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Overcoming Strain-Induced Rearrangement Reactions: A Mild Dehydrative Aromatization Protocol for the Synthesis of Highly Distorted *para*-Phenylenes

Nirmal K. Mitra, Rolande Meudom, Hector H. Corzo, John D. Gorden, and Bradley L. Merner*

Auburn University, Department of Chemistry and Biochemistry, Auburn, AL 36849, United States

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ABSTRACT: *A series of p-terphenyl-based macrocycles, containing highly distorted para-phenylene units, have been synthesized. The biaryl bonds of the nonplanar p-terphenyl nuclei were constructed in the absence of Pd-catalyzed or Ni-mediated cross-coupling reactions, using 1,4-diketones as surrogates to strained arene units. A streamlined synthetic protocol for the synthesis of 1,4-diketo macrocycles has been developed, using only 2.5 mol% of the Hoveyda-Grubbs second-generation catalyst in both metathesis and transfer hydrogenation reactions. Under protic acid-mediated dehydrative aromatization conditions, the central and most strained benzene ring of the p-terphenyl systems was susceptible to rearrangement reactions. To overcome this, a dehydrative aromatization protocol using the Burgess reagent was developed. Under these conditions, no strain-induced rearrangement reactions occur, delivering para-phenylene units with up to 28.4 kcal/mol of SE and deformation angles that sum up to 40°.*

INTRODUCTION

The formation of biaryl bonds via transition metal-catalyzed, or mediated, cross-coupling reactions are venerable transformations in organic synthesis.[1] A plethora of conditions, modifications, and optimizations have been reported over the past 30 years,[1a] and the presence of biaryl systems in natural products,[2] important pharmaceuticals,[3] axially chiral molecules,[4] and designed molecules relevant to materials science[5] has instigated a tireless interest in this area of synthetic method development.[6] Thus, it is surprising to find that such methods have not enjoyed widespread applicability in the synthesis of macrocyclic systems that contain arene-bridged units as they have in the synthesis of acyclic (linear) arene-arene, or polyaryl systems. In fact, biaryl bond formation that results in the construction of strained macrocyclic compounds has proven to be a significant challenge for chemical synthesis.[7] One of the main problems posed by the synthesis of macrocyclic arene-bridged systems is the build up of strain in carbon-carbon (C-C) bond forming reactions that furnish the intended targets. In particular, if the desired cross-coupling reaction requires bending the arene, or multiple arene, unit(s), low-yielding reactions result (mode 1, Figure 1a).[7] Furthermore, if arene-arene bond formation requires stretching or elongating C-C bonds within an alkyl chain upon macrocycle formation, the corresponding macrocyclization can be energetically prohibitive (mode 2, Figure 1a). Recently, arylation reactions that avoid cross-coupling reaction partners have emerged as powerful tools for assembling strained macrocyclic systems.[8]

The synthesis of distorted benzene rings has been ongoing for over 65 years,[9] and the quest to synthesize the most perturbed cyclic 6π system culminated with kinetically stabilized [4]paracyclophane derivatives in 2003.[10] However, this field of chemical synthesis has remained quite vigorous over the past decade. The discovery of natural products containing highly strained *para*-phenylene subunits, particularly the haouamine alkaloids,[11] and the notion that macrocyclic benzenoid hydrocarbons may serve as templates in the

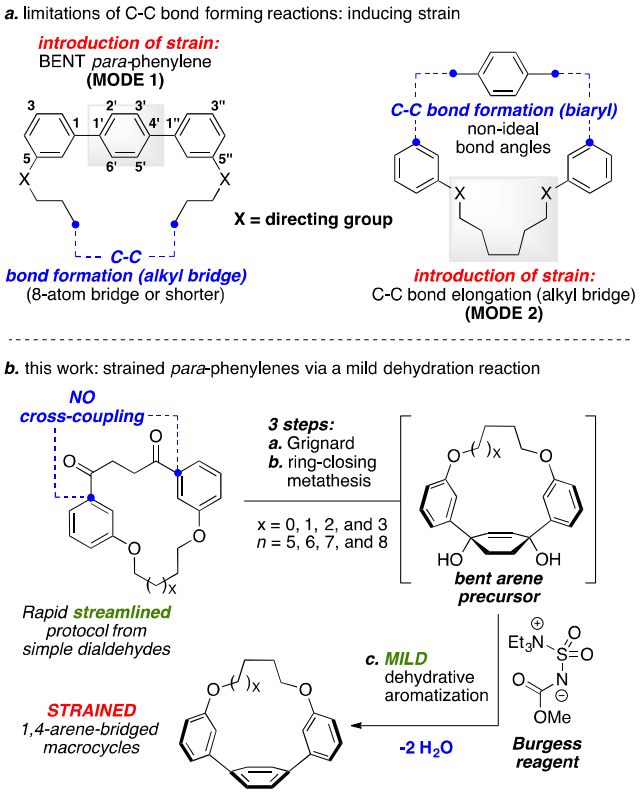


Figure 1. (a) Strain inducing carbon-carbon bond forming reactions; (b) biaryl bond formation using a macrocyclic 1,4-diketone surrogate and a mild dehydrative aromatization reaction

bottom–up chemical synthesis of carbon nanotubes (CNTs)[12] has kept the level of interest in new synthetic method development high. It is noteworthy that in both of the aforementioned examples, the bent *para*-phenylene units are part of biaryl macrocyclic systems. The most distorted benzene rings

to be characterized by X-ray crystallography belong to the paracyclophanes. In the case of Tobe's [6]paracyclophane derivative **1**[13] and Tsuji's [1.1]paracyclophane **2**,[14] the highly distorted pi-systems were obtained upon valence isomerization of Dewar benzene precursors (Figure 2). For a long time, valence isomerization reactions were viewed as the ultimate method for synthesizing severely distorted aromatic systems. In the case of the Dewar benzenes, rupture of the central C-C bond in the bicyclo[2.2.0]hexa-2,5-diene system brought about a release of strain energy (SE) upon destruction of the bicyclic intermediate, and a gain in aromatic stabilization energy (ASE) upon forming the arene system. Until 2014, no bent *para*-phenylene ring with an α angle greater than 15° had been synthesized using a non-valence isomerization approach. The pioneering contributions from the groups of Bertozzi[15] Itami,[16] Yamago,[17] and Jasti[18] on the [*n*]cycloparaphenylenes rejuvenated this area of chemical synthesis, in the context of strained (macrocyclic) benzenoid nanohoops. The 2014 syntheses of [5]CPP[19,20] (**3**) re-wrote the record books for the smallest [*n*]CPP homologue. With an average mean plane deviation angle (α) of 15.6° and a total SE of 119 kcal/mol (*ca.* 24 kcal/mol per benzene ring), [5]CPP is by far the most strained of the carbon nanohoops yet to be synthetized. The synthesis of this impressive nanostructure, and related homologs, has led to the development of powerful aromatization strategies that employ reductive (aromatization) protocols and not valence isomerization reactions (Figure 2).

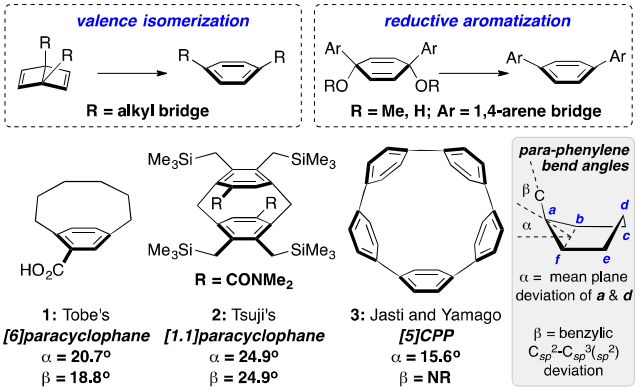


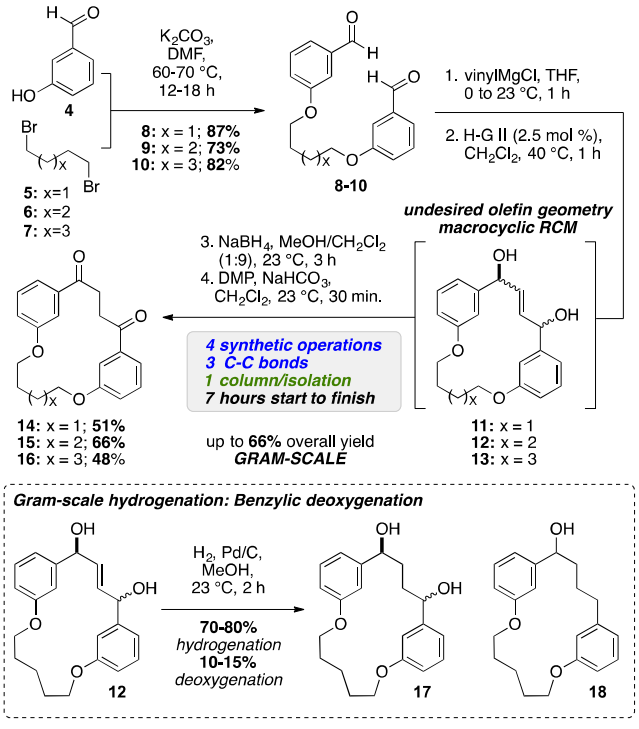
Figure 2. Valence isomerization and reductive aromatization strategies to highly distorted *para*-phenylene-containing molecules

Recently, our group has reported the application of a non-cross-coupling-based approach to an arene-bridged macrocycle, 1,7-dioxa[7](3,3")*p*-terphenylophane (**26**, Scheme 2), which contains nonplanar benzene and *p*-terphenyl units.[21] This strategy relied on the conversion of an unstrained macrocyclic 1,4-diketone to a strained *para*-phenylene unit. Our overlapping interests in the synthesis of natural products containing biaryl, nonplanar *para*-phenylene units and the conversion of macrocyclic benzenoid systems into polycyclic aromatic hydrocarbon-containing macrocycles led us to investigate the utility of 1,4-diketo-bridged macrocycles in the synthesis of highly distorted arene units that comprise biaryl systems. In this Article we report the synthesis of three new members of this class of benzenoid macrocycles, a streamlined synthetic approach to a series of macrocyclic 1,4-diones, an interesting size-dependent, diastereoselective Grignard reaction of vinylmagnesium chloride with macrocyclic 1,4-diones, a new mild dehydrative aromatization protocol for the synthesis of highly strained *para*-phenylenes that are part of a polyaryl system, the X-ray crystal structure of the most distorted homolog, and the computed SE of this compound

RESULTS AND DISCUSSION

Streamlined Synthesis of Macrocyclic 1,4-diketones. The synthesis of macrocyclic 1,4-diketones, that are also [*n*.4]metacyclophanes, was unknown when we began our synthetic investigations on the 1,*n*-dioxa[*n*](3,3")*p*-terphenylophanes. The first-generation approach to these benzenoid macrocyclic systems involved a three-stage synthetic process that commenced with an acyclic dialdehyde (**9**, Scheme 1). The conversion of **9** to macrocyclic ketone **15** was accomplished over four steps, which required purification of three synthetic intermediates.[21] Upon scaling up this process, it was discovered that hydrogenation of the undesired olefin diastereomer (**12**) resulted in the production of a benzylic deoxygenation product (*ca.* 15%) **18**. To circumvent this byproduct formation and streamline the four-step process to furnish gram-scale quantities of a homologous series of macrocyclic 1,4-diones, we explored alternative hydrogenation protocols. Inspired by the recent report of sequential ring-closing metathesis (RCM) and transfer hydrogenation reactions by Peese and co-workers,[22] using the Hoveyda-Grubbs second-generation (H-G II) catalyst, we designed a synthetic sequence that would facilitate the synthesis of macrocyclic 1,4-diketones from acyclic dialdehydes without purification of any intermediates. Indeed, treatment of dialdehydes **8-10** with vinylmagnesium chloride, followed by a H-G II-mediated macrocyclic RCM reaction at 15 mM concentration in dichloromethane afforded **11-13** as mixtures of alkene diastereomers, in which the *trans*-configured (undesired) olefin was

Scheme 1. Streamlined, scalable synthesis of macrocyclic 1,4-diones **11-13**

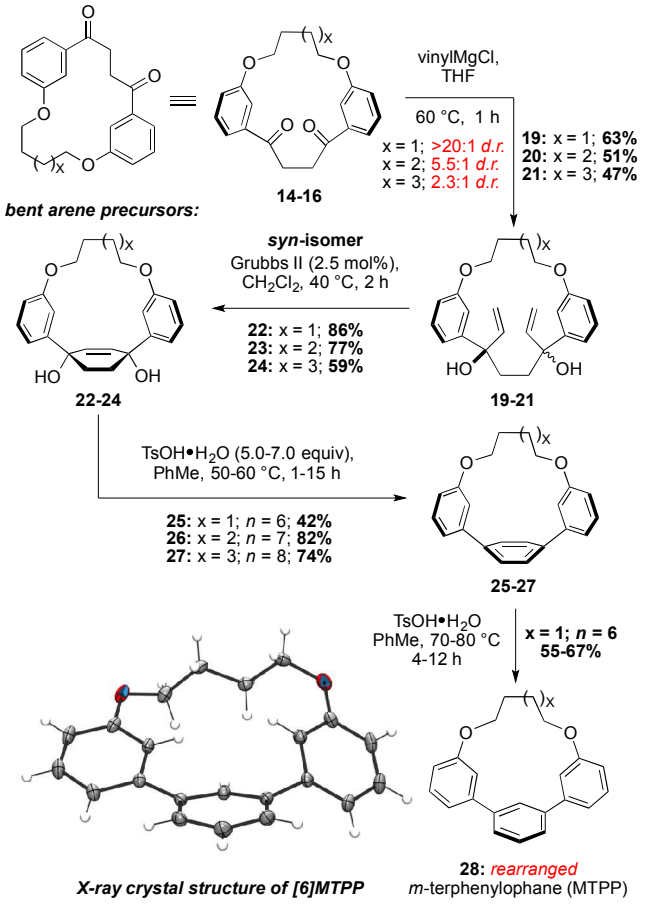


the major product. After evaporation of the solvent, the residue was dissolved in 1:9 methanol/dichloromethane and the addition of 3.0-5.0 equivalents of $NaBH_4$ resulted in smooth transfer hydrogenation of the olefin in less than three hours, without any benzylic deoxygenation. It is noteworthy that only 2.5 mol% of the H-G II catalyst was used in both the metathesis and transfer hydrogenation reactions, all of which was added at the RCM stage. Furthermore, the use of a 1:9 vs a 1:19 methanol/dichloromethane solvent mixture, as originally reported by Peese and co-workers,[22] provided much shorter reaction times in the transfer hydrogenation step. Finally, direct exposure of the crude 1,4-diol mixtures to the Dess-Martin reagent, in the presence of $NaHCO_3$, furnished pure macrocyclic 1,4-diketones **14-16** in up to 66% yield. Running this four-step reaction protocol on a gram-scale provided access to 500-650 milligram quantities of the desired diketone while using less than 500 mL of solvent and 50 g of silica gel for a single chromatographic separation. Furthermore, the desired products can be obtained in less than 7 hours starting from acyclic dialdehydes **8-10**. So far, we have not been able to find a faster and more efficient protocol for the synthesis of macrocyclic 1,4-diketones.

Protic Acid-Mediated Dehydrative Aromatization: Strain-Induced Rearrangements of Severely Distorted Biaryl para-phenylenes. The conversion of the 1,4-diketo-bridging group into a strained 1,4-arene bridge (bent *para*-phenylene) was previously accomplished by employing a three-step reaction protocol. The first of which involved a Grignard reaction with vinylmagnesium chloride. The diastereoselectivity of this reaction was critical to the formation of the desired arene precursor, as only the *syn*-allylic diol (**20**) was converted to the bridged cyclohex-2-ene-1,4-diol system (**23**).[21] After completing the synthesis of a homologous series of macrocyclic 1,4-diketones, it was discovered that the diastereoselectivity of this Grignard reaction is dependent on the size of the macrocyclic system employed. Larger macrocyclic rings (18 and 17-membered) gave lower diastereoselectivities (**21**, x = 3, 2.3:1 *d.r.*; **20**, x = 2, 5.5:1 *d.r.*, Scheme 2), while smaller macrocyclic rings (16 and 15-membered) gave much higher diastereoselectivities (**19**, x = 1, >20:1 *d.r.*, Scheme 2, and **30**, x = 0 >20:1 *d.r.*, Scheme 3a). To the best of our knowledge, no studies have been carried out to explore the origin of diastereoselectivity in related macrocyclic systems. We are currently conducting an extensive investigation of this reaction in our laboratory.

Fortunately, the *syn*-diastereomer is the major product of the vinylmagnesium chloride addition, and the inseparable (minor) *anti*-diastereomer could be easily removed after a RCM reaction.[23] Treatment of **19-21** with the Grubbs second-generation catalyst completed the conversion of the 1,4-dione unit into a six-membered ring, and the precursor macrocycle for a dehydrative aromatization reaction. In the case of **24** (n = 8) and **23** (n = 7), conversion to the bent *p*-terphenyl systems was high yielding and straightforward using TsOH (Scheme 2). For the next smallest macrocycle in the series, **22** (n = 6), clean isolation of the highly distorted *p*-terphenyl system proved to be more challenging and slightly lower yielding at 42%. Controlling the temperature of this reaction is critical to avoid the formation of unwanted by-products, and the reaction *must not* be heated above 60 °C, as the isomeric and less strained (3,3")*m*-terphenylophane derivative is formed. Heating a toluene solution of **25** in the presence of 5.0-7.0 equivalents of TsOH at 80 °C resulted in clean isomerization to **28** (X-ray, Scheme 2), presumably through a strain relief driven protonation of the bridgehead carbon followed by migration of the terminal arene unit.[24] It has been speculated that a similar "backbone" rearrangements occur when CPPs are subjected to protic or Lewis acid-mediated reaction conditions, however, to the best of our knowledge, no supporting structural evidence has been reported to corroborate such a rearrangement.[25]

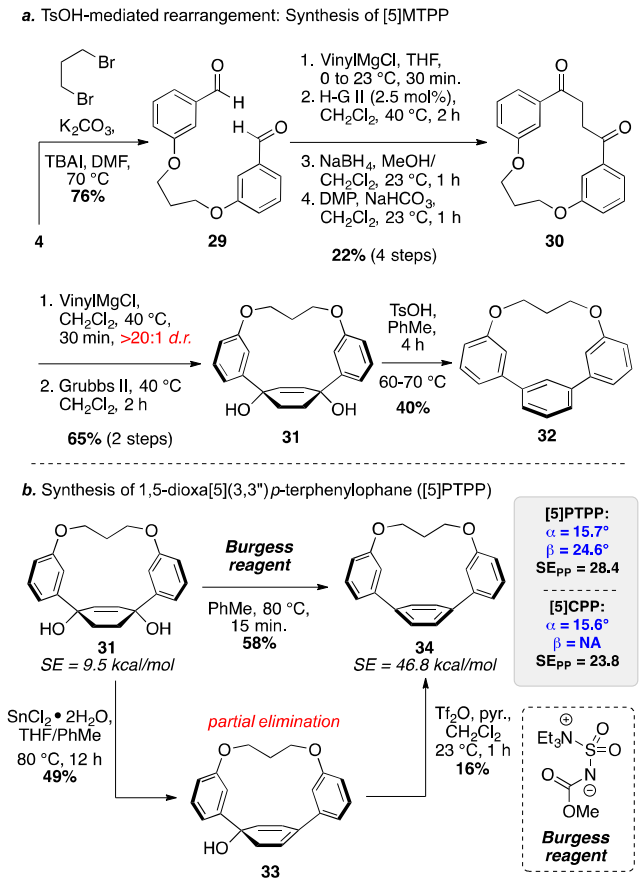
Scheme 2. Conversion of 1,4-diones **14-16** to *p*-terphenylophanes **25-27**



To investigate this strain-induced rearrangement reaction of (3,3")*p*-terphenylophanes to (3,3")*m*-terphenylophanes, we synthesized a smaller macrocyclic homolog **31**. The synthesis of **31** proceeds along the same pathway previously described for **22-24**. It is worth mentioning that the yield of the 4-step 1,4-diketone synthesis is lower than the three previously described homologues (**14-16**) at 22%. We attribute this lower yielding process to the reduced solubility of the macrocyclic RCM product, as well as the propensity for the precursor diene to form a higher molecular weight metathesis by-product at 15 mM concentration.[26] Nonetheless, synthetically useful quantities of **30** can be prepared in short order. The Grignard reaction of **30** with vinylmagnesium chloride demonstrated the same macrocyclic trend as described above (**14-16** to **19-21**, >20:1, *d.r.*, 15-membered 1,4-diketone) and a RCM reaction of the afforded diene gave the cyclohex-2-ene-1,4-diol precursor **31** in 65% overall yield. Treatment of **31** with TsOH in toluene at 60 °C gave, what was believed to be, a partial elimination product, which persisted in solution at this temperature. Increasing the tempera-

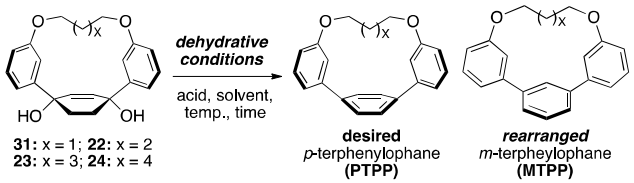
ture to 70 °C furnished only the rearranged 1,5-dioxa[5](3,3")*m*-terphenylophane product after 3 hours (Scheme 3a and Table 1, entry 3). Thin-layer chromatography analysis of the reaction mixture revealed that an initially formed product (**34**, R_f = 0.43) was quantitatively converted into a slightly slower moving by-product (**32**, R_f = 0.41). This analysis is identical, albeit more rapid, to that observed for the conversion of **25** to **28** (Scheme 2), indicating that the desired 1,5-dioxa[5](3,3")*p*-terphenylophane (**34**) is formed during the course of the acid-mediated dehydrative aromatization reaction. In order to demonstrate the utility of cyclohex-2-ene-1,4-diol units as precursors to bent *para*-phenylenes, we sought an alternative dehydration strategy.

Scheme 3. (a) Synthesis of rearranged *m*-terphenylophane **32** under protic acid conditions; (b) Synthesis of [5]PTPP (**34**) under non-protic acid conditions



A Mild Dehydrative Aromatization Protocol. Several different reaction conditions that employ milder acidic reagents were screened to facilitate the synthesis of **25** and **34** from **22** and **31**, respectively. Application of $NaHSO_4$ in the presence of *o*-chloranil, which has been used by Itami and co-workers to aromatize cyclohexane-1,4-diol units of [*n*]CPP macrocyclic precursors,[27] gave a low yield of **25** with the formation of the rearranged isomer **28** (entry 4, Table 1). Using a modification of Yamago and co-workers tin(II) chloride dihydrate-mediated aromatization reaction, which was used successfully to synthesize [5]CPP (**3**),[20] gave only the partial dehydration product **33**. Furthermore, application of the recently reported $SnCl_2$/HCl ate complex (H_2SnCl_4),[28] did not afford the aromatized product. However, treating **33** with Tf_2O in pyridine (Table 1, entry 7) gave a 16% yield of the desired *p*-terphenylophane **34** (8% from **31**, Scheme 3b). Shifting our focus to non-acidic dehydration conditions, we attempted the synthesis of **34** by employing the Burgess reagent. Remarkably, **34** was isolated in 58% yield upon heating a toluene solution of **31** at 80 °C in the presence of the Burgess reagent,[29] without the formation of the rearranged isomer **32**! In comparison, heating toluene solutions of the cyclohex-2-ene-1,4-diol (arene) precursors **22**-**24** at 80 °C in the presence of TsOH for 30 minutes saw rearrangements occur at the n = 7 homolog stage (Table 1, entry 11). Indeed, subjecting all of the remaining cyclohexe-2-ene-1,4-diol precursors (**20**-**22**, n = 8-6, respectively) to identical reaction conditions, with the Burgess reagent, furnished the desired *p*-terphenyl-containing macrocycles in comparable yields (Table 1, entries 8, 9, 10, and 12). To the best of our knowledge, this represents the first application of the Burgess reagent in the synthesis of a nonplanar benzenoid system.

Table 1. Optimized conditions for the conversion of macrocyclic cyclohex-2-ene-1,4-diols **22**-**24**, and **31** to *p*-terphenylophanes **25**-**27**, and **34**, respectively



entry	x (*n*)	reagent	solvent	temp (°C)	time (h)	PTPP (%)	MTPP (%)
1	2 (6)	TsOH	PhMe	60	10	42	0
2	2 (6)	TsOH	PhMe	80	4	trace	**55**
3	1 (5)	TsOH	PhMe	70	3	0	**40**
4	2 (6)	$NaHSO_4$	DMSO/xylenes	130	24	36	trace
5[a]	1 (5)	$SnCl_2$•$2H_2O$	THF/PhMe	80	12	0	0
6[b]	1 (5)	H_2SnCl_4	THF	23	72	0	0
7[c]	1 (5)	Tf_2O	CH_2Cl_2/pyr.	23	0.5	16	0
8	1 (5)	***Burgess***	PhMe	80	0.2	**58**	0
9	2 (6)	***Burgess***	PhMe	80	0.2	**56**	0
10	3 (7)	***Burgess***	PhMe	80	0.2	**68**	0
11	3 (7)	TsOH	PhMe	80	0.2	38	**19**
12	4 (8)	***Burgess***	PhMe	80	0.2	**60**	0
13	4 (8)	TsOH	PhMe	80	0.2	62	0

a. Only the monodehydration product **33** (Scheme 3a) was formed; ***b.*** H_2SnCl_4 was prepared by mixing $SnCl_2$•$2H_2O$ and HCl; ***c.*** This entry refers to the reaction of **33**.

X-Ray Crystal Structure and Strain Energy of a Highly Distorted para-Phenylene Ring. Recrystallization of **34** from dichloromethane and hexanes produced a single crystal suitable for X-ray analysis, revealing the highly distorted *p*-terphenyl nucleus and *para*-phenylene ring of the macrocycle. The central arene unit in the *p*-terphenyl system has an α angle of 15.7°, which is comparable to the α angle found in the bent *para*-phenylene units of [5]CPP – *cf.* 15.6° – and is greater than that found in the natural product haouamine A.[30] It is, however, less than that of the mean plane deviation found in compounds **1** and **2** (Figure 1). The *β* angles found in **34** have an average value of 24.6°, with the largest deviation coming in at 26.8°. This is identical to the largest *β* angle measured in a bent *para*-phenylene unit – Tsuji's [1.1]paracyclophane derivative **2**.[14] The 1,3-propanoxy bridge of **34** severely bends the *p*-terphenyl system from an ideal planar geometry, but also twists and bows the terminal arene units. In fact, the biaryl bonds in **34** are canted forward at an average angle of 9.8° (C11–C22–C23 and C14–C25–C24). The overall SE of **34** has

been computed at the DFT B3LYP level of theory using the 6-31G(d) basis set, and is estimated to be 46.8 kcal/mol. The SE of the *p*-terphenyl system comprises 40.2 kcal/mol of the total SE found in **34**, the majority of which is localized on the central arene unit. At 28.4 kcal/mol, the SE of the *para*-phenylene ring is approximately 4.6 kcal/mol greater than that of the average SE/*para*-phenylene unit in [5]CPP – the most strained CPP homolog to be prepared by chemical synthesis. The SE of [4]CPP, which has yet to be synthesized, is predicted to be 144 kcal/mol,[31] giving an average SE/*para*-phenylene of 36 kcal/mol. Currently, we are pursuing the synthesis of a smaller homolog of **34** as well as a macrocyclic precursor of [4]CPP. Both of these targets will provide the ultimate tests of our Burgess reagent-mediated aromatization protocol of macrocyclic cyclohex-2-ene-1,4-diols.

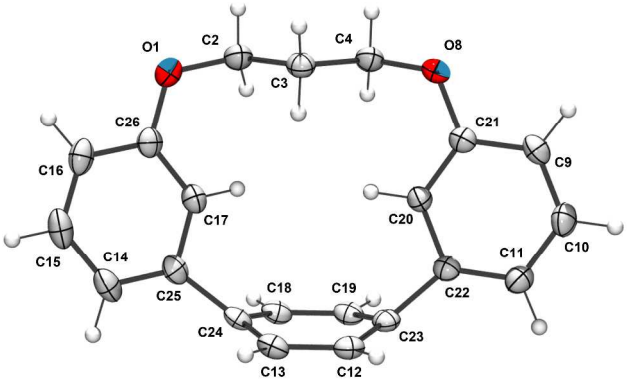


Figure 3. X-ray crystal structure of 1,5-dioxa[5](3,3")*p*-terphenylophane (**34**)

CONCLUSION

In summary, a streamlined synthetic approach that involves the conversion of acyclic dialdehydes to macrocyclic 1,4-diketones has been developed. This four-reaction process can be conducted on a gram-scale, completed in just 7 hours, and requires a single chromatographic separation to afford pure 1,4-diketones. The addition of vinylmagnesium chloride to these macrocyclic 1,4-diketones, gave higher diastereoselectivities when smaller macrocyclic systems were employed (15 to 18-membered rings). The origin of this (macrocyclic) size-dependent diastereoselectivity, as well as its synthetic utility, is currently under investigation in our laboratory. Finally, a non-protic acid-mediated dehydrative aromatization reaction of arene-bridged cyclohex-2-ene-1,4-diol precursors has been demonstrated to be a mild and powerful tool for the synthesis of highly distorted *para*-phenylene units that are part of polyaryl systems, or benzenoid macrocycles. In the case of the smallest homolog synthesized, over 37 kcal/mol of SE is generated upon elimination of two molecules of water (**31** to **34**, Scheme 3b). The application of this reaction to a smaller homolog of **34**, the synthesis of small, functionalized CPPs, and biaryl natural products containing bent benzene rings are underway in our laboratory. The results of these studies will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and all ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at htpp://pubs.acs.org

AUTHOR INFORMATION

Corresponding Author

* Corresponding Author: blm0022@auburn.edu

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ABBREVIATIONS

CNT, carbon nanotube; CPP, cycloparaphenylene; PTPP, (3,3")*p*-terphenylophane; MTPP, (3,3")*m*-terphenylophane; SE, strain energy; DFT, density functional theory; RCM, ring-closing metathesis; TLC, thin layer chromatography; TsOH, *p*-toluene sulfonic acid;

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(24) See Supporting Information for a proposed mechanism.
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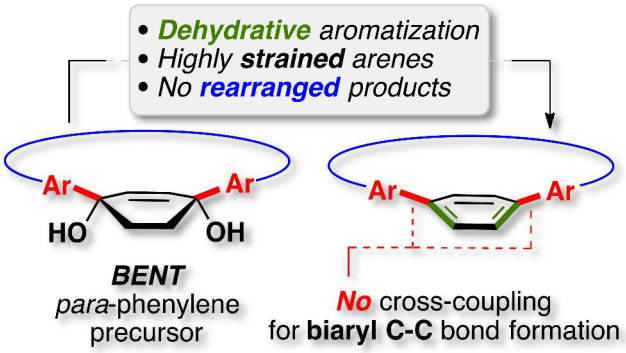

• Dehydrative aromatization
• Highly strained arenes
• No rearranged products
Ar
Ar
HO
OH
BENT
para-phenylene
precursor
Ar
Ar
No cross-coupling
for biaryl C-C bond formation

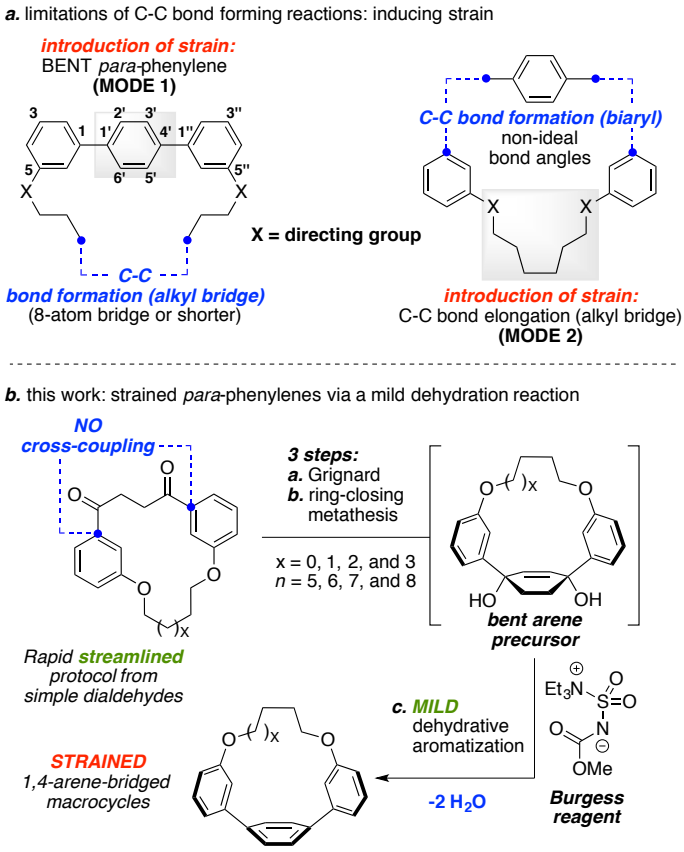


Figure 1. (a) Strain inducing carbon-carbon bond forming reactions; (b) biaryl bond formation using a macrocyclic 1,4-diketone surrogate and a mild dehydrative aromatization reaction

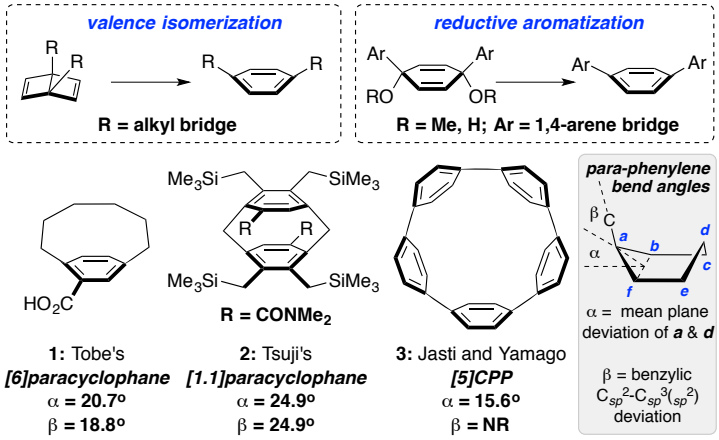
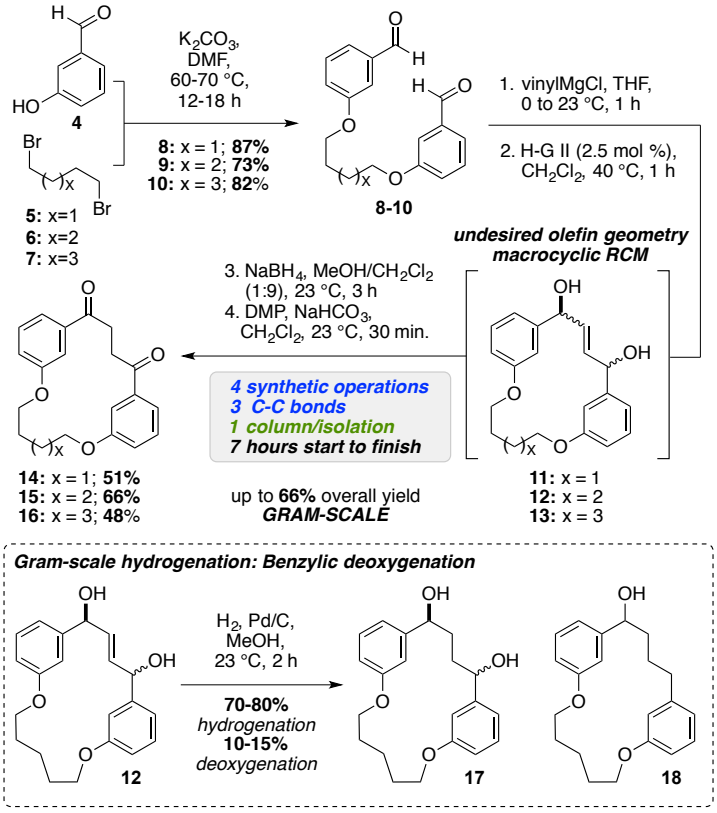
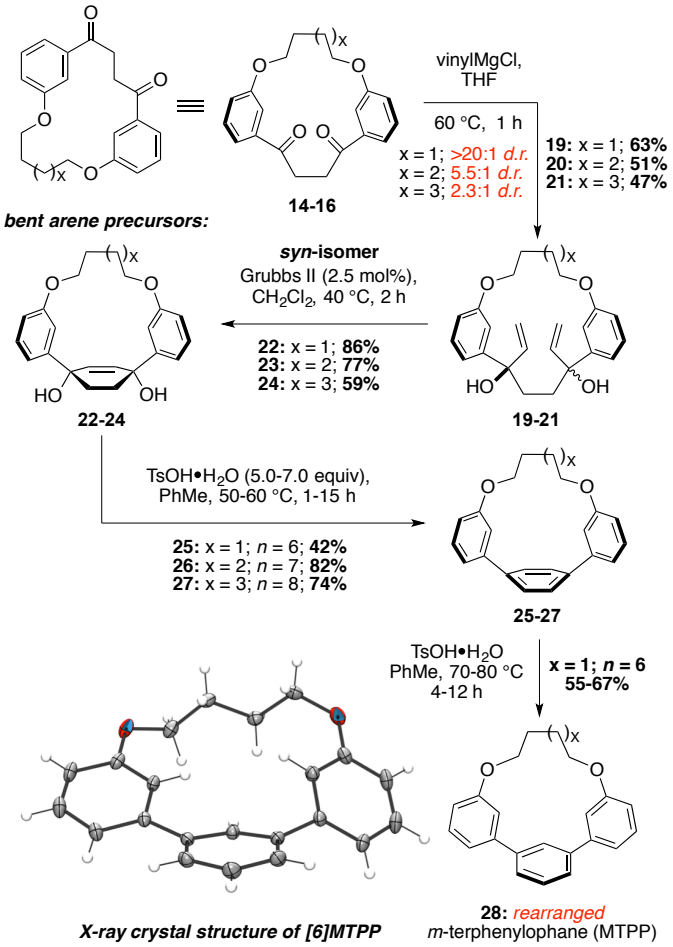


Figure 2. Valence isomerization and reductive aromatization strategies to highly distorted *para*-phenylene-containing molecules

Scheme 1. Streamlined, scalable synthesis of macrocyclic 1,4-diones **11-13**



Scheme 2. Conversion of 1,4-diones **14-16** to *p*-terphenylophanes **25-27**



Scheme 3. (a) Synthesis of rearranged *m*-terphenylophane **32** under protic acid conditions; (b) Synthesis of [5]PTPP (**34**) under non-protic acid conditions

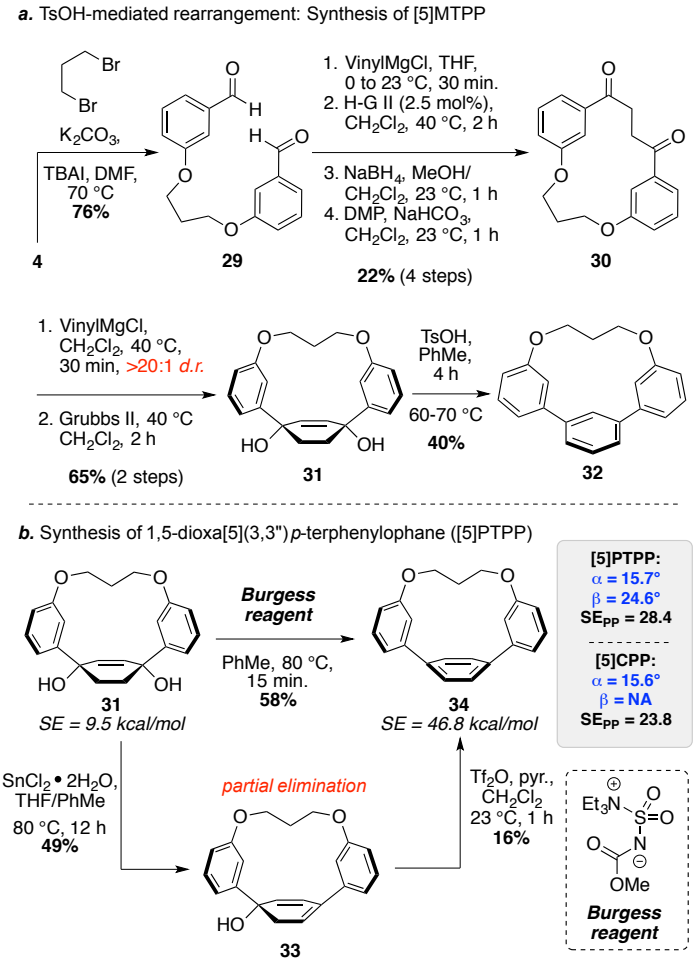
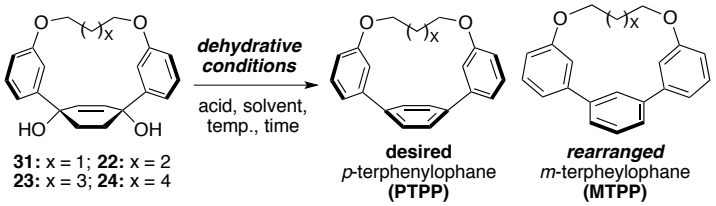


Table 1. Optimized conditions for the conversion of macrocyclic cyclohex-2-ene-1,4-diols **22**-**24**, and **31** to *p*-terphenylophanes **25**-**27**, and **34**, respectively



entry	x (*n*)	reagent	solvent	temp (°C)	time (h)	PTPP (%)	MTPP (%)
1	2 (6)	TsOH	PhMe	60	10	42	0
2	2 (6)	TsOH	PhMe	80	4	trace	**55**
3	1 (5)	TsOH	PhMe	70	3	0	**40**
4	2 (6)	$NaHSO_4$	DMSO/xylenes	130	24	36	trace
5[a]	1 (5)	$SnCl_2•2H_2O$	THF/PhMe	80	12	0	0
6[b]	1 (5)	H_2SnCl_4	THF	23	72	0	0
7[c]	1 (5)	Tf_2O	CH_2Cl_2/pyr.	23	0.5	16	0
8	1 (5)	***Burgess***	PhMe	80	0.2	**58**	0
9	2 (6)	***Burgess***	PhMe	80	0.2	**56**	0
10	3 (7)	***Burgess***	PhMe	80	0.2	**68**	0
11	3 (7)	TsOH	PhMe	80	0.2	38	**19**
12	4 (8)	***Burgess***	PhMe	80	0.2	**60**	0
13	4 (8)	TsOH	PhMe	80	0.2	62	0

a. Only the monodehydration product **33** (Scheme 3a) was formed; ***b.*** H_2SnCl_4 was prepared by mixing $SnCl_2•2H_2O$ and HCl; ***c.*** This entry refers to the reaction of **33**.

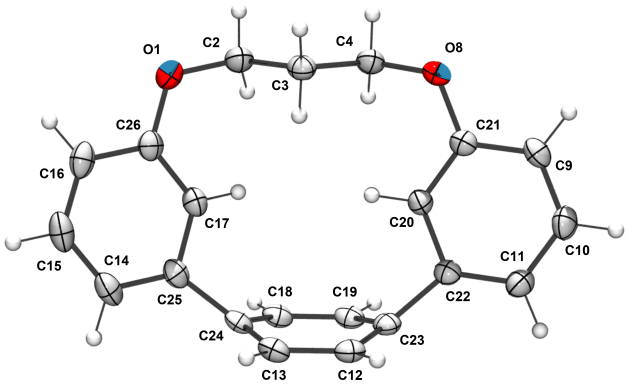


Figure 3. X-ray crystal structure of 1,5-dioxa[5](3,3")*p*-terphenylophane (**34**)

Graphical TOC