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

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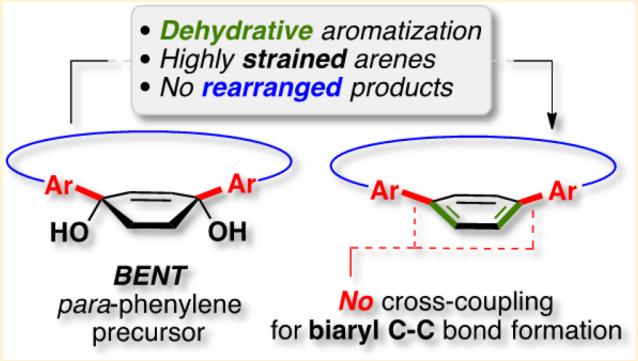
Supporting Information

ABSTRACT: A series of *p*-terphenyl-based macrocycles, containing highly distorted *p*-phenylene units, have been synthesized. 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 *p*-phenylene units with up to 28.4 kcal/mol strain energy and deformation angles that sum up to 40°.



INTRODUCTION

Formation of biaryl bonds via transition metal-catalyzed, or mediated, cross-coupling reaction is a venerable transformation 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 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 buildup 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 unit or multiple arene units, then 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 *p*-phenylene subunits, particularly the haouamine alkaloids,[11] and the notion that macrocyclic benzenoid hydrocarbons may serve as templates in the 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 *p*-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 [6]paracylophane derivative **1** of Tobe et al.[13] and [1.1]paracyclophane **2** of Tsuji and co-workers,[14] the highly distorted π-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 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 formation of the arene system. Until 2014, no bent *p*-

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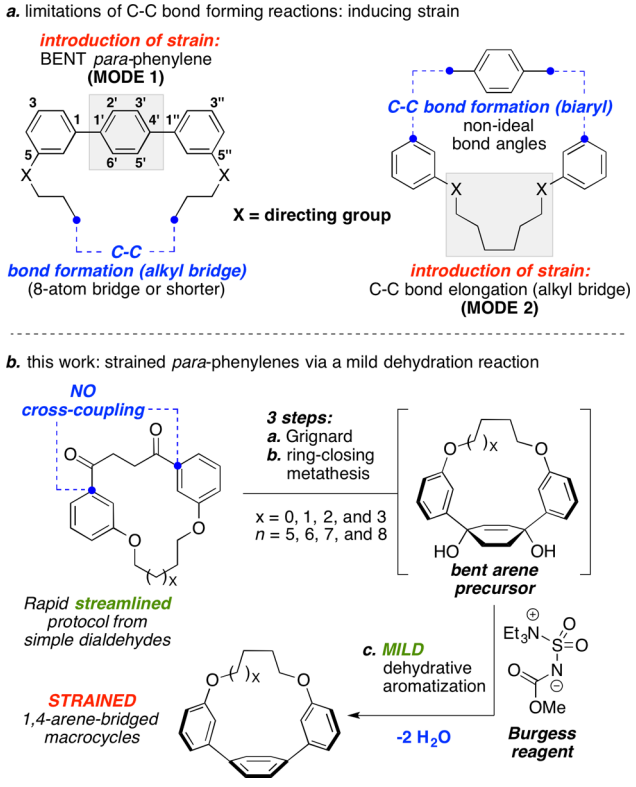


Figure 1. (a) Strain-inducing carbon−carbon bond-forming reactions. (b) Biaryl bond formation using a macrocyclic 1,4-diketone surrogate and a mild dehydrative aromatization reaction.

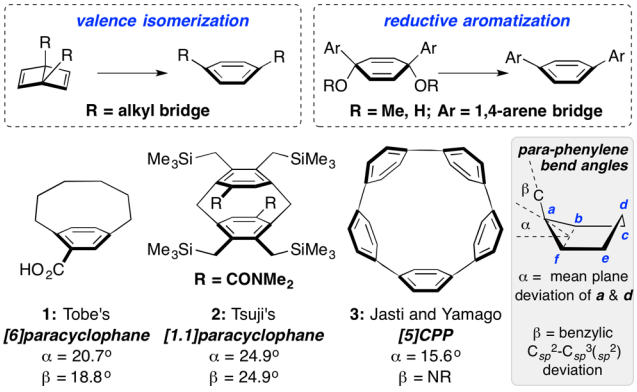


Figure 2. Valence isomerization and reductive aromatization strategies to highly distorted *p*-phenylene-containing molecules.

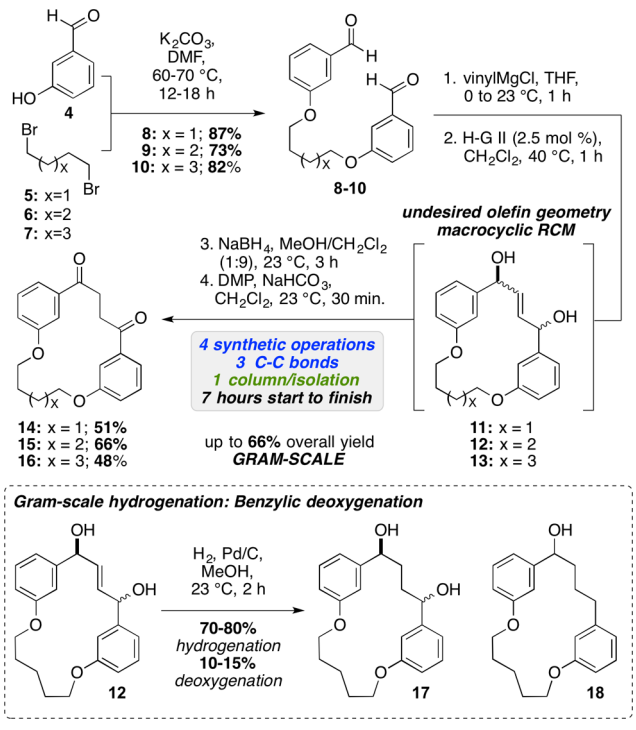
phenylene ring with an α angle greater than 15° had been synthesized by a nonvalence isomerization approach. Pioneering contributions from the groups of Bertozzi,[15] Itami,[16] Yamago,[17] and Jasti[18] on [*n*]cycloparaphenylenes ([*n*]CPP) rejuvenated this area of chemical synthesis, in the context of strained (macrocyclic) benzenoid nanohoops. The 2014 syntheses of [5]CPP[19,20] (**3**) rewrote 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 synthesized. The synthesis of this impressive nanostructure, and related homologues, has led to the development of powerful aromatization strategies that employ reductive (aromatization) protocols and not valence isomerization reactions (Figure 2).

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 *p*-phenylene unit. Our overlapping interests in the synthesis of natural products containing biaryl, nonplanar *p*-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 synthesis of highly strained *p*-phenylenes that are part of a polyaryl system; the X-ray crystal structure of the most distorted homologue; 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). 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**)

Scheme 1. Streamlined, Scalable Synthesis of Macrocyclic 1,4-Diones 11−13



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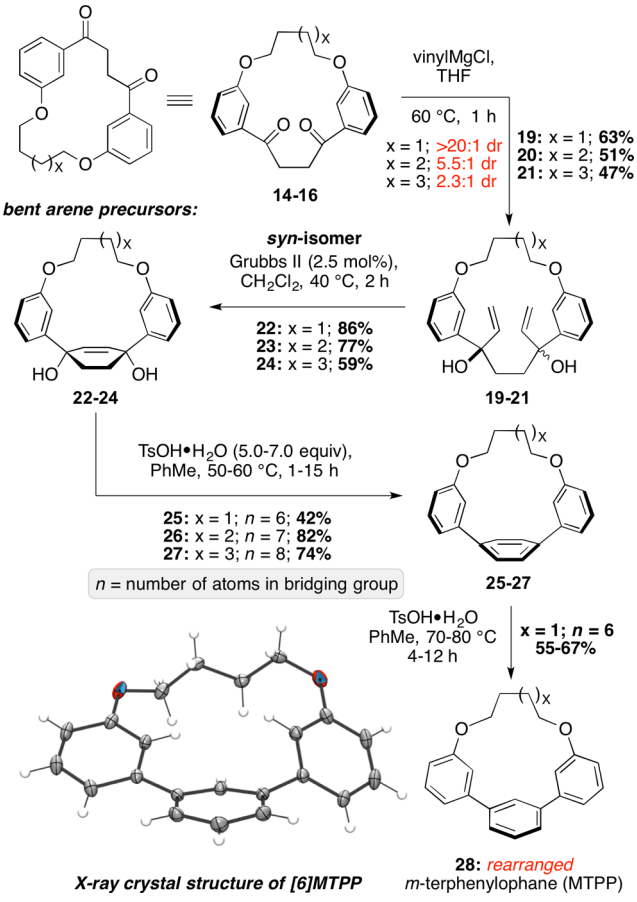
resulted in the production of a benzylic deoxygenation product **18** (ca. 15%). To circumvent this byproduct formation and streamline the four-step process to furnish gram-scale quantities of a homologous series of macrocyclic 1,4-diones, we explored alternative hydrogenation protocols. Inspired by 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 in dichloromethane afforded **11**–**13** as mixtures of alkene diastereomers, in which the trans-configured (undesired) olefin was the major product. After evaporation of the solvent, the residue was dissolved in 1:9 methanol/dichloromethane, and addition of 3.0–5.0 equiv of $NaBH_4$ resulted in smooth transfer hydrogenation of the olefin in less than 3 h, without any benzylic deoxygenation. It is noteworthy that only 2.5 mol % H-G II catalyst was used in both the metathesis and transfer hydrogenation reactions, all of which was added at the RCM stage. Furthermore, use of 1:9 vs 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 mg 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 h 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 *p*-Phenylenes. Conversion of the 1,4-diketo bridging group into a strained 1,4-arene bridge (bent *p*-phenylene) was previously accomplished by employing a three-step reaction protocol. The first step involved a Grignard reaction with vinylmagnesium chloride. The diastereoselectivity of this reaction was critical to 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 the synthesis of a homologous series of macrocyclic 1,4-diketones was completed, 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, diastereomeric ratio (dr) 2.3:1; **20**, x = 2, dr 5.5:1; Scheme 2), while smaller macrocyclic rings (16- and 15-membered) gave much higher diastereoselectivities (**19**, x = 1, dr > 20:1, Scheme 2; **30**, x = 0, dr > 20:1, 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 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 in *p*-toluenesulfonic acid (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 byproducts, 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 equiv 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 similar "backbone" rearrangements occur when CPPs are subjected to protic acid- 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]

To investigate this strain-induced rearrangement reaction of (3,3″)*p*-terphenylophanes to (3,3″)*m*-terphenylophanes, we synthesized a smaller macrocyclic homologue, **31**. Synthesis of **31** proceeds along the same pathway previously described for **22**–**24**. It is worth mentioning that the yield of the four-step 1,4-diketone synthesis is lower than the three previously described homologues (**14**–**16**) at 22%. We attribute this lower

Scheme 2. Conversion of 1,4-Diones 14–16 to *p*-Terphenylophanes 25–27



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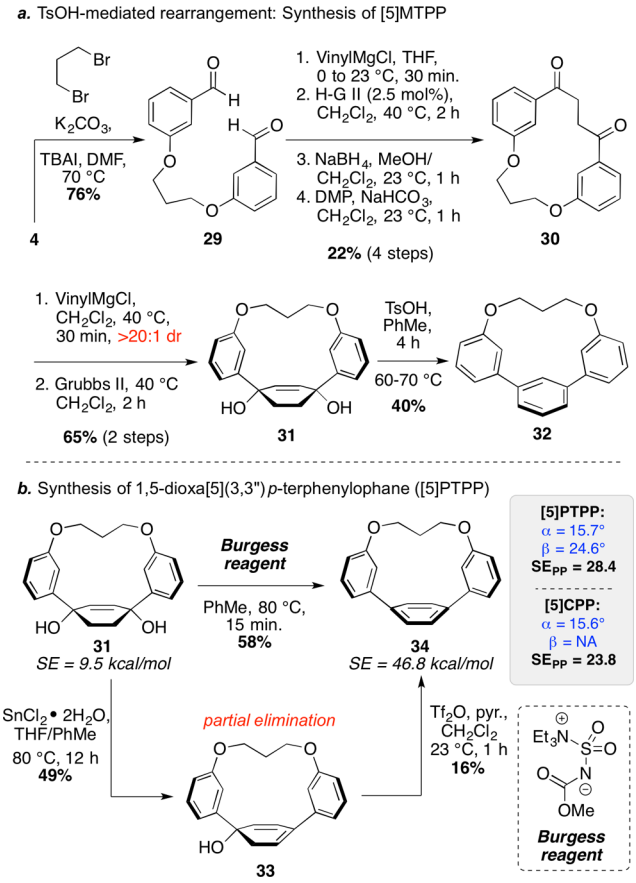
yield process to reduced solubility of the macrocyclic RCM product, as well as the propensity for the precursor diene to form a higher molecular weight metathesis byproduct at 15 mM concentration.[26] Nonetheless, synthetically useful quantities of **30** can be prepared in short order. Grignard reaction of **30** with vinylmagnesium chloride demonstrated the same macrocyclic trend as described above (**14**–**16** to **19**–**21**, dr > 20:1, 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 temperature to 70 °C furnished only the rearranged 1,5-dioxa[5](3,3″)*m*-terphenylophane (**32**) product after 4 h (Scheme 3a and Table 1, entry 3). Thin-layer chromatography

Scheme 3. Synthesis of (a) Rearranged *m*-Terphenylophane 32 under Protic Acid Conditions and (b) [5]PTPP (34) under Nonprotic Acid Conditions



(TLC) analysis of the reaction mixture revealed that an initially formed product (**34**, R_f = 0.43) was quantitatively converted into a slightly slower-moving byproduct (**32**, R_f = 0.41). This analysis is identical, albeit more rapid, to that observed for 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 *p*-phenylenes, we sought an alternative dehydration strategy.

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[27] to aromatize cyclohexane-1,4-diol units of [*n*]CPP macrocyclic precursors, gave a low yield of **25** with formation of the rearranged isomer **28** (entry 4, Table 1). Use of a modification of the tin(II) chloride dihydrate-mediated aromatization reaction of Yamago and co-workers,[20] which was used successfully to synthesize [5]CPP (**3**), 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 nonacidic 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 Burgess reagent,[29] without 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 min saw rearrangements occur at the n = 7 homologue stage (Table 1, entry 11). Indeed, subjecting all remaining cyclohexe-2-ene-1,4-diol precursors (**22**–**24**, 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 8–10 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.

X-ray Crystal Structure and Strain Energy of a Highly Distorted *p*-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 *p*-phenylene ring of the macrocycle (Figure 3). 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 *p*-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 **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 *p*-phenylene unit, the [1.1]paracyclophane derivative **2** of Tsuji and co-workers.[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 B3LYP density functional theory level 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 *p*-phenylene ring is approximately 4.6 kcal/mol greater than that of the average SE/*p*-phenylene unit in [5]CPP, the most strained CPP homologue 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/*p*-phenylene of 36 kcal/mol. Currently, we are pursuing the synthesis of a smaller homologue 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.

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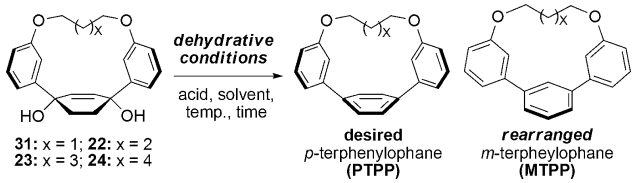
Table 1. Optimized Conditions for Conversion of Macrocyclic Cyclohex-2-ene-1,4-diols 22−24 and 31 to *p*-Terphenylophanes 25−27 and 34



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)	$SnCl_2{\cdot}2H_2O$	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 $SnCl_2{\cdot}2H_2O$ and HCl. [c]This entry refers to reaction of **33**.

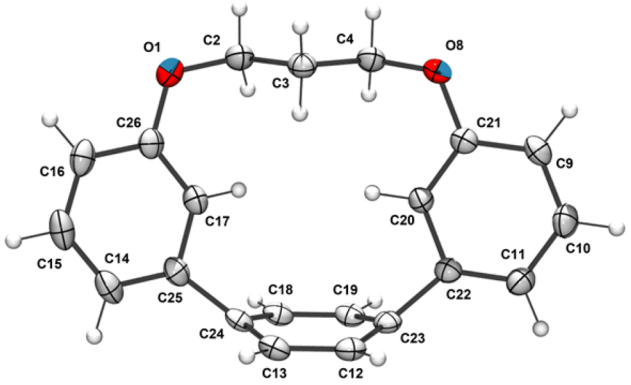


Figure 3. X-ray crystal structure of 1,5-dioxa[5](3,3″)*p*-terphenylophane (**34**).

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, can be completed in just 7 h, 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 nonprotic 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 synthesis of highly distorted *p*-phenylene units that are part of polyaryl systems, or benzenoid macrocycles. In the case of the smallest homologue synthesized, over 37 kcal/mol SE is generated upon elimination of two molecules of water (**31**−**34**, Scheme 3b). Applications of this reaction to a smaller homologue 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00538.

Three figure with structures for **35**−**37**, **34**, and **28**; one scheme with possible mechanistic pathways for *p*- to *m*-terphenyl rearrangement; additional text with detailed experimental procedures and characterization data; ^1H and ^{13}C NMR spectra for all new compounds; four tables listing crystal data and structure refinement and bond lengths and angles for **34** and **28**; and DFT computed strain energies of **31** and **34** (PDF)

Crystallographic file for **34** (CIF)

Crystallographic file for **28** (CIF)

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Notes

The authors declare no competing financial interest.

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