A Remarkable Effect of C−O−C Bond Angle Strain on the Regioselective Double Nucleophilic Substitution of the Acetal Group of Tetraacetal Tetraoxa-Cages and a Novel Hydride Rearrangement of Tetraoxa-Cages

Hsien-Jen Wu* and Jyh-Haur Chern

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, China

Received December 9, 1996[⊗]

A remarkable effect of C−O−C bond angle strain on the regioselective double nucleophilic substitution of the acetal group of tetraacetal tetraoxa-cages and a novel regioselective and stereoselective hydride rearrangement of tetraoxa-cages are reported. Reaction of the tetraacetal tetraoxa-cages **1** with 3 equiv of triethylsilane (at −78 °C), cyanotrimethylsilane (at 25 °C), and allyltrimethylsilane (at −78 °C) in dichloromethane in the presence of $TiCl_4$ gave the double nucleophilic substitution products **2**, **6**, and **7** in 85−90% yields, respectively. No detectable amount of other regioisomers was obtained. Reaction of **1a** with (methylthio)trimethylsilane and (phenylthio)trimethylsilane in dichloromethane in the presence of $TiCl_4$ at −78 °C gave the symmetric products **10a,b** and the unsymmetric products **11a,b** in ratios of 8−10:1. The stereochemistry of the symmetric substitution products was proven by X-ray analysis of the crystalline compound **10a**. The mechanism of the double nucleophilic substitution of the tetraoxa-cages **1** are discussed. Treatment of the tetraoxa-cages **1a,c** and **22a**−**c** with 2 equiv of $TiCl_4$ or $MeSO_3H$ in dichloromethane at 25 °C for 3 h regioselectively and stereoselectively gave the novel hydride rearrangement products **16a,b** and **23a**−**c** respectively. No detectable amount of other regioisomers was observed. The stereochemistry of the hydride rearrangement was proven by DIBAL-H reduction of **16** and **23** and X-ray analysis of the reduction product **24a**. We attribute the high regioselectivity of the double nucleophilic substitution and the hydride rearrangement of the tetraoxa-cages **1** to the bond angle strain of the unusually large bond angle of C(3)−O(4)−C(5) of the tetraoxa-cages.

Introduction

The reaction chemistry of acetals has been greatly expanded by the use of Lewis acidic promoters particularly in conjunction with silicon-containing nucleophiles.[1] In recent times much interest has been shown in the mechanism and origin of stereoselectivity of substitution of chiral acetals,[2] a concept initiated by Johnson *et al.*[3] Usually, acyclic and monocyclic acetals are the objects for study. Recently, we accomplished the synthesis of novel oxa-cage compounds, such as tetraacetal tetraoxa-cages,[4] tetraacetal petaoxa-cages,[5] triacetal trioxa-cages,[6] diacetal trioxa-cages,[7] and pentaacetal pentaoxa-cages (the pentaoxa[5]-peristylanes).[8] For instance, the tetraoxa-cages **B** were synthesized by ozonolysis of 2,3-*endo*-diacylnorbornenes **A** (Scheme 1).[4a] Afterward, we developed a new entry for the synthesis of the unsubstituted (parent) compound **1c** and its 3-alkyl-substituted derivatives **D** via ozonolysis of 2-*endo*-7-*anti*-diacylnorbornenes **C**.[4h] All these oxa-cages contain acetal and ketal groups on the molecule, and they are new systems for the study of the reaction chemistry of acetals. As part of a program that involves the synthesis, chemistry, and applications of new heterocyclic cage compounds, we report here a remarkable effect of the C−O−C bond angle strain on the regioselective double nucleophilic substitution of the acetal group of tetraacetal tetraoxa-cages. We also wish to demonstrate a novel hydride rearrangement of the acetal group of tetraoxa-cages mediated by Lewis acids.

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.

(1) Reviews: (a) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043. (b) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. (c) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200.

(2) (a) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. (b) Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997. (c) Denmark, S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984. (d) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258. (e) Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116. (f) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (g) Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475. (h) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485. (i) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595.

(3) (a) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279. (b) Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188. (c) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (d) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951. (e) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294. (f) Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588. (g) Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 3947. (h) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591. (i) Elliott, J. D.; Steele, J.; Johnson, W. S. *Tetrahedron Lett.* **1985**, *26*, 2535. (j) Silverman, R. I.; Edington, C.; Elliott, J. D.; Johnson, W. S. *J. Org. Chem.* **1987**, *52*, 180. (k) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371. (l) For copper nucleophiles: Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3075. (m) Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3083. (n) Richter, W. J. *J. Org. Chem.* **1981**, *46*, 5119. (o) Alexakis, A.; Mangeney, P. *Tetrahedron Asymm.* **1990**, *1*, 477.

(4) (a) Wu, H. J.; Lin, C. C. *J. Org. Chem.* **1995**, *60*, 7558. (b) Wu, H. J.; Lin, C. C. *J. Org. Chem.* **1996**, *61*. 3820. (c) Lin, C. C.; Wu, H. J. *Tetrahedron Lett.* **1995**, *36*, 9353. (d) Wu, H. J.; Huang, F. J.; Lin, C. C. *J. Chem. Soc., Chem. Commun.* **1991**, 770. (e) Lin, C. C.; Wu, H. J. *J. Chin. Chem. Soc.* **1995**, *42*, 815. (f) Lin, C. C.; Huang, F. J.; Lin, J. C.; Wu, H. J. *J. Chin. Chem. Soc.* **1996**, *43*, 177. (g) Lin, R. L.; Wu, C. Y.; Chern, J. H.; Wu, H. J. *J. Chin. Chem. Soc.* **1996**, *43*, 289. (h) Wu, H. J.; Chern, J. H.; Wu, C. Y. *Tetrahedron* **1997**, *53*, 2401.

(5) Lin, C. C.; Wu, H. J. *Synthesis* **1996**, 715.

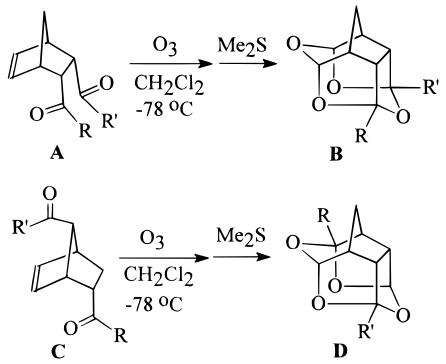
(6) Wu, C. Y.; Lin, C. C.; Lai, M. C.; Wu, H. J. *J. Chin. Chem. Soc.* **1996**, *43*, 187.

(7) (a) Wu, H. J.; Tsai, S. H.; Chung, W. S. *Tetrahedron Lett.* **1996**, *37*, 8209. (b) Tsai, S. H.; Wu, H. J.; Chung, W. S. *J. Chin. Chem. Soc.* **1996**, *43*, 445. (c) Wu, H. J.; Tsai, S. H.; Chern, J. H.; Lin, H. C. *J. Org. Chem.*, submitted for publication.

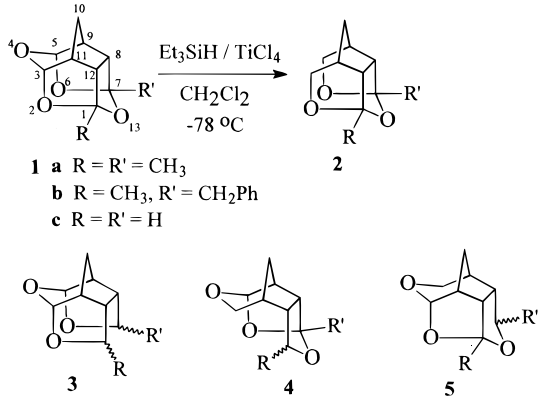
(8) Wu, H. J.; Wu, C. Y. *Tetrahedron Lett.* **1997**, in press.

S0022-3263(96)02285-2 CCC: $14.00

Scheme 1



Scheme 2

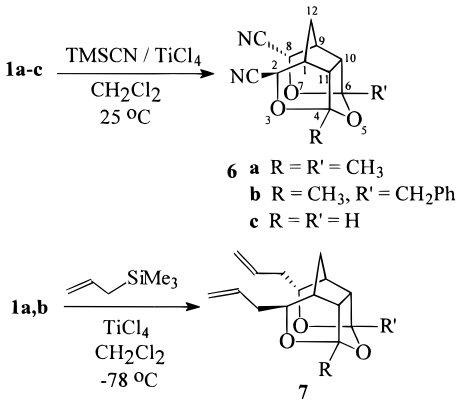


Results and Discussion

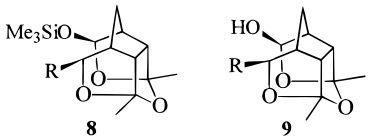
Reaction of the tetraacetal tetraoxa-cages **1a,b**[4a] and **1c**[4h] with 3 equiv of triethylsilane[9] in dichloromethane at −78 °C in the presence of a catalytic amount of $TiCl_4$ for 0.5 h regioselectively gave the substitution products **2a,b** and **2c** in 85−90% yields, respectively (Scheme 2). No detectable amount of the other regioisomers **3**, **4**, or **5** was obtained. We attribute the highly regioselective nucleophilic substitution by cleavage of the C(3)−O(4) or C(5)−O(4) bond of **1** mediated by $TiCl_4$ to the unusually large bond angle of C(3)−O(4)−C(5). While the other C−O−C bond angles of tetraoxa-cages **1** are in between 111−108°, the C(3)−O(4)−C(5) bond angle is 117.5°, remarkably larger than the ordinary bond angles with sp^3-hybridized atoms.[4a] Steric factor for the regioselective nucleophilic substitution of the acetal groups of **1** was excluded since no detectable amount of **3c** was obtained in the case of **1c**.

Reaction of **1a**−**c** with 3 equiv of cyanotrimethylsilane[10] in dichloromethane at 25 °C in the presence of $TiCl_4$ for 1 h regioselectively and stereoselectively gave **6a**−**c** in 85−90% yields (Scheme 3). No detectable amount of other regioisomeric substitution products was obtained. The stereochemistry of the cyano groups of **6** was assigned on the basis of NOE experiments and other similar chemical transformations, such as reaction of **1** with Me_3SiSMe on Scheme 4. Irradiating the proton on C_2 and C_8 of **6a** (δ 4.73) gives 6.8% enhancement for the *syn* proton on the apical carbon C_{12} and less than 1% enhancement for the bridgehead C_1 proton. Treatment of **1a,b** with 3 equiv of allyltrimethylsilane[11,12] in dichloromethane at −78 °C for 0.5 h gave compounds **7a,b** in 90% yields. The nucleophilic substitution reactions took place regioselectively on the C(3)−O(4)−C(5) bonds of **1a**−**c**.

Scheme 3



Reaction of **1a** with 1 equiv of triethylsilane and allyltrimethylsilane in dichloromethane at −78 °C gave **2a** and **7a** in 45% yields and the unreacted compound **1a**. No detectable amount of the monosubstitution products **8** or **9** was obtained. Similarly, reaction of **1a** with 1 equiv of cyanotrimethylsilane in dichloromethane at 25 °C gave **6** in 45% yield and unreacted **1a**. There are two sequential nucleophilic substitution reactions present in each case of the reaction of **1a**−**c** with the silicon-containing nucleophiles. The above experimental results indicate that the second nucleophilic substitution reaction of the acetal group of **1** is faster than the first one in reaction with the silane nucleophiles in the presence of $TiCl_4$.



Reaction of **1a** with 3 equiv of (methylthio)trimethylsilane and (phenylthio)trimethylsilane in dichloromethane in the presence of $TiCl_4$ at −78 °C for 1 h gave the symmetric products **10a** and **10b** (80−85%) and the unsymmetric products **11a** and **11b** (10−8%) in ratios of 8−10:1 (Scheme 4). The stereochemistry of the substit-

(9) (a) Frainnet, E.; Esclamadon, C. *C. R.* **1962**, *254*, 1814. (b) Loim, N. M.; Parnes, Z. N.; Vasil'eva, S. P.; Kursanov, D. N. *Zh. Org. Khim.* **1972**, *8*, 896. (c) For a review on ionic hydrogenation with silanes, see: Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633. (d) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979**, 4679. (e) Olah, G. A.; Yamato, T.; Iyer, P. S.; Prakash, G. K. S. *J. Org. Chem.* **1986**, *51*, 2826. (f) Mori, A.; Ishihara, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 987. (g) Sato, T.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1990**, *112*, 901.

(10) (a) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55. (b) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929. (c) Utimoto, K.; Wakabayashi, Y.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4279. (d) Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967. (e) Kirchmeyer, S.; Mertens, A.; Arvanaghi, M.; Olah, G. A. *Synthesis* **1983**, 498.

(11) (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295. (b) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (c) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. (d) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817. (e) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496.

(12) Reviews: (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Chan, T. H.; Wang, D. *Chem. Rev.* **1992**, *92*, 995. (d) Hoffman, R. W. *Angew. Chem.* **1982**, *94*, 569; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

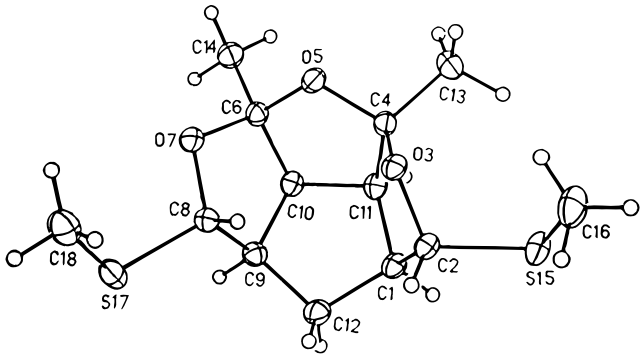
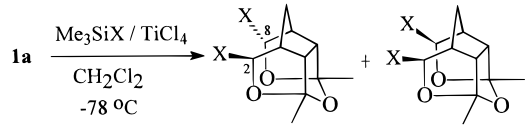
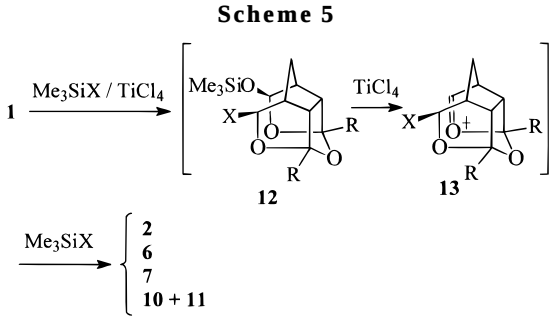


Figure 1. ORTEP diagram of **10a**.

Scheme 4



Scheme 5

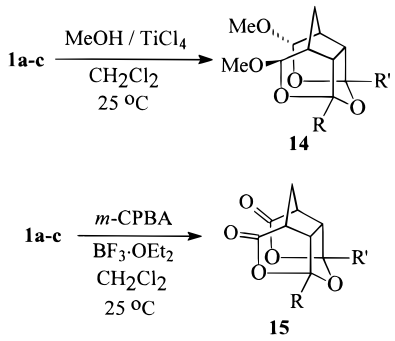


uents on C_2 and C_8 of the symmetric compounds **10a,b** was proven by X-ray analysis of the crystalline compound **10a** (Figure 1).[13]

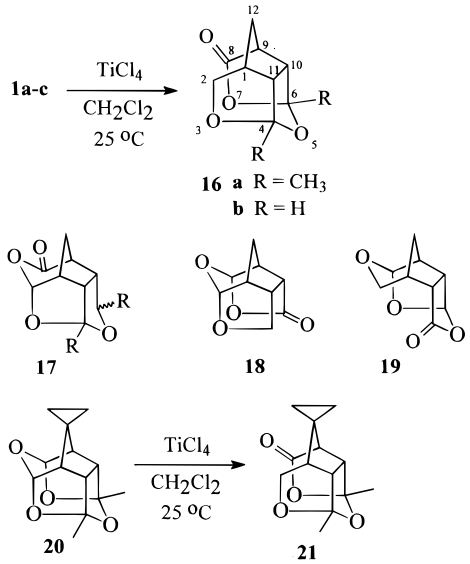
Lewis acid-mediated nucleophilic substitution of acetals can occur by direct displacement (S_N2) or oxocarbenium ion (S_N1) mechanisms.[2] Each case of the above reactions involves double nucleophilic substitution. Since the unsymmetric substitution products **11a** and **11b** were obtained in the reaction of **1a** with TMSX (X = SMe, SPh), a mechanism via double S_N2 direct displacement may be excluded. A mechanism via the intermediates **12** and **13** may be proposed for this double nucleophilic substitution reaction (Scheme 5). Nevertheless, the detailed mechanism of the double nucleophilic substitution is not clear at present. The slight difference in the double nucleophilic substitution reaction of **1** with Me_3SiSR from that with triethylsilane, allyltrimethylsilane, and cyanotrimethylsilane may depend on the nature of the nucleophiles.[2]

Reaction of **1a**−**c** with 4 equiv of methanol in dichloromethane at 25 °C in the presence of $TiCl_4$ for 2 h regioselectively and stereoselectively gave the substitution products **14a**−**c** in 80−85% yields. Treatment of **1a**−**c** with 3 equiv of *m*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane at 25 °C for 1 h gave the bislactones **15a**−**c** in 85% yields

Scheme 6



Scheme 7



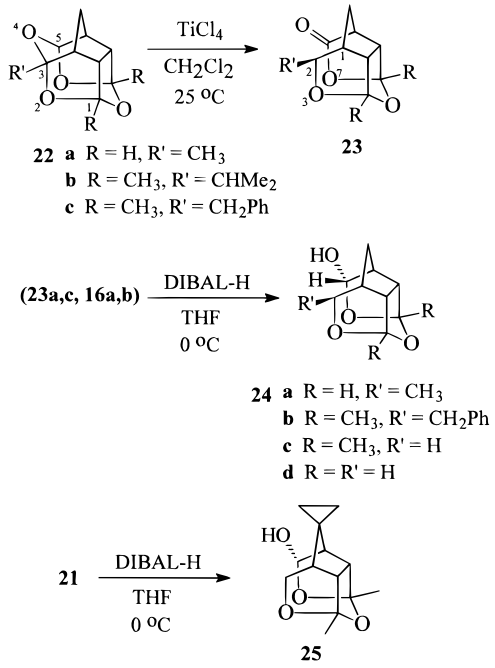
(Scheme 6). This oxidation reaction also takes place regioselectively on the acetal carbons C_3 and C_5 of **1** even in the case of unsubstituted compound **1c**.

A novel regioselective and stereoselective hydride rearrangement was also discovered. Treatment of the symmetric tetraoxa-cages **1a** and **1c** with 2 equiv of Lewis acids, such as $TiCl_4$, $BF_3{-}OEt_2$, and $MeSO_3H$ in dichloromethane at 25 °C for 12 h regioselectively gave the novel hydride rearrangement products **16a** and **16b** in 90% yields (Scheme 7). No detectable amount of the other regioisomer **17** was obtained. In the case of the unsubstituted (parent) compound **1c**, no detectable amount of the other regioisomers **18** or **19** was obtained. Treatment of **1a** and **1c** with a catalytic amount of $TiCl_4$ at 25 °C for 12 h gave **16a** and **16b** in 15−20% yields and the unreacted **1a** and **1b**. Similar to the previous nucleophilic substitution reactions, we attribute the high regioselectivity of the hydride rearrangement to the bond angle strain of the unusually large bond angle of C(3)−O(4)−C(5) of the tetraoxa-cages **1**. In the case of **1c**, with no alkyl substituents on C_1 and C_7, the hydride rearrangement still took place regioselectively between C_3 and C_5. Thus, steric hindrance factor for the hydride rearrangement of **1** to **16** was excluded. Treatment of the tetraoxa-cage **20**[4g] with $TiCl_4$ under the same reaction conditions gave **21** in 90% yield. A three-membered spiro ring on the apical carbon did not interfere with the hydride rearrangement.

The IR spectra of **16a,b** and **21** showed strong absorption at 1770 cm^{-1} for the five-membered lactone carbonyl group. The ^1H NMR spectrum of **16b** revealed two

(13) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 8



doublets at δ 6.04 and 5.97 for the two acetal protons on C_4 and C_6 and two doublets of doublet at δ 4.13 and 3.50 for the methylene protons on C_2. The ^{13}C NMR spectrum of **16b** displayed a singlet at δ 179.09 for the lactone carbonyl, two peaks at δ 112.31 and 106.38 for the acetal carbons C_4 and C_6, and one peak at δ 71.59 for the methylene carbon C_2.

In order to understand the stereochemistry of the hydride rearrangement, we prepared compounds **22a**−**c**[4g] for the rearrangement study. Treatment of **22a**−**c** with 2 equiv of $TiCl_4$ in dichloromethane at 25 °C for 12 h stereoselectively gave compounds **23a**−**c** in 85−90% yields (Scheme 8). The stereochemistry of the alkyl group on C_2 of **23** was assigned on the basis of NOE experiments of **23a** and proven by chemical transformation of **23**. Irradiating the methyl group on C_2 of **23a** gives 8.6% enhancement of the intensity of the C_1 proton. Reduction of **23a,c** and **16a,b** with diisobutylaluminum hydride (DIBAL-H) in dry THF at 0 °C stereoselectively gave compounds **24a**−**d** in 85−90% yields, respectively. The stereochemistry of the hydroxy group and the alkyl substituents on C_2 of **24** was proven by X-ray analysis of the crystalline compound **24a** (Figure 2).[13] Hence, the stereochemistry of the alkyl substituent on C_2 of **23a**−**c** was confirmed. Reduction of **21** with DIBAL-H under the same reaction conditions gave **25** in 85% yield.

A reaction mechanism is proposed for the hydride rearrangement from **22** to **23** (Scheme 9). Coordination of $TiCl_4$ to the oxygen atom O(4) of **22** followed by cleavage of the C(3)−O(4) bond gives the oxocarbenium ion **26**. Repulsion of the hydride on C_5 of **26** by the alkoxide anion followed by nucleophilic addition of the hydride on the oxocarbenium ion from the inside concave face gives the observed products **23**. We propose that the hydride rearrangement is an intramolecular process. From the previous intermolecular nucleophilic substitution reactions (Schemes 3−6), the nucleophiles attack the oxocarbenium ion **26** from the outside convex face. Nevertheless, more experiments, such as the cross-over rearrangement test, are required before the conclusion can be made.

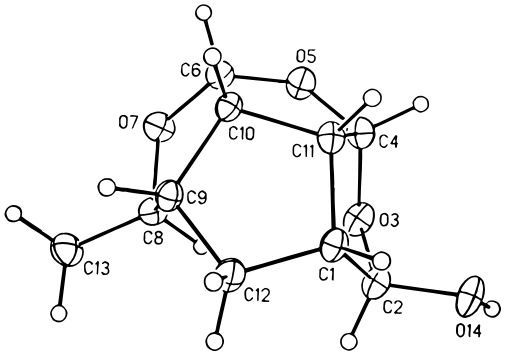
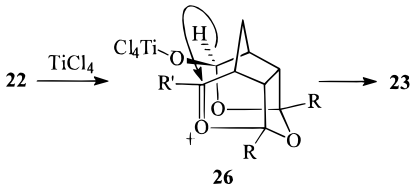


Figure 2. ORTEP diagram of **24a**.

Scheme 9



It is worth to note the stereochemistry of the DIBAL-H reduction of **23a,c** and **16a,b**. The hydride addition from DIBAL-H to the lactone carbonyl group takes place stereoselectively from the inside concave face. We propose that the aluminum atom of DIBAL-H may coordinate to the carbonyl oxygen atom and the oxygen atoms O(3) and O(7) of **23** and **16** in the transition state. Whether these oxa-cages may exhibit such interesting cation-binding properties or not needs to be proven by further extensive studies.

Conclusion

A remarkable regioselective and stereoselective double nucleophilic substitution of the acetal group of tetraacetal tetraoxa-cages with silicon-containing nucleophiles mediated by Lewis acids was demonstrated. We attribute the highly regioselective nucleophilic substitution of the tetraoxa-cages **1** to the C−O−C bond angle strain of the unusually large bond angle of C(3)−O(4)−C(5) of **1**. The stereochemistry of the substitution products was proven by X-ray analysis of the crystalline compound **10a**. There are two sequential nucleophilic substitution reaction present in each case and the second nucleophilic substitution of the acetal group of **1** is faster than the first one. The Lewis acid-mediated substitution may occur by S_N2 or S_N1 mechanisms, but a mechanism via double S_N2 direct displacement may be excluded. A novel regioselective and stereoselective hydride rearrangement of acetal group was also discovered. We also attribute the high regioselectivity of the hydride rearrangement to the C(3)−O(4)−C(5) bond angle strain of the tetraoxa-cages. The stereochemistry of the hydride rearrangement is proven by X-ray analysis of the crystalline compound **24a**. A mechanism via intramolecular manner is proposed for the stereochemistry of the hydride rearrangement.

Experimental Section

General. Melting points were determined in capillary tubes with a Laboratory Devices melting point apparatus and 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 spectra

were determined at 75 MHz, on Fourier transform spectrometers. Chemical shifts are 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. Elemental analyses were performed at the microanalysis laboratory of National Taiwan University. X-ray analysis were carried out on a diffractometer 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.

General Procedure for the Reaction of Tetraacetal Tetraoxa-Cages 1a−c with Triethylsilane in the Presence of $TiCl_4$. To a solution of tetraacetal tetraoxa-cage **1a** (0.21 g, 1.00 mmol) in dichloromethane (20 mL) were added triethylsilane (0.35 g, 3.00 mmol) and $TiCl_4$ (0.020 g, 0.10 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 0.5 h. After addition of water (10 mL) and extraction 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 **2a** (0.17 g, 0.85 mmol) in 85% yield.

4,6-Dimethyl-3,5,7-trioxatetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (2a): white waxy solid; yield 85%; mp 57−58 °C; IR ($CHCl_3$) 2980, 2880, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.01 (dd, J = 8.4 Hz, J = 2.7 Hz, 4H), 3.08 (dd, J = 6.9 Hz, J = 3.0 Hz, 2H), 2.98−2.92 (m, 2H), 2.18−2.04 (m, 1H), 1.78−1.72 (m, 1H), 1.50 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 118.46 (2C), 73.91 ($2CH_2$), 60.98 (2CH), 46.79 (2CH), 37.29 (CH_2), 24.88 ($2CH_3$); LRMS *m/z* (rel inten) 196 (M^+, 23), 181 (100); HRMS (EI) calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1094. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.31; H, 8.22. Found: C, 67.20; H, 8.30.

4-Methyl-6-benzyl-3,5,7-trioxatetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (2b): white waxy solid; yield 90%; mp 66−67 °C; IR ($CHCl_3$) 2980, 2880, 1600, 1060, 750, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 4.02−3.94 (m, 4H), 3.16 (dd, J = 9.6 Hz, J = 9.6 Hz, 1H), 3.10, 2.97 (ABq, J = 13.7 Hz, 2H), 2.83−2.72 (m, 3H), 2.15−2.05 (m, 1H), 1.76−1.72 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 136.77 (C), 130.67 (2CH), 127.86 (2CH), 126.43 (CH), 120.74 (C), 118.98 (C), 74.18 (CH_2), 74.78 (CH_2), 60.75 (CH), 58.37 (CH), 46.39 (CH), 46.23 (CH), 43.59 (CH_2), 38.12 (CH_2), 24.03 (CH_3); LRMS *m/z* (rel inten) 272 (M^+, 15), 195 (100); HRMS (EI) calcd for $C_{17}H_{20}O_3$ 272.1412, found 272.1410. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.96; H, 7.41. Found: C, 74.84; H, 7.50.

3,5,7-Trioxatetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (2c): white waxy solid; yield 85%; mp 53−54 °C; IR ($CHCl_3$) 2980, 2880, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J = 3.9 Hz, 2H), 4.07−3.93 (m, 4H), 3.34−3.30 (m, 2H), 2.94−2.87 (m, 2H), 2.28−2.17 (m, 1H), 1.85−1.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 111.67 (2CH), 73.82 ($2CH_2$), 56.39 (2CH), 45.48 (2CH), 37.60 (CH_2); LRMS *m/z* (rel inten) 168 (M^+, 31), 154 (100); HRMS (EI) calcd for $C_9H_{12}O_3$ 168.0786, found 168.0781. Anal. Calcd for $C_9H_{12}O_3$: C, 64.26; H, 7.20. Found: C, 64.34; H, 7.16.

General Procedure for the Reaction of Tetraoxa-Cages 1a−c with Cyanotrimethylsilane in the Presence of $TiCl_4$. To a solution of tetraoxa-cages **1a** (0.21 g, 1.00 mmol) in dichloromethane (20 mL) were added cyanotrimethylsilane (0.30 g, 3.0 mmol) and $TiCl_4$ (0.020 g, 0.10 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h. After addition of water (10 mL) and extraction 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 **6a** (0.22 g, 0.90 mmol) in 90% yield.

2β,8β-Dicyano-4,6-dimethyl-3,5,7-trioxatetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (6a): white waxy solid; yield 85%; mp 102−103 °C; IR ($CHCl_3$) 2980, 2250, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (d, J = 5.1 Hz, 2H), 3.39−3.26 (m, 4H), 2.48−2.40 (m, 1H), 2.12−2.07 (m, 1H), 1.67 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 120.97 (2CN), 118.00 (2C), 71.52 (2CH), 60.31 (2CH), 52.00 (2CH), 37.29 (CH_2), 25.25 ($2CH_3$); LRMS *m/z* (rel inten) 246 (M^+, 32), 231 (100); HRMS (EI) calcd for $C_{13}H_{14}O_3N_2$ 246.1004, found 246.1007.

2β,8β-Dicyano-4-methyl-6-benzyl-3,5,7-trioxatetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (6b): white waxy solid; yield 90%; mp 80−81 °C; IR ($CHCl_3$) 2980, 2880, 2250, 1600, 1060, 745, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 4.74 (d, J = 5.7 Hz, 1H), 4.70 (d, J = 5.4 Hz, 1H), 3.42 (dd, J = 10.2 Hz, J = 10.2 Hz, 1H), 3.23, 3.09 (ABq, J = 13.8 Hz, 2H), 3.20−3.12 (m, 2H), 2.99 (dd, J = 10.2 Hz, J = 9.6 Hz, 1H), 2.43−2.32 (m, 1H), 2.08−2.03 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 134.89 (C), 130.61 (2CH), 128.22 (2CH), 127.20 (CH), 122.77 (CN), 121.26 (CN), 118.05 (C), 117.85 (C), 71.76 (CH), 71.20 (CH), 59.66 (CH), 58.18 (CH), 51.83 (CH), 51.59 (CH), 43.38 (CH_2), 37.46 (CH_2), 24.29 (CH_3); LRMS *m/z* (rel inten) 322 (M^+, 21), 245 (100); HRMS (EI) calcd for $C_{19}H_{18}O_3N_2$ 322.1317, found 322.1312.

2β,8β-Dicyano-3,5,7-trioxatetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (6c): white waxy solid; yield 85%; mp 92−93 °C; IR ($CHCl_3$) 2980, 2880, 2250, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (d, J = 5.1 Hz, 2H), 4.72 (d, J = 5.1 Hz, 2H), 3.63−3.58 (m, 2H), 3.27−3.19 (m, 2H), 2.63−2.51 (m, 1H), 2.13−2.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 120.97 (2CN), 112.58 (2CH), 71.61 (2CH), 55.79 (2CH), 51.01 (2CH), 37.61 (CH_2); LRMS *m/z* (rel inten) 218 (M^+, 100); HRMS (EI) calcd for $C_{11}H_{10}O_3N_2$ 218.0691, found 218.0678.

General Procedure for the Reaction of Tetraoxa-Cages 1a,b with Allyltrimethylsilane in the Presence of $TiCl_4$. To a solution of tetraoxa-cages **1a** (0.42 g, 2.00 mmol) in dichloromethane (30 mL) were added allyltrimethylsilane (0.68 g, 6.00 mmol) and $TiCl_4$ (0.040 g, 0.20 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 0.5 h. After addition of water (20 mL) and extraction 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 **7a** (0.51 g, 1.8 mmol) in 90% yield.

2β,8β-Diallyl-4,6-dimethyl-3,5,7-trioxatetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (7a): pale yellow oil; yield 90%; IR (neat) 2970, 1620, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78−5.69 (m, 2H), 5.07−4.98 (m, 4H), 4.27−4.20 (m, 2H), 3.03 (dd, J = 7.2 Hz, J = 3.0 Hz, 2H), 2.58−2.54 (m, 2H), 2.32−2.19 (m, 4H), 1.90−1.79 (m, 1H), 1.58−1.54 (m, 1H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 134.07 (2CH), 117.12 ($2CH_2$), 116.09 (2C), 84.21 (2CH), 60.58 (2CH), 53.48 (2CH), 39.73 ($2CH_2$), 33.74 (CH_2), 26.01 ($2CH_3$); LRMS *m/z* (rel inten) 276 (M^+, 45), 261 (100); HRMS (EI) calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1719. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.87; H, 8.76. Found: C, 73.98; H, 8.68.

2β,8β-Diallyl-4-methyl-6-benzyl-3,5,7-trioxatetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (7b): pale yellow oil; yield 90%; IR (neat) 2980, 1600, 1070, 745, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.21 (m, 5H), 5.83−5.71 (m, 2H), 5.11−5.02 (m, 4H), 4.32−4.24 (m, 2H), 3.22−2.92 (m, 4H), 2.60−2.17 (m, 6H), 1.92−1.82 (m, 1H), 1.72−1.67 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 136.76 (C), 134.37 (CH), 134.28 (CH), 130.73 (2CH), 127.76 (2CH), 126.36 (CH), 118.67 (C), 117.18 (C), 117.12 ($2CH_2$), 84.81 (CH), 84.37 (CH), 60.74 (CH), 58.44 (CH), 53.14 (CH), 52.99 (CH), 45.13 (CH_2), 40.14 ($2CH_2$), 34.81 (CH_2), 26.24 (CH_3); LRMS *m/z* (rel inten) 352 (M^+, 64), 275 (100); HRMS (EI) calcd for $C_{23}H_{28}O_3$ 352.2038, found 352.2032. Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.36; H, 8.01. Found: C, 78.45; H, 8.08.

General Procedure for the Reaction of 1a with (Methylthio)trimethylsilane and (Phenylthio)trimethylsilane in the Presence of $TiCl_4$. To a solution of tetraoxa-cage **1a** (0.42 g, 2.00 mmol) in dichloromethane (30 mL) were added methylthiotrimethylsilane (0.72 g, 6.00 mmol) and $TiCl_4$ (0.040 g, 0.20 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h. After addition of water (20 mL) and extraction 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 **10a** (0.46 g, 80%) and **11a** (0.057 g, 10%).

2*β*,8*β*-Bis(methylthio)-4,6-dimethyl-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (10a): white waxy solid; yield 80%; mp 134−135 °C; IR ($CHCl_3$) 2980, 2880, 1380, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (d, J = 6.0 Hz, 2H), 3.20 (dd, J = 6.0 Hz, J = 2.4 Hz, 2H), 2.80−2.70 (m, 2H), 2.15 (s, 6H), 2.10−2.01 (m, 2H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.34 (2C), 90.96 (2CH), 60.68 (2CH), 52.90 (2CH), 37.96 (CH_2), 26.65 ($2CH_3$), 13.95 ($2CH_3$); LRMS *m*/*z* (rel inten) 288 (M$^+$, 12), 241 (100); HRMS (EI) calcd for $C_{13}H_{20}O_3S_2$ 288.0854, found 288.0858.

2*β*,8α-Bis(methylthio)-4,6-dimethyl-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (11a): white waxy solid; yield 10%; mp 85−86 °C; IR ($CHCl_3$) 2980, 2880, 1380, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (d, J = 9.0 Hz, 1H), 4.98 (d, J = 5.4 Hz, 1H), 3.23−3.12 (m, 2H), 3.07−2.96 (m, 1H), 2.64−2.55 (m, 1H), 2.34−2.30 (m, 1H), 2.27 (s, 3H), 2.24 (s, 3H), 2.05−1.97 (m, 1H), 1.60 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.77 (C), 115.99 (C), 89.44 (CH), 87.87 (CH), 61.94 (CH), 60.51 (CH), 52.61 (CH), 48.91 (CH), 33.21 (CH_2), 26.30 (CH_3), 24.00 (CH_3), 15.49 (CH_3), 14.44 (CH_3); LRMS *m*/*z* (rel inten) 288 (M$^+$, 23), 241 (100); HRMS (EI) calcd for $C_{13}H_{20}O_3S_2$ 288.0854, found 288.0842.

2*β*,8*β*-Bis(phenylthio)-4,6-dimethyl-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (10b): pale yellow oil; yield 85%; IR (neat) 2980, 1600, 1060, 750, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.20 (m, 10H), 5.52 (d, J = 5.4 Hz, 2H), 3.25 (dd, J = 6.6 Hz, J = 3.0 Hz, 2H), 2.90−2.86 (m, 2H), 2.36−2.12 (m, 2H), 1.69 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 134.57 (2C), 130.90 (4CH), 128.81 (4CH), 126.94 (2CH), 119.57 (2C), 92.15 (2CH), 60.42 (2CH), 53.05 (2CH), 37.84 (CH_2), 26.68 ($2CH_3$); LRMS *m*/*z* (rel inten) 412 (M$^+$, 56), 303 (100); HRMS (EI) calcd for $C_{23}H_{24}O_3S_2$ 412.1167, found 412.1160.

2*β*,8α-Bis(phenylthio)-4,6-dimethyl-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (11b): pale yellow oil; yield 8%; IR (neat) 2980, 1600, 1060, 750, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.18 (m, 10H), 5.96 (d, J = 8.1 Hz, 1H), 5.23 (d, J = 5.4 Hz, 1H), 3.22−3.13 (m, 3H), 2.80−2.74 (m, 1H), 2.48−2.44 (m, 1H), 2.21−2.08 (m, 1H), 1.63 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 135.04 (C), 134.31 (C), 131.11 (2CH), 130.79 (2CH), 128.83 (2CH), 128.75 (2CH), 127.00 (CH), 126.79 (CH), 120.12 (C), 116.19 (C), 89.76 (CH), 88.22 (CH), 61.56 (CH), 60.07 (CH), 52.47 (CH), 49.47 (CH), 33.44 (CH_2), 26.33 (CH_3), 24.03 (CH_3); LRMS *m*/*z* (rel inten) 412 (M$^+$, 18), 303 (100); HRMS (EI) calcd for $C_{23}H_{24}O_3S_2$ 412.1167, found 412.1175.

General Procedure for the Reaction of Tetraoxa-Cages 1a−c with Methanol in the Presence of $TiCl_4$. To a solution of **1a** (0.21 g, 1.00 mmol) in dichloromethane (20 mL) were added MeOH (0.13 g, 4.0 mmol) and $TiCl_4$ (0.020 g, 0.10 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition of water (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 **14a** (0.21 g, 82%).

2*β*,8*β*-Dimethoxy-4,6-dimethyl-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (14a): white waxy solid; yield 82%; mp 81−82 °C; IR ($CHCl_3$) 2980, 2880, 1380, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (d, J = 1.5 Hz, 2H), 3.35 (s, 6H), 3.22 (dd, J = 5.7 Hz, J = 3.0 Hz, 2H), 2.75−2.70 (m, 2H), 2.32−2.24 (m, 1H), 2.08−1.97 (m, 1H), 1.57 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.66 (2C), 111.06 (2CH), 59.69 (2CH), 55.00 ($2CH_3$), 52.70 (2CH), 36.18 (CH_2), 27.41 ($2CH_3$); LRMS *m*/*z* (rel inten) 256 (M$^+$, 55), 241 (100); HRMS (EI) calcd for $C_{13}H_{20}O_5$ 256.1311, found 256.1307. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.91; H, 7.87. Found: C, 60.82; H, 7.95.

2*β*,8*β*-Dimethoxy-4-methyl-6-benzyl-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (14b): white waxy solid; yield 85%; mp 89−90 °C; IR ($CHCl_3$) 2980, 1600, 1380, 1070, 745, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 4.95 (d, J = 1.5 Hz, 1H), 4.87 (d, J = 1.5 Hz, 1H), 3.41 (s, 3H), 3.31 (s, 3H), 3.27 (dd, J = 8.7 Hz, J = 8.2 Hz, 1H), 3.22, 2.95 (ABq, J = 13.8 Hz, 2H), 2.84 (dd, J = 8.7 Hz, J = 8.5 Hz, 1H), 2.69−2.62 (m, 2H), 2.29−2.17 (m, 1H), 2.00−1.94 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 136.47 (C), 130.73 (2CH), 127.73 (2CH), 126.42 (CH), 121.03 (C), 119.80 (C), 111.15 (CH), 110.92 (CH), 59.26 (CH), 56.98 (CH), 55.41 (CH_3), 54.80 (CH_3), 52.44 (2CH), 45.42 (CH_2), 36.06 (CH_2), 26.36 (CH_3); LRMS *m*/*z* (rel inten) 332 (M$^+$, 100); HRMS (EI) calcd for $C_{19}H_{24}O_5$ 332.1624, found 332.1608. Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.64; H, 7.28. Found: C, 68.72; H, 7.22.

2*β*,8*β*-Dimethoxy-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (14c): white waxy solid; yield 80%; mp 65−66 °C; IR ($CHCl_3$) 2980, 2880, 1380, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (d, J = 5.1 Hz, 2H), 4.94 (d, J = 2.1 Hz, 2H), 3.48−3.40 (m, 2H), 3.37 (s, 6H), 2.72−2.66 (m, 2H), 2.42−2.30 (m, 1H), 2.02−1.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 111.86 (2CH), 111.45 (2CH), 55.30 ($2CH_3$), 55.03 (2CH), 51.36 (2CH), 35.92 (CH_2); LRMS *m*/*z* (rel inten) 228 (M$^+$, 66), 213 (100); HRMS (EI) calcd for $C_{11}H_{16}O_5$ 228.0998, found 228.0991. Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.87; H, 7.07. Found: C, 57.75; H, 7.02.

General Procedure for the Reaction of Tetraoxa-Cages 1a−c with *m*-Chloroperoxybenzoic Acid in the Presence of BF_3·OEt_2. To a solution of **1a** (0.21 g, 1,00 mmol) in dichloromethane (20 mL) were added *m*-CPBA (0.69 g, 4.0 mmol) and BF_3·OEt_2 (0.010 g, 0.10 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition of saturated sodium carbonate (20 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 **15a** (0.19 g, 0.85 mmol) in 85% yield. Compounds **15a** and **15b** were obtained via a different approach, and their spectral data were reported.[4a] On the other hand, **15c** is a new compound.

2,8-Dioxo-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (15c): white waxy solid; yield 85%; mp 255−256 °C; IR ($CHCl_3$) 2960, 1767, 1240, 1107 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 6.19 (d, J = 5.7 Hz, 2H), 4.04 (brs, 2H), 3.34 (brs, 2H), 2.67 (brs, 2H); ^{13}C NMR (75 MHz, CD_3COCD_3, DEPT) δ 177.26 (2CO), 108.03 (2CH), 52.70 (2CH), 46.70 (2CH), 37.93 (CH_2); LRMS *m*/*z* (rel inten) 196 (M$^+$, 5), 97 (78), 152 (100); HRMS (EI) calcd for $C_9H_8O_5$ 196.0372, found 196.0378. Anal. Calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 55.25; H, 4.19.

General Procedure for the Hydride Rearrangement of Tetraoxa-Cages 1a,c, 20, and 22a−c. To a solution of **1a** (0.21 g, 1.00 mmol) in dichloromethane (40 mL) was added $TiCl_4$ (0.38 g, 2.00 mmol) or BF_3·OEt_2 (0.20 g, 2.00 mmol) or $MeSO_3H$ (0.19 g, 2.00 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched by addition of water (30 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 the hydride rearrangement product **16a** (0.19 g, 0.90 mmol) in 90% yield.

2-Oxo-4,6-dimethyl-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (16a): white waxy solid; yield 90%; mp 146−147 °C; IR ($CHCl_3$) 2980, 1770, 1240, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (dd, J = 9.3 Hz, J = 9.3 Hz, 1H), 3.61 (dd, J = 9.3 Hz, J = 8.7 Hz, 1H), 3.40−3.28 (m, 3H), 3.00−2.93 (m, 1H), 2.37−2.25 (m, 2H), 1.67 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 178.54 (CO), 119.39 (C), 115.14 (C), 72.13 (CH_2), 61.23 (CH), 55.82 (CH), 48.39 (CH), 45.30 (CH), 35.86 (CH_2), 26.13 (CH_3), 24.53 (CH_3); LRMS *m*/*z* (rel inten) 210 (M$^+$, 16), 166 (100); HRMS (EI) calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0898. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.83; H, 6.72. Found: C, 62.94; H, 6.79.

2-Oxo-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (16b): white waxy solid; yield 90%; mp 112−113 °C; IR ($CHCl_3$) 2980, 1770, 1240, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (d, J = 5.7 Hz, 1H), 5.97 (d, J = 5.4 Hz, 1H), 4.13 (dd, J = 9.6 Hz, J = 9.0 Hz, 1H), 3.63−3.58 (m, 2H), 3.50 (dd, J = 9.6 Hz, J = 8.4 Hz, 1H), 3.27−3.21 (m, 1H), 2.96−2.89 (m, 1H), 2.42−2.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 179.09 (CO), 112.31 (CH), 106.38 (CH), 71.60 (CH_2), 56.72 (CH), 50.72 (CH), 46.88 (CH), 44.85 (CH), 35.35 (CH_2); LRMS *m*/*z* (rel inten) 182 (M$^+$, 78), 138 (100); HRMS (EI) calcd for $C_9H_{10}O_4$ 182.0579, found 182.0588. Anal. Calcd for $C_9H_{10}O_4$: C, 59.32; H, 5.54. Found: C, 59.46; H, 5.60.

2-Oxo-4,6-dimethyl-12-spiroethylene-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (21): white waxy solid; yield 90%; mp 155−156 °C; IR ($CHCl_3$) 2980, 1770, 1250, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (dd, J = 9.9 Hz, J = 9.9 Hz, 1H), 3.79 (dd, J = 9.9 Hz, J = 8.4 Hz, 1H), 3.51−3.35 (m, 2H), 2.51 (d, J = 9.3 Hz, 1H), 2.36−2.27 (m, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.37−1.31 (m, 1H), 0.61−0.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 176.74 (CO), 119.86 (C), 114.79 (C), 71.52 (CH_2), 59.90 (CH), 55.70 (CH), 53.78 (CH), 53.43 (CH), 30.56 (C), 26.19 (CH_3), 24.38 (CH_3), 16.22 (CH_2), 4.01 (CH_2); LRMS *m*/*z* (rel inten) 236 (M$^+$, 82), 192 (100); HRMS (EI) calcd for $C_{13}H_{16}O_4$ 236.1049, found 236.1041. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.07; H, 6.83. Found: C, 66.18; H, 6.89.

2β-Methyl-8-oxo-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]-dodecane (23a): white waxy solid; yield 85%; mp 141−142 °C: IR ($CHCl_3$) 2980, 1770, 1240, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, J = 6.0 Hz, 1H), 5.95 (d, J = 5.4 Hz, 1H), 3.80−3.74 (m, 1H), 3.66−3.60 (m, 2H), 3.27−3.22 (m, 1H), 2.39−2.27 (m, 3H), 1.28 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 179.28 (CO), 111.28 (CH), 106.21 (CH), 78.92 (CH), 57.19 (CH), 52.59 (CH), 50.59 (CH), 47.04 (CH), 34.87 (CH_2), 19.55 (CH_3); LRMS *m*/*z* (rel inten) 196 (M$^+$, 43), 152 (100); HRMS (EI) calcd for $C_{10}H_{12}O_4$ 196.0736, found 196.0730. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.20; H, 6.17. Found: C, 61.28; H, 6.25.

2β-Isopropyl-4,6-dimethyl-8-oxo-3,5,7-trioxatetracyclo-[7.2.1.0^{4,11}.0^{6,10}]dodecane (23b): white waxy solid; yield 90%; mp 120−121 °C; IR ($CHCl_3$) 2980, 1770, 1380, 1240, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (dd, J = 8.7 Hz, J = 6.6 Hz, 1H), 3.36−3.24 (m, 3H), 2.65−2.57 (m, 1H), 2.38−2.20 (m, 2H), 1.80−1.68 (m, 1H), 1.65 (s, 3H), 1.57 (s, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 178.86 (CO), 118.46 (C), 114.91 (C), 88.39 (CH), 62.23 (CH), 55.93 (CH), 49.12 (CH), 48.45 (CH), 36.41 (CH_2), 33.03 (CH), 26.42 (CH_3), 25.81 (CH_3), 18.81 (CH_3), 18.12 (CH_3); LRMS *m*/*z* (rel inten) 252 (M$^+$, 47), 208 (100); HRMS (EI) calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1368. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.63; H, 7.99. Found: C, 66.75; H, 7.95.

2β-Benzyl-4,6-dimethyl-8-oxo-3,5,7-trioxatetracyclo-[7.2.1.0^{4,11}.0^{6,10}]dodecane (23c): white waxy solid; yield 90%; mp 112−113 °C; IR ($CHCl_3$) 2980, 1770, 1600, 1240, 1070, 740, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.18 (m, 5H), 4.05−4.00 (m, 1H), 3.34−2.98 (m, 4H), 2.80−2.50 (m, 2H), 2.05−1.78 (m, 2H), 1.63 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 178.60 (CO), 136.64 (C), 129.48 (2CH), 128.34 (2CH), 126.53 (CH), 118.37 (C), 114.82 (C), 83.12 (CH), 61.94 (CH), 55.61 (CH), 51.16 (CH), 48.42 (CH), 40.64 (CH_2), 35.10 (CH_2), 26.51 (CH_3), 25.69 (CH_3); LRMS *m*/*z* (rel inten) 300 (M$^+$, 45), 256 (100); HRMS (EI) calcd for $C_{18}H_{20}O_4$ 300.1362, found 300.1366. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.97; H, 6.72. Found: C, 71.90; H, 6.78.

General Procedure for the Reduction of Compounds 23a,c 16a,b and 21 with Diisobutylaluminum Hydride (DIBAL-H). To a solution of **16a** (0.42 g, 2.00 mmol) in dry THF (40 mL) was added DIBAL-H (1.70 g, 2.40 mmol, 20% in *n*-hexane) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. The reaction mixture was quenched by slow addition of water (30 mL) at 0 °C and extracted with ether (5 × 30 mL). The organic layer was washed with saturated sodium bicarbonate and brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the reduction product **24c** (0.38 g, 1.8 mmol) in 90% yield.

2β-Methyl-8β-hydroxy-3,5,7-trioxatetracyclo-[7.2.1.0^{4,11}.0^{6,10}]dodecane (24a): white waxy solid; yield 90%; mp 95−96 °C; IR ($CHCl_3$) 3500−3300, 2970, 1110, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (d, J = 5.4 Hz, 1H), 5.91 (d, J = 5.4 Hz, 1H), 5.51 (d, J = 1.5 Hz, 1H), 4.09−4.00 (m, 1H), 3.89 (brs, 1H), 3.50−3.44 (m, 2H), 2.84−2.78 (m, 1H), 2.34−2.15 (m, 2H), 1.94−1.89 (m, 1H), 1.25 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 112.30 (CH), 110.69 (CH), 106.11 (CH), 79.30 (CH), 57.87 (CH), 54.25 (CH), 53.21 (CH), 52.50 (CH), 34.86 (CH_2), 19.65 (CH_3); LRMS *m*/*z* (rel inten) 198 (M$^+$, 36), 181 (100); HRMS (EI) calcd for $C_{10}H_{14}O_4$ 198.0892, found 198.0898. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.58; H, 7.12. Found: C, 60.65; H, 7.18.

2β-Benzyl-8β-hydroxy-4,6-dimethyl-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (24b): white waxy solid; yield 90%; mp 82−83 °C; IR ($CHCl_3$) 3500−3300, 2970, 1600, 1070, 750, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 5H), 5.32 (s, 1H), 4.26−4.20 (m, 1H), 3.25−3.04 (m, 4H), 2.75−2.63 (m, 2H), 2.53−2.42 (m, 1H), 1.92−1.80 (m, 1H), 1.60 (s, 3H), 1.55 (s, 3H), 1.30−1.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 137.60 (C), 129.39 (2CH), 128.28 (2CH), 126.27 (CH), 119.10 (C), 118.40 (C), 105.82 (CH), 83.44 (CH), 62.87 (CH), 58.70 (CH), 53.66 (CH), 52.26 (CH), 41.05 (CH_2), 35.28 (CH_2), 28.28 (CH_3), 25.92 (CH_3); LRMS *m*/*z* (rel inten) 302 (M$^+$, 52), 285 (100); HRMS (EI) calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1523. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.49; H, 7.34. Found: C, 71.58; H, 7.40.

2β-Hydroxy-4,6-dimethyl-3,5,7-trioxatetracyclo-[7.2.1.0^{4,11}.0^{6,10}]dodecane (24c): white waxy solid; yield 90%; mp 103−104 °C; IR ($CHCl_3$) 3500−3300, 2970, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 5.50 (s, 1H), 4.00 (dd, J = 9.0 Hz, J = 7.8 Hz, 1H), 3.81 (dd, J = 9.0 Hz, J = 8.7 Hz, 1H), 3.46 (brs, 1H), 3.26−3.06 (m, 2H), 2.92−2.80 (m, 2H), 2.26−2.12 (m, 1H), 1.94−1.89 (m, 1H), 1.63 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.41 (C), 119.18 (C), 105.65 (CH), 72.44 (CH_2), 62.05 (CH), 59.00 (CH), 54.08 (CH), 46.38 (CH), 35.60 (CH_2), 28.19 (CH_3), 25.27 (CH_3); LRMS *m*/*z* (rel inten) 212 (M$^+$, 41), 195 (100); HRMS (EI) calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1063. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 62.35; H, 7.68.

2β-Hydroxy-3,5,7-Trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (24d): white waxy solid; yield 85%; mp 121−122 °C; IR ($CHCl_3$) 3500−3300, 2970, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (d, J = 5.4 Hz, 1H), 5.90 (d, J = 5.4 Hz, 1H), 5.51 (s, 1H), 4.02 (ddd, J = 10.2 Hz, J = 9.0 Hz, J = 1.2 Hz, 1H), 3.75 (dd, J = 10.2 Hz, J = 7.2 Hz, 1H), 3.61 (brs, 1H), 3.52−3.38 (m, 2H), 2.86−2.77 (m, 2H), 2.28−2.20 (m, 1H), 1.98−1.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 113.01 (CH), 110.81 (CH), 105.83 (CH), 72.34 (CH_2), 57.17 (CH), 54.33 (CH), 52.59 (CH), 45.23 (CH), 35.43 (CH_2); LRMS *m*/*z* (rel inten) 184 (M$^+$, 61), 167 (100); HRMS (EI) calcd for $C_9H_{12}O_4$ 184.0736, found 184.0732. Anal. Calcd for $C_9H_{12}O_4$: C, 58.67; H, 6.57. Found: C, 58.79; H, 6.75.

2β-Hydroxy-4,6-dimethyl-12-spiroethylene-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (25): white waxy solid; yield 85%; mp 89−90 °C; IR ($CHCl_3$) 3500−3300, 2970, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (s, 1H), 3.95 (dd, J = 9.0 Hz, J = 8.7 Hz, 1H), 3.83 (dd, J = 9.0 Hz, J = 8.1 Hz, 1H), 3.44 (brs, 1H), 3.31 (dd, J = 10.5 Hz, J = 8.7 Hz, 1H), 3.20 (dd, J = 10.5 Hz, J = 9.3 Hz, 1H), 2.28−2.19 (m, 1H), 2.15 (d, J = 8.7 Hz, 1H), 1.56 (s, 3H), 1.46 (s, 3H), 0.87−0.68 (m, 2H), 0.58−0.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.37(C), 118.99 (C), 104.30 (CH), 71.41 (CH_2), 61.33 (CH), 60.74 (CH), 58.76 (CH), 54.19 (CH), 29.54 (C), 27.76 (CH_3), 25.05 (CH_3), 17.79 (CH_2), 5.47 (CH_2); LRMS *m*/*z* (rel inten) 238 (M$^+$, 61), 221 (100); HRMS (EI) calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1202. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.51; H, 7.62. Found: C, 65.43; H, 7.68.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support (Grant No. NSC85-2113-M009-004), and Miss F. L. Liao and Dr. S. L. Wang at the Department of Chemistry, National Tsing Hua University, for carrying out the X-ray crystallographic analysis.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **2a**, **6a**, **7a**, **14a**, and **16a** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO962285X