

Optically Active Calixarenes Conduced by Methylene Substitution

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Calixarenes have become one of the most popular scaffolds for constructing receptors for supramolecular chemistry.¹ In an effort to extend the use of scaffolds to chiral recognition events, there has been an interest in chiral calixarenes. The easiest approach is to covalently attach a chiral molecule to either the upper rim (benzene ring) or lower rim (oxygen) of the calixarene, and this approach has been studied extensively. A much more difficult and much less frequently encountered method is to generate a chiral calixarene by controlling the substitution pattern of the different benzene rings in the calix.² For example, calix[4]arene **1** is chiral when $R^3 = H$ and $R^1, R^2 \neq H$ and can be isolated in optically active form as long as the ring flip to **2** is prevented by having large enough substituents *R* on the phenolic oxygens (at least *n*-propyl for *R* is required) (Figure 1). When the ring flip occurs, **1** becomes racemic, since **2** is its enantiomer. Calix[4]arene **1** can also be obtained in optically active form if $R^3 \neq H$, since in this case the ring flip gives **2**, which is a diastereomer. An even more difficult task is to prepare calixarenes that are chiral as the result of introduction of substituents on the methylene bridges. In fact, although a number of mono-, di-, and tetramethylene-substituted calix[4]arenes have been prepared in the last two decades,³ all were prepared as racemic compounds, and none have been isolated in optically active form. The reason for this is clearly linked to the methods for their preparation, which are based on introduction of the substituents via reactions that involve intermediates with either radicals, cations, or carbanions at the methylene carbon or the intermediacy of compounds that have sp^2 carbons bridging the rings. Calix[4]arene **3** has a plane of symmetry when $R^1 = R^2$ and thus is not chiral; however, if this is not the case and if $R^3 \neq R^4$, then **3** becomes chiral and should be isolable in optically active form, since the ring flip to **4** would give a diastereomer.

We have previously developed a new method for the synthesis of calix[4]arenes that involves triple annulation of the biscarbene complex **5** with bisalkyne **6** in a process that constructs three of the five rings of the calix[4]arene in a single step (Scheme 1).⁴ The yields for this process range only from 22 to 41% but nonetheless are comparable or superior to those for the macrocyclization steps in other methods for the synthesis of unsymmetrical calix[4]arenes. It was envisioned that it should be possible to utilize this method for the synthesis of methylene-substituted calix[4]arenes by incorporating substituents in one or both of the methylenes in the biscarbene complex **5** and/or one or both of the methylenes in diyne **6**. Indeed, we report here a method that for the first time allows the direct construction of calix[4]arenes in optically active form where the chirality results from substitution at the methylene bridges.

The synthesis of the desired bisalkyne **11** is convergent with that of the biscarbene complex **13** (Scheme 2). Diol **10** could be prepared from dialdehyde **8** using Pu's method for the asymmetric addition of alkynes to aldehydes.⁶ This reaction gave diol (*S,S*)-**9** in 56% yield and 99.2% ee along with 42% yield of the corresponding meso compound. After desilylation and methylation

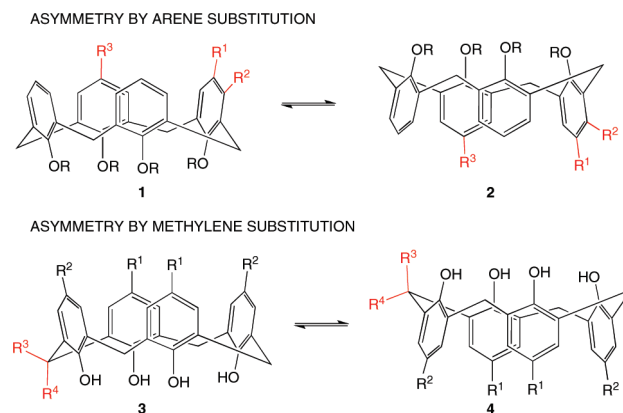
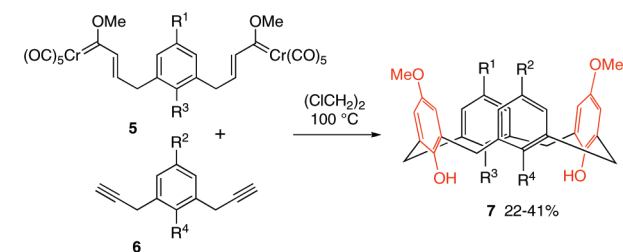
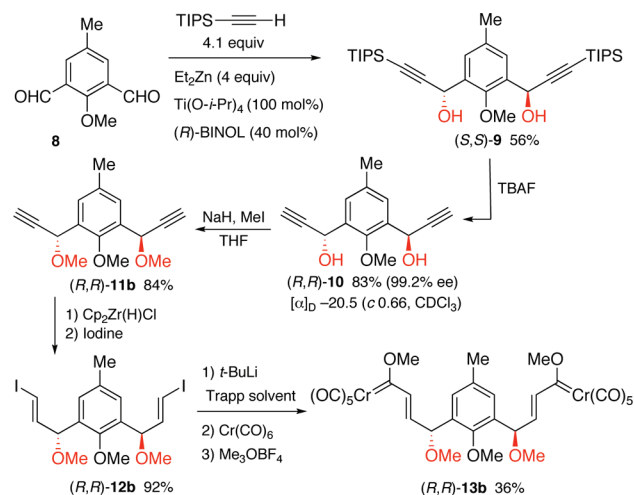


Figure 1. Intrinsically chiral calix[4]arenes.

Scheme 1

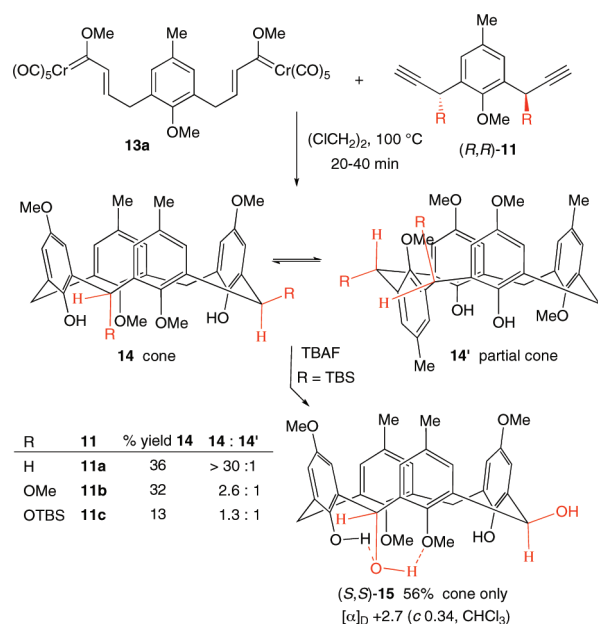


Scheme 2



of diol (*R,R*)-**10**, the alkyne functions in (*R,R*)-**11b** were hydrozirconated, and upon quench with iodine, bis-*trans*-vinyl iodide **12b** was obtained in 92% yield. The biscarbene complex (*R,R*)-**13b** was then prepared by a modification of the Fischer protocol involving the addition of a bisvinyl lithium to chromium hexacarbonyl followed by methylation of the intermediate metal acylate.

Scheme 3

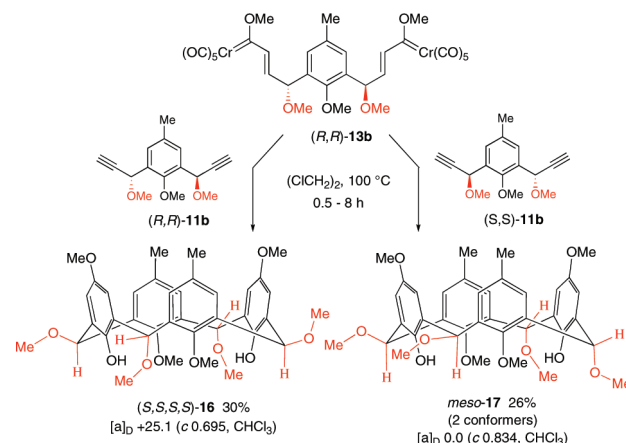


Chiral calix[4]arenes with substitution on two of the methylene bridges can be synthesized by reacting the substituted carbene complex **13a** with the disubstituted diyne **11** (Scheme 3). The dimethoxy diyne **11b** reacted to give calix[4]arene **14b** in 32% yield, which exists as 2.6:1 mixture of rapidly interconverting conformers that can be observed on the NMR time scale.⁷ Extensive analysis of 1D NOE and NOESY experiments allowed the assignment of the major species as the cone conformer **14b**, which has one equatorial and one axial methoxy group.⁸ The minor conformer could be only tentatively assigned as the partial cone conformer **14b'** shown in Scheme 3, as a precise assignment of all the protons and through-space interactions could not be made. The bis-OTBS diyne (S,S)-**11c** reacted to give a lower yield (13%) of the bis-OTBS-substituted calix[4]arene **14c** as a 1.3:1 mixture of the same conformers. Removal of the TBS groups gave calix[4]arene (S,S)-**15**, which exists exclusively as the cone conformer. This shift in conformer equilibrium can be interpreted as a consequence of the hydrogen-bonding interactions that exist in the cone conformer of **15** but not in the partial cone conformer.

The reaction of biscarbene complex (R,R)-**13b** with diyne (R,R)-**11b** gave calix[4]arene **16** in 30% yield (Scheme 4); despite the fact that **16** has two axial and two equatorial methoxy groups, it exists as a single conformer (cone) with a pair of two-hydrogen singlets at 5.05 and 6.08 ppm.⁸ One would predict that the reaction of complex (R,R)-**13b** with diyne (S,S)-**11b** would produce an optically inactive meso calix[4]arene. Indeed, this reaction gave a 26% yield of calix[4]arene **17**, which is optically inactive but exists as a 1:1 mixture of conformers that could not be identified because of the complexity of the ^1H NMR spectrum. Calix[4]arenes **16** and **17** are stereoisomers that differ in that **16** has a trans,cis,trans relative relationship of the methoxy substituents whereas **17** has a cis,trans,cis relative relationship.

In summary, a method for the synthesis of optically active calix[4]arenes that are chiral as a result of substitution on the methylene bridges has been described. It has been shown that this method is suitable for the synthesis of optically active di- and

Scheme 4



tetramethoxy-substituted calix[4]arenes. The stereoregulation possible in this approach has been demonstrated in the controlled synthesis of two different diastereomers of a tetramethoxy-substituted calix[4]arene.

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Supporting Information Available: Synthetic procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001. (b) Sliwa, W.; Kozłowski, C. *Calixarenes and Resorcinarenes: Synthesis, Properties and Applications*; Wiley-VCH: Weinheim, Germany, 2009.
- (2) For recent examples, see: (a) Sarkar, A.; Nethaji, M.; Krishnamurthy, S. S. *J. Organomet. Chem.* **2008**, *693*, 2097. (b) Xu, Z.-X.; Li, G.-K.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2008**, *64*, 8668. (c) Narumi, F.; Matsumura, N.; Sasagawa, N.; Natori, K.; Kajiwara, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1470. (d) Xu, Z.-X.; Zhang, C.; Yang, Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2008**, *10*, 477. (e) Shirakawa, S.; Tanaka, Y.; Kobari, T.; Shimizu, S. *New J. Chem.* **2008**, *32*, 1835. (f) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Eur. J. Org. Chem.* **2008**, 5957.
- (3) (a) Tabatabai, M.; Vogt, W.; Bohmer, V. *Tetrahedron Lett.* **1990**, *31*, 3295. (b) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657. (c) Grüttner, C.; Böhmer, V.; Vogt, W.; Thondorf, I.; Biali, S. E.; Grynspan, F. *Tetrahedron Lett.* **1994**, *35*, 6267. (d) Sartori, G.; Bigi, F.; Porta, C.; Maggi, R.; Peri, F. *Tetrahedron Lett.* **1995**, *36*, 8323. (e) Biali, S. E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynspan, F.; Paulus, E. F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938. (f) Böhmer, V. *Liebigs Ann./Recl.* **1997**, 2019. (g) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pelinghelli, M. A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 13037. (h) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967. (i) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667. (j) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (k) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741. (l) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136. (m) Biali, S. E. *Synlett* **2003**, 1. (n) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 3634. (o) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7685. (p) Simaan, S.; Biali, S. E. *J. Phys. Org. Chem.* **2004**, *17*, 752. (q) Simaan, S.; Biali, S. E. *Org. Lett.* **2005**, *7*, 1817. (r) Kuno, L.; Seri, N.; Biali, S. E. *Org. Lett.* **2007**, *9*, 1577. (s) Columbus, I.; Biali, S. E. *Org. Lett.* **2007**, *9*, 2927. (t) Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 2598. (u) Kuno, L.; Biali, S. E. *J. Org. Chem.* **2009**, *74*, 48.
- (4) (a) Gopalsamuthiram, V.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 13936. (b) For a review of the reactions of Fischer carbene complexes and alkynes, see: Waters, M. L.; Wulff, W. D. *Org. React.* **2008**, *70*, 121.
- (5) Morgan, B.; Dolphin, D. *J. Org. Chem.* **1987**, *52*, 5364.
- (6) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855.
- (7) This reaction was performed on (S,S)-**11b**.
- (8) For a review of the conformations of methylene-substituted calixarenes, see ref 3p.

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