Synthesis of Optically Active Tetraoxa-Cage Compounds by Chemical Resolution

I-Chia Chen (• • • •) and Hsien-Jen Wu* (• • • •)
Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, R.O.C.

The first synthesis of optically active tetraoxa-cage compounds has been accomplished by using (-)-camphanic chloride as a resolving reagent in a short sequence. The synthesis of the tetraoxa-cages with different functional groups on the side chain was also demonstrated.

INTRODUCTION

The synthesis and chemistry of polycyclic cage compounds have attracted considerable attention in recent years.[1] The vast majority of the work reported in this area has dealt with carbocyclic cage compounds. These cage compounds have played a key role in theoretical organic chemistry by providing rigid and often symmetric frameworks for evaluating theories put forth on the physicochemical properties of organic molecules. In addition, some precursors of these cage compounds are important building blocks for the synthesis of polycyclic unnatural and natural products. Heterocyclic cage compounds have also received attention in recent years from synthetic as well as mechanistic considerations. The main purpose for the studies was the desire to compare the reactivity profiles of carbon cage compounds with those of their heterocyclic analogs. Recently, we envisioned that studies on the synthesis and chemistry of heterocyclic cage compounds can greatly expand their scope and utility.[2]

There are some reports regarding the chemisty[3] and synthesis[4-9] of oxa-cage compounds in the literature. This class of heterocyclic cage compounds is synthesized by intramolecular alkene-oxirane (2σ-2π) photocycloaddition,[4] transannular cyclization of suitable compounds,[5] tandem cyclization,[6] dehydration of diols having the proper stereochemistry,[7] base-promoted rearrangement,[8] and intramolecular etherification of an alkene bond with organoselenium reagents.[9] Recently, we utilized a ozonolysis reaction for the synthesis of a series of oxa-cage compounds, such as diacetal trioxa-cages,[10] triacetal trioxa-cages,[11] tetraacetal tetraoxa-cages,[12] tetraacetal pentaoxa-cages,[13] and pentaacetal pentaoxa-cages (the pentaoxa[5]peristylanes).[14] Later on, we investigated the chemical nature of the acetal group of tetraoxa-cages and discovered a hydride rearrangement and an one-pot conversion from oxa-cages to aza-cages.[15] We also developed a method for the synthesis of diacetal trioxa-cages[16] and dioxa-cages[17] by electrophile-induced cyclization reaction. As part of a program that involves the synthesis, chemistry, and applications of new heterocylic cages, we report here the first synthesis of optically active tetraoxa-cage compounds by chemical resolution.

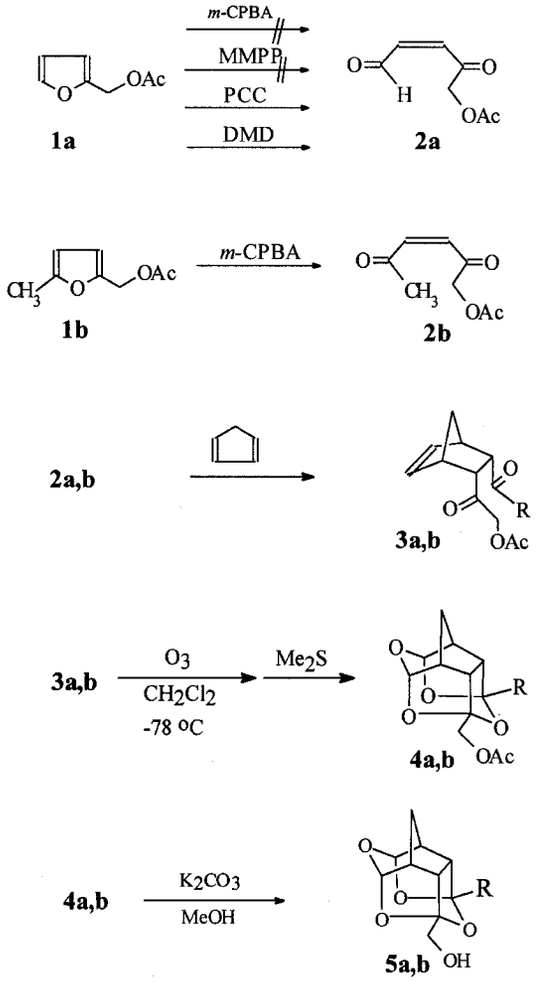
RESULTS AND DISCUSSION

Oxidation of 2-furfuryl acetate (**1a**) with *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane or magnesium monoperoxyphthalate (MMPP) in aqueous THF did not give any detectable amount of compound **2a**. Oxidation of **1a** with pyridinium chlorochromate (PCC) in CH_2Cl_2 gave poor yield of **2a** (10%). Oxidation of **1a** with dimethyldioxirane (DMD)[18] in acetone gave **2a** in about 75% yield.[19] The DMD oxidation was usually carried out on a small scale and was difficult to scale up. On the other hand, oxidation of 5-methyl-2-furfuryl acetate (**1b**) with *m*-CPBA in dichloromethane at 0 °C gave **2b** in 82% yield and this oxidation can be scaled up. Diels-Alder reaction of **2a** and **2b** with cyclopentadiene at room temperature gave the *endo* adducts **3a** and **3b** (84%). Both compounds **2a** and **3a** were difficult to be purified and might be labile. Compound **3a** was subjected to the next ozonolysis reaction without purification. Ozonolysis of **3a** and **3b** in dichloromethane at -78 °C, followed by reduction with dimethyl sulfide, gave the tetraoxa-cage compounds **4a** and **4b** in 80-88% yields (Scheme I). Hydrolysis of **4a** and **4b** with potassium carbonate in methanol gave compounds **5a** and **5b** in 85-92% yields.

Compounds **4a,b** and **5a,b** are chiral and they were obtained as a racemic mixture. First of all, we adopted the chemical resolution method to synthesize optically active tetraoxa-cage compounds. Reaction of the racemic mixture of **5b** with

Dedicated to the memory of the late Professor Ta-shue Chou

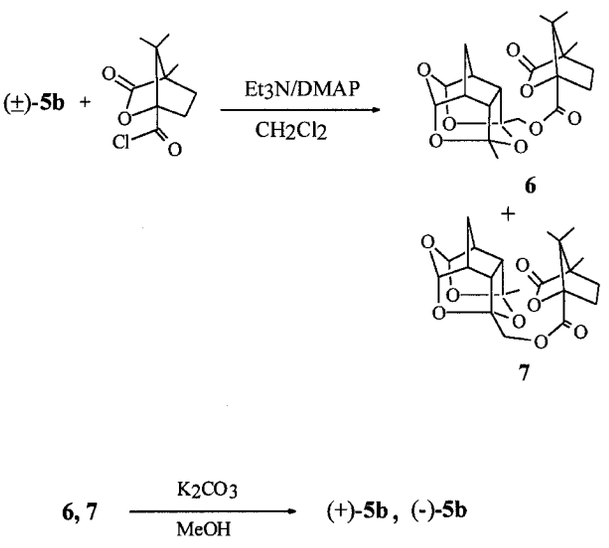
Scheme I



(-)-camphanic chloride and triethylamine in the presence of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) in dichloromethane gave two optically active diastereomers **6** and **7**, which were separable by column chromatography. On the other hand, if (+)-camphor-10-sulfonyl chloride was used as the chemical resolution agent, the diastereomeric mixture of **8** and **9** was very difficult to be separated by column chromatography or by recrystalization. Hydrolysis of **6** and **7** with potassium carbonate in methanol gave (+)-**5b** and (-)-**5b**, respectively, or the opposite (Scheme II). Thus, we have accomplished the first synthesis of optically active tetraoxacage compounds by chemical resolution. The absolute configuration of **6**, **7**, (+)-**5b**, and (-)-**5b** will be determined afterward. Attempts for the enzymatic resolution of the racemic mixture of **4b** with lipase AP6, lipase PS, or L-3126 failed.

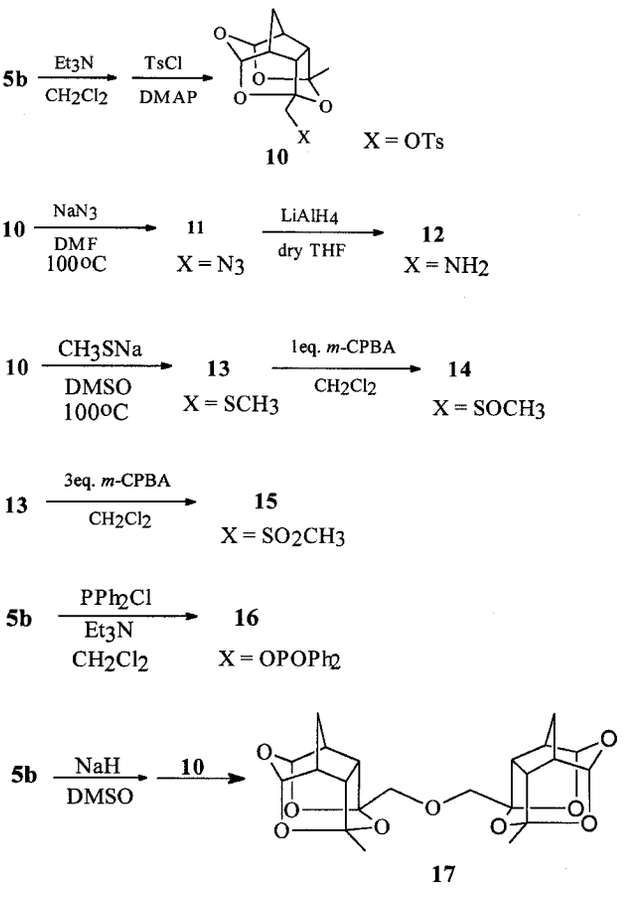
We have also accomplished the synthesis of tetraoxacage compounds with different functional groups on the side chain. Treatment of **5b** with *p*-toluenesulfonyl chloride and triethylamine in the presence of a catalytic amount of DMAP

Scheme II



in dichloromethane gave the tosylate **10**. Reaction of **10** with sodium azide in dimethyl formamide (DMF) at 100 °C gave

Scheme III



compound **11** in 50% yield. Reduction of **11** with $LiAlH_4$ in dry THF gave **12** (Scheme III). Reaction of **10** with CH_3SNa in DMSO at 100 °C gave compound **13** in 75% yield. Oxidation of **13** with one equivalent and three equivents of *m*-CPBA in CH_2Cl_2 gave the sulfoxide **14** and the sulfone **15** in 85-76% yields, respectively. The sulfoxide **14** contained two diastereomers in a ratio of 1:1 based on ^1H NMR spectra. Reaction of **5b** with chlorodiphenylphosphine and triethylamine in CH_2Cl_2 at 25 °C gave compound **16** in 64% yield, in which the phosphine atom might be oxidized by oxygen in the air. Reaction of **5b** with NaH in dry DMSO, followed by treatment with **10**, gave the bistetraoxa-cage compound **17**. Thus, we have also demonstrated the chemostability of the skeleton of the tetraoxa-cage compounds. The synthetic applications of these oxa-cages, such as **5b** and **12-16**, was undertaken.

CONCLUSION

We have accomplished the first synthesis of optically active tetraoxa-cage compounds by chemical resolution in a short sequence. The synthesis of tetraoxa-cages with different functional groups on the side chain was also accomplished.

EXPERIMENTAL SECTION

General

Melting points were determined in capillary tubes with a Laboratory Devices melting point apparatus and are uncorrected. Infrared spectra were recorded in $CHCl_3$ solutions or on neat thin films between NaCl disks. ^1H NMR spectra were determined at 300 MHz, and ^{13}C NMR were determined at 75 MHz on Fourier transform spectrometers. Chemical shifts were reported in ppm relative to TMS in the solvents specified. The multiplicities of ^{13}C signals were determined by DEPT techniques. High resolution mass values were obtained with a high resolution mass spectrometer at the Department of Chemistry, National Tsing Hua University. For thin-layer chromatography (TLC) analysis, precoated TLC plates (Kieselgel 60 F_{254}) were used, and column chromatography was done by using Kieselgel 60 (70-230 mesh) as the stationary phase. THF was distilled immediately prior to use from sodium benzophenone ketyl under nitrogen. CH_2Cl_2 was distilled from CaH_2 under nitrogen.

Oxidation of 5-Methyl-2-furfuryl Acetate (1b) with *m*-CPBA

To a solution of **1b** (1.0 g, 6.5 mmol) in dichloromethane (30 mL) was added *m*-CPBA (1.2 g, 7.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated sodium carbonate (10 mL), and extracted with dichloromethane (3 × 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give **2b** (0.80 g, 82%): pale yellow liquid; IR (neat) 1746, 1730, 1234, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95, 6.90 (ABq, J = 12 Hz, 2H), 4.91 (s, 2H), 2.39 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.55 (CO), 192.96 (CO), 170.15 (CO_2), 137.95 (CH), 132.52 (CH), 67.50 (CH_2), 28.61 (CH_3), 20.42 (CH_3); MS *m/z* (rel int) 170 (M^+, 2), 98 (100).

On the other hand, oxidation of 2-furfuryl acetate (**1a**) with *m*-CPBA under the same reaction conditions did not give any detectable amount of **2a**.

Preparation of Dimethyldioxirane Solution[20,21]

A 250 mL, three-necked, round-bottomed flask, containing a mixture of water (20 mL), acetone (13 mL, 0.177 mmol), sodium bicarbonate (12 g), and a magnetic stirring bar, was equipped with an additional funnel for solids containing potassium monoperoxy sulfate (25 g, 0.041 mol) and an air condenser which was connected to a receiving flask, cooled by means of liquid nitrogen-acetone. While applying a slight vacuum (ca. 180 Torr. water aspirator), the solid potassium monoperoxy sulfate was added in one portion while stirring vigorously at room temperature. The yellow dioxirane-acetone solution (8 mL, 0.11 M) was collected in the receiving flask. The concentration of the dioxirane solution was determined by titration as reported in the literature.[21]

Oxidation of 2-Furfuryl Acetate (1a) with Dimethyldioxirane

To a yellow dioxirane-acetone solution (8.0 mL, 0.11 M), which was collected in a cooled receiving flask, was added a solution of **1a** (0.10 g, 0.70 mmol) in acetone (10 mL) at -78 °C. The reaction mixture was stirred at room temperature for 30 min. To this solution was added 1N HCl (3 mL) and the reaction mixture was stirred at room temperature for 10 min. Saturated sodium carbonate solution (10 mL) was slowly added to neutralize the reaction solution. The reaction mixture was extracted with dichloromethane (3 × 30 mL) and the organic layer was washed with brine, dried over $MgSO_4$, and the solvent was evaporated to give the crude product **2a**, which is a known compound.[18] Since the product was labile, the crude product was used for the next Diels-Alder reaction without purification.

General Procedure for the Diels-Alder Reaction of 2a and 2b with Cyclopentadiene

To a solution of **2b** (2.0 g. 13 mmol) in dichloromethane (20 mL) was added cyclopentadiene (1.6 g, 24 mmol). The reaction mixture was stirred at room temperature for 7 h. The solvent was evaporated and the residue was purified by column chromatography to give the *endo* adduct **3b** (2.6 g, 84%): pale yellow oil; IR (neat) 2978, 1748, 1730, 1710, 1372, 1234, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (dd, J = 5.7, 3.0 Hz, 1H), 5.92 (dd, J = 5.7, 3.0 Hz, 1H), 4.50 (s, 2H), 3.53 (dd, J = 9.3, 3.6 Hz, 1H), 3.17-3.07 (m, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.43-1.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 206.21 (CO), 203.62 (CO), 169.67 (CO_2), 136.09 (CH), 132.35 (CH), 68.09 (CH_2), 58.09 (CH), 52.27 (CH), 48.06 (CH_2), 46.63 (CH), 45.83 (CH), 28.72 (CH_3), 20.22 (CH_3); MS *m/z* (rel int) 236 (M^+, 17), 176 (40), 97 (l00); HRMS (EI) calcd for $C_{13}H_{16}O_4$ 236.1049, found 236.1041.

The same reaction conditions and procedure were applied for the Diels-Alder reaction of the crude compound **2a** with cyclopentadiene to give the *endo* adduct **3a**. Attempts for the purification of **3a** by column chromatography failed and it was subjected to the next ozonolysis reaction without purification.

General Procedure for the Ozonolysis of 3a and 3b. Formation of the Tetraacetal Tetraoxa-Cage Compounds 4a and 4b

The solution of **3b** (1.0 g, 4.2 mmol) in dichloromethane (75 mL) was cooled to -78 °C and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added dimethyl sulfide (0.50 g, 8.0 mmol) at -78 °C. The reaction mixture was stirred at room temperature for 5 h. The solvent was evaporated and the residue was purified by column chromatography to give the tetraoxa-cage compound **4b** (1.0 g, 88%).

1-Acetoxymethyl-7-methyl-2,4,6,13-tetraoxapentacyclo-[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 4b

White solid; yield 88%; mp 126-128 °C; IR ($CHCl_3$) 1744, 1238, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (d, J = 6.0 Hz, 1H), 5.52 (d, J = 6.3 Hz, 1H), 4.21, 4.15 (ABq, J = 11.7 Hz, 2H), 3.34 (dd, J = 10.8, 7.2 Hz, 1H), 3.14 (dd, J = 10.8, 7.5 Hz, 1H), 2.92-2.80 (m, 2H), 2.09 (s, 3H), 2.00-1.78 (m, 2H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 170.24 (CO_2), 117.76 (C), 115.78 (C), 103.19 (CH), 103.05 (CH), 64.70 (CH_2), 56.84 (CH), 55.00 (CH), 45.68 (CH), 45.56 (CH), 29.01 (CH_2), 24.58 (CH_3), 20.56 (CH_3); MS *m/z* (rel int) 268 (M^+, 27), 195 (100), 179 (77); HRMS (EI) calcd for $C_{13}H_{16}0_6$ 268.0947, found 268.0940.

1-Acetoxymethyl-2,4,6,13-tetraoxapentacyclo-[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 4a

Highly viscous oil; yield 80%; IR ($CHCl_3$) 2985, 1745, 1266, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (d, J = 5.4 Hz, 1H), 5.52 (d, J = 6.3 Hz, 1H), 5.49 (d, J = 6.3 Hz, 1H), 4.16 (s, 2H), 3.50-3.41 (m, 1H), 3.28-3.22 (m, 1H), 2.87-2.75 (m, 2H), 2.04 (s, 3H), 1.98-1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 170.42 (CO_2), 116.27 (C), 109.85 (CH), 103.61 (CH), 103.03 (CH), 64.70 (CH_2), 54.14 (CH), 53.62 (CH), 45.69 (CH), 45.32 (CH), 29.35 (CH_2), 20.76 (CH_3); MS *m/z* (rel int) 254 (M^+, 7), 166 (100); HRMS (EI) calcd for $C_{12}H_{14}0_6$ 254.0790, found 254.0795.

General Procedure for the Hydrolysis of 4a and 4b with K_2CO_3 in Methanol

To a solution of **4b** (1.0 g, 3.7 mmol) in methanol (30 mL) was added solid potassium carbonate (1.2 g, 12 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and water (10 mL) was added. The mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography to give the alcohol **5b** (0.80 g, 92%).

1-Hydroxymethyl-7-methyl-2,4,6,13-tetraoxapentacyclo-[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 5b

White waxy solid; yield 92%; mp 93-95 °C; IR ($CHCl_3$) 3500-3300, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.37 (d, J = 5.7 Hz, 1H), 5.33 (d, J = 6.0 Hz, 1H), 3.45, 3.41 (ABq, J = 12 Hz, 2H), 3.27 (dd, J = 10.5, 7.5 Hz, 1H), 2.99 (dd, J = 10.5, 7.5 Hz, 1H), 2.85-2.67 (m, 3H), 1.78-1.62 (m, 2H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.62 (C), 117.47 (C), 103.05 (CH), 102.84 (CH), 63.51 (CH_2), 56.63 (CH), 54.10 (CH), 45.50 (CH), 45.33 (CH), 28.78 (CH_2), 24.32 (CH_3); MS *m/z* (rel int) 226 (M^+, 9), 195 (100); HRMS (EI) calcd for $C_{11}H_{14}0_5$ 226.0841, found 226.0837.

1-Hydroxymethyl-2,4,6,13-tetraoxapentacyclo-[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 5a

White waxy solid; yield 85%; mp 86-88 °C; IR ($CHCl_3$) 3500-3000, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (d, J = 5.4 Hz, 1H), 5.54 (d, J = 6.3 Hz, 1H), 5.51 (d, J = 6.3 Hz, 1H), 3.63 (s, 2H), 3.50-3.41 (m, 1H), 3.37-3.30 (m, 1H), 2.90-2.76 (m, 2H), 1.99-1.83 (m, 2H), 1.70 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 118.22 (C), 109.91 (CH), 103.76 (CH), 103.15 (CH), 63.98 (CH_2), 53.83 (CH), 53.67 (CH), 45.82 (CH), 45.47 (CH), 29.43 (CH_2); MS *m/z* (rel int) 212 (M^+, 13), 181 (100); HRMS (EI) calcd for $C_{10}H_{12}0_5$ 212.0685, found 212.0679.

Chemical Resolution of the Racemic Mixture of 5b with (-)-Camphanic Chloride

To a solution of the racemic mixture of **5b** (0.25 g, 1.1 mmol) in dichloromethane (60 mL) was added (-)-camphanic chloride (0.30 g, 1.2 mmol), triethylamine (0.35 g, 3.4 mmol), and a catalytic amount of DMAP (20 mg) at room temperature. The reaction mixture was refluxed for 24 h. After addition of water (20 mL), the mixture was extracted with dichloromethane (3 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give two optically active diastereomers **6** and **7**. Spectral data for **6**: white solid; yield 35%; mp 168-170 °C; $[\alpha]^{25}$ -25.6° ($CHCl_3$, c = 0.0734 M, 2.98 g/l00 mL); IR ($CHCl_3$) 1789, 1753, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.49 (d, *J* = 6.3 Hz, 1H), 5.47 (d, *J* = 6.3 Hz, 1H), 4.38, 4.20 (ABq, *J* = 11.4 Hz, 2H), 3.38 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.12 (dd, *J* = 10.5, 7.5 Hz, 1H), 2.92-2.82 (m, 2H), 2.48-2.32 (m, 1H), 1.99-1.60 (m, 5H), 1.50 (s, 3H), 1.09 (s, 3H), 1.03 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 178.14 (CO_2), 166.73 (CO_2), 117.97 (C), 115.53 (C), 103.45 (CH), 103.25 (CH), 90.93 (C), 65.35 (CH_2), 57.06 (CH), 55.46 (CH), 54.75 (C), 54.18 (C), 45.87 (CH), 45.77 (CH), 30.65 (CH_2), 29.23 (CH_2), 28.79 (CH_2), 24.75 (CH_3), 16.57 ($2CH_3$), 9.62 (CH_3); MS *m/z* (rel int) 406 (M^+, 27), 195 (82), 109 (100); HRMS (EI) calcd for $C_{21}H_{26}O_8$ 406.1628, found 406.1634.

Spectral data for **7**: white solid; yield 36%; mp 178-180 °C; $[\alpha]^{25}$ -16.8° ($CHCl_3$, c = 0.197 M, 8.00 g/100 mL); IR ($CHCl_3$) 1789, 1753, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.51 (d, *J* = 6.3 Hz, 1H), 5.49 (d, *J* = 6.3 Hz, 1H), 4.29, 4.26 (ABq, *J* = 11.7 Hz, 2H), 3.37 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.11 (dd, *J* = 10.5, 7.5 Hz, 1H), 2.92-2.80 (m, 2H), 2.43-2.33 (m, 1H), 2.02-1.61 (m, 5H), 1.50 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 178.14 (CO_2), 166.80 (CO_2), 118.03 (C), 115.61 (C), 103.49 (CH), 103.29 (CH), 90.98 (C), 65.45 (CH_2), 57.15 (CH), 55.43 (CH), 54.78 (C), 54.17 (C), 45.92 (CH), 45.76 (CH), 30.70 (CH_2), 29.32 (CH_2), 28.85 (CH_2), 24.77 (CH_3), 16.75 (CH_3), 16.63 (CH_3), 9.68 (CH_3); MS *m/z* (rel int) 406 (M^+, 26), 195 (80), 109 (100); HRMS (EI) calcd for $C_{21}H_{26}0_8$ 406.1628, found 406.1636.

General Procedure for the Hydrolysis of 6 and 7 with K_2CO_3 in Methanol

To a solution of **6** (0.40 g, 1.0 mmol) in methanol (20 mL) was added solid potassium carbonate (0.60 g, 6.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated and water (10 mL) was added. The mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give (+)-**5b** (0.16 g, 68%), with $[\alpha]^{25}$ +8.2° ($CHCl_3$, c = 0.056 M, 1.27 g/100 mL), or the opposite. The spectral data of (+)-**5b** are the same as (±)-**5b**. The absolute configuration of (+)-**5b** will be determined afterward.

The same reaction conditions and procedure were applied for the hydrolysis of **7** to give (-)-**5b**, $[\alpha]^{25}$ -8.2° ($CHCl_3$, c = 0.050 M, 1.13 g/100 mL), or the opposite.

Synthesis of the Tosylate 10

To a solution of **5b** (1.0 g, 4.4 mmol) in dichloromethane (50 mL) was added triethylamine (1.0 g, 9.9 mmol), *p*-toluenesulfonyl chloride (1.0 g, 5.3 mmol), and a catalytic amount of DMAP (20 mg) at room temperature. The reaction mixture was stirred at room temperature for 3 h. To this reaction mixture was slowly added 1N HCl (10 mL) and water (20 mL). To this solution was slowly added saturated $NaHCO_3$ (10 mL) to neutralize the solution. The mixture was extracted with dichloromethane (3 × 40 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the tosylate **10** (1.5 g, 89%): white solid; mp 155-156 °C; IR ($CHCl_3$) 1363, 1180, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 5.48 (d, *J* = 6.3 Hz, 1H), 5.41 (d, *J* = 6.3 Hz, 1H), 4.05 (s, 2H), 3.47 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.14 (dd, *J* = 10.5, 7.5 Hz, 1H), 2.90-2.80 (m, 2H), 2.44 (s, 3H), 1.92 (d, *J* = 12.6 Hz, 1H), 1.84-1.75 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 144.97 (C), 132.30 (C), 129.72 (2CH), 127.81 (2CH), 117.79 (C), 114.92 (C), 103.35 (CH), 103.12 (CH), 69.27 (CH_2), 56.81 (CH), 54.96 (CH), 45.70 (CH), 45.53 (CH), 29.00 (CH_2), 24.41 (CH_3), 21.45 (CH_3); MS *m/z* (rel int) 380 (M^+, 40), 195 (100); HRMS (EI) calcd for $C_{18}H_{20}O_7S$ 380.0930, found 380.0924.

Synthesis of the Azido-Cage 11

To a solution of **10** (1.0 g, 2.6 mmol) in dry DMF (30 mL) was added sodium azide (0.50 g, 7.7 mmol) at 25 °C. The reaction mixture was stirred at l00 °C for 64 h. The solvent was evaporated under reduced pressure. After addition of water (20 mL), the mixture was extracted with dichloromethane (4 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the azido-cage **11** (0.33 g, 50%).

1-Azidomethyl-7-methyl-2,4,6,13-tetraoxapentacyclo-[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 11

Highly viscous oil; IR ($CHCl_3$) 2109, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (d, *J* = 6.3 Hz, 1H), 5.51 (d, *J* = 6.3 Hz, 1H), 3.43-3.14 (m, 4H), 2.94-2.82 (m, 2H), 1.96 (d, *J* = 12.3 Hz, 1H), 1.87-1.75 (m, 1H), 1.56 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$, DEPT) δ 117.81 (C), 117.00 (C), 103.16 (CH), 103.00 (CH), 56.91 (CH), 54.88 (CH), 53.54 (CH_2), 45.65 (CH), 45.44 (CH), 28.95 (CH_2), 24.55 (CH_3); MS *m/z* (rel int) 251 (M^+, 38), 195 (100); HRMS (EI) calcd for $C_{11}H_{13}O_4N_3$ 251.0907, found 251.0902.

Synthesis of the Amino-Cage 12

To a solution of **11** (0.50 g, 2.0 mmol) in dry THF (50 mL) was added lithium aluminum hydride (0.11 g, 2.8 mmol) at 0 °C. The reaction mixture was refluxed for 10 h. To this solution was slowly added saturated potassium sodium tartrate (15 mL) at 0 °C to destroy the excess $LiAlH_4$. After filtration, the mixture was extracted with ether (3 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography with basic alumina as the stationary state to give the amino-cage **12** (0.20 g, 44%).

1-Aminomethyl-7-methyl-2,4,6,13-tetraoxapentacyclo-[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 12

Pale yellow solid; mp 98-99 °C; IR ($CHCl_3$) 3400, 3300, 1265, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.50 (d, *J* = 6.3 Hz, lH), 5.45 (d, *J* = 6.3 Hz, lH), 3.38-3.05 (m, 4H), 2.88-2.80 (m, 2H), 1.89 (d, *J* = 12.3 Hz, lH), 1.79-1.73 (m, lH), 1.50 (s, 3H), 1.20 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.64 (C), 117.61 (C), 103.29 (CH), 103.19 (CH), 57.20 (CH), 55.34 (CH), 53.95 (CH_2), 45.91 (CH), 45.84 (CH), 29.26 (CH_2), 24.86 (CH_3); MS *m/z* (rel int) 225 (M^+, 7), 195 (96), 117 (100); HRMS (EI) calcd for $C_{11}H_{15}O_4N$ 225.1002, found 225.1006.

Synthesis of the Methylthio-Cage 13

To a solution of **10** (1.0 g, 2.6 mmol) in dry DMSO (30 mL) was added $NaSCH_3$ (0.40 g, 5.7 mmol) at 25 °C. The reaction mixture was stirred at l00 °C for 24 h. The solvent was evaporated under reduced pressure. After addition of water (20 mL), the mixture was extracted with dichloromethane (5 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the product **13** (0.51 g, 74%).

1-Methylthiomethyl-7-methyl-2,4,6,13-tetraoxapentacyclo-[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 13

Pale yellow solid; mp 106-108 °C; IR ($CHCl_3$) 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (d, *J* = 6.3 Hz, 1H), 5.44 (d, *J* = 6.3 Hz, 1H), 3.34 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.08 (dd, *J* = 10.5, 7.5 Hz, 1H), 2.86-2.78 (m, 2H), 2.75 (s, 2H), 2.13 (s, 3H), 1.89-1.71 (m, 2H), 1.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.64 (C), 117.75 (C), 103.32 (CH), 103.04 (CH), 57.13 (CH), 55.93 (CH), 45.96 (CH), 45.81 (CH), 40.15 (CH_2), 29.05 (CH_2), 24.70 (CH_3), 17.31 (SCH_3); MS *m/z* (rel int) 256 (M^+, 90), 210 (54), 195 (100); HRMS (EI) calcd for $C_{12}H_{16}O_4S$ 256.0770, found 256.0776.

Oxidation of 13 with One Equivalent of *m*-CPBA

To a solution of **13** (0.26 g, 1.0 mmol) in dichloromethane (30 mL) was added one equivalent of *m*-CPBA (0.13 g, 1.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After addition of saturated sodium carbonate (10 mL), the mixture was extracted with dichloromethane (3 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the sulfoxide **14** (0.23 g, 85%). The sulfoxide **14** contained two diastereomers in a ratio of 1:1, which was determined by its ^1H and ^{13}C NMR spectra. The spectral data of **14** were taken as a mixture of two diastereomers since the separation of the diastereomers was difficult.

1-Methylsulfinylmethyl-7-methyl-2,4,6,13-tetraoxapenta-cyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 14

Pale yellow solid; mp 192-196 °C; IR ($CHCl_3$) 1331, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.59 (d, *J* = 6.3 Hz, 1H), 5.52 (d, *J* = 6.3 Hz, 3H), 3.83 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.68 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.32-2.98 (m, 6H), 2.94-2.86 (m, 4H), 2.68 (s, 3H), 2.67 (s, 3H), 2.00-1.78 (m, 4H), 1.57 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.90 (C), 116.97 (C), 114.97 (C), 114.87 (C), 103.45 (CH), 103.18 (CH), 103.13 (CH), 102.39 (CH), 61.56 (CH_2), 60.56 (CH_2), 57.33 (CH), 57.13 (CH), 56.48 (CH), 55.95 (CH), 45.92 (CH), 45.80 (2CH), 45.62 (CH), 37.79 ($2CH_3$), 29.01 ($2CH_2$), 24.74 (CH_3), 24.39 (CH_3); MS *m/z* (rel int) 272 (M^+, 31), 209 (100); HRMS (EI) calcd for $C_{12}H_{16}O_5S$ 272.0719, found 272.0728.

Oxidation of 13 with Three Equivalents of *m*-CPBA

To a solution of **13** (0.26 g, 1.0 mmol) in dichloromethane (30 mL) was added three equivalents of *m*-CPBA (0.39 g, 3.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After addition of saturated sodium carbonate (10 mL), the mixture was extracted with dichloromethane (3 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the sulfone **15** (0.22 g, 76%).

1-Methylsulfonylmethyl-7-methyl-2,4,6,13-tetraoxapenta-cyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 15

Pale yellow solid; mp 159-161 °C; IR ($CHCl_3$) 1339, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (d, *J* = 6.3 Hz, 1H), 5.52 (d, *J* = 6.3 Hz, 3H), 3.82 (dd, *J* = 10.5, 7.5 Hz, 1H),

3.58, 3.47 (ABq, J = 15.6 Hz, 2H), 3.24 (dd, J = 10.5, 7.5 Hz, 1H), 3.03 (s, 3H), 3.00-2.88 (m, 2H), 1.98-1.83 (m, 2H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.67 (C), 113.92 (C), 103.26 (CH), 102.97 (CH), 59.19 (CH_2), 57.08 (CH), 56.72 (CH), 45.81 (CH), 45.56 (CH), 43.05 (CH_3), 28.79 (CH_2), 24.34 (CH_3); MS *m/z* (rel int) 288 (M^+, 46), 139 (100); HRMS (EI) calcd for $C_{12}H_{16}0_6S$ 288.0668, found 288.0661.

Reaction of 5b with Chlorodiphenylphosphine

To a solution of **5b** (0.50 g, 2.2 mmol) in dichloromethane (40 mL) was added triethylamine (0.5 g, 5.0 mmol) and chlorodiphenylphosphine (0.80 g, 3.6 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After addition of water (20 mL), the mixture was extracted with dichloromethane (3 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give compound **16** (0.60 g, 64%), in which the phosphine atom might be oxidized by oxygen in the air: white solid; mp 145-146 °C; IR ($CHCl_3$) 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.74 (m, 4H), 7.53-7.37 (m, 6H), 5.57 (d, J = 6.3 Hz, 1H), 5.52 (d, J = 6.3 Hz, 1H), 4.12-4.00 (m, 2H), 3.67 (dd, J = 10.5, 7.5 Hz, 1H), 3.13 (dd, J = 10.5, 7.5 Hz, 1H), 2.92-2.78 (m, 2H), 1.92 (d, J = 12.3 Hz, 1H), 1.81-1.72 (m, 1H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 132.28 (2CH), 131.61 (2CH), 131.27 (2CH), 129.87 (C), 128.70 (C), 128.42 (2CH), 128.35 (2CH), 118.04 (C), 116.43 (C), 103.51 (CH), 103.18 (CH), 64.76 (CH_2), 56.88 (CH), 54.93 (CH), 45.81 (CH), 45.74 (CH), 29.07 (CH_2), 24.62 (CH_3); MS *m/z* (rel int) 426 (M^+, 48), 219 (100); HRMS (EI) calcd for $C_{23}H_{23}0_6F$ 426.1233, found 426.1240.

Synthesis of the Bistetraoxa-Cage Compound 17

To a solution of **5b** (0.23 g, 1.0 mmol) in dry DMSO (30 mL) was added NaH (0.10 g, 4.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. To this solution was added the tosylate **10** (0.38 g, 1.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 48 h. To this mixture was slowly added water (20 mL) at 0 °C to destroy the excess NaH. The mixture was extracted with dichloromethane (5 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the bistetraoxacage **17** (0.22 g, 51%): white solid; mp 107-108 °C; IR ($CHCl_3$) 1058 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (d, J = 6.3 Hz, 2H), 5.52 (d, J = 6.3 Hz, 2H), 3.63-3.50 (m, 4H), 3.42 (dd, J = 10.5, 7.5 Hz, 2H), 3.13 (dd, J = 10.5, 7.5 Hz, 2H), 2.96-2.80 (m, 4H), 1.98-1.79 (m, 4H), 1.55 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.76 (2C), 117.60 (2C), 103.34 (2CH), 103.16 (2CH), 71.73 ($2CH_2$), 56.94 (2CH), 54.76 (2CH), 45.88 (2CH), 45.72 (2CH), 29.18 ($2CH_2$), 24.81 ($2CH_3$); MS *m/z* (rel int) 434 (M^+, 11), 195 (100); HRMS (EI) calcd for $C_{22}H_{26}0_9$ 434.1577, found 434.1571.

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Key Words

Synthesis of optically active tetraoxa-cages; Chemical resolution; Various functional group substituted tetraoxa-cages.

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