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Introduction of Vinyl and Hydroxymethyl Functionalities at C-4 of Glucose-Derived Substrates: Synthesis of Spirocyclic, Bicyclic, and Tricyclic Nucleosides

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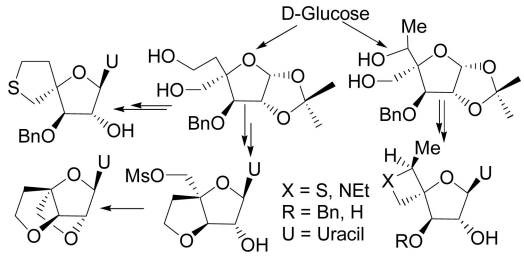

Installing hydroxymethyl and hydroxyethyl substitutions at C-4 through vinylation and hydroboration−oxidation reactions of the C-4 bis-hydroxymethyl derivative of D-glucose based substrate, and inserting heteroatoms thereafter permitted formation of *N*-, *O*-, or *S*-heterocycles leading to [4,5]- or [5,5]-spirocycles and a bicyclo[3.3.0]octane product. Some of the spirocycles were converted to spironucleosides under Vorbrüggen glycosidation reaction conditions. Similarly, the bicyclic product was elaborated to the corresponding bicyclic nucleoside as well as an unexpected tricyclic nucleoside.

Hydantocidin, a pseudonucleoside possessing a spirocyclic ring at the anomeric center, was reported from a natural source.[1] Its unusual structure and bioactivity inspired Miyasaka[2] and others[3] to synthesize C-1′-spironucleosides as conformationally restricted molecules. Subsequently, Paquette[4] introduced the concept of spirocyclic restriction in nucleosides through insertion of a carbocyclic ring (a bulky substituent) at C-4′ of furanose/thiofuranose rings. This was expected to fix the glycosyl torsional angle around the C-4′ bond, while the void space below C-4′ would be sufficient to avoid nonbonded steric superimposition. In addition, the free radical-induced degradation of the ribose ring of nucleosides by C-4′-H abstraction can be precluded. Various other synthetic routes to C-2′-spiro,[5] C-3′-spiro,[6] and C-4′-spironucleosides[4] as conformationally restricted or biased analogues have appeared in the literature. Some of these nucleosides display anti-HIV and antivirus activity.[7] We have earlier reported[8] on the synthesis of spironucleosides having 4- and 7-membered spiro rings at C-4′ through nucleophilic substitution and intramolecular nitrone cycloaddition reaction. The work encouraged us to take up the synthesis of spirocycles based on five-membered heterocyclic rings from a D-glucose-derived precursor carrying two hydroxymethyl groups at C-4. One of these groups was planned to be utilized to introduce a vinyl group via oxidation and Wittig reaction, and then converted to a hydroxyethyl group by hydroboration−oxidation reaction. Subsequent intra/intermolecular cyclization through the participation of oxygen, nitrogen, and sulfur nucleophiles (Figure 1) was expected to furnish the desired heterocyclic systems. In the process, we also encountered newer 4,5-spirocyclic and bicyclo[3.3.0]octane systems. The products could be elaborated to interesting spirocyclic and bicyclic nucleosides in addition to an unexpected 5,5,5-tricyclic conformationally locked nucleoside as discussed in the sequel.

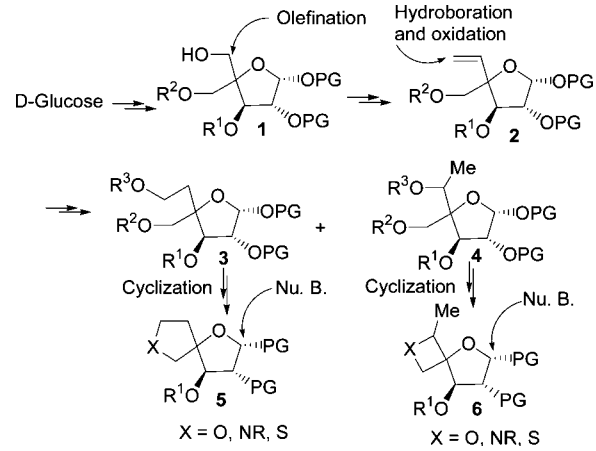

FIGURE 1. An approach to produce spirocycles and spironucleosides.

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(6) Nielsen, P.; Larsen, K.; Wengel, J. *Acta Chem. Scand.* **1996**, *50*, 1030–1035.

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(8) (a) Roy, A.; Achari, B.; Mandal, S. B. *Tetrahedron Lett.* **2006**, *47*, 3875–3879. (b) Tripathi, S.; Roy, B. G.; Drew, M. G. B.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **2007**, *72*, 7427–7430.

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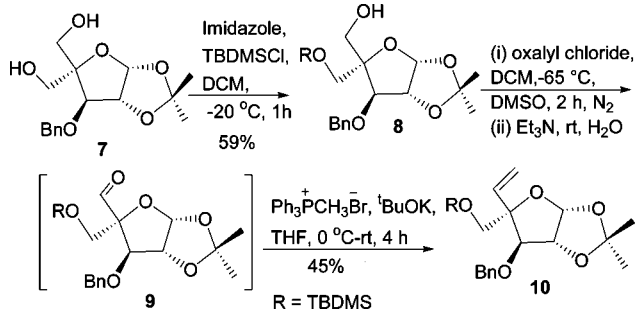
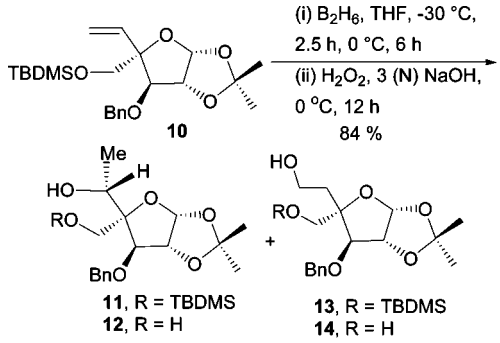
SCHEME 1. Introduction of a Vinyl Group at C-4 of 7



SCHEME 2. Hydroboration−Oxidation Reaction of 10



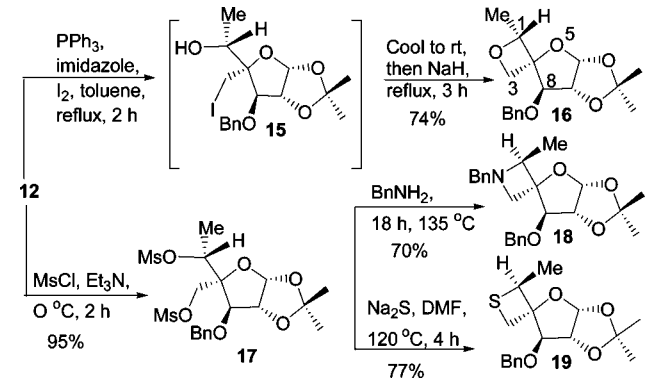
Preparation of Important Intermediates 10, 11, and 14. To realize our goals, we set about as follows. One of the hydroxyl groups of the D-glucose derived substrate **7**[9] (derived from D-glucose in five steps, 36% overall yield) was preferentially protected as *tert*-butyldimethylsilyl ether to provide **8**. Submitting **8** to Swern oxidation (Scheme 1) afforded the aldehyde **9**. When the crude product was subjected to Wittig reaction with methylenetriphenylphosphorane, it yielded the vinylated compound **10** in 45% yield (over two steps).

Diborane reaction of **10** followed by oxidation with alkaline hydrogen peroxide resulted in a mixture of products, which after chromatographic purification and spectroscopic analysis provided (Scheme 2) a mixture of both Markownikov and anti-Markownikov products (**11**, **13**) along with their desilylated derivatives (**12**, **14**) as established by correlation analysis. The expected anti-Markownikov addition products were formed in higher yields (combined yield 49% vs 35% for the other mode).[10]

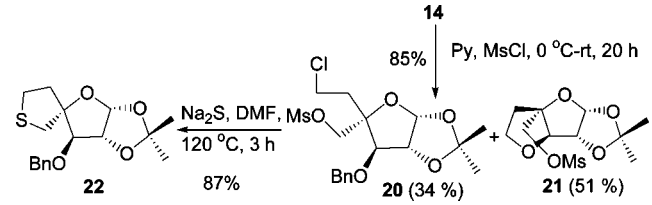
The structure of **8** was deduced from the $^1H-^1H$ COSY, $^1H-^{13}C$ HSQC, $^1H-^{13}C$-HMBC, and NOESY spectra (vide the Supporting Information). The absolute configuration at the newly generated asymmetric center of **11** and **12** was deduced subsequently from an X-ray analysis of the derived product **19**.[11]

Cyclization of 12 to the Heterocycles 16, 18, and 19. Toward the generation of spiroannulated heterocycles, phosphonium ion induced iodination[12] of the primary hydroxyl group of **12** produced (Scheme 3) the expected intermediate **15** without affecting the secondary hydroxyl group. The intermediate was cyclized in situ to the oxetane derivative **16** upon addition of

SCHEME 3. Synthesis of 5/4-Spirocycles 16, 18, and 19



SCHEME 4. Conversion of 14 to Bicycle 21 and Spirocycle 22



sodium hydride. In another approach, mesylation of the same substrate **12** produced the dimesyl derivative **17**, which upon treatment with benzyl amine at elevated temperature cleanly furnished the azetane derivative **18** (70%), wherein inversion of configuration at the azetane methine center is anticipated. In the same vein, compound **17** gave the thietane analogue **19** (77%). The relative configurations of **16** and **18** were easily deduced from the structure of **19** assuming inversion at C-5 during cyclization to **18** and **19** based on mechanistic consideration.

Transformation of 14 to Bicycle 21 and Spirocycle 22. We next turned our attention to convert **14** to its dimesyl derivative in the hope of generating spiroannulated 5-membered *O*-, *N*-, and *S*-heterocycles. Toward this end, mesylation of **14** was carried out with mesyl chloride in pyridine (Scheme 4). Surprisingly, this afforded the chloro mesyl derivative **20** (34%) instead of the expected dimesyl derivative, along with the unexpected product **21** (51%). Fortunately, **20** turned out to be a good substrate for transformation to the spiroannulated thiophene analogue **22** (suggested mechanism for this reaction is given in the Supporting Information).

The structures of **20** and **22** were deduced by spectral analyses (^1H, ^{13}C NMR and MS). However, such analyses could not furnish any conclusive proof for the structure of **21**. Fortunately, this could be achieved by a single-crystal X-ray diffraction analysis.[11]

Synthesis of Spironucleosides 25−29. With a view to generating spironucleosides, cleavage of the 1,2-acetonide rings of **18** and **19** by acid treatment was followed by acetylation to furnish the respective acetylated products **23** and **24** as anomeric mixtures, which without purification were used to instal uracil base at their anomeric centers using the Vorbrüggen glycosidation procedure.[13] This provided the nucleoside analogues **25** and **26** in 56−60% yields. Deacetylation of these products by treatment with K_2CO_3 in MeOH smoothly produced **27** and **28**

(9) Youssefyeh, R. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1979**, *44*, 1301–1309.

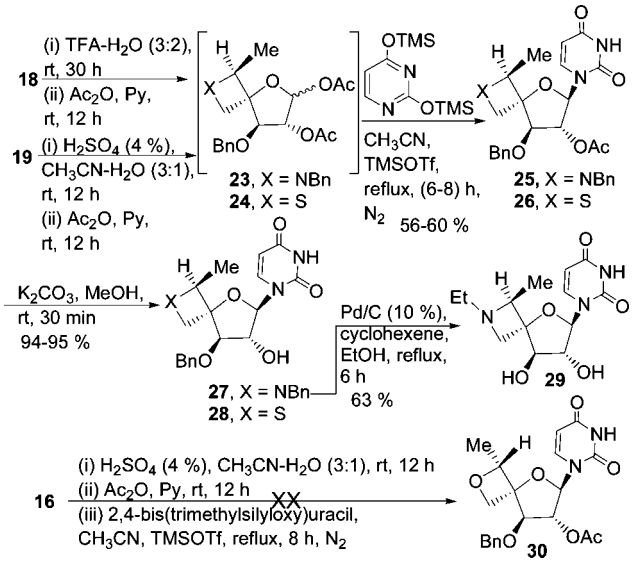
(10) Hydroboration of **10** with 9-BBN was not successful possibly due to the steric hindrance offered to the approach of the reagent by the bulky *tert*-butyldimethylsilyloxymethyl functionality at C-4′.

(11) ORTEP diagram(s) are given in the Supporting Information.

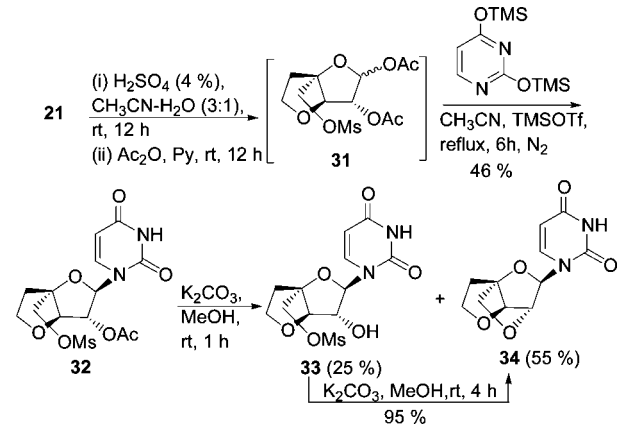
(12) Roy, B. G.; Roy, A.; Achari, B.; Mandal, S. B. *Tetrahedron Lett.* **2006**, *47*, 7783–7787.

(13) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234–1255.

SCHEME 5. Nucleosidation on Spirocycles 18 and 19



SCHEME 6. Conversion of 21 to Bi-/Tricyclic Nucleosides



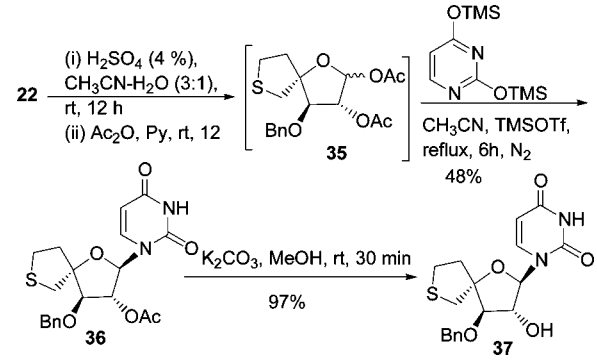
in excellent yields (Scheme 5). Exposure of **27** to transfer hydrogenolysis with cyclohexene and Pd/C in pure EtOH yielded the *N*-ethyl derivative **29** rather than the expected secondary amine. Incorporation of ethyl moiety could be rationalized from the Pd-catalyzed oxidation of EtOH to acetaldehyde,[14,15] which was reductively trapped by the free amine to produce **29**. However, the same reaction with the sulfur compound **28** failed to yield the desired product, possibly due to poisoning of the catalyst. On the other hand, the failure of the oxetane spirocycle **16** to afford any isolable nucleoside is attributed to the vulnerability of the oxetane ring under Vorbrüggen reaction conditions.

Synthesis of Bicyclic Nucleosides 32 and 33, and of the Tricyclic Nucleoside 34. Toward this objective, **21** was subjected to acetonide removal followed by peracetylation to furnish a mixture of anomeric acetates **31**, which was routinely elaborated to the corresponding nucleoside **32** in 46% yield (Scheme 6). Deacetylation of **32** with K_2CO_3 in MeOH produced the expected nucleoside **33** in only 25% yield. The major product was identified as the tricyclic nucleoside **34** (55%), formed

(14) (a) Fu, X.; Cook, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 6910–6912. (b) Bailey, P. D.; Beard, M. A.; Dang, H. P. T.; Phillips, T. R.; Price, R. A.; Whittaker, J. H. *Tetrahedron Lett.* **2008**, *49*, 2150–2153.

(15) The use of 2,2,2-trifluoroethanol as the solvent for debenzylation[14b] of **27** unexpectedly removed the uracil moiety along with removal of benzyl groups.

SCHEME 7. Nucleosidation of Spirocycle 22



through nucleophilic attack by the alkoxide ion on the mesyl bearing carbon. As anticipated, **33** delivered **34** in 95% yield upon prolonged exposure to deacetylation reaction condition. The structures of the nucleosides were determined by spectral analyses.

Synthesis of Spironucleoside 37. Removal of the 1,2-acetonide (Scheme 7) from the spiroannulated sulfur heterocycle **22** followed by peracetylation (furnishing **35**) and nucleosidation by Vorbrüggen methodology produced the nucleoside derivative **36** in 48% yield. This could be deacetylated to furnish **37** (97%). The presence of the four structural units—uracil ring, tetrahydrothiophene moiety, benzyl group, and furanose functionality—was confirmed by the examination of ^1H and ^{13}C NMR spectral data.

In conclusion, utilizing a 4-formyl group of an appropriate precursor to insert a (1- or 2-) hydroxyethyl group through the intermediacy of a vinyl group permitted nucleophilic insertion of heteroatoms in the carbohydrate framework of D-glucose-derived substrates, allowing access to new classes of spironucleosides. An unexpected bicyclic (furano-furan derivative) compound was also encountered. This was eventually transformed to a bicyclic nucleoside and, surprisingly, to a conformationally locked tricyclic nucleoside. The strategy for the precursor assembly for the targeted reactions is simple and attractive.

Experimental Section

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilyloxymethyl-4-vinyl-β-L-arabinofuranose (10). To a solution of oxalyl chloride (2.24 mL, 25.96 mmol) in dry CH_2Cl_2 (20 mL) cooled to −65 °C was added a solution of dry DMSO (4.02 mL, 2.46 mmol) in CH_2Cl_2 (15 mL) dropwise under N_2 and the mixture was stirred for 15 min. A solution of **8** (10.0 g, 23.60 mmol) in CH_2Cl_2 (40 mL) was added to the above mixture during 1 h and the stirring was continued for another 1 h. Et_3N (20 mL) was added to it and the reaction was allowed to reach room temperature. After quenching the reaction by the addition of water (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined extract was washed with water (2 × 30 mL) and dried (Na_2SO_4); the solvent was evaporated in vacuo to furnish the crude aldehyde **9**. This was dried under vacuum (P_2O_5) and subsequently used without further purification. To a solution of methyltriphenylphosphonium bromide (14.32 g, 40.13 mmol) and potassium *tert*-butoxide (3.91 g, 32.08 mmol) in dry THF (80 mL) at 0 °C under N_2 was added a solution of the aldehyde in THF (10 mL) dropwise during 45 min. The mixture was stirred for 2 h at 0 °C and another 2 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (20 mL). The solvent was evaporated in vacuo and the residue was extracted with $CHCl_3$ (3 × 40 mL). The $CHCl_3$ solution was washed with H_2O (2 × 40

mL), dried (Na_2SO_4), and evaporated to a crude product, which was purified by column chromatography on silica gel (60−120 mesh) by using ethyl acetate−petroleum ether (2:23) as eluent to afford **10** (4.854 g, 45%) as a colorless liquid. $[\alpha]_D^{25}$ +15.9 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.40 (s, 3H), 1.61 (s, 3H), 3.55 (d, 1H, J = 10.4 Hz), 3.67 (d, 1H, J = 10.4 Hz), 4.35 (d, 1H, J = 2.1 Hz), 4.59 (d, 1H, J = 11.8 Hz), 4.66 (dd, 1H, J = 2.4, 4.3 Hz), 4.73 (d, 1H, J = 11.8 Hz), 5.24 (dd, 1H, J = 1.5, 10.9 Hz), 5.50 (dd, 1H, J = 1.7, 17.4 Hz), 5.90 (d, 1H, J = 4.6 Hz), 6.08 (dd, 1H, J = 10.9, 17.4 Hz), 7.30−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.6 (CH_3), −5.4 (CH_3), 18.3 (C), 25.8 (3 × CH_3), 27.1 (CH_3), 27.6 (CH_3), 65.7 (CH_2), 72.2 (CH_2), 83.5 (CH), 86.5 (CH), 88.3 (C), 103.6 (CH), 113.2 (C), 115.4 (CH_2), 127.6 (2 × CH), 127.7 (CH), 128.3 (2 × CH), 135.1 (CH), 137.6 (C); ESIMS, *m*/*z* 443 $(M + Na)^+$. Anal. Calcd for $C_{23}H_{36}O_5Si$: C, 65.68; H, 8.63. Found: C, 65.45; H, 8.48.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-mesyl-4-(2-chloroethyl)-β-L-arabinofuranose (20) and 3,6-Anhydro-5-deoxy-1,2-*O*-isopropylidene-4-mesyloxymethyl-β-L-idofuranose (21). Mesyl chloride (1.86 mL, 23.91 mmol) was added to a solution of **14** (900 mg, 2.78 mmol) in pyridine (25 mL) at 0 °C; the mixture was stirred at 0 °C for 30 min and then at room temperature for 20 h. The solvent was evaporated in vacuo and the crude residue was extracted with $CHCl_3$ (3 × 30 mL). The combined extract was washed with water (2 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by silica gel column chromatography by using ethyl acetate−petroleum ether (1:10) to afford **20** (399 mg, 34%) as a colorless liquid, while the same solvents in the ratio 3:22 eluted **21** (417 mg, 51%) as a white solid.

20: $[\alpha]_D^{25}$ −35.6 (*c* 0.23, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 3H), 1.58 (s, 3H), 2.21−2.35 (m, 2H), 3.01 (s, 3H), 3.53−3.71 (m, 2H), 3.93 (s, 1H), 4.25 (d, 1H, J = 10.6 Hz), 4.31(d, 1H, J = 10.6 Hz), 4.53 (d, 1H, J = 11.6 Hz), 4.68 (d, 1H, J = 4.1 Hz), 4.72 (d, 1H, J = 11.6 Hz), 5.91 (d, 1H, J = 4.1 Hz), 7.35−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.7 (CH_3), 26.3 (CH_3), 34.7 (CH_2), 37.7 (CH_3), 39.5 (CH_2), 69.5 (CH_2), 72.3 (CH_2), 83.4 (CH), 84.3 (CH), 87.4 (C), 105.1 (CH), 112.6 (C), 127.8 (2 × CH), 128.2 (CH), 128.6 (2 × CH), 136.6 (C); ESIMS, *m*/*z* 443 $[(M + Na)^+$ for $Cl^{35}]$ and 445 $[(M + Na)^+$ for $Cl^{37}]$. Anal. Calcd for $C_{18}H_{25}O_7SCl$: C, 51.36; H, 5.99. Found: C, 51.09; H, 5.72.

21: mp 92−93 °C; $[\alpha]_D^{25}$ −6.8 (*c* 0.27, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 3H), 1.58 (s, 3H), 2.04−2.25 (m, 2H), 3.13 (s, 3H), 3.81−3.89 (m, 1H), 3.96−4.03 (m, 1H), 4.29 (s, 1H), 4.33 (d, H, J = 11.0 Hz), 4.64−4.67 (m, 2H), 5.93 (d, 1H, J = 3.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.4 (CH_3), 26.2 (CH_3), 36.5 (CH_2), 37.8 (CH_3), 68.1 (CH_2), 71.1 (CH_2), 84.5 (CH), 85.5 (CH), 94.2 (C), 106.8 (CH), 112.1 (C); ESIMS, *m*/*z* 317 $(M + Na)^+$. Anal. Calcd for $C_{11}H_{18}O_7S$: C, 44.89; H, 6.16. Found: C, 44.62; H, 6.03.

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Supporting Information Available: Characteristic spectral analyses of compounds; mechanism for the formation of **20** and **21**; ORTEP diagrams, and CIF files for **19** and **21**; general and experimental details; copies of ^1H and ^{13}C NMR spectra of **8**, **10**−**14**, **16**−**22**, **25**−**29**, **32**−**34**, **36**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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