

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

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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 $-78\text{ }^{\circ}\text{C}$), cyanotrimethylsilane (at $25\text{ }^{\circ}\text{C}$), and allyltrimethylsilane (at $-78\text{ }^{\circ}\text{C}$) 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 $-78\text{ }^{\circ}\text{C}$ 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 $25\text{ }^{\circ}\text{C}$ 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 penta-oxa-cages,⁵ triacetal trioxa-cages,⁶ diacetal trioxa-cages,⁷ and pentaacetal penta-oxa-cages (the penta-oxa[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.

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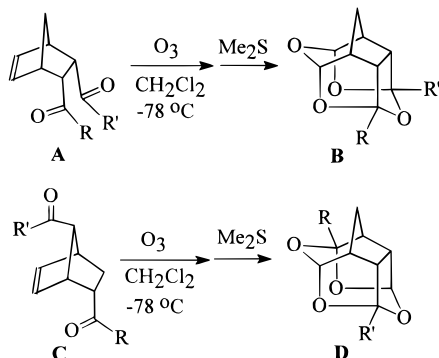
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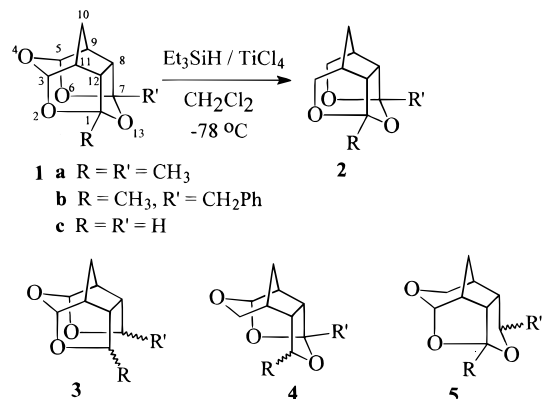
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Scheme 1



Scheme 2

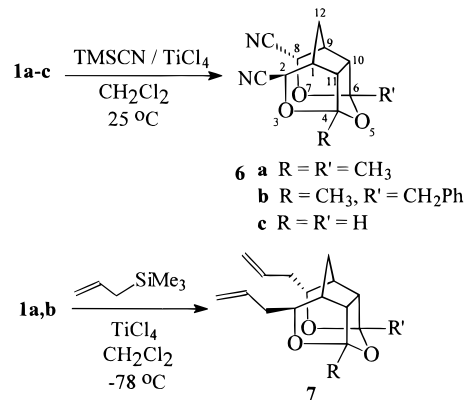


Results and Discussion

Reaction of the tetraacetal tetraoxa-cages **1a,b**^{4a} and **1c**^{4h} with 3 equiv of triethylsilane⁹ in dichloromethane at $-78\text{ }^\circ\text{C}$ 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**.

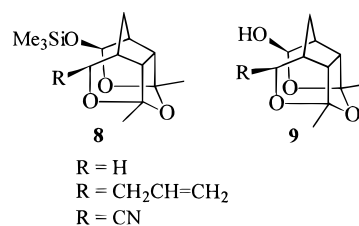
Reaction of **1a–c** with 3 equiv of cyanotrimethylsilane¹⁰ in dichloromethane at $25\text{ }^\circ\text{C}$ in the presence of $TiCl_4$ for 1 h regioselectively and stereoselectively gave **6a–c** in 85–90% yields (Scheme 3). No detectable

Scheme 3



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 C₂ and C₈ of **6a** (δ 4.73) gives 6.8% enhancement for the *syn* proton on the apical carbon C₁₂ and less than 1% enhancement for the bridgehead C₁ proton. Treatment of **1a,b** with 3 equiv of allyltrimethylsilane^{11,12} in dichloromethane at $-78\text{ }^\circ\text{C}$ 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**.

Reaction of **1a** with 1 equiv of triethylsilane and allyltrimethylsilane in dichloromethane at $-78\text{ }^\circ\text{C}$ 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 $25\text{ }^\circ\text{C}$ 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 $-78\text{ }^\circ\text{C}$ 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-

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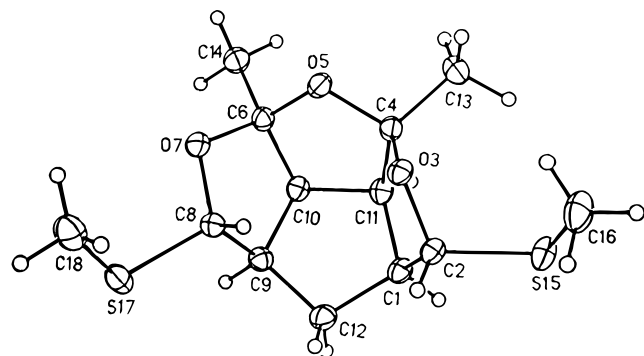
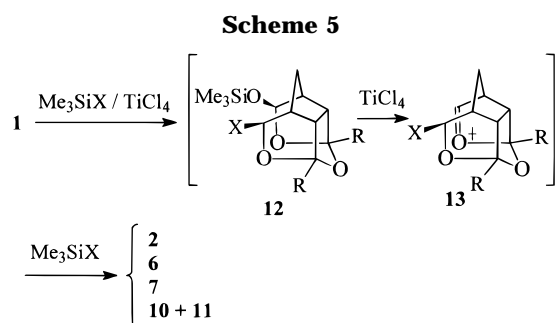
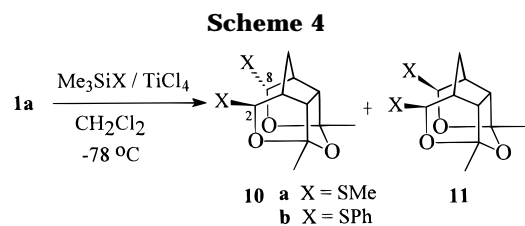


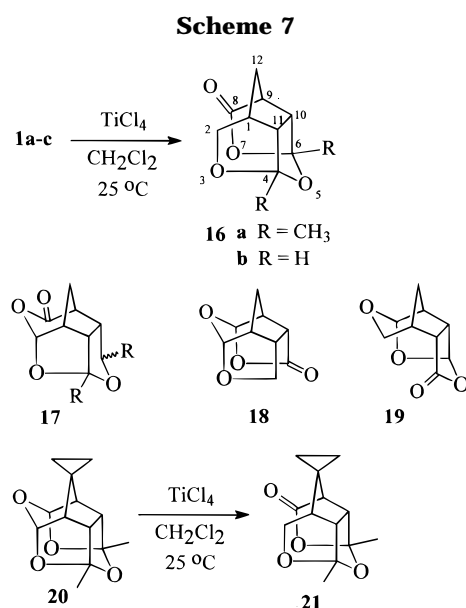
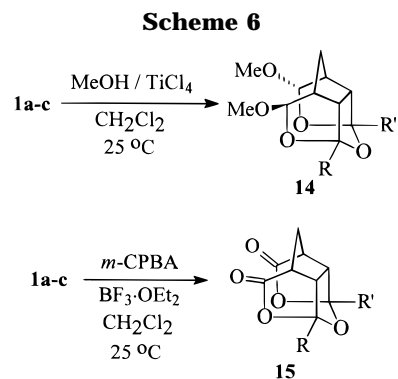
Figure 1. ORTEP diagram of **10a**.



uents on C₂ and C₈ 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 Me₃SiSR 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 TiCl₄ 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 BF₃·OEt₂ in dichloromethane at 25 °C for 1 h gave the bislactones **15a–c** in 85% yields

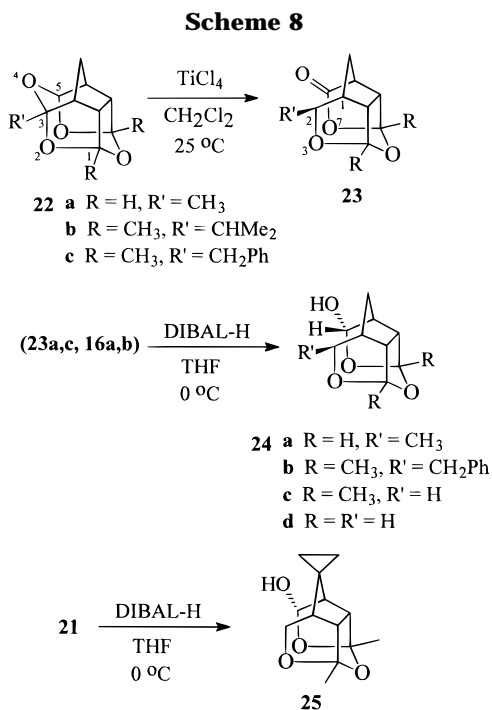


(Scheme 6). This oxidation reaction also takes place regioselectively on the acetal carbons C₃ and C₅ of **1** even in the case of unsubstituted compound **1c**.

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 TiCl₄, BF₃·OEt₂, and MeSO₃H 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 TiCl₄ 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 C₁ and C₇, the hydride rearrangement still took place regioselectively between C₃ and C₅. Thus, steric hindrance factor for the hydride rearrangement of **1** to **16** was excluded. Treatment of the tetraoxa-cage **20**^{4g} with TiCl₄ 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.



doublets at δ 6.04 and 5.97 for the two acetal protons on C₄ and C₆ and two doublets of doublet at δ 4.13 and 3.50 for the methylene protons on C₂. The ¹³C 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 C₄ and C₆, and one peak at δ 71.59 for the methylene carbon C₂.

In order to understand the stereochemistry of the hydride rearrangement, we prepared compounds **22a–c**⁴⁸ for the rearrangement study. Treatment of **22a–c** with 2 equiv of TiCl₄ 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 C₂ of **23** was assigned on the basis of NOE experiments of **23a** and proven by chemical transformation of **23**. Irradiating the methyl group on C₂ of **23a** gives 8.6% enhancement of the intensity of the C₁ 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 C₂ of **24** was proven by X-ray analysis of the crystalline compound **24a** (Figure 2).¹³ Hence, the stereochemistry of the alkyl substituent on C₂ 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 TiCl₄ 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 C₅ 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.

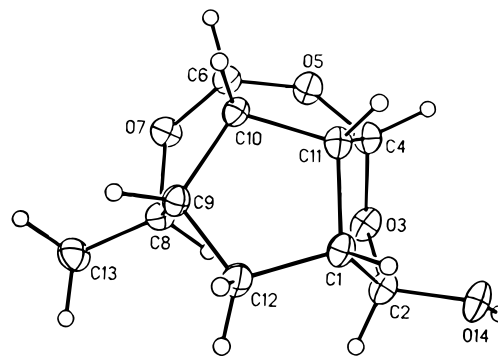
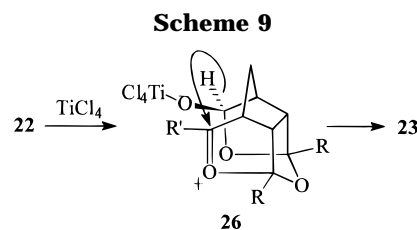


Figure 2. ORTEP diagram of **24a**.



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 CHCl₃ solutions or on neat thin films between NaCl disks. ¹H NMR spectra were determined at 300 MHz, and ¹³C 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 F₂₅₄) 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 $57\text{--}58^\circ\text{C}$; 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 (2CH₂), 60.98 (2CH), 46.79 (2CH), 37.29 (CH₂), 24.88 (2CH₃); LRMS m/z (rel inten) 196 (M^+ , 23), 181 (100); HRMS (EI) calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3$ 196.1099, found 196.1094. Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3$: 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 $66\text{--}67^\circ\text{C}$; 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 (CH₂), 74.78 (CH₂), 60.75 (CH), 58.37 (CH), 46.39 (CH), 46.23 (CH), 43.59 (CH₂), 38.12 (CH₂), 24.03 (CH₃); LRMS m/z (rel inten) 272 (M^+ , 15), 195 (100); HRMS (EI) calcd for $\text{C}_{17}\text{H}_{20}\text{O}_3$ 272.1412, found 272.1410. Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_3$: 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 $53\text{--}54^\circ\text{C}$; 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 (2CH₂), 56.39 (2CH), 45.48 (2CH), 37.60 (CH₂); LRMS m/z (rel inten) 168 (M^+ , 31), 154 (100); HRMS (EI) calcd for $\text{C}_9\text{H}_{12}\text{O}_3$ 168.0786, found 168.0781. Anal. Calcd for $\text{C}_9\text{H}_{12}\text{O}_3$: 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.

2 β ,8 β -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 $102\text{--}103^\circ\text{C}$; 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 (CH₂), 25.25 (2CH₃); LRMS m/z (rel inten) 246 (M^+ , 32), 231 (100); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{14}\text{O}_3\text{N}_2$ 246.1004, found 246.1007.

2 β ,8 β -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 $80\text{--}81^\circ\text{C}$; 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 (CH₂), 37.46 (CH₂), 24.29 (CH₃); LRMS m/z (rel inten) 322 (M^+ , 21), 245 (100); HRMS (EI) calcd for $\text{C}_{19}\text{H}_{18}\text{O}_3\text{N}_2$ 322.1317, found 322.1312.

2 β ,8 β -Dicyano-3,5,7-trioxatetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (6c): white waxy solid; yield 85%; mp $92\text{--}93^\circ\text{C}$; 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 (CH₂); LRMS m/z (rel inten) 218 (M^+ , 100); HRMS (EI) calcd for $\text{C}_{11}\text{H}_{10}\text{O}_3\text{N}_2$ 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.

2 β ,8 β -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 (2CH₂), 116.09 (2C), 84.21 (2CH), 60.58 (2CH), 53.48 (2CH), 39.73 (2CH₂), 33.74 (CH₂), 26.01 (2CH₃); LRMS m/z (rel inten) 276 (M^+ , 45), 261 (100); HRMS (EI) calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3$ 276.1725, found 276.1719. Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3$: C, 73.87; H, 8.76. Found: C, 73.98; H, 8.68.

2 β ,8 β -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 (2CH₂), 84.81 (CH), 84.37 (CH), 60.74 (CH), 58.44 (CH), 53.14 (CH), 52.99 (CH), 45.13 (CH₂), 40.14 (2CH₂), 34.81 (CH₂), 26.24 (CH₃); LRMS m/z (rel inten) 352 (M^+ , 64), 275 (100); HRMS (EI) calcd for $\text{C}_{23}\text{H}_{28}\text{O}_3$ 352.2038, found 352.2032. Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{O}_3$: 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 (CHCl₃) 2980, 2880, 1380, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 119.34 (2C), 90.96 (2CH), 60.68 (2CH), 52.90 (2CH), 37.96 (CH₂), 26.65 (2CH₃), 13.95 (2CH₃); LRMS m/z (rel inten) 288 (M⁺, 12), 241 (100); HRMS (EI) calcd for C₁₃H₂₀O₃S₂ 288.0854, found 288.0858.

2 β ,8 α -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 (CHCl₃) 2980, 2880, 1380, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, 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 (CH₂), 26.30 (CH₃), 24.00 (CH₃), 15.49 (CH₃), 14.44 (CH₃); LRMS m/z (rel inten) 288 (M⁺, 23), 241 (100); HRMS (EI) calcd for C₁₃H₂₀O₃S₂ 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, 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 (CH₂), 26.68 (2CH₃); LRMS m/z (rel inten) 412 (M⁺, 56), 303 (100); HRMS (EI) calcd for C₂₃H₂₄O₃S₂ 412.1167, found 412.1160.

2 β ,8 α -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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, 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 (CH₂), 26.33 (CH₃), 24.03 (CH₃); LRMS m/z (rel inten) 412 (M⁺, 18), 303 (100); HRMS (EI) calcd for C₂₃H₂₄O₃S₂ 412.1167, found 412.1175.

General Procedure for the Reaction of Tetraoxa-Cages 1a–c with Methanol in the Presence of TiCl₄. 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 TiCl₄ (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 \times 20 mL). The organic layer was washed with brine, dried over MgSO₄, 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 (CHCl₃) 2980, 2880, 1380, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 119.66 (2C), 111.06 (2CH), 59.69 (2CH), 55.00 (2CH₃), 52.70 (2CH), 36.18 (CH₂), 27.41 (2CH₃); LRMS m/z (rel inten) 256 (M⁺, 55), 241 (100); HRMS (EI) calcd for C₁₃H₂₀O₅ 256.1311, found 256.1307. Anal. Calcd for C₁₃H₂₀O₅: 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 (CHCl₃) 2980, 1600, 1380, 1070, 745, 695 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, 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 (CH₃), 54.80 (CH₃), 52.44 (2CH), 45.42 (CH₂), 36.06 (CH₂), 26.36 (CH₃); LRMS m/z (rel inten) 332 (M⁺, 100); HRMS (EI) calcd for C₁₉H₂₄O₅ 332.1624, found 332.1608. Anal. Calcd for C₁₉H₂₄O₅: 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 (CHCl₃) 2980, 2880, 1380, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 111.86 (2CH), 111.45 (2CH), 55.30 (2CH₃), 55.03 (2CH), 51.36 (2CH), 35.92 (CH₂); LRMS m/z (rel inten) 228 (M⁺, 66), 213 (100); HRMS (EI) calcd for C₁₁H₁₆O₅ 228.0998, found 228.0991. Anal. Calcd for C₁₁H₁₆O₅: 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 BF₃·OEt₂. 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 BF₃·OEt₂ (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 \times 20 mL). The organic layer was washed with brine, dried over MgSO₄, 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 (CHCl₃) 2960, 1767, 1240, 1107 cm⁻¹; ¹H NMR (300 MHz, CD₃COCD₃) δ 6.19 (d, J = 5.7 Hz, 2H), 4.04 (brs, 2H), 3.34 (brs, 2H), 2.67 (brs, 2H); ¹³C NMR (75 MHz, CD₃COCD₃, DEPT) δ 177.26 (2CO), 108.03 (2CH), 52.70 (2CH), 46.70 (2CH), 37.93 (CH₂); LRMS m/z (rel inten) 196 (M⁺, 5), 97 (78), 152 (100); HRMS (EI) calcd for C₉H₈O₅ 196.0372, found 196.0378. Anal. Calcd for C₉H₈O₅: 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 TiCl₄ (0.38 g, 2.00 mmol) or BF₃·OEt₂ (0.20 g, 2.00 mmol) or MeSO₃H (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 \times 20 mL). The organic layer was washed with brine, dried over MgSO₄, 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 (CHCl₃) 2980, 1770, 1240, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 178.54 (CO), 119.39 (C), 115.14 (C), 72.13 (CH₂), 61.23 (CH), 55.82 (CH), 48.39 (CH), 45.30 (CH), 35.86 (CH₂), 26.13 (CH₃), 24.53 (CH₃); LRMS m/z (rel inten) 210 (M⁺, 16), 166 (100); HRMS (EI) calcd for C₁₁H₁₄O₄ 210.0892, found 210.0898. Anal. Calcd for C₁₁H₁₄O₄: 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 (CHCl₃) 2980, 1770, 1240, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 179.09 (CO), 112.31 (CH), 106.38 (CH), 71.60 (CH₂), 56.72 (CH), 50.72 (CH), 46.88 (CH), 44.85 (CH), 35.35 (CH₂); LRMS m/z (rel inten) 182 (M⁺, 78), 138 (100); HRMS (EI) calcd for C₉H₁₀O₄ 182.0579, found 182.0588. Anal. Calcd for C₉H₁₀O₄: 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 (CHCl₃) 2980, 1770, 1250, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 176.74 (CO), 119.86 (C), 114.79 (C), 71.52 (CH₂), 59.90 (CH), 55.70 (CH), 53.78 (CH), 53.43 (CH), 30.56 (C), 26.19 (CH₃), 24.38 (CH₃), 16.22 (CH₂), 4.01 (CH₂); LRMS *m/z* (rel inten) 236 (M⁺, 82), 192 (100); HRMS (EI) calcd for C₁₃H₁₆O₄ 236.1049, found 236.1041. Anal. Calcd for C₁₃H₁₆O₄: 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 (CHCl₃) 2980, 1770, 1240, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, 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 (CH₂), 19.55 (CH₃); LRMS *m/z* (rel inten) 196 (M⁺, 43), 152 (100); HRMS (EI) calcd for C₁₀H₁₂O₄ 196.0736, found 196.0730. Anal. Calcd for C₁₀H₁₂O₄: 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 (CHCl₃) 2980, 1770, 1380, 1240, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, 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 (CH₂), 33.03 (CH), 26.42 (CH₃), 25.81 (CH₃), 18.81 (CH₃), 18.12 (CH₃); LRMS *m/z* (rel inten) 252 (M⁺, 47), 208 (100); HRMS (EI) calcd for C₁₄H₂₀O₄ 252.1362, found 252.1368. Anal. Calcd for C₁₄H₂₀O₄: 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 (CHCl₃) 2980, 1770, 1600, 1240, 1070, 740, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, 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 (CH₂), 35.10 (CH₂), 26.51 (CH₃), 25.69 (CH₃); LRMS *m/z* (rel inten) 300 (M⁺, 45), 256 (100); HRMS (EI) calcd for C₁₈H₂₀O₄ 300.1362, found 300.1366. Anal. Calcd for C₁₈H₂₀O₄: 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 MgSO₄, 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 (CHCl₃) 3500–3300, 2970, 1110, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, 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 (CH₂), 19.65 (CH₃); LRMS *m/z* (rel inten) 198 (M⁺, 36), 181 (100); HRMS (EI) calcd for C₁₀H₁₄O₄

198.0892, found 198.0898. Anal. Calcd for C₁₀H₁₄O₄: 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 (CHCl₃) 3500–3300, 2970, 1600, 1070, 750, 695 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, 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 (CH₂), 35.28 (CH₂), 28.28 (CH₃), 25.92 (CH₃); LRMS *m/z* (rel inten) 302 (M⁺, 52), 285 (100); HRMS (EI) calcd for C₁₈H₂₂O₄ 302.1518, found 302.1523. Anal. Calcd for C₁₈H₂₂O₄: 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 (CHCl₃) 3500–3300, 2970, 1070 cm⁻¹; ¹H NMR (300 MHz, CHCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 119.41 (C), 119.18 (C), 105.65 (CH), 72.44 (CH₂), 62.05 (CH), 59.00 (CH), 54.08 (CH), 46.38 (CH), 35.60 (CH₂), 28.19 (CH₃), 25.27 (CH₃); LRMS *m/z* (rel inten) 212 (M⁺, 41), 195 (100); HRMS (EI) calcd for C₁₁H₁₆O₄ 212.1049, found 212.1063. Anal. Calcd for C₁₁H₁₆O₄: 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 (CHCl₃) 3500–3300, 2970, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 113.01 (CH), 110.81 (CH), 105.83 (CH), 72.34 (CH₂), 57.17 (CH), 54.33 (CH), 52.59 (CH), 45.23 (CH), 35.43 (CH₂); LRMS *m/z* (rel inten) 184 (M⁺, 61), 167 (100); HRMS (EI) calcd for C₉H₁₂O₄ 184.0736, found 184.0732. Anal. Calcd for C₉H₁₂O₄: 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 (CHCl₃) 3500–3300, 2970, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 119.37 (C), 118.99 (C), 104.30 (CH), 71.41 (CH₂), 61.33 (CH), 60.74 (CH), 58.76 (CH), 54.19 (CH), 29.54 (C), 27.76 (CH₃), 25.05 (CH₃), 17.79 (CH₂), 5.47 (CH₂); LRMS *m/z* (rel inten) 238 (M⁺, 61), 221 (100); HRMS (EI) calcd for C₁₃H₁₈O₄ 238.1205, found 238.1202. Anal. Calcd for C₁₃H₁₈O₄: C, 65.51; H, 7.62. Found: C, 65.43; H, 7.68.

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Supporting Information Available: ¹H and ¹³C 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.