

The synthesis of optically active calix[4]arenes with one or three substituents on the methylene bridges†

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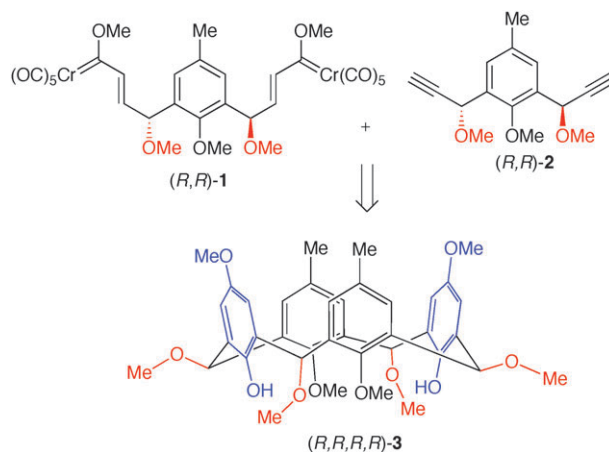
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A facile synthesis of optically active mono and trisubstituted calix[4]arenes is described wherein the chirality at the methylene bridges arises from centers of chirality present in the diyne and the bis-carbene complex from which they are constructed.

Calixarenes are among the small group of privileged scaffolds for the construction of supramolecular hosts.¹ Although a plethora of synthetic methods have been developed for the synthesis of calixarenes, very few methods exist for the preparation of calixarenes with substituents in the methylene bridges of the calix. At present, only a handful of methods have been described in the literature that allow for the preparation of mono-, 1,2 and 1,3-di-, and tetra-substituted calix[4]arenes where all of the substituents are on the methylene bridges.² 1,2,3-Tri-substituted calix[4]arenes with all substituents on the methylene bridges have not been reported. While some of these methods afford the product as a single diastereomer, none of these methods offer the potential to prepare optically active variants. This is a consequence of the methods used for linking the arene rings to the methylene spacers since they involve intermediates with either radicals, cations or carbanions at the methylene carbon or involve the intermediacy of compounds that have sp² carbons bridging the rings.

In this regard, we recently demonstrated the utility of the reaction of diynes with bis-carbene complexes in the first synthesis of optically active di- and tetra-substituted calix[4]arenes (Scheme 1).³ This process generates two of the benzene rings of the calixarene as well as the macrocyclic ring in a single step. With this triple annulation protocol we were able to gain stereoselective access to enantiomerically pure 1,2-dimethoxy calix[4]arenes and to different diastereomers of tetra-methoxy calix[4]arenes also in optically pure form. We would like to report herein the synthesis of the first examples of optically active mono- and tri-substituted calix[4]arenes with all substituents on the methylene bridges.

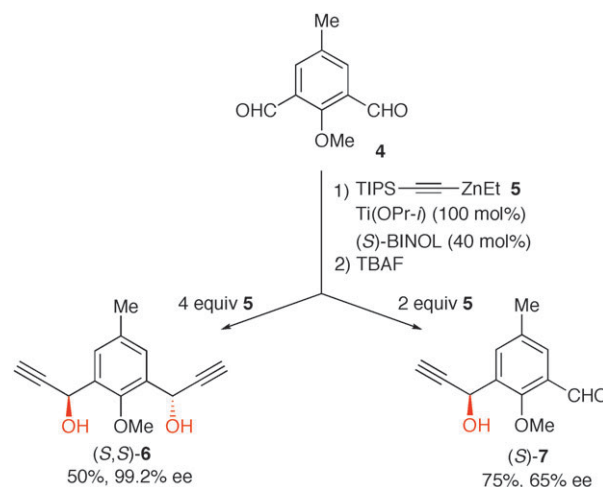
During the optimization studies for the synthesis of bis-alkynols by the addition of zinc acetylide⁴ to the dialdehyde **4**, we noted that the complete conversion of the dialdehyde **4** requires the addition of 4 equivalents of the zinc acetylide and gives, after desilylation, the diol (*S,S*)-**6** in 50% yield and 99.2% ee along with a 38% yield of the meso diol corresponding to **6** (Scheme 2). The use of two equivalents of the zinc acetylide gives the mono-addition product **7** in 75% yield



Scheme 1

and 65% ee along with a 13% yield of the bis-addition product.

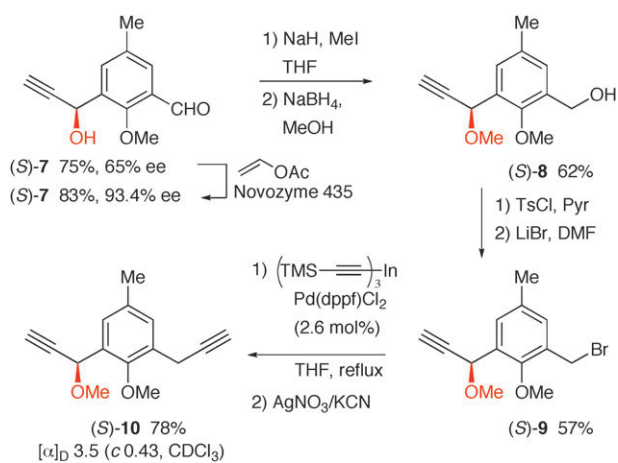
Advantage was taken of this outcome to access the mono-substituted diyne (*S*)-**10** so that a greater diversity of methylene substituted calix[4]arenes could be achieved. The optical purity of **7** was only 65% ee but it was found that this could be increased to 93.4% ee with enzymatic kinetic resolution with Novozyme 435 and vinyl acetate (Scheme 3).⁵ The key carbon-carbon bond forming step in the synthesis of (*S*)-**10** is the alkylation of benzyl bromide **9** which utilizes a palladium catalyzed coupling of an alkynyl indium reagent.⁶ According to the observations of Pu,⁴ the absolute configuration of **7** is expected to be (*S*) when using (*S*)-BINOL. This configurational assignment was confirmed by the method of Horeau (see ESI†). On this basis the assignment of the



Scheme 2

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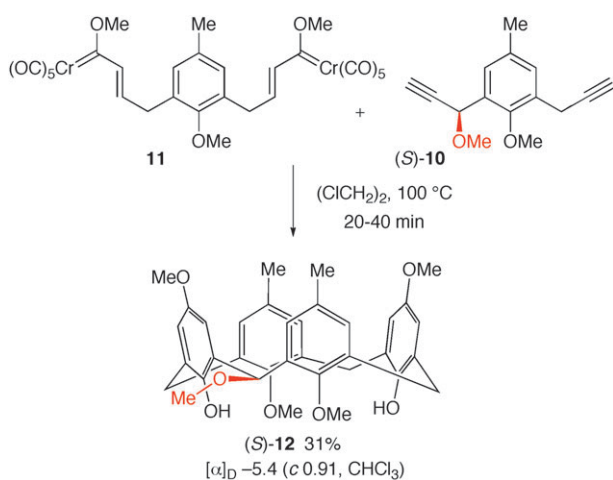


Scheme 3

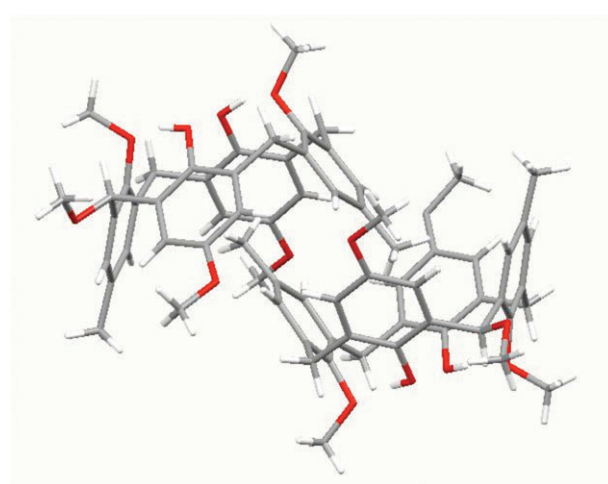
absolute configuration of all calixarenes was made assuming that the configuration of diyne (*S*)-**10** does not change during the triple annulation.

The first chiral calix[4]arene that we attempted to prepare with diyne (*S*)-**10** was the mono-methoxy derivative **12**. The reaction of the unsubstituted carbene complex **11**⁷ and 1 equivalent of the mono-methoxy substituted diyne (*S*)-**10** (93.4% ee) was carried out at 2.5 mM in 1,2-dichloroethane at 100 °C to give a single product as indicated by TLC and ¹H NMR which was isolated in 31% yield and identified as the calix[4]arene (*S*)-**12**. The ¹H NMR spectrum indicated that this compound exists exclusively as the cone conformer and the singlet at δ = 5.98 ppm indicates that the methoxy group is in an equatorial position.^{2,8}

The calixarene (*S*)-**12** as drawn in Scheme 4 would result from the approach of the carbene complex **11** from the backside of (*S*)-**10**. Approach from the frontside of (*S*)-**10** would give a diastereomeric calixarene that is a diastereomer of (*S*)-**12** where the cone conformer would have an axial methoxy group. However, the flip of all the phenyl rings through the annulus would be expected to be rapid for this compound and would produce a compound that would be in identity with (*S*)-**12**. Since only a single diastereomer of (*S*)-**12** is seen, it must be the case that an equatorial methoxy is significantly



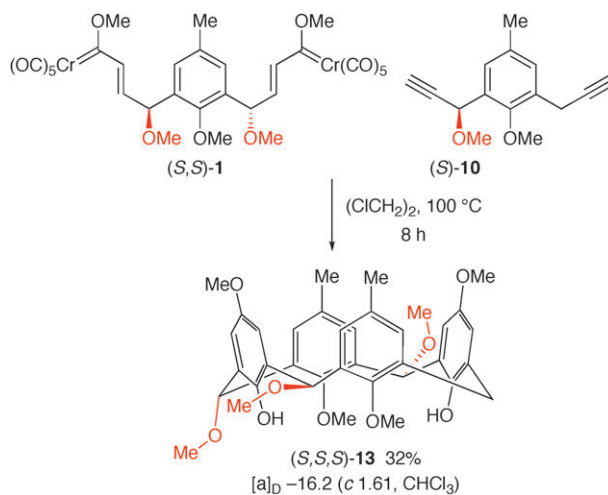
Scheme 4

Fig. 1 Crystal structure of (*S*)-**12** visualized by the Mercury program.

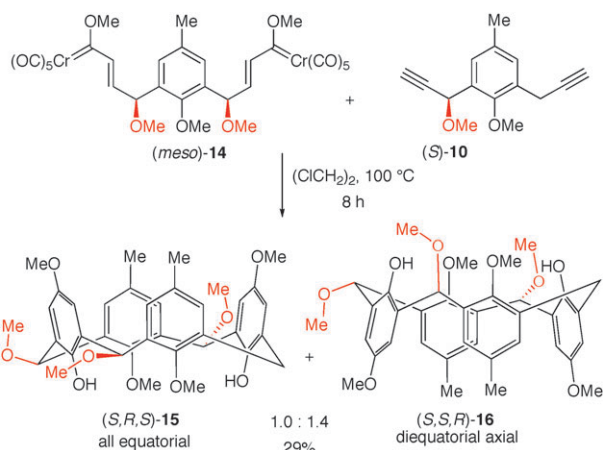
more stable than an axial methoxy. The ¹H NMR assignment of (*S*)-**12** as having the cone conformation was confirmed by an X-ray diffraction analysis (Fig. 1). The X-ray structure reveals that (*S*)-**12** adopts the cone former that has the methoxyl in an equatorial position. Interestingly, the analysis reveals that there are two molecules in the unit cell that are interlocked by the mutual projection of a methyl group on the *para*-position of the outer rim into the bowl of the other calixarene.

The first example of a 1,2,3-trisubstituted calix[4]arene was prepared from the reaction of the diyne (*S*)-**10** and the bis-carbene complex (*S,S*)-**1**³ which has both of its methylenes substituted with methoxy groups. This reaction gave the (*S,S,S*)-tri-methoxycalix[4]arene **13** in 32% yield which by its ¹H NMR spectrum exists as the cone conformer as shown in Scheme 5, which has two equatorial and one axial methoxy groups. As with the formation of (*S*)-**12**, a diastereomer of **13** is possible. This diastereomer has one equatorial and two axial methoxy groups and a ring flip would be expected to preferentially favor (*S*)-**13**.

Two diastereomers are possible from the reaction of diyne (*S*)-**10** with the meso-bis-carbene complex **14**. Indeed, this reaction gave a 1.0 : 1.4 mixture of diastereomers (*S,R,S*)-**15**



Scheme 5



Scheme 6

and **(S,S,R)-16** in a combined 29% yield (Scheme 6). Although they could not be completely separated, careful gradient elution from silica gel did give a pure fraction of the diastereomer **(S,R,S)-15** with the remainder as an enriched fraction of the **(S,S,R)-16** (4.1 : 1.0). The structures of these diastereomers are indicated in Scheme 6 with **15** having all equatorial methoxyl groups and **16** having two equatorial and one axial methoxy groups. These conformers would be expected to be more stable than the ring-flipped diastereomers with three axial methoxyl groups in the case of **15** and two axial and one equatorial methoxy groups in the case of **16**.

In summary, the first synthesis of optically active mono and tri-substituted calix[4]arenes substituted on the methylene carbons has been achieved by transfer of chirality from the unsymmetrical mono-methylene substituted diyne **(S)-10** that has been obtained selectively by controlled addition to dialdehyde **4**.

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