Elsevier Editorial System(tm) for Journal of Molecular Structure
Manuscript Draft

Manuscript Number: MOLSTRUC-D-15-00501R1

Title: Synthesis and conformational studies of calixarene analogoue chiral [3.3.1]metacyclophanes

Article Type: Research Paper

Keywords: Metacyclophanes; Macrocycles; Calixarenes; Intramolecular hydrogen bonding; O-methylation; Chirality

Corresponding Author: Prof. Takehiko Yamato, Ph.D.

Corresponding Author's Institution: Saga University

First Author: Md. Monarul Islam, Mc

Order of Authors: Md. Monarul Islam, Mc; Hirotsugu Tomiyasu, Mc; Pierre Thuéry, PhD; Taisuke Matsumoto, PhD; Junji Tanaka, PhD; Mark R. J. Elsegood, PhD; Carl Redshaw, Prof. PhD.; Takehiko Yamato, Ph.D.

Synthesis and conformational studies of calixarene analogue chiral [3.3.1]metacyclophanes

Md. Monarul Islam[a], Tomiyasu Hirotsugu[a], Pierre Thuery[b], Taisuke Matsumoto[c], Junji Tanaka[c], Mark R. J. Elsegood[d], Carl Redshaw[e] and TakehikoYamato[a]**

[a]*Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi 1, Saga-shi, Saga 840-8502, Japan. Fax: (internat.) + 81(0)952/28-8548.*
[b]*CEA / Saclay SCM, Bat. 125 91191 Gif-sur-Yvette*
[c]*Institute of Material Chemistry and Engineering, Kyushu University, 6-1, Kasugakoen, Kasuga 816-8580, Japan*
[d]*Chemistry Department, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK*
[e]*Department of Chemistry, The University of Hull, Cottingham Road, Hull, Yorkshire, HU6 7RX, UK*

Abstract: Trihydroxy[3.3.1]metacyclophane, which can be regarded as an unsymmetrical or incomplete "homocalix[3]arene", has been prepared from trimethoxy[3.3.1]metacyclophane by demethylation with trimethylsilyl iodide in MeCN. Di-*O*-methylation at the lower rim of trihydroxy[3.3.1]metacyclophane in the presence of K_2CO_3 in acetone afforded a novel inherently chiral calixarene–analogue, namely a macrocyclic [3.3.1]metacyclophane, possessing C_1 symmetry. The inherent chirality of the two conformers was characterized by ^{1}H NMR spectroscopy by addition of an excess of Pirkle's chiral shift reagent [(*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol], which caused a splitting of the OMe group and AB patterns corresponding to the methylene protons.

Keywords: Metacyclophanes / Macrocycles / Calixarenes / Intramolecular hydrogen bonding / *O*–methylation / Chirality.

* Corresponding author. Tel.: +81 952 28 8679; fax: +81 952 28 8548. E-mail address: yamatot@cc.saga-u.ac.jp (T. Yamato)

HIGHLIGHT

♦ Calixarene analogue [3.3.1]metacyclophane was synthesized by TosMIC method followed by Wolf–Kishner reduction.

♦ A chiral [3.3.1]metacyclophane was synthesized by selective *O*-methylation at lower rim of trihydroxy[3.3.1]metacyclophane.

♦ All synthesized [3.3.1]metacyclophanes adopt *partial-cone* conformation except trihydroxy-[3.3.1]metacyclophane.

1. Introduction

Calixarenes and related macrocycles have been receiving considerable attention due to their host–guest chemistry as ionophoric receptors [1,2] and potential enzyme mimics in biology [3–5]. The conformational characteristics of macrocyclic cyclophanes, especially those of calix[*n*]arenes, have been extensively investigated in the past decade [6,7]. Their phenolic hydroxyl groups are well ordered in a cyclic array due to strong intramolecular hydrogen bonding. C.D Gutsche reported [8] the role of hydrogen bonding in conformational mobolities of calix[*n*]arenes (n = 4–20). Kanters *et al*. have reported [9] that 27,28-diethoxy-*p*-*tert*-butylcalix[4]arene exhibits interconversion due to intramolecular hydrogen bondings. Considering the role of the hydrogen bonding, it is surprising that reports on the preparation of calix[3]arenes and their analogues containing three benzene rings and the characterization of their conformational mobility due to hydrogen bonding has been very limited [10–14]. First successful preparation of *p*-halocalix[3]arenes was reported in 1982 and no follow up reports have appeared [10]. This lack of research seems to be due to the much more strained structure of calix[3]arenes than larger calix[*n*]arenes. Homocalixarenes have been the subject of scientific interest for a couple of decades [14] and belong to a general class of calixarenes [1,2] in which the linker methylene bridges are partly or completely replaced by ethano or larger bridges [2,15,16]. Introduction of longer bridge into the methylene bridges of the conventional calixarenes, has rendered homocalixarene unique structural characteristics. One of the salient structural features is the self fine tuning of the conformations and the cavity sizes of the macrocycles. Such compounds have significantly different properties to those of their corresponding calixarene analogues.

Shinkai and co-workers have reported [11,12] that the introduction of substituents at the hydroxyl groups of hexahomotrioxacalix[3]arene led to conformational rigid structures, *i.e*. fixed conformations such as *cone* and *partial-cone*. Among the numerous methods of chemical modification of calixarenes, the *O*-alkylation of the phenolic hydroxyl groups or modification at

upper rim is of great importance which leads to form inherent chirality in conventional calixarenes [12,17–21]. Inherently chiral calixarenes are unusual types of chiral calixarenes which are not based on a chiral subunit but due to the absence of a plane of symmetry or an inversion center in the molecule [22–25]. Inherently chiral calixarenes are considered as promising host molecules for molecular recognition [26,27] and asymmetric catalyst [17]. A large number of racemic inherently chiral calixarenes have been reported and some of them have been resolved into the enantiomerically pure form [22–25]. Replacement of the bridging methylene linkage by hetero-atoms have attracted considerable interest as a new members of calixarene family [28–31] and most recent technique to synthesize inherent chiral calixarene analogues [32]. However, there are few reports concerning the introduction of substituent's at the hydroxyl groups of asymmetric or incomplete homocalix[3]arenes having three conformers; *i.e*. *cone* and 2-*partial-cone* and 3-*partial-cone* conformers (Fig. 1).

Insert Figure 1 in here

Due to the intramolecular hydrogen bond interactions between the lower-rim phenolic hydroxy groups of conventional calix[4]arenes, it adopts stable *cone*, *partial-cone*, 1,3-*alternate* and 1,2-*alternate* conformations [6,7]. In contrast to the conventional calix[4]arenes, the conformational isomerism in the present system is slightly simple. Owing to the intrinsic structural features, we envisioned that calix[3]arenes would provide a unique platform for the construction of inherently chiral macrocycles and prompted us to attempt the synthesis of inherently chiral propane bridged homocalixarene [33]. The main objective of this research is to synthesize asymmetric or incomplete calixarene analogue inherently chiral [3.3.1]metacyclophane bearing two propane bridges.

2. Experimental

General procedures

All melting points (Yanagimoto MP-S1) are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra were recorded on a Nippon Denshi JEOL FT-300 NMR spectrometer and Varian-400MR-vnmrs400 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Mass spectra were obtained on a Nippon Denshi JMS–01SA–2 mass spectrometer at an ionization energy of 70 eV; *m/z* values reported include the parent ion peak. Infrared (IR) spectra were obtained on a Nippon Denshi JIR-AQ2OM spectrophotometer as KBr disks. Elemental analyses were performed by Yanaco MT-5. G.L.C. analyses were performed by Shimadzu gas chromatograph, GC-14A; Silicone OV–1, 2 m; programmed temperature rise, 12 °C min^{-1}; carrier gas nitrogen, 25 mL min^{-1}. Silica gel columns were prepared by use of Merk silica gel 60 (63–200 μm).

Materials: TosMIC adduct **1** was prepared according to our reported data [34,35] and 1,1-bis(3-bromomethyl-5-*tert*-butyl-2-methoxyphenyl)methane **2**, was previously described [36]. 6,15,22-Tri-*tert*-butyl-9,18,25-trimethoxy[3.3.1]metacyclophane-2,11-dione **3** was synthesized by the coupling reaction of TosMIC adduct **1** with **2** according to reported procedure [37].

*2.1 Synthesis of 6,15,22-tri-*tert*-butyl-9,18,25-trimethoxy[3.3.1]metacyclophane (**4**)*

A mixture of **3** (200 mg, 0.33 mmol), NaOH (200 mg, 5.0 mmol), 100 % hydrazine hydrate (0.35 mL, 6.2 mmol), and triethylene glycol (5 mL) was heated at 120 °C for 2 h and then at 200 °C for 3 h. The cooled mixture was poured into water (50 mL), acidified with diluted HCl, and extracted with CH_2Cl_2 (5 × 30 mL), washed with water (2 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified on silica gel using benzene as eluents to give crude **4** as a white solid. Recrystallization from hexanes afforded 6,15,22-tri-*tert*-butyl-9,18,25-trimethoxy[3.3.1]metacyclophane **4** (129 mg, 68 %) as white solid. M.p.

199–200°C. IR: ν_{max} (KBr)/cm^{-1}: 2900, 2800, 1480, 1180 and 1000. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (9H, s, *t*Bu), 1.27(18H, s, *t*Bu × 2), 1.80 (3H, s, O*Me*), 1.98–2.28 (10H, m, *CH*$_2$), 3.01 (2H, d, *J* = 2.19, *CH*$_2$), 3.43 (1H, d, *J* = 12.1 Hz, *CH*$_2$), 3.77 (6H, s, O*Me*), 4.50 (1H, d, *J* = 12.1 Hz, *CH*$_2$), 6.81 (2H, s, Ar–*H*), 6.96 (2H, d, *J* = 2.5, Ar–*H*) and 7.35 (2H,d, *J* = 2.5 Hz, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.67 (CH_2), 30.45 (CH_2), 31.59 ($C(CH_3)_3$), 31.77 ($C(CH_3)_3$), 32.66 (CH_2), 34.02 (CH_2), 34.08 (CH_2), 58.41 (OCH_3), 61.11 (OCH_3), 124.08 (ArC), 125.40 (ArC), 126.72 (ArC), 134.29 (ArC), 134.68 (ArC), 136.35 (ArC), 145.04 (ArC), 145.21 (ArC), 154.32 (ArC) and 155.56 (ArC) ppm. FABMS: *m*/*z*: 584.45 [M^+]. $C_{40}H_{56}O_3$ (584.89): calcd. C 82.14, H 9.65. Found: C 81.98, H 9.67.

*2.2 Synthesis of 6,15,22-tri-tert-butyl-18,25-dihydroxy-9-methoxy[3.3.1]metacyclophane (**5**)*

A solution of BBr_3 (1 mL, 10.6 mmol) in CH_2Cl_2 (3 mL) was added gradually to a solution of **4** (100 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After the reaction mixture had been stirred at room temperature for 4 h, it was poured into ice-water (20 mL), extracted with CH_2Cl_2 (2 × 50 mL), washed with water (2 × 10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude **5** as a white solid. Recrystallization from benzene afforded 6,15,22-tri-*tert*-butyl-18,25-dihydroxy-9-methoxy[3.3.1]metacyclophane **5** (60 mg, 63 %) as white powder. M.p. 209–210 °C. IR: ν_{max} (KBr)/cm^{-1}: 3625, 3320 (OH), 1495 and 1215. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (9H, s, *t*Bu), 1.28(18H, s, *t*Bu × 2), 1.72 (3H, s, O*Me*), 1.76–2.35 (10H, m, *CH*$_2$), 3.04 (2H, m, *CH*$_2$), 3.61 (1H, d, *J* = 13.3 Hz, *CH*$_2$), 4.36 (1H, d, *J* = 13.3 Hz, *CH*$_2$), 6.29 (2H, s, *OH*, Exchanged by D_2O), 6.90 (2H, s, Ar–*H*), 6.96 (2H, d, *J* = 2.5 Hz, Ar–*H*) and 7.25 (2H, s, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.58 (CH_2), 29.92 (CH_2), 31.42 (CH_2), 31.56 ($C(CH_3)_3$), 31.58 ($C(CH_3)_3$), 31.76 (CH_2), 33.93 (CH_2), 34.15 (CH_2), 58.25 (OCH_3), 124.31 (ArC), 125.21 (ArC), 126.81 (ArC), 127.58 (ArC), 128.16 (ArC), 136.36 (ArC), 143.15 (ArC), 145.78 (ArC), 149.15 (ArC) and 154.17 (ArC) ppm. FABMS: *m*/*z*: 556.44 [M^+]. $C_{38}H_{52}O_3$ (556.8): calcd. C 81.97, H 9.41. Found: C 81.67, H 9.17.

*2.3 Synthesis of 6,15,22-tri-tert-butyl-9,18,25-trihydroxy[3.3.1]metacyclophane (**6**)*

To a mixture of CH_3CN (16 mL) and CH_2Cl_2 (12 mL) compound **4** (180 mg, 0.31 mmol) and NaI (1.935 g, 12.9 mmol) was added. After adding trimethylsilyl chloride (2.0 mL), the mixture was stirred at 40–45 °C for 30 h. The reaction mixture was poured into 10 % aqueous thiosulphate solution (40 mL) and stirred for 1 h at room temperature. Then the mixture was stirred with 10 % HCl (20 mL) for 1 h and extracted with CH_2Cl_2 (3 × 40 mL). The combined mixture was washed with 10 % $NaHCO_3$ (20 mL) and water (2 × 20 mL) and dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was purified on silica gel using methanol as eluent to give crude **6** as a white solid. Recrystallisation from CH_2Cl_2 afforded 6,15,22-tri-*tert*-butyl-9,18,25-trihydroxy[3.3.1]metacyclophane **6** (140 mg, 83 %) as white solid. M.p. 230–231 °C. IR: ν_{max} (KBr)/cm^{-1}: 3550, 3320 (OH), 1496 and 1210. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (9H, s, *t*Bu), 1.27(18H, s, *t*Bu × 2), 1.85 (4H, m, *CH*$_2$), 2.30 (4H, m, *CH*$_2$), 2.70 (4H, s, *CH*$_2$), 3.33 (1H, s, O*H*, Exchanged by D_2O), 3.95 (2H, s, *CH*$_2$), 6.25 (2H, s, OH, Exchanged by D_2O), 6.86 (2H, s, Ar–*H*), 6.96 (2H, d, *J* = 4.5 Hz, *Ar*–H) and 7.24 (2H, d, *J* = 2.4 Hz, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.95 (CH_2), 28.99 (CH_2), 31.26 (CH_2), 31.51 ($C(CH_3)_3$), 31.61 ($C(CH_3)_3$), 31.79 (CH_2), 33.88 (CH_2), 33.96 (CH_2), 124.21 (ArC), 125.63 (ArC), 127.00 (ArC), 127.28 (ArC), 128.18 (ArC), 128.29 (ArC), 142.04 (ArC), 143.68 (ArC), 148.50 (ArC) and 148.76 (ArC) ppm. FABMS: *m*/*z*: 542.44 [M^+]. $C_{37}H_{50}O_3$ (542.81): calcd. C 81.87, H 9.28. Found: C 81.76, H 9.19.

*2.4 Synthesis of 6,15,22-tri-tert-butyl-25-hydroxy-9,18-dimethoxy[3.3.1]metacyclophane (**8**) and 6,15,22-tri-tert-butyl-9,18-dihydroxy-25-methoxy[3.3.1]metacyclophane (**7**)*

A mixture of **6** (100 mg, 0.18 mmol) and potassium carbonate (500 mg, 3.62 mmol) in dry acetone (25 mL) was heated at reflux for 1 h under N_2. Then MeI (0.25 mL, 3.7 mmol) was added and the mixture was heated at reflux for 0.5 h. After cooling of the reaction mixture to

room temperature, it was quenched with water, extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with water (2 × 10 mL), dried over Na_2SO_4 and condensed under reduced pressure to afford a residue (yield 91 mg) containing a mixture of compounds **4**, **7** and **8**. The residue was purified on silica gel (Wako, C-300; 100 g) by using hexanes-benzene (1:1) as eluent to give the crude **8** (16 mg, 15 %) as a white solid. Recrystallization from methanol–$CHCl_3$ (3:1) gave 6,15,22-tri-*tert*-butyl-25-hydroxy-9,18-dimethoxy[3.3.1]metacyclophane **8** as white prisms. M.p. 203–204 °C. IR: ν_{max} (KBr)/cm^{-1}: 3566, 3395 (OH), 1492 and 1230. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (9H, s, *t*Bu), 1.19 (9H, s, *t*Bu), 1.20 (9H, s, *t*Bu), 1.58 (3H, s, O*Me*), 1.71–2.21 (10H, m, *CH*$_2$), 2.98–3.10 (2H, m, *CH*$_2$), 3.53 (1H, d, *J* = 13.2 Hz, *CH*$_2$), 3.85 (3H, s, O*Me*), 4.16 (1H, d, *J* = 13.2 Hz, CH_2), 6.78–6.81 (2H, m, *J* = 3.0 Hz, Ar–*H*), 6.89 (1H, d, *J* = 2.4 Hz, Ar–*H*), 6.95 (1H, d, *J* = 2.4 Hz, Ar–*H*), 7.12 (1H, d, *J* = 2.4 Hz, Ar–*H*), 7.26 (1H, d, *J* = 2.4 Hz, Ar–*H*) and 7.91 (1H, s, *OH*, Exchanged by D_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.41 (CH_2), 31.45 ($C(CH_3)_3$), 31.52 ($C(CH_3)_3$), 34.09 ($C(CH_3)_3$), 34.22 (CH_2), 34.31 (CH_2), 37.40 (CH_2), 41.69 (CH_2), 41.99 (CH_2), 42.25 (CH_2), 44.42 (CH_2), 45.27 (CH_2), 46.37 (CH_2), 58.81 (OCH_3), 60.76 (OCH_3), 125.67 (ArC), 125.87 (ArC), 126.10 (ArC), 126.27 (ArC), 126.39 (ArC), 126.55 (ArC), 126.80 (ArC), 126.92 (ArC), 127.03 (ArC), 128.16 (ArC), 128.86 (ArC), 134.14 (ArC), 145.71 (ArC), 145.96 (ArC), 146.54 (ArC), 153.79 (ArC), 154.02 (ArC) and 154.63 (ArC) ppm. FABMS: *m*/*z*: 570.43 [M^+]. $C_{39}H_{54}O_3$ (570.8): calcd. C 82.06, H 9.53. Found: C 82.18, H 9.47.

Recrystallization from hexane-CH_2Cl_2 (1:1) afforded 6,15,22-tri-*tert*-butyl-9,18-dihydroxy-25-methoxy[3.3.1]metacyclophane **7** (12.0 mg, 12 %) as white powder. M.p. 214–215 °C. IR: ν_{max} (KBr)/cm^{-1}: 3564, 3308 (OH), 1498 and 1205. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (9H, s, *t*Bu), 1.26 (9H, s, *t*Bu), 1.27 (9H, s, *t*Bu), 1.76–2.28 (10H, m, *CH*$_2$), 2.85 (1H, s, O*H*, Exchanged by D_2O), 3.08–3.16 (2H, m, *CH*$_2$), 3.58 (1H, d, *J* = 13.5 Hz, *CH*$_2$), 3.93 (3H, s, *OMe*), 4.17 (1H, d, *J* = 13.5 Hz, *CH*$_2$), 6.81 (2H, s, Ar–*H*), 6.99 (2H, d, *J* = 6 Hz, Ar–*H*), 7.22 (1H, s, Ar–*H*), 7.28 (1H, s, Ar–*H*) and 7.95 (1H, s, O*H*, Exchanged by D_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =

27.22 (CH_2), 27.81 (CH_2), 28.30 (CH_2), 29.67 (CH_2), 29.86 (CH_2), 31.36 ($C(CH_3)_3$), 31.53 ($C(CH_3)_3$), 31.62 ($C(CH_3)_3$), 32.00 (CH_2), 32.37 (CH_2), 33.80 (CH_2), 33.89 (CH_2), 34.17 (CH_2), 61.85 (OCH_3), 123.87 (ArC), 124.11 (ArC), 125.17 (ArC), 125.54 (ArC), 127.18 (ArC), 127.67 (ArC), 128.05 (ArC), 128.07 (ArC), 128.53 (ArC), 128.96 (ArC), 133.44 (ArC), 133.53 (ArC), 141.57 (ArC), 142.75 (ArC), 147.52 (ArC), 148.82 (ArC), 149.73 (ArC) and 152.3 (ArC) ppm. FABMS: *m/z*: 556.38 [M^+]. $C_{38}H_{52}O_3$ (556.81): calcd. C 81.97, H 9.41. Found: C 81.86, H 9.31.

*2.5 Synthesis of 6,15,22-tri-tert-butyl-25-hydroxy-9,18-dimethoxy[3.3.1]metacyclophane (**8**)*

A mixture of **6** (100 mg, 0.18 mmol) and potassium carbonate (500 mg, 3.62 mmol) in dry acetone (25 mL) was heated at reflux for 1 h under N_2. Then MeI (0.25 mL, 3.7 mmol) was added and the mixture was heated at reflux for 0.5 h. After cooling of the reaction mixture to room temperature, it was quenched with water, extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with water (2 × 10 mL), dried over Na_2SO_4 and condensed under reduced pressure to afford a residue. The crude product was purified on silica gel (Wako, C-300; 100 g) by using hexanes-benzene (1:1) as eluent to give the product **8** (85 mg, 83 %) as a white solid.

3. Results and Discussion

6,15,22-Tri-*tert*-butyl-9,18,25-trimethoxy[3.3.1]metacyclophane-2,11-dione **3** was prepared by the coupling reaction of 2,6-bis(bromomethyl)-4-*tert*-butylanisole TosMIC adduct **1** with 1,1-bis(5-*tert*-butyl-2-methoxyphenyl)methane **2** according to reported procedure [34–37]. The modified Wolff–Kishner reduction of diketone **3** afforded 6,15,24-tri-*tert*-butyl-9,18,27-trimethoxy[3.3.1]MCP **4** in 68 % yield (Scheme 1) as previously reported for the preparation of [3.3]metacyclophane [34].

Insert Scheme 1 in here

The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of macrocycle **4** presents two sets of doublets at δ 3.43, 4.50 ppm (J = 12.1 Hz) for the Ar*CH*$_2$Ar methylene protons and two single peaks at δ 1.80 and 3.77 ppm for the methoxy protons. In this case, the two methoxy groups in the compound point up and another one is point down, folded into the π-cavity formed by two benzene rings, shielded and appeared up field at δ 1.80 ppm. Thus, the compound **4** adopts an asymmetric 2-*partial-cone* conformation at room temperature as observed by two sets of doublets for the methylene protons. Demethylation of **4** with BBr_3 in methylene dichloride afforded 6,15,22-tri-*tert*-butyl-18,25-dihydroxy-9-methoxy[3.3.1]metacyclophane **5** in 63 % yield. Attempts to further demethylate **5** with a large excess of BBr_3 or by prolonging the reaction time were unsuccessful. No formation of the triol **6** was observed, and only the starting compound **5** was recovered in quantitative yield. Different reactivities towards BBr_3 were thus observed in the present system.

Insert Scheme 2 in here

This phenomenon could be attributed due to the 9–methoxy group of compounds **4** and **5** inside the π–cavity of the two benzene rings of the diarylmethane being inert to attack by BBr_3. These results are consistent with the difference of chemical shifts between these methoxy groups in **4**. Yang *et al* developed a BBr_3 and TMSI-mediated one-pot demethylation to synthesize an antifungal tricyclic *o*-hydroxy-*p*-quinone methide diterpenoid and analogues [38]. Interestingly, an extended demethylation reaction of **4** and **5** with trimethylsilyl iodide in MeCN afforded the desired triol **6** in 83 % and 90 % yield, respectively.

The IR (KBr) spectrum of **5** shows the absorption for the hydroxyl stretching vibration at around 3320 cm^{-1}. The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) exhibits signals for the hydroxyl groups at around δ 6.29 ppm (exchanged by D_2O). This data is consistent with the existence of intramolecular hydrogen bonding between the two hydroxyl groups of the diarylmethane linkage of cyclic product **5**, but not the diarylpropane linkage. The intramolecular hydrogen bonded O–H

band is a broad peak appear at 3320 cm^{-1} and the free O–H band is a sharp peak appear at 3625 cm^{-1}. The ^{1}H NMR spectrum of macrocycle **5** presents two sets of doublets at δ 3.61 and 4.36 ppm (J = 13.3 Hz) for the ArCH_2Ar methylene protons and one single peak at δ 1.72 ppm for the methoxy protons. These patterns correspond to the former conformer given that the two methylene protons ArCH_2Ar and methoxy protons are all in different environments, whereas the latter conformer should exhibit a set of doublets for the methylene protons ArCH_2Ar and a singlet for the methoxy protons due to the C_2-symmetry (Fig. 1).

Insert Figure 2 in here

The crystal structure of **5** (CCDC 908364) was found to belong to the monoclinic crystal system with space group $P2_1/n$ (SI Table S1). The X-ray structure also supports the ^{1}H NMR spectrum (Fig. 2). It is clear that one methoxy group is present between two aromatic rings which is experiencing ring current by the π-aromatic electrons as predicted from the ^{1}H NMR data. The distance between H (OH) and O_1 (OH) is 1.82 Å, which is a reasonable distance for intramolecular hydrogen bonding. In contrast, both the ^{1}H NMR spectrum and single crystal analysis confirmed the 2-*partial-cone* conformation of macrocycle **5**.

The IR (KBr) spectrum of **6** shows the absorption of the hydroxyl stretching vibration a broad band at around 3320 cm^{-1} for intramolecular hydrogen bonding and a sharp peak at 3550 cm^{-1} for free hydroxyl stretching. The ^{1}H NMR spectrum (in $CDCl_3$) exhibits the signals for the hydroxyl groups at around δ 3.33 and 6.25 ppm (exchanged by D_2O) which is the evidence for the formation of intramolecular hydrogen bonding between two hydroxyl groups of the diarylmethane linkage of cyclic product **6**. However, it is weaker than the corresponding calix[4]arenes due to the flexibility of the propane linkages in spite of having a smaller ring size. The ^{1}H NMR spectrum of **6** indicates that it adopts a *cone* conformation at room temperature [23] and the methylene proton appears as a singlet at δ 3.95 ppm. Gutsche and co-workers

reported [6] that the strong intramolecular hydrogen bonding of calix[4]arenes may fix the *cone* conformation.

We have succeeded in synthesizing both trihydroxy[3.3.1]metacyclophane **6** and dihydroxy[3.3.1]metacyclophane **5**; one regio–isomer expected to have a chirality monohydroxy[3.3.1]metacyclophane **8** is still remains to be synthesized. Thus, there is substantial interest to synthesize this compound via *O*-methylation of the phenolic oxygen using MeI in the presence of base.

Insert Scheme 3 in here

Insert Table 1 in here

O-Methylation of trihydroxy[3.3.1]metacyclophane **6** using MeI in presence of NaH as a base, exclusively afforded the corresponding tri-*O*-methylated product **4** in 90 % yield. On the other hand, when Na_2CO_3 is employed, only the trihydroxy compound **6** was recovered in 92 %, even when a large excess of Na_2CO_3 was used. Interestingly, when K_2CO_3 is used in this reaction for 0.5 h, the mono-*O*-methylated product **7** and di-*O*-methylated product **8** were obtained in 21 and 26 % yields, along with the recovery of the starting compound **6** in 53 % yield. On increasing the reaction time to 3 h, the yield of the di-*O*-methylation product **8** increased to 93 %. Thus, in the case of K_2CO_3, selective di-*O*-methylation was observed. On increasing further the reaction time to 12 h, the yield of the tri-*O*-methylation product **4** was increased to 85 %. In contrast, when Cs_2CO_3 is employed, the reaction was completed within 3 h with the exclusive formation of the tri-*O*-methylated product **4** and the *O*-methylation results are summarized in Table 1.

Insert Table 2 in here

The ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of macrocycle **7** showed three single peaks for the *tert*-butyl protons at δ = 1.21, 1.26 and 1.27 ppm (relative intensity 1:1:l). These signals correspond to an unsymmetrical structure. Two hydroxyl groups give singlet peaks at δ 2.85 and 7.95 ppm and both are exchanged by D_2O. The peak at high field (δ 7.95 ppm) indicates the formation of intramolecular hydrogen bonding between MeO···HO. The IR (KBr) spectrum of **7** shows the absorption peaks of the hydroxyl stretching vibration at around 3564 and 3308 cm^{-1} evidence for the existence of intramolecular hydrogen bonding. The splitting pattern of the ArCH_2Ar methylene protons at δ 3.58 and 4.17 ppm (J = 13.5 Hz) indicates that compound **7** adopts a 2-*partial-cone* conformation.

The ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of macrocycle **8** exhibits two sets of doublets due to the bridging methylene protons and three single peaks for the *tert*-butyl protons at δ = 1.15, 1.19 and 1.20 ppm (relative intensity 1:1:l). This indicates that macrocycle **8** adopts an asymmetric 2-*partial-cone* conformation at room temperature. In this conformation, the one methoxy group in the compound **8** is point up and another is point down with folded into the π–cavity by two benzene rings which causes upfield shift of this methoxy group at δ 1.58 ppm. The IR (KBr) spectrum of **8** shows the absorption for the hydroxyl stretching vibration at around 3566 and 3395 cm^{-1} due to free and intramolecular hydrogen bonding of hydroxyl group. The ^{1}H NMR spectral data of [3.3.1]MCPs **4**, **5**, **6**, **7** and **8** are summarized in Table 2.

Insert Figure 3 in here

Macrocycle **8** is expected to have a plane of chirality, because it has two types of substituents and bridged linkages which are fixed and the C_1 symmetrical conformer does not show conformational change at room temperature. Shinkai and co-workers introduced two kinds of substituents at the lower rim of homo-oxacalix[3]arenes to synthesis C_2 symmetry inherent chirality [12]. Böhmer and co-workers [39,40] demonstrated the chirality of dissymmetric

calix[4]arenes with C_2 and C_4symmetry by interaction with Pirkle's reagent [(*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol]. The ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **8** in the absence and the presence of Pirkle's reagent is shown in Fig. 3. It is reported [39] that hydroxyl groups which do not participate in intramolecular hydrogen bonding are necessary for an effective interaction between chiral calix[4]arenes and Pirkle's reagent. In the spectrum of compound **8**, one of the singlet peaks of the methoxy groups and all peaks of the bridged protons are splitted on addition of Pirkle's reagent due to the formation of two diastereomeric complexes (Fig. 3). These findings suggest that one methoxy and a hydroxyl group of **8** play an important role to coordinate with Pirkle's reagent.

Insert Figure 4 in here

Chromatographic resolution using a chiral column was attempted for the present di-*O*-methylation derivative **8**. Interestingly, compound **8** exhibits two well resolved peaks in the ratio of 50:50 for *P* and *M*-enantiomers as presented in Fig. 4(a). This finding strongly suggests that the resolution of racemic **8** could be achieved by chromatographic separation using a chiral column. In fact, we have succeeded in resolving each *P* and *M*-enantiomers. The circular dichroism (CD) spectra of the separated enantiomers with perfect mirror images are shown in Fig. 4(b). In fact, we have succeeded to generate inherent chirality in metacyclophane system containing three benzene rings by regio-selective *O*-methylation at lower rim of calixarene analogue [3.3.1]metacyclophane **6**.

Conclusions

We have for the first time provided an effective and practical method for the synthesis of calixarene analogue trihydroxy[3.3.1]metacyclophanes **6**, which is regarded as an unsymmetrical or incomplete "homocalixarene", bearing one methylene and two propane bridges. Di-*O*-methylation of the hydroxyl groups of triol **6** with MeI in presence of K_2CO_3 afforded to yield a

2-*partial-cone* conformer **8**, which has a plane of chirality, given that the two types of substituent and bridges are fixed in a C_1-symmetrical structure. All synthesized [3.3.1]metacyclophanes exhibit rigid 2-*partial-cone* conformations in solution except trihydroxy[3.3.1]metacyclophane **6** which has a flexible *cone* conformation at room temperature. Further mechanistic details of *O*-alkylation and uses as enantioselective artificial receptors, are ongoing and will be reported in future.

Acknowledgments

We would like to thank the OTEC at Saga University for financial support. This work was performed under the Cooperative Research Program of "Network Joint Research Center for Materials and Devices (Institute for Materials Chemistry and Engineering, Kyushu University)".

References

[1] B. Xu, T.M. Svager, J. Am. Chem. Soc.115 (1993) 1159–1160.

[2] S.G. Bott, A.W. Coleman, J.L. Atwood, J. Chem. Soc. Chem. Commun. 8 (1986) 610–611.

[3] S. Shinkai, Tetrahedron 49 (1993) 8933–8968.

[4] J.M. Lehn, Angew. Chem., Int. Ed. Engl. 27 (1988) 89–112.

[5] D.J. Cram, Angew. Chem., Int. Ed. Engl. 27 (1988) 1009–1020.

[6] (a) C.D. Gutsche, Calixarenes, Royal Society of Chemistry, Cambridge, 1989; (b) C.D. Gutsche, Acc. Chem. Res. 16 (1983) 161–170.

[7] J. Vicens, V. Böhmer, CALIXARENES: A Versatile Class of Macrocyclic Compounds, Kluwer Academic Publishers, Cambridge, 1990.

[8] D.R. Stewart, C.D. Gutsche, J. Am. Chem. Soc. 121 (1999) 4136–4146.

[9] J.A. Kanters, A. Schouten, E. Steinwender, J.H. van der Maas, L.C. Groenen, D.N. Reinhoudt, J. Mol. Struct. 269 (1992) 49–64.

[10] A.A. Moshfegh, F. Beladi, L. Radnia, A.S. Hosseini, S. Tofigh, G.H. Hakimelahi, Helv. Chim. Acta. 65 (1982) 1264–1270.

[11] (a) K. Araki, N. Hashimoto, H. Otsuka, S. Shinkai, J. Org. Chem. 58 (1993) 5958–5963; (b) K. Araki, K. Inada, H. Otsuka, S. Shinkai, Tetrahedron. 49 (1993) 9465–9478.

[12] K. Araki, K. Inada, S. Shinkai, Angew. Chem. Int. Ed. Engl. 35 (1996) 72–74.

[13] A. Tsuge, T. Sawada, S. Mataka, N. Nishiyama, H. Sakashita, M. Tashiro, J. Chem. Soc., Perkin Trans. 1 (1992) 1489–1494.

[14] S. Ibach, V. Prautzsch, F. Vögtle, C. Chartroux, K. Gloe, Acc. Chem. Res. 32 (1999) 729–740.

[15] G. Brodesser, F.Vögtle, J. Incl. Phenom. Mol. Recognit. Chem. 19 (1994) 111–135.

[16] J. Schmitz, F. Vögtle, M. Nieger, K. Gloe, H. Stephen, O. Heitzsch, H.-J. Buschmann, W. Hasse, K. Cammann, Chem. Ber. 126 (1993) 2483–2491.

[17] (a) S. Shirakawa, A. Moriyama, S. Shimizu, Eur. J. Org. Chem. 2008 (2008) 5957–5964; (b) S. Shirakawa,S. Shimizu, New J. Chem. 34 (2010) 1217–1222.

[18] F. Narumi, T. Hattori, W. Yamabuki, C.Kabutoc, H. Kameyamaa, Tetrahedron: Asymmetry. 16 (2005) 793–800.

[19] J Havlíček, R Krátký, M Růžičková, P Lhoták, I Stibor, J. Mol. Struct. 563–564 (2001) 301–307.

[20] M.O. Vysotsky, M.O. Tairov, V.V. Pirozhenko, V. I Kalchenko, Tetrahedron Lett. 39 (1998) 6057–6060.

[21] K. Iwamoto, A. Yanagi, T. Arimura, T. Matsuda, S. Shinkai, Chem. Lett. 19 (1990) 1901–1904.

[22] V. Böhmer, D. Kraft,M. Tabatabai, J. Incl. Phenom. Mol.Recog. Chem. 19 (1994) 17–39.

[23] Y.-S. Zheng, J. Luo, J. Incl. Phenom. Macrocylic. Chem. 71 (2011) 35–56.

[24] S.-Y. Li, Y.-W. Xu, J.-M. Liu, C.-Y. Su, Int. J. Mol. Sci. 12 (2011) 429–455.

[25] M.J. McIldowie, M. Mocerino, M.I. Ogden, Supramol. Chem. 22 (2010) 13–39.

[26] Z.-X. Xu, G.-K. Li,C.-F. Chen, Z.-T. Huang, Tetrahedron 64 (2008) 8668–8675.

[27] A.V. Yakovenko, V.I. Boyko, O. Danylyuk, K. Suwinska, J. Lipkowski, V.I. Kalchenko, Org. Lett. 9 (2007) 1183–1185.

[28] C. Yang, Y. Chen, D.-X. Wang, L. Zhao, M.-X. Wang, Org. Lett.15 (2013) 4414–4417.

[29] L.-X. Wang, D.-X. Wang, Z.-T. Huang, M.-X. Wang, J. Org. Chem. 75 (2010) 741–745.

[30] M. Li, M.-L. Ma, X.-Y. Li, K. Wen, Tetrahedron 65 (2009) 4639–4643.

[31] W. Liu, Q.-Q. Wang, Z.-T. Huang, D.-X. Wang, Tetrahedron Lett. 55 (2014) 3172–3175.

[32] (a) J.-T. Li, L.-X. Wang, D.-X. Wang, L. Zhao, M.-X. Wang, J. Org. Chem. 79 (2014) 2178−2188; (b) J.-T. Li, D.-X. Wang, L. Zhao, M.-X. Wang, Tetrahedron Lett. 55 (2014) 3259–3262.

[33] T. Yamato, L.K. Doamekpor, H. Tsuzuki, Liebigs Ann. Recueil. (1997) 1537–1544.

[34] K. Tazoe, X. Feng, B. Sharma, S. Miyamoto, T. Yamato, Can. J. Chem. 90 (2012) 222–229.

[35] T. Yamato, L. K. Doamekpor, K. Koizumi, K. Kishi, M. Haraguchi, M. Tashiro, Liebigs Ann. 7 (1995) 1259–1267.

[36] T. Yamato, J. Matsumoto, S. Ide, K. Tokuhisa, K. Suehiro, M. Tashiro, J. Org. Chem. 57 (1992) 5243–5246.

[37] M.M. Islam, T. Hirotsugu, T. Matsumoto, J. Tanaka, S. Rahman, P.E. Georghiou, C. Redshaw, T. Yamato, Org. Biomol. Chem. submitted on 01 April (OB-ART-04-2015-000647).

[38] J. Huang, D. Foyle, X. Lin, J. Yang, J. Org. Chem. 78 (2013) 9166–9173.

[39] A. Wolff, V. Böhmer, W. Fogt, F. Ugozzoli, G.D. Andreetti, J. Org. Chem. 55 (1990) 5665–5667.

[40] S.T. Pickard, W.H. Pirkle, M. Tabatabai, W. Vogt, V. Böhmer, Chirality 5 (1993) 310–314.

Dear Editor:

We would like to submit the manuscript entitled “Synthesis and conformational studies of calixarene analogue chiral [3.3.1]metacyclophanes” for consideration as an article in *Journal of Molecular Structure*.

A homocalixarene is analogue to calixarene, where methylene groups of the bridge linkage were changed to other functional groups partially or totally. All of these calixarenes analogous have the similar characteristics to that of calixarene. Furthermore, with different bridge linkage, they have special properties. Homocalixarenes have been utilized in different fields of chemistry like conformational analysis, molecular recognition, organic catalysts etc. There are few reports concerning on the unsymmetric or uncomplete calix[n]arenes. Again it is surprising that reports on the preparation of calix[3]arenes and their analogue containing three benzene rings have been very limited. This facts seem to be due to the much more strained structure of calix[3]arenes than calix[n]arenes containing the larger ring

Herein, we have synthesized for the first time trihydroxy[3.3.1]metacyclophane, which is regarded as an unsymmetrical or incomplete "homocalix[3]arene" from trimethoxy[3.3.1]-metacyclophane by demethylation with trimethylsilyl iodide in MeCN. Weak intramolecular hydrogen bonding was observed in the trihydroxy[3.3.1]metacyclophane. An interesting result was obtained by *O*-methylation of the trihydroxy[3.3.1]metacyclophane with methyl iodide in presence of K_2CO_3, which formed the inherently chiral di-*O*-methylation product. Inherently chiral calixarenes are considered as promising host molecules for enantio-recognition and enantio-separation of chemically and/or biologically important chiral guest molecules.

I certify that this paper consists of original, unpublished work which has not been submitted to any other journal.

Your sincerely

Prof. Dr.Takehiko Yamato (corresponding author)
Department of Applied Chemistry, Faculty of Science and Engineering
Saga University
Honjo-machi 1, Saga-shi, Saga 840-8502, Japan
Fax: (internet.) + 081-952-28-8548
E-mail: yamatot@cc.saga-u.ac.jp

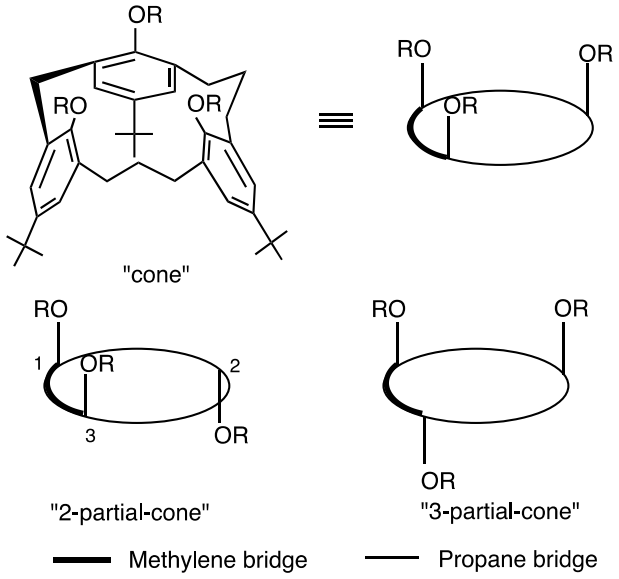


Fig. 1. Possible conformers for [3.3.1]metacyclophanes.

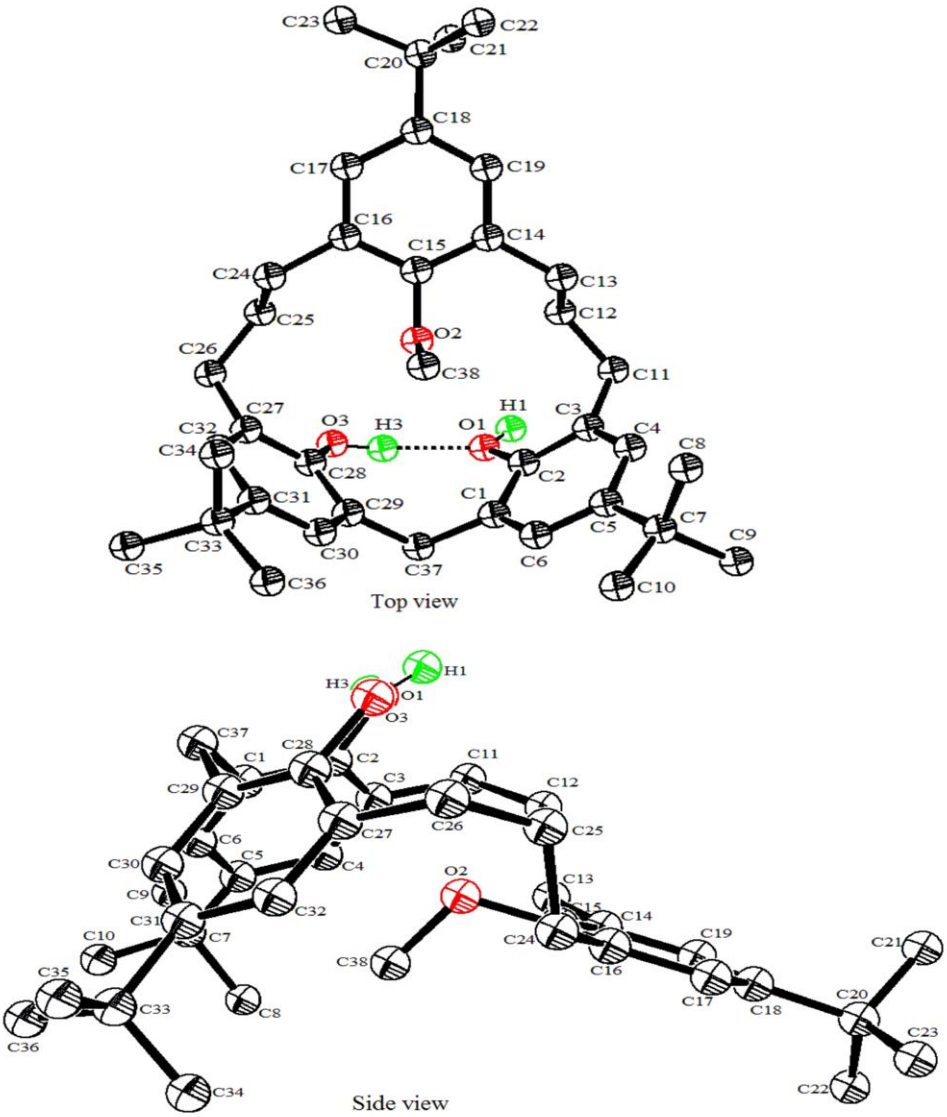


Fig. 2. Ortep drawing of [3.3.1]metacyclophane **5**. Thermal ellipsoids are drawn at the 50 % probability level. All hydrogen atoms except two are omitted for clarity

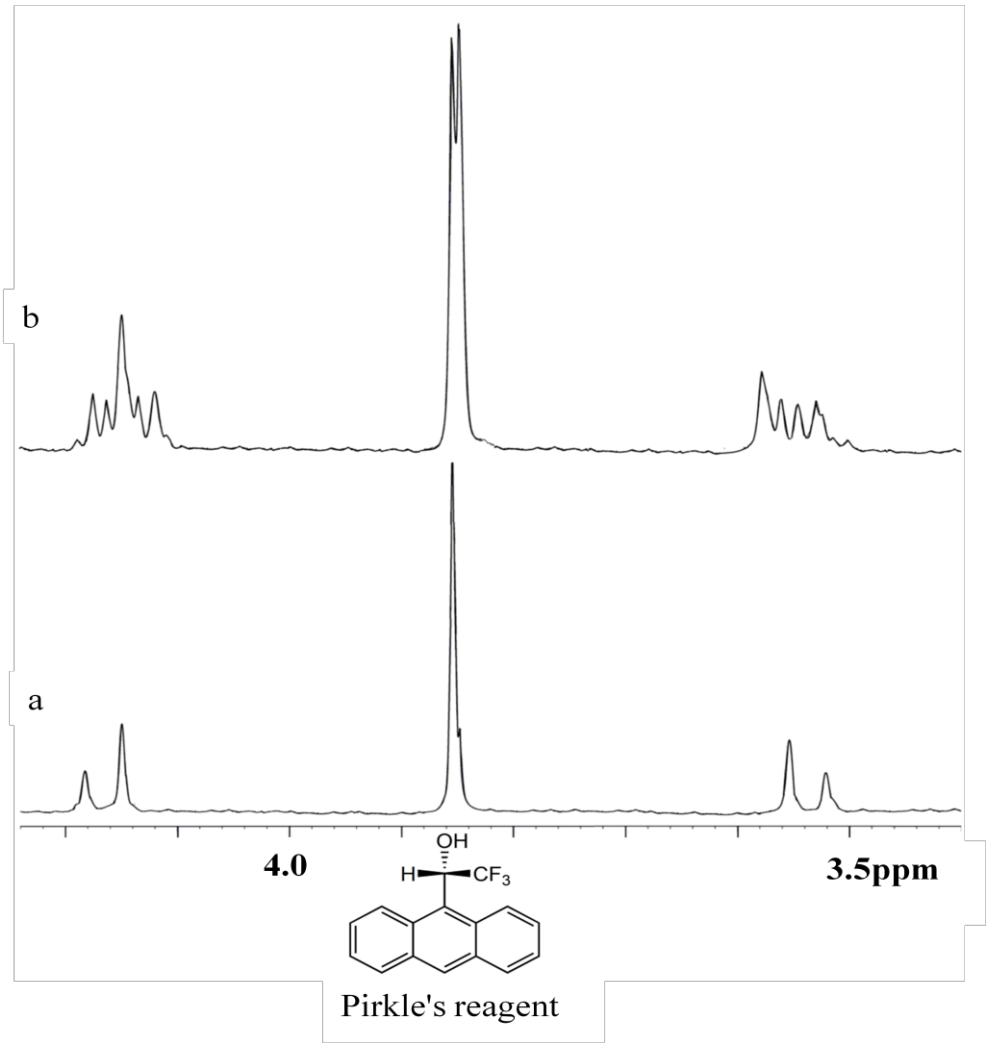


Fig. 3. Partial ^{1}H NMR spectra ($CDCl_3$; 400 MHz); (a) **8**, (b) **8**+ Pirkle's reagent.

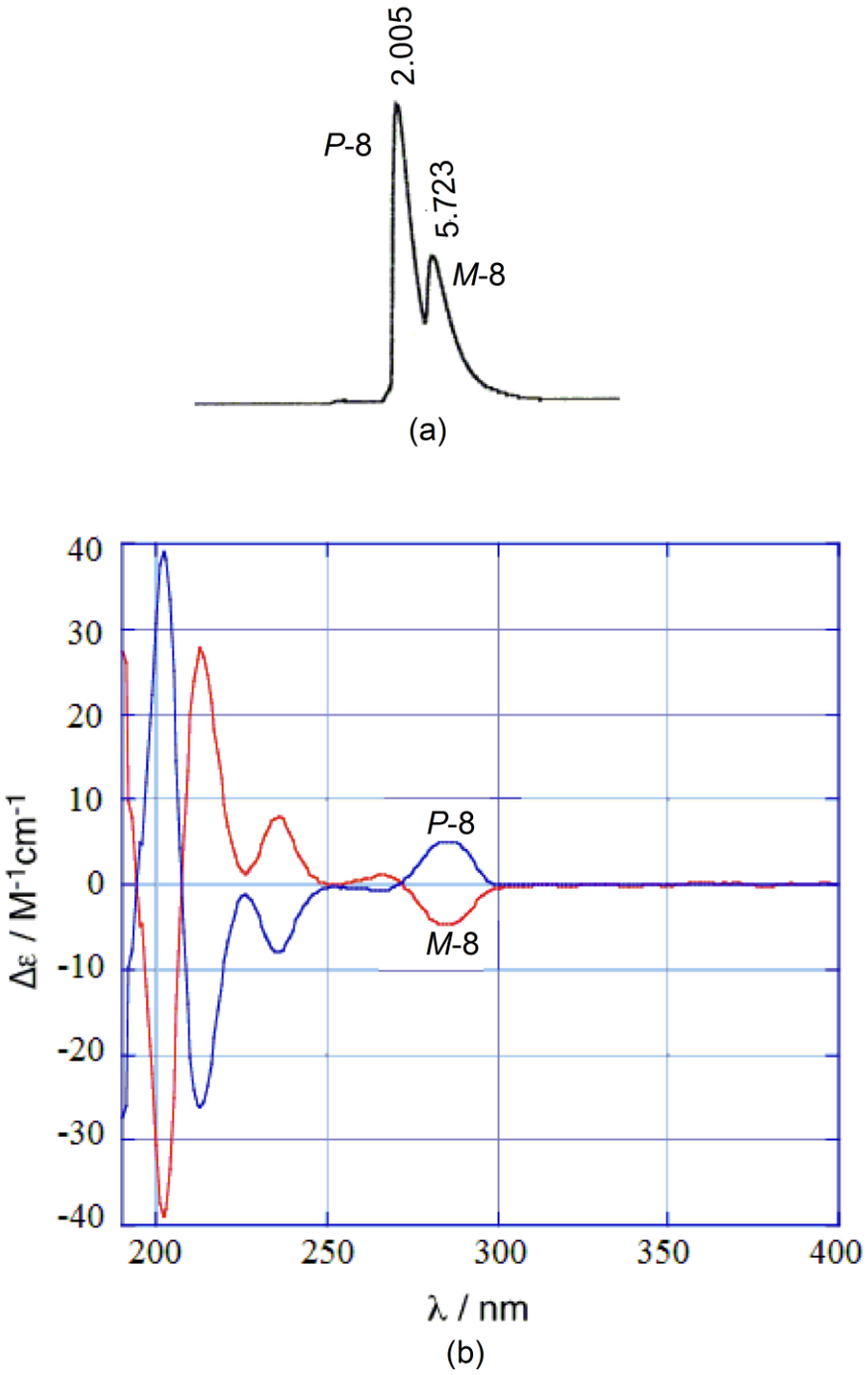
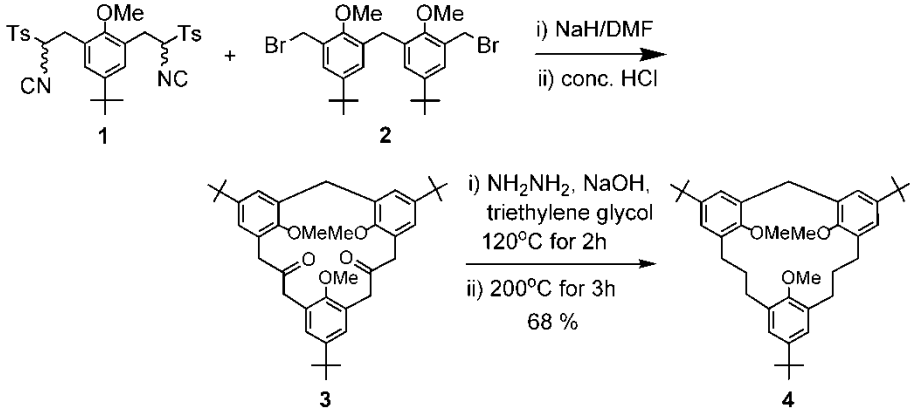
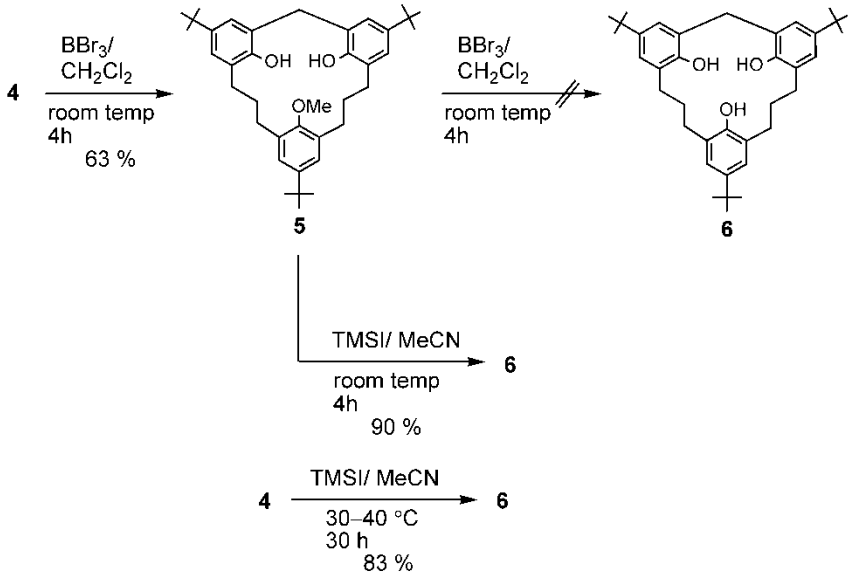


Fig. 4. (a) Chromatogram of **8** (HPLC on chiral column). Daicel chiralpak AD–H. Eluent: hexanes. (b) CD spectra of *P*- and *M*-enantiomers of inherently chiral MCP **8**.

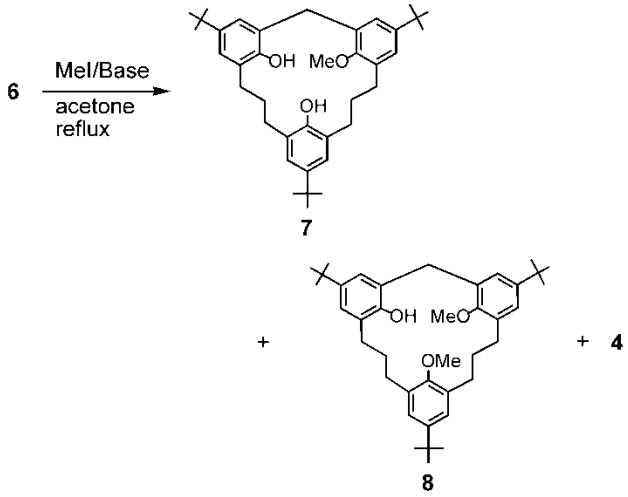
Scheme 1



Scheme 2



Scheme 3



Graphical abstract

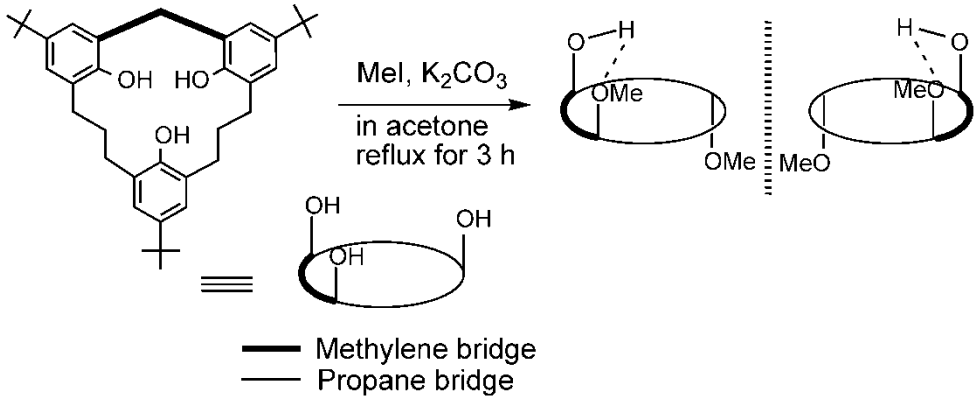


Table 1 *O*-Methylation of 9,18,25-trihydroxy[3.3.1]metacyclophane **6** with MeI in the presence of M_2CO_3 or NaH.

Run	Base	Time (hr)	Products Yield(%)[a,b] Recovered			
			7	**8**	**4**	**6**
1	NaH[c]	3	0	0	100 (90)	0
2	Na_2CO_3	12	0	0	0	100 (92)
3	K_2CO_3	0.5	21 (12)	26 (15)	0	53
4	K_2CO_3	3	0	93 (83)	7	0
5	K_2CO_3	12	0	15	85 (65)	0
6	Cs_2CO_3	3	0	0	100 (81)	0

[a]Yields were determined by ^{1}H-NMR analyses. [b]Isolated yields are shown in parentheses. [c]Solvent: THF-DMF (4:1 v/v).

Table 2 ^{1}H-NMR data for the [3.3.1]metacyclophanes **4**–**8** in $CDCl_3$.[a]

Compound	Methylene bridge protons			OH-Protons	O-Me protons	Assignment
	e	*a*	*J* (Hz)			
4	3.43	4.50	12.1	–	1.80, 3.77	*partial-cone*
5	3.61	4.36	13.3	6.29	1.72	*partial-cone*
6	3.95	–	singlet	3.33, 6.25	–	*cone*
7	3.58	4.17	13.5	2.85, 7.95	3.93	*partial-cone*
8	3.60	4.23	13.1	7.91	1.58, 3.85	*partial-cone*

[a]Chemical shifts are expressed in ppm (δ) against TMS as internal standard; coupling constants are given in Hz, *a* stands for *axial*, *e* for *equatorial*.

Supporting information for

Synthesis and conformational studies of calixarene analogue chiral [3.3.1]metacyclophanes

Md. Monarul Islam[a], Tomiyasu Hirotsugu[a], Pierre Thuery[b], Taisuke Matsumoto[c], Junji Tanaka[c], Mark R.J. Elsegood[d], Carl Redshaw[e] and Takehiko Yamato[a,*]

[a] Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi 1, Saga-shi, Saga 840-8502, Japan, *E-mail: yamatot@cc.saga-u.ac.jp*

[b] *CEA / Saclay SCM, Bat. 125 91191 Gif-sur-Yvette*

[c] *Institute of Material Chemistry and Engineering, Kyushu University, 6-1, Kasugakoen, Kasuga 816-8580, Japan*

[d] *Chemistry Department, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK*

[e] *Department of Chemistry, The University of Hull, Cottingham Road, Hull, Yorkshire, HU6 7RX, UK*

Table Contents

Copy of NMR Spectra

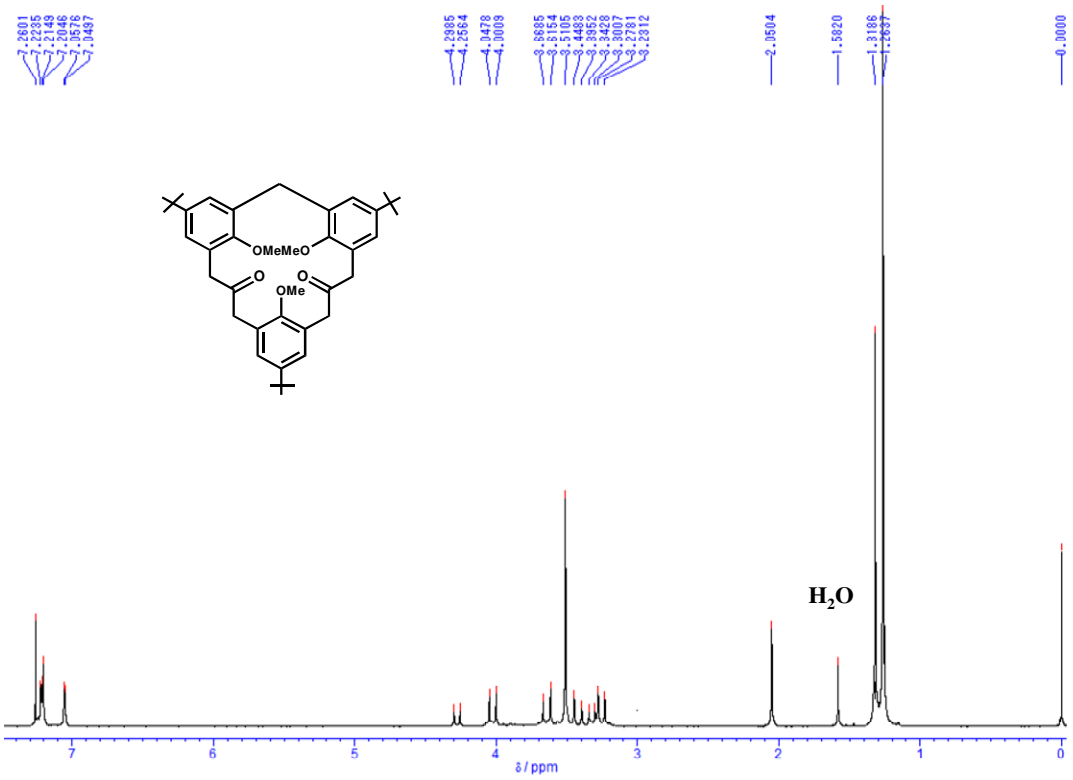


Figure S1-1 ^{1}H-NMR spectrum (300 MHz, 298 K, * $CDCl_3$) for **3**.

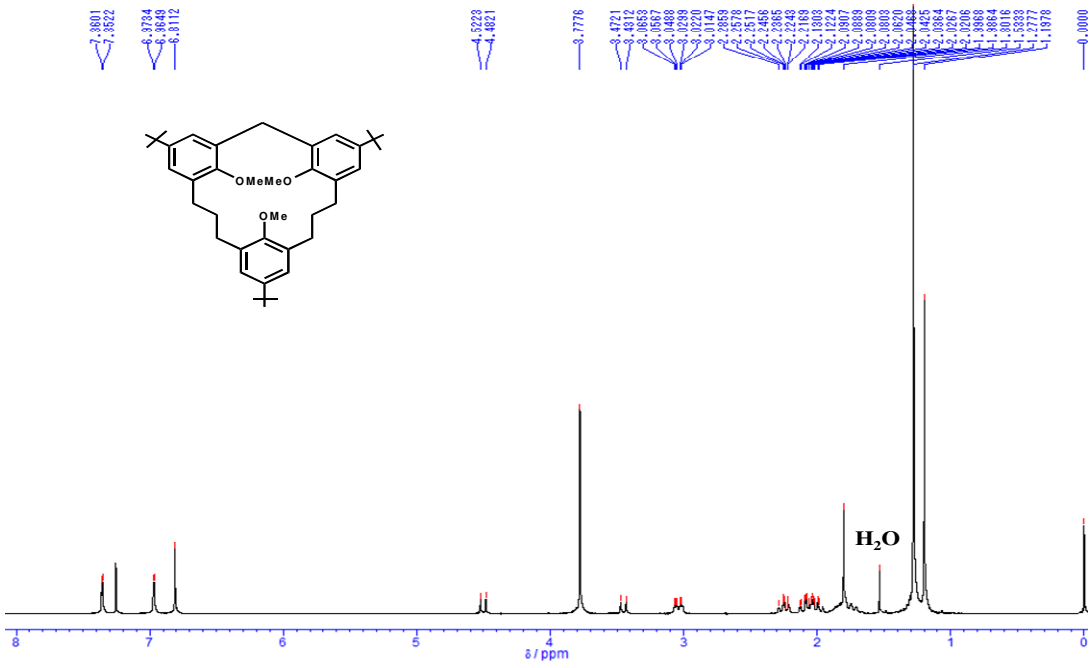


Figure S1-2 ^{1}H-NMR spectrum (300 MHz, 298 K, * $CDCl_3$) for **4.**

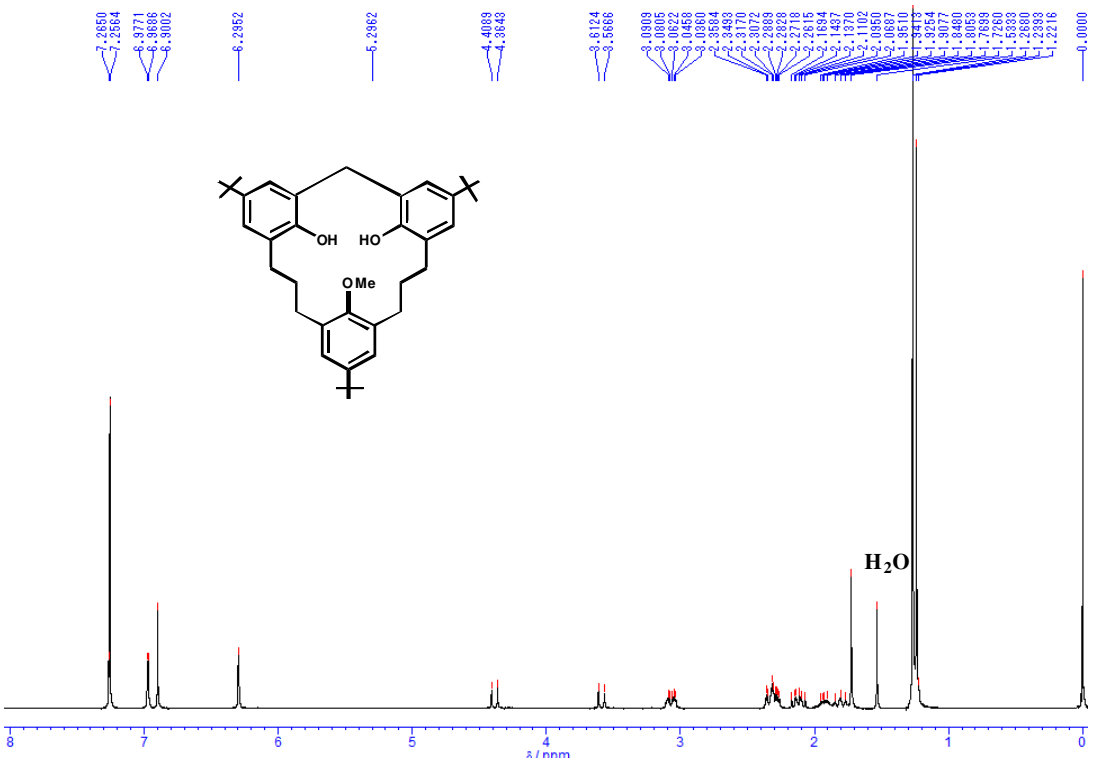


Figure S1-3 ^{1}H-NMR spectrum (300 MHz, 298 K, * $CDCl_3$) for **5.**

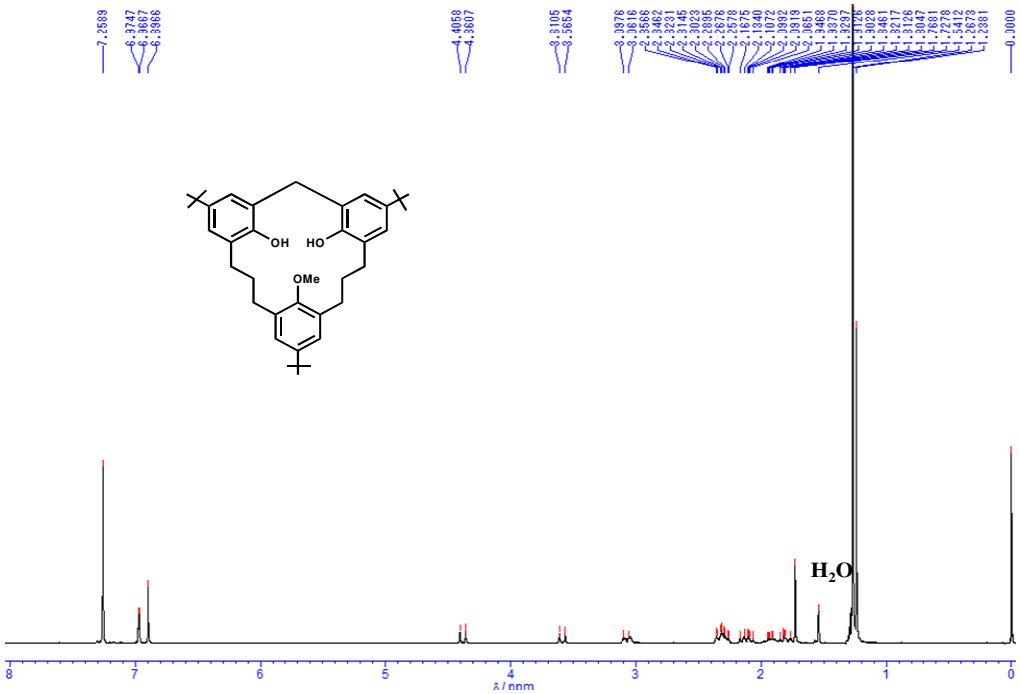


Figure S1-4 ^{1}H-NMR spectrum (300 MHz, 298 K, * $CDCl_3$) for **5** with D_2O.

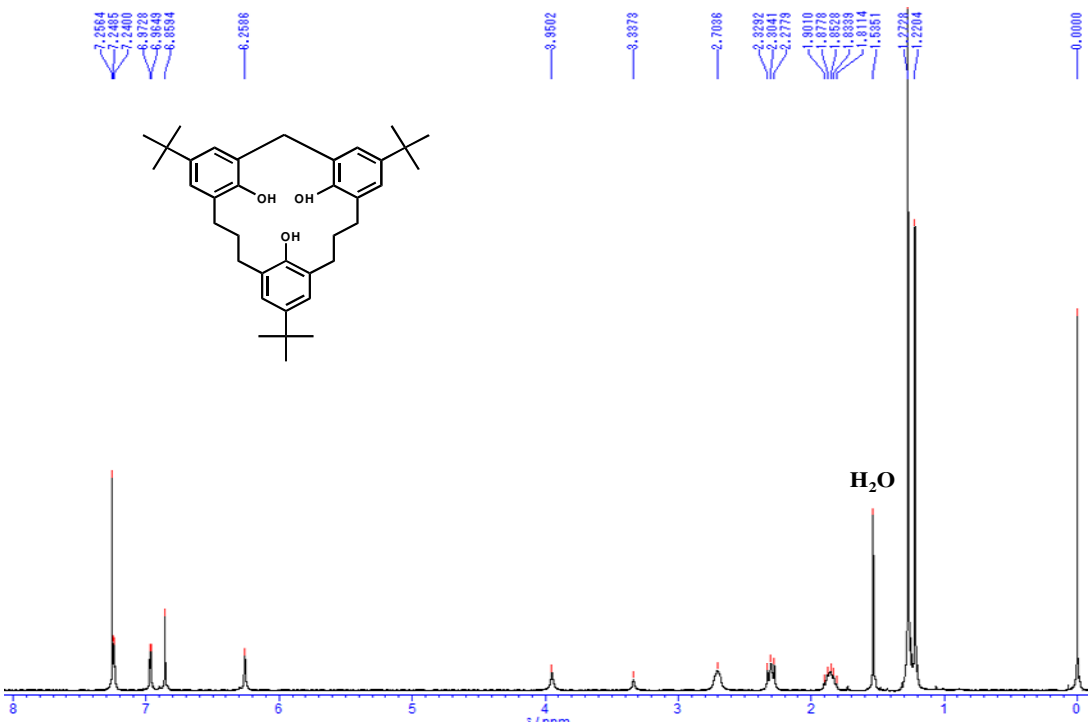


Figure S1-5 ^{1}H-NMR spectrum (300 MHz, 298 K, * $CDCl_3$) for **6.**

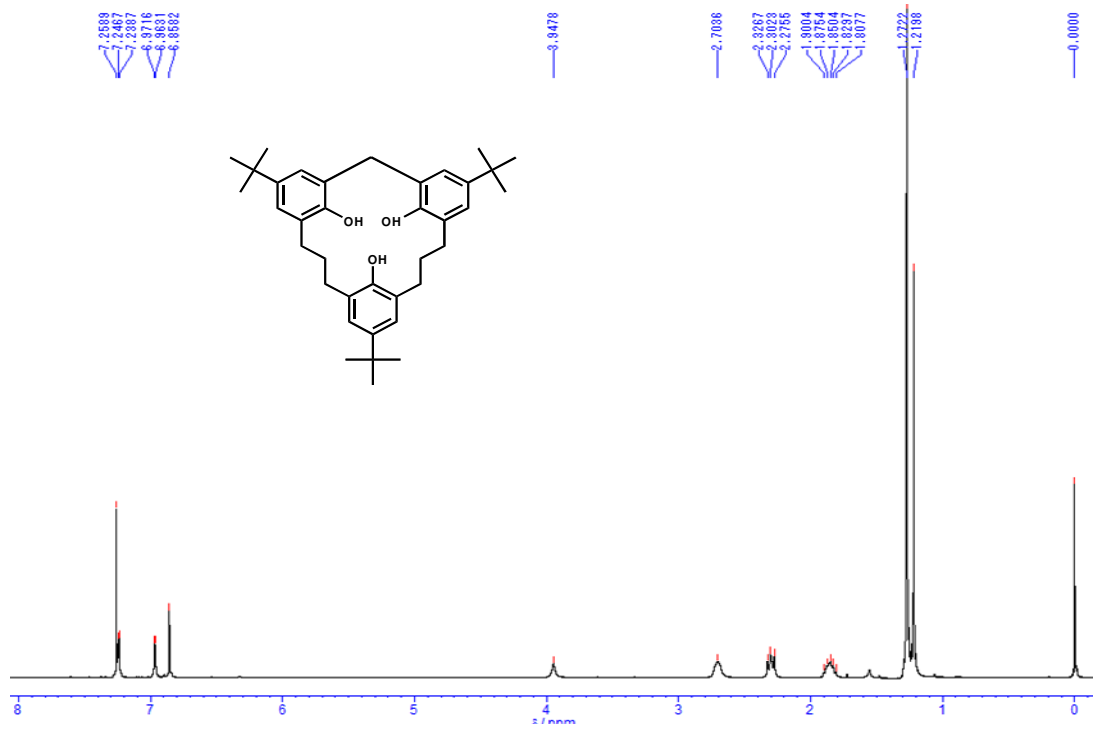


Figure S1-6 ^{1}H-NMR spectrum (300 MHz, 298 K, * $CDCl_3$) for **6** with D_2O.

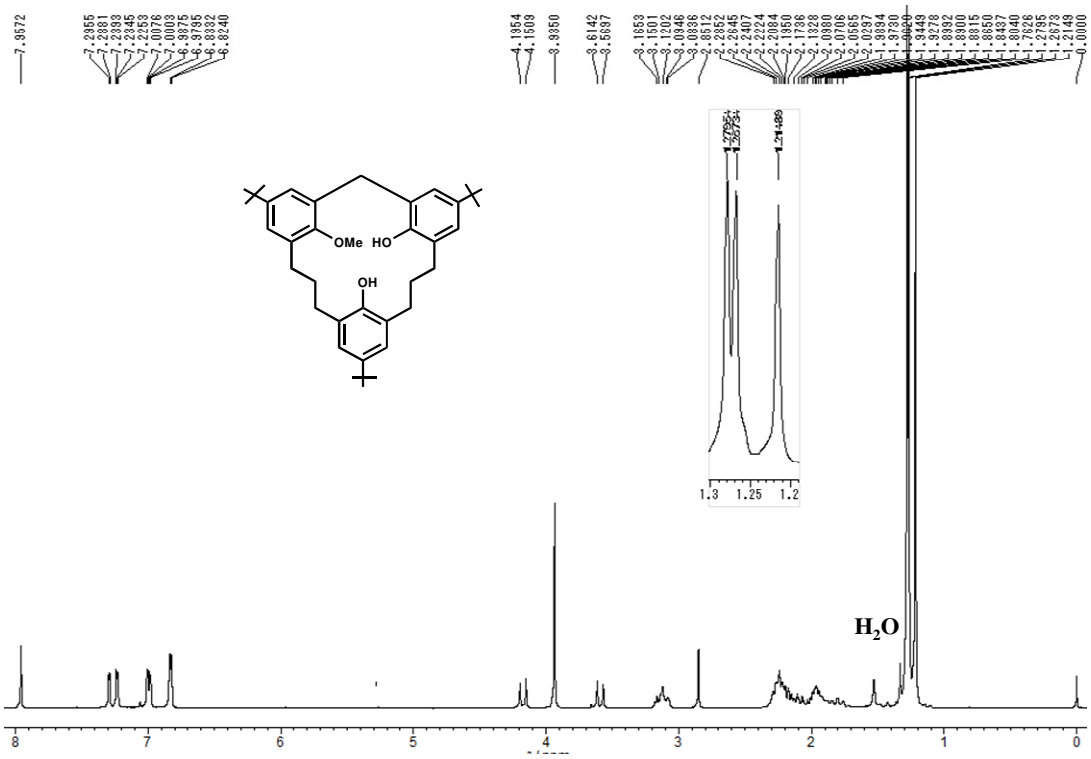


Figure S1-7 ^{1}H-NMR spectrum (100 MHz, 298 K, * $CDCl_3$) for **7.**

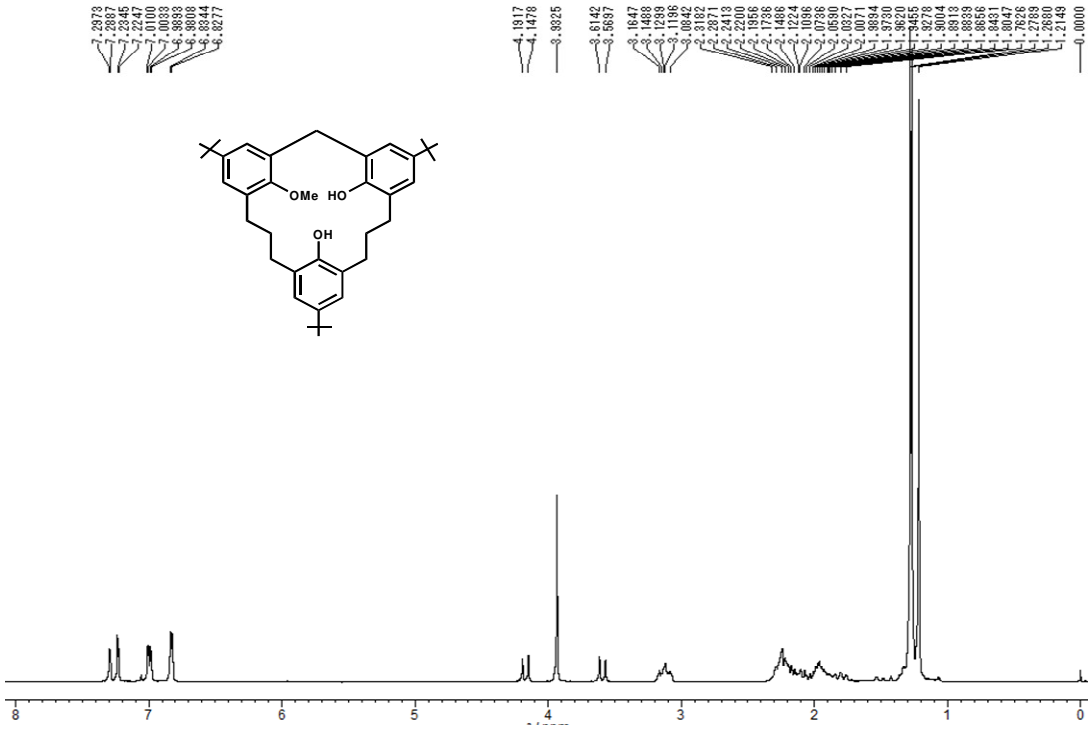


Figure S1-8 ^{1}H-NMR spectrum (300 MHz, 298 K, * $CDCl_3$) for **7** with D_2O.

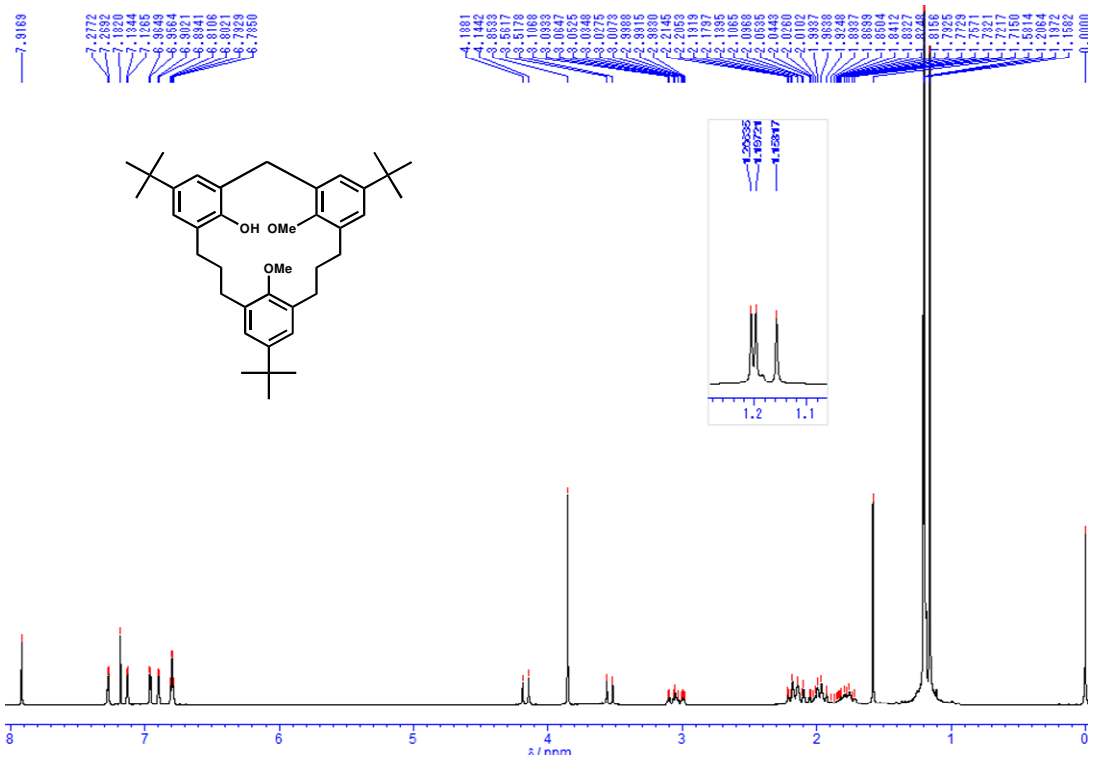


Figure S1-9 ^{1}H-NMR spectrum (300 MHz, 298 K, * $CDCl_3$) for **8.**

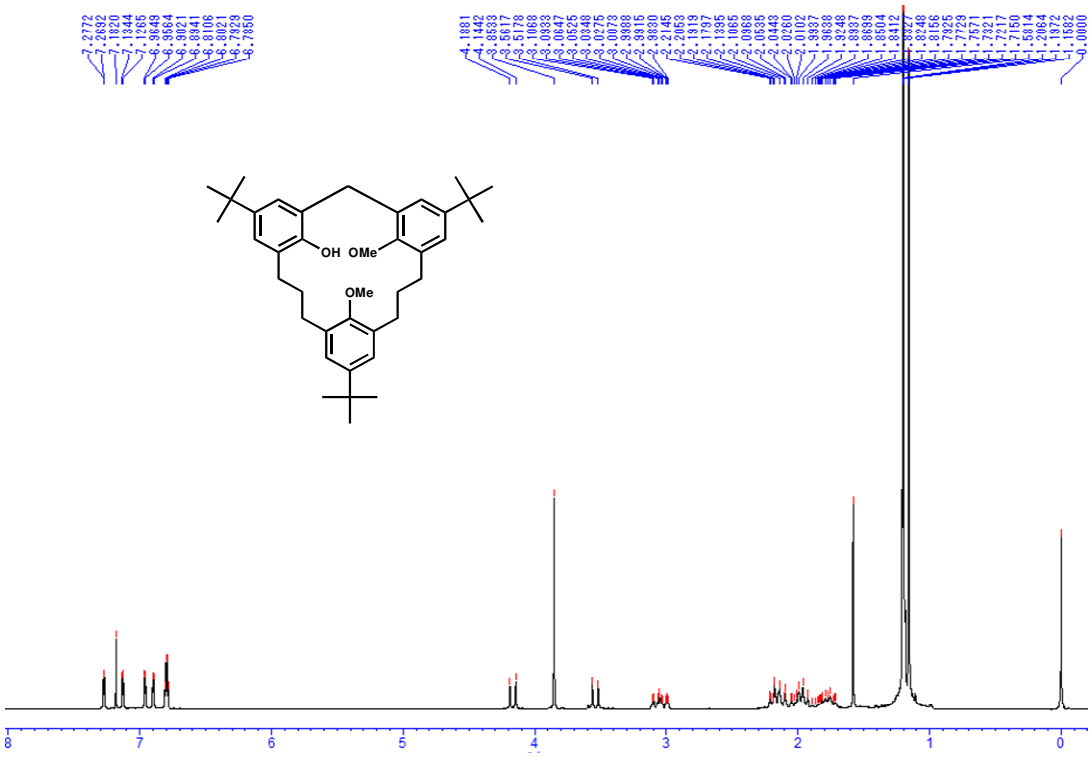


Figure S1-10 ^{1}H-NMR spectrum (300 MHz, 298 K, * $CDCl_3$) for **8** with D_2O.

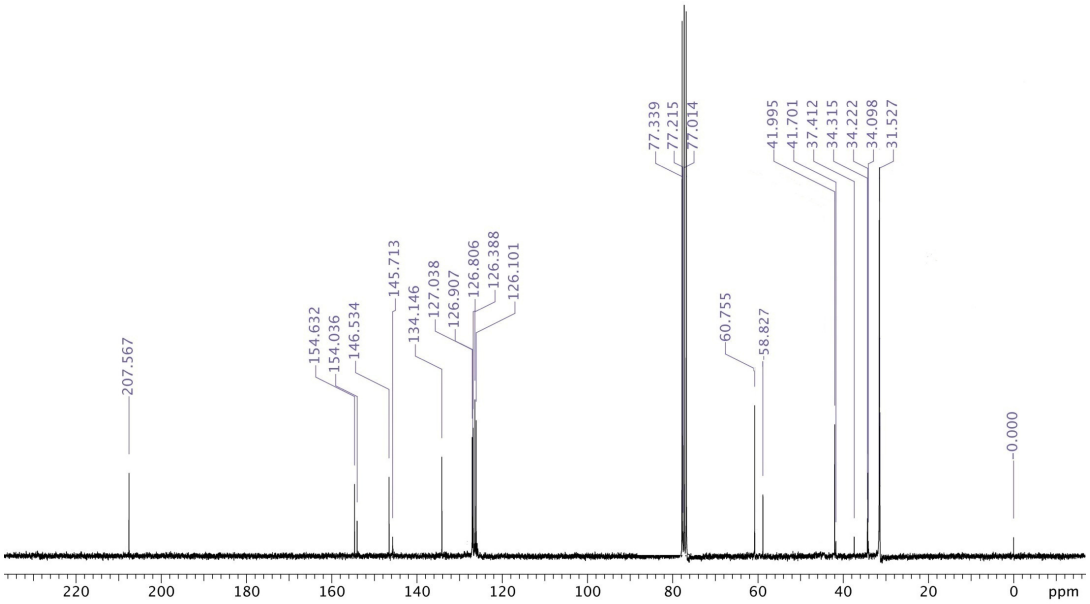


Figure S1-11 ^{13}C-NMR spectrum (100 MHz, 298 K, * $CDCl_3$) for **3.**

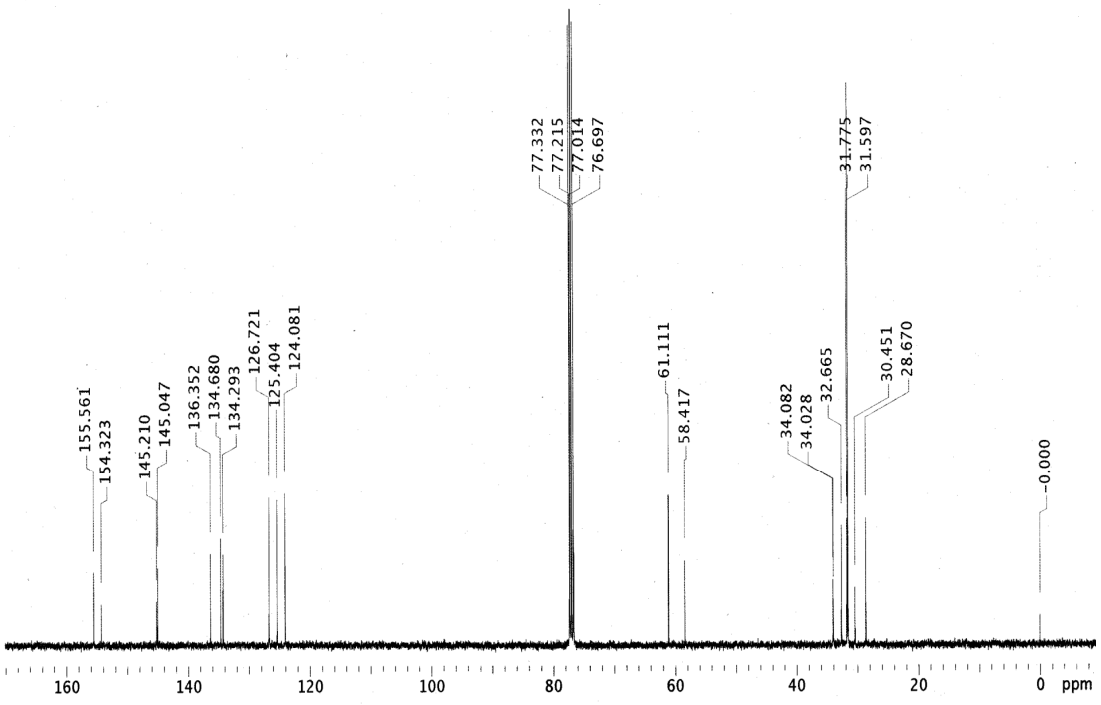


Figure S1-12 ^{13}C-NMR spectrum (100 MHz, 298 K, * $CDCl_3$) for **4**.

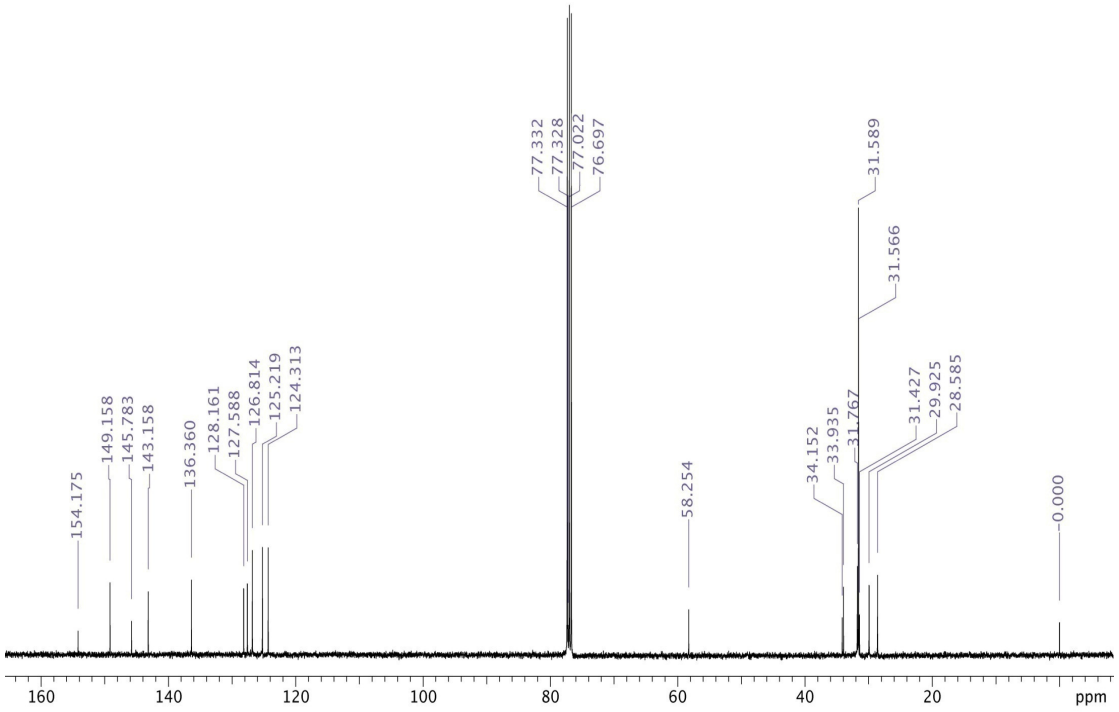


Figure S1-13 ^{13}C-NMR spectrum (100 MHz, 298 K, * $CDCl_3$) for **5.**

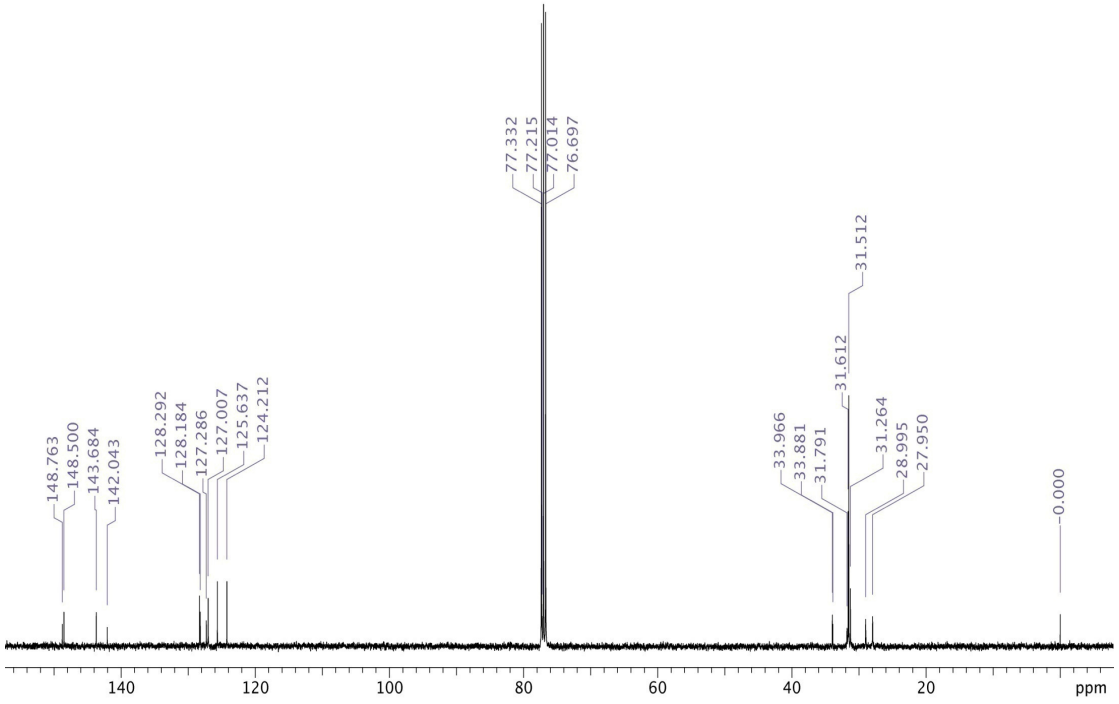


Figure S1-14 ^{13}C-NMR spectrum (100 MHz, 298 K, * $CDCl_3$) for **6.**

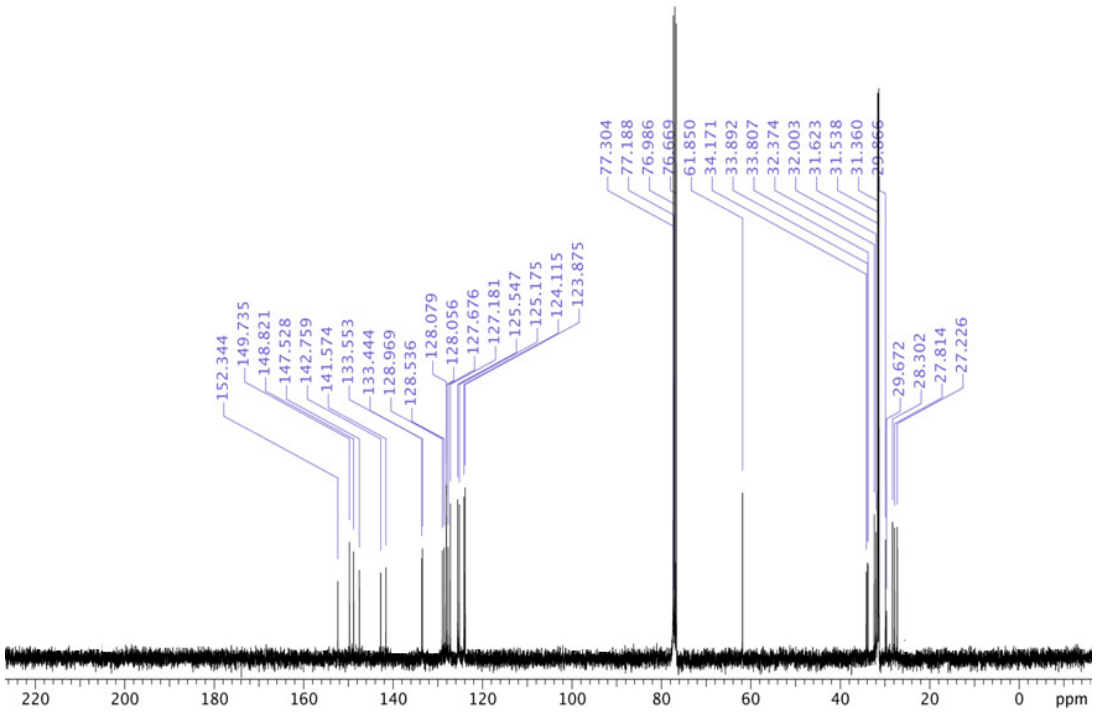


Figure S1-15 ^{13}C-NMR spectrum (100 MHz, 298 K, * $CDCl_3$) for **7.**

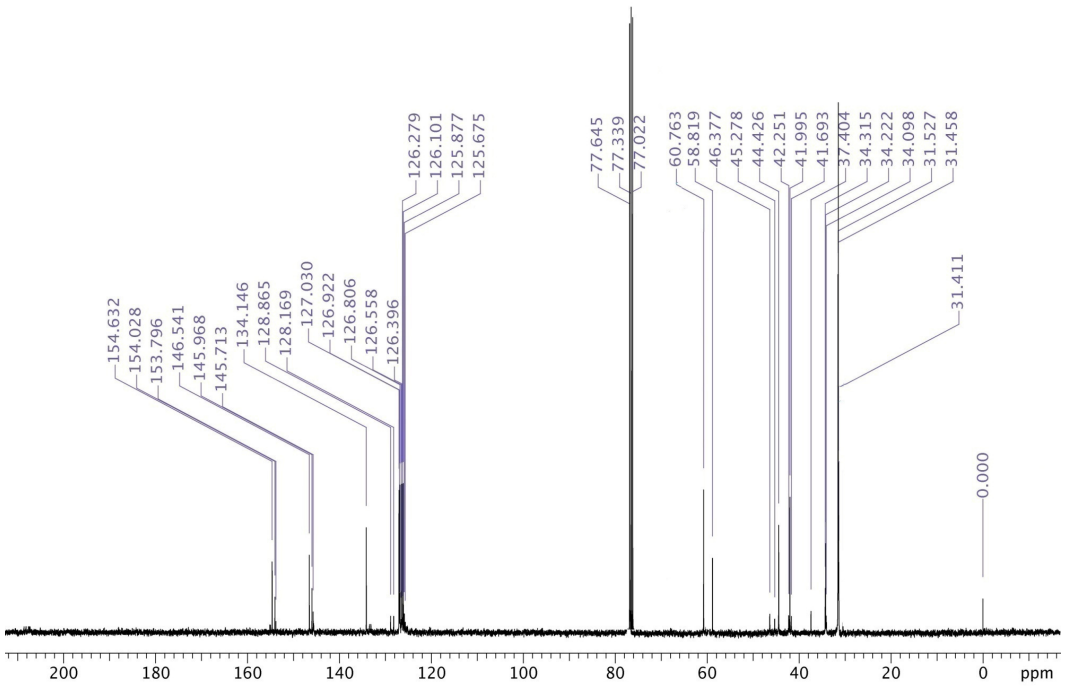


Figure S1-16 ^{13}C-NMR spectrum (100 MHz, 298 K, * $CDCl_3$) for **8.**

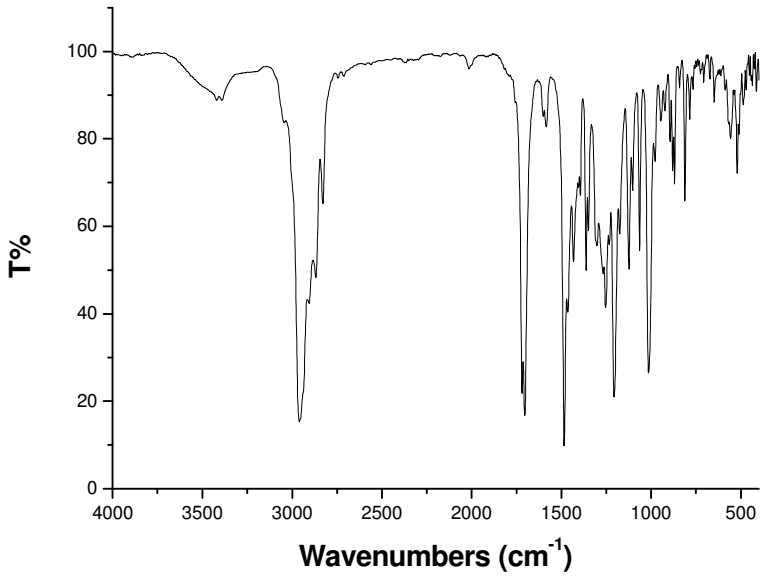


Figure S2-1 FT-IR spectrum for **3.**

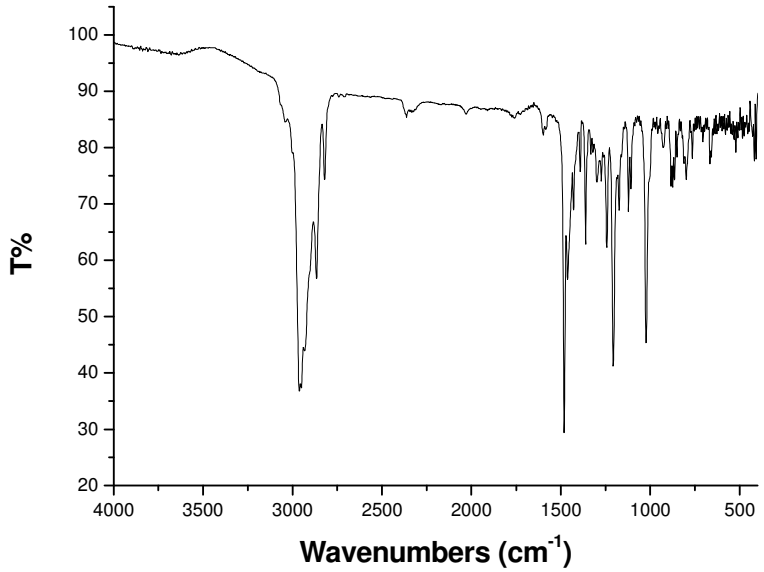


Figure S2-2 FT-IR spectrum for **4.**

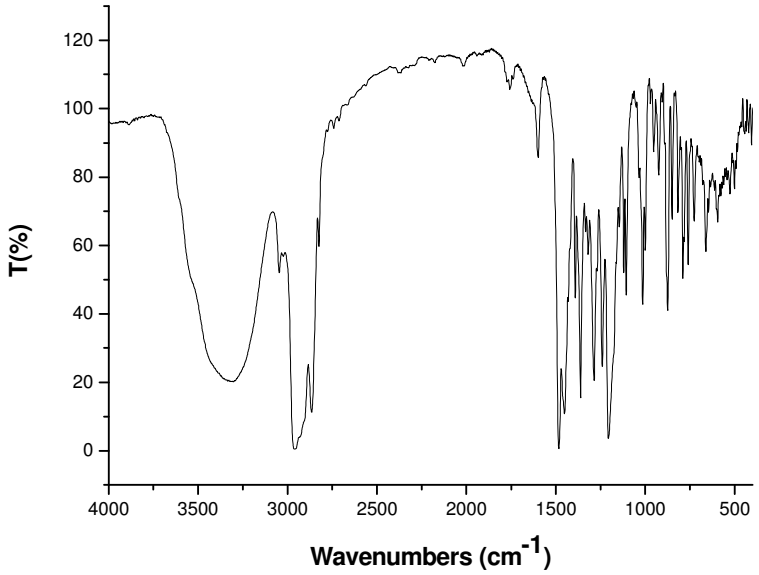


Figure S2-3 FT-IR spectrum for **5.**

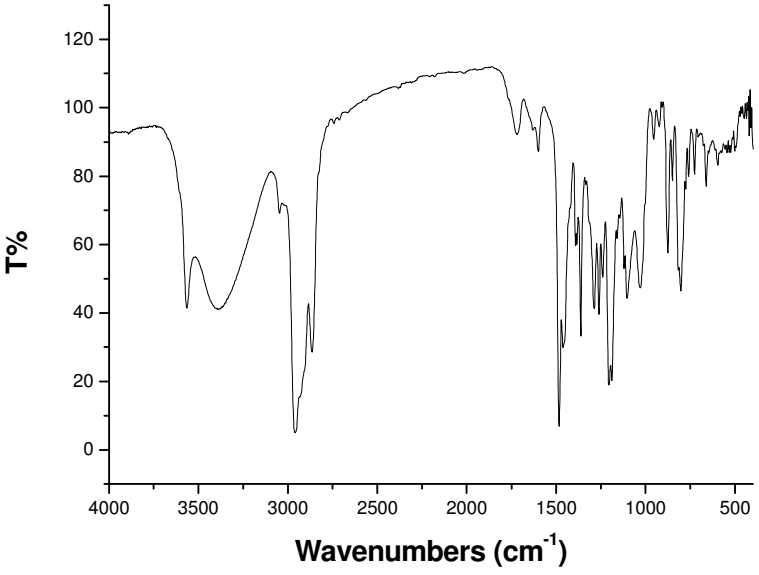


Figure S2-4 FT-IR spectrum of the compound **6.**

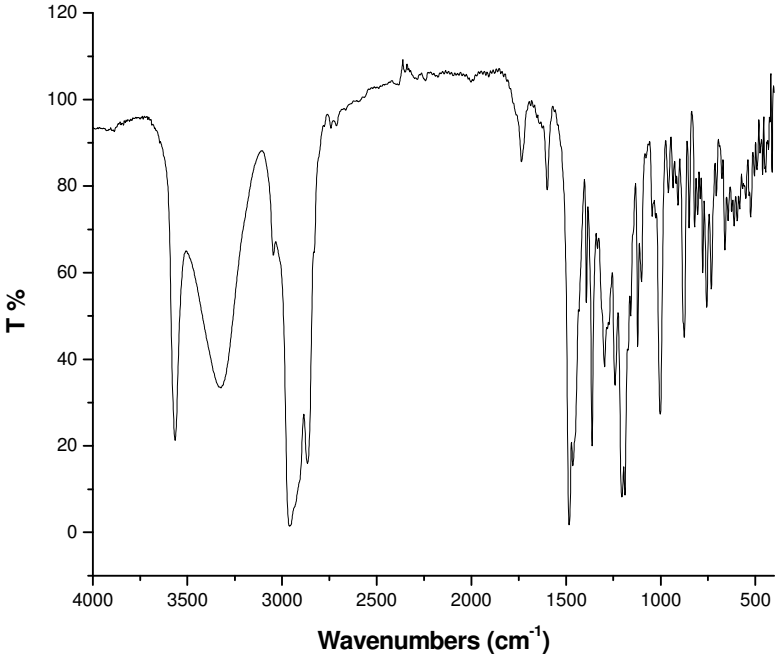


Figure S2-5 FT-IR spectrum for **7.**

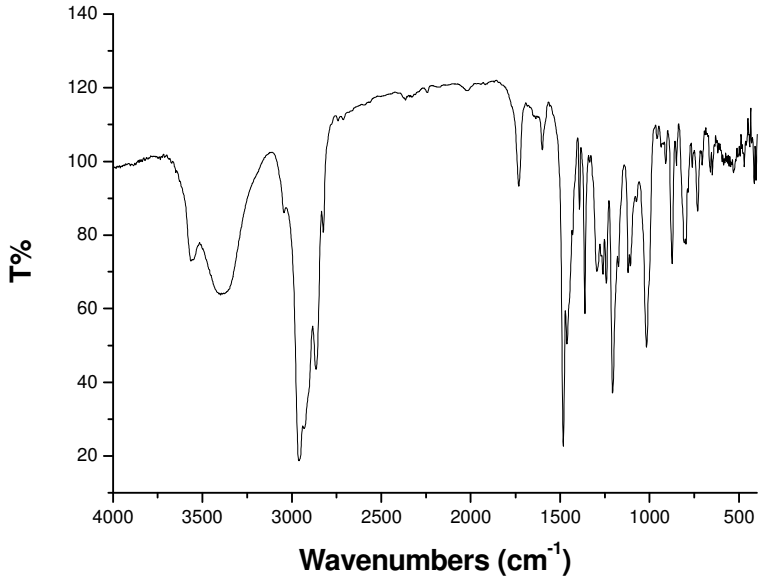


Figure S2-6 FT-IR spectrum for **8.**

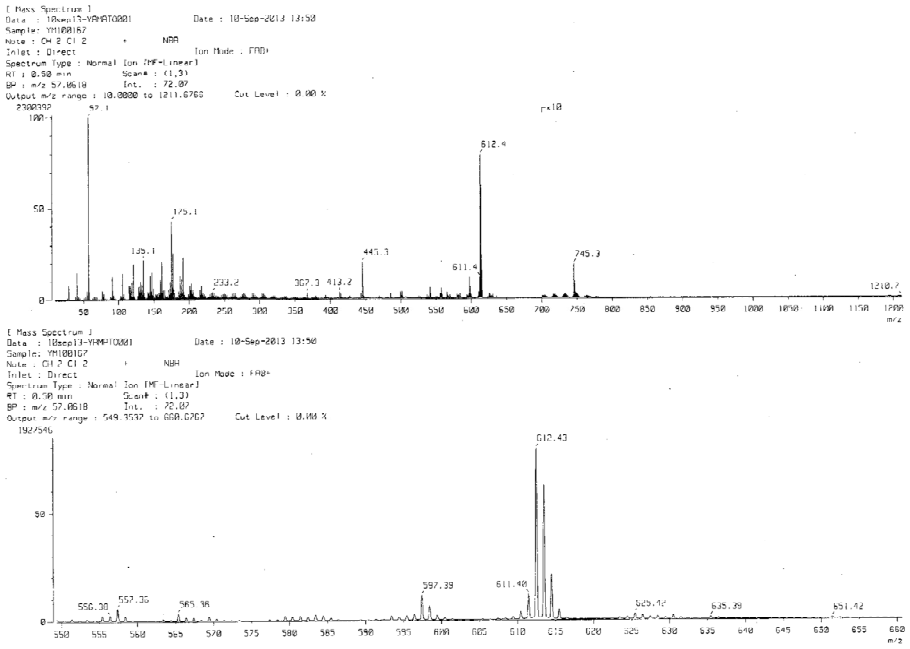


Figure S3-1 Mass spectrum for **3**.

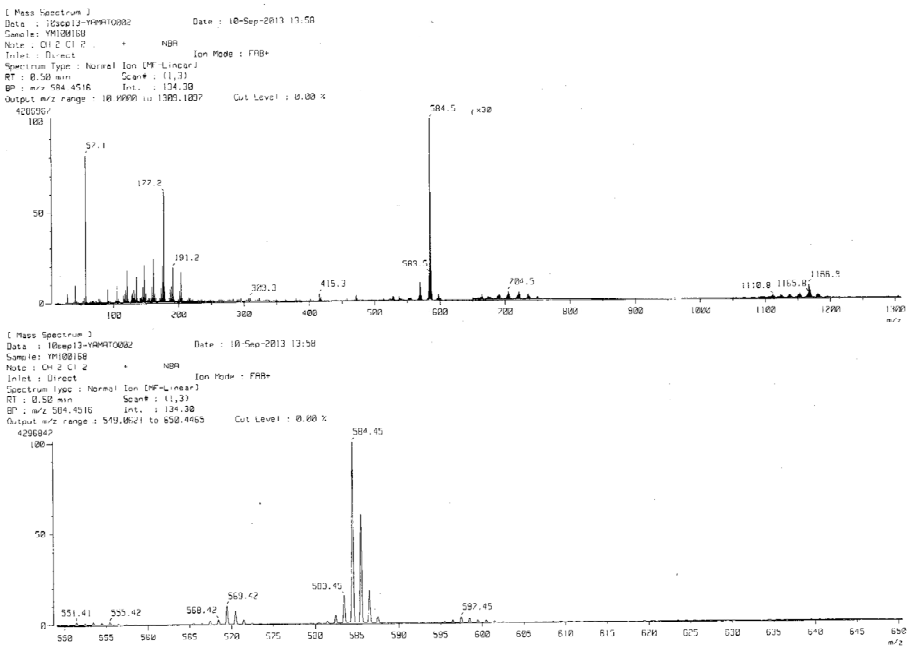


Figure S3-2 Mass spectrum for **4.**

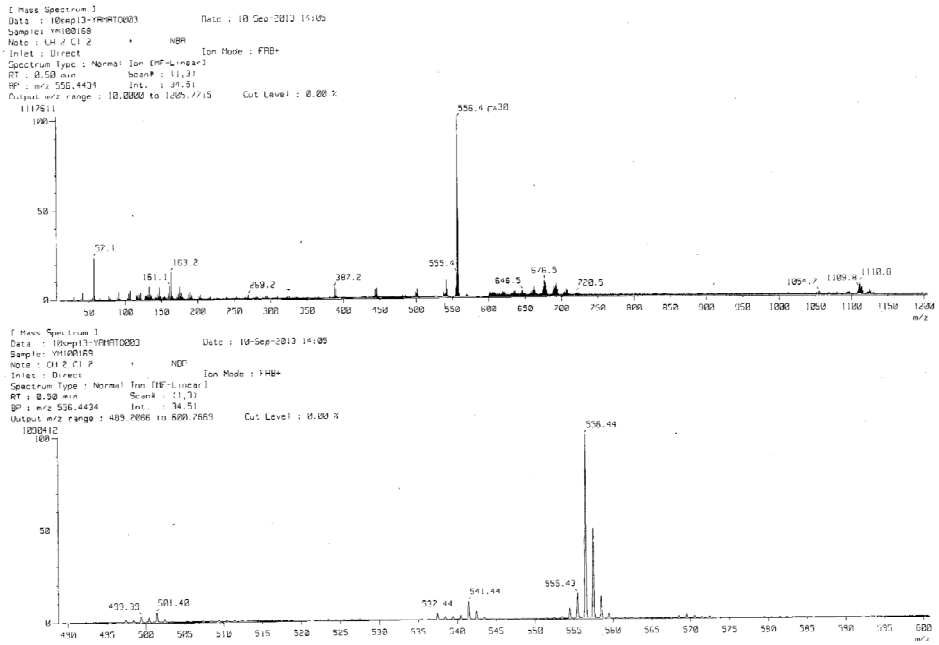


Figure S3-3 Mass spectrum for **5.**

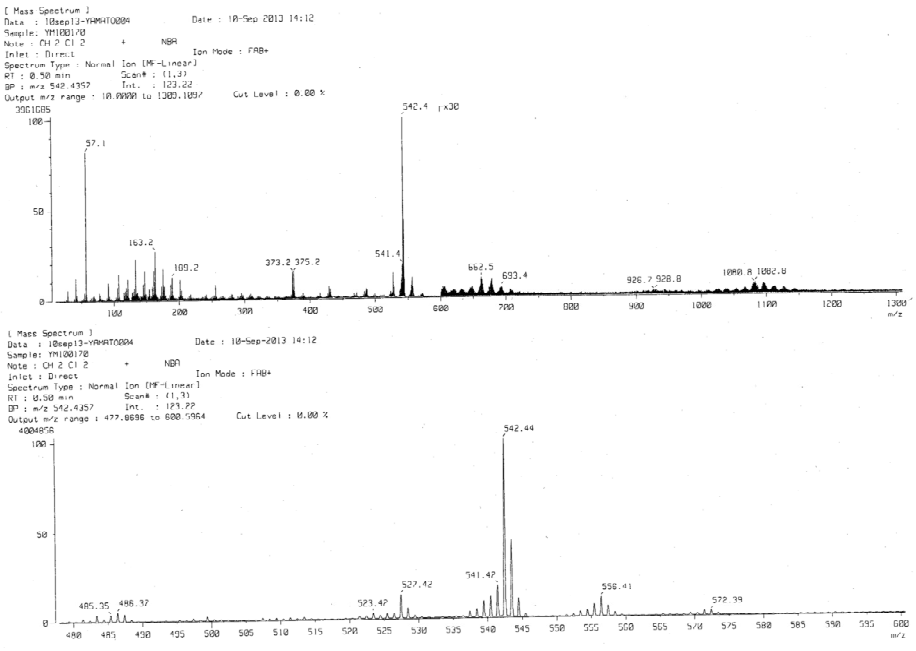


Figure S3-4 Mass spectrum for **6.**

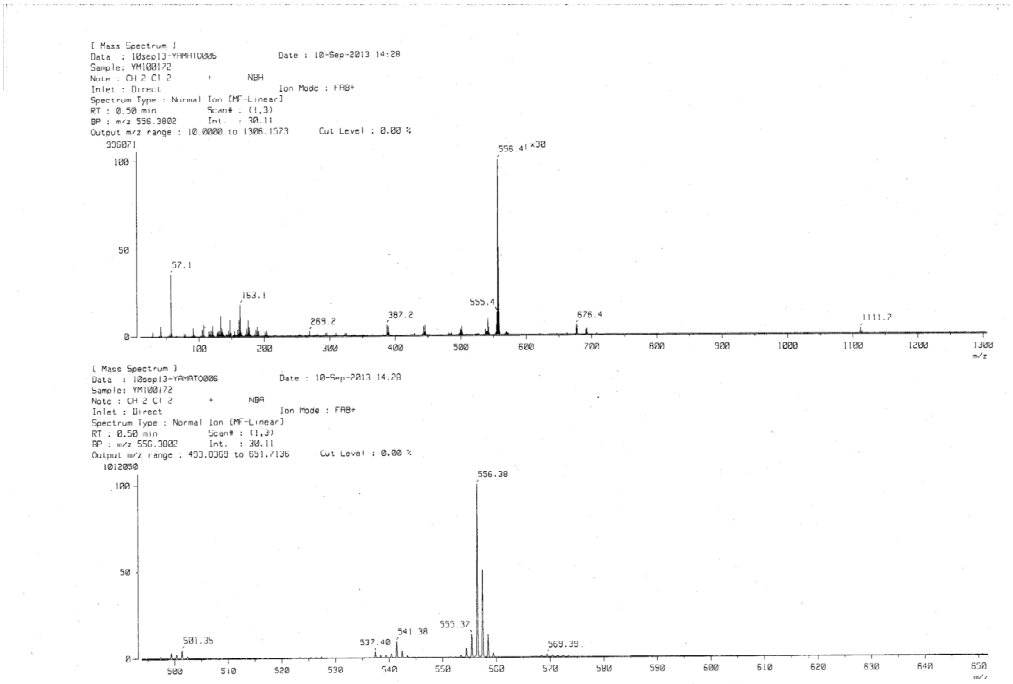


Figure S3-5 Mass spectrum for **7.**

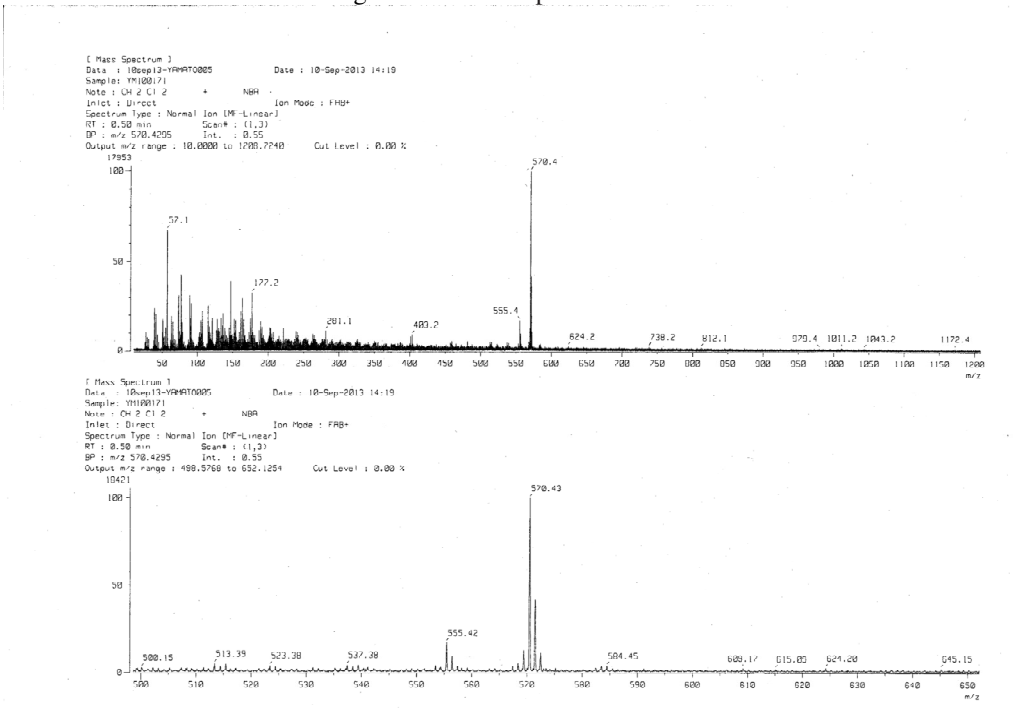


Figure S3-6 Mass spectrum for **8.**

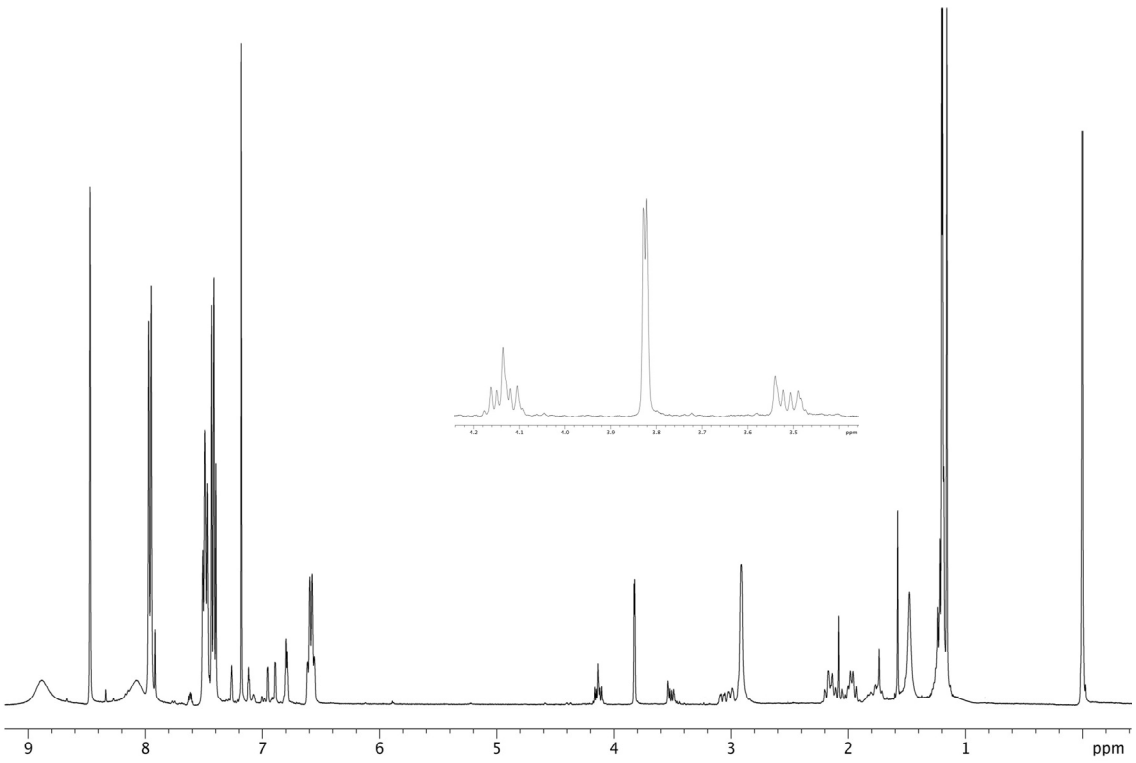


Figure S4-1 ^{1}H-NMR spectrum ($CDCl_3$; 400 MHz) for **8** with Pirkle's reagent.

X-ray crystallography

Table S1 Summary of crystal data for **5**.[a,b]

Parameter	**5**
Empirical formula	$C_{38}\ H_{52}\ O_3$
Formula weight [g mol^{-1}]	556.80
Crystal system	monoclinic
Space group	$P2_1/n$
A [Å]	13.1224(5)
B [Å]	14.4709(10)
C [Å]	17.6162(12)
α [°]	90.0000
β [°]	91.595(4)
γ [°]	90.0000
Volume [Å^3]	3343.9(3)
Z	4
Density, calcd [g m^{-3}]	1.106
Temperature [K]	100(2)
Unique reflns	6270
Obsd reflns	4089
Parameters	381
R_{int}	0.0973
R[I>2σ(I)][a]	0.0586
wR[I>2σ(I)][b]	0.1503
GOF on F^2	1.030

[a] Conventional R on F_{hkl}: $\Sigma||F_o| - |F_c||/\sigma|F_o|$. [b] Weighted R on $|F_{hkl}|^2$: $\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]^{1/2}$

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) I

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: I

```
Bond precision:  C-C = 0.0032 A          Wavelength=0.71073

Cell:            a=13.1224(5)    b=14.4709(10)      c=17.6162(12)
                 alpha=90        beta=91.595(4)     gamma=90
Temperature:     100 K

                 Calculated                Reported
Volume           3343.9(3)                 3343.9(3)
Space group      P 21/n                    P 21/n
Hall group       -P 2yn                    ?
Moiety formula   C38 H52 O3                ?
Sum formula      C38 H52 O3                C38 H52 O3
Mr               556.80                    556.80
Dx,g cm-3        1.106                     1.106
Z                4                         4
Mu (mm-1)        0.068                     0.068
F000             1216.0                    1216.0
F000'            1216.49
h,k,lmax         15,17,21                  15,17,21
Nref             6349                      6270
Tmin,Tmax        0.985,0.995
Tmin'            0.985

Correction method= Not given

Data completeness= 0.988          Theta(max)= 25.680

R(reflections)= 0.0586( 4089)     wR2(reflections)= 0.1503( 6270)

S = 1.030                 Npar= 381
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

```
PLAT420_ALERT_2_B D-H Without Acceptor       O1     -   H1     ...     Please Check
```

Alert level C

```
PLAT048_ALERT_1_C MoietyFormula Not Given .......................     Please Do !
PLAT125_ALERT_4_C No '_symmetry_space_group_name_Hall' Given .....     Please Do !
PLAT242_ALERT_2_C Low       Ueq as Compared to Neighbors for .....         C7 Check
```

Alert level G

```
PLAT005_ALERT_5_G No _iucr_refine_instructions_details  in the CIF     Please Do !
PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ..............          2 Report
PLAT899_ALERT_4_G SHELXL97   is Deprecated and Succeeded by SHELXL       2014 Note
```

---

0 **ALERT level A** = Most likely a serious problem - resolve or explain
1 **ALERT level B** = A potentially serious problem, consider carefully
3 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
3 **ALERT level G** = General information/check it is not something unexpected

1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
2 ALERT type 2 Indicator that the structure model may be wrong or deficient
0 ALERT type 3 Indicator that the structure quality may be low
2 ALERT type 4 Improvement, methodology, query or suggestion
2 ALERT type 5 Informative message, check

---

checkCIF publication errors

Alert level A

```
PUBL004_ALERT_1_A  The contact author's name and address are missing,
            _publ_contact_author_name and _publ_contact_author_address.
PUBL005_ALERT_1_A  _publ_contact_author_email, _publ_contact_author_fax and
            _publ_contact_author_phone are all missing.
            At least one of these should be present.
PUBL006_ALERT_1_A  _publ_requested_journal is missing
            e.g. 'Acta Crystallographica Section C'
PUBL008_ALERT_1_A  _publ_section_title is missing. Title of paper.
PUBL009_ALERT_1_A  _publ_author_name is missing. List of author(s) name(s).
PUBL010_ALERT_1_A  _publ_author_address is missing. Author(s) address(es).
PUBL012_ALERT_1_A  _publ_section_abstract is missing.
            Abstract of paper in English.
```

Alert level G

```
PUBL017_ALERT_1_G The _publ_section_references section is missing or
            empty.
```

---

7 **ALERT level A** = Data missing that is essential or data in wrong format
1 **ALERT level G** = General alerts. Data that may be required is missing

---

Publication of your CIF

You should attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the nature of your study may justify the reported deviations from journal submission requirements and the more serious of these should be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. *checkCIF* was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

If level A alerts remain, which you believe to be justified deviations, and you intend to submit this CIF for publication in a journal, you should additionally insert an explanation in your CIF using the Validation Reply Form (VRF) below. This will allow your explanation to be considered as part of the review process.

Validation response form

Please find below a validation response form (VRF) that can be filled in and pasted into your CIF.

```
# start Validation Reply Form
_vrf_PUBL004_GLOBAL
;
PROBLEM: The contact author’s name and address are missing,
RESPONSE: ...
;
_vrf_PUBL005_GLOBAL
;
PROBLEM: _publ_contact_author_email, _publ_contact_author_fax and
RESPONSE: ...
;
_vrf_PUBL006_GLOBAL
;
PROBLEM: _publ_requested_journal is missing
RESPONSE: ...
;
_vrf_PUBL008_GLOBAL
;
PROBLEM: _publ_section_title is missing. Title of paper.
RESPONSE: ...
;
_vrf_PUBL009_GLOBAL
;
PROBLEM: _publ_author_name is missing. List of author(s) name(s).
RESPONSE: ...
;
_vrf_PUBL010_GLOBAL
;
PROBLEM: _publ_author_address is missing. Author(s) address(es).
RESPONSE: ...
;
_vrf_PUBL012_GLOBAL
;
```

```
PROBLEM: _publ_section_abstract is missing.
RESPONSE: ...
;
# end Validation Reply Form
```

If you wish to submit your CIF for publication in Acta Crystallographica Section C or E, you should upload your CIF via the web. If your CIF is to form part of a submission to another IUCr journal, you will be asked, either during electronic submission or by the Co-editor handling your paper, to upload your CIF via our web site.

PLATON version of 20/08/2014; check.def file version of 18/08/2014

Datablock I - ellipsoid plot