Tetrahedron: *Asymmetry* 19 (2008) 1470–1475

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Resolution of inherently chiral *anti*-*O*,*O*′-dialkylthiacalix[4]arenes and determination of their absolute stereochemistries

Fumitaka Narumi [a,*], Nobuji Matsumura [b], Nariaki Sasagawa [b], Koichi Natori [b], Takashi Kajiwara [c], Tetsutaro Hattori [b,*]

[a] *Department of Basic Sciences, School of Science and Engineering, Ishinomaki Senshu University, 1 Shinmito, Minamisakai, Ishinomaki 986-8580, Japan*
[b] *Department of Environmental Studies, Graduate School of Environmental Studies, Tohoku University, 6-6-11 Aramaki-Aoba, Aoba-ku, Sendai 980-8579, Japan*
[c] *Department of Chemistry, Graduate School of Science, Tohoku University, Aramaki-Aoba, Aoba-ku, Sendai 980-8578, Japan*

ARTICLE INFO

Article history:
Received 1 May 2008
Accepted 19 May 2008
Available online 27 June 2008

ABSTRACT

Inherently chiral *anti*-*O*,*O*′-dibenzyl- and *anti*-*O*,*O*′-dibutyl-*p*-*tert*-butylthiacalix[4]arenes **4** and **6** are resolved as (*S*)-2-methoxy-2-(naphthalen-1-yl)propionic esters by flash chromatography. The absolute stereochemistries were determined to be (S_a)-(+)-**4** and (S_a)-(+)-**6** by X-ray crystallographic analyses.

1. Introduction

Over the last decade, interest in the development of chiral host molecules with a calixarene skeleton has increased.[1] A variety of chiral calixarenes have been prepared by introducing chiral substituents at the lower rim through the phenolic oxygens or at the *para* positions, and applied as chromogenic receptors,[2] additives in capillary electrophoresis,[3] chiral stationary phases for GC and HPLC,[4] chiral solvating agents for NMR,[5] and so on.[6] On the other hand, although a certain number of inherently chiral calixarenes have been prepared, their chiral recognition abilities have hardly been investigated, seemingly due to the poor accessibility to this type of compounds in enantiopure form;[7,8] they have, in most cases, been resolved on an analytical scale by chiral HPLC[9] and it is seldom that resolution techniques easy to scale-up were successfully applied to these compounds.[8,10]

anti-*O*,*O*′-Dialkylthiacalix[4]arenes, for example, compounds **4** and **6**, are one of the simplest inherently chiral calixarenes and expected to show high complexation ability toward metal ions by the cooperative coordination of the two neighboring hydroxy groups with the interpositioned epithio linkage to the metal center.[11,12] Therefore, the development of a synthetic method toward them is highly desirable for designing synthetic receptors, as well as meal catalysts.[13] Previously, we succeeded in the synthesis of methylene-bridged analogues, *anti*-*O*,*O*′-dialkylcalix[4]arenes, via 1,2-*O*-tetraisopropyldisiloxane (TIPDS)-capping by the *O*,*O*′-disiloxylation of calix[4]arene with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, followed by the base-catalyzed dialkylation of the remaining hydroxy groups with an alkyl halide, and subsequent deprotection of the TIPDS moiety.[14] The resolution of the resulting diethers could be achieved by a diastereomeric method.[15] However, the racemic synthesis could not be applied to thiacalix[4]arene **1**, which, on being treated in a similar manner, selectively gave *syn* stereoisomers (e.g., compounds **5** and **7**).[14] This was attributed to the bulkiness of the TIPDS moiety, which allows the attack of an alkyl halide to an anionic intermediate of the thiacalixarene from only the opposite side to the TIPDS moiety with respect to the mean plane defined by the macrocycle, giving a diether of 1,2-alternate conformation. Recently, we found that *syn*-*O*,*O*′-bistriflate ester of thiacalix[4]arene **3**, bearing T_f capping groups smaller than TIPDS for two adjacent hydroxy groups, can be prepared by a base-catalyzed isomerization of *syn*-*O*,*O*″-counterpart **2** and shows good *anti* selectivity in the dialkylation.[16] With a method for the racemic synthesis in hand, we herein report the resolution of *anti*-*O*,*O*′-dialkylthiacalix[4]arenes **4** and **6** on a gram-scale by flash chromatography after conversion into the diastereomeric esters of (*S*)-2-methoxy-2-(naphthalen-1-yl)propionic acid [(*S*)-MNPA].[17] Also reported are the absolute stereochemistries determined by X-ray crystallographic analysis. To the best of our knowledge, this is the first report on the synthesis of optically active *anti*-*O*,*O*′-dialkylthiacalix[4]arenes.

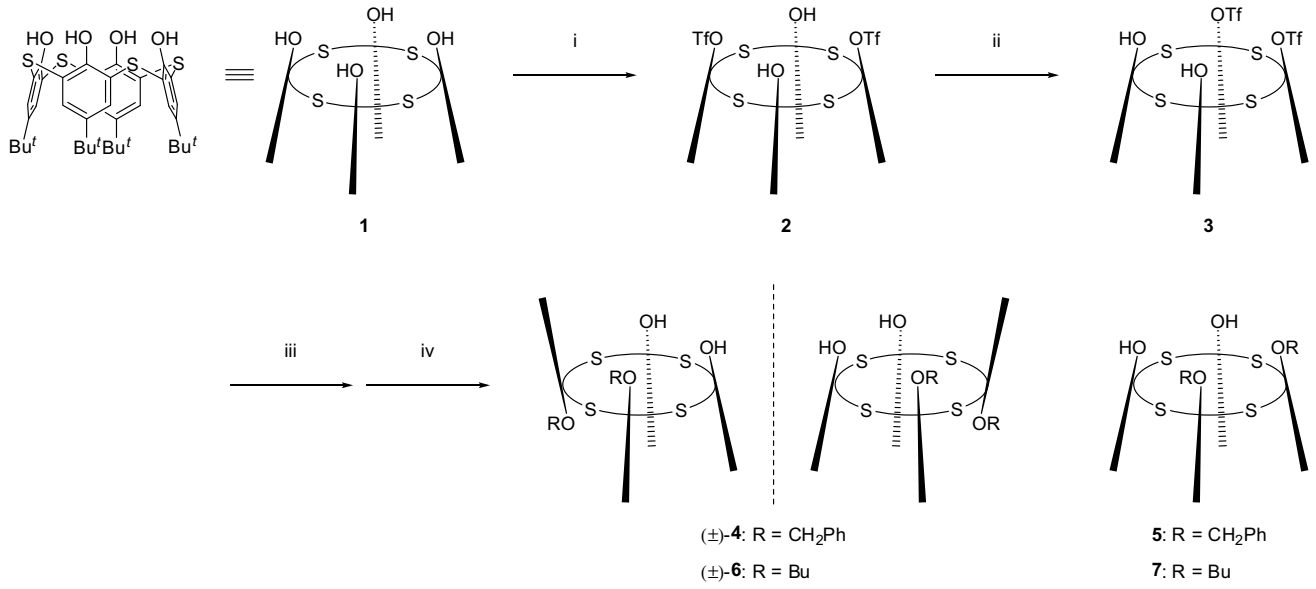
2. Results and discussion

2.1. Synthesis and resolution of *O*,*O*′-dialkylthiacalix[4]arenes 4 and 6

Racemic diethers **4** and **6** were prepared on a gram-scale, according to the reported procedure (Scheme 1).[16] Commercially available thiacalix[4]arene **1** was allowed to react with 2.9 mol equiv of triflic anhydride in the presence of pyridine in dichloromethane at room temperature to give *syn*-*O*,*O*″-bistriflate ester **2** (76%), which was isomerized by heating at 60 °C in DMSO in the presence of 4.4 mol equiv of triethylamine to give

* Corresponding authors. Tel.: +81 225 22 7716; fax: +81 225 22 7746 (F.N.).
E-mail addresses: fnarumi@isenshu-u.ac.jp (F. Narumi), hattori@orgsynth.che.tohoku.ac.jp (T. Hattori).

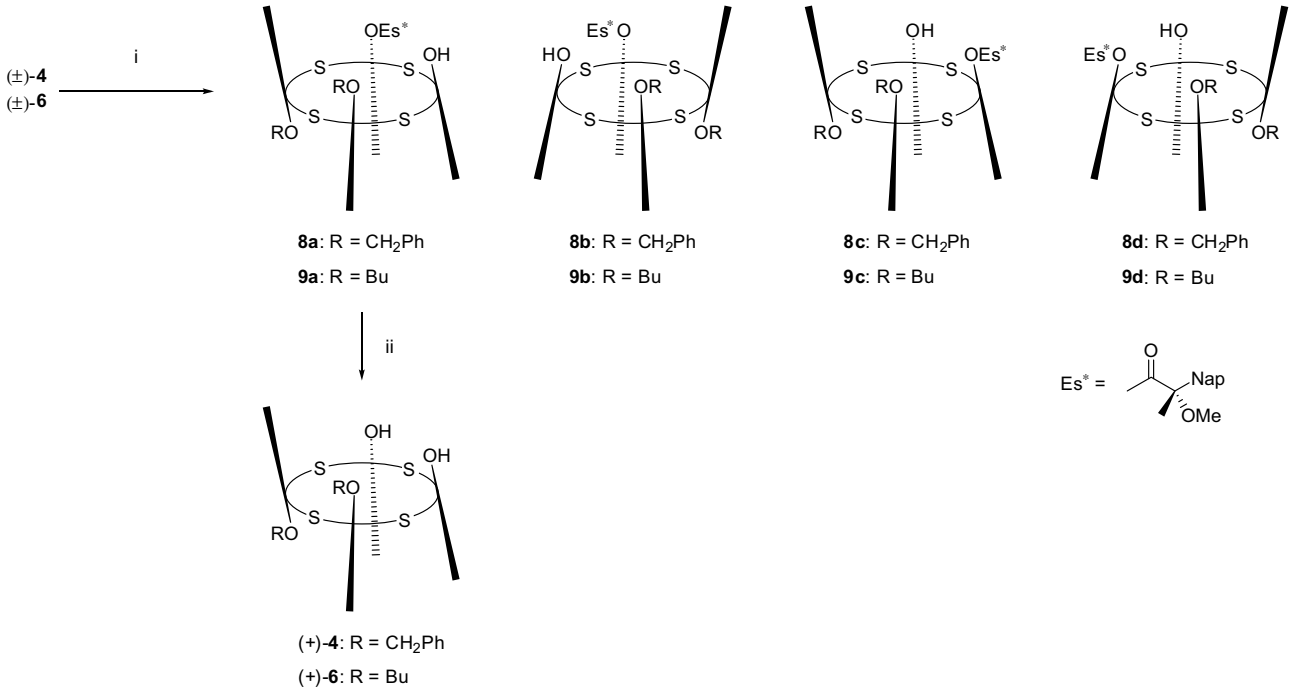
0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.05.034



Scheme 1. Reagents: (i) triflic anhydride, Py, dichloromethane; (ii) NEt_3, DMSO; (iii) benzyl bromide or 1-iodobutane, K_2CO_3, acetone; (iv) NaOH aq, EtOH, THF.

syn-*O*,*O*′-counterpart **3** (92%). The dialkylation was performed by the treatment of diester **3** with 12 mol equiv of benzyl bromide in the presence of K_2CO_3 in refluxing acetone to give a mixture of three stereoisomers of *syn*-*O*,*O*′-bistriflate ester of *O*″,*O*‴-dibenzylthiacalix[4]arene,[16] which was hydrolyzed without separation under basic conditions to give, after recrystallization, *anti*-*O*,*O*′-dibenzyl ether (±)-**4** in 67% yield. The filtrate was purified by column chromatography to give *syn*-*O*,*O*′-dibenzyl ether **5** (28%) with an additional crop of (±)-**4** (2%). By using the same dialkylation procedure, *anti*- and *syn*-*O*,*O*′-dibutyl ether (±)-**6** and **7** were obtained in 71% and 23% yields, respectively.

The resolution of diethers (±)-**4** and (±)-**6** was examined by using (*S*)-MNPA as a chiral derivatizing agent (Scheme 2). The treatment of racemic dibenzyl ether (±)-**4** with (*S*)-MNPA in dichloromethane in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) gave a mixture of four possible diastereomeric monoesters **8a**–**d**, from which ester **8a** was successfully separated by flash chromatography in 36% yield (see Section 4). The stereochemistry of ester **8a** was determined by an X-ray crystallographic analysis (vide infra). The removal of the MNPA moiety from ester **8a** by conversion into the methyl ester with sodium methoxide gave enantiopure diether (+)-**4** in 95% yield. The resolution of dibutyl ether (±)-**6** was achieved by the same procedure (Scheme 2). Flash chromatography of a mixture of **9a**–**d** isolated ester **9a** (36%), which gave, after the removal of the MNPA moiety, diether (+)-**6** in almost quantitative yield.



Scheme 2. Reagents: (i) (*S*)-MNPA, DCC, PPy, dichloromethane; (ii) sodium methoxide, methanol, water.

2.2. Determination of the absolute stereochemistries of compounds (+)-4 and (+)-6

In our previous paper,[15] we reported that the absolute stereochemistries of *anti*-*O*,*O*′-dialkylcalix[4]arenes could be determined by the CD exciton chirality method:[18] The two etherified phenol units showed an exciton-split CD pattern at the UV band of ca. 230 nm, which represents the axial twist of the two etherified phenol units. However, the CD method could not be applied to thiacalixarene derivatives (+)-**4** and (+)-**6**, because their CD patterns were ambiguous, presumably due to the auxochromous epithio linkages (Figs. 1 and 2).

We next tried X-ray crystallographic analysis: The recrystallization of ester **8a** from chloroform–acetonitrile gave single crystals, one of which was subjected to X-ray crystallographic analysis. The crystal of **8a** belongs to the monoclinic system with a *C*2 space group. In the asymmetric unit, there are two crystallographically independent molecules, which adopt similar conformations to each other. Figure 3 shows the X-ray structure of one of the two independent molecules. Compound **8a** adopts a partial-cone conformation in the crystal. Interestingly, the benzyl moiety attached to the inverted phenol unit of the calix macrocycle is included into the cavity formed by the other three phenol units. As previously reported,[15] the axial chirality of *anti*-*O*,*O*′-dialkylcalix[4]arenes can be defined by the spatial arrangement of the four aromatic carbons at the *ortho*-positions to the epithio linkage between the two etherified phenol units. By this definition, the absolute stereochemistry of ester **8a**, as well as that of dibenzyl ether (+)-**4**, was assigned to be (S_a) by using the (*S*)-MNPA moiety as the internal reference.

A single crystal of ester **9a**, obtained by recrystallization from diethyl ketone–acetonitrile, was analyzed by X-ray diffraction. It was shown that the crystal belongs to the triclinic system with a *P*1 space group. The asymmetric unit contains two independent molecules of similar conformations, one of which is shown in Figure 4. Compound **9a** adopts a partial-cone conformation and an acetonitrile molecule is included in the calix cavity. From the X-ray structure, the absolute configuration of ester **9a**, as well as that of dibutyl ether (+)-**6**, was determined to be (S_a) by using the (*S*)-MNPA moiety as the internal reference.

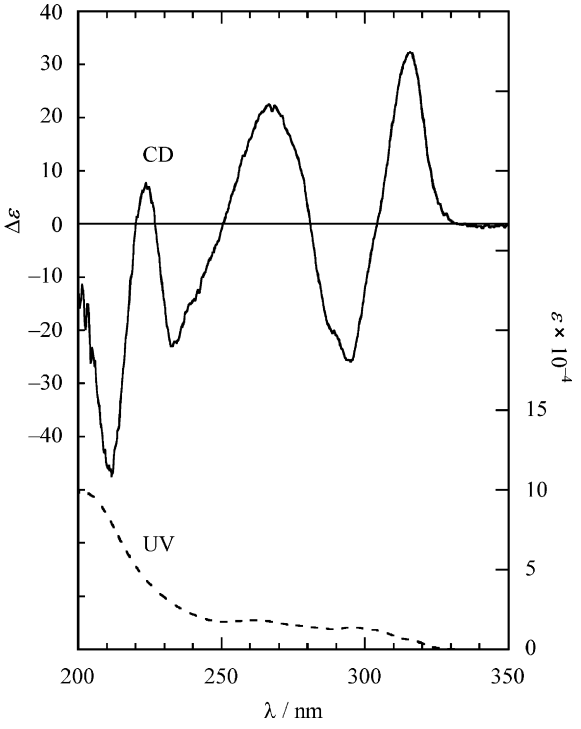


Figure 1. CD and UV spectra of dibenzyl ether (+)-**4** (0.18 mM) in ethanol at 25 °C.

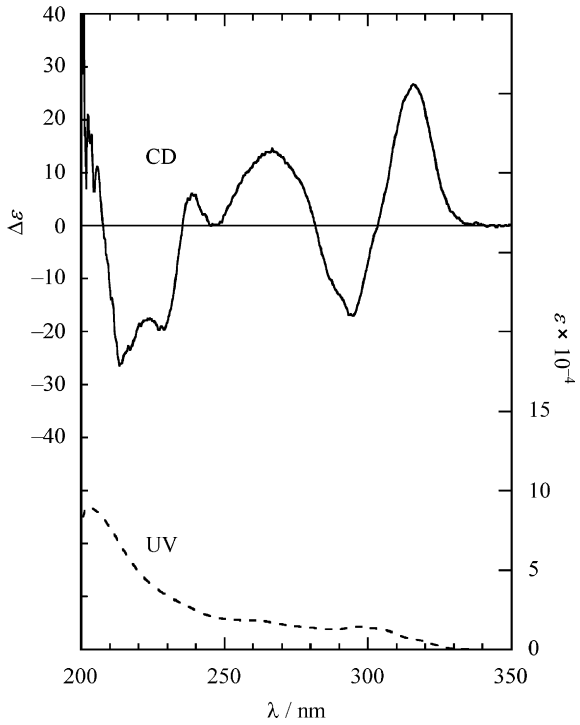


Figure 2. CD and UV spectra of dibutyl ether (+)-**6** (0.19 mM) in ethanol–dioxane (9:1) at 25 °C.

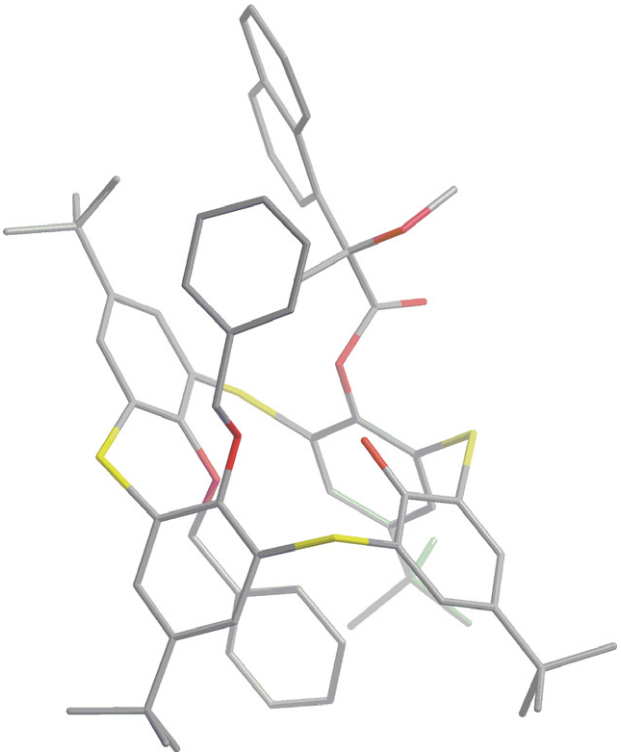


Figure 3. X-ray structure of diastereomeric ester **8a**.

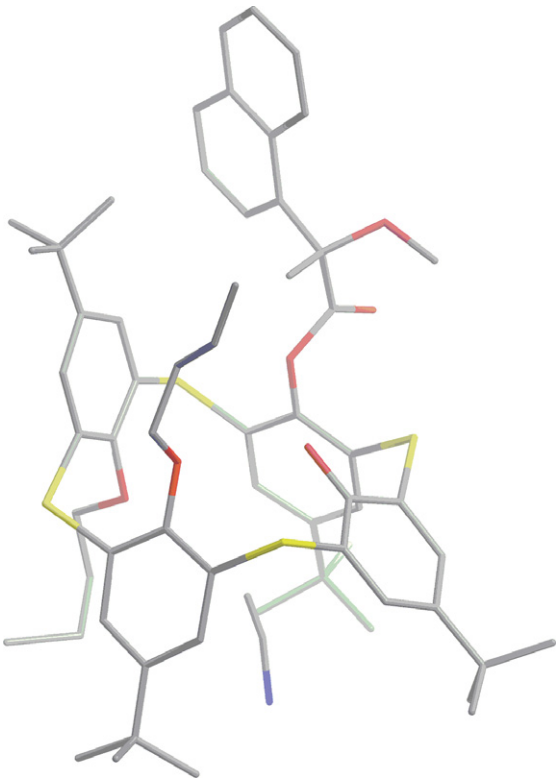


Figure 4. X-ray structure of diastereomeric ester **9a**.

3. Conclusion

In conclusion, we have reported a practical method to prepare enantiopure *anti*-*O*,*O*′-diethers of thiacalix[4]arenes (+)-**4** and (+)-**6** on a gram-scale. The synthesis of racemates was achieved by our recently reported di-*O*-protection method with Tf moieties. The racemates could be resolved as the (*S*)-MNPA esters by flash chromatography. The absolute stereochemistries were determined to be (S_a)-(+)-**4** and (S_a)-(+)-**6** by X-ray analyses.

4. Experimental

4.1. General

Melting points were taken using a Mitamura Riken MP-P or a Yamato IA-9000 apparatus. Microanalyses were carried out in the Microanalytical Laboratory of the Institute of Multidisciplinary Research for Advanced Materials, Tohoku University. Optical rotations were measured on a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400, DRX-500, or JEOL JNM-ECA300 spectrometer using tetramethylsilane (^{1}H NMR) or chloroform (^{13}C NMR) as the internal standard and $CDCl_3$ as solvent. *J*-Values are given in Hertz. Open columns and flash columns were prepared by using Kanto Kagaku Silica Gel 60N (spherical, neutral, 63–210 μm) and Silica Gel 60N (spherical, neutral, 40–50 μm), respectively. Mass spectra were measured on a JEOL JMS-DX602 spectrometer. Triethylamine was distilled from calcium hydride and stored under nitrogen. Other materials were used as purchased.

4.2. Synthesis of *syn*-*O*,*O*′-bistriflate ester of thiacalix[4]arene 3

This compound was prepared on a large scale via *syn*-*O*,*O*″-bistriflate ester **2**, according to the reported procedure.[16,19] To an ice-cold suspension of thiacalix[4]arene **1** (21.6 g, 30.0 mmol) in anhydrous dichloromethane (40 mL) were added anhydrous pyridine (d = 0.983 g mL^{-1}, 14.5 mL, 0.180 mol) and triflic anhydride (d = 1.72 g mL^{-1}, 14.5 mL, 88.3 mmol) under nitrogen. After stirring at room temperature for 3 h, the mixture was quenched with 2 M HCl and the mixture extracted with chloroform. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by recrystallization from dichloromethane–methanol to give *syn*-*O*,*O*″-bistriflate ester **2**[19] (22.6 g, 76%) as a colorless powder.

A mixture of compound **2** (22.6 g, 22.9 mmol), triethylamine (d = 0.726 g mL^{-1}; 14.0 mL, 0.100 mol), and anhydrous DMSO (300 mL) was heated at 60 °C for 8 h under nitrogen. After cooling, the reaction was quenched with 2 M HCl (200 mL) to give a precipitate, which was collected by filtration, washed successively with 2 M HCl and water, and then dried under an air stream. The crude product was purified by recrystallization from dichloromethane–methanol to give *syn*-*O*,*O*′-bistriflate ester **3** (20.7 g, 92%), the spectroscopic data of which were identical with those reported previously.[16]

4.3. Synthesis of *anti*-*O*,*O*′-dibenzylthiacalix[4]arene (±)-4

This compound was prepared on a large scale according to the reported procedure.[16] To a solution of compound **3** (9.86 g, 10.0 mmol) in anhydrous acetone (100 mL) were added K_2CO_3 (16.6 g, 0.120 mol) and benzyl bromide (d = 1.44 g mL^{-1}; 14.0 mL, 0.118 mol), after which the mixture was refluxed for 6 h under nitrogen. After cooling, the reaction was quenched with 2 M HCl and the mixture extracted with dichloromethane. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was recrystallized from methanol to give a mixture of three stereoisomers of *syn*-*O*,*O*′-bistriflate ester of *O*″,*O*‴-dibenzylthiacalix[4]arene[16] (11.3 g) as a colorless powder, which was dissolved in a 1:1 mixture of THF and ethanol (400 mL). To the solution was added 20 M NaOH (25 mL) after which the mixture was heated at reflux for 8 h. After cooling, most of the organic solvents were evaporated and the residue extracted with chloroform. The extract was washed successively with 2 M HCl and water, dried over $MgSO_4$, and evaporated. The residue was purified by recrystallization from dichloromethane–methanol to give *anti*-*O*,*O*′-dibenzyl ether (±)-**4** (6.02 g) as a colorless powder. Furthermore, the filtrate was evaporated and the residue purified by column chromatography with hexane–chloroform (2:1) as an eluent to give an additional crop (0.22 g) for a total yield of 6.24 g (69%). The chromatography also isolated the *syn*-counterpart **5** (2.56 g, 28%,) as a colorless solid. The spectral data of these diethers were identical with those reported previously.[14b]

4.4. Synthesis of *anti*-*O*,*O*′-dibutylthiacalix[4]arene (±)-6

This compound was prepared by the same procedure as mentioned for the preparation of compound (±)-**4** by using ester **3** (7.88 g, 8.00 mmol), anhydrous acetone (80 mL), K_2CO_3 (13.3 g, 96.2 mmol), and 1-iodobutane (d = 1.60 g mL^{-1}; 11.1 mL, 96.3 mmol). The crude product was recrystallized from chloroform–ethanol to give *anti*-*O*,*O*′-dibutyl ether (±)-**6** (3.61 g) as a colorless powder. The filtrate was then evaporated and the residue was purified by column chromatography with hexane–chloroform (2:1) as an eluent to give an additional crop (1.13 g) for a total yield of 4.74 g (71%), mp 217–219 °C (Anal. Calcd for $C_{48}H_{64}O_4S_4$: C, 69.19; H, 7.74; S, 15.39. Found: C, 68.89; H, 7.71; S, 15.58.); δ_H (400 MHz) 0.53 (6H, t, *J* 7.4, CH_2CH_3), 0.86–0.91 (4H, m, CH_2CH_3), 1.05–1.26 (4H, m, OCH_2CH_2), 1.25 [18H, s, $C(CH_3)_3$], 1.30 [18H, s, $C(CH_3)_3$], 3.70–3.80 (2H, m, OCH_2), 4.01–4.11 (2H, m, OCH_2), 7.46 (2H, d, *J* 2.5, ArH), 7.48 (2H, d, *J*

2.5, ArH), 7.51 (2H, d, *J* 2.5, ArH), 7.58 (2H, d, *J* 2.5, ArH), 8.53 (2H, s, OH); δ_C (75 MHz) 13.73, 18.68, 30.92, 31.23, 31.32, 34.07, 34.42, 71.97, 120.28, 120.68, 127.52, 128.30, 129.29, 131.73, 132.09, 133.52, 142.90, 147.27, 155.39, 156.50; *m*/*z* (FAB) 833 [$(M+1)^+$]. This chromatography also isolated *syn* counterpart **7** (1.55 g, 23%) as a colorless solid, the spectroscopic data of which were identical with those reported previously.[14b]

4.5. Resolution of *anti-O,O′*-dibenzyl ether (±)-4

4.5.1. Esterification of dibenzyl ether (±)-4 to diastereomeric monoesters 8a–d

To an ice-cold solution of dibenzyl ether (±)-**4** (3.61 g, 4.00 mmol) in anhydrous dichloromethane (40 mL) were added (*S*)-MNPA (1.84 g, 8.00 mmol), 4-pyrrolidinopyridine (4-PPy) (1.78 g, 12.0 mmol), and DCC (2.48 g, 12.0 mmol) under nitrogen. After stirring at room temperature for 24 h, the mixture was quenched with 2 M HCl and the mixture extracted with dichloromethane. The extract was washed with 1 M NaOH to recover unreacted (*S*)-MNPA, and then with 2 M HCl and water, dried over $MgSO_4$, and evaporated. The residue was passed through a short silica gel column with hexane–diethyl ether (4:1) as an eluent to give a mixture of four diastereomeric monoesters **8a–d**. Flash chromatography of the mixture, eluting with hexane–chloroform (1:1–2:3), gave an inseparable mixture of **8b–d** as the first fraction, while the second fraction gave diastereomerically pure **8a** (1.59 g, 36%) as a colorless powder, mp 193–195 °C (dichloromethane–methanol) (Anal. Calcd for $C_{68}H_{72}O_6S_4$: C, 73.34; H, 6.52; S, 11.52. Found: C, 73.33; H, 6.51; S, 11.66.); $[\alpha]_D^{28} = -75.0$ (*c* 1.02, chloroform); δ_H (300 MHz) 0.68 [9H, s, $C(CH_3)_3$], 0.70 [9H, s, $C(CH_3)_3$], 0.84 [9H, s, $C(CH_3)_3$], 1.20 (3H, s, CH_3), 1.40 [9H, s, $C(CH_3)_3$], 3.43 (3H, s, OCH_3), 4.85 (1H, d, *J* 12.0, OCH_2Ph), 4.86 (1H, d, *J* 9.6, OCH_2Ph), 4.96 (1H, d, *J* 12.0, OCH_2Ph), 5.25 (1H, d, *J* 9.6, OCH_2Ph), 6.02 (2H, d, *J* 7.6, OCH_2Ph), 6.36 (2H, t, *J* 7.6, OCH_2Ph), 6.74 (1H, t, *J* 7.6, OCH_2Ph), 6.92 (1H, d, *J* 2.4, ArH), 7.12 (1H, d, *J* 2.4, ArH), 7.18 (1H, d, *J* 2.4, ArH), 7.23–7.37 (6H, m, ArH × 3 and Nap × 3), 7.49–7.58 (5H, m, OCH_2Ph × 3 and Nap × 2), 7.71 (1H, d, *J* 2.7, ArH), 7.81–7.87 (4H, m, ArH × 1, OCH_2Ph × 2 and Nap × 1), 8.39 (1H, s, OH), 8.54 (1H, d, *J* 8.6, Nap); δ_C (75 MHz) 22.18, 30.41, 30.47, 30.67, 31.52, 33.81, 33.84, 33.97, 34.18, 53.57, 67.38, 86.22, 119.78, 122.06, 124.36, 124.57, 124.90, 125.17, 125.43, 125.82, 126.16, 126.50, 126.72, 127.01, 127.27, 127.45, 127.82, 128.14, 128.56, 128.59, 128.75, 128.85, 128.90, 129.45, 129.94, 130.41, 131.23, 131.29, 133.67, 134.85, 135.09, 135.44, 135.65, 136.77, 137.00, 142.62, 146.95, 148.56, 148.65, 149.74, 154.77, 156.62, 157.63, 171.29.

4.5.2. Hydrolysis of ester 8a to *anti-O,O′*-dibenzyl ether (+)-4

To a solution of ester **8a** (1.59 g, 1.43 mmol) in anhydrous THF (5 mL) was added a 28% solution of sodium methoxide in methanol (10 mL) under nitrogen and the mixture was heated at reflux. After 4 h, water (1 mL) was added and the mixture refluxed for a further 30 min. After cooling, the organic solvents were evaporated and the residue extracted with dichloromethane. The extract was washed successively with 2 M HCl and water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography with hexane–chloroform (2:1) as eluent to give dibenzyl ether (+)-**4** (1.22 g, 95%,) as a colorless solid, $[\alpha]_D^{28} = +4.5$ (*c* 1.00, chloroform). The enantiomeric purity of the sample was determined to be 99.9% ee by HPLC on a Sumika SUMICHIRAL OA-2000 column (4.6 mm i.d. × 25 cm) with hexane–chloroform (9:1, 1.0 mL min^{-1}) as the eluent. The retention times for (+)- and (−)-**4** enantiomers were 19.0 and 23.8 min, respectively. The spectroscopic data of the sample were identical with those of the racemate.[14b]

4.6. Resolution of *anti-O,O′*-dibutyl ether (±)-6

4.6.1. Esterification of dibutyl ether (±)-6 to diastereomeric monoesters 9a–d

Racemic dibutyl ether (±)-**6** was esterified by the same manner as described for dibenzyl ether **4** by using (±)-**6** (4.17 g, 5.00 mmol), anhydrous dichloromethane (50 mL), (*S*)-MNPA (2.30 g, 10.0 mmol), 4-PPy (2.22 g, 15.0 mmol), and DCC (3.09 g, 15.0 mmol). The mixture of diastereomeric monoesters **9a–d** were loaded on a flash column and eluted with hexane–chloroform (1:1) to give, in addition to an inseparable mixture of **9b–d**, diastereomerically pure **9a** (1.86 g, 36%) as a colorless powder, mp 154–158 °C (dichloromethane–methanol) (Anal. Calcd for $C_{62}H_{76}O_6S_4$: C, 71.22; H, 7.33; S, 12.27. Found: C, 71.00; H, 7.28; S, 12.16); $[\alpha]_D^{28} = -118.2$ (*c* 1.21, chloroform); δ_H (300 MHz, $CDCl_3$) 0.75 (9H, s, $C(CH_3)_3$), 0.82 (3H, t, *J* 7.2, CH_2CH_3), 0.88 (3H, t, *J* 7.2, CH_2CH_3), 1.06 (9H, s, $C(CH_3)_3$), 0.96–1.16 (1H, m, OCH_2CH_2), 1.19 (9H, s, $C(CH_3)_3$), 1.21–1.36 (4H, m, CH_2CH_3), 1.33 (9H, s, $C(CH_3)_3$), 1.38–1.71 (3H, m, OCH_2CH_2), 2.07 (3H, s, CCH_3), 3.52 (3H, s, OCH_3), 3.70 (1H, td, *J* 7.9 and 7.9, $OCHCH_2$), 3.86–3.94 (1H, m, $OCHCH_2$), 4.03–4.11 (1H, m, $OCHCH_2$), 4.35 (1H, td, *J* 8.2 and 4.8, $OCHCH_2$), 7.20 (1H, d, *J* 2.4, ArH), 7.28 (1H, d, *J* 2.4, ArH), 7.38 (1H, d, *J* 2.4, ArH), 7.41 (1H, d, *J* 2.4, ArH), 7.47 (1H, d, *J* 2.4, ArH), 7.49–7.57 (4H, m, ArH × 2 and Naph × 2), 7.61 (1H, t, *J* 7.7, Naph), 7.69 (1H, d, *J* 2.4, ArH), 7.78 (1H, s, OH), 7.88–7.92 (2H, m, Naph × 2), 8.14 (1H, d, *J* 7.2, Naph), 8.75 (1H, d, *J* 7.5, Naph); δ_C (75 MHz) 13.79, 13.90, 18.90, 18.96, 24.88, 30.57, 30.93, 31.08, 31.25, 31.45, 31.88, 33.83, 34.06, 34.17, 34.34, 54.03, 70.78, 74.23, 86.20, 119.91, 122.64, 124.76, 125.07, 125.36, 125.99, 126.24, 127.08, 127.30, 128.04, 128.41, 128.90, 129.25, 129.77, 129.81, 130.35, 131.44, 131.65, 131.89, 132.45, 132.87, 134.30, 134.33, 134.47, 134.85, 135.83, 142.07, 145.83, 147.50, 147.79, 150.01, 156.62, 156.70, 158.43, 171.68; *m*/*z* (FAB) 1044 (M^+).

4.6.2. Hydrolysis of ester 9a to *anti-O,O′*-dibutyl ether (+)-6

The hydrolysis of ester **9a** was carried out by a similar procedure to that described for ester **8a** by using **9a** (1.72 g, 1.64 mmol), anhydrous THF (10 mL), and a 28% solution of sodium methoxide in methanol (10 mL). The crude product was recrystallized from dichloromethane–methanol to give dibutyl ether (+)-**6** (1.33 g, 97%) as a colorless powder, $[\alpha]_D^{27} = +16.3$ (*c* 1.00, chloroform). The enantiomeric purity of the sample was determined to be 99.8% ee by HPLC on a Sumika SUMICHIRAL OA-2000 column (4.6 mm i.d. × 25 cm) with hexane–chloroform (9:1, 1.0 mL min^{-1}) as the eluent. The retention times for enantiomers (+)- and (−)-**6** were 11.5 and 13.1 min, respectively. The spectroscopic data of the sample were identical with those of the racemate (vide supra).

4.7. X-ray analysis of ester 8a

The single crystals were obtained by the slow diffusion of acetonitrile into a chloroform solution of ester **8a**. Data were collected on a Bruker SMART CCD diffractometer employing graphite monochromated MoKα radiation (λ = 0.71073 Å). The data integration and reduction were undertaken with SAINT and XPREP.[20] The structure was solved by the direct methods with SHELXS-97[21] and refined by the full-matrix least squares methods with SHELXL-97.[22] Crystal data and refinement statistics are as follows: $C_{140}H_{149}Cl_6NO_{12}S_8$, *M* = 2506.96, monoclinic, *a* = 26.5621(14), *b* = 15.7462(8), *c* = 32.2129(17) Å, β = 95.062(2)°, *V* = 13420.6(12) $Å^3$, *T* = 200(2) K, space group *C*2, *Z* = 4, μ(MoKα) = 0.311 mm^{-1}, 57219 reflections measured, 23543 unique (R_{int} = 0.061). Final R_1 = 0.059 for 14318 data [$I > 2\sigma(I)$] and wR_2 = 0.145 for all data, *GOF* = 0.883. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary Publication No. CCDC 685855.[23] The absolute stereochemistry of ester **8a**, as well as that

of dibenzyl ether (+)-**4**, was assigned to be (S_a) by using the (*S*)-MNPA moiety as an internal reference.

4.8. X-ray analysis of ester 9a

The single crystals were obtained by slow diffusion of acetonitrile into a diethylketone solution of ester **9a**. Data were collected on a Rigaku/MSC Mercury CCD diffractometer using MoKα radiation ($\lambda = 0.71073$ Å). The calculation was performed using the software package TEXSAN (v. 1.11).[24] The structure was solved by the direct methods with SIR2002[25] and refined by full-matrix least squares methods with SHELXL-97.[22] Crystal data and refinement statistics are as follows: $C_{130}H_{161}N_3O_{12}S_8$, $M = 2214.19$, triclinic, $a = 14.719(5)$, $b = 15.420(6)$, $c = 17.010(7)$ Å, $\alpha = 104.985(9)°$, $\beta = 107.366(7)°$, $\gamma = 90.097(8)°$, $V = 3546(2)$ Å^3, $T = 200.2$ K, space group *P*1, $Z = 1$, μ(MoKα) = 0.177 mm^{-1}, 44185 reflections measured, 24474 unique ($R_{int} = 0.046$). Final $R_1 = 0.082$ for 20363 data [$I > 2\sigma(I)$] and $wR_2 = 0.278$ for all data, $GOF = 1.113$. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 685856.[23] The absolute stereochemistry of ester **9a**, as well as that of (+)-**6**, was assigned to be (S_a) by using the (*S*)-MNPA moiety as an internal reference.

References

1. Vysotsky, M.; Schmidt, C.; Böhmer, V. *Adv. Supramol. Chem.* **2000**, *7*, 139–233.
2. (a) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522–524; (b) Bitter, I.; Koszegi, E.; Grun, A.; Bako, P.; Pal, K.; Grofcsik, A.; Kubinyi, M.; Balazs, B.; Toth, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1025–1035; (c) Qing, G.-Y.; He, Y.-B.; Zhao, Y.; Hu, C.-G.; Liu, S.-Y.; Yang, X. *Eur. J. Org. Chem.* **2006**, 1574–1580.
3. (a) Sanchez Pena, M.; Zhang, Y.; Thibodeaux, S.; McLaughlin, M. L.; Munoz de la Pena, A.; Warner, I. M. *Tetrahedron Lett.* **1996**, *37*, 5841–5844; (b) Sanchez Pena, M.; Zhang, Y.; Warner, I. M. *Anal. Chem.* **1997**, *69*, 3239–3242.
4. (a) Narumi, F.; Iki, N.; Suzuki, T.; Onodera, T.; Miyano, S. *Enantiomer* **2000**, *5*, 83–93; (b) Krawinkler, K. H.; Maier, N. M.; Ungaro, R.; Sansone, F.; Casnati, A.; Lindner, W. *Chirality* **2003**, *15*, S17–S29.
5. (a) He, Y.; Xiao, Y.; Meng, L.; Zeng, Z.; Wu, X.; Wu, C.-T. *Tetrahedron Lett.* **2002**, *43*, 6249–6253; (b) Zheng, Y.-S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189–1192; (c) Garrier, E.; Gac, S. L.; Jabin, I. *Tetrahedron: Asymmetry* **2005**, *16*, 3767–3771.
6. (a) Grady, T.; Harris, S. J.; Smyth, M. R.; Diamond, D. *Anal. Chem.* **1996**, *68*, 3775–3782; (b) Guo, W.; Wang, J.; Wang, C.; He, J.-Q.; He, X.-W.; Cheng, J. -P. *Tetrahedron Lett.* **2002**, *43*, 5665–5667; (c) Jennings, K.; Diamond, D. *Analyst* **2001**, *126*, 1063–1067; (d) Lynam, C.; Jennings, K.; Nolan, K.; Kane, P.; McKervey, M. A.; Diamond, D. *Anal. Chem.* **2002**, *74*, 59–66; (e) Gaeta, C.; Rosa, M. D.; Fruilo, A. S.; Neri, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2333–2340; (f) Amato, M. E.; Ballistreri, F. P.; Pappalardo, A.; Tomaselli, G. A.; Toscano, R. M.; Williams, D. J. *Eur. J. Org. Chem.* **2005**, 3562–3570; (g) Zheng, Y.-S.; Ji, A.; Chen, X.-J.; Zhou, J.-L. *Chem. Commun.* **2007**, 3398–3400.
7. Narumi, F.; Hattori, T.; Matsumura, N.; Onodera, T.; Katagiri, H.; Kabuto, C.; Kameyama, H.; Miyano, S. *Tetrahedron* **2004**, *60*, 7827–7833.
8. (a) Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, *17*, 2508–2517; (b) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2005**, *61*, 8517–8528; (c) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117–3119.
9. (a) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, *115*, 3997–4006; (b) Ferguson, G.; Gallagher, J. F.; Giunta, L.; Neri, P.; Pappalardo, S.; Parisi, M. *J. Org. Chem.* **1994**, *59*, 42–53; (c) Arnaud-Neu, F.; Caccamese, S.; Fuangswasdi, S.; Pappalardo, S.; Parisi, M. F.; Petringa, A.; Principato, G. *J. Org. Chem.* **1997**, *62*, 8041–8048; (d) Jin, T. *Chem. Commun.* **1998**, *13*, 1357–1358; (e) Caccamese, S.; Bottino, A.; Cunsolo, F.; Parlato, S.; Neri, P. *Tetrahedron: Asymmetry* **2000**, *11*, 3103–3112; (f) Hesek, D.; Inoue, Y.; Drew, M. G. B.; Beer, P. D.; Hembury, G. A.; Ishida, H.; Aoki, F. *Org. Lett.* **2000**, *2*, 2237–2240; (g) Tairov, M. A.; Vysotsky, M. O.; Kalchenko, O. I.; Pirozhenko, V. V.; Kalchenko, V. I. *J. Chem. Soc., Perkin Trans. 1* **2002**, *11*, 1405–1411; (h) Csokai, V.; Simon, A.; Balázs, B.; Tóth, G.; Bitter, I. *Tetrahedron* **2006**, *62*, 2850–2856.
10. (a) Narumi, F.; Yamabuki, W.; Hattori, T.; Kameyama, H.; Miyano, S. *Chem. Lett.* **2003**, *32*, 320–321; (b) Cao, Y.-D.; Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Wang, M.-X.; Huang, Z.-T. *J. Org. Chem.* **2004**, *69*, 206–208; (c) Miao, R.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *J. Org. Chem.* **2005**, *70*, 7662–7671; (d) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Chem. Eur. J.* **2005**, *11*, 5917–5928; (e) Yakovenko, A. V.; Boyko, V. I.; Danylyuk, O.; Suwinska, K.; Lipkowski, J.; Kalchenko, V. I. *Org. Lett.* **2007**, *9*, 1183–1185; (f) Xu, Z.-X.; Zhang, C.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2007**, *9*, 4447–4450.
11. Reviews: Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291–5316.
12. Morohashi, N.; Iki, N.; Sugawara, A.; Miyano, S. *Tetrahedron* **2001**, *57*, 5557–5563.
13. Morohashi, N.; Yokomakura, K.; Hattori, T.; Miyano, S. *Tetrahedron Lett.* **2006**, *47*, 1157–1161.
14. (a) Narumi, F.; Morohashi, N.; Matsumura, N.; Iki, N.; Kameyama, H.; Miyano, S. *Tetrahedron Lett.* **2002**, *43*, 621–625; (b) Narumi, F.; Hattori, T.; Morohashi, N.; Matsumura, N.; Yamabuki, W.; Kameyama, H.; Miyano, S. *Org. Biomol. Chem.* **2004**, *2*, 890–898.
15. Narumi, F.; Hattori, T.; Yamabuki, W.; Kabuto, C.; Kameyama, H. *Tetrahedron: Asymmetry* **2005**, *16*, 793–800.
16. Serizawa, R.; Tanaka, S.; Morohashi, N.; Narumi, F.; Hattori, T. *Tetrahedron Lett.* **2007**, *48*, 6281–6285.
17. (a) Kuwahara, S.; Fujita, K.; Watanabe, M.; Harada, N.; Ishida, T. *Enantiomer* **1999**, *4*, 141–145; (b) Harada, N.; Watanabe, M.; Kuwahara, S.; Sugio, A.; Kasai, Y.; Ichikawa, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1249–1253.
18. Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy–Exciton Coupling in Organic Stereochemistry*; University Science Books: CA, 1983.
19. Tanaka, S.; Serizawa, R.; Morohashi, N.; Hattori, T. *Tetrahedron Lett.* **2007**, *48*, 7660–7664.
20. SMART, SAINT and XPREP, Area detector control and data integration and reduction software, Bruker Analytical X-ray Instruments, Madison, WI, 1995.
21. SADABS, Empirical Absorption Correction Program for Area Detector Data; Sheldrick, G. M. University of Göttingen, Germany, 1996.
22. Sheldrick, G. M. SHELXLS-97, *Program for the Solution of Crystal Structures*; University of Göttingen: Germany, 1998.
23. CCDC 685855 and 685856 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
24. TEXSAN Single Crystal Structure Analysis Software, 1999. Molecular Structure Corporation, 3200 Research Forest Drive, The Woodlands, TX 77381, USA; Rigaku, 3-9-12 Akishima, Tokyo, Japan.
25. Burla, M. C.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **2003**, *36*, 1103.