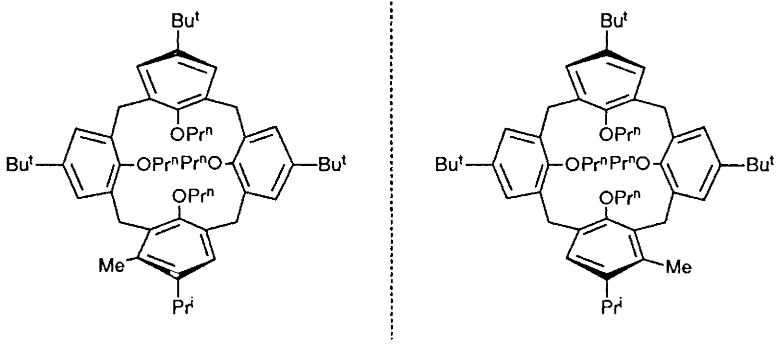
Synthesis and Optical Resolution of an Asymmetrically Substituted Calix[4]arene

Seiji Shinkai,* Takashi Arimura, Hirosuke Kawabata, Hiroto Murakami, Koji Araki, Koji Iwamoto and Tsutomu Matsuda

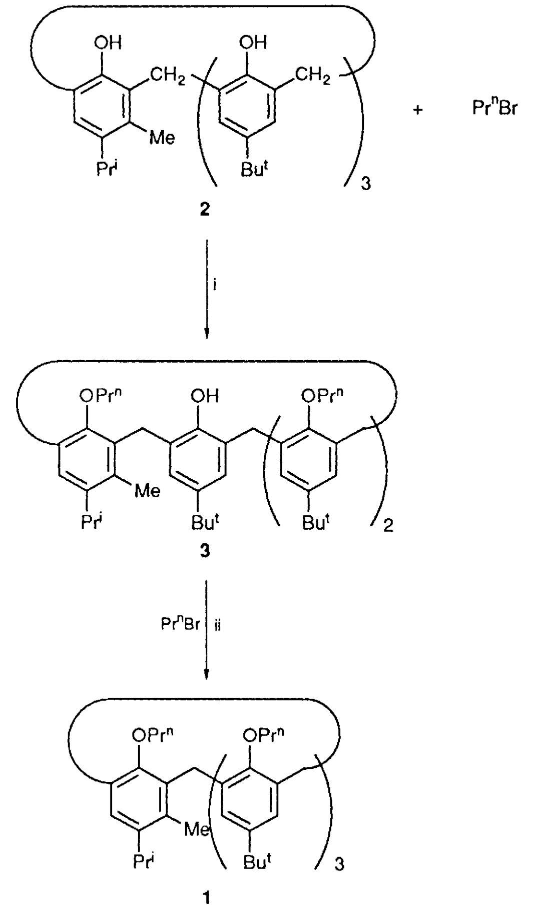
Department of Organic Synthesis, Faculty of Engineering, Kyusyu University, Higashi-ku, Fukuoka 812, Japan

A cone-shaped, asymmetrically substituted calix[4]arene, **1**, has been synthesized and successfully optically resolved for the first time.

Calix[4]arenes are cyclic tetramers made up of phenol and formaldehyde. Recently, Böhmer[1] and Vicens[2] synthesized calix[4]arenes without a plane of symmetry. Their research aimed to provide evidence for the existence of the optical isomers expected for this class of asymmetrically substituted calix[4]arenes. For example, calix[4]arenes with four different substituents should result in racemates. However, they were unable to discover any evidence for such asymmetry, probably owing to racemisation *via* rapid ring inversion. The dynamic ^{1}H NMR spectrum of the ArCH$_2$Ar methylene protons of calix[4]arenes shows a pair of doublets at low temperature and a sharp singlet at high temperature.[3,4] This indicates that in conventional calix[4]arenes ring inversion takes place at a speed comparable with that of the NMR time scale.[5] This suggests that optical resolution should be possible under conditions where the ring inversion is sufficiently suppressed. The ring inversion can be readily inhibited by introducing bulky substituents (*e.g.* Pr^n) on the OH groups.[6,7] However, O-substitution results in a mixture of conformational isomers known for calix[4]arenes (*e.g.* 'cone,' 'partial cone,' *etc.*). Thus, one has to isolate, prior to optical resolution, a pair of racemates from many conformational isomers. A new *O*-substitution method is required which selectively affords only one conformational isomer. After trial-and-error, we found that when Ba(OH)$_2$ is used as base, the O-substitution reaction affords only a 'cone' isomer. This breakthrough enabled us to synthesize conformationally-fixed, cone-shaped **1** and to optically resolve the racemates by an HPLC method. In **1**, the



1
(showing possible racemates)



Scheme 1 *Reagents*: i, BaO, $\mathrm{Ba(OH)_2{\cdot}8H_2O}$, dimethylformamide (DMF); ii, NaH, tetrahydrofuran (THF)–DMF

m-methyl group serves as a source of ring asymmetry. This is the first example of the successful optical resolution of an asymmetrically substituted calix[4]arene.

$\mathrm{Ba(OH)_2}$ is used for the synthesis of tri-*O*-alkylcalix[4]arenes.[6] In the reaction of *p*-t-butylcalix[4]arene and $\mathrm{Pr^nBr}$, we unexpectedly obtained cone-shaped tri-*O*-n-propyl-*p*-t-butylcalix[4]arene. The conformation of calix[4]arenes is determined when the third $\mathrm{Pr^n}$ group enters and remains unaltered when the fourth $\mathrm{Pr^n}$ group enters.[8] We thus designed reaction Scheme 1 for the synthesis of asymmetrically-substituted, cone-shaped **1**.† Compound **2** was synthesized from 2,6-bis(bromomethyl)-4-isopropyl-3-methylphenol and 2,6-bis(2-hydroxy-5-t-butylphenylmethyl)-4-*t*-butylphenol under high dilution conditions ($\mathrm{TiCl_4}$, reflux in dioxane):‡ m.p. 265–266 °C, yield 9%, *m/z* 648.§

Compound **2** was tri-*O*-propylated with $\mathrm{Pr^nBr}$ in the presence of $\mathrm{Ba(OH)_2{\cdot}8H_2O}$ and BaO in DMF (Scheme 1) to give **3** (m.p. 251–253 °C, yield 45%, *m/z* 774). The conformation of **3** was assigned as 'cone' from the ^{1}H NMR spectrum: the signals for the $\mathrm{ArCH_2Ar}$ protons appeared as four pairs of

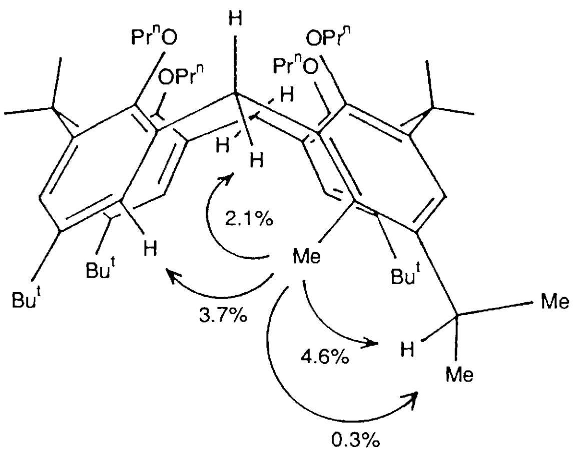


Fig. 1 Cone structure proposed for **1**. The numbers indicate NOE data with respect to the *m*-methyl group ($\mathrm{CDCl_3}$, 30 °C).

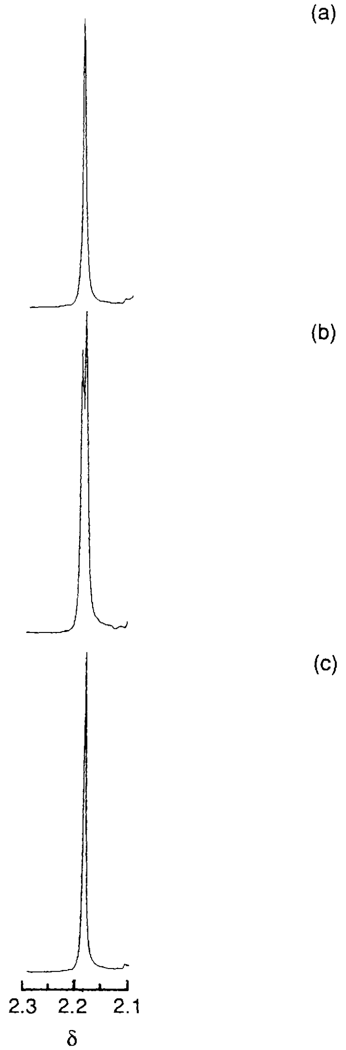


Fig. 2 Partial ^{1}H NMR spectrum for the *m*-methyl protons of **1** ($\mathrm{CDCl_3}$, 50 °C): (a) racemic **1**, (b) racemic **1** + Pirkle's reagent (1 : 20 mol/mol), (c) (+)-**1** + Pirkle's reagent (1 : 2 mol/mol). In (b), the peak to higher field is assigned to (+)-**1**.

---

† When **2** was directly tetra-*O*-propylated with $\mathrm{Pr^nBr}$ in the presence of NaH (this is the most typical method for *O*-alkylation), we obtained a mixture of conformational isomers (at least six spots were detected by TLC).

‡ A similar calix[4]arene including a 4-isopropyl-3-methylphenol unit has been synthesized by Vicens *et al.*[2]

§ Products were identified by their IR, ^{1}H NMR, and mass spectra and by elemental analysis.

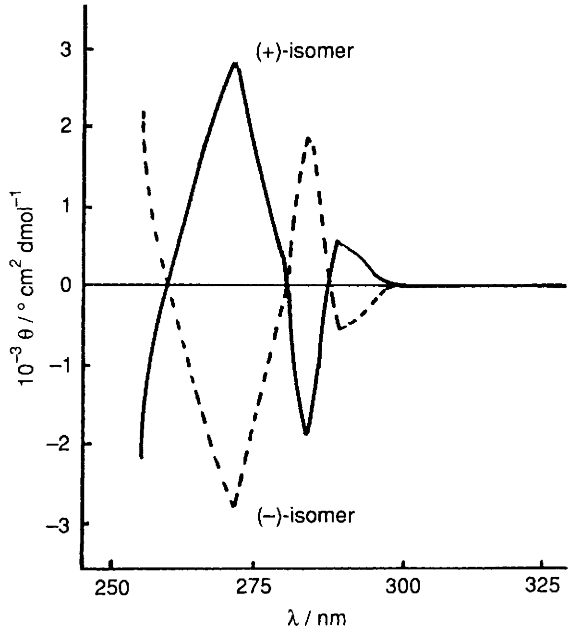


Fig. 3 CD spectra of **1** ($CHCl_3$, 25 °C)

doublets.¶ Finally, the fourth OH group in compound **3** was propylated with Pr^nBr in the presence of NaH in DMF–THF: m.p. 163–164 °C, yield 72%. The product was identified as **1** by spectroscopy and elemental analysis. The conformation of **1** (determined by ^1H NMR) was 'cone',|| indicating that the conformational change does not take place during this step. The proposed cone structure is illustrated in Fig. 1 with the NOE data.

In order to ascertain that **1** consists of a pair of ring-originating racemates, we measured the ^1H NMR spectrum in the presence of a chiral shift reagent, Pirkle's reagent [(*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol]. In $CDCl_3$, most signals were split into pairs (Fig. 2).

Racemic **1** was optically resolved by a LC method using a chiral packing column [Daicel Chiralpak OP(+)]. The mobile phase was n-hexane–propan-2-ol–methanol (1:3:16 v/v/v). The peak separation was almost complete. We separated the eluent into three fractions and obtained about 35 mg of (+)-**1** from the first fraction and 25 mg of (−)-**1** from the third fraction from 100 mg of racemic **1**.

The ^1H NMR spectrum in the presence of Pirkle's reagent and the HPLC analysis showed that the optical purity of (+)-**1** is 100% (Fig. 2), whereas that of (−)-**1** is somewhat inferior because of 'tailing' of (+)-**1** (95% optical purity); (+)-**1** showed $[\alpha]_D^{25}$ + 255° (*c* 0.08, $CHCl_3$). The circular dichroism spectra are shown in Fig. 3: λ_{max} 271 (θ +2830) and 284 nm (θ − 1890 deg cm^2 $dmol^{-1}$) for (+)-**1**. The symmetrical spectra indicate that these compounds are optical isomers.

We are indebted to Dr K. Tachibana (Daicel Co. Ltd.) for the separation of racemic **1**.

Received, 18th June 1990; Com. 0/02716B

¶ *NMR Data* for **3**: δ_H ($CDCl_3$) 3.15, 3.16, 3.19, 3.37 (H_{exo}), 4.27, 4.29, 4.41, 4.46 (H_{endo}). This split pattern is commensurate with a 'cone' conformation. Detailed examination of the ^1H NMR spectrum (including NOE studies) indicates that the phenol unit proximal to the 4-isopropyl-3-methylphenol unit remains unpropylated.

|| *NMR Data* for **1**: δ_H ($CDCl_3$) 3.10, 3.11, 3.12, 3.37 (H_{exo}), 4.40, 4.41, 4,42, 4.43 (H_{endo}). This split pattern is commensurate with a 'cone' conformation.

References

1 V. Böhmer, F. Marschollek and L. Zetta, *J. Org. Chem.*, 1987, **52**, 3200.
2 H. Casabianca, J. Royer, A. Satrallah, A. Taty-C and J. Vicens, *Tetrahedron Lett.*, 1987, **28**, 6595.
3 C. D. Gutsche, *Acc. Chem. Res.*, 1983, **16**, 161.
4 C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.*, 1985, **107**, 6052.
5 K. Araki, S. Shinkai and T. Matsuda, *Chem. Lett.*, 1989, 581.
6 C. D. Gutsche, B. Dhawan, J. A. Levined, K. Hyun and L. J. Bauer, *Tetrahedron*, 1983, **39**, 409.
7 K. Araki, K. Iwamoto, S. Shinkai and T. Matsuda, *Chem. Lett.*, 1989, 1747.
8 K. Iwamoto and S. Shinkai, *J. Am. Chem. Soc.*, to be submitted.