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Diastereoselective Additions of Allylmetal Reagents to Free and Protected *syn*-α,β-Dihydroxyketones Enable Efficient Synthetic Routes to Methyl Trioxacarcinoside A

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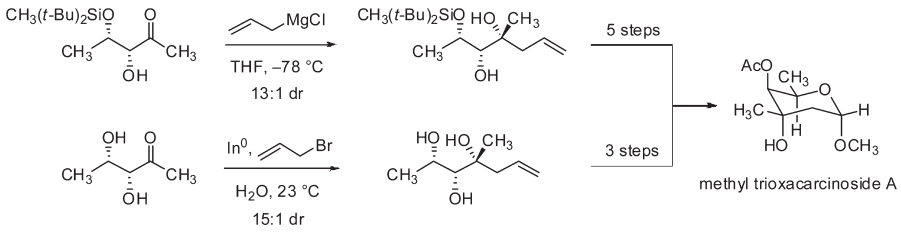
ABSTRACT



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

Trioxacarcinose A (**1**) is a rare deoxysugar found within many trioxacarcins, densely oxygenated bacterial metabolites with antiproliferative effects in cultured human cancer cells.[1] Trioxacarcin A (**2**), the most potent member of the trioxacarcin natural product class (Figure 1), contains both trioxacarcinose A and B residues, each with an α-linkage. The desacetyl form of trioxacarcinose A, axenose (**3**), is also naturally occurring and was earlier known, appearing within the natural products axenomycin, polyketomycin, and dutomycin.[2] Two prior synthetic routes to axenose have been published.[3,4] The first proceeded in 13 steps (1.6% yield) from L-fucose as starting material,[3a] and the second proceeded in 12 steps (~4% yield) from 2-deoxy-D-ribose as starting material.[3b] Here we describe two different synthetic routes to the axenose−trioxacarcinose A carbohydrate class. Both routes rely upon diastereoselective addition reactions of allylmetal reagents to α,β-dioxygenated ketones and employ the crystalline substance 4-phenylbenzyl (2*R*,3*S*)-dihydroxybutyrate as starting material.[5] The routes we present have allowed us to prepare gram quantities of optically pure trioxacarcinose A in a form suitable for glycosidic coupling reactions.

Considering the open-chain or aldehydic form of trioxacarcinose 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.

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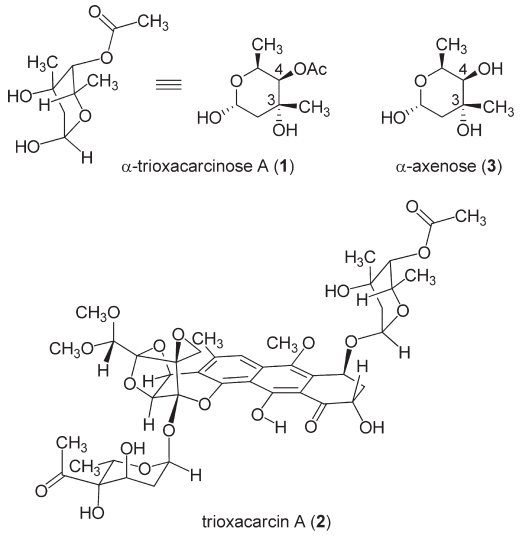
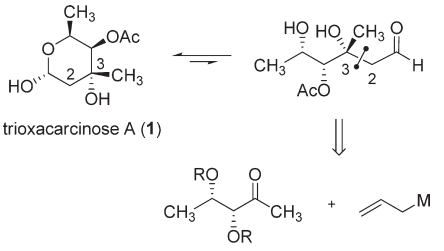


Figure 1. Structures of α-trioxacarcinose A (**1**), trioxacarcin A (**2**), and α-axenose (**3**).

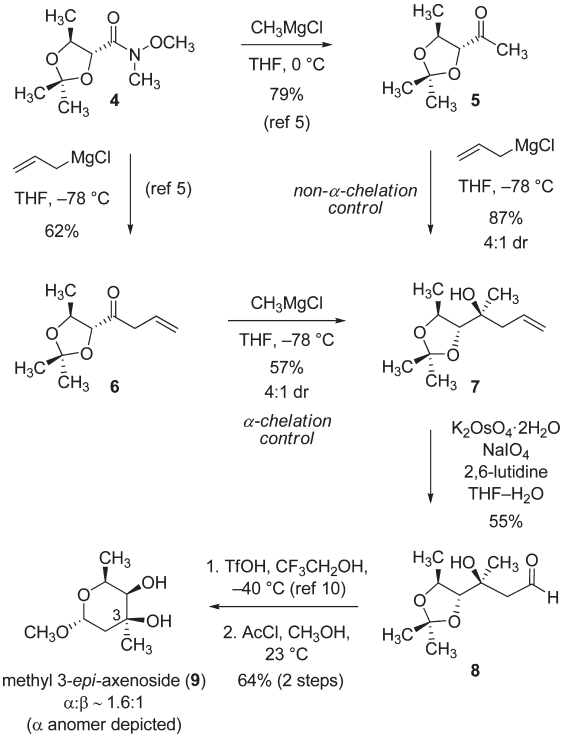
operations that would disconnect carbons 2 and 3. This led us to envision, in the synthetic direction, stereocontrolled addition of an allyl Grignard reagent to (3*R*,4*S*)-dihydroxy-2-pentanone with the expectation that our selection of diol protective group(s) might influence the addition; however,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

We briefly explored additions of Grignard reagents to acetonide-protected *syn*-2,3-dihydroxyketones **5** (methyl ketone) and **6** (allyl ketone)[9] 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).[4,10] The observed stereochemical course is consistent with either "polar Felkin–Anh"[11] or *β*-chelation-controlled transition structures, but not an α-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 α-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.[12]

(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.[5]

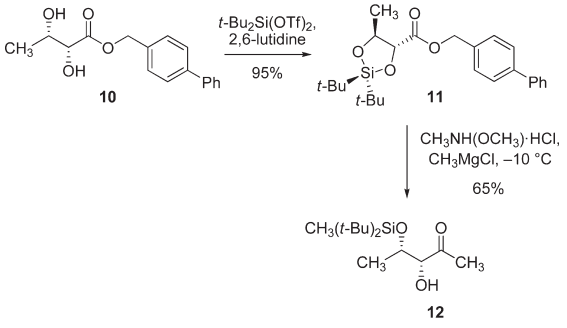
(10) Cleavage of the acetonide protective group required the use of triflic acid in trifluoroethanol, conditions first described by the Hirama group in the context of their synthesis of N1999A2; see: Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *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*-butylsiloxane ester derivative **11** as a substrate (95% yield, 12.7 g, Scheme 3),[13] which was easily achieved using the readily available, optically pure diol ester **10** as starting material.[5] Fortuitously, we observed that upon attempted transformation of the di-*tert*-butylsiloxane ester **11** into the corresponding methyl ketone using the Merck single-step process (via the Weinreb amide derivative)[14,15] 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*-butylsiloxane derivatives with *n*-butyllithium have been described,[16] we are unaware of corresponding transformations with Grignard reagents.

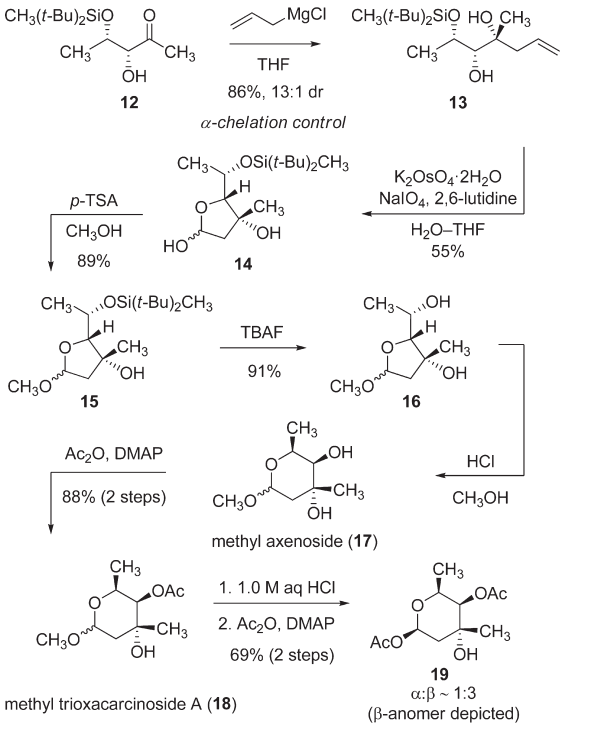
Scheme 3. Synthesis of Methyl Ketone **12**



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 α-hydroxyketone **12** in THF at −78 °C proceeded with 13:1 diastereoselectivity favoring the tertiary alcohol product **13**, consistent with an α-chelation-controlled addition mechanism (3.59 g, 86% yield).[17] 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,[18] providing the furanose derivative **14** as a mixture of anomers (1.97 g, 55% yield, α:β ≈ 1:5).

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



Deprotection of the di-*tert*-butylmethylsilyl ether, a sterically hindered and robust protective group,[19] 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 α- and β-axenoside) with methanolic HCl at 23 °C, a known transformation.[3b,20] Analytical data were in accord with those previously reported for methyl axenoside.[3] Selective *O*-acetylation of **17** provided methyl trioxacarcinoside A **18** (970 mg, 88% over two steps). Analytical data were in agreement with values reported for the same substance derived from natural sources.[21] 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 (α:β ≈ 1:3). 1-*O*-Acetyl glycosides are known to be effective glycosyl donors, do not require activation for

(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 α-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.

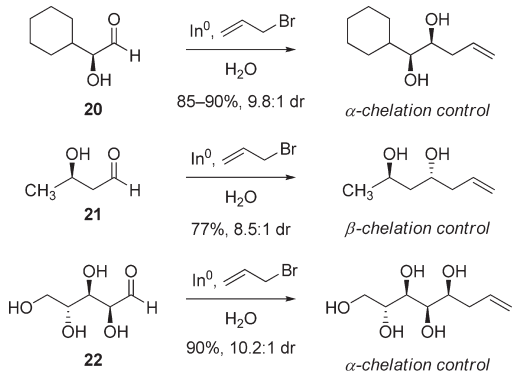
(19) Nicolaou, K. C.; Yue, E. W.; la Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; de Riccardis, F. *Chem.—Eur. J.* **1995**, *1*, 467–494.

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

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

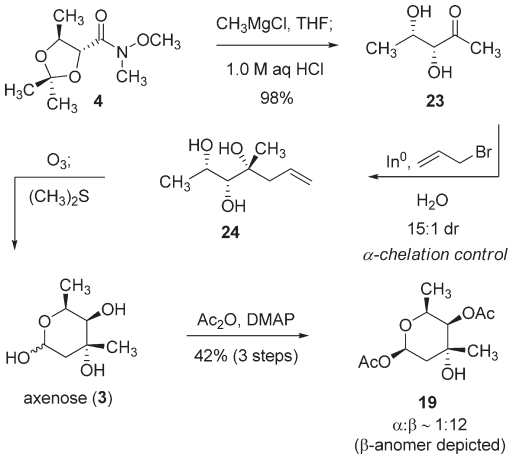
coupling,[22] and can also be transformed into a number of other different types of glycosyl donors.[23]

Scheme 5. Indium-Mediated Allylations of Hydroxyaldehydes as Described by Paquette and Mitzel[24a]



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.[24] For example (summarized in Scheme 5), Paquette and Mitzel showed that In-mediated allylation of the α-hydroxyaldehyde **20** proceeded with high diastereoselectively to afford mainly the syn product, consistent with an α-chelation-controlled addition mechanism, while allylation of the *β*-hydroxyaldehyde **21** provided primarily the anti product, consistent with a *β*-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 α- and *β*-hydroxyl groups were nonreinforcing (and the effects of *γ*- and *δ*-hydroxyl groups were unknown); the product of apparent α-chelation control was formed with high diastereoselectivity.[24a] 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 α- and *β*-directing effects, might proceed in the desired sense (with α-chelation control) to provide a practicable and extraordinarily short sequence to trioxacarcinose A.

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**[5,9] 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,[24b] using In powder (1.6 equiv) and allyl bromide (1.6 equiv) in water at 23 °C, did indeed proceed with predominant α-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, α:*β* ≈ 1:12) in >95% purity after chromatographic purification.[25]

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 anomerically activated form.

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Supporting Information Available. Experimental procedures and characterization data (^{1}H and ^{13}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.

(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.