] Interestingly, attempted acetylation of the 4-hydroxyl of **7a** (to give **8a**) under a variety of conditions gave either returned starting material or complex mixtures. Temporary protection of the carboxylic acid of compounds **7** as the benzyl ester affords derivatives **9**; acetylation of compounds **9** proceeds smoothly, giving **10**. Transfer hydrogenolysis (triethylammonium formate, Pd/C, EtOH) removes both benzyl groups, affording **11**, at which point the acid is reesterified, providing desired targets **1a** and **1b**.

The route described herein allows facile preparation of differentially protected C(6)-carboxylate analogues of *N*-acetylmuramic acid. Since it is known that small peptides with a free amino terminus will react with lactones such as **6**,[6] this synthesis provides a particularly efficient route to the preparation of MDP analogues as well. The use of the lactone to allow selective oxidation at carbon-6, and the finding that the ruthenium chloride/sodium periodate protocol effects clean oxidation (where other standard reagents fail), are particularly noteworthy.

Experimental Section

General. ^1H NMR spectra were determined at 300 MHz. Unless otherwise specified, all NMR spectra were recorded in $CDCl_3$, and the chemical shifts are expressed in ppm downfield from tetramethylsilane. Data are presented in the order multiplicity, coupling constant in hertz, number of hydrogens. IR values are in inverse centimeters. Specific rotations, $[\alpha]$, were measured at the sodium D line.

Benzyl 2-Acetamido-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside (2).[4] *N*-Acetyl-α-D-glucosamine (10.0 g, 45.2 mmol) was suspended in benzyl alcohol (70 mL) and was warmed to 95 °C. A saturated solution of anhydrous HCl in benzyl alcohol (5 mL) was added. The suspended material dissolved and turned dark over 20 min. The solution was filtered through glass wool into vigorously stirring diethyl ether (400 mL). The precipitated glycoside was removed by filtration, washed thoroughly with ether, air dried, and used without further purification.

The crude glycoside was suspended in a mixture of acetone (200 mL) and 2,2-dimethoxypropane (80 mL). *p*-Toluenesulfonic acid monohydrate (700 mg) was added, and the mixture was stirred for 2 h at room temperature, during which time it became a clear, light yellow solution. The solvent was evaporated under reduced pressure, and the residue was taken up in methylene chloride, washed (dilute sodium bicarbonate, water, and brine), dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The resulting light brown oil was subjected to column chromatography on silica gel (600 g), eluting with 2.5% methanol/chloroform to yield **2** as an amorphous solid (10.6 g, 30.2 mmol, 67%), $[\alpha]^{23}$ +99.6° (*c*, 0.895, $CHCl_3$), lit.[4] $[\alpha]^{25}$ +117° (*c* 1, $CHCl_3$): IR (KBr) 3411, 1662, 1544, 1126, 1074; ^1H NMR δ 7.41–7.26 (m, 5 H), 5.92 (d, *J* = 9.0, 1 H), 4.85 (d, *J* = 4.8, 1 H), 4.71 (d, *J* = 12, 1 H) 4.45 (d, *J* = 12, 1 H), 4.16 (dt, *J* = 10.0, 5.0, 1 H), 3.83–3.61 (m, 4 H), 3.04–3.02 (d, *J* = 3.9, 1 H), 1.97 (s, 3 H), 1.52 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR δ 171.35, 136.80, 128.63, 128.23, 128.05, 99.84, 97.18, 74.69, 70.80, 69.81, 63.66, 62.18, 54.05, 29.04, 23.19, 19.06; mass spectrum *m/z* 352.0 (M + 1).

Benzyl 2-Acetamido-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside (3).[4] Sodium hydride (3.30 g, 60% in oil, 1.98 g as NaH, 82.5 mmol) was placed in a three-neck flask fitted with an addition funnel and mechanical stirrer. It was washed with three portions of hexane and was suspended in dry THF (25 mL). A solution of compound **2** (10.6 g, 30.2 mmol) in dry THF (50 mL) was added dropwise over 20 min. A solution of (*S*)-(−)-2-chloropropionic acid (3.05 mL, 3.6 g, 33.2 mmol; Fluka) in dry THF (20 mL) was added dropwise over 20 min, and the reaction mixture was heated at 50 °C for 18 h. The mixture was cooled, quenched with ethanol (2 mL), and diluted with ether. The ether was separated, and the aqueous layer was washed with two more portions of ether. The aqueous solution was acidified with 1 M phosphoric acid and was extracted with three portions of ethyl acetate. The combined organic phase was washed (2 × water, 1 × brine), dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator to afford **3** (12.2 g) contaminated with (*S*)-(−)-2-chloropropionic acid. This material was generally carried on without further purification; an analytical sample was prepared by recrystallization from ether/hexane, mp 54–56 °C, $[\alpha]^{23}$ +117° (*c* 0.959, $CHCl_3$), lit.[4] mp 92 °C, $[\alpha]^{25}$ +129° (*c* 1, $CHCl_3$): IR (KBr), 2800–3600 br, 3450, 3430, 1719, 1630, 1558, 1122; ^1H NMR δ 7.28 (m, 5 H), 7.14 (d, *J* = 9, 1 H), 5.19 (d, *J* = 4, 1 H), 4.64 (d, *J* = 12, 1 H), 4.45 (d, *J* = 12, 1 H), 4.17 (q, *J* = 6, 1 H), 3.95 (m, 1 H), 3.70 (m, 5 H), 1.98 (s, 3 H), 1.49 (s, 3 H), 1.41 (d, *J* = 6, 3 H), 1.39 (s, 3 H); HRMS calcd for $C_{21}H_{30}NO_8$ (M + 1) 424.1971, found 424.1958.

Benzyl 2-Acetamido-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-α-D-glucopyranoside (4).[5] Compound **3** (12.2 g, contaminated with (*S*)-(−)-2-chloropropionic acid) was dissolved in a mixture of ethanol (125 mL), water (40 mL), and acetic acid (25 mL) and was heated at reflux for 2 h. The solvent was evaporated, azeotroping with toluene and ethanol, to yield 11.8 g of crude **4** as a yellow glass, which was used without further purification. An analytical sample was prepared by recrystallization from toluene/ethyl acetate, mp 161–162 °C: $[\alpha]^{23}$ +163.9° (*c* 0.107, MeOH), lit.[5] mp 160–161 °C, $[\alpha]^{20}$ +168° (*c* 1.25, MeOH); IR (KBr) 3401–3277 br, 3400–2800 br, 1745, 1649, 1553, 1326, 1053; ^1H NMR (d_6-DMSO) δ 13.05 (br s, 1 H), 8.01 (d, *J* = 3.6, 1 H), 7.32 (m, 5 H), 5.35 (br s, 1 H), 4.98 (s, 1 H), 4.65 (d, *J* = 12, 1 H), 4.40 (d, *J* = 12.1 H), 4.61 (br s, 1 H), 4.50 (q, *J* = 6.9, 1 H), 3.51 (m, 5 H), 1.83 (s, 3 H), 1.30 (d, *J* = 6.9, 3 H); mass spectrum *m/z* 384.1 (M + 1).

Benzyl 2-Acetamido-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-α-D-glucopyranoside 1′,4-Lactone (5).[6] Compound **4** (11.8 g, crude) was dissolved in acetonitrile (200 mL). *p*-Toluenesulfonic acid monohydrate (934 mg) was added, and the mixture was heated at reflux under nitrogen for 3 h. The acetonitrile was removed under reduced pressure, and the residue was taken up in chloroform (400 mL), washed (2 × saturated $NaHCO_3$, brine), dried (magnesium sulfate), filtered, and concentrated with a rotary evaporator. The residue was taken up in hot acetonitrile and was allowed to cool slowly to room temperature; it was then refrigerated for 4 h. The precipitated product was filtered, washed with ether, and dried in a vacuum oven at 30 °C, to yield **5** (4.28 g). A second crop (0.21 g) was isolated from the mother liquor, to give a total of 4.49 g of **5** (12.3 mmol, 41% from **2**), mp 204–208 °C, $[\alpha]^{23}$ +180.9° (*c* 0.131, MeOH), lit.[6] mp 210–212 °C, $[\alpha]^{25}$ + 155° (*c* 1, $CHCl_3$): IR (KBr) 3500–3200 br, 1750, 1660, 1550; ^1H NMR δ 7.32 (m, 5 H), 5.61 (d, *J* = 8.4, 1 H), 4.97 (d, *J* = 3.6, 1 H), 4.72 (d, *J* = 12, 1 H), 4.68 (d, *J* = 12, 1 H) 4.66 (q, *J* = 6.9,

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1 H), 4.42 (t, J = 9.3 1 H), 4.29 (dt, J = 3.6, 9.8, 1 H), 3.82 (m, 4 H), 1.96 (s, 3 H), 1.46 (d, J = 6.9, 3 H); ^{13}C NMR (d_6-DMSO) 169.89, 169.53, 137.43, 128.28, 127.74, 127.65, 95.95, 74.74, 70.05, 69.78, 68.47, 58.93, 51.24, 22.42, 17.68; mass spectrum m/z 366.1 (M + 1).

Benzyl 2-Acetamido-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-α-D-glucopyranosiduronic Acid 1′,4-Lactone (6). Compound **5** (2.52 g, 6.90 mmol) was stirred vigorously in a mixture of acetonitrile (15.5 mL), carbon tetrachloride (15.5 mL), and water (22.7 mL) at 5 °C. Sodium periodate (6.56 g, 30.7 mmol) was added, followed by ruthenium trichloride hydrate (156 mg). The mixture was allowed to warm to room temperature and was stirred 40 min, occasionally cooling in a water bath. At the end of 40 min the reaction mixture began to darken. It was immediately poured into ethyl acetate chilled in an ice bath, and a dilute solution of sodium bisulfite was added slowly with vigorous stirring until all of the dark brown color was dispelled. The green aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were washed (dilute sodium bisulfite, water, brine), dried over magnesium sulfate, filtered, and concentrated to afford **6** (1.78 g, 4.7 mmol, 68%), mp 210–215 dec, $[\alpha]^{23}$ +137° (c 0.126, 1% MeOH/$CHCl_3$): IR (KBr) 3500–2850 br, 1750, 1604, 1565, 1379, 1220, 1184, 1051; ^{1}H NMR (d_6-DMSO) δ 8.25 (d, J = 7.5, 1 H), 7.35 (m, 5 H), 4.88 (d, J = 2.4, 1 H), 4.77 (q, J = 6.6, 1 H), 4.75 (d, J = 12, 1 H), 4.52 (d, J = 12, 1 H), 4.57 (t, J = 10.5, 1 H), 4.21 (d, J = 9.9, 1 H), 4.00 (m, 2 H), 1.83 (s, 3 H), 1.37 (d, J = 6.6, 3 H); ^{13}C NMR (d_6-DMSO) 169.56, 169.27, 168.57, 137.10, 128.29, 127.71, 127.41, 96.59, 76.23, 70.31, 69.06, 68.47, 67.59, 50.89, 22.35, 17.62; mass spectrum m/z 380.2 (M + 1). Anal. Calcd for $C_{18}H_{21}NO_8$: C, 56.99; H, 5.58; N, 3.69. Found: C, 56.63, H, 5.58, N, 3.42.

Benzyl 2-Acetamido-3-*O*-[(*R*)-1-carbamoylethyl]-2-deoxy-α-D-glucopyranosiduronic Acid (7a). Compound **6** (1.30 g, 3.44 mmol) was dissolved in saturated methanolic ammonia (35 mL) and was allowed to stand at room temperature for 18 h. The solvent was evaporated, and the residue was dissolved in methanol and treated with Amberlite H^+ ion exchange resin. The solvent was removed under reduced pressure to yield **7a** (1.27 g, 3.22 mmol, 93%), mp 110 °C dec, $[\alpha]^{23}$ +140° (c 0.081, MeOH): IR (KBr) 3294, 3500–2900 br, 1711, 1654, 1121, 1056; ^{1}H NMR (d_6-DMSO) δ 8.52 (d, J = 6.3, 1 H), 7.30 (m, 5 H), 7.28 (br s, 1 H), 7.21 (br s, 1 H), 4.97 (d, J = 3.3, 1 H), 4.63 (d, J = 12.3, 1 H), 4.42 (d, J = 12.3, 1 H), 4.32 (q, J = 6.3, 1 H), 3.74 (d, J = 8.7, 1 H), 3.65 (m, 1 H), 3.41 (m, 2 H), 1.82 (s, 3 H), 1.25 (d, J = 6.3, 3 H); ^{13}C NMR (d_6-DMSO) 176.25, 171.50, 169.60, 137.66, 128.25, 127.52, 127.44, 127.40, 96.13, 77.98, 75.96, 72.44, 71.37, 68.43, 52.94, 22.61, 19.43; HRMS calcd for $C_{18}H_{25}N_2O_8$ (M + 1) 397.1611, found 397.1601.

Benzyl 2-Acetamido-2-deoxy-3-*O*-[(*R*)-1-(methoxycarbonyl)ethyl]-α-D-glucopyranosiduronic Acid (7b). Compound **6** (1.78 g, 4.70 mmol) was heated at reflux for 18 h in methanol. The solvent was removed under reduced pressure to give **7b** (1.74 g, 4.23 mmol, 90%), mp 60–63 °C, $[\alpha]^{23}$ +134° (c 0.132, $CHCl_3$): IR (KBr) 3400–2500 br, 1730, 1660, 1620, 1550, 1230, 1120, 1060; ^{1}H NMR δ 7.97 (d, J = 4.0, 1 H), 7.29 (m, 5 H), 5.51 (d, J = 2.4, 1 H), 4.80 (m, 2 H), 4.75 (d, J = 12, 1 H), 4.52 (d, J = 12, 1 H), 4.07 (d, J = 10.0, 1 H), 3.79 (m, 4 H), 3.73 (s, 3 H), 2.03 (s, 3 H), 1.40 (d, J = 6.9, 3 H); mass spectrum m/z 412.3 (M + 1). Anal. Calcd for $C_{19}H_{25}NO_9$: C, 55.47; H, 6.12; N, 3.40. Found: C, 55.21; H, 6.04; N, 3.23.

Benzyl 2-Acetamido-3-*O*-[(*R*)-1-carbamoylethyl]-2-deoxy-α-D-glucopyranosiduronic Acid Benzyl Ester (9a). Compound **7a** (1.26 g, 3.17 mmol) was dissolved in dry DMF (8 mL). Sodium bicarbonate (655 mg, 7.79 mmol) was added, followed by benzyl bromide (1.14 mL, 1.64 g, 9.6 mmol). The mixture was stirred under nitrogen at 60 °C for 18 h. It was then cooled, diluted with ethyl acetate, washed (2 × water, brine), dried over magnesium sulfate, filtered, and concentrated. The residue was subjected to column chromatography on silica gel (40 g), eluting with 3.5% methanol/chloroform, to yield **9a** (1.23 g, 2.53 mmol, 80%), mp 205–206 °C dec $[\alpha]^{23}$ +116.5° (c 0.099, MeOH); IR (KBr) 3497, 3355, 3302, 1739, 1710, 1636, 1548, 1124, 1053; ^{1}H NMR (d_6-DMSO) δ 8.57 (d, J = 6.0, 1 H), 7.39 (m, 5 H), 7.36 (m, 5 H), 7.36 (br s, 1 H), 7.31 (br s, 1 H), 5.77 (d, J = 7.8, 1 H), 5.20 (d, J = 12, 1 H), 5.17 (d, J = 12, 1 H), 5.01 (d, J = 2.7, 1 H), 4.66 (d, J = 12.6, 1 H), 4.45 (d, J = 12.6, 1 H), 4.30 (q, J = 6.9, 1 H), 4.03 (d, J = 9.6, 1 H), 3.68 (m, 1 H), 3.67 (t, J = 10, 1 H), 1.82 (s, 3 H), 1.25 (d, J = 6.9, 3 H); ^{13}C NMR (d_6-DMSO) 176.03, 169.66, 168.86, 137.38, 135.65, 128.46, 128.27, 128.16, 128.08, 128.03, 127.84, 127.59, 96.67, 77.47, 76.20, 72.17, 71.88, 69.04, 66.20, 53.02, 22.54, 19.30; HRMS calcd for $C_{25}H_{31}N_2O_8$ (M + 1) 487.2081, found 487.2092.

Benzyl 2-Acetamido-2-deoxy-3-*O*-[(*R*)-1-(methoxycarbonyl)ethyl]-α-D-glucopyranosiduronic Acid Benzyl Ester (9b). Compound **7b** (1.74 g, 4.23 mmol) was dissolved in dry DMF (10 mL). Sodium bicarbonate (739 mg, 8.8 mmol) was added, followed by benzyl bromide (1.30 mL, 1.87 g, 10.9 mmol). The mixture was stirred under nitrogen for 16 h at 60 °C. It was then cooled and diluted with ethyl acetate, washed (2 × water, brine), dried over magnesium sulfate, filtered, and concentrated. The residue was subjected to column chromatography on silica gel (93 g), eluting with 2% methanol/chloroform, to yield **9b** (1.89 g, 3.77 mmol, 89%), mp 44–47 °C, $[\alpha]^{23}$ +108° (c 0.148, $CHCl_3$): IR (KBr) 3330, 1750, 1660, 1550, 1130, 1050; ^{1}H NMR δ 7.61 (d, J = 3.6, 1 H), 7.36 (m, 5 H), 7.27 (m, 5 H), 5.48 (d, J = 3.3, 1 H), 5.25 (d, J = 12, 1 H), 5.23 (d, J = 12, 1 H), 4.70 (m, 1 H), 4.67 (d, J = 12, 1 H), 4.53 (d, J = 12, 1 H), 4.12 (d, J = 10.0, 1 H), 3.76 (m, 3 H), 3.73 (s, 3 H), 3.28 (d, J = 2.1, 1 H), 1.99 (s, 3 H), 1.39 (d, J = 6.6, 3 H); mass spectrum m/z 502.2 (M + 1). Anal. Calcd for $C_{26}H_{31}NO_9$: C, 62.27; H, 6.23; N, 2.79. Found: C, 61.99; H, 5.98; N, 2.60.

Benzyl 2-Acetamido-4-*O*-acetyl-3-*O*-[(*R*)-1-carbamoylethyl]-2-deoxy-α-D-glucopyranosiduronic Acid Benzyl Ester (10a). Compound **9a** (1.11 g, 2.29 mmol) was suspended in methylene chloride (50 mL) at room temperature. Triethylamine (1.30 mL, 944 mg, 9.3 mmol) was added, followed by 4-(dimethylamino)pyridine (12 mg) and acetic anhydride (0.94 mL, 1.0 g, 10 mmol). The mixture was stirred for 40 min at room temperature, during which time the starting material dissolved. The reaction was diluted with methylene chloride, washed (1 M phosphoric acid, dilute sodium bicarbonate, water, brine), dried over magnesium sulfate, filtered, and concentrated to yield **10a** (1.17 g, 2.22 mmol, 97%), mp 202–203 °C dec, $[\alpha]^{23}$ +90° (c 0.065, $CHCl_3$): IR (KBr) 3376, 3304, 1746, 1637, 1540, 1237, 1130, 1055; ^{1}H NMR δ 7.31 (m, 10 H), 6.49 (br s, 1 H), 5.92 (d, J = 9.6, 1 H), 5.43 (br s, 1 H), 5.17 (d, J = 12.3, 1 H), 5.05 (d, J = 12.3, 1 H), 5.09 (m, 1 H), 4.94 (d, J = 3.6, 1 H), 4.71 (d, J = 11.7, 1 H), 4.49 (d, J = 11.7, 1 H), 4.35 (dt, J = 3.6, 10, 1 H), 4.24 (d, J = 9.9, 1 H), 3.93 (q, J = 6.9, 1 H), 3.64 (t, J = 9.3, 1 H), 1.86 (s, 3 H), 1.80 (s, 3 H), 1.27 (d, J = 6.9, 3 H); ^{13}C NMR (d_6-DMSO) 174.78, 169.72, 169.15, 167.48, 137.23, 135.08, 128.50, 128.40, 128.28, 127.71, 96.59, 76.60, 75.38, 71.22, 69.52, 68.69, 66.89, 52.95, 22.51, 20.30, 18.78; mass spectrum m/z 529.2 (M + 1). Anal. Calcd for $C_{27}H_{32}N_2O_9$: C, 61.36; H, 6.10; N, 5.30. Found: C, 61.24; H, 6.12; N, 5.19.

Benzyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[(*R*)-1-(ethoxycarbonyl)ethyl]-α-D-glucopyranosiduronic Acid Benzyl Ester (10b). Compound **9b** (1.82 g, 3.63 mmol) was dissolved in methylene chloride (70 mL) at room temperature. Triethylamine (2 mL, 1.45 g, 14.3 mmol) was added, followed by 4-(dimethylamino)pyridine (20 mg) and acetic anhydride (1.48 mL, 1.60 g, 15.7 mmol). The mixture was stirred for 1 h, diluted with methylene chloride, washed (1 M phosphoric acid, sat'd sodium bicarbonate, brine), dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue was subjected to column chromatography on silica gel (100 g), eluting with 65:35 ethyl acetate/hexane, to yield **10b** (1.22 g, 2.24 mmol, 62%), mp 146–147 °C, $[\alpha]^{23}$ +108° (c 0.148, $CHCl_3$): IR (KBr) 3330, 1750, 1660, 1550, 1500, 1130, 1050; ^{1}H NMR δ 7.67 (d, J = 3.9, 1 H), 7.35 (m, 5 H), 7.29 (m, 5 H), 5.53 (d, J = 3.3, 1 H), 5.14 (m, 1 H), 5.13 (d, J = 12, 1 H), 5.05 (d, J = 12, 1 H), 4.67 (d, J = 12, 1 H), 4.52 (d, J = 12, 1 H), 4.25 (q, J = 6.9, 1 H), 4.18 (d, J = 10, 1 H), 3.84 (m, 2 H), 3.74 (s, 3 H), 1.99 (s, 3 H), 1.81 (s, 3 H), 1.32 (d, J = 6.9, 3 H); mass spectrum m/z 544.1 (M + 1). Anal. Calcd for $C_{28}H_{33}NO_{10}$: C, 61.87; H, 6.12; N, 2.58. Found: C, 61.57; H, 5.84; N, 2.38.

2-Acetamido-4-*O*-acetyl-3-*O*-[(*R*)-1-carbamoylethyl]-2-deoxy-D-glucopyranosiduronic Acid (11a). A mixture of compound **10a** (347 mg, 0.660 mmol), formic acid (0.25 mL), and triethylamine (0.66 mL, 490 mg, 44.8 mmol) was heated at 65 °C in ethanol (50 mL) under nitrogen. To this was added 10% Pd/C (480 mg), and the mixture was stirred vigorously for 30 min. It was then filtered, concentrated, taken up in methanol, and treated

with 2 g of Amberlite H^+ ion exchange resin. The solvent was removed under reduced pressure to yield **11a** (190 mg, 0.550 mmol, 83%), mp 130 °C dec. ^1H NMR analysis of the mixture showed the ratio of anomers to be about 9:1 α/β: IR (KBr) 3515, 3417, 3100–2400 br, 1751, 1720, 1639, 1377, 1262, 1115; ^1H NMR (d_6-DMSO, α-anomer) δ 8.36 (d, J = 6.6, 1 H), 7.32 (s, 1 H), 7.07 (d, J = 3.9, 1 H), 7.03 (s, 1 H), 5.16 (t, J = 3.9, 1 H), 4.89 (t, J = 9.0, 1 H), 4.17 (d, J = 10, 1 H), 4.08 (q, J = 6.6, 1 H), 3.74 (m, 1 H), 3.63 (t, J = 9.6, 1 H), 2.04 (s, 3 H), 1.82 (s, 3 H), 1.15 (d, J = 6.6, 3 H); ^{13}C NMR (d_6-DMSO), 174.94, 169.75, 169.70, 169.10, 90.62, 76.51, 75.61, 71.56, 68.31, 53.62, 22.66, 20.70, 18.80; HRMS (FAB) calcd for $C_{13}H_{21}N_2O_9$ (M + 1) 349.1247, found 349.1248.

2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[(*R*)-1-(methoxycarbonyl)ethyl]-D-glucopyranosiduronic Acid (11b). Compound **10b** (1.2 g, 2.2 mmol) was dissolved in ethanol (150 mL) and was heated at 65 °C under nitrogen. Triethylamine (2.2 mL, 1.6 g, 15.8 mmol) and formic acid (0.83 mL, 18 mmol) were added, followed by 10% Pd/C (1.6 g). Vigorous evolution of gas was observed, which subsided after about 15 min. After 45 min, the mixture was cooled and filtered. The solvent was removed under reduced pressure, and the residue was taken up in methanol and treatd with Amberlite H^+ ion exchange resin. The methanol was removed with a rotary evaporator to yield **11b** (780 mg, 2.14 mmol, 97%) as a glass, which was used without further purification. ^1H NMR analysis indicated that the ratio of anomers was about 3:1 α/β: IR (KBr) 3400–2500 br, 3300, 1740, 1660, 1550, 1375, 1230, 1125; ^1H NMR (d_6-DMSO, α-anomer) δ 7.89 (m, 1 H), 5.75 (d, J = 3, 1 H), 5.04 (br s, 1 H), 4.79 (m, 1 H), 4.27 (m, 1 H), 4.19 (d, J = 8, 1 H), 3.71 (m, 2 H), 3.61 (s, 3 H), 3.43 (m, 1 H), 2.03 (s, 3 H), 1.81 (s, 3 H), 1.18 (d, J = 6, 3 H); ^{13}C NMR (d_6-DMSO) 172.78, 169.49, 169.29, 169.04, 90.85, 76.31, 75.46, 71.23, 68.02, 52.95, 51.81, 22.57, 20.56, 18.54. Anal. Calcd for $C_{14}H_{21}NO_{10}$: C, 46.28; H, 5.83; N, 3.86. Found: C, 46.53; H, 5.73; N, 3.31.

2-Acetamido-4-*O*-acetyl-3-*O*-[(*R*)-1-carbamoylethyl]-2-deoxy-D-glucopyranosiduronic Acid Benzyl Ester (1a). Compound **11a** (333 mg, 0.960 mmol) was dissolved in dry DMF (7 mL) under nitrogen. Sodium bicarbonate (160 mg, 1.91 mmol) was added, followed by benzyl bromide (0.22 mL, 325 mg, 1.91 mmol). The mixture was stirred at 45 °C for 18 h. The solvent was removed under reduced pressure, and the residue was triturated with acetone and filtered. The residue was then triturated with water and filtered again, and the solid was washed with acetone and dried in a vacuum oven at 40 °C to yield **1a** (372 mg, 0.85 mmol, 88%), mp 220 °C dec. ^1H NMR analysis of the mixture showed the ratio of anomers to be greater than 9:1 α/β: IR (KBr) 3429, 3312, 3300–3100 br, 1744, 1678, 1378, 1245, 1121; ^1H NMR (d_6-DMSO) δ 8.41 (d, J = 6.6, 1 H), 7.36 (m, 5 H), 7.31 (s, 1 H), 7.13 (br s, 2 H), 5.16 (d, J = 3.3, 1 H), 5.10 (d, J = 11.7, 1 H), 5.01 (d, J = 11.7, 1 H), 4.85 (t, J = 10, 1 H), 4.31 (d, J = 10, 1 H), 4.10 (q, J = 6.9, 1 H), 3.70 (m, 1 H), 3.63 (t, J = 9, 1 H), 1.88 (s, 3 H), 1.81 (s, 3 H), 1.13 (d, J = 6.9, 3 H); ^{13}C NMR (d_6-DMSO) 174.85, 169.74, 167.93, 135.23, 128.50, 128.39, 90.80, 76.54, 75.37, 71.51, 68.12, 66.74, 53.54, 22.61, 20.39, 18.77; mass spectrum m/z 439.1 (M + 1). Anal. Calcd for $C_{20}H_{26}N_2O_9$: C, 54.79; H, 5.98; N, 6.39. Found: C, 54.69; H, 6.00; N, 6.41.

2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[(*R*)-1-(methoxycarbonyl)ethyl]-D-glucopyranosiduronic Acid Benzyl Ester (1b). Compound **11b** (705 mg, 1.94 mmol) was dissolved in dry DMF (10 mL). Sodium bicarbonate (326 mg, 3.88 mmol) was added, followed by benzyl bromide (0.46 mL, 661.5 mg, 3.87 mmol). The mixture was stirred under nitrogen at 45 °C for 16 h. The mixture was cooled to room temperature, and most of the DMF was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed (water, brine), dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue was subjected to column chromatography on silica gel (40 g), eluting with ethyl acetate, to give **1b** (402 mg, 0.890 mmol, 46%), mp 55–58 °C: IR (KBr) 3330, 1740, 1660, 1550, 1375, 1230, 1125; ^1H NMR δ 7.98 (d, J = 2.4, 1 H), 7.32 (m, 5 H), 5.79 (s, 1 H), 5.12 (t, J = 7.5, 1 H), 5.10 (d, J = 12.3, 1 H), 5.01 (d, J = 12.3, 1 H), 4.53 (m, 1 H), 4.42 (d, J = 10, 1 H), 4.28 (q, J = 6.9, 1 H), 3.80 (m, 2 H), 3.75 (s, 3 H), 2.01 (s, 3 H), 1.80 (s, 3 H), 1.32 (d, J = 6.9, 3 H); ^{13}C NMR (d_6-DMSO) 172.77, 169.23, 169.21, 167.91, 135.24, 128.53, 91.06, 76.20, 75.53, 71.32, 68.03, 66.77, 52.93, 51.86, 22.60, 20.36, 18.57; HRMS (FAB) calcd for $C_{21}H_{28}NO_{10}$ (M + 1) 454.1713, found 454.1706.

Registry No. α-**1a**, 129392-02-5; β-**1a**, 129392-15-0; α-**1b**, 129392-08-1; β-**1b**, 129392-16-1; **2**, 66026-10-6; **3**, 69323-67-7; **4**, 15892-26-9; **5**, 62959-83-5; **6**, 129392-03-6; **7a**, 129392-04-7; **7b**, 129392-09-2; **9a**, 129392-05-8; **9b**, 129392-10-5; **10a**, 129392-06-9; **10b**, 129392-11-6; α-**11a**, 129392-07-0; β-**11a**, 129392-13-8; α-**11b**, 129392-12-7; β-**11b**, 129392-14-9; $NaIO_4$, 7790-28-5; *N*-acetyl-α-D-glucosamine, 10036-64-3; (*S*)-(−)-2-chloropropionic acid, 29617-66-1; ruthenium trichloride hydrate, 14898-67-0.

Supplementary Material Available: NMR spectra for compounds **1b**, **7a**, **9a**, and **11a** (8 pages). Ordering information is given on any current masthead page.

The 1,5-Addition Reaction of Lithium Diorganocuprates to Methylenecyclopropyl Ketones

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In the last two decades, methylenecyclopropane chemistry has been advanced by numerous synthetic[2] and mechanistic[3] studies. The biologically active natural product hypoglycin[4] contains this moiety. More recently, (methylenecyclopropyl)acetyl-CoA was synthesized as a tool to study enzyme-catalyzed reactions.[5] Despite all this research, few have investigated the reaction of nucleophiles with this ring system.[6]

Due to our interest in employing methylenecyclopropanes as 4-carbon synthons,[7] we viewed methylenecyclopropyl ketones **1a** and **1b** as intriguing substrates for nucleophilic substitution reactions. These compounds contain a monoactivated strained ring due to the exomethylene group, in contrast to other monoactivated cyclopropanes which will not undergo nucleophilic addition on a ring, unless the ring is part of a larger strained ring system.[8] Bertz has studied specifically the reaction of dialkylcuprates with cyclopropanes and also concluded that double activation of the ring is necessary for good yields, while only in special strained systems would monoactivated compounds undergo reaction.[9] Falck and Mioskoski found

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