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Syntheses of Cyclotriveratrylene Analogues and Their Long Elusive Triketone Congeners

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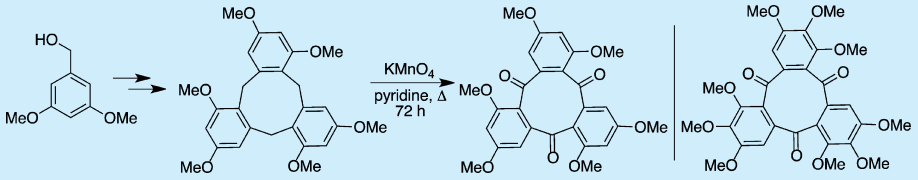
Supporting Information



ABSTRACT: Although interest in cyclotriveratrylene and its analogues has been significant, limitations in the ability to adjust its structure fully have hampered studies into their complete range of properties. A unique strategy to synthesize a previously unobtainable cyclotriveratrylene analogue and a procedure which adjusts the inner methylene bridges of that material to a triketone is reported. A second triketone synthesis and computational studies indicate the parameters needed for success.

Since its correct structural assignment in 1965,[1,2] cyclotriveratrylene (**1**, Figure 1) has received significant attention due its unique, three-dimensional shape. Indeed, with a rigid bowl-like architecture as shown in the additional depiction, one also referred to as a "crown conformation",[3] this compound and many of its close analogues (such as **2**) have been studied in an array of host−guest complexes, several of which have led to exciting applications.[4] Among these are size-selective buckminsterfullerene hosting,[5] anion and cation binding,[6] as well as the generation of self-assembled organic frameworks.[7] When these units are explicitly combined into a dimeric framework, as with cryptophane **3**,[8] entirely new opportunities for binding result. Compound **3** and its close analogues, for instance, show a particularly high affinity for xenon, a property that is being exploited for improved MRI-based diagnostic techniques, including the detection of matrix metalloproteinase activity.[9]

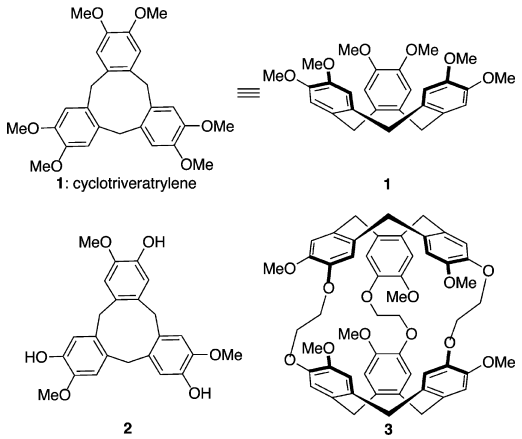


Figure 1. Structure of cyclotriveratrylene (**1**) and analogues (**2** and **3**).

Yet, despite the increasing number of applications for this class of molecules, the ability to access a full array of structural congeners to maximize properties remains an unattained goal. At present, elaborating the aromatic rings, or "outer rim" of cyclotriveratrylene and its analogues, has proven achievable. For instance, aryl derivatives of **2** have been accessed that allow for the controlled appendage of additional groups to obtain extended-cavity cyclotriveratrylenes with greater affinity for certain guest molecules.[10] By contrast, synthetic manipulation of the methylene bridges, or "inner rim" of these molecules, to other cyclotriveratrylene congeners has proven far more challenging.

For instance, Cookson and co-workers reported in 1968 that the oxidation of cyclotriveratrylene (obtained in a single step from alcohol **4** as shown in Scheme 1) with chromic acid could afford its corresponding monoketone (**5**) and a small amount of symmetric triketone **6**.[11] However, the Baldwin group refuted this claim later that same year, proving that spirocycle **8**, not **6**, was the obtained fully oxidized product; that material likely resulted through the indicated transannular rearrangement of **6** by way of intermediate **7**.[12] Indeed, a similar result was observed in 1997 upon oxidation of the parent unfunctionalized [1,1,1]orthocyclophane **9**,[13] with mono- and diketone products **10** and **11** obtained alongside an analogous spirocycle (**12**).[14] In fact, no report of successfully accessing the triketone of cyclotriveratrylene or any related analogue has ever been issued, with some authors suggesting that such an outcome is unachieveable.[12,13,15] Herein, we disclose a unique route to synthesize a novel cyclotriveratrylene-like analogue, one that may prove extendable to other synthetically challenging congeners, and a procedure that successfully oxidized that material to a triketone. In addition, we show that a second cyclotriveratrylene-

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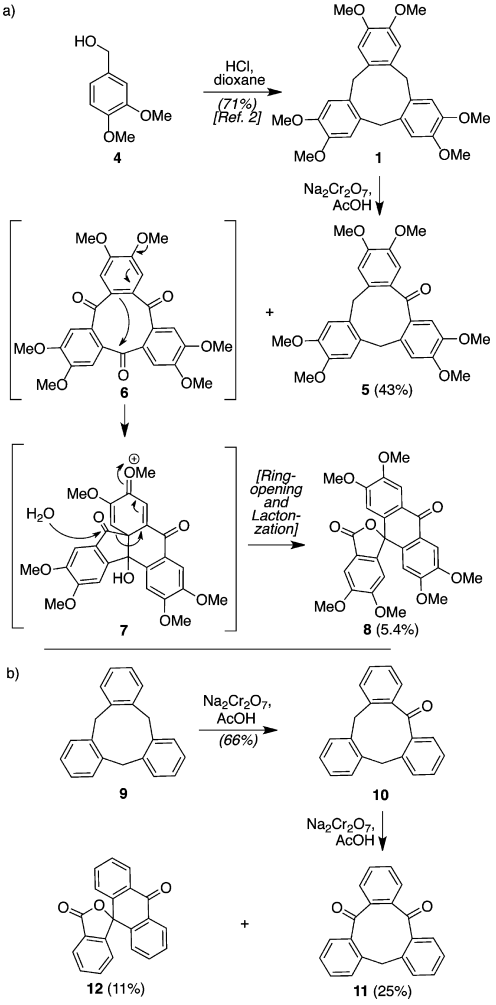
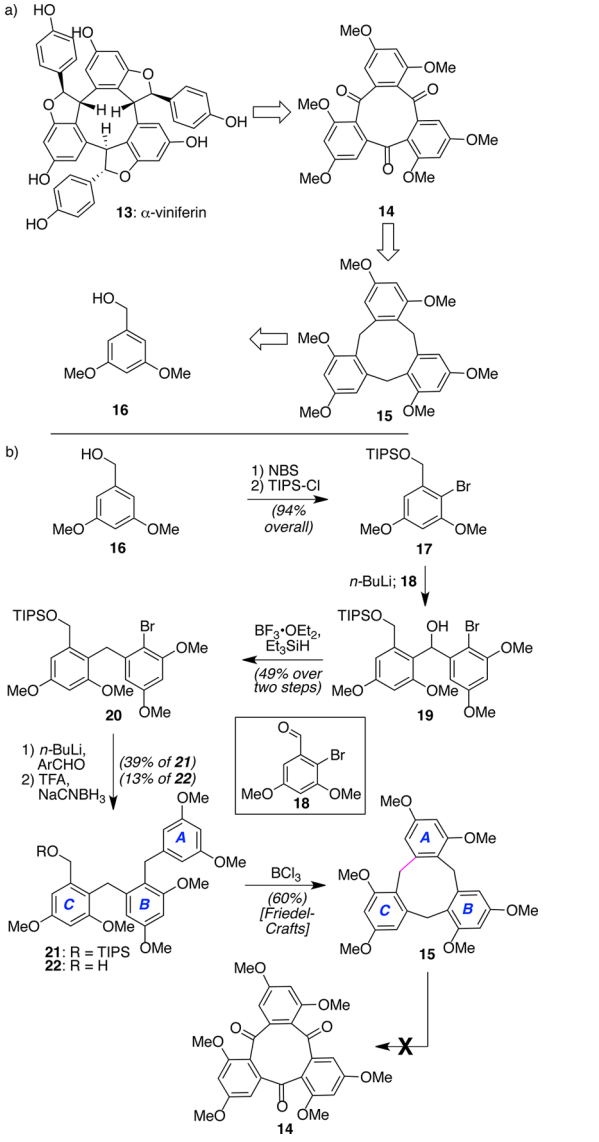
Scheme 1. Synthesis of Cyclotriveratrylene (1) and Its (a) Oxidation to Spirocycle 8, Presumably through Triketone 6, and (b) Similar Reactivity Observed with 9



Scheme 2. (a) Inspiration for 9-Membered Ring Exploration and (b) Synthesis and Attempted Oxidation of Cyclotriveratrylene Derivative 15



like substrate is capable of forming a similar triketone, establishing in the process what we believe are the structural guidelines for when triketones can be formed with electron-rich substrates in preference to the spirocycles observed in past studies.

Our interest in this unique class of compounds derived from our efforts[16] to synthesize 9-membered rings within the resveratrol natural products family, of which α-viniferin (**13**)[17] is representative (Scheme 2a). In one design, we viewed triketone **14** as a key intermediate, hoping that simultaneous elaboration of all three of its carbonyl moieties would lead to the rapid construction of the natural product. Our first attempted route to that triketone invoked cyclotriveratrylene analogue **15** as a precursor, hoping we could find conditions capable of effecting its oxidation without rearrangement to a spirocycle. We began our efforts by attempting to trimerize **16**, in line with the precedents discussed earlier (cf. Scheme 1). Unfortunately, we did not observe any 9-membered ring formation.

This outcome was not unexpected since all successful instances of one-step trimerizations involve substrates with an electron-donating substituent *para* to the benzylic alcohol, a group that likely assists in cation generation and thus increases the reaction rate toward desired processes. As a result, we embarked on an alternate, stepwise strategy to achieve the desired intermediate as shown in Scheme 2b. Here, site-specific monobromination and protection of benzylic alcohol **16** gave coupling precursor **17** in 94% overall yield. This material, upon lithiation, was then added into aldehyde **18** to give bis-benzylic alcohol **19**. Subsequent reductive removal of the hydroxyl group then furnished the methylene bridge of **20**, with repetition of the same general sequence ultimately affording cyclization precursors **21**/**22**. As previously reported,[16,18] we found that treatment of **21** with BCl_3 accomplished the desired cyclization to **15** in 60% yield through a Friedel–Crafts cyclization,[19] with X-ray crystallographic analysis revealing that **15** adopts a crown conformation much like cyclotriveratrylene.

Overall, this result was gratifying in that not only had the core carbon framework of our targeted natural product been formed, but we had also synthesized an entirely new cyclotriveratrylene analogue. Furthermore, the facility of the sequence and possibilities for interchanging the three aromatic coupling partners could potentially serve as a roadmap for the construction of other cyclotriveratrylene analogues unobtainable

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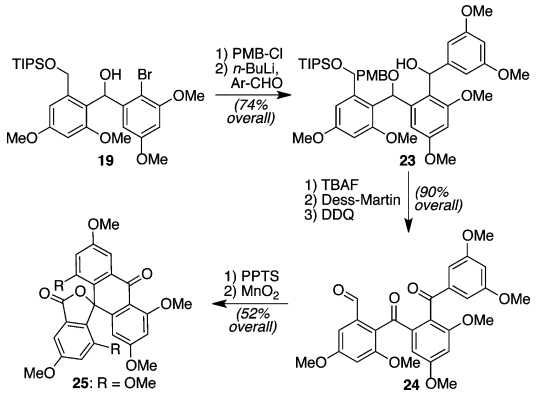
Scheme 3. Attempted Cyclization of Preoxidized Intermediate 24



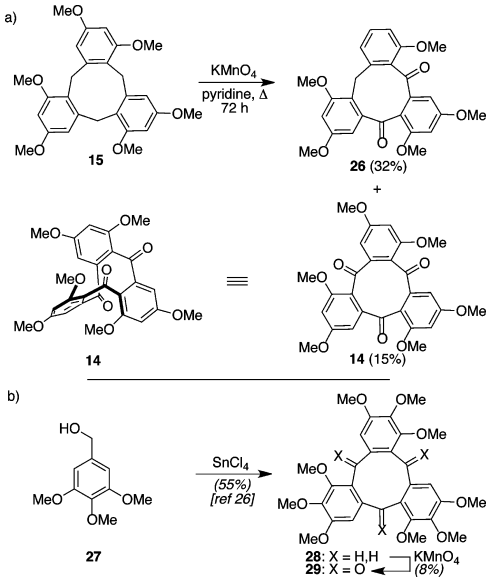
by the conventional, one-step acid-catalyzed trimerization method. Unfortunately, attempted oxidation of this material (**15**) with chromic acid afforded minimal oxidation of any type with no **14** observed. Attempts to deploy other conventional benzylic oxidations (such as $Pd(OAc)_2$/*t*-BuOOH[20] and DDQ) were likewise met with poor conversion. Given the similar electronic environment of **15** and cyclotriveratrylene (**1**), we reasoned that the positioning of a methoxy group *ortho* to the methylenes within **15** might be responsible, with its steric bulk effectively blocking any incoming oxidant.

Given this failure, we next sought to preinstall the needed carbonyls before 9-membered ring formation so as to obviate the need for any benzylic oxidation postcyclization. Starting from the previously synthesized TIPS-protected bromide **19** (Scheme 3), protection of its free hydroxyl with a PMB group, followed by lithiation and addition of the final aromatic ring, smoothly furnished triaryl **23** in 74% yield. Next, TIPS removal using TBAF, oxidation of the two free alcohol groups with Dess–Martin periodinane, and PMB excision followed by in situ alcohol oxidation smoothly delivered diketoaldehyde **24**, poised to attempt closure to a 9-membered ring.[21]

Our explorations focused on treating diketoaldehyde **24** with various Lewis and Brønsted acids. Regrettably, these attempts consistently afforded the same product after subsequent benzylic oxidation with MnO_2, namely spirocyclic lactone **25** as confirmed by X-ray crystallographic analysis of a demethylated analogue. Unclear is whether this spirocycle formed directly or if 9-membered ring formation occurred first and was followed by a transannular rearrangement of the type detailed in Scheme 1. In any event, resigned to the unattainability of the desired triketone **14** in line with past reports, we engaged other strategies toward the synthesis of 9-membered ring-containing natural products, ultimately synthesizing a related natural product through a unique Friedel–Crafts cyclization.[16]

Quite some time after our initial pursuit of the triketone in the context of Scheme 2, a publication appeared which reported new conditions for the oxidation of cyclotriveratrylene (**1**) using $KMnO_4$ and MnO_2 in refluxing pyridine.[22] Although no triketone was obtained, the authors did report a significantly higher yield of the mono- and diketones than any previous approach. With some **15** still in hand, we attempted its oxidation using these same conditions. Much to our surprise, we obtained a small amount of what appeared to be a fully oxidized product distinct from the previously obtained spirocycle **25**. Optimization studies led to a slightly modified protocol which allowed us to isolate that material in higher yield (Scheme 4), and with the

Scheme 4. (a) Successful Oxidation of 15 to 14 and (b) Application to a Two-step Synthesis of Triketone Analogue 29



support of NMR, mass spectrometry, and a preliminary X-ray crystal structure (see the Supporting Information), we were able to identify this product as the elusive triketone (**14**).

As indicated, diketone **26** is the favored product of this process, and interestingly, despite recovery of a small amount of starting material **15**, no trace of the monoketone was observed.[23] Significantly, resubmission of diketone **26** to the same conditions gave additional triketone **14** in 20% yield along with 30% recovered **26**. On the basis of these results, the first and third oxidations would appear to occur slowly, while the second oxidation to the diketone is more rapid.[24,25] X-ray crystallography revealed that diketone **26** and triketone **14** possess a saddle-like conformation (shown explicitly for **14**).

On initial reflection, it may seem curious that we did not see rearrangement to the spirocyclic lactone **25** (cf. Scheme 3) from triketone **14** as observed previously with very similar substrates; we can stipulate that no observable trace of such a product was obtained having already synthesized **25** by other means with full knowledge of its spectral and chromatographic properties. We originally postulated that the steric penalties of the requisite intermediates needed in such a rearrangement, particularly those of type **7** (cf. Scheme 1), might be prohibitively high when methoxy groups are *ortho*- to the methylene positions, as compared to those previous cases where no such substitution was present. To test that theory, a series of DFT calculations (B3LYP/6-31g*) were performed considering the energies of the hypothetical triketone **6**, triketone **14**, and the corresponding intermediates following transannular attack of both of those triketones under acidic conditions. In the case of **6** to **7**, that process is downhill energetically by ~3 kcal/mol; by contrast, the same process with **14** is uphill by 0.7 kcal/mol. The difference appears not to be due to sterics, but rather stabilization of the protonated triketone by the neighboring *o*-methoxy groups in **14** that causes substantial twisting, forcing the attacking aryl group to be orthogonal to the protonated ketone (see the Supporting Information for structures), thereby preventing the transannular rearrangement. To support this overall theory for successful triketone formation from materials possessing a methoxy group *ortho* to a methylene, and assuming the relative energies are

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similar under the basic conditions of our developed procedure, we submitted cyclotriveratrylene analogue **29**, obtained in one step from **28**,[26] to the same oxidation protocol. As shown, our prediction for oxidation without rearrangement proved correct, with triketone **30** formed in 8% yield, just a mere two steps from commercially available alcohol **28**.[27]

In conclusion, we have developed a stepwise synthetic strategy toward cycloveratrylene analogue **15**, a compound unavailable through the conventional single step approach previously developed for cyclotriveratrylene and other related derivatives. We believe this strategy may be generalized for other cyclotriveratrylene analogues that do not possess the necessary substitution pattern for a one-step, acid-catalyzed trimerization. Furthermore, we have accomplished the first reported examples of synthesizing cyclotriveratrylene-like triketones. Not only does this key finding address a longstanding challenge in the field, it also illustrates the conditions and structural requirements needed for the formation of such materials, opening the door to further elaboration and study of these previously unexplored "inner rim" cycloveratrylene derivatives for new applications.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details, copies of spectral data, computational details/structures, X-ray crystal structures, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) This molecule was first synthesized in 1915 but was misassigned as a dimeric structure: Robinson, G. M. *J. Chem. Soc. Trans.* **1915**, 267–276. It was not until 1965 that **1** was correctly identified as a trimer: Lindsay, A. S. *J. Chem. Soc.* **1965**, 1685–1692.

(2) For a selected, recent synthesis of cyclotriveratrylene, see: Vargas-Rodriguez, Y. M.; Vargas, M.; Miranda, R.; Francisco, B.; Nogues, O.; Morales-Serna, J. A.; Salmon, M. *Org. Commun.* **2012**, *5*, 58–63.

(3) (a) Collet, A. *Tetrahedron* **1987**, *43*, 5725–5759. (b) Collet, A.; Gabard, J. *J. Org. Chem.* **1980**, *45*, 5400–5401.

(4) For an excellent review on recent cyclotriveratrylene chemistry and applications, see: Hardie, M. J. *Chem. Soc. Rev.* **2010**, *39*, 516–527.

(5) Steed, J. W.; Junk, P. C.; Atwood, J. L.; Barnes, M. J.; Raston, C. L.; Burkhalter, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 10346–10347.

(6) (a) Holman, K. T.; Halihan, M. M.; Jurisson, S. S.; Atwood, J. L.; Burkhalter, R. S.; Mitchell, A. R.; Steed, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9567–9576. (b) Gawenis, J. A.; Holman, K. T.; Atwood, J. L.; Jurisson, S. S. *Inorg. Chem.* **2002**, *41*, 6028–6031. (c) Abrahams, B. F.; Fitzgerald, N. J.; Hudson, T. A.; Robson, R.; Waters, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 3129–3132.

(7) Xu, D.; Warmuth, R. *J. Am. Chem. Soc.* **2008**, *130*, 7520–7521.

(8) Brotin, T.; Dutasta, J.-P. *Chem. Rev.* **2009**, *109*, 88–130.

(9) (a) Bartik, K.; Luhmer, M.; Dutasta, J.-P.; Collet, A.; Reisse, J. *J. Am. Chem. Soc.* **1998**, *120*, 784–791. (b) Wei, Q.; Seward, G. K.; Hill, P. A.; Patton, B.; Dimitrov, I. E.; Kuzma, N. N.; Dmochowski, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 13274–13283.

(10) Huerta, E.; Metselaar, G. A.; Fragoso, A.; Santos, E.; Bo, C.; de Mendoza, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 202–205.

(11) Cookson, R. C.; Halton, B.; Stevens, I. D. R. *J. Chem. Soc. B* **1968**, 767–774.

(12) Baldwin, J. E.; Kelly, D. P. *Chem. Commun.* **1968**, 1664–1665.

(13) The structure of **9** was also originally misassigned. It was first prepared by Cannizaro in 1854 and reported as a cyclic hydrocarbon with a general formula of $(C_7H_6)_n$: (a) Cannizaro, S. *Ann. Chem. Pharm.* **1854**, *90*, 113–117. (b) Cannizaro, S. *Ann. Chem. Pharm.* **1854**, *90*, 252–254. Only in 2008 was the correct assignment made: (c) Grealis, J. P.; Muller-Bunz, H.; Casey, M.; McGlinchey, M. J. *Tetrahedron Lett.* **2008**, *49*, 1527–1530.

(14) Yamato, T.; Sakaue, N. *J. Chem. Res., Synop.* **1997**, *21*, 440–441.

(15) (a) Lutz, M. R.; Zeller, M.; Sarsah, S. R. S.; Filipowicz, A.; Wouters, H.; Becker, D. P. *Supramol. Chem.* **2012**, *24*, 803–809. For examples of related oxidation difficulty with congeners possessing double bonds in place of the aromatic rings of the cycloveratrylene structure, see: (b) Person, G.; Keller, M.; Prinzbach, H. *Liebigs. Ann.* **1996**, 507–527. (c) Pleschke, A.; Grier, J.; Keller, M.; Wörth, J.; Knothe, L.; Prinzbach, H. *Eur. J. Org. Chem.* **2007**, 4867–4880.

(16) Wright, N. E.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 3409–3413.

(17) Pryce, R. J.; Langcake, P. *Phytochemistry* **1977**, *16*, 1452–1454.

(18) Although we disclosed the key Friedel–Crafts step in this precedent, the route utilized to prepare the cyclization precursor (i.e., **22**) was not delineated.

(19) An additional 20% of the material was recovered as the corresponding benzyl chloride; it could be resubmitted to the reaction conditions and increase material throughput.

(20) (a) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727–2730. (b) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232–3233. (c) Snyder, S. A.; Sherwood, T. C.; Ross, A. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 5146–5150.

(21) For example, see: Torricelli, F.; Bosson, J.; Besnard, C.; Chekini, M.; Burgi, T.; Lacour, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1796–1800.

(22) Sarsah, S. R. S.; Lutz, M. R.; Zeller, M.; Crumrine, D. S.; Becker, D. P. *J. Org. Chem.* **2013**, *78*, 2051–2058.

(23) Original explorations of this process with the conditions of ref 22 did afford a small amount of the monoketone, obtained impure upon all attempted isolations. A pure sample of that monoketone was obtained, albeit in poor yield, from a slightly modified approach for characterization purposes (see the Supporting Information).

(24) For reasons presently unclear, in each $KMnO_4$ oxidation we could cleanly recover only ~50–55% of the material balance, with no other products or decomposition observed.

(25) In ref 22., the authors report heating compound **1** with $KMnO_4$ for 1 day; we have re-exposed **1** to our optimized conditions (3 days of reaction time), and observed no formation of triketone or spirocycle **8**.

(26) Ding, Y.; Li, B.; Zhang, G. *ARKIVOC* **2007**, *14*, 322–326.

(27) The reaction can be performed on both small and large scales (up to ~1 mmol). On a larger scale, the yield for the triketone products is typically less, with the ideal for improved throughput being several smaller scale reactions and doing a single purification. $KMnO_4$ equivalents can range from 100–140, but less leads to inefficient oxidation.