Natural Product Synthesis

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Total Synthesis of Trioxacarcin DC-45-A2**

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Dedicated to Professor Stephen Hanessian on the occasion of his 80th birthday

Abstract: *An enantioselective total synthesis of trioxacarcin DC-45-A2 (**1**) featuring a novel Lewis acid-induced cascade rearrangement of epoxyketone **6** to forge the polyoxygenated 2,7-dioxabicyclo[2.2.1]heptane core of the molecule is described.*

Trioxacarcin DC-45-A2 (**1**, Figure 1)[1] is a naturally occurring antitumor antibiotic that serves as a biosynthetic precursor to a variety of other biologically active members of the family, including the highly potent DC-45-A1 (**2**), trioxacarcin A (**3**), and LL-D49194α1 (**4**) (Figure 1).[1] Possessing a highly oxygenated and complex architecture, trioxacarcin DC-45-A2 (**1**) presents an appealing synthetic challenge and provides opportunities for method and strategy development, chemical biology, and drug discovery efforts.[2] Recent synthetic studies have culminated in a total synthesis of this target molecule and a number of its congeners.[3] In this Communication, we report an enantioselective and distinctively different approach to the total synthesis of the parent trioxacarcin DC-45-A2 (**1**) that could be applied to the synthesis of all other members of the class and their designed analogues.

The polyoxygenated 2,7-dioxabicyclo[2.2.1]heptane system of the trioxacarcins is a most intriguing structural motif requiring special attention with regard to strategy and experimentation for its construction. Figure 2 presents our designed strategy toward DC-45-A2 (**1**) in retrosynthetic format. Thus, disconnection of the hemiacetal moiety of **1** followed by functional group transformations led to advanced precursor **5**, whose conversion to the target molecule could be envisioned through sequential and selective deprotection/oxidations. Dismantling of the bicyclo[2.2.1]heptane system within **5** through an epoxyketone rearrangement[4] revealed epoxyketone **6** as a precursor, whose origin could be traced back to key building blocks **7**–**10** through the disconnections indicated in Figure 2 [that is, a) Hauser–Kraus annulation; b) Stille reaction; c) asymmetric Jørgensen epoxidation; and d) Baylis–Hillman reaction]. The key epoxyketone rearrangement (**6**→**5**, Figure 2) was presumed to be inducible in a stereo- and regioselective manner through the action of a suitable monodentate Lewis acid that would involve inversion of configuration at C6, as indicated in Figure 2 (see arrows on structure **6**).

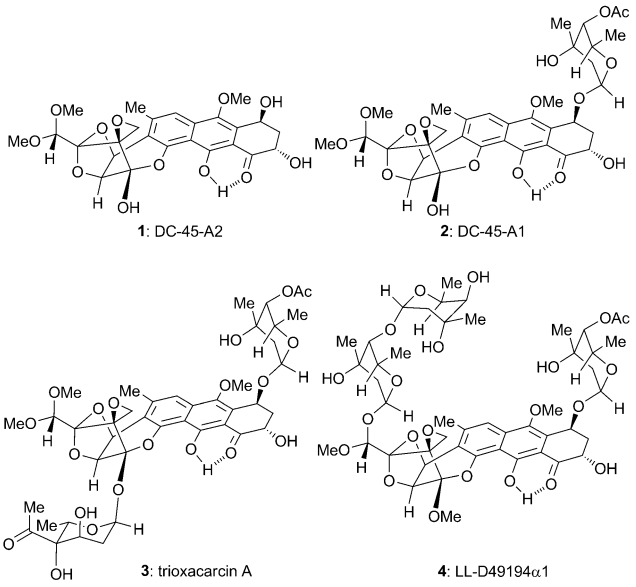

Figure 1. Molecular structures of trioxacarcins DC-45-A2 (**1**), DC-45-A1 (**2**), A (**3**), and LL-D49194α1 (**4**).

The required cyclohexenone **10** was prepared enantioselectively from cyclohexadiene **11**, as summarized in Scheme 1. Thus, **11** was subjected to Upjohn dihydroxylation (OsO_4 cat., NMO, 50% yield) and the resulting diol **12** was silylated to afford bis-TBS ether **13** (TBSCl, 92% yield). Epoxidation of the latter (*m*CPBA, 89% yield) led selectively to epoxide **14**, whose regioselective opening with (−)-norephedrine-derived amine **15** in the presence of *n*BuLi furnished allylic alcohol **16** in 94% yield and 89% *ee*.[5] Protection of this alcohol with 4-methoxybenzyl-2,2,2-trichloroacetimidate (PMBTCA) followed by TBAF-induced desilylation led to PMB-ether diol **17** in 84% yield. Selective oxidation of the allylic alcohol of

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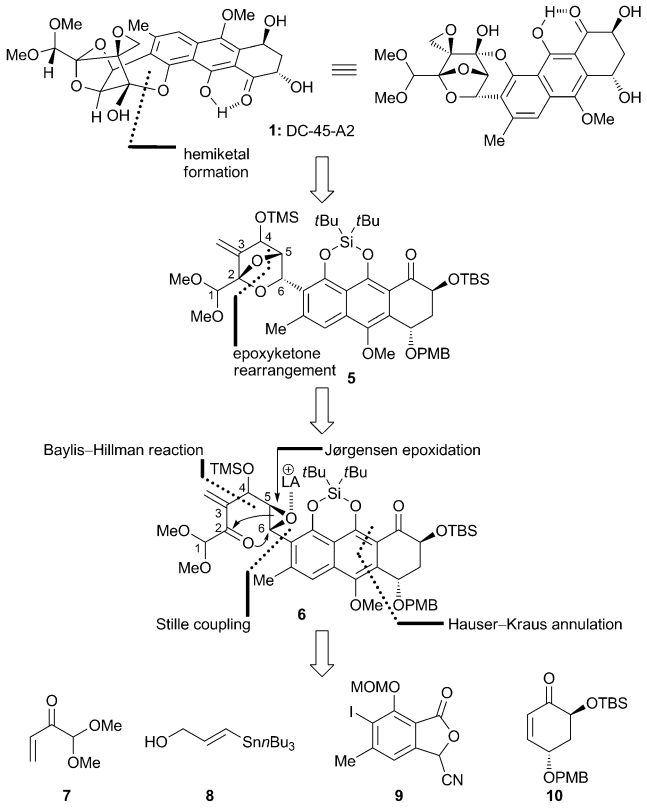
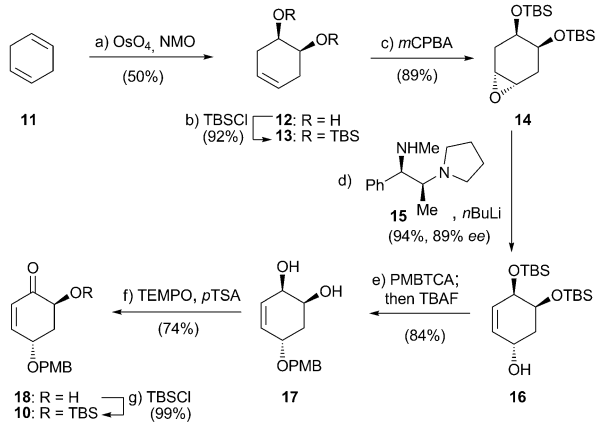


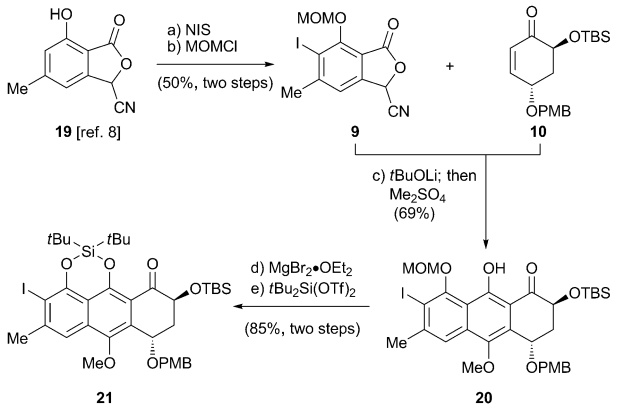
Figure 2. Retrosynthetic analysis of trioxacarcin DC-45-A2 (**1**). MOM = methoxymethyl, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.



Scheme 1. Synthesis of key building block **10**. Reagents and conditions: a) OsO_4 (4% w/v aq. solution, 0.02 equiv), NMO (1.0 equiv), acetone, 25 °C, 72 h, 50%; b) TBSCl (2.4 equiv), imidazole (5.0 equiv), CH_2Cl_2, 25 °C, 48 h, 92%; c) *m*CPBA (1.4 equiv), $NaHCO_3$ (2.0 equiv), cyclohexane, 25 °C, 17 h, 89%; d) **15** (2.0 equiv), *n*BuLi (2.0 equiv), THF, 0→25 °C, 18 h, 94%, 89% *ee*; e) PMBTCA (2.5 equiv), $TrBF_4$ (0.05 equiv), THF, 25 °C, 1 h; then TBAF (7.0 equiv), THF, 66 °C, 4 h, 84%; f) TEMPO (3.0 equiv), *p*TSA (3.0 equiv), CH_2Cl_2, 0 °C, 45 min, 74%; g) TBSCl (1.8 equiv), imidazole (3.0 equiv), CH_2Cl_2, 25 °C, 1.5 h, 99%. *m*CPBA = *meta*-chloroperoxybenzoic acid, NMO = *N*-methylmorpholine-*N*-oxide, PMBTCA = *para*-methoxybenzyl-2,2,2-trichloroacetimidate, *p*TSA = *para*-toluenesulfonic acid, TBAF = tetra-*n*-butylammonium fluoride, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, THF = tetrahydrofuran, $TrBF_4$ = trityltetrafluoroborate.

the latter (TEMPO, *p*TSA, 74% yield)[6] furnished hydroxyenone **18**, whose silylation (TBSCl, 99% yield) led to the targeted key building block enone **10**.

Enone **10** was coupled with the easily accessible iodocyanophthalide derivative **9** through a Hauser–Kraus annulation,[7] and the product was elaborated to intermediate **21** as shown in Scheme 2. Thus, iodocyanophthalide **9** [prepared

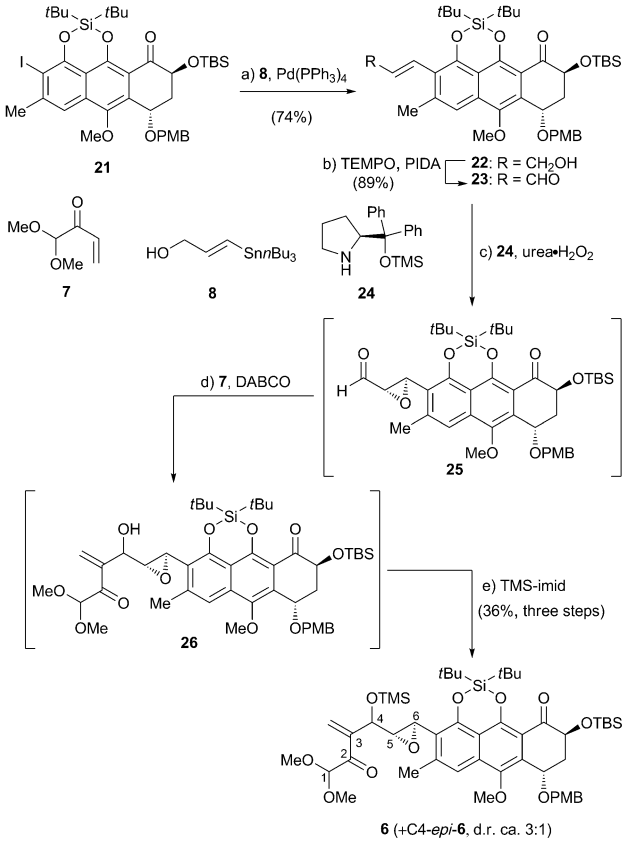


Scheme 2. Synthesis of key building block **21**. Reagents and conditions: a) NIS (1.4 equiv), DCE, −10 °C, 6 h; b) MOMCl (1.3 equiv), DIPEA (3.0 equiv), CH_2Cl_2, 25 °C, 6 h, 50% over two steps; c) **9** (1.0 equiv), **10** (1.0 equiv), *t*BuOLi (3.0 equiv), THF, −78 °C, 0.5 h; then Me_2SO_4 (10 equiv), 0 °C, 5 h, 69%; d) $MgBr_2{\cdot}OEt_2$ (3.0 equiv), THF, 0 °C, 15 min; e) $tBu_2Si(OTf)_2$ (1.2 equiv), 2,6-lutidine (2.5 equiv), DMF, 0 °C, 0.5 h, 85% over two steps. DCE = 1,2-dichloroethane, DIPEA = *N*,*N*-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide, NIS = *N*-iodosuccinimide.

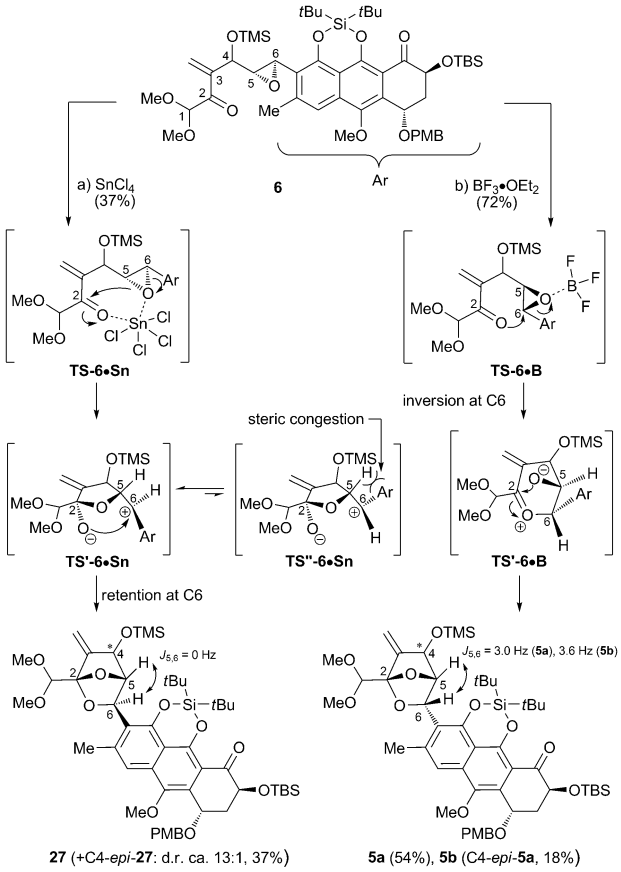
from the known cyanophthalide **19**[8] by sequential iodination (NIS) and MOM protection (MOMCl, DIPEA, 50% overall yield)] was reacted with enone **10** in the presence of *t*BuOLi (−78 °C)[3,8] and the resulting *p*-dihydroquinone derivative was selectively methylated with Me_2SO_4 to afford tricyclic system **20** in 69% overall yield. Removal of the MOM group from the latter intermediate with $MgBr_2{\cdot}OEt_2$,[9] followed by treatment with $tBu_2Si(OTf)_2$ and 2,6-lutidine then gave silylated product **21** in 85% overall yield.

Intermediate **21** was advanced to the key cyclization precursor **6**, as summarized in Scheme 3. Thus, Stille coupling of aryl iodide **21** with stannane **8**[10] proceeded in the presence of CuTC and catalytic amounts of $Pd(PPh_3)_4$[11] to afford allylic alcohol **22** (74% yield), whose oxidation with TEMPO and PIDA gave aldehyde **23** (89% yield). Jørgensen asymmetric epoxidation of α,β-unsaturated aldehyde **23** (**24** cat., urea·H_2O_2)[12] led to epoxyaldehyde **25**, which was subjected without purification to Baylis–Hillman reaction with enone **7**[13] (DABCO, 4-nitrophenol) to give labile hydroxyepoxide **26**. The latter was immediately protected with *N*-trimethylsilylimidazole (TMS-imid) to furnish the targeted precursor **6** (+C4-*epi*-**6**, d.r. ca. 3:1) in 36% yield over the three steps.

With the penultimate bis-cyclization precursor **6** in hand, the stage was now set for the coveted cascade ring closures to forge the targeted 2,7-dioxabicyclo[2.2.1]heptane system of the growing molecule. To this end, and as shown in Scheme 4,



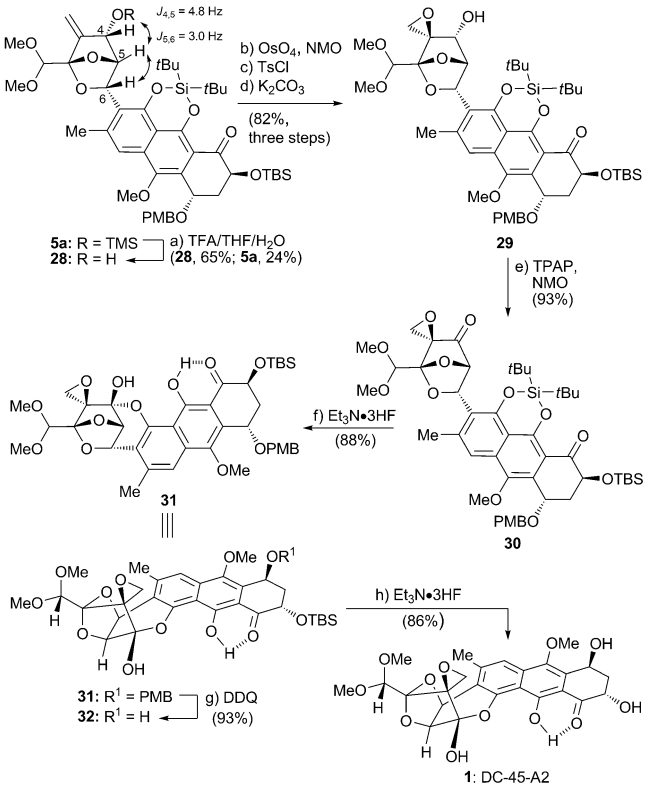
Scheme 3. Synthesis of bis-cyclization precursor epoxyketone **6**. Reagents and conditions: a) $Pd(PPh_3)_4$ (0.2 equiv), **8** (3.0 equiv), CuTC (1.2 equiv), DMF/THF 1:1, 85 °C, 12 h, 74%; b) TEMPO (0.1 equiv), PIDA (1.3 equiv), CH_2Cl_2, 25 °C, 4 h, 89%; c) **24** (0.2 equiv), urea·H_2O_2 (7.0 equiv), $CHCl_3/H_2O$ 20:1, 25 °C, 7 h; d) **7** (10 equiv), DABCO (0.5 equiv), 4-nitrophenol (0.5 equiv), THF, 25 °C, 12 h; e) TMS-imid (1.0 equiv), CH_2Cl_2, 25 °C, 0.5 h, 36% over three steps, d.r. ca. 3:1 at C4. CuTC = copper(I)-thiophene-2-carboxylate, DABCO = 1,4-diazabicyclo[2.2.2]octane, PIDA = iodobenzene diacetate, TMS-imid = *N*-trimethylsilylimidazole.



Scheme 4. Bis-cyclization of precursor epoxyketone **6**. Reagents and conditions: a) $SnCl_4$ (0.05 equiv), CH_2Cl_2, −78 °C, 1 h, d.r. ca. 13:1 at C4, 37%; b) $BF_3{\cdot}OEt_2$ (0.3 equiv), CH_2Cl_2, −78 °C, 3 h, 54% (**5a**), 18% (**5b**).

epoxyketone **6** (ca. 3:1 mixture of C4-diastereoisomers) was reacted with catalytic amounts of $BF_3{\cdot}OEt_2$ (monodentate Lewis acid) in CH_2Cl_2 at −78 °C, furnishing the desired product as a mixture of C4-diastereoisomers (d.r. ca. 3:1) (**5a**, C4-α-diastereoisomer, 54% yield; **5b**, C4-β-diastereoisomer, 18% yield). The assignments of the C4 and C6 configurations of diastereoisomers **5a** and **5b** were based on their H4, H5, H6 coupling constants (**5a**:[14] $J_{4,5} = 4.8$ Hz, $J_{5,6} = 3.0$ Hz; **5b**:[14] $J_{4,5} = 0$ Hz, $J_{5,6} = 3.6$ Hz).[15] Both compounds were obtained as single diastereoisomers at C6 (inverted configuration). The reaction is presumed to proceed through transition states **TS-6·B** and **TS′-6·B** as shown in Scheme 4. In contrast, reaction of substrate **6** with catalytic amounts of bidentate Lewis acid $SnCl_4$ in CH_2Cl_2 at −78 °C led to the opposite diastereoisomers at C6 ($J_{5,6} = 0$ Hz), **27** (+C4-*epi*-**27**) (37% yield, d.r. ca. 13:1). This reaction is presumed to proceed through transition states **TS-6·Sn** and **TS′-6·Sn**, the latter being favored over its more sterically congested alternative conformer **TS″-6·Sn** that would have led to inversion of configuration at C6 (see Scheme 4). These results support our originally proposed monodentate Lewis acid-catalyzed epoxyketone rearrangement upon which the strategy for the construction of the dioxabicyclo[2.2.1]heptane structural motif possessing the desired configurations was based.

Having succeeded in building the most challenging structural domain of the targeted molecule, we proceeded to complete the remaining tasks of the synthesis that included installation of the epoxide moiety, oxidation at C4, and deprotection. Thus, advanced intermediate **5a** (major diastereoisomer) was converted to the targeted natural product (**1**) as shown in Scheme 5. Selective cleavage of the TMS-ether of **5a** gave allylic alcohol **28** (TFA, 65% yield) and recovered **5a** (24% yield). Due to difficulties in obtaining the desired epoxide **29** from **28** through *m*CPBA or *t*BuOOH/VO(acac)$_2$ epoxidations, we resorted to a three-step process involving diastereoselective Upjohn dihydroxylation of the olefinic bond within **28** (OsO_4 cat., NMO) followed by selective monotosylation of the resulting triol (TsCl, Et_3N, DMAP cat.) and epoxide formation (K_2CO_3, MeOH, 82% overall yield). TPAP-catalyzed oxidation of hydroxyepoxide **29** led to ketoepoxide **30** (93% yield), which could be sequentially and selectively deprotected to afford trioxacarcin derivatives **31** ($Et_3N{\cdot}3HF$, 3.0 equiv, 15 min, 88% yield) and **32** (DDQ, 93% yield). Finally, trioxacarcin DC-45-A2 (**1**) was liberated



Scheme 5. Completion of the total synthesis of trioxacarcin DC-45-A2 (**1**). Reagents and conditions: a) TFA (0.1 M, 10 equiv), THF/H_2O 5:1, 25 °C, 6 h, 65% and recovered **5a**, 24%; b) OsO_4 (4% w/v, aq. solution, 0.2 equiv), NMO (0.48 M aq. solution, 4.0 equiv), acetone, 25 °C, 12 h; c) TsCl (5.0 equiv), Et_3N (10 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0→25 °C, 5 h; d) K_2CO_3 (2.0 equiv), MeOH, 0 °C, 3 h, 82% over three steps; e) TPAP (0.2 equiv), NMO·H_2O (3.0 equiv), CH_2Cl_2, 0 °C, 2 h, 93%; f) $Et_3N{\cdot}3HF$ (3.0 equiv), CH_3CN, 25 °C, 15 min, 88%; g) DDQ (2.0 equiv), CH_2Cl_2/H_2O 10:1, 25 °C, 1 h, 93%; h) $Et_3N{\cdot}3HF$ (20 equiv), CH_3CN, 25 °C, 13 h, 86%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = *N*,*N*-dimethyl-4-aminopyridine, TFA = trifluoroacetic acid, TPAP = tetra-*n*-propylammonium perruthenate, Ts = 4-toluenesulfonyl.

from its TBS-ether **32** by exposure to $Et_3N{\cdot}3HF$ (excess, 13 h, 86% yield). Synthetic **1** exhibited identical physical properties (i.e., ^1H and ^{13}C NMR and mass spectra) to those reported in the literature.[1e,3a]

The total synthesis described herein provides rapid access to the parent trioxacarcin DC-45-A2 (**1**) and could be deployed to reach all other members of the trioxacarcin family of compounds. Furthermore, the developed synthetic strategy and technologies could be applied to the construction of designed analogues for structure activity relationship studies and drug discovery efforts. Of particular interest is the design and synthesis of potent trioxacarcins equipped with handles that could be employed to attach them onto specific antibodies to construct antibody drug conjugates (ADCs) for targeted chemotherapy purposes. These objectives are currently being pursued.

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