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Synthesis of a Carbon Analogue of *N*-Acetylmannosamine via Acetolysis on a Relatively Stable Ozonide

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Abstract: After a 2-methylpropenyl group was added to a carbohydrate framework through regioselective opening of a glucose-derived epoxide, hydrolysis or acetolysis of the methyl glycoside in various derivatives was problematic. Ozonolysis of the olefin followed by brief treatment with dimethyl sulfide gave a mixture of diastereomeric ozonides that proved to be stable for weeks at room temperature. Acetolysis of these ozonides at low temperature allowed selective cleavage of the methyl glycoside in the presence of the 1,2,4-trioxolane as well as selective formation of the α-acetate.

Ozonolysis is an important method for conversion of alkenes into ketones and aldehydes. A generally accepted mechanism involves initial formation of an unstable primary ozonide that undergoes cycloreversion and subsequent cycloaddition to give a more stable secondary ozonide.[1] The resulting ozonides usually are reduced to ketones or aldehydes without isolation,[2] but recently, there has been increased interest in direct transformations in which ozonides serve as precursors for compounds other than carbonyl compounds.[3−5] In this paper, we wish to report isolation of unusually stable carbohydrate-derived ozonides and a novel acetolysis reaction to cleave the methyl glycosidic bond in the presence of the ozonide. [6]

In connection with studies on the elasticity of sialic acid biosynthesis, we became interested in carbon analogues of *N*-acetylmannosamine (**1**, Figure 1). In the target compound **2** and its peracetylated derivative **3**, the nitrogen atom is formally replaced with a methylene group, resulting in a ketone in place of the amide functional group. If compound **2** or **3** could enter the sialic acid biosynthesis pathway and be incorporated into cell surface glycoconjugates, the ketone group presumably could be detected through reaction with biotin hydrazide.[7,8]

In our synthetic approach, it was envisioned that the branched sugars **2** or **3** could be obtained from the methyl mannoside derivative **4** after oxidative cleavage of the olefin and a series of deprotections. Compound **4** in turn might be obtained from the known epoxide **5** if an appropriate nucleophile were used to open the epoxide and the equatorial orientation of the C-3 hydroxyl group in compound **4** could be secured.

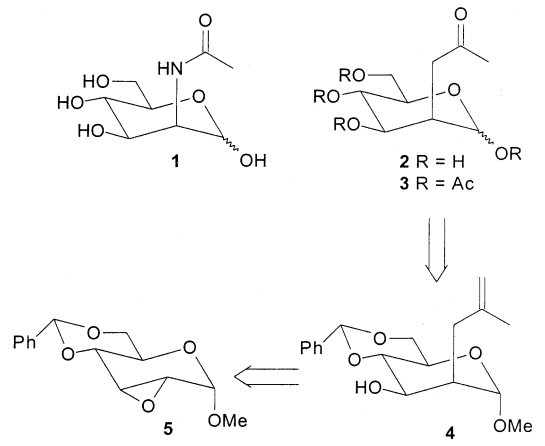

FIGURE 1.

In the actual synthesis, epoxide **5** was prepared by a one-flask procedure in which commercially available methyl glucoside **6** was treated with tosyl chloride in the presence of base followed by cyclization under phase-transfer catalysis conditions (Scheme 1).[9] When treated with the Grignard reagent derived from 3-chloro-2-methylpropene, epoxide **5** was opened regioselectively in almost quantitative yield to give methyl glycoside **7** with the expected D-altro configuration.[10] Inversion of the C-3 hydroxyl group was accomplished through an oxidation−reduction sequence. The free hydroxyl group of compound **7** was oxidized through a Swern procedure[10] to give ketone **8** in excellent yield. The desired reduction of this ketone would require an attack of hydride from the β face, but previous studies have shown that in similar ketones reduction with $NaBH_4$ results in preferred attack from the β face.[11] However, Fraser-Reid and co-workers have found that hydride attack might be reversed in orientation if DIBAL were used.[12] When these conditions were applied to ketone **8**, the desired isomer **4** was obtained as the major product in a 6:1 ratio along with the C-3 epimer **7**.

The olefin **4** could serve as a precursor for the needed ketone moiety in the target compounds through a sequence involving cleavage of the methyl glycosidic bond followed by ozonolysis of the alkene. Alternatively, the double bond could be converted to a ketone group first

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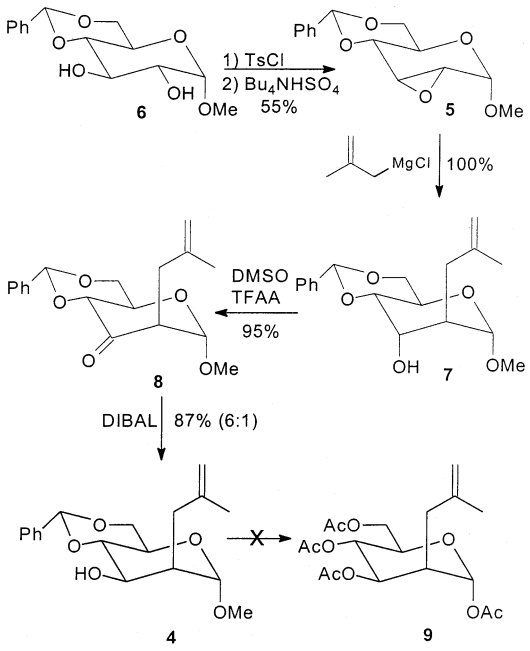
SCHEME 1

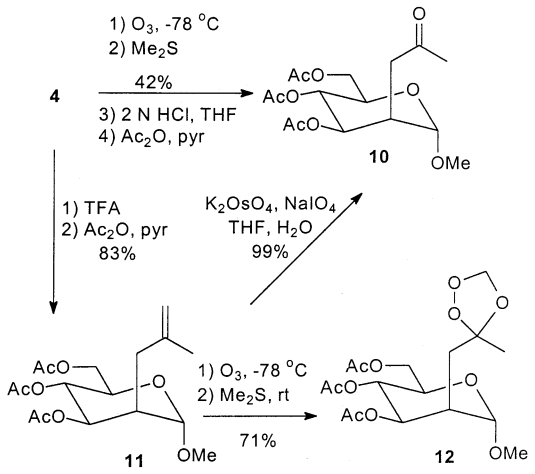


and the protecting group then removed to furnish the target compound **2**. To examine the first approach, various acetolysis conditions (Ac_2O and H_2SO_4,[13] Ac_2O and $FeCl_3$,[14] and Ac_2O and Tf_2O[15]) were applied to attempt conversion of compound **4** into the acetylated derivative **9**. Unfortunately, each of these conditions produced a complex mixture based on TLC analysis. When acidic hydrolysis of methyl glycoside **4** was explored, the glycosidic methyl group could not be removed without compromise of the olefin, based on ^{1}H NMR analysis of the resulting mixture.

The limited success of this approach encouraged efforts to convert the olefin into a ketone prior to attempting hydrolysis. Ozonolysis of olefin **4** and subsequent reductive workup gave the corresponding ketone in low yield. When this ketone was subjected to mild acidic hydrolysis and subsequent acetylation, the acetylated methyl glycoside **10** (Scheme 2) was isolated in very low yield along with a complex mixture of other carbohydrate derivatives including both furanose and pyranose forms of the carbohydrate.

After these attempts at cleaving the glycosidic bond went unrewarded, a more stepwise approach was explored. Removal of the benzylidene group in sugar **4** under mild acidic conditions followed by acetylation produced the acetylated methyl glycoside **11** in 83% overall yield (Scheme 2) without significant loss of the olefin. Sugar **11** was treated with ozone and then with dimethyl sulfide for 6 h at room temperature. Surprisingly, a 1.5:1 mixture of the diastereomeric ozonides **12** was obtained after flash column chromatography, which may be due in part to the low reactivity of dimethyl sulfide.[17] Each of these two compounds exhibited ^{13}C

SCHEME 2



NMR signals at ~108 and ~94 ppm, values that are consistent with literature values of similar ozonides.[16] While no effort was taken to separate the two isomers, formation of diastereomers was reasonable given the chiral environment imposed by the carbohydrate motif.

The isolated ozonides **12** proved to be surprisingly stable, with no apparent decomposition after 6 weeks at room temperature, as judged by both ^{1}H and ^{13}C NMR experiments, and both satisfactory HRMS and analytical data were obtained. To compare ozonides **12** with the analogous ketone, sugar **11** was treated with potassium osmate and sodium periodate to give ketone **10** in almost quantitative yield. The NMR spectra of ketone **10** were substantially different from those of ozonides **12**. Most notably, the ketone carbonyl carbon of compound **10** was observed at 206 ppm in the ^{13}C NMR spectrum.

When ozonides **12** were subjected to acetolysis under dilute conditions[18] at −25 °C, the reaction proceeded slowly. After 24 h, compound **13** was isolated in 70% yield as a 1.5:1 mixture of two diastereomers (Scheme 3), indicating that the 1,2,4-trioxolane was relatively stable under these conditions while the methyl glycoside was more reactive. Because the diastereomeric ratio did not differ from that of compound **12**, it would be reasonable to assume that the two diastereomers originated from the 1,2,4-trioxolane stereochemistry instead of the C-1 position of the sugar ring. For this reason, the α orientation was assigned to C-1 in compound **13**. Both the greater reactivity of the methyl glycoside and selective formation of the α anomer could be rationalized by a transition state[19] where a trioxolane oxygen stabilizes a positive charge at the anomeric position while shielding the *β*-face from an approaching nucleophile.

When the acetolysis of compound **12** was conducted at 0 °C, a mixture of compound **13** and the corresponding ketone **14** was obtained in a ratio of ~2.5:1. However, the target compound **14** could be obtained more efficiently

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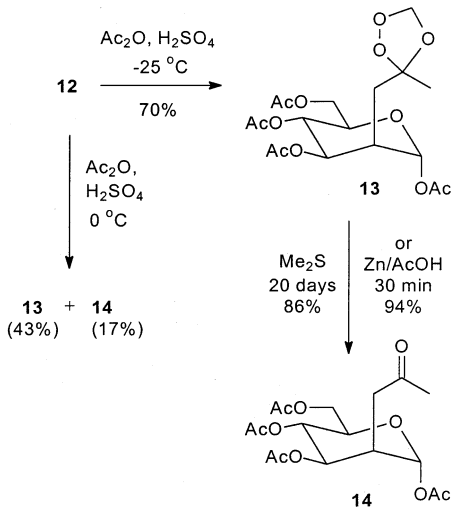
SCHEME 3



from ozonides **13** by reduction of the 1,2,4-trioxolane ring to the desired ketone.[2,20−23] When ozonides **13** were treated with 3.3 equiv of dimethyl sulfide at room temperature, only ∼50% completion was observed even after 10 days. After an additional 13.2 equiv of dimethyl sulfide was added, complete reaction was observed after 10 more days and the target compound **14** was obtained as a single isomer, presumably the α isomer, in 86% yield. In contrast, when compounds **13** were treated with zinc/acetic acid,[23] the starting material was consumed in 30 min and the target compound **14** was obtained as a single isomer in 94% yield. The ^{1}H NMR spectra of the products from both reductions were identical.

In conclusion, the target ketone **14** was obtained from the commercially available methyl glucoside **6** through chemical transformations including regioselective opening of epoxide **5**, stereoselective reduction of ketone **8**, and most notably, selective acetolysis of ozonides **12**. The NMR data of the final product were in agreement with those very recently reported by Bertozzi and co-workers for material prepared by a different route.[24] This confirms that the product reported here is indeed the α isomer and highlights the utility of the unusually stable ozonide **12** as a control element during acetolysis.

Experimental Section

Methyl 4,6-*O*-Benzylidene-2-deoxy-2-(2-methylallyl)-α-D-mannopyranoside (4). To a solution of compound **8**[10] (971 mg, 3.05 mmol) in anhydrous THF (12 mL) at 0 °C was added DIBAL (1.0 M in THF, 18.3 mL, 18.3 mmol) over 20 min. After the addition was complete, the mixture was allowed to warm to rt. After the reaction mixture was stirred at rt for 2 h, the mixture was cooled to 0 °C and water (5 mL) was added slowly. The resulting gel was dissolved with 1 N HCl and extracted with EtOAc. The combined organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine and then dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by flash column chromatography (15−25% EtOAc/hexanes) to give compound **7**[10] as a white solid (120 mg, 12%) and compound **4** as a clear syrup that solidified after standing at rt (736 mg, 75%): mp 69−71 °C; $[\alpha]^{24}_D$ +27.7 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.45 (m, 2H), 7.41−7.32 (m, 3H), 5.56 (s, 1H), 4.83 (s, 1H), 4.75 (s, 1H), 4.61 (s, 1H), 4.30−4.22 (m, 2H), 3.84−3.74 (m, 2H), 3.63 (dd, *J* = 9.4, 9.4 Hz, 1H), 3.34 (s, 3H) 2.56 (d, *J* = 14.2 Hz, 1H), 2.35 (ddd, *J* = 12.0, 5.7, 1.7 Hz, 1H), 2.07 (dd, *J* = 14.3, 12.1 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 137.3, 129.2, 128.3 (2C), 126.2 (2C), 112.3, 102.2, 101.2, 79.7, 69.0, 67.5, 63.1, 54.9, 42.3, 32.4, 22.2. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.24; H, 7.79.

Methyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2-methylallyl)-α-D-mannopyranoside (11). A solution of compound **4** (1.01 g, 3.16 mmol) in a mixture of MeOH (32 mL), water (3.2 mL), and TFA (2.1 mL) was allowed to stir at rt for 3 h. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, water, and brine, and then dried (Na_2SO_4) and filtered. The filtrate was concentrated and dried in vacuo to give a white solid. After the solid was dissolved in anhydrous pyridine (20 mL), acetic anhydride (1.80 mL, 19.1 mmol) was added dropwise. The mixture was allowed to stir at rt for 24 h and concentrated. After the resulting residue was dissolved in EtOAc and washed with 1 N HCl, saturated $NaHCO_3$, and brine, the organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the resulting residue was purified by flash column chromatography (25% EtOAc/hexanes) to give compound **11** as a clear syrup (940 mg, 83%): $[\alpha]^{24}_D$ +46.2 (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (dd, *J* = 9.8, 5.5 Hz, 1H), 5.12 (dd, *J* = 9.9, 9.9 Hz, 1H), 4.82 (s, 1H), 4.74 (s, 1H), 4.63 (s, 1H), 4.20 (dd, *J* = 12.2, 5.1 Hz, 1H), 4.14 (dd, *J* = 12.1, 2.5 Hz, 1H), 3.92 (ddd, *J* = 10.0, 5.0, 2.5 Hz, 1H), 3.36 (s, 3H), 2.45 (dddd, *J* = 11.1, 5.4, 3.6, 1.7 Hz, 1H), 2.30 (dd, *J* = 14.4, 2.60 Hz, 1H), 2.17 (dd, *J* = 14.4, 11.2 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.9, 169.8, 142.4, 112.6, 100.3, 70.9, 68.1, 66.4, 62.7, 55.0, 40.4, 33.2, 22.2, 20.8, 20.7 (2C); HRFABMS calcd for $C_{17}H_{26}O_8Na$ $(M + Na)^+$ 381.1525, found 381.1530. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 57.01; H, 7.38.

Methyl 2-Acetonyl-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-mannopyranoside (10). Compound **11** (305 mg, 0.85 mmol) was dissolved in a mixture of THF (6 mL) and water (6 mL). A solution of sodium periodate and potassium osmate dihydrate in water (3 mL) was added dropwise, and the mixture was allowed to stir at rt for 2 h. After addition of water (5 mL), the mixture was extracted with EtOAc. The combined organic extract was washed with 1 N $NaHSO_3$, water, saturated $NaHCO_3$, and brine and then dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (50% EtOAc/hexanes) to give compound **10** as a clear syrup that solidified after standing at rt (304 mg, 99%): mp 64−66 °C; $[\alpha]^{28}_D$ +49.3 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (dd, *J* = 9.9, 5.5 Hz, 1H), 5.03 (dd, *J* = 10.0, 10.0 Hz, 1H), 4.58 (s, 1H), 4.24 (dd, *J* = 12.2, 5.1 Hz, 1H), 4.09 (dd, *J* = 12.2, 2.3 Hz, 1H), 3.93 (ddd, *J* = 10.0, 5.1, 2.3 Hz, 1H), 3.37 (s, 3H), 2.93−2.86 (m, 1H), 2.82 (dd, *J* = 18.3, 3.9 Hz, 1H), 2.59 (dd, *J* = 18.3, 9.4 Hz, 1H), 2.19 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 170.6, 170.0, 169.5, 100.9, 69.6, 67.8, 66.6, 62.6, 55.1, 39.2, 38.1, 30.3, 20.8, 20.7, 20.6; HRFABMS calcd for $C_{16}H_{24}O_9Na$ $(M + Na)^+$ 383.1318, found 383.1310. Anal. Calcd for $C_{16}H_{24}O_9$: C, 53.31; H, 6.72. Found: C, 53.10; H, 6.76.

Methyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-*C*-((3-methyl-1,2,4-trioxolan-3-yl)methyl)-α-D-mannopyranoside (12). Compound **11** (609 mg, 1.70 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) and cooled to −78 °C. Ozone was bubbled through the solution for 15 min, and the resulting blue solution was flushed with argon until it was clear. Dimethyl sulfide (0.20 mL, 2.7 mmol) was added, and the reaction mixture was allowed to warm to rt and stirred at rt for 6 h. The mixture was diluted with CH_2Cl_2, washed with 1 N HCl and then with saturated $NaHCO_3$, and dried (Na_2SO_4). After filtration, the filtrate was

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concentrated and the residue was purified by flash column chromatography (35% EtOAc/hexanes) to give ozonide **12** as a clear syrup (493 mg, 71%) consisting of a 1.5:1 mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (dd, J = 10.0, 5.5 Hz, 0.6H), 5.31 (dd, J = 9.1, 5.5 Hz, 0.4H), 5.14 (s, 0.6H), 5.12 (s, 0.4H), 5.06 (s, 0.6H), 5.05 (s, 0.4H), 4.99 (dd, J = 10.1, 10.1 Hz, 0.4H), 4.98 (dd, J = 10.1, 10.1 Hz, 0.6H), 4.80 (d, J = 1.1 Hz, 0.6H), 4.76 (d, J = 1.1 Hz, 0.4H), 4.22 (dd, J = 12.2, 5.1 Hz, 0.6H), 4.21 (dd, J = 12.2, 5.0 Hz, 0.4H), 4.10 (dd, J = 12.2, 2.4 Hz, 1H), 3.90 (ddd, J = 10.0, 5.1, 2.4 Hz, 1H), 3.37 (s, 3H), 2.61−2.54 (m, 0.4H), 2.54−2.47 (m, 0.6H), 2.20−2.12 (m, 0.6H), 2.12−2.07 (m, 3.4H), 2.06−1.86 (m, 7H), 1.44 (s, 1.2 H), 1.43 (s, 1.8H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 170.6, 169.9, 169.8, 109.1, 101.6, 94.3, 70.2, 67.8, 66.4, 62.6, 55.1, 38.3, 31.7, 23.3, 20.9, 20.7, 20.7; HRFABMS calcd for $C_{17}H_{26}O_{11}Na$ $(M + Na)^+$ 429.1373, found 429.1371. Anal. Calcd for $C_{17}H_{26}O_{11}$: C, 50.23; H, 6.45. Found: C, 50.44; H, 6.57.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-*C*-((3-methyl-1,2,4-trioxolan-3-yl)methyl)-α-D-mannopyranose (13). To a solution of ozonide **12** (266 mg, 0.65 mmol) and acetic anhydride (0.10 mL, 1.1 mmol) in anhydrous CH_2Cl_2 (7 mL) at −25 °C was added 1 M sulfuric acid in anhydrous CH_2Cl_2 (0.37 mL). The resulting mixture was allowed to stir at −25 °C for 24 h, and then saturated $NaHCO_3$ was added. After it had warmed to rt, the mixture was diluted with EtOAc, washed with water and brine, and then dried (Na_2SO_4). After filtration, the filtrate was concentrated and the residue was purified by flash column chromatography (40% EtOAc in hexanes) to give ozonide **13** as a clear syrup (198 mg, 70%) consisting of a 1.5:1 mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 1.5 Hz, 0.6H), 6.19 (d, J = 1.5 Hz, 0.4H), 5.36 (dd, J = 10.1, 5.4 Hz, 0.6H), 5.33 (dd, J = 10.0, 5.4 Hz, 0.4H), 5.16−5.03 (m, 3H), 4.21 (dd, J = 12.3, 4.7 Hz, 0.6H), 4.20 (dd, J = 12.3, 4.8 Hz, 0.4H), 4.09 (dd, J = 12.3, 2.4 Hz, 0.4H), 4.08 (dd, J = 12.4, 2.4 Hz, 0.6H), 4.06−3.98 (m, 1H), 2.61−2.53 (m, 1H), 2.24−1.90 (m, 14H), 1.48 (s, 1.8H), 1.46 (s, 1.2H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 170.5, 169.8, 169.6, 168.6, 108.6, 94.2, 94.0, 70.2, 69.5, 65.7, 62.1, 37.3, 31.5, 23.7, 20.9, 20.7, 20.6, 20.5; HRFABMS calcd for $C_{18}H_{26}O_{12}Na$ $(M + Na)^+$ 457.1322, found 457.1317.

2-Acetonyl-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-mannopyranose (14).[24] To a solution of ozonide **13** (59 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt were added zinc dust (95 mg, 1.4 mmol) and acetic acid (0.20 mL). The reaction mixture was allowed to stir for 30 min and filtered. After the filtrate was concentrated, toluene was added and the solution was concentrated in vacuo. The resulting residue was purified by flash column chromatography (50% EtOAc/hexanes) to give compound **14** as a clear syrup (51 mg, 94%): $[\alpha]^{24}_D$ +51.7 (*c* 1.20, $CHCl_3$); both ^{1}H and ^{13}C NMR data were identical to the reported values.[24]

Acknowledgment. Financial support from the NIH (DK 54759) and the Cystic Fibrosis Foundation is gratefully acknowledged.

Supporting Information Available: General experimental conditions and the ^{1}H and ^{13}C NMR spectra for compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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