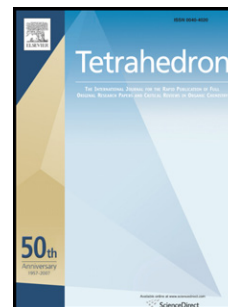


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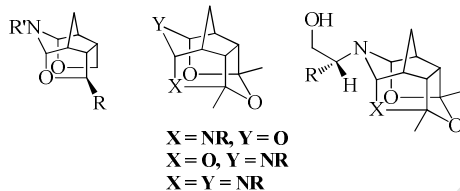
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**Synthesis of New Acetal Aza-Cage
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Chung-Yi Wu^{a, b}, Hui-Chang Lin^{a, c}, and Hsien-Jen Wu^{a, d, *}



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Synthesis of new acetal aza-cage compounds via ozonolysis of bis-*endo*-diol- and diacylnorbornene derivatives

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ABSTRACT

We synthesized acetal aza-cage compounds directly via ozonolysis of 2,3-bis-*endo*-diol- and diacylnorbornenes in dichloromethane at -78 °C. Ozonolysis of the diols followed by addition of amines gave the aza-cage compounds in high yields. The reaction mechanism for the formation of this type of aza-cage compounds is proposed to proceed via the hydroperoxide intermediate. Ozonolysis of the diacetyl norbornene followed by addition of (1) primary amines gave monoaza-cages and diaza-cage, (2) *t*-butylamine gave hydroxyl lactone and diaza-cages, and (3) amino acid ester gave optically active aza-cages, in which one compound was converted into chiral amino alcohol and structure of another was proven by X-ray analysis. A mechanism via the final ozonide and the imine intermediates is proposed for the formation of this type of aza-cages.

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1. Introduction

The synthesis and chemistry of polycyclic cage compounds have attracted considerable attention in recent years.¹ The vast majority of the work reported in this area has dealt with carbocyclic cage compounds, which have played a key role in theoretical organic chemistry by providing rigid and often symmetric frameworks for evaluating theories put forth on the physical-chemical properties of organic molecules. In addition, some precursors of these cage compounds are important building blocks for the synthesis of polycyclic synthetic and natural products. Moreover, heterocyclic cage compounds have also received attention from both synthetic and mechanistic considerations for comparing the reactivity pattern of carbon cage compounds with their heterologues.

There have been many studies regarding the chemistry² and synthesis³⁻⁸ of oxa-cage compounds. This class of heterocyclic cage compounds can be synthesized by intramolecular alkene-oxirane ($2\sigma-2\pi$) photocycloaddition,³ transannular cyclization of suitable compounds,⁴ tandem cyclization,⁵ dehydration of diols

that have the proper stereochemistry,⁶ base-promoted rearrangement,⁷ intramolecular etherification of an alkene bond with organoselenium reagents,⁸ and tandem radical cyclization,⁹ Previously, our group utilized ozonolysis reaction for the synthesis of a series of oxa-cage compounds, such as diacetal trioxa-cages,¹⁰ triacetal trioxa-cages,¹¹ tetraacetal tetraoxa-cages,¹² tetraacetalpentaoxa-cages,¹³ and pentaacetal pentaoxa-cages (the pentaoxal[5]-peristylenes).¹⁴ In the meantime, Mehta's group also independently published the syntheses of [n]oxa[n]peristylane ($n = 3-6$) oxa-cages system via ozonolysis reaction.¹⁵ We also investigated the chemical nature of the acetal group of tetraoxa-cages and discovered hydride rearrangement.¹⁶ We further developed a method for the synthesis of dioxo-cages¹⁷ and diacetal trioxa-cages¹⁸ derivatives via the iodine-induced cyclization reaction. Moreover, we also used the dimethyldioxirane induced sequential cyclization reaction to synthesize the diacetal trioxa-cages and found that dimethyldioxirane is a more powerful electrophile for inducing sequential cyclization reaction of bicyclo[2,2,1]heptanes and bicyclo[2,2,2]octenes.¹⁹ On the other hand, there are only a few

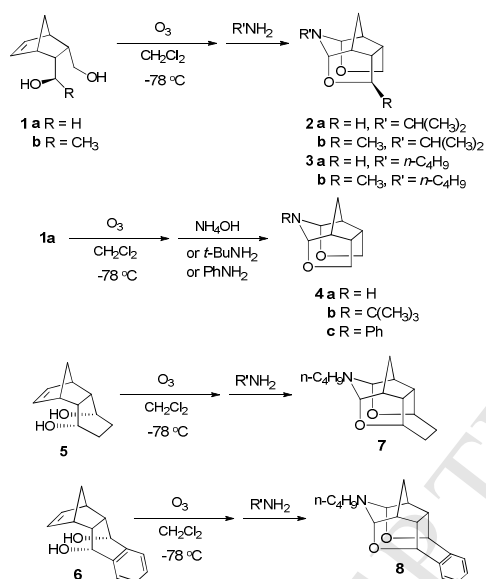
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examples for the synthesis of aza-cage compounds in the literature.^{4f,4g,9b,20} We had developed a one-pot conversion from oxa-cages to aza-cages.²¹ In this study, we report a new method to synthesize acetal aza-cage compounds directly via ozonolysis of 2,3-bis-endo-diol- and diacylnorbornene derivatives.

2. Results and discussion

Ozonolysis of the diols **1a,b** in dichloromethane at $-78\text{ }^{\circ}\text{C}$, followed by addition of isopropylamine and *n*-butylamine, gave the aza cage compounds **2a,b** and **3a,b** in 70-75% yields, respectively (Scheme 1). Ozonolysis of **1a** in dichloromethane at $-78\text{ }^{\circ}\text{C}$ followed by addition of aqueous ammonia, *t*-butylamine, and aniline, gave the aza-cage compounds **4a-c** in 60-70% yield. Therefore, various primary amines, such as *n*-butylamine, isopropylamine, *t*-butylamine, aniline, and aqueous ammonia are able to incorporate into the molecule to form the aza-cages. The steric effect of *t*-butylamine and the benzene ring of aniline did not affect the incorporation of the amine molecule to form the aza-cages. The aza-cage compound **7** and **8** were also obtained in 70-75% by ozonolysis of compounds **5** and **6** followed by addition of *n*-butylamine.

Scheme 1

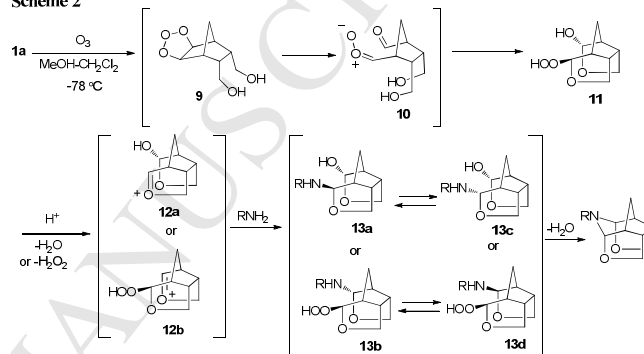


We proposed a reaction mechanism for the formation of the aza cage compounds (Scheme 2). 1,3-Dipolar cycloaddition of an ozone molecule with the alkene bond of **1a** via the *exo* face gave the 1,2,3-trioxolane (primary ozonide) **9**. Fragmentation of **9** leading to the carbonyl oxide **10**, which was followed by intramolecular nucleophilic addition of the hydroxyl groups to the carbonyl oxide group and the aldehyde group, gave the hydroperoxide **11**. The hydroperoxide **11** was isolated in the synthesis of diacetal trioxa-cage compounds.¹⁰ The stereochemistry of the hemiacetal protons of **11** was assigned on the basis of the coupling constant ($J = 0\text{ Hz}$) of the hemiacetal protons. Also, the ozonated dichloromethane blank solution was found to be acidic. Protonation of the hydroxyl group or the hydroperoxy group of **11** followed by loss of a H₂O or a H₂O₂ molecule gave the oxonium ion **12a** or **12b**. Nucleophilic addition of the amine molecule on the oxonium ion **12** followed by dehydration gave the aza-cage compounds probably via the intermediates **13a** or **13b** and **13c** or **13d**.

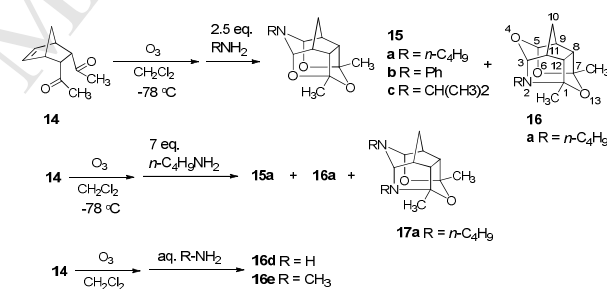
We further extend the synthesis of aza-cages. Ozonolysis of the diacetyl compound **14**^{12a} in dichloromethane at $-78\text{ }^{\circ}\text{C}$

followed by addition of 2.5 equivalents of *n*-butylamine gave the aza-cages compounds **15a** in 38% yield and **16a** in 26% yield (Scheme 3). When isopropylamine and aniline, instead of *n*-butylamine, were added in the ozonolysis reaction, the aza-cage compounds **15b** and **15c** were obtained in 55-60% yields, respectively. The amount of **16b** and **16c** was too small to be isolated. Ozonolysis of **14** in dichloromethane at $-78\text{ }^{\circ}\text{C}$ followed by addition of 7 equivalents of *n*-butylamine gave the aza-cage compounds **15a** (26%), **16a** (22%) and **17a** (14%). If *n*-butylamine and dichloromethane (1:1) were used as cosolvents for the ozonolysis reaction, a messy mixture was obtained. Ozonolysis of **14** in dichloromethane at $-78\text{ }^{\circ}\text{C}$ followed by addition of large excess of aqueous ammonia and aqueous methylamine gave the aza-cages **16d** (45%) and **16e** (68%), respectively. The amount of the other monoaza-cages **15d,e** and the diaza-cages **17d,e** was too small to be isolated.

Scheme 2



Scheme 3

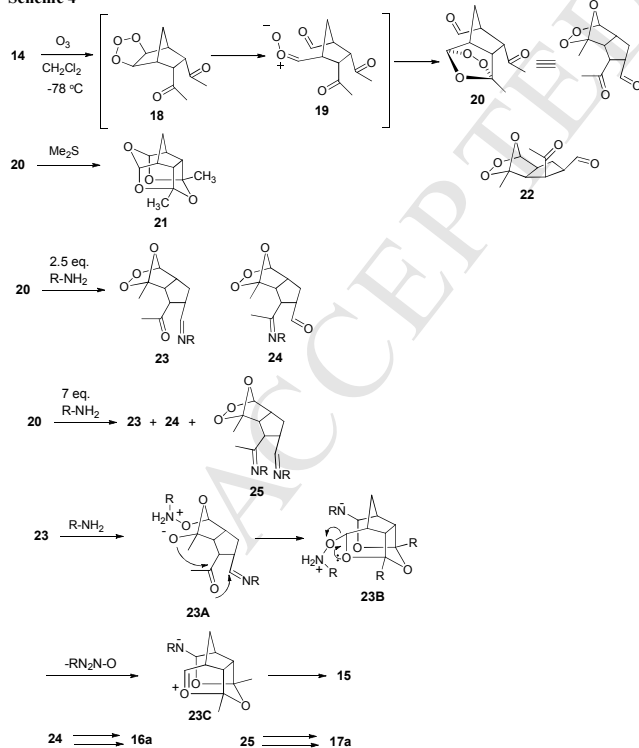


The ¹H NMR spectrum of the monoaza-cage **15a** revealed one doublet at δ 5.01 for the two acetal protons on C₃ and C₅ and one singlet at δ 1.52 for the angular methyl protons. The ¹³C NMR spectrum of **15a** displayed one peak at δ 115.1 for the quaternary carbons, one peak at δ 93.1 for the azaacetal carbons, and one peak at δ 25.9 for the angular methyl carbons. Both ¹H and ¹³C NMR spectra showed that compounds **15a-c** possess a symmetry plane. On the other hand, the ¹H NMR spectrum of **16a** revealed one doublet at δ 5.39 for the acetal proton on C₅, one doublet at δ 4.95 for the azaacetal proton on C₃, and two singlets at δ 1.43 and 1.38 for the angular methyl protons. The ¹³C NMR spectrum of **16a** displayed one peak at δ 115.8 for the quaternary carbon C₇, one peak at δ 103.6 for the other quaternary carbon C₁, one peak at δ 102.9 for the acetal carbon C₅, one peak at δ 89.9 for the azaacetal carbon C₃, and two peaks at δ 25.8 and 25.4 for the angular methyl carbons. Both ¹H and ¹³C NMR spectra showed that compound **16a** do not possess a symmetry plane.

The aza-cage **15a** remained unchanged when it was dissolved in an ozonated CH₂Cl₂ solution with added *n*-butylamine. The aza-cage **16a** also remained unchanged under the same reaction conditions. Therefore, the mutual transformation between **15a** and **16a** during the ozonolysis reaction was ruled out. Moreover,

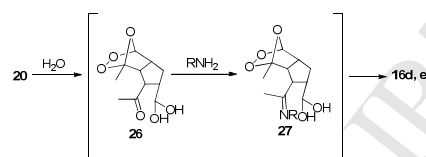
neither the conversion from **15a** to **17** nor from **16a** to **17** was observed. Based on above information, we proposed a mechanism for the ozonolysis of **14** to form the aza-cage compounds **15**, **16**, and **17** (Scheme 4). 1,3-Dipolar cycloaddition of an ozone molecule with the alkene bond of **14** via the *exo* face gave the 1,2,3-trioxolane (primary ozonide) **18**. A least-motion fragmentation²²⁻²³ from **18** leads to the *syn*-oriented carbonyl oxide **19**. At $-78\text{ }^{\circ}\text{C}$, before free rotation of the carbonyl oxide group, the rapid intramolecular 1,3-dipolar cycloaddition of the *syn* carbonyl oxide group to the *endo* acetyl group gave the final ozonide **20** with *endo* stereochemistry. Based on the reduction of **20** with dimethyl sulfide in dichloromethane at $-78\text{ }^{\circ}\text{C}$ to give the tetraoxa-cage **21** and NOE experiments, we concluded that the stereochemistry of the final ozonide was consistent with the *endo* product **20** rather than the *exo* isomer **22**.^{12a} Reaction of the carbonyl groups of the final ozonide **20** with the primary amines gave the imines **23** and **24**. When large excess of *n*-butylamine (7 equi.) was added, the imine **25** may also formed as the intermediate. In reaction with final ozonides, amines can act as reducing agents.²⁰ Electron donation from the primary amine to the *endo* peroxide bond of the final ozonide **23** followed by heterolytic cleavage of the peroxide bond and sequential cyclization to the adjacent carbonyl and imine groups of **23** gave the intermediate **23B** via **23A**. Loss of an N-oxide molecule from **23B** followed by intramolecular nucleophilic addition of the amide anion to oxonium ion gave the aza-cage **15**. Similarly, reduction of **24** and **25** with the primary amine under the same sequence gave the aza-cages **16a** and **17a**, respectively. The mechanism for the aza-cage formation from the imine intermediates **23-25** is similar to that for the tetraoxa-cage formation from the final ozonide **20**. In the case of the aza-cage formation, the primary amines act as nucleophiles in reaction with the carbonyls to give the imine groups and act as a reducing agent in reaction with the peroxide bond of the final ozonides **23-25**.

Scheme 4



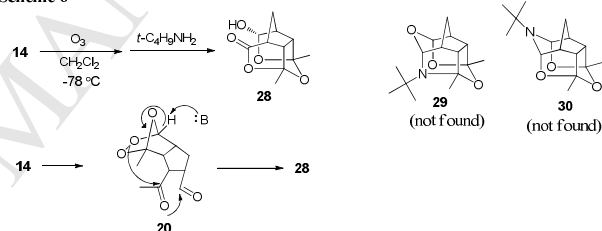
The formation mechanism for **16d,e** from the final ozonide **20** may proceed via the intermediates **26** and **27** (Scheme 5). In the reaction of the final ozonide with aqueous ammonia and methylamine, large excess water molecule reacts with the aldehyde group to form the hydrate **26**; then, the amine molecule reacts with the ketone group to form the intermediate **27**. Reaction of the peroxide bond of **27** with amine molecule, which was followed by similar sequence to the formation of **16a** from **24** in the scheme 4, gave the aza-cages **16d,e**.

Scheme 5



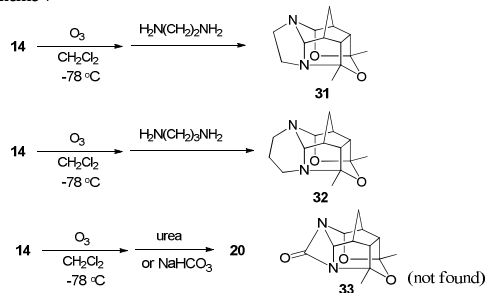
Ozonolysis of **14** in dichloromethane at $-78\text{ }^{\circ}\text{C}$ followed by addition of *t*-butylamine gave the hydroxyl lactone **28** in 68% yield (Scheme 6). No detectable amount of the aza-cages **29** or **30** was obtained. The hydroxyl lactone **28** was also obtained by ozonolysis of **14** in CH_2Cl_2 followed by triethylamine treatment.^{12a} In this reaction, both *t*-butylamine and triethylamine act as a base, instead of as reducing agent and a nucleophile, to abstract the 1,2,4-trioxolane ring proton of the final ozonide **20**. After heterolytic cleavage of the peroxide bond and sequential nucleophilic addition of the newly-formed alkoxide ions to the adjacent carbonyl groups, the observed product **28** is obtained.

Scheme 6



Ozonolysis of **14** in dichloromethane at $-78\text{ }^{\circ}\text{C}$ followed by addition of excess ethylenediamine and 1,3-propylenediamine gave the cyclic diaza-cage compound **31** (62%) and **32** (76%), respectively (Scheme 7). Ozonolysis of **14** in dichloromethane at $-78\text{ }^{\circ}\text{C}$ followed by addition of urea or NaHCO_3 gave the final ozonide **20** in 86% yield. No detectable amount of the aza-cage compound **33** was obtained. The final ozonide **20** was clean without purification and was stable at $25\text{ }^{\circ}\text{C}$ for taking its ^1H and ^{13}C NMR spectra.

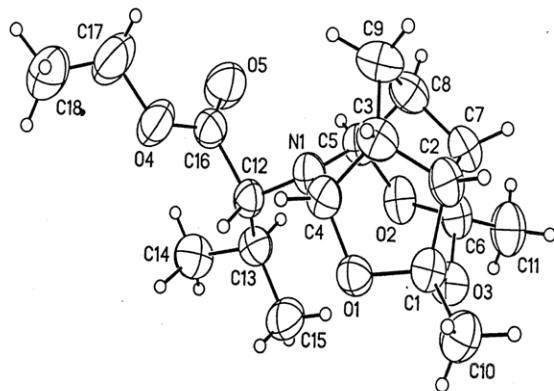
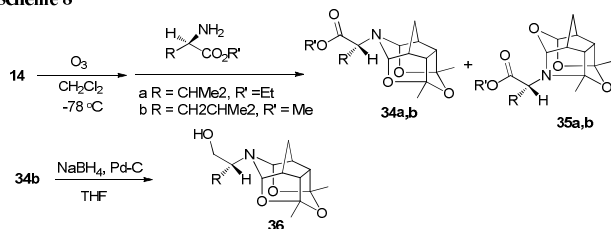
Scheme 7



Ozonolysis of **14** in dichloromethane at $-78\text{ }^{\circ}\text{C}$ followed by addition of L-Valine ethyl ester and L-Leucine methyl ester gave the aza-cages **34a,b** (35%) and **35a,b** (10%), respectively (Scheme 8). The aza-cages **34a,b** and **35a,b** are optically active compounds. The structure **34a** was confirmed by X-ray analysis

(Figure 1). Reduction of **34b** with NaBH₄ in THF in the presence of Pd-C gave the aminoalcohol cage compound **36** in 83% yield. Compound **36** possesses cage skeleton and aminoalcohol function group, which might be a useful new chiral aminoalcohol.

Scheme 8

Figure 1. ORTEP diagram of **34a**.

3. Conclusion

We have accomplished the synthesis of new acetal aza-cage compounds with different types of skeleton in a short sequence. Ozonolysis of the diol **1a,b**, **5**, and **6** in dichloromethane at -78 °C followed by addition of various amines gave the aza-cages **2a,b**, **3a,b**, **4a-c**, **7** and **8** in high yields. We proposed a mechanism via an intramolecular nucleophilic addition of the hydroxyl group of the diols to the carbonyl oxide group for the formation of the aza-cages. Ozonolysis of **14** in CH₂Cl₂ at -78 °C followed by addition of different equivalents of primary amines gave the monoaza-cages **15** and **16** and the diaza-cage **17**. When adding aqueous amines, only the monoaza-cages **16d** and **16e** were obtained. When adding *t*-butylamine, only the hydroxyl lactone **28** was obtained. We also proposed another mechanism via the final ozonide **20** and the imine intermediates **23-25** to the formation of the aza-cage compounds (**15**, **16** and **17**). In this case, the primary amines act as a nucleophile and as a reducing agent. On the other hand, *t*-butylamine and triethylamine act only as base in reaction with the final ozonide **20**. We further synthesized optically active aza-cages **34** and **35**. The aza-cage **34b** was also converted into a new type of aminoalcohol.

4. Experimental selection

4.1. General

Melting points were determined in capillary tubes with a Laboratory Device melting point apparatus and are uncorrected. Infrared spectra were recorded in CHCl₃ solutions or as 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 ¹³C signals were determined by DEPT techniques. High resolutions 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 the same department. X-ray analyses were also 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. CH₂Cl₂ was distilled from CaH₂ under nitrogen.

4.2 General procedure for the synthesis of aza-cages **2a, b**

A solution of **1a** (0.500 g, 3.25 mmol) in dichloromethane (80 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added isopropylamine (1.20 g, 20.0 mmol) at -78 °C. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the crude product was purified by column chromatography to give **2a** (0.5 g, 72%). Spectral data for **2a**: white waxy solid; mp 94-95 °C; IR (CHCl₃) 2880, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.10 (d, *J* = 7.5 Hz, 2H), 3.92 (d, *J* = 9.0 Hz, 2H), 3.78 (dd, *J* = 9.0, 5.1 Hz, 2H), 3.28-3.17 (m, 1H), 2.69-2.65 (m, 2H), 2.60 (brs, 2H), 1.63-1.46 (m, 2H), 1.17 (d, *J* = 6.3 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 91.7 (2CH), 67.0 (2CH₂), 50.7 (CH), 45.6 (2CH), 44.3 (2CH), 25.8 (CH₂), 22.7 (2CH₃); LRMS *m/z* (re lint) 209 (M⁺, 13), 166 (100); HRMS (EI) calcd for C₁₂H₁₉O₂N 209.1415, found 209.1419. Anal. Calcd for C₁₂H₁₉O₂N: C, 68.85; H, 9.16; N, 6.70. Found C, 68.94; H, 9.22; N, 6.62.

2b: Pale yellow oil; IR (CHCl₃) 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.12 (d, *J* = 7.2 Hz, 1H), 5.08 (d, *J* = 7.2 Hz, 1H), 4.14 (q, *J* = 6.3 Hz, 1H), 3.97 (d, *J* = 9.0 Hz, 1H), 3.74 (dd, *J* = 9.0, 5.4 Hz, 1H), 3.23-3.14 (m, 1H), 2.81-2.76 (m, 1H), 2.66-2.52 (m, 2H), 2.28-2.22 (m, 1H), 1.56-1.45 (m, 2H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 92.1 (CH), 91.4 (CH), 73.6 (CH), 67.4 (CH₂), 50.6 (CH), 50.2 (CH), 45.3 (CH), 44.7 (CH), 44.3 (CH), 25.7 (CH₂), 24.0 (CH₃), 22.8 (CH₃), 22.7 (CH₃); LRMS *m/z* (rel int) 223 (M⁺, 20), 208(100); HRMS (EI) calcd for C₁₃H₂₁O₂N 223.1572, found 223.1576.

4.3 General procedure for the synthesis of aza-cages **3a-b**

A solution of **1b** (0.59 g, 2.7 mmol) in dichloromethane (80 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added *n*-butylamine (1.0 g, 14 mmol) at -78 °C. The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the crude product was purified by column chromatography to give **3b** (0.48 g, 75%). Spectral data for **3b**: pale yellow oil; IR (CHCl₃) 2980, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.96 (d, *J* = 7.2 Hz, 1H), 4.92 (d, *J* = 7.2 Hz, 1H), 4.15 (q, *J* = 6.6 Hz, 1H), 3.97 (d, *J* = 9.0 Hz, 1H), 3.78 (dd, *J* = 9.0, 5.4 Hz, 1H), 2.87-2.78 (m, 2H), 2.74-2.67 (m, 1H), 2.62-2.56 (m, 1H), 2.31-2.25 (m, 1H), 1.67-1.24 (m, 7H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 92.7 (2CH), 74.0 (CH), 67.6 (CH₂), 58.3 (CH), 47.2 (CH₂), 45.3 (CH), 44.8 (CH), 44.1 (CH), 29.6 (CH₂), 25.4 (CH₂), 24.1 (CH₃), 20.3 (CH₂), 13.9 (CH₃); LRMS *m/z* (rel int) 237 (M⁺, 20), 194 (100); HRMS (EI) calcd for C₁₄H₂₃O₂N 237.1728, found 237.1736.

3a: Pale yellow oil; IR (CHCl₃) 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.94 (d, *J* = 7.8 Hz, 2H), 3.92 (d, *J* = 9.0 Hz, 2H), 3.82 (dd, *J* = 9.0, 5.1 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.75-2.96 (m, 2H), 2.66-2.60 (m, 2H), 1.65-1.62 (m, 2H), 1.55-1.44 (m, 2H), 1.38-1.26 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 92.5 (2CH), 67.3 (2CH₂), 47.2 (CH₂), 45.3 (2CH), 44.2 (2CH), 29.5 (CH₂), 25.4 (CH₂), 20.2 (CH₂), 13.9 (CH₃); LRMS *m/z* (rel int) 223 (M⁺, 12), 108(100); HRMS (EI) calcd for C₁₃H₂₁O₂N 223.1572, found 223.1582.

4.4 General procedure for the synthesis of aza-cages **4a-c**

The same reaction conditions and procedure for the synthesis of **2a, b** were applied for the synthesis of **4a-c**. Spectral data for **4b**: white waxy solid; mp 88-89 °C; IR (CHCl₃) 1380, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.35 (d, *J* = 7.2 Hz, 2H), 3.93 (d, *J* = 9.0 Hz, 2H), 3.75 (dd, *J* = 9.0, 5.1 Hz, 2H), 2.67-2.58 (m, 4H), 1.60-1.52 (m, 1H), 1.41-1.36 (m, 1H), 1.25 (s, 9H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 89.9 (2CH), 66.8 (2CH₂), 53.7 (C), 45.7 (2CH), 44.3 (2CH), 30.5 (3CH₃), 25.8 (CH₂); LRMS *m/z* (rel int) 223 (M⁺, 15), 166 (100); HRMS (EI) calcd for C₁₃H₂₁O₂N 223.1572, found 223.1578.

4a: White solid; mp 103-104 °C; IR (CHCl₃) 3350, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.99 (d, *J* = 7.8 Hz, 2H), 3.90 (d, *J* = 9.0 Hz, 2H), 3.74 (dd, *J* = 9.0, 5.1 Hz, 2H), 3.52 (brs, 1H), 2.71-2.62 (m, 2H), 2.59-2.55 (m, 2H), 1.62-1.55 (m, 2H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 89.2 (2CH), 67.7 (2CH₂), 45.3 (2CH), 26.0 (CH₂); LRMS *m/z* (rel int) 167 (M⁺, 100); HRMS (EI) calcd for C₉H₁₃O₂N 167.0946, found 167.0941.

4c: Colorless solid; mp 94-96 °C; IR (CHCl₃) 1610, 1060, 750, 690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.10 (m, 5H), 5.73 (d, *J* = 7.8 Hz, 2H), 4.05 (d, *J* = 9.3 Hz, 2H), 3.91 (dd, *J* = 9.3, 5.1 Hz, 2H), 2.75-2.70 (m, 2H), 1.82-1.69 (m, 2H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 146.7 (C), 129.1 (2CH), 120.5 (CH), 117.2 (2CH), 90.1 (2CH), 68.1 (2CH₂), 45.6 (2CH), 44.1 (2CH), 25.2 (CH₂); LRMS *m/z* (rel int) 243 (M⁺, 20), 166 (100); HRMS (EI) calcd for C₁₅H₁₇O₂N 243.1259, found 243.1297.

4.5 General procedure for the synthesis of aza-cages **7** and **8**

The same reaction conditions and procedure for the synthesis of **3a, b** were applied for the synthesis of **7** and **8**. Spectral data for **7**: white solid; mp 135-136 °C; IR (CHCl₃) 2980, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.65 (d, *J* = 7.2 Hz, 2H), 4.09-4.05 (m, 2H), 2.58-2.48 (m, 4H), 2.15-2.12 (m, 2H), 1.44-1.02 (m, 8H), 0.65 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 92.1 (2CH), 73.3 (2CH), 47.0 (CH₂), 45.9 (2CH), 41.8 (2CH), 28.9 (CH₂), 25.2 (CH₂), 22.1 (2CH₂), 19.9 (CH₂), 13.5 (CH₃); LRMS *m/z* (rel int) 249 (M⁺, 20), 166 (100), 208 (100); HRMS (EI) calcd for C₁₅H₂₃O₂N 249.1726, found 249.1729.

Spectral data for **8**: white solid; mp 175-176 °C; IR (CHCl₃) 2990, 1600, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.23 (m, 4H), 5.02-4.92 (m, 4H), 3.02-2.96 (m, 2H), 2.89-2.85 (m, 2H), 2.73 (t, *J* = 6.9 Hz, 2H), 1.82-1.80 (m, 2H), 1.44-1.34 (m, 2H), 1.26-1.15 (m, 2H), 0.83 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 136.7 (2C), 130.1 (2CH), 128.5 (2CH), 92.9 (2CH), 78.2 (2CH), 47.4 (CH₂), 46.4 (4CH), 29.3 (CH₂), 28.1 (CH₂), 20.3 (CH₂), 13.9 (CH₃); LRMS *m/z* (rel int) 297 (M⁺, 15), 255 (100); HRMS (EI) calcd for C₁₉H₂₃O₂N 297.1730, found 297.1724.

4.6 General procedure for the synthesis of aza-cages **15a-c** and **16a**

A solution of **14** (0.50 g, 2.8 mmol) in dichloromethane (80 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was

added *n*-butylamine (0.51 g, 7.0 mmol) at -78 °C. The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the crude product was purified by column chromatography to give **15a** (0.29 g, 38%) and **16a** (0.18 g, 26%).

4.6.1 *N*-*n*-Butyl-1,7-dimethyl-4-aza-2,6,13-trioxapentacyclo[5.5.1.0^{3,11}.0^{5,9}.0^{8,12}]tridecane **15a**:

Pale yellow oil; IR (neat) 2850, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.01 (d, *J* = 7.2 Hz, 2H), 3.14-3.11 (m, 2H), 2.94-2.84 (m, 4H), 1.87-1.82 (m, 1H), 1.71-1.63 (m, 1H), 1.52 (s, 6H), 1.50-1.26 (m, 4H), 0.91 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 115.1 (2C), 93.1 (2CH), 59.9 (2CH), 47.4 (CH₂), 45.1 (2CH), 30.4 (CH₂), 29.3 (CH₂), 25.9 (2CH₃), 20.3 (CH₂), 13.9 (CH₃); LRMS *m/z* (rel int) 265 (M⁺, 8), 222 (100); HRMS (EI) calcd for C₁₅H₂₃O₃N 265.1677, found 265.1670. Anal. Calcd for C₁₅H₂₃O₃N: C, 67.88; H, 8.74; N, 5.28. Found: C, 67.98; H, 8.82; N, 5.23.

15b: White solid; mp 186-188 °C; IR (CHCl₃) 1610, 1060, 750, 690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.22 (m, 5H), 5.77 (d, *J* = 7.8 Hz, 2H), 3.22 (dd, *J* = 5.1, 3.0 Hz, 2H), 3.08-3.00 (m, 2H), 1.92-1.76 (m, 2H), 1.53 (s, 6H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 146.8 (C), 129.1 (2CH), 121.4 (CH), 118.8 (2CH), 115.9 (2C), 91.3 (2CH), 59.8 (2CH), 45.4 (2CH), 30.2 (CH₂), 25.8 (2CH₃); LRMS *m/z* (rel int) 285 (M⁺, 42), 214 (100); HRMS (EI) calcd for C₁₇H₁₉O₃N 285.1364, found 285.1369.

15c: White solid; mp 77-78 °C; IR (CHCl₃) 1610 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.18 (d, *J* = 7.5 Hz, 2H), 3.33-3.24 (m, 1H), 3.12-3.08 (m, 2H), 2.85-2.80 (m, 2H), 1.70-1.62 (m, 2H), 1.48 (s, 6H), 1.24 (d, *J* = 6.3 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 114.8 (2C), 92.2 (2CH), 59.9 (2CH), 50.9 (CH), 45.3 (2CH), 30.5 (CH₂), 26.1 (2CH₃), 22.4 (2CH₃); LRMS *m/z* (rel int) 251 (M⁺, 8), 207 (100); HRMS (EI) calcd for C₁₄H₂₁O₃N 251.1521, found 251.1516.

4.6.2 *N*-*n*-Butyl-1,7-dimethyl-2-aza-4,6,13-trioxapentacyclo[5.5.1.0^{3,11}.0^{5,9}.0^{8,12}]tridecane **16a**:

Pale yellow oil; IR (neat) 2855, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.39 (d, *J* = 7.2 Hz, 1H), 4.95 (d, *J* = 6.9 Hz, 1H), 3.04-2.95 (m, 3H), 2.77-2.62 (m, 3H), 1.94-1.89 (m, 1H), 1.69-1.65 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.42-1.27 (m, 4H), 0.89 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 115.9 (C), 103.6 (C), 102.9 (CH), 89.9 (CH), 58.5 (CH), 58.5 (CH), 46.0 (CH), 42.4 (CH), 40.6 (CH₂), 30.4 (CH₂), 29.8 (CH₂), 25.8 (CH₃), 25.5 (CH₃), 20.5 (CH₂), 14.0 (CH₃); LRMS *m/z* (rel int) 265 (M⁺, 11), 222 (100); HRMS (EI) calcd for C₁₅H₂₃O₃N 265.1677, found 265.1683.

4.7 Synthesis of aza-cage **17a**

A solution of **14** (0.53 g, 3.0 mmol) in dichloromethane (80 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added *n*-butylamine (1.6 g, 22 mmol) at -78 °C. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the crude product was purified by column chromatography to give **15a** (0.20 g, 26%), **16a** (0.18 g, 22%), and **17a** (0.11 g, 14%).

4.7.1 *N,N'*-Bis-*n*-butyl-1,7-dimethyl-2,4-diaza-6,13-dioxapentacyclo[5.5.1.0^{3,11}.0^{5,9}.0^{8,12}]tridecane **17a**

Spectral data: pale yellow oil; IR (neat) 2855, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.99 (d, *J* = 7.2 Hz, 1H), 4.33 (d, *J* = 7.2 Hz, 1H), 3.20-2.51 (m, 8H), 1.62-1.19 (m, 10H), 1.43 (s, 3H), 1.36 (s, 3H), 0.87 (t, *J* = 6.6 Hz, 3H), 0.85 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 113.7 (C), 103.2 (C), 94.1

(CH), 77.3 (CH), 60.2 (CH), 59.9 (CH), 51.8 (CH₂), 45.3 (CH), 42.7 (CH), 42.2 (CH₃), 31.8 (CH₂), 31.0 (CH₂), 30.9 (CH₂), 26.5 (CH₃), 26.2 (CH₃), 20.6 (CH₂), 19.9 (CH₂), 14.0 (CH₃), 13.9 (CH₃); LRMS *m/z* (rel int) 320 (M⁺, 42), 277 (100); HRMS (EI) calcd for C₁₉H₃₂O₂N₂ 320.2463, found 320.2468. Anal. Calcd for C₁₉H₃₂O₂N₂: C, 71.20; H, 10.07; N, 8.75. Found: C, 71.32; H, 10.16; N, 8.67.

4.8 General procedure for the synthesis of aza-cages **16d,e**

A solution of **14** (0.53 g, 3.0 mmol) in dichloromethane (80 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added large excess of aqueous ammonia (10 mL) at -78 °C. The reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated, and the crude product was purified by column chromatography to give **16d** (0.29 g, 45%).

4.8.1 1,7-Dimethyl-2-aza-4,6,13-trioxapentacyclo[5.5.1.0^{3,11}.0^{5,9}.0^{8,12}]tridecane **16d**

White waxy solid; mp 78-79 °C; IR (CHCl₃) 3350, 2280, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.45 (d, *J* = 7.2 Hz, 1H), 5.05 (d, *J* = 6.6 Hz, 1H), 3.14-3.08 (m, 1H), 3.01-2.99 (m, 1H), 2.81-2.76 (m, 3H), 1.94-1.90 (m, 1H), 1.75-1.68 (m, 1H), 1.49 (s, 3H), 1.46 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 116.8 (C), 103.1 (CH), 102.6 (C), 89.2 (CH), 58.8 (CH), 57.8 (CH), 46.1 (CH), 44.8 (CH), 29.5 (CH₂), 28.0 (CH₃), 24.6 (CH₃); LRMS *m/z* (rel int) 209 (M⁺, 35), 208 (100); HRMS (EI) calcd for C₁₁H₁₅O₃N 209.1051, found 209.1062.

16e: White waxy solid; mp 72-73 °C; IR (CHCl₃) 1610 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.40 (d, *J* = 6.6 Hz, 1H), 4.82 (d, *J* = 6.3 Hz, 1H), 3.06-3.00 (m, 2H), 2.80-2.76 (m, 1H), 2.69-2.62 (m, 1H), 2.51 (s, 3H), 1.95-1.90 (m, 1H), 1.73-1.66 (m, 1H), 1.49 (s, 3H), 1.41 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 116.0 (C), 103.0 (C), 102.9 (CH), 93.6 (CH), 58.8 (CH), 58.5 (CH), 46.0 (CH), 42.4 (CH), 29.8 (CH₂), 28.3 (CH₃), 25.5 (CH₃), 24.9 (CH₃); LRMS *m/z* (rel int) 223 (M⁺, 12), 135 (100); HRMS (EI) calcd for C₁₂H₁₇O₃N 223.1208, found 223.1217.

4.9 General procedure for the reaction of **15a** and **16a** with *n*-butylamine in ozonated CH₂Cl₂ solution

Dichloromethane (70 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added compound **15a** (0.27 g, 1.0 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min. Then, to this solution was added *n*-butylamine (0.15 g, 2.0 mmol) at -78 °C, and the reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the crude product was purified by column chromatography to give **15a**.

4.10 Formation of the hydroxylactone **28**

A solution of **14** (0.53 g, 3.0 mmol) in dichloromethane (90 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added *t*-butylamine (1.2 g, 16 mmol) at -78 °C, and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the crude product was purified by column chromatography to give the hydroxylactone **28** (0.47 g, 70%), which was a known compound.^{11a}

4.11 General procedure for the synthesis of aza-cages **31** and **32**

A solution of **14** (0.50 g, 2.8 mmol) in dichloromethane (80 mL) was cooled to -78 °C, and ozone was bubbled through it at

-78 °C until the solution turned light blue. To this solution was added 1,2-ethylenediamine (0.27 g, 4.5 mmol) at -78 °C and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the crude product was purified by column chromatography to give the aza-cage **31** (0.41 g, 62%).

4.11.1 Spectral data for **31**

Pale yellow oil; IR (neat) 2880, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.12 (d, *J* = 7.2 Hz, 1H), 4.28 (d, *J* = 7.2 Hz, 1H), 3.32-3.25 (m, 2H), 3.16-2.98 (m, 6H), 1.98-1.93 (m, 1H), 1.70-1.65 (m, 1H), 1.53 (s, 3H), 1.41 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 113.5 (C), 105.4 (C), 93.3 (CH), 76.0 (CH), 60.2 (CH), 59.9 (CH), 47.3 (CH₂), 44.7 (CH), 41.3 (CH), 40.9 (CH₂), 28.9 (CH₂), 26.3 (CH₃), 26.3 (CH₃); LRMS *m/z* (rel int) 234 (M⁺, 18), 205 (100); HRMS (EI) calcd for C₁₃H₁₈O₂N₂ 234.1368, found 234.1361.

4.11.2 Spectral data for **32**

Pale yellow oil; IR (neat) 2880, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.03 (d, *J* = 7.2 Hz, 1H), 4.24 (d, *J* = 7.2 Hz, 1H), 3.38-3.29 (m, 2H), 3.18-3.03 (m, 3H), 2.78-2.54 (m, 3H), 1.96-1.92 (m, 1H), 1.66-1.59 (m, 1H), 1.50 (s, 3H), 1.40 (s, 3H) 1.06-1.01 (m, 2H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 114.5 (C), 103.6 (C), 94.9 (CH), 76.6 (CH), 60.9 (CH), 60.0 (CH), 47.9 (CH₂), 45.0 (CH), 42.0 (CH), 41.1 (CH₂), 29.1 (CH₂), 26.5 (2CH₃), 22.0 (CH₃); LRMS *m/z* (rel int) 248 (M⁺, 22), 205 (100); HRMS (EI) calcd for C₁₄H₂₀O₂N₂ 248.1525, found 248.1534.

4.12 Formation of the final ozonide **20**

A solution of **14** (0.53 g, 3.0 mmol) in dichloromethane (100 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added excess of saturated urea or NaHCO₃ solution and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was extracted with chloroform (4 x 30 mL). The combined organic layer was washed with brine, dried over MgSO₄, and evaporated to give the final ozonide **20** (0.58 g, 86%). Spectral data for **20**: Pale yellow oil; IR (neat) 1710, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.64 (s, 1H), 5.60 (s, 1H), 3.07 (dd, *J* = 7.2 Hz, 1H), 2.97-2.77 (m, 3H), 2.21 (s, 3H), 2.14-2.01 (m, 2H), 1.52 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, DEPT) δ 205.5 (CO), 201.9 (CHO), 110.5 (C), 104.7 (CH), 57.8 (CH), 51.5 (CH), 50.1 (CH), 46.6 (CH), 29.6 (CH₃), 28.4 (CH₂), 13.9 (CH₃); LRMS *m/z* (rel int) 226 (M⁺, 4), 194 (100).

4.13 General procedure for the synthesis of aza-cages **34a,b** and **35a,b**

A solution of **14** (0.53 g, 3.0 mmol) in dichloromethane (80 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added L-Valine ethyl ester (0.66 g, 4.5 mmol) at -78 °C and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was extracted with chloroform (4 x 40 mL). The combined organic layer was washed with brine, dried over MgSO₄, and evaporated. The residue was purified by column chromatography to give the aza-cage **34a** (0.34 g, 35%) and **35a** (0.10 g, 10%).

4.13.1 Spectral data for **34a**

White waxy solid; mp 92-93 °C; [α]_D²⁵ = -19.3° (c = 5.4, CHCl₃); IR (KBr) 2860, 1740, 1230, 1085 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.25 (d, *J* = 7.2 Hz, 1H), 5.07 (d, *J* = 7.2 Hz, 1H), 4.18 (q, *J* = 6.9 Hz, 2H), 3.20 (d, *J* = 9.6 Hz, 1H), 3.12-3.08 (m, 2H), 2.88-2.84 (m, 2H), 2.26-2.16 (m, 1H), 1.74-1.64 (m, 2H),

1.47 (s, 3H), 1.45 (s, 3H), 1.30 (t, $J = 6.6$ Hz, 3H), 1.07 (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3 , DEPT) δ 172.4 (CO_2), 114.9 (C), 114.8 (C), 93.1 (CH), 92.5 (CH), 69.9 (CH), 60.1 (CH_2), 59.4 (2CH), 45.5 (CH), 45.4 (CH), 30.1 (CH_3), 28.0 (CH_3), 25.8 (CH_3), 19.7 (CH_3), 18.9 (CH_3), 13.9 (CH_3); LRMS m/z (rel int) 337 (M^+ , 2), 264 (100); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{27}\text{O}_5\text{N}$ 337.1889, found 337.1884.

34b: Highly viscous oil; $[\alpha]_{\text{D}}^{25} = +5.8^\circ$ ($c = 3.8$, CHCl_3); IR (KBr) 1740, 1075, 1230 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.15 (d, $J = 7.8$ Hz, 1H), 4.92 (d, $J = 7.2$ Hz, 1H), 3.65 (t, $J = 6.9$ Hz, 1H), 3.60 (s, 3H), 3.02-2.97 (m, 2H), 2.80-2.72 (m, 2H), 1.78-1.54 (m, 5H), 1.37 (s, 6H), 0.88-0.80 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3 , DEPT) δ 174.1 (CO_2), 115.0 (C), 114.9 (C), 93.6 (CH), 91.8 (CH), 61.3 (CH), 59.6 (CH), 59.4 (CH), 51.5 (CH_3), 45.5 (CH), 45.5 (CH), 39.3 (CH_2), 30.2 (CH_2), 25.8 (2 CH_3), 24.6 (CH), 22.58 (CH_3), 22.2 (CH_3); LRMS m/z (rel int) 337 (M^+ , 1), 278 (100); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{27}\text{O}_5\text{N}$ 337.1889, found 337.1880.

4.13.2 Spectral data for 35a

Highly viscous oil; $[\alpha]_{\text{D}}^{25} = +14.3^\circ$ ($c = 2.8$, CHCl_3); IR (KBr) 2860, 1740, 1230, 1080 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.46 (d, $J = 7.2$ Hz, 1H), 5.43 (d, $J = 7.2$ Hz, 1H), 4.17 (q, $J = 6.9$ Hz, 2H), 3.45 (d, $J = 8.4$ Hz, 1H), 3.05-3.01 (m, 2H), 2.82-2.76 (m, 1H), 2.66-2.60 (m, 1H), 2.40-2.30 (m, 1H), 1.90-1.84 (m, 1H), 1.72-1.62 (m, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.26 (t, $J = 6.9$ Hz, 3H), 1.22 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3 , DEPT) δ 174.0 (CO_2), 115.9 (C), 103.7 (CH), 103.2 (C), 90.1 (CH), 63.4 (CH), 60.0 (CH_2), 59.5 (CH), 58.4 (CH), 46.1 (CH), 43.3 (CH), 30.6 (CH), 29.5 (CH_2), 25.7 (CH_3), 25.2 (CH_3), 21.0 (CH_3), 19.5 (CH_3), 14.2 (CH_3); LRMS m/z (rel int) 337 (M^+ , 2), 264 (100); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{27}\text{O}_5\text{N}$ 337.1889, found 337.1881.

35b: Highly viscous oil; $[\alpha]_{\text{D}}^{25} = +61.5^\circ$ ($c = 2.4$, CHCl_3); IR (KBr) 1740, 1070 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.42 (d, $J = 6.3$ Hz, 1H), 5.33 (d, $J = 6.3$ Hz, 1H), 3.88 (dd, $J = 9.9$, 6.0 Hz, 1H), 3.69 (s, 3H), 3.05-3.00 (m, 2H), 2.78-2.72 (m, 1H), 2.65-2.60 (m, 1H), 2.10-2.00 (m, 1H), 1.86-1.60 (m, 4H), 1.45 (s, 3H), 1.39, s, 3H), 0.99-0.88 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3 , DEPT) δ 175.5 (CO_2), 115.9 (C), 103.5 (C), 103.1 (CH), 89.4 (CH), 58.9 (CH), 58.4 (CH), 59.5 (CH), 51.5 (CH_3), 46.0 (CH), 42.9 (CH), 41.4 (CH_2), 29.6 (CH_2), 25.6 (CH_3), 25.4 (CH_3), 25.1 (CH), 23.2 (CH_3), 21.9 (CH_3); LRMS m/z (rel int) 337 (M^+ , 2), 278 (100); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{27}\text{O}_5\text{N}$ 337.1889, found 337.1895

4.14 Preparation of the aminoalcohol cage compound 36.

To a solution of **34b** (0.40 g, 1.2 mmol) in dry THF (50 mL) was added NaBH_4 (0.38 g, 10 mmol) and a catalytic amount of Pd-C (10%) (0.10 g) at 0°C . The reaction mixture was stirred at room temperature for 4 h. After addition of 1N HCl (20 mL), the reaction mixture was extracted with ether (5 x 30 mL). The combined organic layer was washed with brine, dried over MgSO_4 , and evaporated. The residue was purified by column chromatography to give the aminoalcohol cage compound **36** (0.31 g, 83%). Spectral for **36**: White solid; mp 240°C (decomposed); $[\alpha]_{\text{D}}^{25} = -8.2^\circ$ ($c = 2.5$, CHCl_3); IR (KBr) 3500-3300, 1070 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.09 (d, $J = 7.2$ Hz, 1H), 4.95 (d, $J = 7.2$ Hz, 1H), 3.83 (dd, $J = 9.9$, 3.9 Hz, 1H), 3.58-3.40 (m, 2H), 3.20-3.15 (m, 2H), 3.04-2.98 (m, 3H), 1.70-1.50 (m, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.10-1.00 (m, 1H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3 , DEPT) δ 115.8 (C), 115.7 (C), 98.2 (CH), 89.2 (CH),

66.1 (CH_2), 63.3 (CH), 60.7 (CH), 60.5 (CH), 46.8 (CH), 46.1 (CH), 38.3 (CH_2), 31.2 (CH_2), 26.3 (CH_3), 26.2 (CH_3), 24.9 (CH), 23.9 (CH_3), 21.8 (CH_3); LRMS m/z (rel int) 309 (M^+ , 4), 292 (100); HRMS (EI) calcd for $\text{C}_{17}\text{H}_{27}\text{O}_4\text{N}$ 309.1940, found 309.1948.

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