Pergamon

Tetrahedron 54 (1998) 5967–5982

TETRAHEDRON

Chemical Transformation of Tetraacetal Tetraoxa-Cages to Aza-Cages and Amido-Cages Mediated by Iodotrimethylsilane and the Combination of Chlorotrimethylsilane and Sodium Iodide in Nitriles

Jyh-Haur Chern and Hsien-Jen Wu*

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

Received 23 December 1997; revised 24 March 1998; accepted 26 March 1998

Abstract: An one-pot conversion of tetraacetal tetraoxa-cages **1a-e** to aza-cages **2a-e** mediated by iodotrimethylsilane in alkyl nitriles at 25 ℃ via the ring expansion compound **9** as the reaction intermediate was discovered. A Ritter-type reaction was proposed for the mechanism of this conversion. On the other hand, reaction of tetraacetal tetraoxa-cages **1** with Me_3SiCl and NaI in nitriles at 25 ℃ gave the amido-cages **12**. Conjugated nitriles and Lewis acids, such as $TiCl_4$ or $BF_3{\cdot}OEt_2$ were found to be ineffective for the conversion of oxa-cages to aza-cages. The structures of **2a** and chemical transformation product **16** were proven by X-ray analysis.

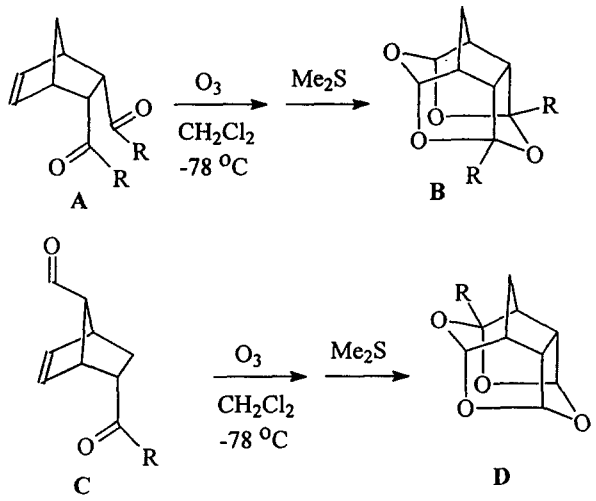
Introduction

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 pentaoxa-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-bis-*endo*-diacylnorbornenes **A** (Scheme 1).[4a] Afterward, we developed a new entry for the synthesis of tetraoxa-cages **D** *via* ozonolysis of 2-*endo*-7-*anti*-diacylnorbornenes **C**.[4e] 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. Thus, we also investigated the chemical nature of the acetal group of tetraoxa-cages and discovered 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

0040-4020/98/$19.00
PII: S0040-4020(98)00277-4

rearrangement of tetraoxa-cages.[9] As part of a program that involves the synthesis, chemistry, and applications of new heterocyclic cages, we report here the full detail of the conversion of tetraacetal tetraoxa-cages to aza-cages mediated by iodotrimethylsilane in nitriles.[10] We also wish to demonstrate that, in reaction with the combination of chlorotrimethylsilane and sodium iodide in nitriles, the tetraoxa-cages were converted to the amido-cages rather than the aza-cages.

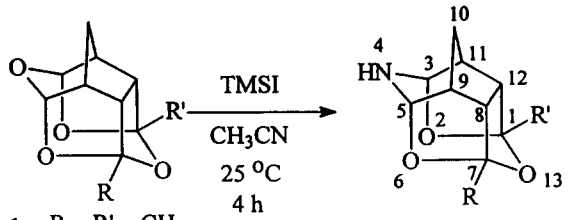
Scheme 1



Results and Discussion

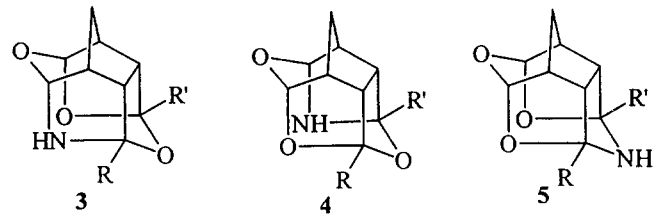
The tetraacetal tetraoxa-cages **1a-e**, desired for the chemical transformations, were prepared via Scheme 1.[4] Reaction of **1a-e** with three equivalents of iodotrimethylsilane in acetonitrile at 25 °C for 4 h gave the aza-cages **2a-e** in 80-85% yields (Scheme 2). No detectable amount of the other regioisomers **3**, **4**, or **5** was obtained. The IR spectra of **2a-e** showed absorptions near 3350 cm^{-1} for the NH group. The ^1H NMR spectrum of **2a** revealed one doublet at δ 5.17 for the two azaacetal protons on C-3 and C-5, which exhibited 0.26 ppm upfield shift in comparison with the acetal protons of **1a**, while the other proton absorptions of **2a** remained almost unchanged as **1a**. The ^{13}C NMR spectrum of **2a** displayed one peak at δ 89.67 for the azaacetal carbons, which exhibited 13.1 ppm upfield shift in comparison with the acetal carbons of **1a**, while the other carbon absorptions of **2a** remained almost unchanged as **1a**. Both ^1H and ^{13}C NMR spectra showed that compounds **2a-c** possess a symmetry plane. The mass spectra of **2a-e** showed odd numbers for the parent molecular ion peaks with correct values for each compounds. Thus, we have discovered an one-pot conversion of tetraacetal tetraoxa-cages to aza-cages mediated by iodotrimethylsilane in acetonitrile, a convenient and efficient method for the synthesis of aza-cages.

Scheme 2



1a R = R' = CH_3
b R = R' = H
c R = R' = Ph
d R = H, R' = CH_3
e R = CH_3, R' = CH_2Ph

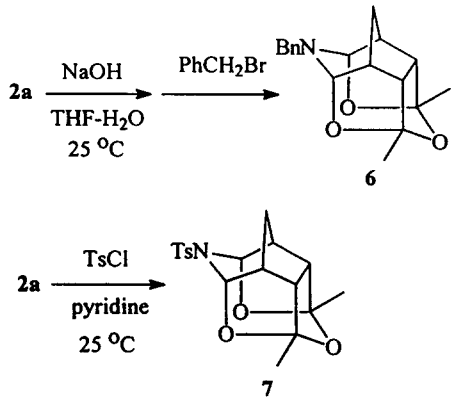
2



3 **4** **5**

Treatment of **2a** with sodium hydroxide in aqueous THF, followed by addition of benzyl bromide at 25 °C, gave the N-benzylation product **6** in 65% yield. Tosylation of **2a** with tosyl chloride in pyridine at 25 °C gave the sulfonamide **7** in 90% yield (Scheme 3). The structure of these heterocyclic cages **2a-e** was finally proven by X-ray analysis of the crystalline compound **2a** (Figure 1). The nitrogen atom N-4 is shown to be in the boat comformation with respect to the apical carbon atom C-10. The bond angles of C(3)-N(4)-C(5) and C(9)-C(10)-C(11) are 119.5° and 100.3°, respectively.

Scheme 3



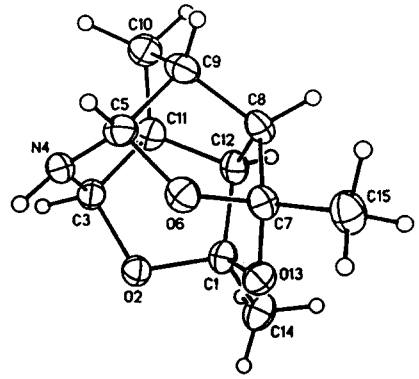


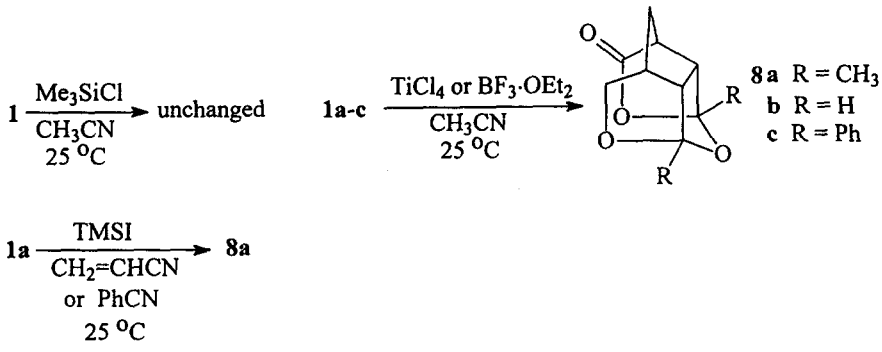
Figure 1. ORTEP diagram of **2a**.

This one-pot conversion from oxa-cages to aza-cages takes place regioselectively on the C(3)-O(4)

or O(4)-C(5) bond of **1**. We attribute the highly regioselective oxygen-nitrogen conversion reaction to the unusually large bond angle of C(3)-O(4)-C(5) of the tetraoxa-cages **1**. While the other C-O-C bond angles of these tetraoxa-cages 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] In the case of **1b**, only **2b** was obtained. Thus, the steric factor for the regioselective conversion was excluded. The stability and size of the ring may also play an important factor for the high regioselectivity.

Reaction of **1** with excess of chlorotrimethylsilane in acetonitrile at 25 °C remained unchanged. Reaction of **1a-c** with Lewis acids, such as $TiCl_4$ and $BF_3{\cdot}OEt_2$, in acetonitrile at 25 °C for 4 h gave the hydride rearrangement products **8a-c** in 80-85% yields (Scheme 4). No detectable amount of the corresponding aza-cages **2a-c** was obtained. In the case of **1b**, only **8b** was obtained. We attribute the highly regioselective hydride rearrangement to the unusually large bond angle of C(3)-O(4)-C(5) of the tetraoxa-cages **1**. Reaction of **1a** with three equivalents of iodotrimethylsilane in acrylonitrile or benzonitrile at 25 °C for 4 h gave the hydride rearrangement product **8a**. No detectable amount of the aza-cage **2a** was obtained. Thus, carbon-carbon double bond conjugated nitriles are inactive for the one-pot conversion from oxa-cages to aza-cages.

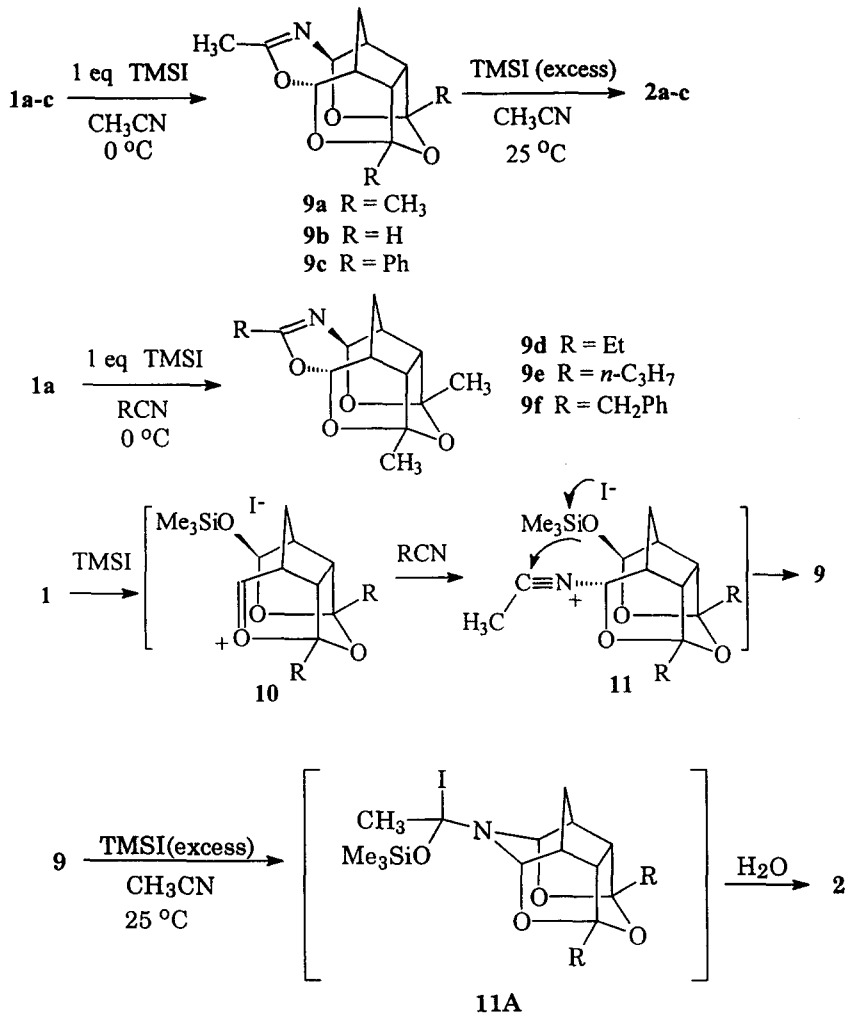
Scheme 4



In order to understand the reaction mechanism for the conversion of tetraoxa-cages to monoazatrioxa-cages, various reaction conditions were performed. Reaction of **1a-c** with one equivalent of iodotrimethylsilane in acetonitrile at 0 °C for 2 h gave the ring expansion products **9a-c** in 80-85% yields (Scheme 5). Treatment of **9a-c** with excess of iodotrimethylsilane in acetonitrile at 25 °C gave the aza-cages **2a-c** in 80% yields. Thus, the ring expansion compound **9** is the intermediate for the conversion of oxa-cage **1** to aza-cage **2**. Reaction of **1a** with one equivalent of iodotrimethylsilane in propionitrile, butyronitrile, and benzyl cyanide at 0 °C for 2 h gave the ring expansion products **9d-f** in 80-85% yields. The proposed mechanism for this interesting reaction involves a Ritter-type reaction[11] of the oxonium ion **10** with alkyl nitriles via the nitrilium ion **11** to

give the intermediate **9**. Reaction of **9** with excess of iodotrimethylsilane may proceed via the intermediate **11A**, which followed by aqueous hydrolysis, to give the aza-cages **2**.

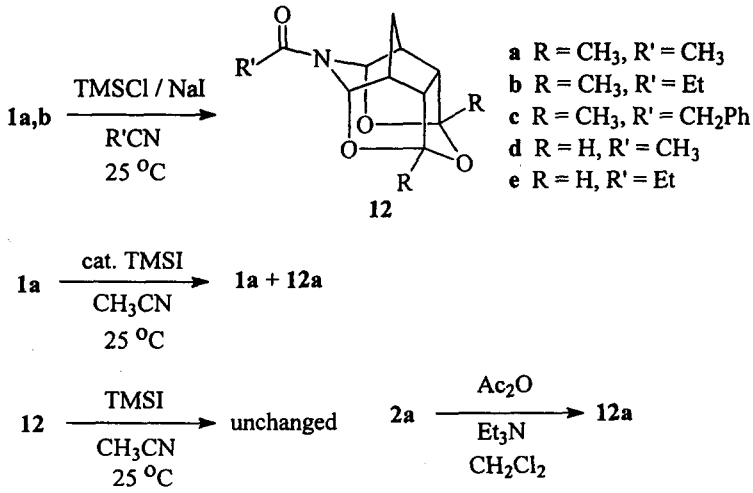
Scheme 5



We also prepared iodotrimethylsilane *in situ*[12] for the conversion of oxa-cages to aza-cages. Treatment of **1a** and **1b** with excess of sodium iodide and chlorotrimethylsilane in acetonitrile, propionitrile, and benzyl cyanide at 25 °C for 48 h gave the amido-cages **12a-e** in 85-90% yields (Scheme 6). Reaction of **1a** with a catalytic amount of iodotrimethylsilane in acetonitrile at 25 °C for 48 h gave the amido-cage **12a** in 8% with a large amount of unreacted compound **1a**. Reaction of **12** with iodotrimethylsilane in acetonitrile at 25 °C remained unchanged. The IR spectra of **12a-e** showed strong absorptions near 1670 cm^{-1} for the amide group. The ^1H NMR spectrum of **12a**

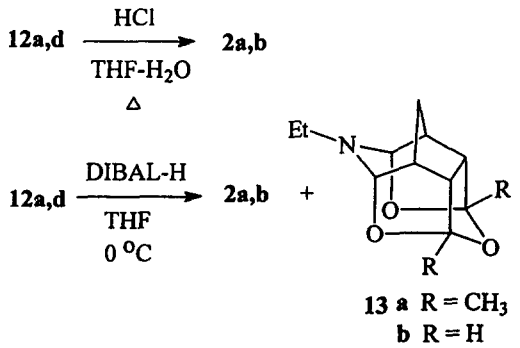
revealed two doublets at δ 6.33 and 5.75 for the two azaacetal protons, which exhibited the partial double bond character for the amide C-N bond due to resonance. The amido-cage **12a** was also obtained by treatment of **2a** with acetic anhydride and triethylamine in dichloromethane at 25 °C. Thus, We have demonstrated that, in reaction with oxa-cages **1**, the combination of chlorotrimethylsilane and sodium iodide in acetonitrile behaves different nature from iodotrimethylsilane. The reaction mechanism for the formation of the amido-cages **12** is not clear.

Scheme 6



Hydrolysis of **12a,d** with concentrated HCl in aqueous THF at refluxing temperature for 4 h gave the aza-cages **2a,b** in 75-80% yields (Scheme 7). Treatment of **12a,d** with diisobutylaluminum hydride (DIBAL-H) in dry THF at 0 °C gave **2a,b** (55-60%) and compounds **13a,b** (10-15%). This results provide another procedure for the preparation of aza-cages.

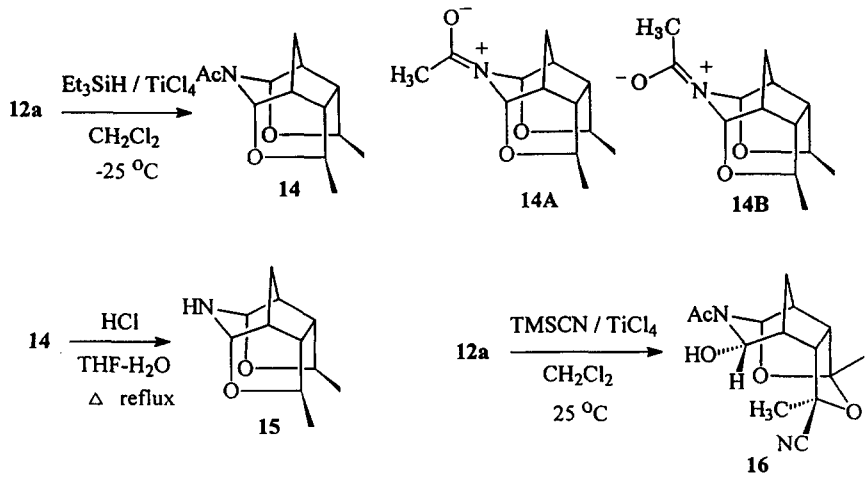
Scheme 7



Treatment of **12a** with triethylsilane in the presence of $TiCl_4$ in dichloromethane at -25 °C gave

compound **14**. The ^{1}H and ^{13}C NMR spectra of **14** revealed one pair of conformational isomers as **14A** and **14B**, an interesting spectral phenomena. Hydrolysis of **14** with concentrated HCl in aqueous THF at refluxing temperature gave the aza-cage **15** in 70% yield. Treatment of **12a** with cyanotrimethylsilane in the presence of $TiCl_4$ in dichloromethane at 25 °C gave compound **16** in 75% yield. The structure of **16** was finally proven by X-ray analysis (Figure 2).

Scheme 8



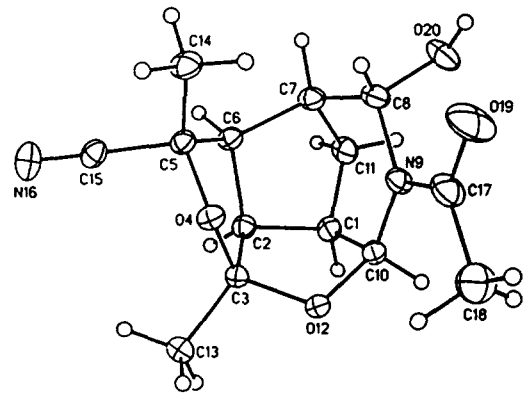


Figure 2. ORTEP diagram of **16**.

Conclusion

We have discovered an one-pot conversion of tetraacetal tetraoxa-cages to aza-cages mediated by iodotrimethylsilane in alkyl nitriles at 25 °C. The ring expansion compounds **9a-f** were found to be the reaction intermediates. The reaction mechanism for the conversion of oxa-cages **1** to aza-cages **2** may involve a Ritter-type reaction of the oxonium ion **10** with nitriles via the nitrilium ion **11** to give the intermediate **9**. We have also demonstrated that reaction of oxa-cages **1** with the combination of

chlorotrimethylsilane and sodium iodide in nitriles gave the amido-cages **12**, different results from the reaction of **1** with iodotrimethylsilane. Carbon-carbon double bond conjugated nitriles and Lewis acids, such as $TiCl_4$ or $BF_3{\cdot}OEt_2$, are ineffective for the oxa-cages to aza-cages conversion. Instead, a hydride rearrangement took place. Chemical transformations of amido-cages with triethylsilane and cyanotrimethylsilane were also performed. The structures of the aza-cages **2** and compound **16** were proven by X-ray analysis of the crystalline compounds **2a** and **16**.

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 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. 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 One-Pot Conversion of Tetraoxa-Cages 1a-e to Aza-Cages 2a-e. To a solution of **1a** (0.21 g, 1.0 mmol) in acetonitrile (30 mL) was added iodotrimethylsilane (0.60 g, 3.0 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 4 h. To this solution was added saturated $Na_2S_2O_3$ solution (20 mL). After extraction with ether (3 x 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the aza-cage **2a** (0.18 g, 85%).

1,7-Dimethyl-4-aza-2,6,13-trioxapentacyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 2a: white waxy solid; mp 81-82 °C; IR ($CHCl_3$) 3350, 2980, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.17 (d, J = 7.2 Hz, 2H), 3.17 (dd, J = 5.1 Hz, J = 2.7 Hz, 2H), 2.94-2.89 (m, 3H), 1.89 (d, J = 11.7 Hz, 1H), 1.74-1.68 (m, 1H), 1.50 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 115.34 (2C), 89.67 (2CH), 59.61 (2CH), 44.95 (2CH), 30.99 (CH_2), 25.81 ($2CH_3$); LRMS m/z (rel int) 209 (M^+, 100); HRMS (EI) calcd for $C_{11}H_{15}O_3N$ 209.1052, found 209.1047.

4-Aza-2,6,13-trioxapentacyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 2b: white waxy solid; mp 70-71 °C;

yield 80%; IR ($CHCl_3$) 3350, 2980, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (d, J = 5.7 Hz, 2H), 5.17 (d, J = 7.2 Hz, 2H), 3.45-3.41 (m, 2H), 3.00 (brs, 1H), 2.88-2.81 (m, 2H), 1.93 (d, J = 11.7 Hz, 1H), 1.87-1.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 108.15 (2CH), 89.50 (2CH), 55.15 (2CH), 44.45 (2CH), 31.26 (CH_2); LRMS m/z (rel int) 181 (M^+, 100); HRMS (EI) calcd for $C_9H_{11}O_3N$ 181.0739, found 181.0733.

1,7-Diphenyl-4-aza-2,6,13-trioxapentacyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 2c: white waxy solid; mp 92-93 °C; yield 80%; IR ($CHCl_3$) 3350, 2980, 1600, 1070, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.58 (m, 4H), 7.40-7.29 (m, 6H), 5.51 (d, J = 7.2 Hz, 2H), 3.55 (dd, J = 5.1 Hz, J = 2.7 Hz, 2H), 3.22 (brs, 1H), 3.14-3.07 (m, 2H), 2.03 (d, J = 11.7 Hz, 1H), 1.83-1.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 142.32 (2C), 128.08 (4CH), 127.93 (2CH), 125.57 (4CH), 116.51 (2C), 90.64 (2CH), 62.69 (2CH), 45.36 (2CH), 31.11 (CH_2); LRMS m/z (rel int) 333 (M^+, 100); HRMS (EI) calcd for $C_{21}H_{19}O_3N$ 333.1365, found 333.1358.

1-Methyl-4-aza-2,6,13-trioxapentacyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 2d: white waxy solid; mp 66-68 °C; yield 80%; IR ($CHCl_3$) 3350, 2980, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (d, J = 6.0 Hz, 1H), 5.17 (d, J = 7.2 Hz, 1H), 5.16 (d, J = 7.2 Hz, 1H), 3.54-3.46 (m, 1H), 3.10 (dd, J = 10.8 Hz, J = 7.2 Hz, 1H), 2.96-2.80 (m, 3H), 1.91 (d, J = 11.7 Hz, 1H), 1.80-1.73 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 115.69 (C), 108.12 (CH), 89.88 (CH), 89.41 (CH), 58.56 (CH), 56.23 (CH), 45.01 (CH), 44.51 (CH), 31.17 (CH_2), 25.43 (CH_3); LRMS m/z (rel int) 195 (M^+, 100); HRMS (EI) calcd for $C_{10}H_{13}O_3N$ 195.0895, found 195.0891.

1-Methy-7-benzyl-4-aza-2,6,13-trioxapentacyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 2e: white waxy solid; mp 55-56 °C; yield 85%; IR ($CHCl_3$) 3350, 2980, 1600, 1070, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.22 (m, 5H), 5.15 (d, J = 7.2 Hz, 1H), 5.11 (d, J = 7.2 Hz, 1H), 3.14 (dd, J = 10.2 Hz, J = 7.5 Hz, 1H), 3.02 (brs, 3H), 2.94 (dd, J = 10.2 Hz, J = 7.2 Hz, 1H), 2.83, 2.43 (ABq, J = 18 Hz, 2H), 1.78 (d, J = 12.6 Hz, 1H), 1.61-1.54 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 136.91 (C), 130.52 (2CH), 127.81 (2CH), 126.39 (CH), 117.06 (C), 115.55 (C), 89.73 (CH), 89.67 (CH), 59.14 (CH), 56.90 (CH), 44.98 (CH), 44.89 (CH), 43.99 (CH_2), 30.88 (CH_2), 25.37 (CH_3); LRMS m/z (rel int) 285 (M^+, 22), 208 (100); HRMS (EI) calcd for $C_{17}H_{19}O_3N$ 285.1365, found 285.1360.

***N*-Benzylation of 2a**. To a solution of **2a** (0.21 g, 1.00 mmol) in THF (20 mL) and H_2O (5 mL) was added NaOH solution (1 M, 5 mL) and benzyl bromide (0.17 g, 1.0 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. To this reaction mixture was added saturated NH_4Cl (20 mL). After extraction with ether (4 x 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the *N*-benzylation product **6** (0.19 g, 63%): pale yellow oil; IR ($CHCl_3$) 2970, 1600, 1070, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H), 4.95 (d, J = 7.5 Hz, 2H), 4.10 (s, 2H), 3.14 (dd, J = 5.1 Hz, J = 3.0 Hz, 2H),

2.88-2.85 (m, 2H), 1.98-1.94 (m, 1H), 1.74-1.67 (m, 1H), 1.51 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 138.43 (C), 128.77 (2CH), 128.28 (2CH), 126.97 (CH), 115.31 (2C), 92.91 (2CH), 59.93 (2CH), 51.77 (CH_2), 45.17 (2CH), 30.53 (CH_2), 25.90 ($2CH_3$); LRMS *m/z* (rel int) 299 (M^+, 11), 91 (100).

Tosylation of 2a. To a solution of **2a** (0.21 g, 1.0 mmol) in pyridine (20 mL) was added tosyl chloride (0.28 g, 1.5 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. To this mixture was added 1 M HCl (30 mL) at 0 °C. After extraction with ether (4 x 30 mL), the organic layer was washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the sulfonamide **7** (0.33 g, 90%): white waxy solid; mp 137-138 °C; IR ($CHCl_3$) 3020, 2980, 1610, 1350, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.99 (d, J = 7.5 Hz, 2H), 3.15-3.12 (m, 2H), 3.05-3.01 (m, 2H), 2.40 (s, 3H), 1.82-1.79 (m, 2H), 1.41 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 143.08 (C), 137.90 (C), 129.01 (2CH), 128.00 (2CH), 116.91 (2C), 88.63 (2CH), 58.66 (2CH), 45.86 (2CH), 30.17 (CH_2), 25.38 ($2CH_3$), 21.55 (CH_3); LRMS *m/z* (rel int) 363 (M^+, 100); HRMS (EI) calcd for $C_{18}H_{21}O_5NS$ 363.1140, found 363.1132.

General Procedure for the Reaction of 1a-c with Lewis Acids, such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ in Acetonitrile. To a solution of **1a** (0.11 g, 0.52 mmol) in acetonitrile (10 mL) was added $TiCl_4$ (0.19 g, 1.00 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 4 h. To this mixture, H_2O (20 mL) was added. After extraction with ether (4 x 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 **8a** which was obtained by a different reaction procedure.[9]

General Procedure for the Reaction of 1a with Me_3SiI in Acrylonitrile and Benzonitrile. To a solution of **1a** (0.11g, 0.52 mmol) in acrylonitrile (10 mL) was added iodotrimethylsilane (0.30 g, 1.5 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 4 h. To this solution was added saturated $Na_2S_2O_3$ solution (10 mL). After extraction with ether (3 x 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 **8a** which is a known compound.[9]

General Procedure for the Formation of the Ring Expansion Compounds 9a-f. To a solution of **1a** (0.42 g, 2.0 mmol) in acetonitrile (30 mL) was added iodotrimethylsilane (0.40 g, 2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h. To this solution was added saturated $Na_2S_2O_3$ solution (30 mL). After extraction with ether (3 x 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the ring expansion intermediate **9a** (0.46 g, 85%).

1,5,9-Trimethyl-4-aza-2,6,8,15-tetraoxapentacyclo[7.5.1.0^{3,13}.0^{7,11}.0^{10,14}]-5-pentadecene 9a: white waxy solid; mp 57-58.5 °C; IR ($CHCl_3$) 2980, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.1 Hz, 1H), 6.06 (d, J = 7.2 Hz, 1H), 3.30-3.28 (m, 2H), 3.14-3.10 (m, 2H), 2.84 (s, 3H), 1.92-1.86 (m, 1H), 1.81-1.77 (m, 1H), 1.56 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 208.46 (C), 117.83 (2C), 89.46 (CH), 89.40 (CH), 59.13 (CH), 59.05 (CH), 45.46 (CH), 44.84 (CH), 34.03 (CH_3), 28.86 (CH_2), 25.26 (CH_3), 25.21 (CH_3); LRMS m/z (rel int) 251 (M^+, 100); HRMS (EI) calcd for $C_{13}H_{17}O_4N$ 251.1158, found 251.1152.

5-Methyl-4-aza-2,6,8,15-tetraoxapentacyclo[7.5.1.0^{3,13}.0^{7,11}.0^{10,14}]-5-pentadecene 9b: white waxy solid; mp 82-83 °C; yield 80%; IR ($CHCl_3$) 2980, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 7.8 Hz, 1H), 6.05 (d, J = 7.5 Hz, 1H), 5.87 (d, J = 3.6 Hz, 1H), 5.86 (d, J = 3.6 Hz, 1H), 3.58-3.54 (m, 2H), 3.09-3.05 (m, 2H), 2.85 (s, 3H), 2.06-1.99 (m, 1H), 1.90-1.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 209.00 (C), 110.04 (2CH), 89.33 (CH), 89.22 (CH), 54.65 (CH), 54.61 (CH), 44.82 (CH), 44.23 (CH), 34.09 (CH_3), 28.85 (CH_2); LRMS m/z (rel int) 223 (M^+, 100); HRMS (EI) calcd for $C_{11}H_{13}O_4N$ 223.0845, found 223.0849.

1,9-Diphenyl-5-methyl-4-aza-2,6,8,15-tetraoxapentacyclo[7.5.1.0^{3,13}.0^{7,11}.0^{10,14}]-5-pentadecene 9c: highly viscous oil; yield 85%; IR ($CHCl_3$) 2980, 1600, 1060, 755, 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (m, 5H), 7.43-7.32 (m, 6H), 6.38 (d, J = 7.5 Hz, 1H), 3.68-3.64 (m, 2H), 3.35-3.29 (m, 2H), 2.92 (s, 3H), 1.99-1.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 209.08 (C), 140.71 (2C), 128.56 (2CH), 128.35 (2CH), 128.17 (2CH), 125.77 (2CH), 125.56 (2CH), 118.85 (2C), 90.18 (2CH), 62.27 (CH), 62.03 (CH), 46.11 (CH), 45.37 (CH), 34.36 (CH_3), 29.06 (CH_2); LRMS m/z (rel int) 375 (M^+, 25), 298 (100); HRMS (EI) calcd for $C_{23}H_{21}O_4N$ 375.1471, found 375.1479.

1,9-Dimethyl-5-ethyl-4-aza-2,6,8,15-tetraoxapentacyclo[7.5.1.0^{3,13}.0^{7,11}.0^{10,14}]-5-pentadecene 9d: highly viscous oil; yield 82%; IR ($CHCl_3$) 2980, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.1 Hz, 1H), 6.10 (d, J = 7.2 Hz, 1H), 3.29-3.26 (m, 2H), 3.14-3.10 (m, 2H), 3.01-2.94 (m, 2H), 1.91-1.85 (m, 1H), 1.78-1.74 (m, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 214.71 (C), 117.91 (C), 117.80 (C), 89.70 (CH), 88.74 (CH), 59.23 (2CH), 45.53 (CH), 44.98 (CH), 37.44 (CH_2), 29.03 (CH_2), 25.33 ($2CH_3$), 14.07 (CH_3); LRMS m/z (rel int) 265 (M^+, 100); HRMS (EI) calcd for $C_{14}H_{19}O_4N$ 265.1314, found 265.1321.

1,9-Dimethyl-5-*n*-propyl-4-aza-2,6,8,15-tetraoxapentacyclo[7.5.1.0^{3,13}.0^{7,11}.0^{10,14}]-5-pentadecene 9e: highly viscous oil; yield 80%; IR ($CHCl_3$) 2980, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.1 Hz, 1H), 6.08 (d, J = 7.5 Hz, 1H), 3.29-3.26 (m, 2H), 3.14-3.08 (m, 2H), 2.97 (t, J = 8.1 Hz, 2H), 1.90-1.84 (m, 2H), 1.77-1.71 (m, 2H), 1.57 (s, 3H), 1.55 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 213.25 (C), 117.89 (C), 117.77 (C), 89.63 (CH), 88.90 (CH), 59.17 (2CH), 46.53 (CH_2), 45.48 (CH), 44.92 (CH), 29.03 (CH_2), 25.27 ($2CH_3$), 23.25 (CH_2), 13.82 (CH_3); LRMS m/z (rel int) 279 (M^+, 100); HRMS (EI) calcd for $C_{15}H_{21}O_4N$ 279.1471, found 279.1467.

1,9-Dimethyl-5-benzyl-4-aza-2,6,8,15-tetraoxapentacyclo[7.5.1.0^{3,13}.0^{7,11}.0^{10,14}]-5-pentadecene

9f: highly viscous oil; yield 80%; IR ($CHCl_3$) 2980, 1600, 1060, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (m, 6H), 5.93 (d, J = 7.5 Hz, 1H), 4.65, 4.36 (ABq, J = 15.3 Hz, 2H), 3.24-3.19 (m, 2H), 3.10-3.08 (m, 1H), 2.86-2.84 (m, 1H), 1.79-1.71 (m, 2H), 1.58 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 209.07 (C), 136.19 (C), 128.83 (2CH), 127.62 (2CH), 126.98 (CH), 118.07 (C), 117.93 (C), 89.89 (CH), 89.57 (CH), 59.23 (CH), 59.17 (CH), 51.73 (CH_2), 45.35 (CH), 45.08 (CH), 29.03 (CH_2), 25.36 (CH_3), 25.29 (CH_3); LRMS m/z (rel int) 327 (M^+, 24), 250 (100); HRMS (EI) calcd for $C_{19}H_{21}O_4N$ 327.1471, found 327.1477.

General Procedure for the Conversion of 9a-c to Aza-Cages 2a-c. The same reaction conditions and procedure for the conversion of tetraoxa-cages **1a-c** to the aza-cages **2a-c** were applied for the conversion of **9a-c** to **2a-c**.

General Procedure for the Reaction of 1a,b with Me_3SiCl and NaI in Nitriles. Formation of the Amido-Cages 12a-e. To a solution of **1a** (0.21 g, 1.0 mmol) in acetonitrile (20 mL) were added NaI (0.45 g, 3.00 mmol) and Me_3SiCl (0.65 g, 6.00 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 48 h. To this mixture was added saturated $Na_2S_2O_3$ solution (20 mL). After extraction with ether (3 x 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the amido-cage **12a** (0.23 g, 90%).

1,7-Dimethyl-4-acetamido-2,6,13-trioxapentacyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 12a: white waxy solid; mp 99-100 °C; IR ($CHCl_3$) 2970, 1670, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.33 (d, J = 7.2 Hz, 1H), 5.75 (d, J = 7.2 Hz, 1H), 3.22 (dd, J = 5.1 Hz, J = 3.0 Hz, 2H), 3.10-3.00 (m, 2H), 2.26 (s, 3H), 1.89-1.80 (m, 1H), 1.73-1.69 (m, 1H), 1.53 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 172.89 (CO), 117.21 (C), 117.09 (C), 88.95 (CH), 84.72 (CH), 59.17 (2CH), 45.33 (CH), 44.51 (CH), 29.54 (CH_2), 25.43 ($2CH_3$), 22.25 (CH_3); LRMS m/z (rel int) 251 (M^+, 12), 209 (100); HRMS (EI) calcd for $C_{13}H_{17}O_4N$ 251.1158, found 251.1155.

1,7-Dimethyl-4-propioamido-2,6,13-trioxapentacyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 12b: highly viscous oil; yield 81%; IR ($CHCl_3$) 2970, 1670, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ d 6.37 (d, J = 7.2 Hz, 1H), 5.81 (d, J = 7.2 Hz, 1H), 3.22 (dd, J = 5.1 Hz, J = 2.4 Hz, 2H), 3.08-3.00 (m, 2H), 2.60-2.50 (m, 2H), 1.85-1.78 (m, 1H), 1.71-1.67 (m, 1H), 1.53 (s, 6H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 175.98 (CO), 117.09 (C), 117.03 (C), 87.93 (CH), 84.93 (CH), 59.14 (2CH), 45.24 (CH), 44.54 (CH), 29.57 (CH_2), 27.06 (CH_2), 25.43 ($2CH_3$), 8.85 (CH_3); LRMS m/z (rel int) 265 (M^+, 24), 209 (100); HRMS (EI) calcd for $C_{14}H_{19}O_4N$ 265.1314, found 265.1318.

1,4-Dimethyl-4-homobenzoylamido-2,6,13-trioxapentacyclo[5.5.1.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]tridecane 12c: highly viscous oil; yield 80%; IR ($CHCl_3$) 2970, 1670, 1600, 1070, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 6.37 (d, J = 7.2 Hz, 1H), 5.77 (d, J = 7.2 Hz, 1H), 3.96, 3.84 (ABq, J = 15.3

Hz, 2H), 3.20-3.18 (m, 2H), 3.01 (brs, 1H), 2.93 (brs, 1H), 1.77-1.70 (m, 1H), 1.53 (s, 6H), 1.53-1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 173.07 (CO), 134.44 (C), 128.58 (2CH), 128.50 (2CH), 126.72 (CH), 117.18 (C), 117.13 (C), 88.23 (CH), 84.98 (CH), 59.00 (2CH), 45.11 (CH), 44.56 (CH), 41.27 (CH_2), 29.44 (CH_2), 25.34 ($2CH_3$); LRMS *m/z* (rel int) 327 (M^+, 8), 209 (100); HRMS (EI) calcd for $C_{19}H_{21}O_4N$ 327.1471, found 327.1463.

4-Acetamido-2,6,13-trioxapentacyclo[5.5.1.0^{3,11}.0^{5,9}.0^{8,12}]tridecane 12d: white waxy solid; mp 68-69 °C; yield 80%; IR ($CHCl_3$) 2970, 1670, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, *J* = 7.2 Hz, 1H), 5.81 (d, *J* = 5.1 Hz, 2H), 5.74 (d, *J* = 7.2 Hz, 1H), 3.50 (brs, 2H), 3.04-2.96 (m, 2H), 2.28 (s, 3H), 1.99-1.93 (m, 1H), 1.81-1.77 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 173.01 (CO), 109.49 (CH), 109.40 (CH), 88.71 (CH), 84.55 (CH), 54.54 (2CH), 44.57 (CH), 43.81 (CH), 29.51 (CH_2), 22.19 (CH_3); LRMS *m/z* (rel int) 223 (M^+, 17), 181 (100); HRMS (EI) calcd for $C_{11}H_{13}O_4N$ 223.0845, found 223.0840.

4-Propioamido-2,6,13-trioxapentacyclo[5.5.1.0^{3,11}.0^{5,9}.0^{8,12}]tridecane 12e: white waxy solid; mp 54-55 °C; yield 83%; IR ($CHCl_3$) 2970, 1670, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, *J* = 7.2 Hz, 1H), 5.81 (d, *J* = 5.1 Hz, 2H), 5.76 (d, *J* = 7.2 Hz, 1H), 3.50 (brs, 2H), 3.02-2.97 (m, 2H), 2.61-2.51 (m, 2H), 1.99-1.92 (m, 1H), 1.79-1.75 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 176.04 (CO), 109.40 (2CH), 87.72 (CH), 84.78 (CH), 54.54 (2CH), 44.54 (CH), 43.84 (CH), 29.54 (CH_2), 26.94 (CH_2), 8.70 (CH_3); LRMS *m/z* (rel int) 278 (M^+, 26), 181 (100); HRMS (EI) calcd for $C_{12}H_{15}O_4N$ 237.1001, found 237.1007.

General Procedure for the Hydrolysis of 12a,d to Give 2a,b. To a solution of **12a** (0.25 g, 1.0 mmol) in THF (10 mL) and H_2O (10 mL) was added 1 M HCl (5 mL) at 25 °C. The reaction mixture was refluxed for 4 h. After cooling, saturated $NaHCO_3$ solution (20 mL) was added to the solution. After extraction with ether (4 x 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the aza-cage **2a** (0.16 g, 75%).

General Procedure for the Reduction of 12a,d with Diisobutylaluminum Hydride (DIBAL-H). To a solution of **12a** (0.25 g, 1.00 mmol) in dry THF (30 mL) was added DIBAL-H (0.85 g, 1.2 mmol, 20% in *n*-hexane) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. To this solution was dropwise added H_2O at 0 °C to destroy the excess DIBAL-H. After extraction with ether (4 x 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the aza-cage **2a** (0.15 g, 70%) and compound **13a** (0.040 g, 15%).

1,7-Dimethyl-4-ethyl-4-aza-2,6,13-trioxapentacyclo[5.5.1.0^{3,11}.0^{5,9}.0^{8,12}]tridecane 13a: highly viscous oil; IR ($CHCl_3$) 2880, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ d 5.04 (d, *J* = 7.8 Hz, 2H), 3.12

(dd, J = 5.1 Hz, J = 3.0 Hz, 2H), 2.97 (q, J = 7.2 Hz, 2H), 2.88-2.84 (m, 2H), 1.87-1.83 (m, 1H), 1.71-1.65 (m, 1H), 1.50 (s, 6H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 115.07 (2C), 92.66 (2CH), 59.90 (2CH), 45.04 (2CH), 42.24 (CH_2), 30.33 (CH_2), 25.90 ($2CH_3$), 12.80 (CH_3); LRMS m/z (rel int) 237 (M^+, 34), 222 (100); HRMS (EI) calcd for $C_{13}H_{19}O_3N$ 237.1365, found 237.1372.

4-Ethyl-4-aza-2,6,13-trioxapentacyclo[5.5.1.0^{3,11}.0^{5,9}.0^{8,12}]tridecane 13b: highly viscous oil; yield 17%; IR ($CHCl_3$) 2880, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (d, J = 5.1 Hz, 2H), 5.01 (d, J = 8.1 Hz, 2H), 3.39-3.36 (m, 2H), 2.97 (q, J = 6.6 Hz, 2H), 2.80-2.76 (m, 2H), 1.89-1.85 (m, 1H), 1.81-1.76 (m, 1H), 1.13 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 108.10 (2CH), 92.56 (2CH), 55.43 (2CH), 44.59 (2CH), 42.48 (CH_2), 30.59 (CH_2), 12.89 (CH_3); LRMS m/z (rel int) 209 (M^+, 15), 194 (100); HRMS (EI) calcd for $C_{11}H_{15}O_3N$ 209.1052, found 209.1058.

Reaction of 12a with Triethylsilane in the Presence of $TiCl_4$. To a solution of **12a** (0.25 g, 1.0 mmol) in dichloromethane (30 mL) were added triethylsilane (0.35 g, 3.00 mmol) and $TiCl_4$ (0.020 g, 0.10 mmol) at -25 °C. The reaction mixture was stirred at -25 °C for 6 h. To this solution, H_2O (10 mL) was added. After extraction with CH_2Cl_2 (3 x 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give compound **14** (0.20 g, 85%), which ^{1}H and ^{13}C NMR spectra revealed one pair of conformational isomers: pale yellow oil; IR ($CHCl_3$) 2880, 1670, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13-6.11 (m, 1H), 5.63-5.61 (m, 1H), 4.83-4.78 (m, 1H), 4.30-4.26 (m, 1H), 2.97-2.91 (m, 1H), 2.86-2.80 (m, 1H), 2.39-2.36 (m, 2H), 2.24 (s, 3H), 1.75-1.68 (m, 1H), 1.57-1.53 (m, 1H), 1.49-1.46 (m, 3H), 1.29-1.26 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 173.41 (CO), 173.01 (CO), 89.75 (CH), 87.45 (CH), 86.09 (CH), 83.19 (CH), 77.31 (CH), 77.19 (CH), 75.85 (CH), 75.65 (CH), 48.48 (CH), 48.17 (CH), 47.88 (CH), 47.81 (CH), 46.93 (CH), 46.10 (CH), 45.86 (CH), 45.14 (CH), 24.14 (CH_2), 24.11 (CH_2), 22.50 (CH_3), 22.17 ($2CH_3$), 21.86 (CH_3), 15.42 (CH_3), 15.38 (CH_3); LRMS m/z (rel int) 237 (M^+, 14), 195 (100); HRMS (EI) calcd for $C_{13}H_{19}O_3N$ 237.1365, found 237.1359.

Hydrolysis of 14. The same reaction conditions and procedure for the hydrolysis of **12a,d** were applied for the hydrolysis of **14** to give compound **15** in 65% yield: pale yellow oil; IR ($CHCl_3$) 3350, 2880, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (d, J = 6.6 Hz, 1H), 5.07 (d, J = 7.5 Hz, 1H), 4.80-4.77 (m, 1H), 4.20-4.16 (m, 1H), 2.81-2.74 (m, 1H), 2.68-2.64 (m, 1H), 2.36-2.28 (m, 2H), 1.59-1.52 (m, 3H), 1.48 (d, J = 7.5 Hz, 3H), 1.20 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 89.63 (CH), 88.32 (CH), 75.62 (CH), 74.13 (CH), 49.51 (CH), 48.20 (CH), 47.18 (CH), 45.94 (CH), 25.81 (CH_2), 23.58 (CH_3), 15.98 (CH_3); LRMS m/z (rel int) 195 (M^+, 18), 83 (100); HRMS (EI) calcd for $C_{11}H_{17}O_2N$ 195.1259, found 195.1263.

Reaction of 12a with Cyanotrimethylsilane in the Presence of $TiCl_4$. To a solution of **12a**

(0.25 g, 1.0 mmol) in dichloromethane (30 mL) were added cyanotrimethylsilane (0.30 g, 3.0 mmol) and $TiCl_4$ (0.020 g, 0.1 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 8 h. To this solution, H_2O (10 mL) was added. After extraction with CH_2Cl_2 (3 x 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give compound **16** (0.19 g, 70%): white waxy solid; mp 86-87 °C; IR ($CHCl_3$) 3500-3300, 2880, 2250, 1675, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (d, J = 7.8 Hz, 1H), 5.59 (s, 1H), 5.13 (d, J = 2.7 Hz, 1H), 3.35 (dd, J = 8.4 Hz, J = 8.4 Hz, 1H), 3.17-3.15 (m, 1H), 2.95 (dd, J = 8.7 Hz, J = 6.9 Hz, 1H), 2.57-2.53 (m, 1H), 2.25 (s, 3H), 2.20-2.16 (m, 1H), 1.88 (s, 3H), 1.72 (s, 3H), 1.65-1.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 176.35 (CO), 121.40 (CN), 117.83 (C), 88.99 (CH), 78.33 (CH), 76.17 (C), 58.06 (CH), 54.28 (CH), 44.75 (CH), 41.25 (CH), 28.48 (CH_2), 24.50 (CH_3), 22.81 (CH_3), 20.74 (CH_3); LRMS m/z (rel int) 278 (M^+, 26), 236 (100); HRMS (EI) calcd for $C_{14}H_{18}O_4N_2$ 278.1267, found 278.1261.

Acknowledgment. We thank the National Science Council of the Republic of China for financial Support (Grant No. NSC86-2113-M009-001) and Dr. Sue-Lein Wang and Miss Fen-Ling Liao at the Department of Chemistry, National Tsing Hua University, for their help in carrying out the X-ray crystallographic analysis.

References and Notes

(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 Asymmetry* **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) Wu, H. J.; Chern, J. H.; Wu, C. Y. *Tetrahedron* **1997** *53*, 2401. (f) Lin, C. C.; Wu, H. J. *J. Chinese Chem. Soc.* **1995**, *42*, 815. (g) Lin, C. C.; Huang, F. J.; Lin, J. C.; Wu, H. J. *J. Chinese Chem. Soc.* **1996**, *43*, 177. (h) Lin, R. L.; Wu, C. Y.; Chern, J. H.; Wu, H. J. *J. Chinese Chem. Soc.* **1996**, *43*, 289.

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

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

(7) (a) Wu, H. J.; Tsai, S. H.; Chern, J. H.; Lin, H. C. *J. Org. Chem.* **1997**, *62*, 6367. (b) Wu, H. J.; Tsai, S. H.; Chung, W. S. *Tetrahedron Lett.* **1996**, *37*, 8209. (c) Wu, H. J.; Tsai, S. H.; Chung, W. S. *J. Chem. Soc., Chem. Commun.* **1996**, 375. (d) Tsai, S. H.; Wu, H. J.; Chung, W. S. *J. Chinese. Chem. Soc.* **1996**, *43*, 445.

(8) (a) Wu, H. J.; Wu, C. Y. *Tetrahedron Lett.* **1997**, *38*, 2493. (b) Mehta, G.; Vidya, R. *Tetrahedron Lett.* **1997**, *38*, 4173.

(9) (a) Wu, H. J.; Chern, J. H. *J. Org. Chem.* **1997**, *62*, 3208. (b) Wu, H. J.; Chern, J. H. *J. Chem. Soc., Chem. Commun.* **1997**, 547.

(10) Wu, H. J.; Chern, J. H. *Tetrahedron Lett.* **1997**, *38*, 2887.

(11) (a) Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; *Tetrahedron Lett.* **1995**, *36*, 3993. (b) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. (c) Bishop, R. *Comprehensive Org. Syn.* **1991**, *6*, 261.

(12) (a) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225. (b) Olah, G. A.; Narang, S. C.; Balaram Gupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.