ORGANIC LETTERS

2011
Vol. 13, No. 20
5584–5587

Short and Efficient Synthetic Route to Methyl α-Trioxacarcinoside B and Anomerically Activated Derivatives

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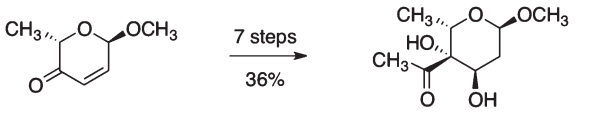
Received August 25, 2011

ABSTRACT



methyl α-trioxacarcinoside B

A 9-step synthetic route to the complex carbohydrate methyl α-trioxacarcinoside B from 2-acetylfuran is described. Anomerically activated forms, including 1-phenylthio, 1-*O*-(4′-pentenyl), 1-fluoro, and 1-*O*-acetyl derivatives are also prepared.

The eight-carbon 2-deoxysugar trioxacarcinose B (**1**) is a constituent of both trioxacarcins and quinocyclines, structurally distinct classes of bacterial fermentation products with antiproliferative and antibiotic effects.[1] Trioxacarcin A (**2**) and quinocycline B (**3**), depicted in Figure 1, are representative members of each structural class; in both cases, the trioxacarcinose B sugar residue is found in α-glycosidic linkage with the aglycon core. Members of both natural product series have also been identified that contain an α-linked 7-(*S*)-dihydrotrioxacarcinose B (**4**) residue. To date, one route for the synthesis of trioxacarcinose B and two routes to 7-(*S*)-dihydrotrioxacarcinose B have been reported. Paulsen and Sinnwell first described a 7-step sequence to methyl α-7-(*S*)-dihydrotrioxacarcinoside B using L-rhamnal diacetate as starting material (2.2% yield).[2] Suami and co-workers later developed an 11-step route to methyl α-trioxacarcinoside B from the same precursor (4.3% yield).[3] More recently, Koert and co-workers reported a 15-step route to methyl α-7-(*S*)-dihydrotrioxacarcinoside B (6.4% yield) by *de novo* construction of the carbohydrate residue, using a lipase to resolve an early intermediate.[4]

Here we describe a short and practical sequence for the synthesis of trioxacarcinose B and anomerically activated forms using 2-acetylfuran as starting material (Scheme 1). Reduction of 2-acetylfuran by Noyori's protocol (dihydrogen, 50 bar, *trans*-$RuCl_2$-[(*R*)-xylbinap][(*R*)-daipen], 0.005 mol %, purification by distillation) afforded the (*S*)-alcohol **6** (94 g) in 77% yield and ≥99% ee.[5,6] This versatile building block is also commercially available. Oxidative ring expansion[7] of furan **6** with bromine in methanol, also a known transformation,[8] provided an anomeric mixture ($\alpha:\beta \approx 1.2:1$) of methyl acetals from which the pure α-anomer **7** could be obtained by medium pressure liquid chromatography (5.3 g, 20%). Conjugate reduction of **7** (5.2 g) with lithium tri-*sec*-butylborohydride (1.2 equiv) in tetrahydrofuran at −78 °C and trapping of the resulting enolate with Comins' reagent[9] (1.1 equiv) afforded the vinyl triflate

(1) (a) Matern, U.; Grisebach, H. *Eur. J. Biochem.* **1972**, *29*, 1–4. (b) Shirahata, K.; Iida, T.; Hirayama, N. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1981**, *24*, 199–206.

(2) Paulsen, H.; Sinnwell, V. *Chem. Ber.* **1978**, *111*, 869–878.

(3) (a) Suami, T.; Nakamura, K.; Hara, T. *Chem. Lett.* **1982**, 1245–1248. (b) Suami, T.; Nakamura, K.; Hara, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1431–1434.

(4) König, C. M.; Harms, K.; Koert, U. *Org. Lett.* **2007**, *9*, 4777–4779.

(5) Noyori, R.; Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749–1751.

(6) $[\alpha]_D^{25} = -20.2$ ($c = 1.06$, $CHCl_3$), ref 4 $[\alpha]_D^{24} = -20.1$ ($c = 1.00$, $CHCl_3$).

(7) Achmatowicz, O.; Bukowksi, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973–1996.

(8) Sammes, P. G.; Thetford, D. *J. Chem. Soc., Perkin Trans. I* **1988**, 111–123.

(9) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *42*, 6299–6302.

10.1021/ol202315m
Published on Web 09/29/2011

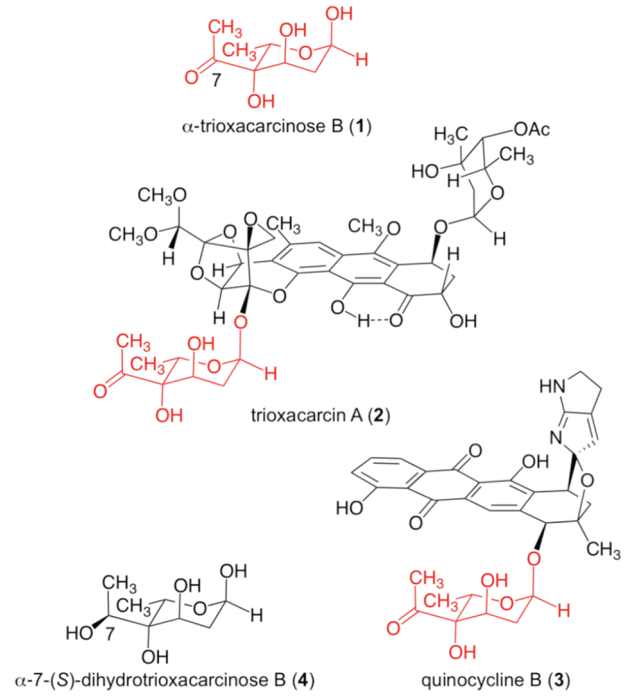


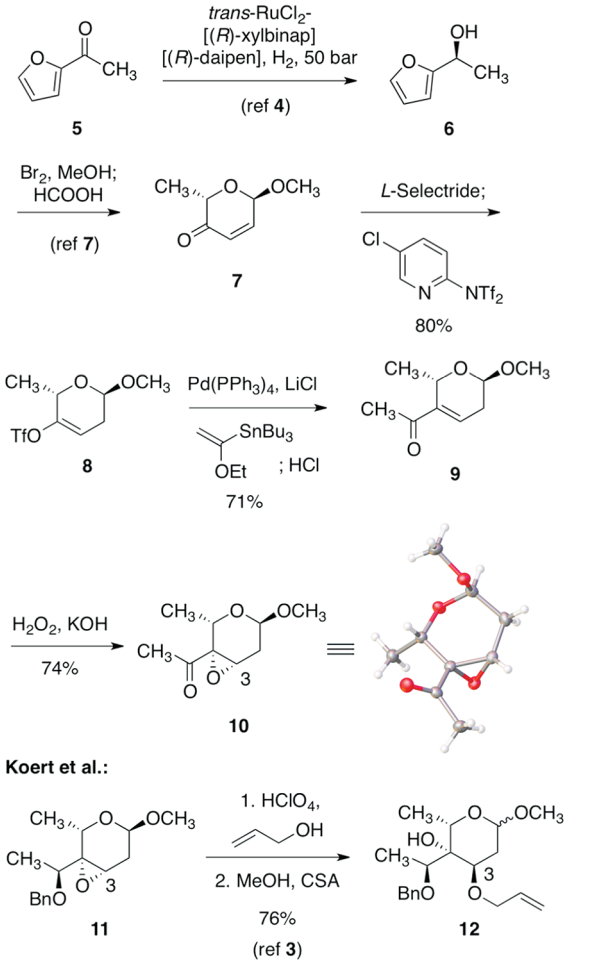
Figure 1. Structures of α-trioxacarcinose B (**1**), trioxacarcin A (**2**), quinocycline B (**3**), and α-7-(*S*)-dihydrotrioxacarcinose B (**4**).

8 in 80% yield. Use of *N*-phenyl-bis(trifluoromethanesulfonimide) as a trapping agent also provided vinyl triflate **8**, but in lower yield (60%).[10] Heating a solution of vinyl triflate **8**, tri*n*-butyl(1-ethoxyvinyl)tin (2.5 equiv), tetrakis-(triphenylphosphine)palladium(0) (5 mol %), and LiCl (2.5 equiv) at 70 °C for 8 h led to formation of an acid-labile dienyl ether. Rapid hydrolysis of the dienyl ether occurred upon acidic workup; column chromatography afforded enone **9** in pure form in 71% yield (3.3-g scale).

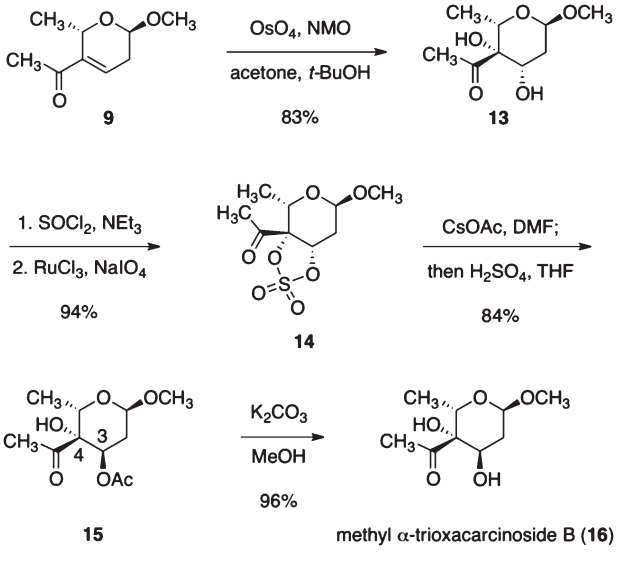
Exposure of enone **9** to alkaline hydrogen peroxide (30% H_2O_2, KOH, MeOH) provided the epoxide **10** as a single diastereomer in 74% yield as a colorless, crystalline solid. X-ray crystallographic analysis established that the stereochemistry of the epoxide was as depicted in structure **10** (Scheme 1). Interestingly, when the corresponding *β*-anomeric enone substrate was subjected to the same epoxidation conditions, a 1:1 mixture of diastereomeric expoxides was formed. Numerous efforts to bring about regioselective opening of epoxide **10** (derived from the α-anomer) by nucleophilic addition to position C3 were not successful. This lack of success stands in contrast to the prior findings of Koert and co-workers in their synthesis of methyl α-7-(*S*)-dihydrotrioxacarcinoside B using epoxide **11** as substrate (Scheme 1, bottom).[4] Evidently, the more highly oxidized substrate **10** we examined has a lesser propensity toward acid-promoted epoxide opening. In retrospect, this is perhaps not surprising.

(10) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982.

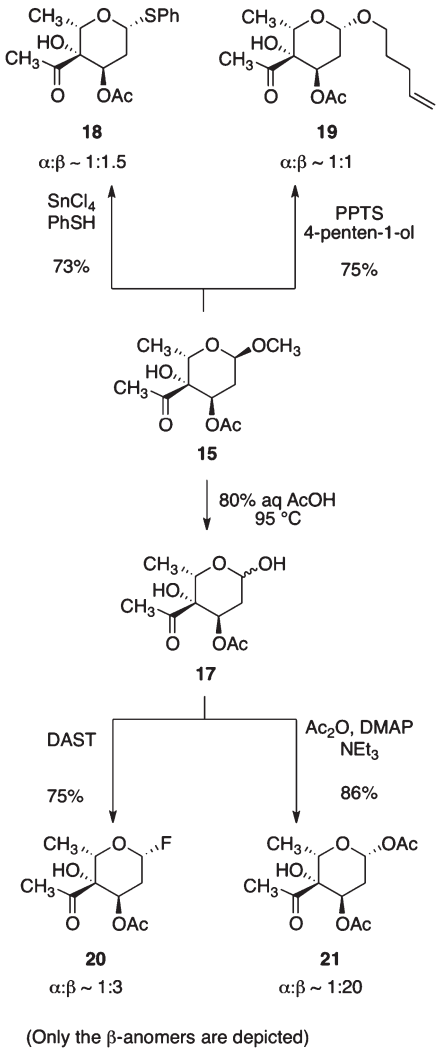
Scheme 1. Synthesis and X-ray Structure of Epoxide **10**



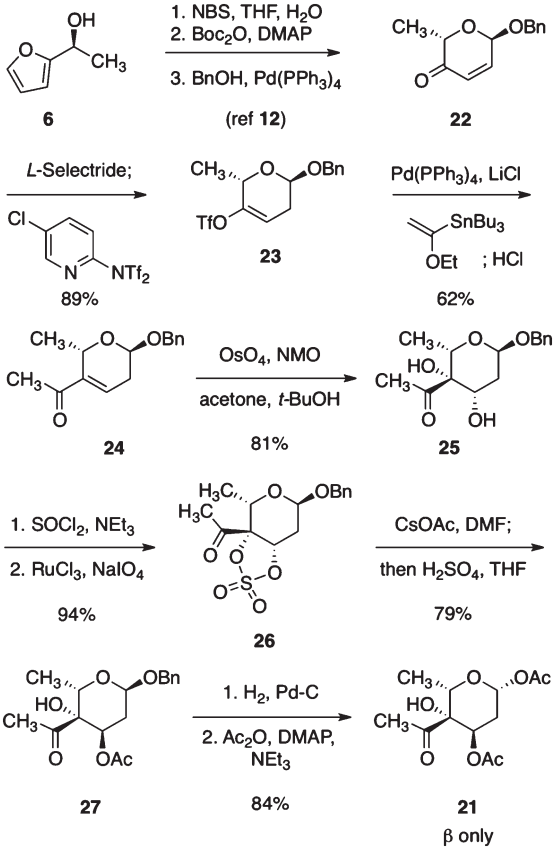
Scheme 2. Synthesis of Methyl α-Trioxacarcinoside B (**16**)



Scheme 3. Preparation of Anomerically Activated Derivatives of Trioxacarcinose B



Scheme 4. Optimized Synthesis of 1-*O*-Acetyl Glycoside **21**



We elected to adapt our strategy by replacing the epoxide function of substrate **10** with the corresponding cyclic sulfate. In fundamental work, Gao and Sharpless reported that cyclic sulfates are more reactive than epoxides toward nucleophilic opening.[11] Dihydroxylation of enone **9** (OsO_4, *N*-methylmorpholine-*N*-oxide) provided the *cis*-diol **13** in 83% yield (2.7 g) as a white solid (Scheme 2). Formation of the cyclic sulfite (thionyl chloride, triethylamine) followed by oxidation ($RuCl_3$, $NaIO_4$) provided the cyclic sulfate **14** in 94% yield. Regioselective ring-opening of **14** with cesium acetate (1.1 equiv, *N*,*N*-dimethylformamide, 50 °C) followed by acid-promoted hydrolysis of the monosulfate ester gave the acetate **15** in 84% yield. Careful control of the reaction temperature and the amount of cesium acetate were necessary to avoid the formation of byproducts during the acetate addition reaction. While Gao and Sharpless reported that cyclic sulfates derived from trans α,β-unsaturated esters undergo regioselective opening with carboxylate nucleophiles by attack at the α-position, with the α,α-disubstituted cyclic sulfate **14** as substrate nucleophilic addition proceeds by attack at the β-position. This can be rationalized by the additional substitution at the α-position and by the fact that β-attack leads to a trans-diaxial disposition of the two C−O bonds at C3 and C4. Saponification of the acetate **15** afforded methyl α-trioxacarcinoside B **16** (175 mg, 96%). Analytical data (HRMS, ^{1}H NMR, ^{13}C NMR, mp, and optical rotation) were identical with those reported in the literature in all respects (see Supporting Information).[2,12]

With an efficient protocol for the synthesis of acetate **15** our efforts turned toward developing an appropriate means of anomeric activation (Scheme 3). We first prepared the corresponding 1-phenylthioglycosides **18** (87 mg, 73%) by subjection of acetate **15** to thiophenol in the presence of tin(IV) chloride at −78 °C. The anomeric mixture of phenylthioglycosides (α:β ≈ 1:1.5) was readily separated by flash-column chromatography on silica gel. We next prepared the 1-*O*-(4′-pentenyl) derivatives **19**. Exposure of a solution of acetate **15** in dichloroethane to

(11) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539. (b) Lohray, B. B. *Synthesis* **1992**, 1035–1052.

(12) (a) Matern, U.; Grisebach, H. *Eur. J. Biochem.* **1972**, *29*, 1–4. (b) Matern, U.; Grisebach, H. *Z. Naturforsch.* **1974**, *29c*, 407–413. (c) Shirahata, K.; Iida, T.; Hirayama, N. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1981**, *24*, 199–206.

pyridinium *p*-toluenesulfonate (PPTS) and 4-penten-1-ol at 80 °C afforded the 1-*O*-(4′-pentenyl) glycosides **19** as a 1:1 mixture of anomers (41 mg, 84%). Lastly, we synthesized both the 1-fluoro and 1-*O*-acetyl glycosides from the hemiacetals **17**, prepared from acetate **15** by hydrolysis with aqueous acetic acid at 95 °C. Addition of (diethylamino)sulfur trifluoride (DAST) to a solution of hemiacetals **17** in tetrahydrofuran at −40 °C gave the moisture- and acid-sensitive glycosyl fluorides **20** (7.6 mg, 75%). Analysis of the ^{1}H NMR spectrum of the crude reaction product revealed that the β-anomer predominated (α:$\beta \approx$ 1:3). The 1-*O*-acetyl glycosides **21** were also obtained from hemiacetals **17**. Treating a solution of hemiacetals **17** in dichloromethane with acetic anhydride, *N*,*N*-dimethyl-4-aminopyridine and triethylamine provided the 1-*O*-acetyl glycosides **21** (240 mg, 86%, α:$\beta \approx$ 1:20), along with two minor inseparable byproducts, believed to be isomers (see Supporting Information for further details).

We found that by use of a benzyl acetal function in lieu of the methyl acetal a substantial improvement in the overall efficiency and operational simplicity of the route was achieved (Scheme 4). By this sequence, the 1-*O*-acetyl glycoside **21**, a preferred donor for the introduction of trioxacarcinose B α-glycosides, could be synthesized in 1-g amounts. Advantages of this improved sequence include the fact that the intermediates throughout the route were less volatile and that the benzyl acetal **22** was more easily purified (see Supporting Information).[13] The milder conditions for cleavage of the benzyl acetal **27** (H_2, 10% Pd−C, ethyl acetate) also proved advantageous, for the byproducts that were formed during acidic hydrolysis of the methyl acetal (**15** → **17**, Scheme 3) were not observed.

Acknowledgment. Financial support from the National Institutes of Health (Grant CA047148) and the Austrian Science Fund (FWF, Schrödinger postdoctoral fellowship J3000-B11 to T.M.) is gratefully acknowledged.

Supporting Information Available. Experimental procedures and tabulated spectral 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.

(13) Shan, M.; Xing, Y.; O'Doherty, G. A. *J. Org. Chem.* **2009**, *74*, 5961–5966.