

# Diastereoselective Additions of Allylmetal Reagents to Free and Protected *syn*- $\alpha,\beta$ -Dihydroxyketones Enable Efficient Synthetic Routes to Methyl Trioxacarcinoside A

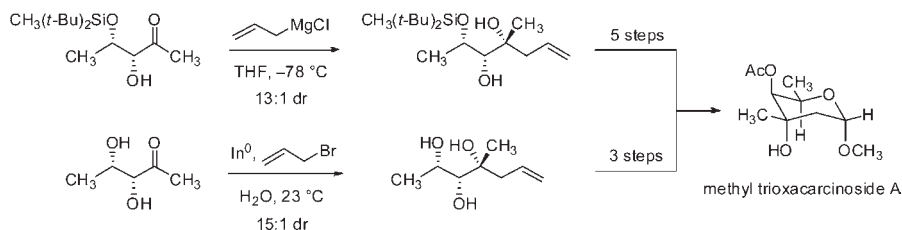
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## ABSTRACT



Two routes to the 2,6-dideoxysugar methyl trioxacarcinoside A are described. Each was enabled by an apparent  $\alpha$ -chelation-controlled addition of an allylmetal reagent to a ketone substrate containing a free  $\alpha$ -hydroxyl group and a  $\beta$ -hydroxyl substituent, either free or protected as the corresponding di-*tert*-butylmethyl silyl ether. Both routes provide practical access to gram quantities of trioxacarcinoside A in a form suitable for glycosidic coupling reactions.

Trioxacarcinoside A (**1**) is a rare deoxysugar found within many trioxacarcins, densely oxygenated bacterial metabolites with antiproliferative effects in cultured human cancer cells.<sup>1</sup> Trioxacarcin A (**2**), the most potent member of the trioxacarcin natural product class (Figure 1), contains both trioxacarcinoside A and B residues, each with an  $\alpha$ -linkage. The desacetyl form of trioxacarcinoside A, axenose (**3**), is also naturally occurring and was earlier known, appearing within the natural products axenomycin, polyketomycin, and dutomycin.<sup>2</sup> Two prior synthetic routes to

axenose have been published.<sup>3,4</sup> The first proceeded in 13 steps (1.6% yield) from L-fucose as starting material,<sup>3a</sup> and the second proceeded in 12 steps (~4% yield) from 2-deoxy-D-ribose as starting material.<sup>3b</sup> Here we describe two different synthetic routes to the axenose–trioxacarcinoside A carbohydrate class. Both routes rely upon diastereoselective addition reactions of allylmetal reagents to  $\alpha,\beta$ -dioxynated ketones and employ the crystalline substance 4-phenylbenzyl (2*R*,3*S*)-dihydroxybutyrate as starting material.<sup>5</sup> The routes we present have allowed us to prepare gram quantities of optically pure trioxacarcinoside A in a form suitable for glycosidic coupling reactions.

Considering the open-chain or aldehydic form of trioxacarcinoside A (Scheme 1), we focused on retrosynthetic

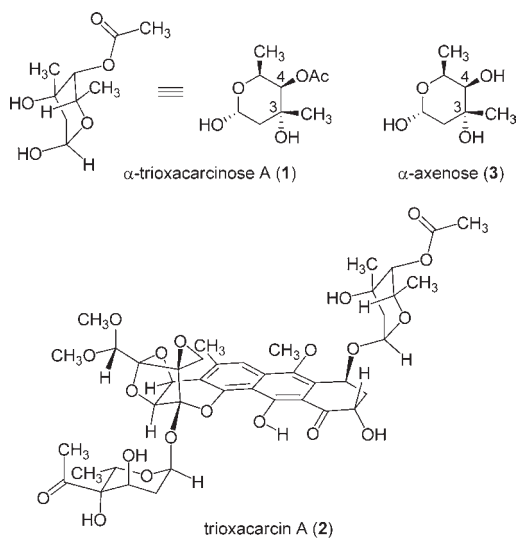
(1) (a) Tomita, F.; Tamaoki, T.; Morimoto, M.; Fujimoto, K. *J. Antibiot.* **1981**, *34*, 1519–1524. (b) Tamaoki, T.; Shirahata, K.; Iida, T.; Tomita, F. *J. Antibiot.* **1981**, *34*, 1525–1530.

(2) Axenomycin: (a) Arcamone, F.; Barbieri, W.; Franceschi, G.; Penco, S.; Vigevani, A. *J. Am. Chem. Soc.* **1973**, *95*, 2008–2009. Polyketomycin: (b) Momosa, I.; Chen, W.; Kinoshita, N.; Iinuma, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1998**, *51*, 21–25. (c) Momosa, I.; Chen, W.; Nakamura, H.; Naganawa, H.; Iinuma, H.; Takeuchi, T. *J. Antibiot.* **1998**, *51*, 26–32. Dutomycin: (d) Xuan, L.-J.; Xu, S.-H.; Zhang, H.-L. *J. Antibiot.* **1992**, *45*, 1974–1976.

(3) (a) Garegg, P. J.; Norberg, T. *Acta Chem. Scand.* **1975**, *29*, 506–513. (b) Giuliano, R. M.; Villani, F. J., Jr. *J. Org. Chem.* **1995**, *60*, 202–211.

(4) For a synthetic route to 3-*epi*-axenose, see: Roush, W.; Hagadorn, S. *Carbohydr. Res.* **1985**, *136*, 187–193.

(5) Smaltz, D. J.; Myers, A. G. *J. Org. Chem.* **2011**, *76*, 8554–8559. The Sharpless asymmetric dihydroxylation reaction was central to this preparation of 4-phenylbenzyl (2*R*,3*S*)-dihydroxybutyrate; for a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

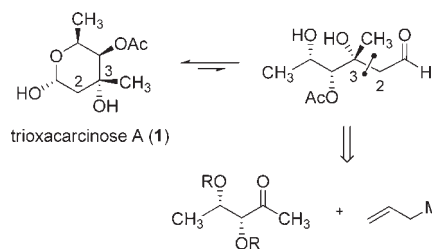


**Figure 1.** Structures of  $\alpha$ -trioxacarcinose A (1), trioxacarcin A (2), and  $\alpha$ -axenose (3).

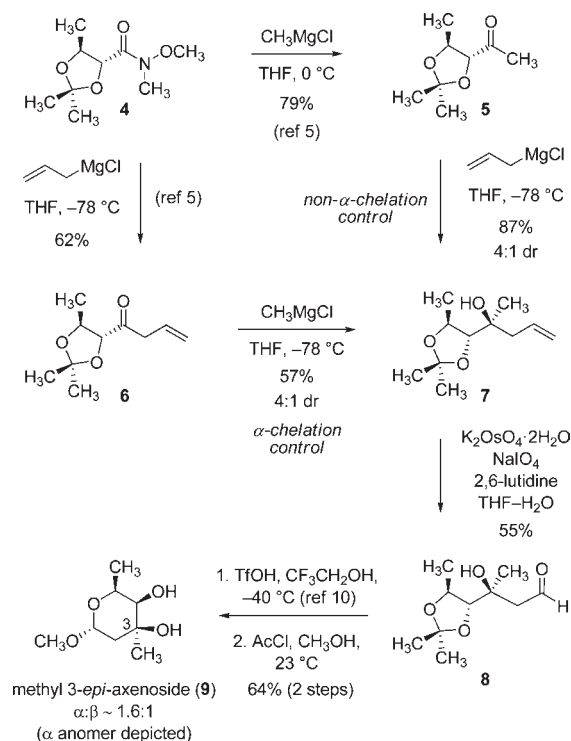
operations that would disconnect carbons 2 and 3. This led us to envision, in the synthetic direction, stereocontrolled addition of an allyl Grignard reagent to (3*R*,4*S*)-dihydroxy-2-pentanone with the expectation that our selection of diol protective group(s) might influence the addition; however, the literature did not offer clear guidance on what diol-protecting scheme might ensure the desired stereochemical outcome. While  $\alpha$ -chelation-controlled<sup>6</sup> additions of Grignard reagents to 2-tetrahydrofuranyl and  $\alpha$ -benzyloxy ketones have been featured in landmark syntheses of stereochemically complex natural products,<sup>7</sup> additions of Grignard reagents to ketones with acyclic side chains bearing both  $\alpha$ - and  $\beta$ -oxygenated substituents are of a less certain stereochemical outcome.<sup>8</sup>

We briefly explored additions of Grignard reagents to acetonide-protected *syn*-2,3-dihydroxyketones **5** (methyl ketone) and **6** (allyl ketone)<sup>9</sup> as summarized in Scheme 2; however, in neither case was the stereochemical outcome favorable for the purpose of synthesizing **1**. Thus, addition of allylmagnesium chloride to methyl ketone **5** afforded predominantly the stereoisomer **7**, which is not congruent

### Scheme 1. Retrosynthetic Analysis of Trioxacarcinose A (1)



### Scheme 2. Additions to Acetonide-Protected *syn*-2,3-Dihydroxyketones



with trioxacarcinose A at position C3, established by conversion of the adduct **7** to methyl 3-*epi*-axenoside (**9**) in a 3-step sequence (Scheme 2).<sup>4,10</sup> The observed stereochemical course is consistent with either “polar Felkin–Anh”<sup>11</sup> or  $\beta$ -chelation-controlled transition structures, but not an  $\alpha$ -chelation-controlled addition. Interestingly, addition of methylmagnesium chloride to the allyl ketone **6** also afforded the tertiary alcohol **7** as the major product, which in this case corresponds to an  $\alpha$ -chelation-controlled process. This is not the first instance where the stereochemical outcomes of addition reactions of allyl and methyl Grignard reagents to a common ketone substrate have been different.<sup>12</sup>

(6) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748–2755. (b) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *11*, 1031–1034. Reviews: (c) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462–468. (d) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223. (e) Reetz, M. T. *Angew. Chem., Int. Ed.* **2003**, *23*, 556–569.

(7) (a) Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, *19*, 2745–2748. (b) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1979**, *102*, 2117–2120.

(8) (a) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843–2846. (b) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422–424.

(9) Both substrates **5** and **6** were derived from 4-phenylbenzyl (2*R*,3*S*)-dihydroxybutyrate via the Weinreb amide acetonide **4**, as summarized in Scheme 2.<sup>5</sup>

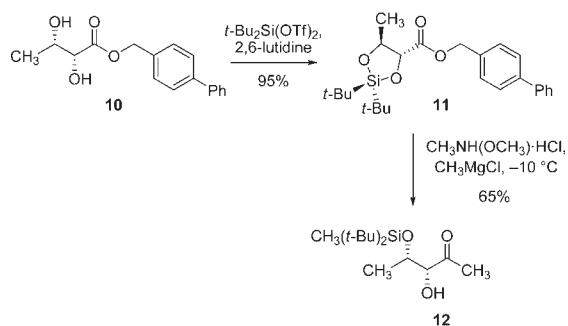
(10) Cleavage of the acetonide protective group required the use of triflic acid in trifluoroethanol, conditions first described by the Hiram group in the context of their synthesis of N1999A2; see: Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hiram, M. *J. Am. Chem. Soc.* **2001**, *123*, 2887–2888.

(11) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–162.

(12) Carda, M.; González, F.; Rodríguez, S.; Marco, J. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1799–1802.

In light of the unfavorable stereochemical outcomes of addition reactions to the acetonide-protected ketone substrates **5** and **6**, we were led to prepare the di-*tert*-butylsiloxy ester derivative **11** as a substrate (95% yield, 12.7 g, Scheme 3),<sup>13</sup> which was easily achieved using the readily available, optically pure diol ester **10** as starting material.<sup>5</sup> Fortuitously, we observed that upon attempted transformation of the di-*tert*-butylsiloxy ester **11** into the corresponding methyl ketone using the Merck single-step process (via the Weinreb amide derivative)<sup>14,15</sup> concomitant, regioselective cleavage of the cyclic siloxane group occurred, giving rise to the di-*tert*-butylmethyl silyl ether **12** (5.3 g, 65% yield). Although regioselective openings of di-*tert*-butylsiloxy derivatives with *n*-butyllithium have been described,<sup>16</sup> we are unaware of corresponding transformations with Grignard reagents.

**Scheme 3.** Synthesis of Methyl Ketone **12**



The selective transformation of the cyclic siloxane **11** to the monosilyl ether **12** proved to be quite useful, as it enabled our first synthetic route to trioxacarcinose A (Scheme 4). Addition of excess allylmagnesium chloride to  $\alpha$ -hydroxyketone **12** in THF at  $-78$  °C proceeded with 13:1 diastereoselectivity favoring the tertiary alcohol product **13**, consistent with an  $\alpha$ -chelation-controlled addition mechanism (3.59 g, 86% yield).<sup>17</sup> The product (**13**) is stereochemically congruent with trioxacarcinose A (**1**), as established by its conversion to methyl axenoside (**17**), en route to **1**, as detailed below.

Oxidative cleavage of the alkenyl side chain of **13** occurred in the presence of potassium osmate and sodium metaperiodate,<sup>18</sup> providing the furanose derivative **14** as a mixture of anomers (1.97 g, 55% yield,  $\alpha$ : $\beta$   $\approx$  1:5).

(13) (a) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999–5002. (b) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871–4874.

(14) Williams, J.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

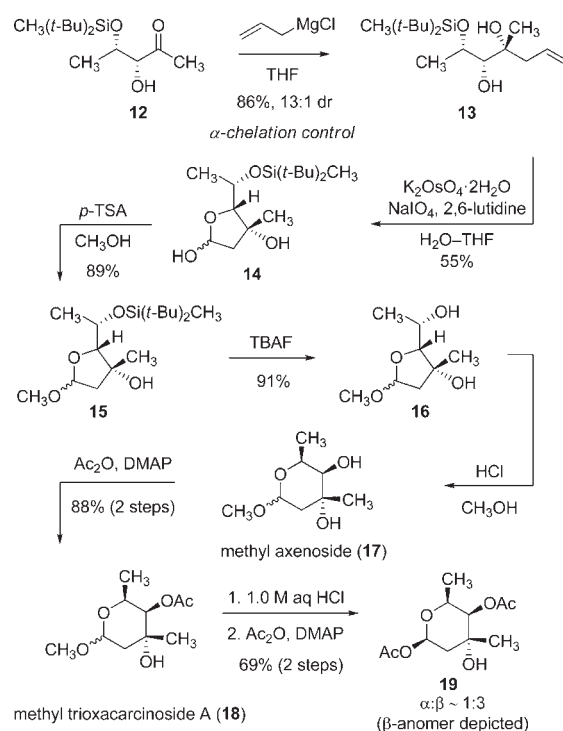
(15) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

(16) (a) Mukaiyama, T.; Shiina, I.; Kimura, K.; Akiyama, Y.; Iwadare, H. *Chem. Lett.* **1995**, *24*, 229–230. (b) Tanino, K.; Shimizu, T.; Kuwahara, M.; Kuwajima, I. *J. Org. Chem.* **1998**, *63*, 2422–2423.

(17) Chelation-controlled Grignard additions of  $\alpha$ -hydroxyketones, while relatively uncommon, are known. For an example, see: (a) Matsunaga, N.; Kaku, T.; Ojida, A.; Tasaka, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2021–2028.

(18) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.

**Scheme 4.** Syntheses of Methyl Axenoside (**17**) and Methyl Trioxacarcinose A (**18**)



Deprotection of the di-*tert*-butylmethylsilyl ether, a sterically hindered and robust protective group,<sup>19</sup> was accomplished in two steps. The cyclic hemiacetal **14** was first transformed into the more stable methyl glycoside derivative **15** with *p*-toluenesulfonic acid in methanol (89% yield). The methyl glycoside then underwent smooth desilylation with TBAF at 23 °C to provide methyl furanosides **16** in 91% yield (890 mg). The latter product was isomerized to the more stable methyl pyranosides **17** (methyl  $\alpha$ - and  $\beta$ -axenoside) with methanolic HCl at 23 °C, a known transformation.<sup>3b,20</sup> Analytical data were in accord with those previously reported for methyl axenoside.<sup>3</sup> Selective *O*-acetylation of **17** provided methyl trioxacarcinose A **18** (970 mg, 88% over two steps). Analytical data were in agreement with values reported for the same substance derived from natural sources.<sup>21</sup> Hydrolysis of **18** in 1.0 M aqueous hydrochloric acid provided trioxacarcinose A itself (**1**), which was acetylated at the anomeric position to give 1-*O*-acetyl glycoside **19** in 69% yield over two steps ( $\alpha$ : $\beta$   $\approx$  1:3). 1-*O*-Acetyl glycosides are known to be effective glycosyl donors, do not require activation for

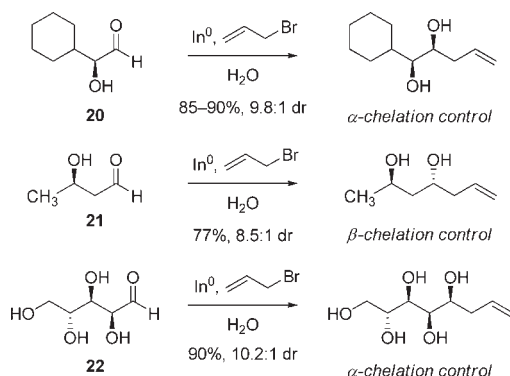
(19) Nicolaou, K. C.; Yue, E. W.; la Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; de Riccardis, F. *Chem.—Eur. J.* **1995**, *1*, 467–494.

(20) The product is a (presumably, thermodynamic) mixture of methyl pyranoside and furanoside isomers:  $\beta$ -pyranoside, 62%;  $\alpha$ -pyranoside, 34%;  $\beta$ -furanoside, 4%;  $\alpha$ -furanoside, < 1%.

(21) Shirahata, K.; Iida, T.; Hirayama, N. *Symposium on the Chemistry of Natural Products* **1981**, *24*, 199–206.

coupling,<sup>22</sup> and can also be transformed into a number of other different types of glycosyl donors.<sup>23</sup>

**Scheme 5.** Indium-Mediated Allylations of Hydroxyaldehydes as Described by Paquette and Mitzel<sup>24a</sup>



While the route outlined in Scheme 4 provided an effective and scalable means of synthesizing trioxacarcinose A and derivatives, an even shorter sequence was considered for investigation based upon a remarkable series of publications from Paquette et al. describing diastereoselective, indium-mediated allylation reactions of aldehyde and ketone substrates containing free hydroxyl groups, in water as solvent.<sup>24</sup> For example (summarized in Scheme 5), Paquette and Mitzel showed that In-mediated allylation of the  $\alpha$ -hydroxyaldehyde **20** proceeded with high diastereoselectivity to afford mainly the syn product, consistent with an  $\alpha$ -chelation-controlled addition mechanism, while allylation of the  $\beta$ -hydroxyaldehyde **21** provided primarily the anti product, consistent with a  $\beta$ -chelation-controlled mechanism. They also reported the very interesting case of In-mediated allylation of the polyol D-arabinose **22**, where in principle the directing effects of the  $\alpha$ - and  $\beta$ -hydroxyl groups were nonreinforcing (and the effects of  $\gamma$ - and  $\delta$ -hydroxyl groups were unknown); the product of apparent  $\alpha$ -chelation control was formed with high diastereoselectivity.<sup>24a</sup> The latter result was particularly germane, for it suggested that allylation of the specific dihydroxy ketone substrate (3*R*,4*S*)-dihydroxy-2-pentanone (**23**), with nonreinforcing  $\alpha$ - and  $\beta$ -directing effects, might proceed in the desired sense (with  $\alpha$ -chelation control) to provide a practicable and extraordinarily short sequence to trioxacarcinose A.

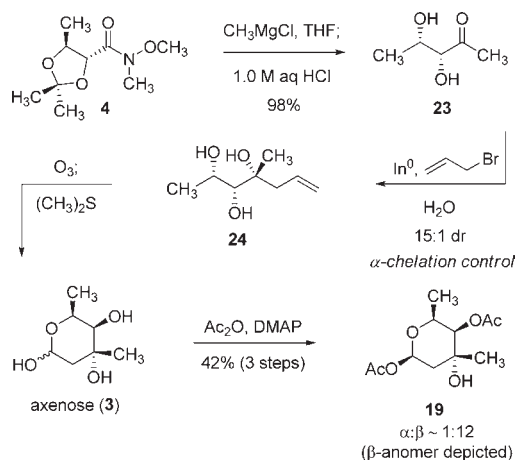
(22) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531.

(23) (a) Ogawa, T.; Kitajima, T.; Nukada, T. *Carbohydr. Res.* **1983**, *123*, C8–C11. (b) Hayashi, M.; Hashimoto, S.; Noyori, R. *Chem. Lett.* **1984**, *13*, 1747–1750. (c) Kihlberg, J. O.; Leigh, D. A.; Bundle, D. R. *J. Org. Chem.* **1990**, *55*, 2860–2863. (d) Sarkar, S.; Lombardo, S. A.; Herner, D. N.; Talan, R. S.; Wall, K. A.; Sucheck, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 17236–17246.

(24) (a) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863–6866. (b) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931–1937. (c) Paquette, L. A.; Lobben, P. C. *J. Org. Chem.* **1998**, *63*, 5604–5616.

(25) The highly polar intermediates **24** and **3** were difficult to purify chromatographically and so were carried through subsequent transformations without purification. We believe that this contributed to the moderate yield of **19** over the three-step sequence.

**Scheme 6.** Second-Generation Synthesis of 1-*O*-Acetyl Trioxacarcinose A (**19**)



To investigate the feasibility of the shorter sequence we envisioned, we first transformed the Weinreb amide substrate **4**<sup>5,9</sup> into ketone **23** (9.89 g, 98% yield), in a single operation (Scheme 6). Allylation of the latter product (**23**, 3.43 g) under conditions typical of those employed by Paquette and Mitzel,<sup>24b</sup> using In powder (1.6 equiv) and allyl bromide (1.6 equiv) in water at 23 °C, did indeed proceed with predominant  $\alpha$ -chelation control to provide the water-soluble triol **24** as a 15:1 mixture of diastereomers. Direct ozonolysis followed by reductive quenching with dimethylsulfide led to cleavage of the terminal alkene(s) to afford axenose (**3**), predominantly in its pyranose form. The crude product was then acetylated to afford 1-*O*-acetyl trioxacarcinose A (**19**, 42% yield over three steps from **23**, 2.97 g,  $\alpha$ : $\beta$   $\approx$  1:12) in >95% purity after chromatographic purification.<sup>25</sup>

Methanolysis of 1-*O*-acetyl trioxacarcinose A (**19**) synthesized by this second route (using acetyl chloride in methanol) produced methyl trioxacarcinoside A (**18**, 74% yield, see Supporting Information), which provided analytical data indistinguishable from those of **18** from our first route, described above. By virtue of its greater brevity and convenience, the second synthetic route provides an especially useful means of access to trioxacarcinose A in an anomericly activated form.

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**Supporting Information Available.** Experimental procedures and characterization data (<sup>1</sup>H and <sup>13</sup>C NMR, FT-IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.