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Study on Metal-Induced Reactions of α-Diazocarbonyl Glucosides

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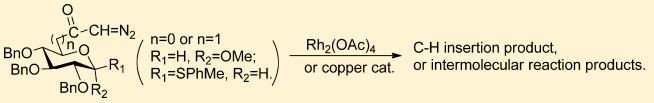
Supporting Information

ABSTRACT: Conversions of diazocarbonyl carbohydrate compounds catalyzed by a series of rhodium and copper catalysts in conventional heating or microwave conditions were investigated. C−H insertion product was obtained in the presence of $Rh_2(OAc)_4$. Intermolecular reactions rather than intramolecular reactions occurred in the presence of copper catalysts.



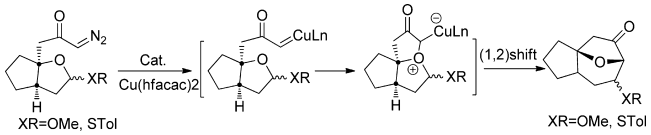
1. INTRODUCTION

α-Diazocarbonyl compounds play an important role in synthetic organic chemistry. The discovery of metal catalysts, especially rhodium and copper catalysts, allowed α-diazocarboids to be developed as synthetically attractive intermediates involved in a wide variety of chemical transformations such as C−H insertion,[1,2] α,α-substitution,[3] Wolff rearrangement,[4] ylide formation,[5−7] dimerization,[8] etc. On the other hand, carbohydrate derivatives are chemically and biologically interesting molecules due to their important roles in biological processes and potential applications in the biomedical field. Introducing diazoketone to the carbohydrate structure should be an interesting attempt at constructing novel carbohydrate derivatives.

So far, only a few works about catalytic conversion of diazosugar have been reported, most of which focused on rhodium catalysts. Rhodium catalyst induced decomposition of diazoester attached at O-3 of glucofuranose giving rise to an intramolecular C-2 insertion process was described by D. F. Berndt and P. Norris.[9] In H. M. Branderhorst and co-workers' work,[10] the C−H insertion aromatic ring of benzyl groups in glucoside was the most favorable reaction. If benzyls were replaced by methyl groups in the glucose system, glucoside carbene dimers (cis and trans isomer mixture) were obtained as major products.

We were interested to learn more about the transformations of active carbene in different carbohydrate structures exposed to metal catalysts. In 2005, Graham K. Murphy and F. G. West described Stevens [1,2]-shift reactions of two cyclic mixed acetals with diazoketone side chains catalyzed by $Cu(hfacac)_2$[11] in which cyclic acetals rearranged to afford ether-bridge cycloheptane ring products through oxonium ylide intermediates (Scheme 1). We also wondered if this rearrangement could occur on the diazocarbonyl carbohydrate derivatives. If not, what would happen? Therefore, key intermediates **1**−**4** were designed and synthesized (Figure 1). Methoxy and *p*-thiocresol were selected as anomeric position protecting groups on the basis of Graham K. Murphy's work. Compounds **2** and **4** with a longer side chain on the C5-position were designed considering that they might geometrically favor C−H insertion or Stevens rearrangement.

Scheme 1. Stevens [1,2]-Shift Reactions of Two Cyclic Acetals with Diazoketone Side Chains



The key transformation was explored with rhodium and copper catalysts, including $Rh_2(OAc)_4$, $Cu(hfacac)_2$, $Cu(tfacac)_2$, $Cu(acac)_2$, and Cu^0. $Rh_2(OAc)_4$ was used since it is a versatile catalyst widely used in reactions involving α-diazocarbonyl groups. The copper catalysts were applied because they had never been used in reactions of diazoketone carbohydrates and their costs are relatively low.[12]

2. RESULTS AND DISCUSSION

Intermediate **1** was synthesized starting from α-methyl glucose (**5**). Compound **6** was readily prepared following the literature procedures.[13,14] The hydroxy group of **6** was oxidized by (diacetoxyiodo)benzene (BAIB) and 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) in CH_2Cl_2/H_2O (2:1) to give acid **7**, in which a catalytic amount of TEMPO was used in combination with a catalytic amount of BAIB as stoichiometric oxidants.[15] Compound **7** reacted with isobutyl chloroformate followed by diazomethane to provide desired diazoketone

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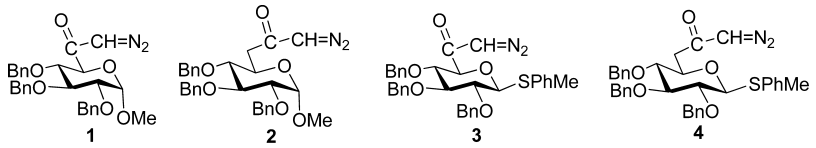
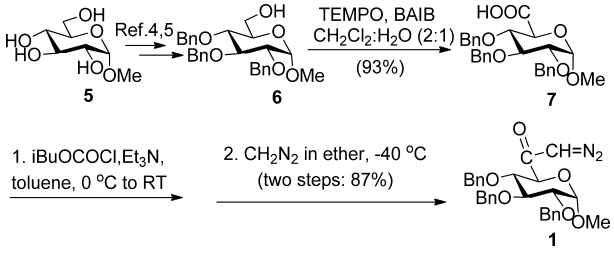


Figure 1. Structures of key intermediates **1**–**4**.

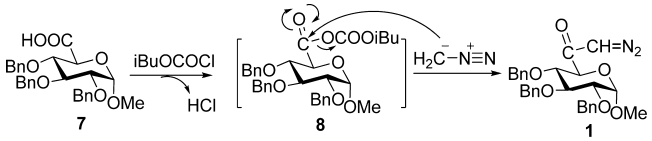
derivative **1** (Scheme 2). The process of conversion into diazoketone should be realized through a carbonic anhydride

Scheme 2. Synthesis of Diazoketone Derivative 1



intermediate, **8**, and at the same time generated hydrochloric acid (Scheme 3).[16] Diazomethane was added to the reaction at −40 °C, and then the reaction was warmed to room temperature to provide **1** in good yield.

Scheme 3. Proposed Mechanism for Formation of Diazoketone 1



The 6-hydroxy group of compound **6** was oxidized by pyridinium chlorochromate (PCC), giving aldehyde **9**.[17] Wittig reaction of **9** with $Ph_3P^+CH_2Br^-$ afforded alkene **10** in 56% yield. Hydroboration with borane dimethyl sulfide and oxidation with hydrogen peroxide converted **10** to alcohol **11** in 80% yield.[18] Oxidation of alcohol **11** by BAIB and TEMPO in CH_2Cl_2 and water (2:1) gave acid **12**.[19] Treatment of **12** with oxalyl chloride followed by a solution of diazomethane in ether furnished diazoketone intermediate **2** with one more carbon at the 6-position (Scheme 4). Isobutyl chloroformate was not applied here because of byproduct **12a** formation (Scheme 5).

The preparation of intermediate **3** started from D-glucose **13** (Scheme 6). Alcohol **14** was obtained according to the literature procedures.[20] A synthetic route similar to that of compound **1** was applied to give desired intermediate **3**. The oxidation of **14** to **15** should be carefully monitored by TLC and timely quenched with aqueous thiosulfate solution to avoid unwanted sulfoxide or sulfone formation.[9] **15** was converted to diazoketone **3** via intermediate **16** (Scheme 7). The acid chloride formed during the reaction process would result in decomposition of thioacetal, which could be avoided by using 2,6-lutidine as a mild hindered base. Isobutyl chloroformate was not suitable in this case due to its unacceptable low yield.[9]

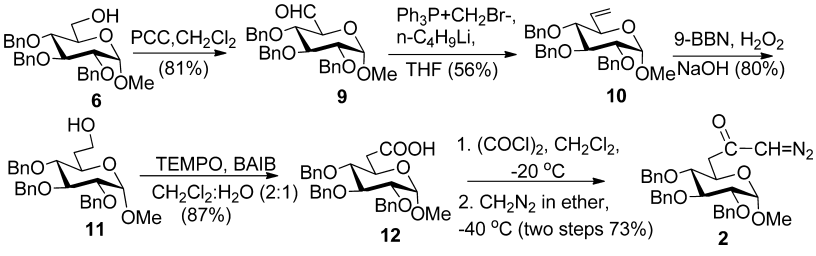
Desired intermediate **4** was obtained through a route similar to that of intermediate **2** (Scheme 8). It should be noted that a high concentration (>1M) was necessary for completing oxidation of **14** to provide aldehyde **17** in a short time (about 1 h). Aldehyde product could be obtained in high yield when the reaction was performed in CH_2Cl_2 within a proper reaction time, so the reaction should be carefully monitored by TLC and timely quenched. While water was added (CH_2Cl_2/H_2O, 2:1), only carboxylic acid product **20** was obtained. **20** was then converted to diazoketone intermediate **4** using oxalyl chloride followed by freshly prepared diazomethane. Here the active hydrogen of the carboxyl of **20** could transfer to diazomethane and finally provided **20a** as a byproduct (Scheme 9).

The key transformation was explored afterward with rhodium and copper catalysts: $Rh_2(OAc)_4$, $Cu(hfacac)_2$, $Cu(tfacac)_2$, $Cu(acac)_2$, and Cu^0.

In the presence of rhodium catalyst (rhodium acetate), only diazosugar **1** provided major product **21**. The result indicated that C−H insertion reaction was favorable under rhodium acetate (Scheme 10), in which the carbon of the methylene was activated by the next oxygen. The aromatic cycloaddition was not favorable, which might be ascribed to the more remote distance of the benzyl protecting group.

The structure of **21** was identified by NMR analysis and mass spectrometry (M + NH_4^+, 492.2383). The disappearance of one of the three carbon signals of CH_2 of the benzyl groups at about 75 ppm indicated that the reaction should occur at CH_2 of the benzyl group. The structure could be identified by ^1H–^1H COSY, HMQC, and NOESY. A strong correlation in NOESY between the proton of $COCH_2$ (H-3 of compound **21**) and *CH*Ph (H-2 of compound **21**) confirmed the structure of **21** (Figure 2). Formation of the C−H insertion product **21** might be ascribed to the proper distance between C4 and the

Scheme 4. Synthesis of Key Intermediate 2



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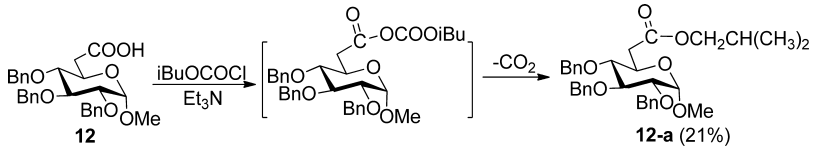
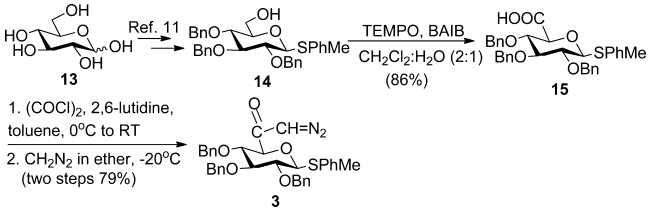
Scheme 5. Formation of Byproduct 12a in the Presence of Isobutyl Chloroformate



Scheme 6. Synthesis of Key Intermediate 3



diazoketone group of compound **1** and the stability of the six-membered ring.

While catalyzed by $Cu(acac)_2$, **1** provided **22** as the major product (Scheme 11). Under the same conditions, compound **2** gave dimer **23** as the main product (Scheme 12). NMR analysis showed a mixture of cis and trans dimers, in which one isomer (**23a**) was obtained as the main product when the reaction was finished, but **23a** transformed slowly and continuously to the other isomer (**23b**) with a lower R_f value. It was difficult to get a very pure **23a** since it was always in the company of **23b**. After storage at room temperature for about four weeks, **23b** became the major product in the mixture. The chemical shifts of the proton signals of CH=CH were at 6.69 (**23a**) and 6.18 (**23b**) ppm. Both isomers displayed signals of a monosaccharide due to their symmetrical structures.

When exposed to $Cu(tfacac)_2$, compound **1** produced two relatively major products: C−H insertion product **21** and dimerization product **22**. NMR analysis of **22** showed a mixture of cis and trans dimers with a ratio of 1.5:1. Compound **2** afforded dimerization mixture **23a** and **23b** in a low yield.

In the presence of $Cu(hfacac)_2$, all the diazocarbonoid intermediates gave complex products. The complex products were mixtures of a lot of products in TLC. There was no main product, and it was hard to isolate one of them. The results are summarized in Table 1. They suggested that the greater the number of fluorine substitutions in copper catalysts, the more active the copper catalysts are in the reaction.

Exposure of all the diazosugar intermediates to copper catalysts in methanol with heating by microwave provided methyl ether products **24**−**27** (Figure 3) through intermolecular α,α-substitution.

MeOH was chosen as the solvent because it is a good solvent for microwave absorption. Dichloromethane was also used to avoid α,α-substitution of solvent molecules. In such cases, compounds **1** and **2** preferred C−H insertion and dimer formation as well (Table 2).

3. CONCLUSION

C−H insertion, α,α-substitution, or dimer products were obtained when anomeric methoxy glucosides were exposed to $Rh_2(OAc)_4$ or copper catalysts in different conditions. The reactions depend greatly on the structures of the diazo precursor, catalysts applied, and reaction reagents selected. Any change of these factors might give different results. Compared with the glucoside with anomeric methoxide, the thioglycoside displayed poor selectivity and gave more complicated products for *p*-thiocresol at the e bond position might also participate in the reaction.

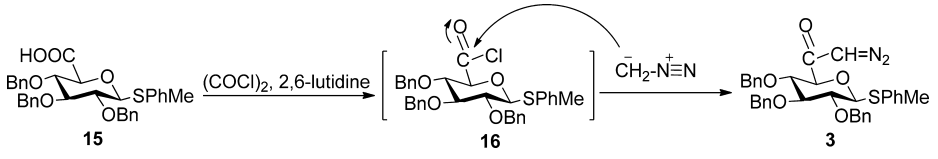
The synthesis of marine polycyclic ethers is an attractive topic for organic chemists for their unique and complex structures and potent biological activities.[21] It is worthwhile to note that the formation of a C−H insertion product provides a novel method for constructing bicyclic ether rings from carbohydrates, and the dimer formation is interesting since it might be applied to connect sugar residues in an oligosaccharide. The catalytic reaction of diazoketone on sugars would provide various novel carbohydrate derivatives which are considered to possess biological and chemical interests and are worthwhile to further explore.

4. EXPERIMENTAL SECTION

General Procedures. ^1H NMR chemical shifts were referenced to residual protic solvent ($CDCl_3$, δ_H = 7.30). ^{13}C NMR chemical shifts were referenced to the solvent signal (δ_C = 77.0 for the central line of $CDCl_3$). Reactions were monitored by thin-layer chromatography (TLC) on a precoated silica gel 60 F_{254} plate (layer thickness 0.2 mm) and detected with cerium molybdate solution. Column chromatography was performed on silica gel 60 (230−400 mesh or 200−300 mesh). Microwave experiments were carried out using a single mode cavity synthesizer.

1-Methyl-2,3,4-tri-*O*-benzyl-7-deoxy-7-diazo-α-D-glucoheptopyran-6-ulose (1). Carboxylic acid **7** (110 mg, 0.23 mmol) was dissolved in anhydrous toluene (2 mL), and the solution was cooled to 0 °C. Triethylamine (64 μL, 0.46 mmol) was added followed by iBuOCOCl (60 μL, 0.46 mmol). The solution was allowed to reach room temperature and stirred for 12 h. The reaction solution was cooled to −40 °C, and then a solution of diazomethane[22] in ether (4 mL, excess) was added. The resulting reaction mixture was stirred for 2 h, and then excess diazomethane was removed by bubbling argon through the solution for another 5 min. The solvent was removed by evaporation, and the residue was purified by silica gel chromatography using cyclohexane/EtOAc (10:1) to give **1** as a yellow syrup (100 mg, 87%): R_f = 0.29 (cyclohexane/EtOAc, 5:1); $[\alpha]_D$ = +56 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 15H, 3 × Ph), 5.47 (br, 1H, CH=N_2), 5.00−4.64 (m, 6H, 3 × PhCH_2), 4.63 (d, 1H, $J_{1,2}$ = 3.5 Hz, H_1), 4.09−4.01 (m, 2H, H_3, H_5), 4.06 (dd, 1H, $J_{1,2}$ = 3.5

Scheme 7. Formation of Intermediate 3



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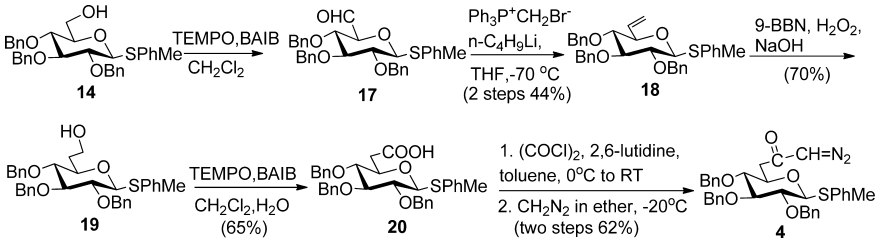
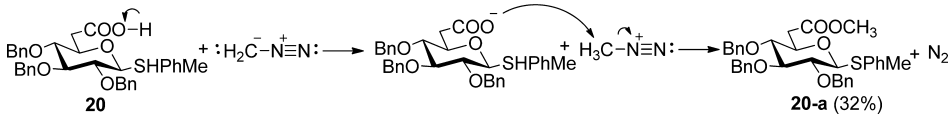
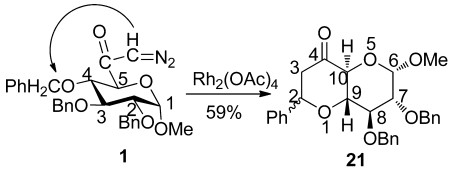
Scheme 8. Synthesis of Key Intermediate 4



Scheme 9. Formation of the Byproduct 20a



Scheme 10. Formation of Product 21



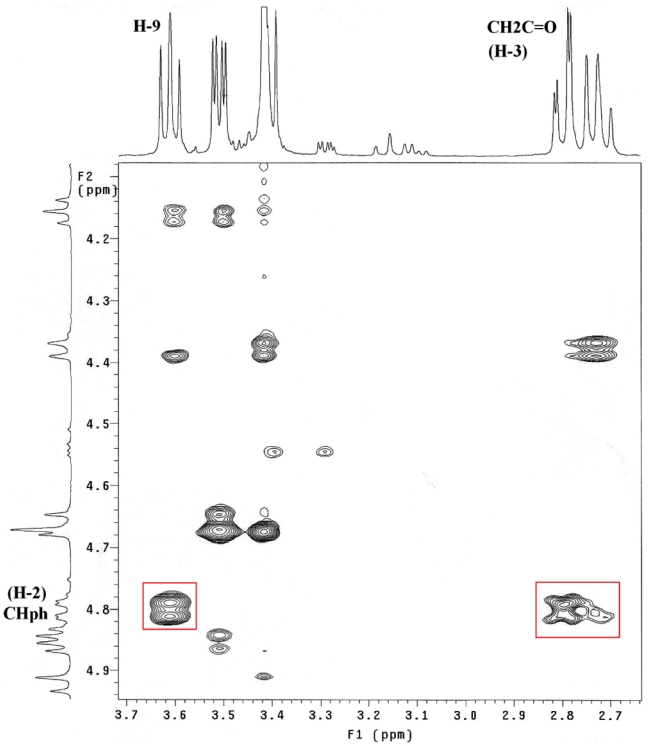


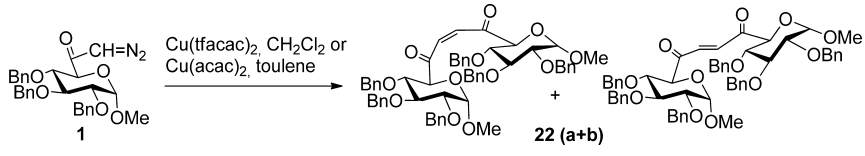
Figure 2. NOESY spectrum of compound **21**.

Hz, $J_{2,3}$ = 9.6 Hz, H_2), 3.64 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, H_4), 3.41 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.90 (C═O), 139.0, 138.4, 138.2, 129.0, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.1 (18C, 3 × Ph), 99.1 (C_1), 82.1 (C_3), 80.0 (C_4), 79.7 (C_2), 76.4, 75.6, 74.0 (3 × PhCH_2), 73.8 (C_5), 56.1 (OCH_3), 55.4 (CH═N_2); HRMS (FAB, M + Na^+) m/z calcd for $C_{29}H_{30}O_6N_2Na$ 525.2002, found 525.2006.

1-Methyl-2,3,4-tri-*O*-benzyl-8-deoxy-8-diazo-α-D-glucoheptopyran-7-ulose (2). Carboxylic acid **12** (337 mg, 0.685 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) along with anhydrous DMF (500 μL), and the solution was cooled to −20 °C. Oxalyl chloride (120 μL, 1.37 mmol) was added. The reaction mixture was stirred for 12 h and then cooled to −40 °C. A solution of diazomethane in ether (10 mL) was added and the resulting mixture stirred for 1 h. Excess diazomethane was removed by bubbling of argon through the reaction mixture for another 10 min. The solvent was removed by evaporation. Silica gel chromatography of the residue, using cyclohexane/EtOAc (8:1), afforded **2** as a yellow syrup (265 mg, 73%): R_f = 0.32 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +63 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 15H, 3 × Ph), 5.24 (br, 1H, CH═N_2), 5.05−4.62 (m, 6H, 3 × PhCH_2), 4.54 (d, 1H, $J_{1,2}$ = 3.5 Hz, H_1), 4.18−4.13 (m, 1H, H_3), 4.04 (t, 1H, $J_{4,5}$ = $J_{5,6b}$ = 9.3 Hz, H_5), 3.53 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.6 Hz, H_2), 3.43 (s, 3H, OCH_3), 3.33−3.26 (m, 1H, H_4), 2.73 (dd, 1H, $J_{5,6a}$ = 2.7 Hz, J_{gem} = 14.8 Hz, H_{6a}), 2.34 (d, 1H, $J_{5,6b}$ = 9.3 Hz, H_{6b}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4 (C═O), 139.1, 138.5, 138.5, 128.9, 128.9, 128.9, 128.54, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1 (18C, 3 × Ph), 98.3 (C_1), 82.4 (C_5), 81.4 (C_4), 80.5 (C_2), 67.6 (C_3), 55.8 (OCH_3), 43.3 (CH_2CO); HRMS (FAB, M + Na^+) m/z calcd for $C_{30}H_{32}O_6N_2Na$ 539.2158, found 539.2144.

1-*p*-Tolyl-2,3,4-tri-*O*-benzyl-7-deoxy-7-diazo-1-thio-β-D-glucoheptopyran-6-ulose (3). A solution of carboxylic acid **15** (100 mg, 0.17 mmol) in anhydrous toluene (1 mL) was cooled to 0 °C. Oxalyl chloride (76 μL, 0.88 mmol) was added dropwise followed by 2,6-lutidine (102 μL, 0.88 mmol). The solution was allowed to reach room temperature and stirred overnight. Then it was cooled to −20 °C. A solution of CH_2N_2 in Et_2O (3 mL) was added and the resulting solution stirred for 1 h. CH_2Cl_2 and aqueous NaCl solution were added. The organic phase was separated and dried over $MgSO_4$. After concentration under reduced pressure, the resulting residue was purified by silica gel chromatography (cyclohexane/EtOAc, 15:1) to

Scheme 11. Conversion of 1 to 22 in the Presence of Cu(tfacac)$_2$ or Cu(acac)$_2$



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Scheme 12. Conversion of 2 to 23 in the Presence of $Cu(tfacac)_2$ or $Cu(acac)_2$

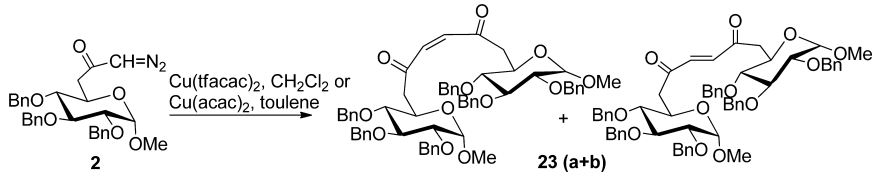

Table 1. Diazoketone Decomposition Catalyzed by Rh or Cu Catalysts under Conventional Conditions

compd	$Rh_2(OAc)_4/CH_2Cl_2$	$Cu(hfacac)_2/CH_2Cl_2$	$Cu(tfacac)_2/CH_2Cl_2$	$Cu(acac)_2$/toluene	Cu/toluene
1	**21** (mixture of isomers, 9:1, 59%)[a]	complex[b]	**21** (42%) + **22a** + **22b** (1.5:1, 23%)	**22a** + **22b** (1.5:1, 53%)[b]	no reaction[c]
2	complex[a]	complex[b]	**23a** + **23b** (22%)	**23a** + **23b** (58%)[b]	no reaction[c]
3	complex[a]	complex[b]	complex[b]	complex[b]	no reaction[c]
4	complex[a]	complex[b]	complex[b]	complex[b]	complex[c]

[a]Conditions: refluxed, 10 min. [b]Conditions: refluxed, 5 min. [c]Conditions: refluxed, 2 h.

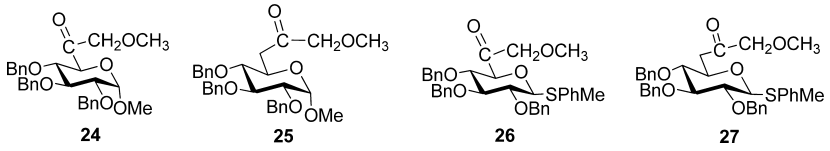

Figure 3. Structures of methyl ether products **24**–**27**.

Table 2. Microwave Diazoketone Decomposition Catalyzed by Copper Catalysts

	$Cu(tfacac)_2$		$Cu(acac)_2$	
compd	CH_3OH	CH_2Cl_2	CH_3OH	CH_2Cl_2
1	**24** (60%)[a]	**21**(53%)[b]	**24** (62%)[a]	**21**(21%) + **22** (21%)
2	**25** (66%)[a]	**23a** + **23b** (49%)[b]	**25** (76%)[a]	**23a** + **23b** (53%)[b]
3	**26** (60%)[a]	complex[b]	**26** (67%)[a]	no reaction
4	**27** (62%)[a]	complex[b]	**27** (64%)[a]	decomposed

[a]Conditions: 100 °C, 5 min. [b]Conditions: 80 °C, 5–10 min.

give **3** as a white solid (80 mg, 79%): R_f = 0.30 (P-E/EtOAc, 3:1); mp 131.0–132.5 °C; $[\alpha]_D$ = −24 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.17 (m, 19H, 3 × *Ph*CH_2, *SPh*CH_3), 5.58 (br, 1H, CH═N_2), 4.94–4.69 (m, 6H, 3 × Ph*C*H_2), 4.66 (d,1H, $J_{1,2}$ = 9.7 Hz, H_1), 3.83 (d, 1H, $J_{4,5}$ = 8.4 Hz, H_5), 3.76–3.70 (m, 2H, H_3, H_4), 3.49 (dd, 1H, $J_{1,2}$ = 9.7 Hz, $J_{2,3}$ = 8.4 Hz, H_2), 2.38 (s, 3H, SPh*C*H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3 (C=0), 138.8, 138.6, 138.3, 138.0, 133.5, 130.2, 129.4, 128.9, 128.9, 128.9, 128.8, 128.8, 128.6, 128.4, 128.3, 128.2 (24C, 3*Ph*CH_2, *SPh*CH_3), 88.3 (C_1), 86.1 (C_3), 81.9 (C_5), 80.8 (C_2), 79.4 (C_4), 76.2, 75.8, 75.2 (3 × Ph*C*H_2), 21.6 (SPh*C*H_3); HRMS (CI, M + H^+) *m*/*z* calcd for $C_{35}H_{35}O_5N_2S$ 595.2267, found 595.2278.

1-*p*-Tolyl-2,3,4-tri-*O*-benzyl-8-deoxy-8-diazo-1-thio-β-D-glucooctopyrano-7-ulose (4) and *p*-Tolyl 2,3,4-Tri-*O*-benzyl-1-thio-β-D-glucoheptopyranoside 7-Methanate (20a). A solution of **20** (120 mg, 0.20 mmol) in anhydrous toluene (3 mL) was cooled to −15 °C. $(COCl)_2$ (21 μL, 0.24 mmol) was added followed by 2,6-lutidine (28 μL, 0.24 mmol). The solution was allowed to reach room temperature and stirred for 15 h. The reaction was cooled to −45 °C. CH_2N_2 in Et_2O (5 mL) was added and the resulting solution stirred for 30 min. Excess CH_2N_2 and solvent were removed by evaporation. The residue was isolated by silica gel chromatography with cyclohexane/EtOAc (8:1) to provide **4** as a light yellow solid (75 mg, 62%) and **20a** as a white amorphous solid (38 mg, 32%).

Data for compound **4**: R_f = 0.37 (cyclohexane/EtOAc, 3:1); mp 138.0–140.0 °C; $[\alpha]_D$ = −17.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.13 (m, 19H, 3 × *Ph*CH_2, *SPh*CH_3), 5.11 (br, 1H, CH═N_2), 4.97–4.64 (m, 7H, 3 × Ph*C*H_2, H_1), 3.75–3.71 (m, 2H, H_3, H_5), 3.51 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.6 Hz, H_2), 3.37 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz, H_4), 2.69 (dd, 1H, J_{gem} = 14.5 Hz, $J_{5,6b}$ = 1.7 Hz, H_{6b}), 2.42–2.32 (m, 4H, H_{6a}, SPh*C*H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3 (C=0), 138.6, 138.3, 138.2, 132.8, 130.2, 128.9, 128.9, 128.7, 128.4, 128.4, 128.4, 128.3, 128.2 (24C, 3 × *Ph*CH_2, *SPh*CH_3), 88.2 (C_1), 87.0 (C_3), 81.8 (C_2), 81.0 (C_4), 76.4 (C_5), 76.3, 76.0, 75.5 (3C, 3 × Ph*C*H_2), 43.4 (*C*H_2C═O), 21.5 (SPh*C*H_3); HRMS (FAB, M + Na^+) *m*/*z* calcd for $C_{36}H_{36}O_5N_2SNa$ 631.2243, found 631.2243.

Data for compound **20a**: R_f = 0.53 (cyclohexane/EtOAc, 3:1); $[\alpha]_D$ = +21 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.14 (m, 19H, 3 × *Ph*CH_2, *SPh*CH_3), 4.98–4.66 (m, 6H, 3 × Ph*C*H_2), 4.64 (d, 1H, $J_{1,2}$ = 9.8 Hz, H_1), 3.79 (ddd, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 3.4 Hz, $J_{5,6b}$ = 8.9 Hz, H_5), 3.74 (t, 1H, $J_{2,3}$ = $J_{3,4}$ =8.9 Hz, H_3), 3.62 (s, 3H, OCH_3), 3.49 (dd, 1H, $J_{1,2}$ = 9.8 Hz, $J_{2,3}$ = 8.9 Hz, H_2), 3.38 (dd, 1H, $J_{3,4}$ = 8.9 Hz, $J_{4,5}$ = 9.6 Hz, H_4), 2.78 (dd, 1H, J_{gem} = 15.3 Hz, $J_{5,6a}$ = 3.4 Hz, H_{6a}), 2.48 (dd, 1H, J_{gem} = 15.3 Hz, $J_{5,6b}$ = 8.9 Hz, H_{6b}), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (C═O), 138.7, 138.4, 138.2, 137.9, 132.4, 130.5, 130.0, 128.9, 128.9, 128.8, 128.6, 128.4, 128.3, 128.3, 128.2, 128.2 (24C, 3 × *Ph*CH_2, *SPh*CH_2), 88.3 (C_1), 87.0 (C_3), 81.8 (C_2), 81.0 (C_4), 76.2, 75.9, 75.5 (3 × Ph*C*H_2), 76.1 (C_5), 52.1 (OCH_3), 37.7 (C_6), 21.5 (SPh*C*H_3); HRMS (FAB, M + Na^+) *m*/*z* calcd for $C_{36}H_{38}O_6SNa$ 621.2287, found 621.2297.

1-Methyl-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucoheptopyranuronic Acid (12). To a solution of **11** (200 mg, 0.42 mmol) and TEMPO (13 mg, 0.08 mmol) in CH_2Cl_2 and H_2O (2:1, 1.5 mL) was added BAIB (336 mg, 1.05 mmol). The mixture was stirred at room temperature for 2 h and then diluted with CH_2Cl_2 (5 mL). The solvent was removed by evaporation, and the residue was purified by silica gel chromatography with cyclohexane/EtOAc (5:1) to provide **12** as a colorless syrup (180 mg, 87%): R_f = 0.24 (cyclohexane/EtOAc, 1:1); $[\alpha]_D$ = +34 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 15H, 3 × Ph), 5.04–4.67 (m, 6H, 3 × Ph*C*H_2), 4.54 (d, 1H, $J_{1,2}$ = 3.4 Hz, H_1), 4.11 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6a}$ = 2.7 Hz, $J_{5,6b}$ = 9.6 Hz, H_5), 4.03 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H_3), 3.53 (dd, 1H, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 9.5 Hz, H_2), 3.40 (s, 3H, OCH_3), 3.28 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H_4), 2.80 (dd, 1H, J_{gem} = 15.6 Hz, $J_{5,6a}$ = 2.7 Hz, H_{6a}), 2.34 (dd, 1H, J_{gem} = 15.6 Hz, $J_{5,6b}$ = 9.6 Hz, H_{6b}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C═O), 139.0, 138.5, 138.4, 129.0, 128.9, 128.9, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1 (18C, 3 × Ph), 98.3 (C_1), 82.3 (C_3), 81.2 (C_2), 80.5 (C_4), 76.2, 75.5, 73.8 (3 × Ph*C*H_2), 67.4 (C_5), 55.8 (OCH_3), 37.4 (C_6); HRMS (ESI, M + Na^+) *m*/*z* calcd for $C_{29}H_{32}O_7Na$ 515.2046, found 515.2048.

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Methyl 2,3,4-Tri-*O*-benzyl-α-D-glucoheptopyranoside 7-Isobutyrate (12a). Carboxylic acid **12** (120 mg, 0.25 mmol) was dissolved in dry toluene (2 mL), and the solution was cooled to 0 °C. Triethylamine (68 μL, 0.49 mmol) was added followed by iBuOCOCl (63 μL, 0.49 mmol). The solution was allowed to reach room temperature and stirred for 12 h. The reaction solution was cooled to −40 °C, and then a solution of diazomethane in Et_2O (4 mL, excess) was added. The reaction mixture was stirred for 1 h, and then excess diazomethane was removed by bubbling argon through the solution for another 5 min. Solvent was removed by evaporation. Silica gel chromatography, using cyclohexane/EtOAc (10:1), provided **2** as a yellow syrup (56 mg, 44%) and **12a** as a white amorphous solid (30 mg, 21%): R_f = 0.62 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +20 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.32 (m, 15H, 3 × Ph), 5.05−4.61 (m, 6H, 3 × PhCH_2), 4.56 (d, 1H, $J_{1,2}$ = 3.5 Hz, H_1), 4.14 (ddd, 1H, $J_{5,6a}$ = 2.9 Hz, $J_{4,5}$ = 9.6 Hz, $J_{5,6b}$ = 9.8 Hz, H_5), 4.04 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H_3), 3.92 (dd, 1H, *J* = 10.6 Hz, *J* = 6.8 Hz, one of OCH_2), 3.82 (dd, 1H, *J* = 10.6 Hz, *J* = 6.8 Hz, one of OCH_2), 3.54 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.6 Hz, H_2), 3.43 (s, 3H, OCH_3), 3.29 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H_4), 2.81 (dd, 1H, J_{gem} = 15.3 Hz, $J_{5,6a}$ = 2.9 Hz, H_{6a}), 2.36 (dd, 1H, J_{gem} = 15.3 Hz, $J_{5,6b}$ = 9.8 Hz, H_{6b}), 1.98−1.89 (m, 1H, $CH(CH_3)_2$), 0.93 (d, 6H, *J* = 6.7 Hz, CH (CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (C═O), 139.1, 138.5, 128.9, 128.9, 128.8, 128.6, 128.4, 128.4, 128.3, 128.2, 128.1 (18C, 3 × Ph), 98.3 (C_1), 82.4 (C_3), 81.5 (C_4), 80.5 (C_2), 76.2, 75.5, 73.8 (3 × PhCH_2), 71.2 ($COOCH_2CH$), 67.7 (C_5), 55.7 (OCH_3), 37.6 (C_6), 28.1 ($CH(CH_3)_2$), 19.5, 19.5 (2C, 2 × CH_3); HRMS (FAB, M + Na^+) *m*/*z* calcd for $C_{33}H_{40}O_7Na$ 571.2672, found 571.2671.

1-*p*-Tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranuronic Acid (15). BAIB (1.4 g, 4.25 mmol) was added to a solution of **14** (1 g, 1.7 mmol) and TEMPO (56 mg, 0.36 mmol) in CH_2Cl_2 and H_2O (2 mL + 1 mL). The reaction mixture was stirred at room temperature for 2 h. $Na_2S_2O_3$ aqueous solution (1 mL) was added to quench the reaction. The organic phase was washed with NaCl aqueous solution and dried over Mg_2SO_4. After concentration, the residue was purified by silica gel chromatography, using cyclohexane/EtOAc (7:1), to provide **15** as a yellow syrup (830 mg, 86%): R_f = 0.27 (P-E/EtOAc, 1:1); $[\alpha]_D$ = −10 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.18 (m, 19H, 3 × *Ph*CH_2, S*Ph*CH_3), 4.98−4.68 (m, 7H, 3 × PhCH_2, H_1), 4.00 (d, 1H, $J_{4,5}$ = 9.2 Hz, H_5), 3.86 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.2 Hz, H_4), 3.78 (t, 1H, $J_{3,4}$ = 9.2 Hz, $J_{2,3}$ = 8.4 Hz, H_3), 3.57 (dd, 1H, $J_{2,3}$ = 8.4 Hz, $J_{1,2}$ = 9.6 Hz, H_2), 2.38 (s, 3H, SPhCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (C=0), 138.8, 138.4, 138.2, 137.7, 133.5, 130.3, 129.5. 129.0, 129.0, 128.9, 128.9, 128.9, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3 (24C, 3 × *Ph*CH_2, S*Ph*CH_3), 88.8 (C_1), 85.8 (C_3), 80.6 (C_2), 79.1 (C_4), 77.8 (C_5), 76.2, 75.8, 75.5 (3 × PhCH_2), 21.6 (SPhCH_3); HRMS (CI, M + NH_4^+) *m*/*z* calcd for $C_{34}H_{38}O_6NS$ 588.2420, found 588.2402.

***p*-Tolyl 2,3,4-Tri-*O*-benzyl-1-thio-β-D-glucohexodialdo-1,5-pyranoside (17) and *p*-Tolyl 2,3,4-Tri-*O*-benzyl-6,7-dideoxy-1-thio-β-D-glucohept-6-enopyranoside (18).** BAIB (4.86 g, 15.1 mmol) was added to a solution of **16** (7 g, 12.6 mmol) and TEMPO (205 mg, 1.3 mmol) in CH_2Cl_2 (7 mL). The reaction mixture was stirred at room temperature for 3 h and then diluted with CH_2Cl_2 (10 mL). The mixture was washed with aqueous $Na_2S_2O_3$ solution, aqueous $NaHCO_3$ solution, and brine and dried over $MgSO_4$. The filtrate was concentrated and isolated by silica gel chromatography, using P-E/EtOAc (10:1) as the eluent, to afford 5 g of crude product **17** as a colorless syrup.

A mixture of MeP^+Ph_3Br (4.8 g, 13.5 mmol) in THF (200 mL) was cooled to −70 °C. Butyllithium (2.2 M, 6.7 mL, 13.5 mmol) was slowly injected to give a yellow solution. After this solution was stirred at −70 °C for 1 h, aldehyde **17** (5 g, 0.36 mmol) dissolved in 50 mL of THF was slowly added. The mixture was stirred for 30 min, then warmed to 0 °C, and stirred overnight. Aqueous NH_4Cl and ether were added. The organic phase was washed with water (2×) and brine, dried over $MgSO_4$, and concentrated to a residue that was purified by silica gel chromatography, using P-E/EtOAc as the eluent, to afford **18** as a light yellow syrup (2.4 g, 35% for two steps). The starting material **16** (1.5 g) was recovered.

Data for compound **18**: R_f = 0.66 (P-E/EtOAc, 3:1); $[\alpha]_D$ = +4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.17 (m, 19H, 3 × *Ph*CH_2, S*Ph*CH_3), 6.04 (m, 1H, *CH*═CH_2), 5.57 (dt, 1H, one of CH═*CH*$_2$), 5.53 (dt, 1H, one of CH═*CH*$_2$), 4.99−4.70 (m, 7H, 3 × PhCH_2, H_1), 3.86 (dd, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6}$ = 3.6 Hz, H_5), 3.77 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 8.9 Hz, H_3), 3.54 (dd, 1H, $J_{2,3}$ = 8.9 Hz, $J_{1,2}$ = 9.8 Hz, H_2), 3.40 (t, 1H, $J_{3,4}$ = 8.9 Hz, $J_{4,5}$ = 9.6 Hz, H_4), 2.40 (s, 3H, SPh*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.6, 138.4, 138.3, 133.4, 130.1, 128.9, 128.9, 128.7, 128.5, 128.5, 128.3, 128.2 (24C, 3 × *Ph*CH_2, S*Ph*CH_3), 135.0 (*CH*═CH_2), 118.7 (CH═*CH*$_2$), 88.2 (C_1), 86.8 (C_3), 82.5 (C_4), 81.3 (C_2), 80.2 (C_5), 76.4, 75.9, 75.6 (3 × PhCH_2), 21.6 (SPh*CH*$_3$); HRMS (FAB, M + Na^+) *m*/*z* calcd for $C_{35}H_{36}O_4SNa$ 575.2232, found 575.2211.

***p*-Tolyl 2,3,4-Tri-*O*-benzyl-6-deoxy-1-thio-β-D-glucohepto-pyranoside (19).** Alkene **18** (1.1 g, 1.99 mmol) was added to 0.5 M 9-BBN in THF (20 mL, 9.96 mmol). The mixture was stirred at room temperature until TLC showed complete conversion of starting material. The solution was cooled to 0 °C. NaOH aqueous solution (2 M, 2.2 mL, 4.4 mmol) was added followed by 30% H_2O_2 (8.7 M, 1 mL, 8.8 mmol). The mixture was stirred for 3 h at room temperature. NH_4Cl solution and CH_2Cl_2 were added. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to a residue. Silica gel chromatography with P-E/EtOAc (10:1) gave alcohol **19** as a colorless syrup (800 mg, 70%): R_f = 0.45 (P-E/EtOAc, 2:1); $[\alpha]_D$ = +34 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.17 (m, 19H, 3 × *Ph*CH_2, S*Ph*CH_3), 4.97−4.66 (m, 6H, 3 × PhCH_2), 4.65 (d, 1H, $J_{1,2}$ = 8.9 Hz, H_1), 3.75−3.69 (m, 3H, CH_2CH_2OH, H_5), 3.52−3.44 (m, 2H, H_3, H_2), 3.35 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.2 Hz, H_4), 2.37 (s, 3H, CH_3), 2.13−2.06 (m, 1H, one of CH_2CH_2OH), 1.79−1.72 (m, 1H, one of CH_2CH_2OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.7, 138.4, 138.2, 133.4, 132.7, 130.4, 130.3, 129.6, 128.9, 128.9, 128.9, 128.7, 128.6, 128.5, 128.4, 128.4, 128.4, 128.2, 128.2 (24C, 3 × *Ph*CH_2, S*Ph*CH_2), 88.4 (C_1), 87.0 (C_5), 81.8, 81.6 (2C, C_4, C_3), 79.2 (C_2), 76.3, 75.9, 75.8 (3 × PhCH_2), 61.1 (CH_2CH_2OH), 34.5 (CH_2CH_2OH), 21.6 (SPhCH_3); HRMS (FAB, M + Na^+) *m*/*z* calcd for $C_{35}H_{38}O_5SNa$ 593.2338, found 593.2327.

1-*p*-Tolyl-2,3,4-tri-*O*-benzyl-6-deoxy-1-thio-β-D-glucohepto-pyranuronic Acid (20). BAIB (160 mg, 0.48 mmol) was added to a solution of **19** (110 mg, 0.19 mmol) and TEMPO (6 mg, 0.04 mmol) in CH_2Cl_2 and water (0.5 mL + 0.25 mL). The solution was stirred at room temperature for 1 h and diluted with CH_2Cl_2 (5 mL). The reaction solution was quenched with $Na_2S_2O_3$ aqueous solution and then washed with NaCl aqueous solution. The organic phase was dried over $MgSO_4$ and concentrated to a residue. Silica gel chromatography with cyclohexane/EtOAc (5:1) gave **20** (70 mg, 63%) as a colorless syrup: R_f = 0.33 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +6 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.09 (m, 19H, 3 × *Ph*CH_2, S*Ph*CH_3), 5.00−4.66 (m, 7H, 3 × PhCH_2, H_1), 3.80 (ddd, 1H, $J_{5,6a}$ = 3.2 Hz, $J_{5,6b}$ = 9.2 Hz, $J_{4,5}$ = 9.5 Hz, H_5), 3.75 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 8.9 Hz, H_3), 3.51 (t, 1H, $J_{2,3}$ = 8.9 Hz, $J_{1,2}$ = 9.6 Hz, H_2), 3.40 (t, 1H, $J_{3,4}$ = 8.9 Hz, $J_{4,5}$ = 9.5 Hz, H_4), 2.84 (dd, 1H, $J_{5,6a}$ = 3.2 Hz, J_{gem} = 16.1 Hz, H_{6a}), 2.52 (dd, 1H, $J_{5,6b}$ = 9.2 Hz, J_{gem} = 16.1 Hz, H_{6b}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (C=0), 138.6, 138.4, 138.1, 138.1, 132.4, 130.3, 130.1, 129.0, 129.0, 128.9, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2 (24C, 3 × *Ph*CH_2, S*Ph*CH_3), 88.5 (C_1), 87.1 (C_3), 81.7 (C_2), 80.7 (C_4), 76.2, 75.9, 75.6 (3 × PhCH_2), 75.7 (C_5), 37.4 (C_6), 21.6 (SPhCH_3); HRMS (ESI, M + Na^+) *m*/*z* calcd for $C_{35}H_{36}O_6SNa$ 607.2130, found 607.2132.

(6*S*,7*R*,8*S*)-7,8-Bis(benzyloxy)-6-methoxy-2-phenylhexahydropyrano[3,2-*b*]pyran-4-one (21). A solution of **1** (46 mg, 0.092 mmol) in CH_2Cl_2 (2.3 mL) was added dropwise to a solution of $Rh_2(OAc)_4$ (1.2 mg, 0.003 mmol) in CH_2Cl_2 (7.5 mL) under argon. The reaction solution was stirred at room temperature for 15 min and then washed with 0.5 M K_2CO_3 aqueous solution. The aqueous layer was extracted with CH_2Cl_2 (2×). The organic phases were combined, washed with NaCl aqueous solution, and dried over $MgSO_4$. After concentration, the residue was purified by silica gel chromatography, using cyclohexane/EtOAc (5:1) as the eluent, to provide **21** as a light yellow amorphous solid (27 mg, 59%, mixture of two isomers in a 9:1 ratio): R_f = 0.45 (cyclohexane/EtOAc, 1:1); ^{1}H

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NMR (400 MHz, $CDCl_3$) δ 7.43−7.28 (m, 15H, 3 × Ph), 4.97−4.81 (m, 4H, PhCH_2, one of PhCH_2, H_2), 4.70−4.67 (m, 2H, one of PhCH_2, H_6), 4.42−4.39 (d, 1H, $J_{9,10}$ = 10.5 Hz, H_{10}), 4.18 (t, 1H, $J_{7,8}$ = $J_{8,9}$ = 9.1 Hz, H_8), 3.63 (dd, 1H, $J_{8,9}$ = 9.1 Hz, $J_{9,10}$ = 10.5 Hz, H_9), 3.53 (dd, 1H, $J_{7,8}$ = 9.1 Hz, $J_{6,7}$ = 3.5 Hz, H_7), 3.44 (s, 3H, OCH_3), 2.85−2.72 (m, 2H, H_{3a}, H_{3b}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5 (C_4), 140.2, 138.9, 138.3, 129.2, 129.1, 129.1, 128.8, 128.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.5, 128.5,128.1, 125.9 (18C, 3 × Ph), 99.7 (C_6), 82.3 (C_9), 80.5 (C_2), 79.6 (C_8), 78.7 (C_7), 75.9, 74.5 (2 × PhCH_2), 74.2 (C_{10}), 56.5 (OCH_3), 49.8 (C_3); HRMS (CI, M + NH_4^+) m/z calcd for $C_{29}H_{34}O_6N$ 492.2386, found 492.2383.

1-Methyl-2,3,4-tri-*O*-benzyl-β-D-glucopyrano-2(*Z*)-butene-5,5′-dione and 1-Methyl-2,3,4-tri-*O*-benzyl-β-D-glucopyrano-2(*E*)-butene-5,5′-dione (22a + 22b). *Method 1.* To a solution of **1** (50 mg, 0.10 mmol) in dry CH_2Cl_2 (5 mL) was added $Cu(tfacac)_2$ (3.7 mg, 0.01 mmol). The reaction mixture was refluxed for 5 min before being concentrated. Silica gel chromatography of the resulting residue, using cyclohexane/EtOAc (7:1) as the eluent, afforded **22a** + **22b** (13 mg, 23%) and **21** (24 mg, 42%).

Method 2. To a solution of **1** (50 mg, 0.10 mmol) in dry toluene (5 mL) was added $Cu(acac)_2$ (1.6 mg, 6.1 × 10^{-3} mmol). The reaction mixture was refluxed for 5 min before being concentrated. The resulting residue was separated by silica gel chromatography with cyclohexane/EtOAc (7:1) to afford **22a** + **22b** (30 mg, 53%).

Data for **22a** + **22b**: R_f = 0.40 (cyclohexane/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.18 (m, 30H, 6 × Ph), 6.35 (s, 2H, CH═CH), 5.02−4.52 (m, 14H, 6 × PhCH_2, 2 × H_1), 4.55−4.52 (m, 2H, 2 × H_5), 4.09−4.01 (m, 2H, 2 × H_3), 3.67−3.61 (m, 2H, 2 × H_4), 3.57−3.54 (m, 2H, 2 × H_2), 3.40 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 195.6 (2 × C═O), 138.9, 138.8, 138.3, 138.3, 138.1, 137.9, 134. 7, 129.0, 129.0, 128.9, 128.9, 128.9, 128.8, 128.8, 128.6, 128.6,128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1 (30C, 6 × Ph), 135.5, 134.7 (2C, CH═CH), 99.2, 98.9 (2C, 2 × C_1), 82.3, 82.1 (2C, 2 × C_3), 79.7, 79.7 (2C, 2 × C_2), 79.0, 79.0 (2C, 2 × C_4), 76.4, 76.3, 75.4, 74.1, 74.0 (6C, 6 × PhCH_2), 74.2, 74.2 (2C, 2 × C_5), 56.4, 56.2 (2C, 2 × OCH_3); HRMS (ESI, M + Na^+) m/z calcd for $C_{58}H_{60}O_{12}Na$ 971.3977, found 971.3982.

1-Methyl-2,3,4-tri-*O*-benzyl-β-D-glucoheptopyrano-2(*Z*)-butene-6,6′-dione and 1-Methyl-2,3,4-tri-*O*-benzyl-β-D-glucoheptopyrano-2(*E*)-butene-6,6′-dione (23a + 23b). *Method 1.* Compound **2** (40 mg, 0.078 mmol) was converted to a **23a** + **23b** mixture (10 mg, 22%) as a light yellow amorphous solid using the same procedure as method 1 described for **22** with refluxing (3 min).

Method 2. Compound **2** (89 mg, 0.17 mmol) was converted to **23a** + **23b** mixture (48 mg, 58%) as a light yellow amorphous solid using the same procedure as method 2 described for **22** with refluxing (10 min).

Data for compound **23a** (mixture containing 14% **23b**; NMR data of **23b** are described individually after the data of **23a**): R_f = 0.40 (cyclohexane/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 30H, 6 × Ph), 6.69 (s, 2H, CH═CH), 5.06−4.59 (m, 6H, 3 × PhCH_2), 4.49 (d, 2H, $J_{1,2}$ = 3.5 Hz, 2 × H_1), 4.22−4.16 (ddd, 2H, $J_{4,5}$ = 9.5 Hz, $J_{5,6a}$ = 2.6 Hz, $J_{5,6b}$ = 9.6 Hz, 2 × H_5), 4.06−4.01 (t, 2H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, 2 × H_3), 3.53−3.50 (dd, 2H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, 2 × H_2), 3.41 (s, 6H, 2 × OCH_3), 3.28−3.24 (t, 2H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, 2 × H_4), 2.86−2.81 (dd, 2H, J_{gem} = 16.1 Hz, $J_{5,6a}$ = 2.6 Hz, 2 × H_{6a}), 2.62−2.56 (dd, 2H, J_{gem} = 16.1 Hz, $J_{5,6b}$ = 9.6 Hz, 2 × H_{6b}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2 (C═O), 139.0, 138.5, 138.4, 138.9, 138.9, 128.9, 128.9, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2 (30C, 6 × Ph), 136.9 (2C, CH═CH), 98.3 (2C, 2 × C_1), 82.3 (2C, 2 × C_3), 81.1 (2C, 2 × C_4), 80.5 (2C, 2 × C_2), 76.2, 75.4, 73.8 (6C, 6 × PhCH_2), 66.8 (2C, 2 × C_5), 55.9 (2C, 2 × OCH_3), 42.1 (2C, 2 × C_6); HRMS (ESI, M + K^+) m/z calcd for $C_{60}H_{64}O_{12}K$ 1015.4024, found 1015.4042.

Data for compound **23b**: R_f = 0.36 (cyclohexane/EtOAc, 3:1); $[\alpha]_D$ = +8 (c 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.23 (m, 30H, 6 × Ph), 6.18 (s, 2H, CH═CH), 4.98−4.55 (m, 12H, 6 × PhCH_2), 4.45 (d, 2H, $J_{1,2}$ = 3.5 Hz, 2 × H_1), 4.12−4.08 (ddd, 2H, $J_{4,5}$ = 9.5 Hz, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 9.5 Hz, 2 × H_5), 3.98−3.95 (t, 2H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, 2 × H_3), 3.48−3.45 (dd, 2H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, 2 × H_2), 3.33 (s, 6H, 2 × OCH_3), 3.21−3.17 (t, 2H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, 2 × H_4), 2.93−2.89 (dd, 2H, J_{gem} = 15.5 Hz, $J_{5,6a}$ = 3.0 Hz, 2 × H_{6a}), 2.57−2.52 (dd, 2H, J_{gem} = 15.5 Hz, $J_{5,6b}$ = 9.5 Hz, 2 × H_{6b}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2 (2 × C═O), 138.6, 138.1, 138.0, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7 (30C, 6 × Ph), 135.6 (2C, CH═CH), 97.9 (2C, 2 × C_1), 81.9 (2C, 2 × C_3), 81.0 (2C, 2 × C_4), 80.0 (2C, 2 × C_2), 75.8, 74.9, 73.3 (6C, 6 × PhCH_2), 66.8 (2C, 2 × C_5), 55.5 (2C, 2 × OCH_3), 44.7 (2C, 2 × C_6); HRMS (ESI, M + K^+) m/z calcd for $C_{60}H_{64}O_{12}K$ 1015.4024, found 1015.4025.

1,7-Dimethyl-2,3,4-tri-*O*-benzyl-β-D-glucopyrano-6-ulose (24). *Method 1.* To a solution of **1** (12 mg, 0.024 mmol) in anhydrous MeOH (1 mL) was added $Cu(tfacac)_2$ (1 mg, 0.0024 mmol, 10 mol %). The mixture was heated in a microwave at 100 °C with stirring for 5 min. The solution was concentrated and purified by silica gel chromatography with P-E/EtOAc (8:1) to give **24** (7 mg, 60%) as a colorless syrup.

Method 2. To a solution of **1** (21 mg, 0.042 mmol) in anhydrous MeOH (2 mL) was added $Cu(acac)_2$ (0.5 mg, 0.002 mmol, 5 mol %). The mixture was heated in a microwave at 100 °C with stirring for 5 min. The solution was concentrated and purified by silica gel chromatography with P-E/EtOAc (8:1) to give **24** (13 mg, 62%) as a colorless syrup.

Data for compound **24**: R_f = 0.35 (P-E/EtOAc, 2:1); $[\alpha]_D$ = +9 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.14 (m, 15H, 3 × PhCH_2), 4.92−4.51 (m, 7H, 3 × PhCH_2, H_1), 4.16−4.10 (m, 3H, H_5, $COCH_2O$), 3.94 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H_3), 3.62 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.0 Hz, H_4), 3.47−3.44 (dd, 1H, $J_{1,2}$ = 3.3 Hz, $J_{2,3}$ = 9.0 Hz, H_2), 3.33 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 127.9, 127.8, 127.7 (15C, 3 × PhCH_2), 98.8 (C_1), 81.7 (C_3), 79.4 (C_2), 78.6 (C_4), 76.5 ($COCH_2O$), 75.9, 75.2, 73.6 (3C, 3 × PhCH_2), 70.9 (C_5), 59.3 (OCH_3), 55.7 (OCH_3); HRMS (ESI, M + Na^+) m/z calcd for $C_{30}H_{34}O_7Na$ 529.2202, found 529.2197.

1,8-Dimethyl-2,3,4-tri-*O*-benzyl-β-D-glucooctopyrano-7-ulose (25). *Method 1.* Compound **2** (11 mg, 0.021 mmol) was converted to compound **25** (7 mg, 66%) as a colorless syrup by a procedure similar to method 1 described for **24**.

Method 2. Compound **2** (25 mg, 0.048 mmol) was converted to compound **25** (19 mg, 76%) as a colorless syrup by a procedure similar to method 2 described for **24**.

Data for compound **25**: R_f = 0.37 (P-E/EtOAc, 2:1); $[\alpha]_D$ = +8 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.25 (m, 15H, 3 × PhCH_2), 5.00−4.57 (m, 6H, 3 × PhCH_2), 4.47 (d, 1H, $J_{1,2}$ = 3.5 Hz, H_1), 4.20−4.15 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 9.5 Hz, H_5), 4.01−3.97 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H_3), 3.95 (s, 2H, $COCH_2O$), 3.49−3.47 (dd, 1H, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H_2), 3.39 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.24−3.20 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 10.0 Hz, H_4), 2.68−2.64 (dd, 1H, J_{gem} = 15.5 Hz, $J_{5,6a}$ = 3.0 Hz, H_{6a}), 2.51−2.46 (dd, 1H, J_{gem} = 15.5 Hz, $J_{5,6b}$ = 9.5 Hz, H_{6b}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1 (C═O), 138.6, 138.1, 138.1, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7 (15C, 3 × PhCH_2), 81.9 (C_3), 81.1 (C_4), 80.1 (C_2), 78.2 ($COCH_2O$), 75.8, 74.9, 73.3 (3C, 3 × PhCH_2), 66.4 (C_5), 59.2 (OCH_3), 55.4 (OCH_3), 40.7 (C_6); HRMS (ESI, M + Na^+) m/z calcd for $C_{31}H_{36}O_7Na$ 543.2353, found 543.2352.

1-*p*-Tolyl-2,3,4-tri-*O*-benzyl-7-methyl-1-thio-β-D-glucoheptopyrano-6-ulose (26). *Method 1.* Compound **3** (45 mg, 0.075 mmol) was converted to compound **26** (27 mg, 60%) as a colorless syrup by a procedure similar to method 1 described for **24**.

Method 2. Compound **3** (27 mg, 0.045 mmol) was converted to compound **26** (18 mg, 67%) as a colorless syrup by a procedure similar to method 2 described for **24**.

Data for compound **26**: R_f = 0.53 (P-E/EtOAc, 2:1); $[\alpha]_D$ = −27 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.12 (m, 19H, 3 × PhCH_2, SPhCH_3), 4.89−4.63 (m, 7H, 3 × PhCH_2, H_1), 4.24−4.17 (dd, 2H, J_{gem} = 19.5 Hz, $COCH_2O$), 3.92 (d, 1H, $J_{4,5}$ = 9.0 Hz, H_5), 3.80−3.77 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.0 Hz, H_4), 3.73−3.70 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H_3), 3.50−3.46 (dd, 1H, $J_{2,3}$ = 9.0 Hz, $J_{1,2}$ = 9.5 Hz, H_2), 3.36 (s, 3H, OCH_3), 2.35 (s, 3H, SPhCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2 (C=0), 138.4, 138.0, 37.8, 137.5, 133.4, 129.8, 128.7, 128.5, 128.4, 128.4, 128.2, 128.2, 127.9, 127.9, 127.8, 127.7 (24C, 3 ×

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PhCH_2, S*Ph*CH_3), 88.1 (C_1), 85.6 (C_3), 80.2 (C_2), 79.6 (C_5), 78.1 (C_4), 75.9, 75.6, 75.3, 74.8 (4C, 3 × Ph*CH_2*, CO*CH_2*O), 59.3 (OCH_3), 21.1 (SPh*CH_3*); HRMS (ESI, M+Na^+) *m*/*z* calcd for $C_{36}H_{38}O_6SNa$ 621.2287, found 621.2281.

***p*-Tolyl-2,3,4-tri-*O*-benzyl-8-methyl-1-thio-β-D-glucooctopyrano-7-ulose (27).** *Method 1.* Compound **4** (8 mg, 0.013 mmol) was converted to compound **27** (5 mg, 62%) as a colorless syrup by a procedure similar to method 1 described for **24**.

Method 2. Compound **4** (23 mg, 0.038 mmol) was converted to compound **27** (15 mg, 64%) as a colorless syrup by a procedure similar to method 2 described for **24**.

Data for compound **27**: R_f = 0.31 (P-E/EtOAc, 3:1); $[\alpha]_D$ = +9 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.10 (m, 19H, 3 × *Ph*CH_2, S*Ph*CH_3), 4.94−4.61 (m, 7H, 3 × Ph*CH_2*, H_1), 3.93−3.86 (dd, 2H, J_{gem} = 19.5 Hz, COCH_2O), 3.84−3.80 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 9.0 Hz, H_5), 3.72−3.68 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H_3), 3.48−3.44 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.5 Hz, H_2), 3.36−3.32 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H_4), 3.31 (s, 3H, OCH_3), 2.71−2.68 (dd, 1H, J_{gem} = 15.5 Hz, $J_{5,6a}$ = 3.0 Hz, H_{6a}), 2.62−2.57 (dd, 1H, J_{gem} = 15.5 Hz, $J_{5,6b}$ = 9.0 Hz, H_{6b}), 2.32 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8 (C═O), 138.2, 137.9, 137.5, 131.6, 129.9, 129.7, 128.5, 128.4, 128.1, 127.9, 127.8, 127.8, 127.8 (24C, 3 × *Ph*CH_2, S*Ph*CH_3), 87.8 (C_1), 86.6 (C_3), 81.3 (C_2), 80.6 (C_4), 78.1 (CO*CH_2*O), 75.8, 75.5, 75.0, 74.9 (4C, 3 × Ph*CH_2*, C_5), 59.2 (OCH_3), 41.0 (C_6), 21.1 (SPh*CH_3*); HRMS (ESI, M + Na^+) *m*/*z* calcd for $C_{37}H_{40}O_6SNa$ 635.2438, found 635.2438.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR for compounds **1**−**4**, **12**, **12a**, **15**, **18**−**20**, **20a**, and **21**−**27** and COSY and HMQC for compound **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Meerwein, S.; Rathjen, H. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1610−1622.
(2) Ye, T.; Mckervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160.
(3) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, *19*, 4233−4236.
(4) Linder, M. R.; Steurer, S.; Podlech, J. *Organic Syntheses*; Wiley & Sons: New York, 2004; Collect. Vol. *X*, pp 194−199. Linder, M. R.; Steurer, S.; Podlech, J. *Org. Synth.* **2002**, *79*, 154−159.
(5) Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878−6880.
(6) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385−4388.
(7) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062−6063.
(8) Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731−734.
(9) Berndt, D. F.; Norris, P. *Tetrahedron Lett.* **2002**, *43*, 3961−3962.
(10) Branderhorst, H. M.; Kemmink, J.; Liskamp, R. M. J.; Pieters, R. J. *Tetrahedron Lett.* **2002**, *43*, 9601−9603.
(11) Murphy, G. K.; West, F. G. *Org. Lett.* **2005**, *7*, 1801−1804.
(12) West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6892−6894.
(13) Ronald, E. B. Y.; Schuerch, C. *Carbohydr. Res.* **1974**, *34*, 79−90.
(14) Berner, von B.; Vasell, A. *Helv. Chim. Acta* **1979**, *62* (204), 1990−2016.
(15) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi A. Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974−6977.
(16) Marmsäter, F. P.; Murphy, G. K.; West, F. G. *J. Am. Chem. Soc.* **2003**, *125*, 14724−14725.
(17) Wang, W.; Zhang, Y. M.; Sollogoub, M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39* (14), 2466−2467.
(18) Dong, W. L.; Jespersen, T.; Bols, M.; Skrydstrup, T.; Sierks, M. R. *Biochemistry* **1996**, *35*, 2788−2795.
(19) Van Den Bos, L. J.; Codée, J. D. C.; Van Der Toorn, J. C.; Boltje, T. J.; Van Boom, J. H.; Overkleeft, H. S.; Van Der Marel, G. A. *Org. Lett.* **2004**, *6* (13), 2165−2168.
(20) France, R. R.; Compton, R. G.; Davis, B. G.; Fairbanks, A. J.; Tees, N. V.; Wadhawan, J. D. *Org. Biomol. Chem.* **2004**, *2*, 2195−2202.
(21) Suzuki, K.; Nakata, T. *Org. Lett.* **2002**, *4* (16), 2739−2741.
(22) Moore, J. A.; Reed, D. E. *Organic Syntheses*; Wiley & Sons: New York, 1973; Collect. Vol. *V*, pp 351−355.