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A Facile and Practical Synthesis of Peracylated 4-Thio-D-ribofuranoses from D-Glucose

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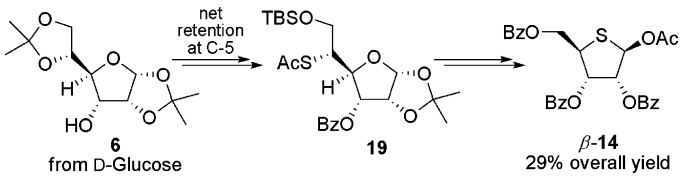

A practical synthesis of a peracylated 4-thio-D-ribofuranose **14** starting from inexpensive D-glucose is described. The C2−C6 portion of D-glucose was utilized, in which sulfur was introduced to C5 in two consecutive displacement reactions with net retention of configuration under mild conditions.

In the search for effective antiviral and antitumor agents, nucleosides are among the most prominent and promising candidates. Over the past 15 years, 4′-thionucleosides (**1**), in which the lactol ring oxygen is replaced by a sulfur atom, have attracted much attention due to their potent biological activity[1] and unique metabolic stability.[1a,2] Furthermore, certain 4′-thionucleosides, when incorporated into RNA strands, lead to enhanced thermal stability of the resulting modified RNA duplex.[3] As the parent building block for 4′-thionucleosides, 4-thiopentofuranoses have been the subject of many synthetic efforts since the pioneering work of Reist and Whistler.[4] A literature survey revealed that it usually required lengthy steps and high-cost starting materials, such as unnatural carbohydrates, and the overall yields were often unsatisfactory. Improved syntheses of 4-thiofuranoses of L-*arabino*,[5] 2-deoxy-D-*ribo*,[6] and D-*galacto*[7] configurations have appeared in recent years; however, the practical synthesis of 4-thio-D-ribofuranose (**2**) still remains a challenge, and this has presumably impeded the development of 4′-thioribonucleosides. To our knowledge, there are only a handful of syntheses of **2** and its derivatives, all starting from costly L-lyxose.[4,8] As an alternative, Matsuda[9] and Yoshimura[10] recently published elegant new protocols for the synthesis of 4′-thioribonucleosides via the Pummerer reaction.[11] In view that the thioglycosylation of the 4-thioribofuranose scaffold usually proceeded with useful to good β-selectivity,[8b,12] we felt that an efficient preparation of **2** and its peracyl derivatives would suffice to make 4′-β-thioribonucleosides more accessible. Further elaboration at C2 after appropriate protection of 3,5-hydroxyls could also be explored to afford valuable synthetic precursors to 2′-modified 4′-thionucleosides possessing potent biological activities, for example, 4′-thioFAC (**3**) and 4′-thioDMDC (**4**).[1e] Herein we wish to report a concise and practical synthesis of derivatives of **2** starting from cheap D-glucose derivative **5**.

We envisioned that the C2−C6 portion of D-glucose could be utilized as the carbon skeleton in our target molecule after adjustment of the stereochemistry of C3 and C5, whereas C1 was to be taken off by oxidative cleavage of vicinal diol (Figure 1). Inversion at C3 of glucose is routine, thus the key to the above strategy is the introduction of sulfur with retention of configuration at C5,[13] which has received little attention and its synthetic utility for thiosugars is not fully appreciated yet.

Initially, a synthetic route adapted from Yoshimura's improved synthesis of 4′-thioFAC was probed[1f] (Scheme 1). 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose (**6**) was easily prepared from the corresponding D-glucose derivative (**5**) in two steps.[14] Benzoylation, selective deprotection of the 5,6-isopro-

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(5) For examples, see: (a) Whistler, R. L.; Nayak, U. G.; Perkins, A. W., Jr. *Chem. Commun.* **1968**, 1339. (b) Whistler, R. L.; Nayak, U. G.; Perkins, A. W., Jr. *J. Org. Chem.* **1970**, *35*, 519. (c) Jeong, L. S.; Moon, H. R.; Choi, Y. J.; Chun, M. W.; Kim, H. O. *J. Org. Chem.* **1998**, *63*, 4821. (d) Satoh, H.; Yoshimura, Y.; Sakata, S.; Miura, S.; Machida, H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 989. (e) Wirsching, J.; Voss, J. *Eur. J. Org. Chem.* **1999**, 691.

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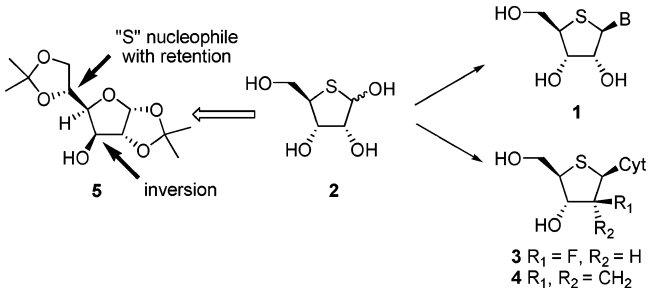


FIGURE 1. Retrosynthetic strategy for 4-thio-D-ribofuranose.

SCHEME 1

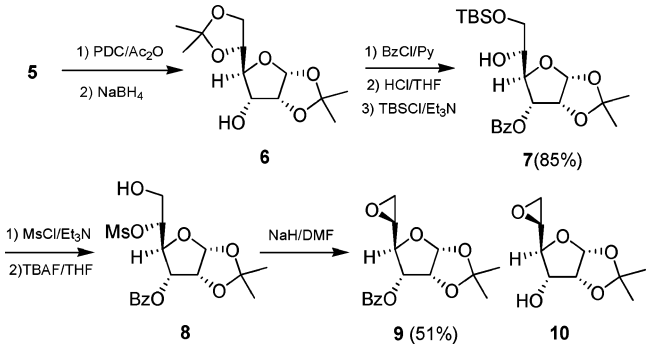


TABLE 1. Conditions for the Epoxide Formation

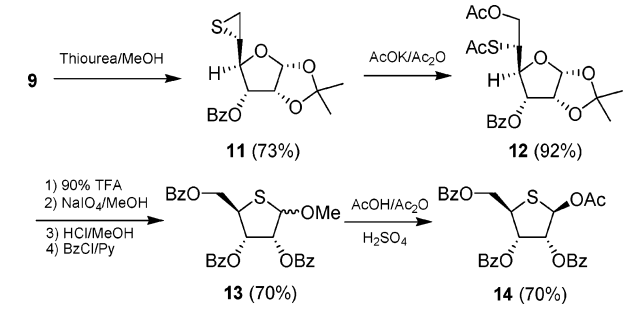
entry	base (equiv)	solvent	temp	**9** (%)[a]
1	NaH (1.4)	THF	rt	trace
2	NaH (1.2)	DMF	rt	30
2	NaH (1.2)	DMF	0 °C	51
3	*t*-BuOK (1.4)	THF	rt	18
4	*t*-BuOK (1.4)	toluene	rt	32
5	KHMDS (1.2)	THF	0 °C	33
6	NaOMe (3.0)	MeOH	rt	trace[b]
7	DBU (1.5)	toluene	90 °C	0[c]

[a] Isolated yield. [b] Along with ca. 15% **10**. [c] Extensive decomposition of starting material. No reaction at rt.

pylidene, followed by TBS protection of the primary alcohol afforded known compound **7** uneventfully.[15] Benzoyl was chosen as the protection for 3-hydroxyl for its ease of introduction and removal, as compared to benzyl, especially in the case of thiosugar synthesis. Mesylation of 5-hydroxyl and subsequent TBAF deblocking of TBS provided compound **8** which was used without purification. Next, various bases were screened for the transformation of **8** to epoxide **9**, and the results are summarized in Table 1. Fair to moderate yields were obtained, with NaH/DMF at 0 °C as the optimum condition. Using sodium methoxide as base could afford neither the desired product **9** nor its debenzoylated form **10** in acceptable yield, although the latter was expected from an analogous literature precedence.[16] The structure of **9** was unambiguously established by X-ray crystallography.

As shown in Scheme 2, compound **9** was treated with thiourea to afford episulfide **11** in good yield,[17] with the desired stereochemistry at C5 correctly installed as the result of two inversions. **11** subsequently underwent ring-opening reaction upon exposure to potassium acetate in refluxing acetic anhydride

SCHEME 2



and acetic acid to give **12** in 92% yield.[16] Sequential deprotection of the 1,2-acetonide, sodium periodate degradation, acidic hydrolysis of *S*-acetyl with concomitant thioglycoside formation, and finally benzoyl protection smoothly converted **12** to methyl 2,3,5-tri-*O*-benzoyl-4-thioribofuranoside **13** in 70% yield without purification of the intermediates. Routine acetolysis afforded a peracylated 4-thioribofuranose **14** almost quantitatively, with an anomeric ratio of $\alpha/\beta = 18/82$, as estimated by NMR of the crude product. Pure β-**14** was obtained by a single recrystallization from MeOH in 70% yield. The structure of compound β-**14** was also confirmed by X-ray crystallography.

So far, albeit successful, the above route has the drawback of being low yielding for the formation of epoxide, as well as employing a harsh condition (prolonged exposure to 150 °C) to open the episulfide ring. Also it would be much preferable to reduce the overall number of steps. With these in mind, another synthesis of β-**14** was launched.

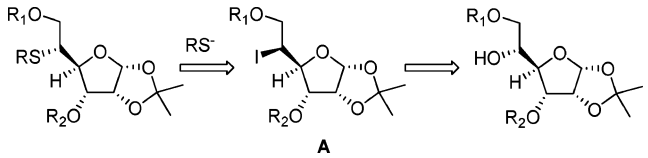


FIGURE 2. Introduction of sulfur to C5 in two steps.

In order to install sulfur to C5 of a D-hexofuranose with net retention of configuration, nucleophilic substitution of the corresponding 5-halo-5-deoxy-L-hexofuranose derivative (**A**) by sulfur nucleophiles would be a rational choice. Conceivably, the 5-halo derivative with the requisite C5 configuration could be obtained by Garegg's protocol[18] (Figure 2). Although similar strategy has been realized for the introduction of azido,[19] amino,[20] and alkoxy[21] substitutions, surprisingly, there is no report of using external sulfur nucleophiles,[22] and 5-halo derivatives in general have received much less scrutiny than sulfonates in carbohydrate chemistry.

Thus work along this line was carried out (Schemes 3 and 4). Starting from **7**, iodination proceeded smoothly in ether/

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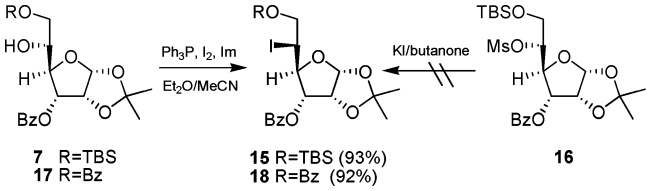
(22) (a) A single example of intramolecular displacement of 5-Cl by 6-thiol to form a 5,6-thiirane has been reported: Chiu, C.-W.; Whistler, R. L. *J. Org. Chem.* **1973**, *38*, 832. (b) Whistler also examined the substitution of 5-tosylate by AcSK, but the starting material was prepared in a much roundabout way; see: Nayak, U. G.; Whistler, R. L. *J. Org. Chem.* **1969**, *34*, 97.

SCHEME 3. Stereospecific Iodination

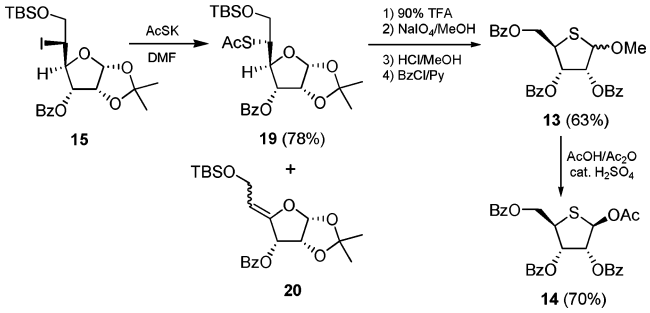


acetonitrile (3:1) instead of xylene (140 °C)[19] under mild conditions (60−70 °C) to give the desired iodide **15** in excellent yield with complete inversion of configuration at C5. It is worthy of note that reaction of mesylate **16** (prepared from **7**) under simple Finkelstein conditions did not proceed at all. Using potassium iodide in dipolar aprotic solvents such as HMPA at higher reaction temperature was avoided due to epimerization at C5 already documented.[23] Notably, the protective group for the 6-hydroxyl is of great importance. TBS proved to be the protective group of choice, as TBDPS resulted in sluggish reaction and posed difficulty for the next step, while acyl such as benzoyl worked well for the iodination but was also problematic in the next step (vide infra).

With the key intermediate **15** in hand, the introduction of sulfur was investigated. To our delight, **15** reacted smoothly with potassium thioacetate in DMF at 100 °C, affording the desired product **19** in 60−70% yield, along with varying amounts (20−25%) of elimination byproduct **20**. Lowering the reaction temperature to 50 °C effectively increased the selectivity to 6:1, and **19** was obtained in 78% yield on multigram scale. In this connection, TBS was the only choice for the protection of 6-hydroxyl, as the bulkier TBDPS significantly retarded the reaction at 50 °C, while at elevated temperature, poor selectivity was obtained. TBS also merited in that the 6-siloxy did not act as an internal nucleophile which would inevitably complicate the stereochemical outcome of the S_N2 process, hence **19** was free of its 5-epimer, which was prepared separately from the reaction of **16** with AcSK. This is in sharp contrast with the case of **18**, which produced an inseparable mixture through participation of the neighboring 6-benzoate group.[24] Conversion of **19** to **13** proceeded in 63% overall yield, affording product identical to that obtained from the previous route. The yield for **14** is 29% from compound **6** over six steps. Conceivably, changing the acylating reagent in the last step leading to **13** could afford other peracylated 4-thioribofuranoses. Furthermore, selective 3,5-protection was possible using bifunctional silyl reagents such as $(t\text{-Bu})_2SiCl_2$, providing an access to 4-thioribofuranoses with differentiated hydroxyls.

In summary, we have accomplished an efficient and practical nine-step synthesis of a peracylated 4-thio-D-ribofuranose **14** using commercially available D-glucose derivative **5** as the starting material. Application of this strategy to the synthesis of other 4-thiofuranoses of more structural diversity and complexity will be explored. Further protective group manipulations, C2 modifications, as well as studies on thioglycosylation to provide biologically active 4-thiofuranosides are currently underway and will be reported in due course.

SCHEME 4



Experimental Section

6-*O*-*tert*-Butyldimethylsilyl-5-iodo-5-deoxy-3-*O*-benzoyl-1,2-*O*-isopropylidene-α-L-talofuranose (15). To a stirred solution of alcohol **7** (10.58 g, 24.2 mmol), Ph_3P (9.53 g, 36.4 mmol), and imidazole (3.32 g, 48.8 mmol) in anhydrous ether (100 mL) and acetonitrile (33 mL) under argon was added iodine (9.24 g, 36.4 mmol) in one portion at rt. The resulting slurry was stirred for 12 h under gentle reflux (bath temp 60 °C), cooled in an ice bath, and quenched with 10% aq $Na_2S_2O_3$. The aqueous phase was extracted with EtOAc (50 mL), and the combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was triturated with ether/hexane (1:1) and filtered through a sintered glass funnel; the filter cake was washed thoroughly with the same solvent. The combined filtrate was concentrated, and the residue was purified by silica gel column chromatography (EtOAc/hexane = 1/12) to afford **15** (11.53 g, 93% borsm) as a colorless oil. Further eluation (EtOAc/hexane = 1/6) recovered unreacted **7** (655 mg): $[\alpha]^{23}_D$ +82.5 (*c* 1.64, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.06 (m, 2H), 7.60 (t, 1H, J = 7.4 Hz), 7.46 (t-like, 2H, J = 7.4 Hz), 5.93 (d, 1H, J = 4.5 Hz), 4.99−4.92 (m, 2H), 4.28 (ddd, 1H, J = 9.4, 5.8, 2.0 Hz), 4.05−3.91, (m, 3H), 1.54 (s, 3H), 1.33 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.6, 133.4, 129.9, 128.4, 113.3, 104.6, 77.52, 77.48, 75.3, 66.2, 36.9, 26.8, 26.7, 25.8, 18.2, −5.3, −5.4. EI-MS *m*/*z* 533 ($M^+ - CH_3$, 0.63%); HR-MS *m*/*z* calcd for $C_{21}H_{30}O_6SiI$ 533.0838, found 533.0856.

6-*O*-*tert*-Butyldimethylsilyl-5-(*S*)-acetyl-5-thio-3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-allofuranose (19). To a solution of iodide **15** (13.95 g, 25.4 mmol) in DMF (40 mL) under argon was added AcSK (8.90 g, 78.1 mmol) in one portion. The solution was stirred at 50 °C for 36 h, cooled to rt, and diluted with ether (60 mL) and water (80 mL), and the aqueous layer was extracted with ether (30 mL). The combined organic layer was washed with water (2 × 40 mL) and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/30 to 1/12) to afford **19** (9.90 g, 78%) as a pale yellow oil: $[\alpha]^{23}_D$ +97.8 (*c* 2.06, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.09 (m, 2H), 7.58 (m, 1H), 7.46 (t-like, 2H, J = 7.8 Hz), 5.86 (d, 1H, J = 3.5 Hz), 5.00−4.94 (m, 2H), 4.56 (t, 1H, J = 6.6 Hz), 3.97−3.88 (m, 2H), 3.83−3.76 (m, 1H), 2.16 (s, 3H), 1.51 (s, 3H), 1.31 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 194.6, 165.4, 133.2, 129.9, 129.5, 128.4, 113.1, 104.0, 77.9, 76.6, 75.2, 62.7, 47.2, 30.4, 26.8, 26.6, 25.8, 18.2. EI-MS *m*/*z* 481 ($M^+ - CH_3$, 1.96%); HR-MS *m*/*z* calcd for $C_{23}H_{33}O_7SiS$ 481.1709, found 481.1716.

Methyl 2,3,5-tri-*O*-benzoyl-α,β-4-thio-D-ribofuranoside (13). A solution of **19** (3.25 g, 6.55 mmol) in 90% aqueous TFA (15 mL) was stirred at 0 °C for 2 h. The volatiles were removed under

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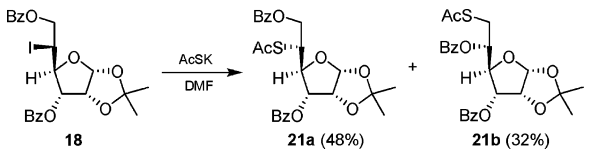
(24) For a detailed mechanistic study, see: Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1053. Accordingly, we observed the following results:



reduced pressure below 20 °C. The residue was taken up in EtOAc (100 mL) and washed with water, saturated $NaHCO_3$ until neutral, and brine and dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, the residue dissolved in MeOH (27 mL) and cooled to 0 °C, and a solution of $NaIO_4$ (1.40 g, 6.55 mmol) in water (27 mL) was added dropwise. The suspension was stirred at 0 °C for 30 min and quenched by ethylene glycol (0.92 mL), stirred for 30 min at rt, and diluted with MeOH (135 mL). The mixture was filtered through Celite, washed with MeOH, and the combined filtrate concentrated under reduced pressure. The residue was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was refluxed in 2% HCl in MeOH (32 mL) for 2 h, cooled in an ice bath, and neutralized with $NaHCO_3$. The inorganic salts were removed by filtration and washed with EtOAc, and the combined filtrate was concentrated under reduced pressure and dried on a pump. The resulting brown syrup was dissolved in pyridine (30 mL), and BzCl (7.9 mL) was added dropwise at 0 °C; the mixture was stirred overnight at rt, re-cooled to 0 °C, and quenched by MeOH. The volatiles were removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed several times with dilute HCl, then saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/20 to 1/8) to afford **13** (2.05 g, 63%) as a yellow syrup (mixture of α- and *β*-anomers): ^{1}H NMR ($CDCl_3$) *δ* 8.10−7.85 (m, 6H), 7.64−7.30 (m, 9H), 6.00−5.90 (m, 2H), 5.08 (br s, 1H), 4.68 (dd, 1H, *J* = 11.4, 6.6 Hz), 4.55 (dd, 1H, *J* = 11.4, 6.0 Hz), 4.24 (dt, 1H, *J* = 8.4, 6.0 Hz), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 166.0, 165.3, 165.2, 133.5, 133.2, 133.0, 130.0, 129.8, 129.7, 129.66, 129.4, 129.3, 129.0, 128.5, 128.3, 128.2, 89.6, 77.9, 76.0, 65.8, 56.6, 45.4. ESI-MS *m*/*z* 515.1 ($M + Na^+$); HR-ESI-MS *m*/*z* calcd for $C_{27}H_{24}NaO_7S$ 515.1140, found 515.1216.

2,3,5-Tri-*O*-benzoyl-1-*O*-acetyl-*β*-4-thio-D-ribofuranose (14). To a solution of **13** (670 mg, 1.36 mmol) in AcOH (5 mL) and Ac_2O (5 mL) was added concd H_2SO_4 (0.15 mL) under cooling. The solution was stirred at rt for 1 h, neutralized with excess NaOAc, and stirred for an additional 1 h. The volatiles were removed under reduced pressure, and the residue was diluted with CH_2Cl_2 and treated with saturated $NaHCO_3$ followed by solid $NaHCO_3$ until neutral. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give **14** (700 mg) as an off-white solid. Recrystallization from MeOH afforded pure *β*-**14** (495 mg): mp 159−160 °C; $[\alpha]^{23}_D$ +6.6 (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 8.04 (m, 2H), 7.97 (m, 2H), 7.90 (m, 2H), 7.62 (t-like, 1H, *J* = 7.4 Hz), 7.55−7.44 (m, 4H), 7.36−7.28 (m, 4H), 6.06 (d, 1H, *J* = 1.6 Hz), 5.99 (dd, 1H, *J* = 3.5, 1.6 Hz), 5.91 (dd, 1H, *J* = 8.6, 3.5 Hz), 4.74 (dd, 1H, *J* = 11.7, 5.3 Hz), 4.53 (dd, 1H, *J* = 11.3, 5.3 Hz), 4.25 (dt, 1H, *J* = 8.6, 6.3 Hz), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 169.3, 165.9, 165.4, 165.0, 133.7, 133.4, 133.1, 129.9, 129.7, 129.6, 129.4, 128.9, 128.8, 128.6, 128.4, 128.3, 79.7, 76.8, 75.1, 65.1, 46.1, 20.9. ESI-MS *m*/*z* 653.0 ($M + Cs^+$); HR-ESI-MS *m*/*z* calcd for $C_{28}H_{24}CsO_8S$ 653.0246, found 653.0289; *m*/*z* calcd for $C_{26}H_{21}O_6S$ ($M - AcO^-$) 461.1059, found 461.1055.

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Supporting Information Available: Experimental details for **9**, **11**, and **12**. Characterization data, ^{1}H and ^{13}C NMR spectra for all new compounds, X-ray crystallographic data for **9** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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