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Total Synthesis of Trioxacarcins DC-45-A1, A, D, C, and C7″-*epi*-C and Full Structural Assignment of Trioxacarcin C

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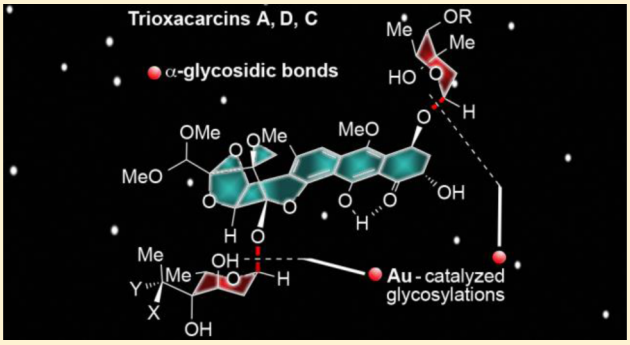
Supporting Information

ABSTRACT: Trioxacarcins DC-45-A2, DC-45-A1, A, D, C7″-*epi*-C, and C have been synthesized through stereoselective strategies involving $BF_3{\cdot}Et_2O$-catalyzed ketone−epoxide opening and gold-catalyzed glycosylation reactions, and the full structural assignment of trioxacacin C was deciphered via the syntheses of both of its C7″ epimers. The gathered knowledge sets the foundation for the design, synthesis, and biological evalution of analogues of these natural products as potential payloads for antibody−drug conjugates and other delivery systems for targeted and personalized cancer chemotherapy.



1. INTRODUCTION

The trioxacarcin family of naturally occurring compounds comprises a number of highly potent cytotoxic agents whose challenging molecular structures and potential in targeted cancer chemotherapies have elevated them to attractive synthetic targets.[1,2] Isolated from *Streptomyces bottropensis* DO-45, these molecules are characterized by a modified anthraquinone scaffold, a polyoxygenated 2,7-dioxabicyclo[2.2.1]heptane core carrying a spiroepoxide moiety, and a varying number of carbohydrate units. Their mechanism of action as cytotoxic agents involves binding to double-stranded DNA followed by covalent modification of the genetic material through proximity-facilitated nucleophilic attack from a DNA base[3] on the trioxacarcin epoxide moiety. X-ray crystallographic analyses of complexes of trioxacarcin A (**3**) (Figure 1)[4,5] and related compounds[6] with an 8-mer duplex DNA segment or guanine revealed intercalation of the aromatic structural domain of the molecule into DNA. A covalent bond between the N7 atom of a nearby guanine base and the terminal carbon of the spiroepoxide unit formed through nucleophilic attack of the former upon the latter was also observed.[5] It is this DNA-damaging event that leads to the lethal potencies of these molecules, making them desirable payloads for antibody−drug conjugates (ADCs)[7] and other drug delivery systems.[8]

Because of their structural novelty and desirability as potential payloads, the trioxacarcins have been the subject of several synthetic efforts,[9−11] notably by the Myers group[10] and our laboratory.[11] Myers reported the total synthesis of trioxacarcins DC-45-A2 (**1**), DC-45-A1 (**2**), and A (**3**) based on an elegant 1,3-dipolar cycloaddition strategy,[10] while we recently described the total synthesis of DC-45-A2 (**1**) through an alternative strategy relying on a $BF_3{\cdot}Et_2O$-catalyzed

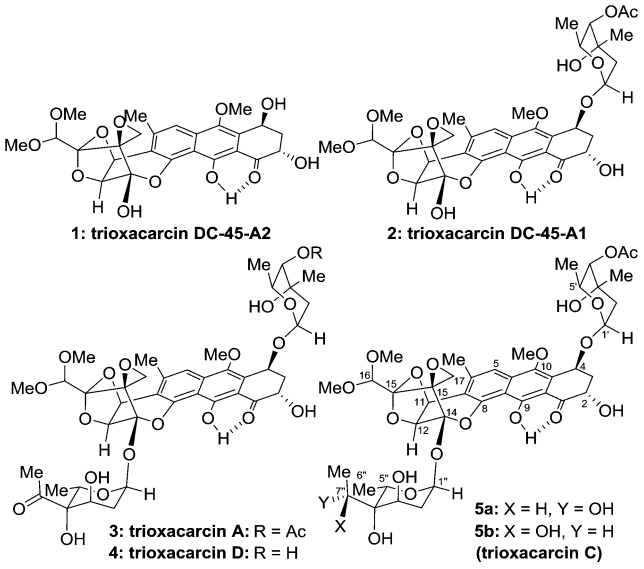


Figure 1. Molecular structures of trioxacarcins DC-45-A2 (**1**), DC-45-A1 (**2**), A (**3**), D (**4**), and C (originally assigned as **5a** or **5b**).

epoxyketone rearrangement/ring closure to afford the 2,7-dioxabicyclo[2.2.1]heptane structural motif of the molecule.[11]

In this article we describe the total synthesis of trioxacarcins DC-45-A2 (**1**), DC-45-A1 (**2**), A (**3**), and D (**4**) as well as trioxacarcins C (**5b**) and C7″-*epi*-C (**5a**). The latter syntheses enabled the full stereochemical assignment of trioxacarcin C as depicted by structure **5b** [i.e., C7″-(*S*)].

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2. RESULTS AND DISCUSSION

2.1. Retrosynthetic Analysis and Rationale. The main synthetic challenges posed by the trioxacarcins are the construction of the polyoxygenated 2,7-dioxabicyclo[2.2.1]-heptane structural motif (for **1**–**5**) and the α-glycosidic bonds (for **2**–**5**) linking the carbohydrate moieties to the aglycon of the molecule, as indicated in Figure 2. While the former challenge was met through the aforementioned $BF_3{\cdot}Et_2O$-catalyzed epoxyketone rearrangement/cyclization,[11] the latter task remained, particularly because of the steric demands of the carbohydrate donors and their stereoselective attachment to the equally hindered aglycon. Our approach for solving this problem relied on the recently developed gold-catalyzed glycosylation reactions utilizing glycosyl *o*-alkynylbenzoates as donors.[12] Thus, retrosynthetic disconnection of the carbohydrate units from the aglycon of trioxacarcins A, D and C (**3**–**5**) revealed key intermediates **II**–**IV** as potential precursors.

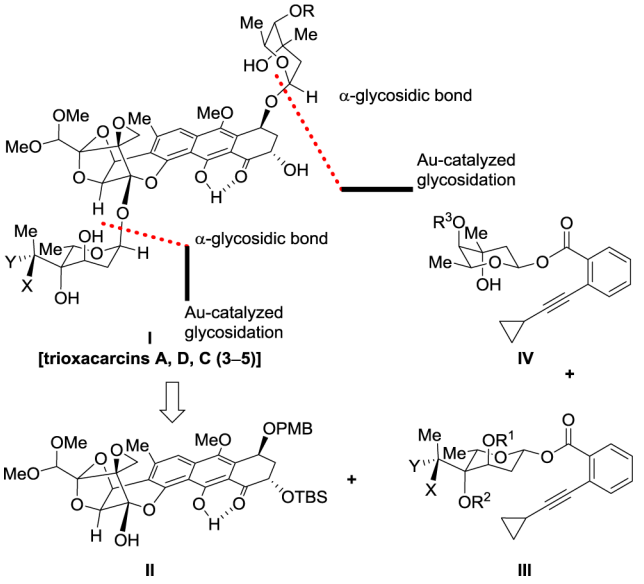
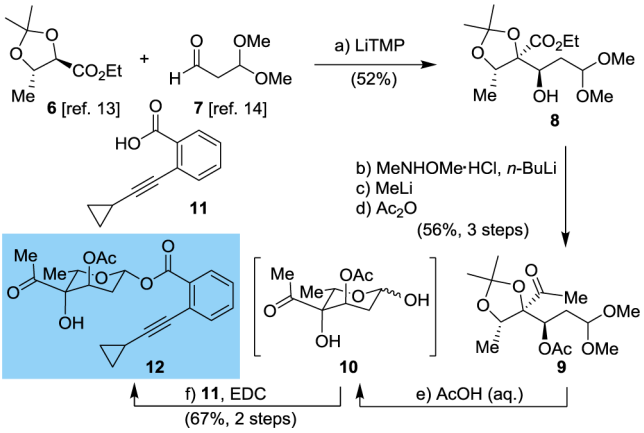


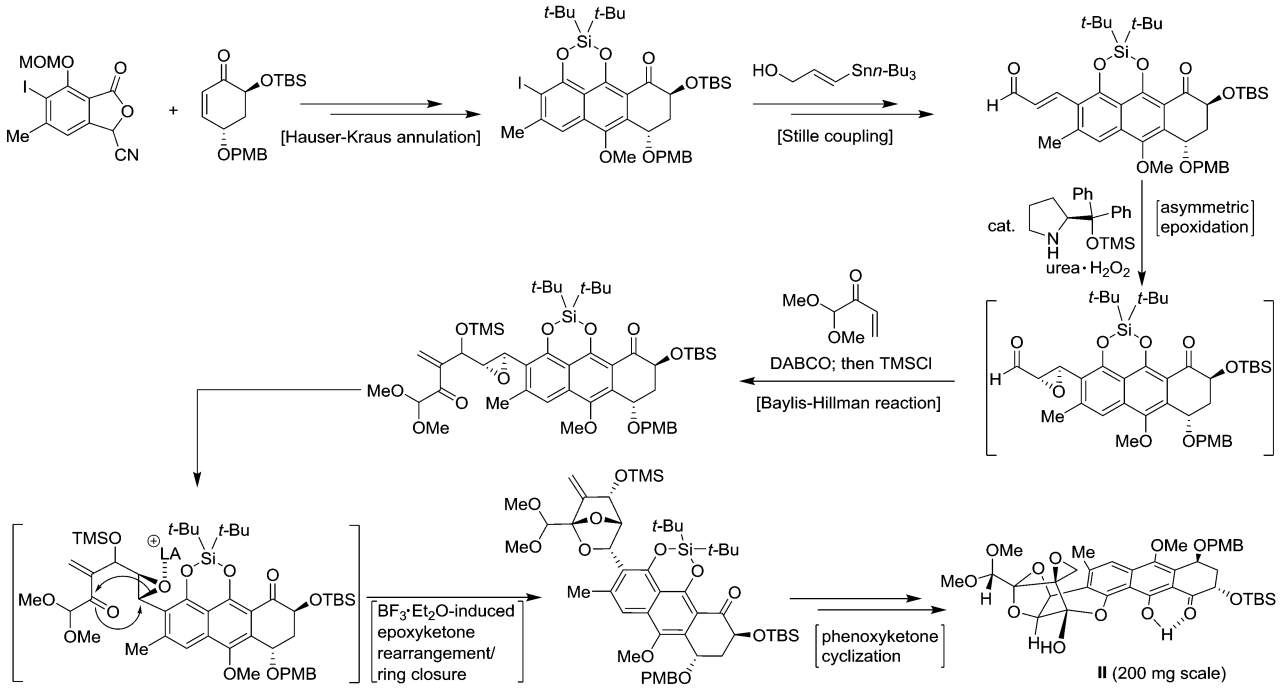
Figure 2. Retrosynthetic analysis of the trioxacarcins defining aglycon common precursor **II** and glycosyl donors **III** and **IV** as key building blocks.

Scheme 2. Construction of Glycosyl *o*-Alkynylbenzoate Donor 12[a]



[a]Reagents and conditions: (a) LiTMP (1.2 equiv), −78 °C, 2 h, then **7** (1.3 equiv), THF, −100 °C, 4 h, 52% for **8** plus 40% total for the other isomers; (b) MeNHOMe·HCl (3.0 equiv), *n*-BuLi (5.0 equiv), −50 to −30 °C, 1 h, then **8**, THF, −78 to −50 °C, 3 h; (c) MeLi (4.0 equiv), THF, −78 to −50 °C, 5 h; (d) Ac_2O (2.0 equiv), DMAP (0.2 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 2 h, 56% over the three steps; (e) 3:1 $AcOH/H_2O$, 80 °C, 3 h; (f) **11** (1.2 equiv), EDC (1.4 equiv), DMAP (1.0 equiv), DIPEA (1.8 equiv), CH_2Cl_2, 6 h, 67% over the two steps. LiTMP = lithium tetramethylpiperidide; EDC = 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide; DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DIPEA = *N*,*N*-diisopropylethylamine.

Scheme 1. Summary of the Synthesis of Common Trioxacarcin Precursor II[11]



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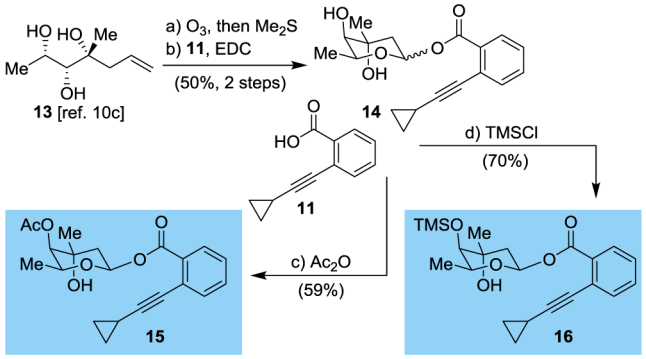
Scheme 3. Synthesis of Glycosyl *o*-Alkynylbenzoate Donors 15 and 16[a]



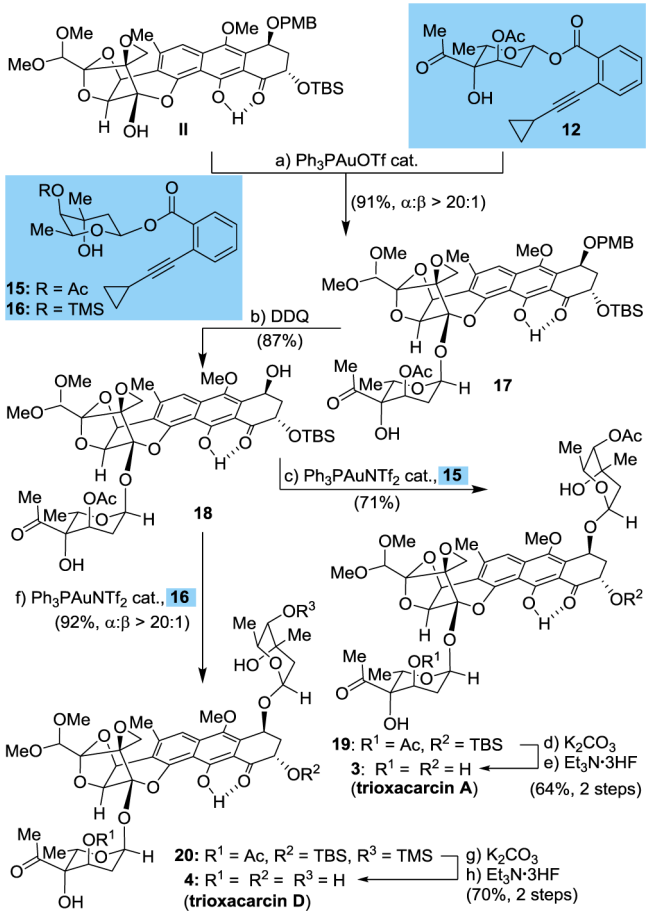
[a]Reagents and conditions: (a) O_3, 0.5 h, then Me_2S (10 equiv), MeOH, 12 h; (b) **11** (1.0 equiv), EDC (1.4 equiv), DMAP (1.0 equiv), DIPEA (1.8 equiv), CH_2Cl_2, 4 h, 50% over two steps (α:β anomers ca. 1:4.3 dr); (c) Ac_2O (2.0 equiv), DMAP (0.2 equiv), pyridine, 25 °C, 3 h, 59%; (d) TMSCl (1.5 equiv), imidazole (3.0 equiv), CH_2Cl_2, 0 °C, 1 h, 70% (β-anomer exclusively). TMS = trimethylsilyl.

Equipped with hydroxyl groups that are well-differentiated by reactivity and appropriate protecting groups, aglycon intermediate **II**[11] was well-suited for manipulation so as to serve as a common precursor to all of the targeted trioxacarcins. On the other hand, the carbohydrate donors **III** and **IV** could be fine-tuned by changes in their protecting groups (R^1, R^2, and R^3) and substituents (X and Y) to respond to any reactivity or stereochemistry issues that might arise at the glycosylation stage. The choice of the gold-catalyzed glycosylation reaction and glycosyl donors **III** and **IV** was based on the previous studies by Yu et al.[12]

2.2. Construction of Key Intermediates. Scheme 1 summarizes the construction of the common key precursor **II** for the synthesis of all of the targeted trioxacarcins [i.e., DC-45-A2 (**1**), DC-45-A1 (**2**), A (**3**), D (**4**), and C (**5a** and **5b**)]. The details of the synthesis of **II** and the conversion of this precursor to trioxacarcin DC-45-A2 (**1**) were described previously[11] and will not be elaborated further here.

Scheme 2 depicts the construction of glycosyl *o*-alkynylbenzoate carbohydrate donor **12** from readily available ethyl ester acetonide **6**[13] and dimethoxy acetal aldehyde **7**.[14] Addition of the anion generated from **6** and LiTMP to **7** proceeded smoothly to afford a mixture of four diastereoisomers from which the desired isomer **8** was chromatographically isolated in 52% yield. The rest of the chromatographically obtained materials consisted of a mixture of the remaining three isomers of **8** (40% combined yield). The stereochemical identity of **8** was based on its conversion to a literature-known compound[10b] (i.e., the β-anomeric acetate of compound **10**; see the Supporting Information (SI) for details). Conversion of ethyl ester **8** to methyl ketone **9** was achieved through a three-step sequence involving Weinreb amide generation (MeNHOMe·HCl, *n*-BuLi), ketone formation (MeLi), and acetylation in 56% overall yield. Acetonide methyl ketone **9** was then exposed to $AcOH/H_2O$ to afford, upon cleavage of the acetonide and ring closure, carbohydrate **10** as a mixture of anomers. After a short column filtration, the latter was reacted with *o*-alkynylbenzoic acid **11** in the presence of EDC to furnish the desired glycosyl *o*-alkynylbenzoate ester **12**[12c] in 67% overall yield for the two steps). Glycosyl donor **12** was formed diastereoselectively as

Scheme 4. Total Synthesis of Trioxacarcins A (3) and D (4)[a]



[a]Reagents and conditions: (a) **II** (1.0 equiv), $Ph_3PAuOTf$ (0.2 equiv), **12** (10 equiv), 4 Å molecular sieves, CH_2Cl_2, −20 °C, 5 min, 91%, α:β > 20:1; (b) DDQ (2.0 equiv), 4:1 CH_2Cl_2/H_2O (pH 7.0 buffer), 25 °C, 87%; (c) $Ph_3PAuNTf_2$ (0.2 equiv), **15** (2.0 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 5 min, 71%; (d) K_2CO_3 (2.0 equiv), MeOH, 0 °C, 40 min; (e) $Et_3N{\cdot}3HF$ (20 equiv), CH_3CN, 25 °C, 12 h, 64% over the two steps; (f) $Ph_3PAuNTf_2$ (0.2 equiv), **16** (2.0 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 5 min, 92%, α:β > 20:1; (g) K_2CO_3 (2.0 equiv), MeOH, 0 °C, 40 min; (h) $Et_3N{\cdot}3HF$ (20 equiv), CH_3CN, 25 °C, 12 h, 70% over the two steps. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

the β-anomer (separated by chromatography from trace amounts of the α-anomer), as confirmed by the observed ^1H NMR coupling constants of its anomeric proton ($\delta_{H\text{-}1}$ 6.29 ppm, dd, ^3J = 10.4, 2.5 Hz; see the SI for the expanded ^1H NMR region of this signal). The preference for the formation of the β-anomer is presumed to be due to steric hindrance provided by the bulky *o*-alkynylbenzoate residue in the α-anomer, as seen with manual molecular models.

The synthesis of β-anomeric glycosyl donors **15** and **16** is shown in Scheme 3. Ozonolysis of the known olefinic triol **13**[10c] followed by treatment of the resulting ozonide with Me_2S resulted in the formation of the corresponding pyranose, whose exposure to *o*-alkynylbenzoic acid **11** in the presence of EDC led to the desired building block **14** (50% overall yield for the two steps; inseparable mixture of anomers, β:α = 4.3:1 dr). Reaction of **14** with Ac_2O in the presence of DMAP and pyridine led to the corresponding acetoxy derivatives, whose anomers were separated by chromatography to furnish β-

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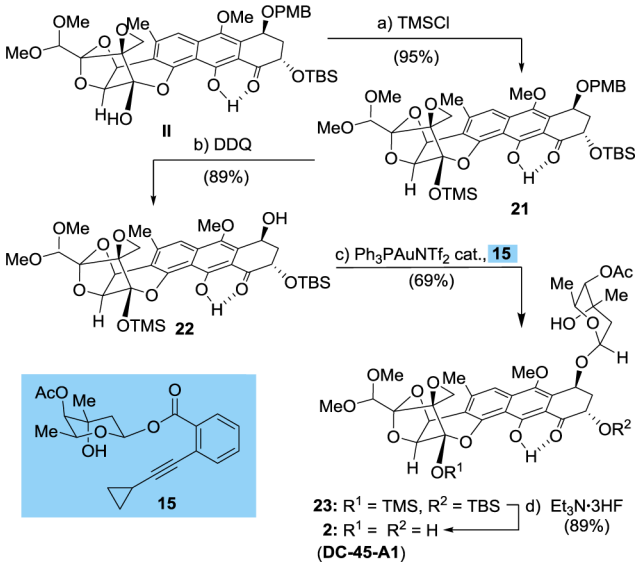
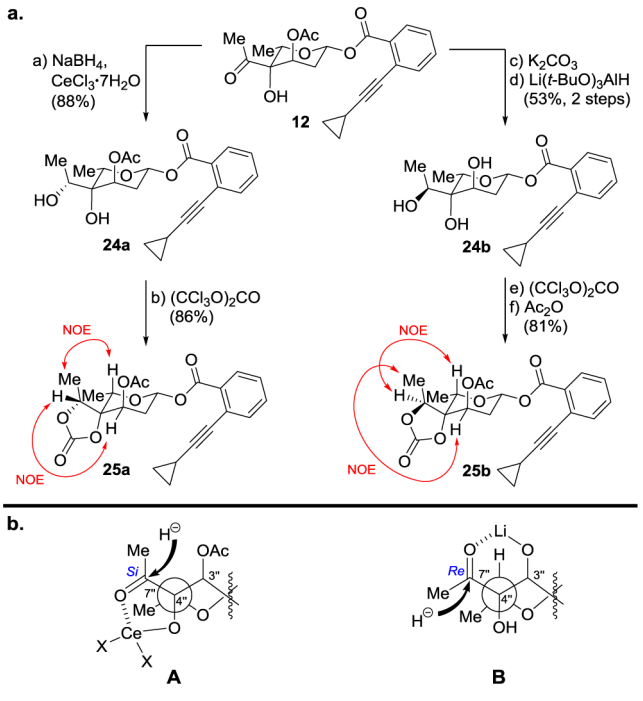
Scheme 5. Total Synthesis of Trioxacarcin DC-45-A1 (2)[a]



[a]Reagents and conditions: (a) TMSCl (2.0 equiv), imidazole (4.0 equiv), CH_2Cl_2, 0 °C, 95%; (b) DDQ (2.0 equiv), 4:1 CH_2Cl_2/H_2O (pH 7.0 buffer), 25 °C, 89%; (c) $Ph_3PAuNTf_2$ (0.2 equiv), **15** (2.0 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 5 min, 69%; (d) $Et_3N{\cdot}3HF$ (20 equiv), CH_3CN, 25 °C, 12 h, 89%.

Scheme 6. Synthesis of Anomerically Activated Derivatives of 2[*H*]-Trioxacarcinoside B (25a and 25b)[a]



[a]Reagents and conditions: (a) $NaBH_4$ (2.0 equiv), $CeCl_3{\cdot}7H_2O$ (1.2 equiv), MeOH, −78 °C, 5 h, 88%; (b) triphosgene (3.0 equiv), pyridine (5.0 equiv), CH_2Cl_2, 0 °C, 0.5 h, 86%; (c) K_2CO_3 (2.0 equiv), MeOH, 0 °C, 15 min, 76%; (d) Li(*t*-BuO)$_3$AlH (1.5 equiv), THF, 0 °C, 2 h, 53% over the two steps; (e) triphosgene (1.2 equiv), pyridine (4.0 equiv), CH_2Cl_2, 0 °C, 0.5 h; (f) Ac_2O (2.0 equiv), DMAP (0.5 equiv), pyridine (5.0 equiv), CH_2Cl_2, 25 °C, 0.5 h, 81% over two steps.

anomer **15** in 59% yield, as confirmed by NMR spectroscopic analysis (anomeric proton $\delta_{H\text{-}1}$ 6.26 ppm, dd, ^3J = 9.8, 2.7 Hz; see the SI for the expanded ^{1}H NMR region of this signal). Analogously, **14** was reacted with TMSCl in the presence of imidazole to afford TMS derivative **16** in 70% yield (pure *β*-anomer after purification, anomeric proton $\delta_{H\text{-}1}$ 6.22 ppm, dd, ^3J = 10.1, 2.4 Hz; see the SI for the expanded ^{1}H NMR region of this signal).

2.3. Total Synthesis of Trioxacarcins A, D, and DC-45-A1. With all of the building blocks available, we then turned our attention to their assembly into the various naturally occurring trioxacarcins. The first to be targeted were trioxacarcins A (**3**) and D (**4**). Their stereoselective total syntheses were accomplished as planned (Scheme 4). Coupling of trioxacarcin carbohydrate acceptor **II** with glycosyl donor **12** in the presence of $Ph_3PAuOTf$ catalyst and 4 Å molecular sieves in CH_2Cl_2 at −20 °C stereoselectively furnished the desired and expected *α*-glycoside **17** (91% yield, *α*:*β* > 20:1, anomeric proton $\delta_{H\text{-}1''}$ 5.82 ppm, dd, ^3J = 4.2, 2.1 Hz; see the SI for the expanded ^{1}H NMR region of this signal). In preparation for the attachment of the second sugar on the growing molecule, the PMB protecting group was removed from **17** (DDQ, 87% yield), affording hydroxy compound **18** (see Scheme 4) ready for the second glycosylation. The reaction of carbohydrate acceptor **18** with carbohydrate donor **15** in the presence of $Ph_3PAuNTf_2$ catalyst and 4 Å molecular sieves in CH_2Cl_2 at 0 °C afforded the desired *α*-glycoside **19** (71% yield, anomeric protons $\delta_{H\text{-}1''}$ 5.81 ppm, ^3J = 3.9, 2.3 Hz and $\delta_{H\text{-}1'}$ 5.35 ppm, apparent dd, ^3J = 3.1, 3.1 Hz; see the SI for the expanded ^{1}H NMR region of these signals). Sequential exposure of the latter to K_2CO_3 in MeOH (deacetylation) followed by $Et_3N{\cdot}3HF$ (desilylation) then furnished the coveted trioxacarcin A (**3**)[1f,10d] in 64% overall yield. The ^{1}H and ^{13}C NMR spectral data for synthetic **3** were identical to those reported for the natural product[10c] (see the SI). On the other hand, glycosylation of substrate **18** with glycosyl donor **16** under the influence of the same catalyst ($Ph_3PAuNTf_2$, 0.2 equiv) and conditions furnished the targeted bisglycosylated product **20** in 92% yield (*α*:*β* > 20:1, anomeric protons $\delta_{H\text{-}1''}$ 5.81 ppm, dd, ^3J = 4.1, 2.3 Hz and $\delta_{H\text{-}1'}$ 5.32, apparent dd, ^3J = 3.1, 3.1 Hz; see the SI for the expanded ^{1}H NMR region of these signals). Sequential and selective deprotection of the latter (K_2CO_3, MeOH, then $Et_3N{\cdot}3HF$) finally yielded trioxacarcin D (**4**)[1c] in 70% overall yield for the last two steps. The ^{1}H and ^{13}C NMR spectral data for synthetic **4** were identical to those reported for the natural product[1c] (see the SI).

Trioxacarcin DC-45-A1 (**2**) was synthesized from fragments **II** and **15** as summarized in Scheme 5. Lactol substrate **II** was protected (TMSCl, imidazole, 95% yield), and the resulting TMS ether (**21**) was treated with DDQ to liberate the C4 hydroxyl group, furnishing carbohydrate acceptor **22** in 89% yield. The latter was united with carbohydrate donor **15** in the presence of $Ph_3PAuNTf_2$ catalyst and 4 Å molecular sieves in CH_2Cl_2 at 0 °C to afford glycoside **23** (69% yield, anomeric proton $\delta_{H\text{-}1'}$ 5.36 ppm, apparent dd, ^3J = 2.9, 2.9 Hz; see the SI for the expanded ^{1}H NMR region of this signal). Concurrent removal of the TMS and TBS groups from the latter ($Et_3N{\cdot}3HF$) gave the coveted trioxacarcin DC-45-A1 (**2**) in 89% yield. The ^{1}H and ^{13}C NMR spectral data for synthetic **2** were identical to those reported for the natural product (see the SI).[1d,10d]

2.4. Total Synthesis of Trioxacarcin C and C7″-*epi*-Trioxacarcin C. The synthesis of trioxacarcins C (**5a**) and C7″-*epi* C (**5b**) proved to be more challenging than those of the other targeted trioxacarcins in that the two required 2[*H*]-

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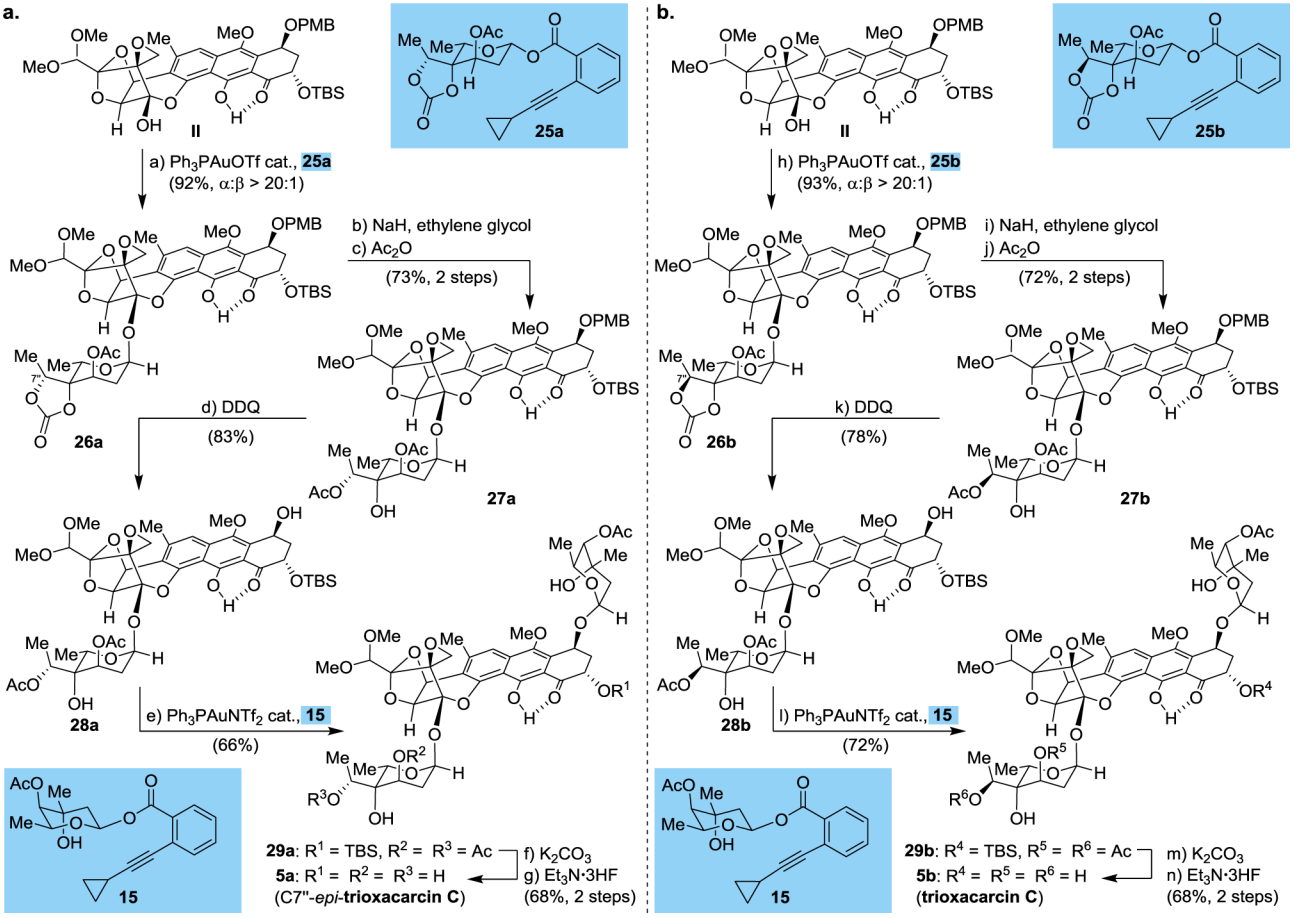
Scheme 7. Total Synthesis of C7″-*epi*-Trioxacarcin C (5a) and Trioxacarcin C (5b)[a]



[a]Reagents and conditions: (a) **II** (1.0 equiv), $Ph_3PAuOTf$ (0.3 equiv), **25a** (5 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 15 min, 92%, α:β > 20:1; (b) NaH (10 equiv), 10:1 THF/ethylene glycol, 25 °C; (c) Ac_2O (8.0 equiv), DMAP (1.0 equiv), pyridine (12 equiv), CH_2Cl_2, 25 °C, 3 h, 73% over the two steps; (d) DDQ (2.0 equiv), 4:1 CH_2Cl_2/H_2O (pH 7.0 buffer), 25 °C, 83%; (e) $Ph_3PAuNTf_2$ (0.2 equiv), **15** (2.0 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 5 min, 66%; (f) K_2CO_3 (2.0 equiv), MeOH, 0 °C, 1 h; (g) $Et_3N{\cdot}3HF$ (20 equiv), CH_3CN, 25 °C, 12 h, 68% over the two steps; (h) **II** (1.0 equiv), $Ph_3PAuOTf$ (0.3 equiv), **25b** (5 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 15 min, 93%, α:β > 20:1; (i) NaH (10 equiv), 10:1 THF/ethylene glycol, 25 °C; (j) Ac_2O (8.0 equiv), DMAP (1.0 equiv), pyridine (12 equiv), CH_2Cl_2, 25 °C, 3 h, 72% over the two steps; (k) DDQ (2.0 equiv), 4:1 CH_2Cl_2/H_2O (pH 7.0 buffer), 25 °C, 78%; (l) $Ph_3PAuNTf_2$ (0.2 equiv), **15** (2.0 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 5 min, 72%; (m) K_2CO_3 (2.0 equiv), MeOH, 0 °C, 1 h; (n) $Et_3N{\cdot}3HF$ (20 equiv), CH_3CN, 25 °C, 12 h, 68% over the two steps.

trioxacarcinoside B donors **25a** and **25b** (Scheme 6) had to be prepared selectively and attached to the growing molecule through the desired α-glycosidic bond. While the latter stereoselectivity was expected on the basis of the anomeric effect, the diastereoselective reduction of hydroxyketo acetate precursor **12** had to be investigated. Scheme 6 depicts the selective synthesis of glycosyl donors **25a** and **25b** from **12** and the mechanistic rationale for the stereoselectivity of the two reductions involved. Exposure of hydroxyketo acetate **12** to $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ furnished diol **24a** exclusively, presumably through transition state **A** (shown as a Newman projection in Scheme 6b), in which the initially formed Ce complex orients the carbonyl moiety in such a way as to favor reduction from the *Si* face (front; the *Re* face is blocked by the Me group on C5″, back). On the other hand, treatment of hydroxyketo acetate **12** with K_2CO_3 (removal of Ac) followed by Li(*t*-BuO)$_3$AlH reduction led to the opposite diastereoisomer **24b** in 53% overall yield (single isomer). The observed stereoselectivity in this reduction may be explained by invoking transition state **B** (Scheme 6b), in which the newly liberated secondary alcohol (C3″) participates in forming the six-membered metallacycle with concurrent rotation of the C4″/C5″ bond, orienting the carbonyl group to a position favoring reduction from the *Re* face (front), with the C5″ Me group no longer in the way. With the hydroxyl groups installed stereoselectively, intermediates **24a** and **24b** were smoothly converted to glycosyl donors **25a** [$(CCl_3O)_2CO$, 86% yield] and **25b** [$(CCl_3CO)_2CO$, Ac_2O, 81% overall yield] as shown in Scheme 6. The structural assignments of compounds **25a** and **25b** were based on the observed nuclear Overhauser effects (NOEs) as shown in Scheme 6a and the ^3J coupling constants of their anomeric protons (anomeric proton of **25a** $\delta_{H\text{-}1}$ 6.25 ppm, dd, ^3J = 8.0, 2.7 Hz; anomeric proton of **25b** $\delta_{H\text{-}1}$ 6.21 ppm, apparent dd, ^3J = 6.3, 6.3 Hz; see the SI for the expanded ^{1}H NMR region of these signals). The carbonate derivatives of these glycosyl donors were chosen on the basis of manual molecular modeling and in order to rigidify them and cap both hydroxyl groups, a tactic that resulted in high-yielding glycosylation reactions (see below).

Scheme 7 summarizes the coupling of trioxacarcin aglycon derivative **II** with glycosyl donors **25a** (Scheme 7a) and **25b** (Scheme 7b) and the elaboration of the products to give the

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two C7″ diastereomeric trioxacarins C (**5a** and **5b**). Reaction of **II** with excess **25a** or **25b** in the presence of $Ph_3PAuOTf$ catalyst and 4 Å molecular sieves in CH_2Cl_2 at 0 °C furnished glycoside **26a** or **26b** in 92% and 93% yield, respectively, and α:β > 20:1 dr (anomeric proton of the α-anomer of **26a** $\delta_{H\text{-}1''}$ 5.77 ppm, dd, ^3J = 3.7, 2.0 Hz; anomeric proton of the α-anomer of **26b** $\delta_{H\text{-}1''}$ 5.79 ppm, d, ^3J = 4.2 Hz; see the SI for the expanded ^{1}H NMR region of these signals). Reaction of **26a** with ethylene glycol and NaH resulted in the cleavage of both the carbonate and acetate groups from the growing molecule, liberating all three hydroxyl groups (see Scheme 7a). Acetylation of the resulting compound (Ac_2O, DMAP, py) then led to bisacetate **27a** in 73% overall yield. The latter compound was treated with DDQ, causing cleavage of the PMB group and furnishing intermediate glycosyl acceptor **28a** (83% yield). Reaction of **28a** with glycosyl donor **15** in the presence of $Ph_3PAuNTf_2$ catalyst and 4 Å molecular sieves in CH_2Cl_2 furnished protected trioxacarcin C (**29a**) (66% yield, anomeric protons $\delta_{H\text{-}1''}$ 5.72 ppm, apparent dd, ^3J = 2.5, 2.5 Hz and $\delta_{H\text{-}1'}$ 5.35, apparent dd, ^3J = 3.0, 3.0 Hz; see the SI for the expanded ^{1}H NMR region of these signals), from which C7″-(*R*)-trioxacarcin C (**5a**) was obtained upon sequential treatment with K_2CO_3 in MeOH (selective deacetylation due to different steric environments) and $Et_3N{\cdot}3HF$ (desilylation) in 68% overall yield. A similar sequence starting from the C7″-epimeric substrate **26b** and the same carbohydrate donor (i.e., **15**) led to the formation of C7″-(*S*)-trioxacarcin C (**5b**) via intermediates **26b**–**29b** in similar yields, as shown in Scheme 7b. That this series of compounds were formed predominantly as the α-anomers (α:β > 20:1 anomeric ratio) as expected was confirmed by their ^{1}H NMR spectra, which exhibited the anticipated ^3J coupling constants for their anomeric protons (**26b** $\delta_{H\text{-}1''}$ 5.79 ppm, d, ^3J = 4.2 Hz; **29b** $\delta_{H\text{-}1''}$ 5.73 ppm, d, ^3J = 4.0 Hz and $\delta_{H\text{-}1'}$ 5.35, apparent dd, ^3J = 3.1, 3.1 Hz). Comparison of the ^{1}H and ^{13}C NMR spectroscopic data for the two synthetic trioaxacarcins C (**5a** and **5b**) revealed the identity of the naturally occurring trioxacarcin C as structure **5b** possessing the C7″-(*S*)-configuration (see the SI for ^{1}H and ^{13}C NMR spectral comparisons).[1e] This finding leads to the designation of **5a** as C7″-*epi*-trioxacarcin C. Synthetic trioxacarcin C (**5b**) exhibited ^{1}H and ^{13}C spectral data identical to those reported for the natural product (see the SI).

3. CONCLUSION

The herein-described total syntheses of trioxacarcins DC-45-A1 (**2**), A (**3**), D (**4**), C (**5b**), and C7″-*epi*-C (**5a**) provide access to these potent antitumor agents and open the way for the synthesis of other members of the class, natural or designed. The high yields and stereoselectivities of the gold-catalyzed glycosylation reactions are particularly impressive given the complexity and sensitivity of the substrates employed, suggesting their potential for applications in other challenging situations. The described chemistry is expected to facilitate the design and synthesis of more or less complex analogues of the trioxacarcins aiming at highly potent cytotoxic agents as required for ADCs and other drug delivery systems for targeted cancer chemotherapy. Our studies toward this goal will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12687.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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