Synthesis of Diacetal Trioxa-Cage Compounds via a Sequential Cyclization Reaction of Norbornene Derivatives Induced by Electrophiles

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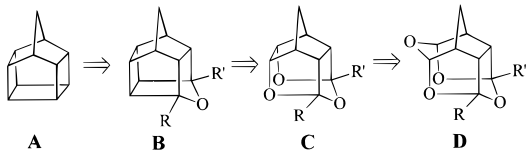
The synthesis of diacetal trioxa-cage compounds via a sequential cyclization reaction of norbornene derivatives induced by electrophiles in a short sequence is reported. Treatment of the norbornene derivatives **2a**−**d** and **10b** with I_2 in aqueous THF in the presence of KI at 25 °C regioselectively gave the iodo-cage compounds **3a**−**d** and **11** in 80−90% yields, respectively, via a iodine-induced sequential cyclization reaction. No detectable amount of other regioisomers or monocyclization products was obtained. The synthesis of trioxa-cages **14a**−**e** was accomplished from **3a**−**d** and **11** in a two-step sequence. Treatment of diacylnorbornenes **15a**−**f** with I_2 in aqueous THF at 25 °C regioselectively and stereoselectively gave the sequential cyclization products **16a**−**f**, respectively, which were converted in one step to the diacetal trioxa-cages **24a**−**f** in high yields. The structure of these trioxa-cages was proven by X-ray analysis of the crystalline compound **14e**. Other electrophiles, such as bromine, *m*-CPBA, and $Hg(OAc)_2$, were also found to be effective for the sequential cyclization reaction. Oxymercuration of **15a**−**f** and **2a**−**c** with $Hg(OAc)_2$ in aqueous THF followed by reduction with $NaBH_4$ at 25 °C gave compounds **28a**−**f** and **30b**,**d**,**c** in high yields, respectively.

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. On the other hand, the synthesis and chemistry of heterocyclic cage compounds have received less attention. However, there are some reports regarding the chemistry[2] and synthesis[3−8] of oxa-cage compounds in the literature. This class of heterocyclic cage compounds is synthesized by intramolecular alkene−oxirane ($2\sigma-2\pi$) photocycloaddition,[3] by transannular cyclization of suitable compounds,[4] by tandem cyclization,[5] by dehydration of diols having the proper stereochemistry,[6] by base-promoted rearrangement,[7] and by intramolecular etherification of an alkene bond with organoselenium reagents.[8]

Scheme 1



We visualized that elaboration of oxa-cages from carbocyclic cages might be achieved by replacing the skeletal carbon atoms with oxygen atoms at the proper positions and by extending the skeletal backbone. For instance, starting with homopentaprismane (**A**), one might be able to "create" the following three different types of oxa-cage compounds, types **B**, **C**, and **D** (Scheme 1). We viewed types **C** and **D** oxa-cages as cage-backboned diacetal and tetraacetal crown ethers, respectively, both of which might exhibit interesting cation-binding properties. Whereas types **B** monooxa-cage compounds are known, type **C** oxa-cages are novel. Recently, we accomplished the synthesis of tetraacetal tetraoxa-cages (type **D**),[9] tetraacetal pentaoxa-cages,[10] and pentaacetal pentaoxa-cages (the pentaoxa[5]peristylanes)[11] by ozonolysis reaction.

The halocyclization of an alkene bond is a powerful process in synthetic organic chemistry, especially for regioselective and stereoselective functionalization of double bonds.[12] Usually, the ring closure takes place with participation of a number of electron-donating groups, such as OH, NHR, COOH, COOR, and CONHR.

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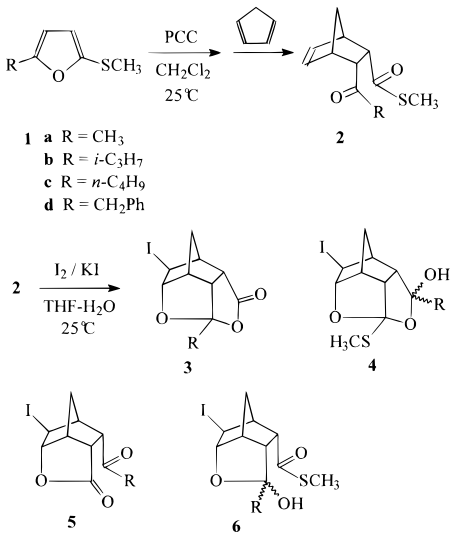
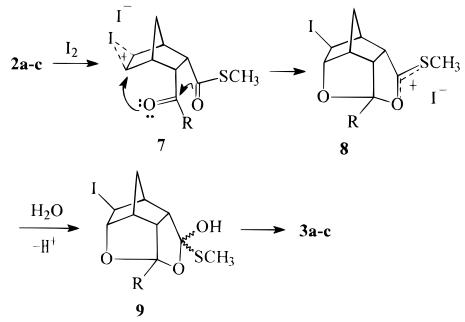
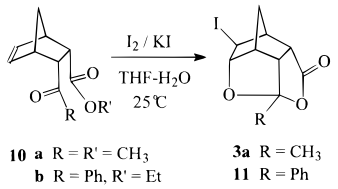
Scheme 2



Scheme 3



Scheme 4



There are some reports regarding the electrophile-induced lactonization of norbornene derivatives.[13] Recently, we discovered a iodine-induced sequential cyclization reaction of norbornene derivatives by the ring closure with participation of carbonyl and thioester groups leading to the formation of novel iodo-cage compounds.[14] In this paper we report the full details of this sequential cyclization reaction of norbornene derivatives induced by several electrophiles. As part of a program that involves the synthesis and chemistry of new heterocyclic cage compounds, we also report here for the first time the application of the sequential cyclization reaction for the synthesis of diacetal trioxa-cages (type **C**).

Results and Discussion

Oxidation of 2-(methylthio)-5-alkylfurans **1a**−**d** with 2 equiv of pyridinium chlorochromate (PCC) in dichloromethane at 25 °C followed by addition of cyclopentadiene gave the *endo* adducts **2a**−**d** in 65−70% yield.[15] Treatment of **2a**−**d** with I_2 in aqueous THF in the presence of KI at 25 °C for 6 h gave the iodo-cage compounds **3a**−**d** in 80−85% yields (Scheme 2). No detectable amount of the other regioisomer **4** was obtained. Also, no detectable amount of the monocyclization products **5** or **6** was obtained.

A mechanism is proposed for the formation of the iodo-cage compounds **3a**−**c** (Scheme 3). Electrophilic attack of an iodine molecule at the alkene bond of **2** from the *exo* face gives the iodonium ion **7**. Sequential intramolecular nucleophilic addition of the *endo* acyl and thioester groups to the iodonium ion followed by addition of water molecule gives the intermediate **9**. Loss of the methylthio group of **9** leads to the lactones **3**. Since only the regioisomers **3a**−**d** are obtained, we propose that the exclusive regioselective cleavage of the partial carbon−iodine bond of **7** may be preferentially affected through space by the acyl carbonyl group rather than by the thioester group.

To compare the nucleophilic cyclization of an ester group with that of an acyl group to the iodonium ion, compounds **10a**,**b** were prepared.[9b] Treatment of **10a**,**b** with I_2 in aqueous THF in the presence of KI at 25 °C for 6 h gave the iodo-cage compounds **3a** and **11** in 80% yields, respectively (Scheme 4). No detectable amount of other regioisomers and monocyclization products was obtained. Thus, we propose that the regioselective cleavage of the partial carbon−iodine bond may be preferentially affected by the acyl group rather than by the ester group.

The synthesis of diacetal trioxa-cage compounds (type **C** in Scheme 1) was accomplished from **3** and **11** by a two-step sequence. Reduction of the iodo-cage compounds **3a**−**d** and **11** with $NaBH_4$ in methanol at 0 °C for 4 h gave the hemiacetals **12a**−**e**, instead of the stereoisomers **13a**−**e**, in 70−80% yields, respectively (Scheme 5). The ^1H NMR spectrum of **12a** revealed one doublet at δ 5.42 (J = 2.4 Hz) for the hemiacetal proton on C_3. The small coupling constant implies that the proton on C_3 is *trans* to the proton on C_2. The stereochemistry of the hydroxy group of **12** was also determined by NOE experiments of **12a**. Irradiating the acetal proton on C_3 of **12a** (δ 5.42) gives 12.3% enhancement for the C_9 proton absorptions and 5.7% enhancement for the C_1 proton absorptions. Irradiating the C_9 proton (δ 4.23) gives 9.9% enhancement for the acetal proton peak, 4.4% enhancement for the C_1 proton peak, and 3.3% enhancement for the C_8 proton peak. Nucleophilic addition of $NaBH_4$ to the lactone carbonyl group of **3** and **11** may take place from the less hindered *exo* face, leading to formation of the stereoisomers **13a**−**e**, which, followed by anomerization, gave the thermodynamical products **12a**−**e**. Treatment of **12a**−**e** with KH in dry THF at 0 °C for 2 h gave the diacetal trioxa-cage compounds **14a**−**e** in 90% yield, respectively. The structure of the diacetal trioxa-cages **14** was proven by X-ray analysis of the crystalline compound **14e**. A mechanism was proposed

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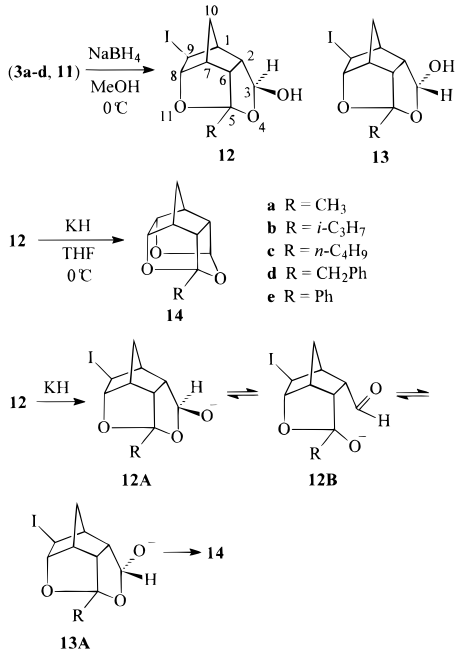
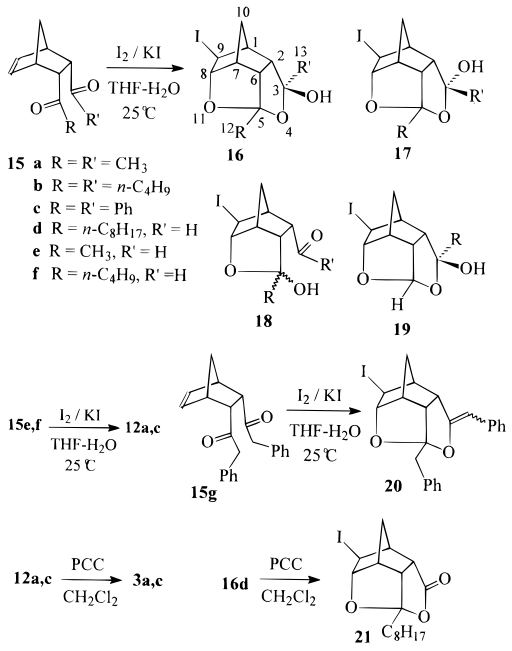
Scheme 5



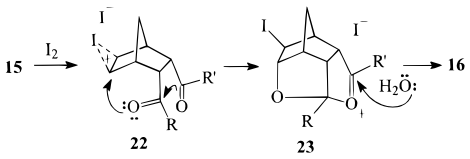
Scheme 6



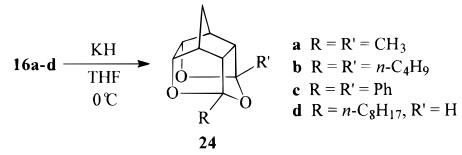
for the conversion of **12a**−**e** to the trioxa-cages **14a**−**e** via the base-promoted anomerization intermediates **12A**, **12B**, and **13A** (Scheme 5).

To extend the iodine-induced sequential cyclization of norbornene derivatives and the synthesis of diacetal trioxa-cage compounds, the bis-endodiacylnorbornenes **15a**−**g** were prepared.[9] Treatment of **15a**−**d** with I_2 in aqueous THF in the presence of KI at 25 °C for 6 h gave the iodo-cage compounds **16a**−**d** in 80−90% yields (Scheme 6). The stereochemistry of the hydroxy group of **16a**−**d** was determined on the basis of NOE epxeriments of **16a**. Irradiating the C_9 proton (δ 4.42) gives 8.4% enhancement for the intensity of the angular methyl protons on C_{13}, 2.2% enhancement for the C_8 proton peak, and 3.2% enhancement for the C_1 proton absorption. Quantities of the other stereoisomers **17a**−**d** were too small to be isolated. No detectable amount of the

Scheme 7



Scheme 8



monocyclization product **18** was obtained. Reaction of **15e**,**f** with I_2 under the same reaction conditions gave the iodo-cages **12a**,**c** in 80% yields. For the cases of reactions of **15d**−**f** with I_2, the other regioisomers **19d**−**f** were formed in too small amounts to be isolated. Treatment of compound **15g** with I_2 under the same reaction conditions gave the dehydration iodo-cage **20** in 80% yield. Oxidation of **12a**,**c** and **16d** with PCC in CH_2Cl_2 at 25 °C gave **3a**,**c** and **21** in 80% yields, respectively.

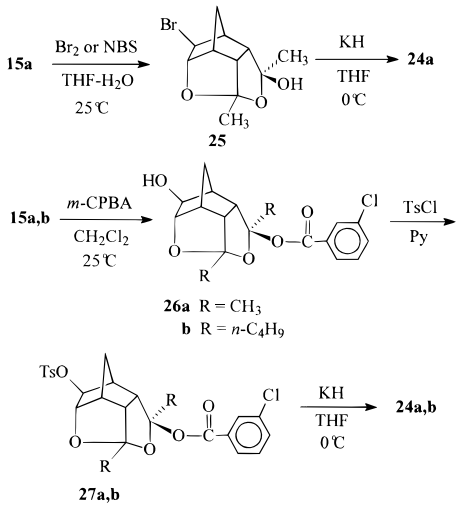
A reaction mechanism is proposed for the formation of **16** from **15** (Scheme 7). Electrophilic attack of iodine molecule to the alkene bond of **15** from the *exo* face gives the iodonium ion **22**. Sequential intramolecular nucleophilic addition of the *endo* acyl groups to the iodonium ion gives the oxonium ion **23**. Addition of a water molecule to **23** from the less hindered convex face, followed by loss of a proton, gave the observed product **16**.

The synthesis of diacetal trioxa-cages was accomplished from **16** by a one-step procedure. Reaction of **16a**−**d** with KH in dry THF at 0 °C for 2 h gave the diacetal trioxa-cage compounds **24a**−**d** in 90% yields (Scheme 8). A mechanism via the base-promoted anomerization, similar to Scheme 5, was proposed for the conversion of **16** to **24**. Thus, we have developed a general method for the synthesis of diacetal trioxa-cages via a sequential cyclization of diacylnorbornenes induced by iodine in a short sequence.

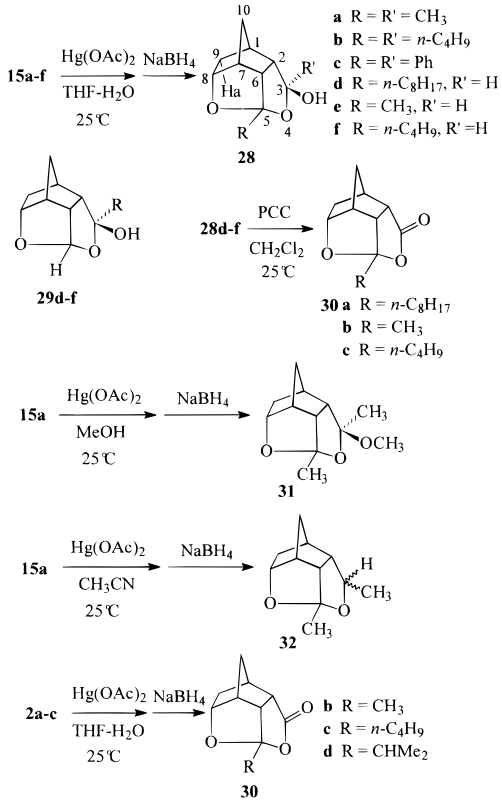
We have also tried with other electrophiles to induce the sequential cyclization reaction of norbornene derivatives. Reaction of **15a** with bromine or NBS in aqueous THF at 25 °C for 2 h gave the bromo-cage compound **25** in 85% yield. Treatment of **25** with KH in dry THF at 0 °C for 2 h gave the trioxa-cage **24a** in 90% yield (Scheme 9). Reaction of **15a**,**b** with *m*-CPBA in dichloromethane at 25 °C gave compounds **26a**,**b**, in 80% yields, which were converted to the tosylates **27a**,**b**. Treatment of **27a**,**b** with KH in dry THF at 0 °C gave the trioxa-cages **24a**,**b** in 80% yields. Thus, the sequential cyclization was also effective with bromine or *m*-CPBA as electrophiles.

Oxymercuration of **15a**−**f** with $Hg(OAc)_2$ in aqueous THF at 25 °C followed by reduction with $NaBH_4$ gave the sequential cyclization compounds **28a**−**f** in 70−80% yields (Scheme 10). For the case of reactions of **15d**−**f** with $Hg(OAc)_2$, the other regioisomers **29d**−**f** were formed in amounts too small to be isolated. The regiochemistry of the alkyl group of **28d**−**f** was confirmed by the following chemical transformation. Oxidation of **28d**−**f** with PCC in CH_2Cl_2 at 25 °C gave the lactones **30a**−**c** in 80% yields. The ^1H NMR spectrum of **28e** revealed one singlet at δ 5.36 for the hemiacetal proton on C_3. The coupling constant (J = 0 Hz) implies that

Scheme 9



Scheme 10



the proton on C_3 is *trans* to the proton on C_2. The stereochemistry of the hydroxy group of **28** was also determined by NOE experiments of **28a** and **28e**. Irradiating the acetal proton on C_3 of **28e** (δ 5.36) gives 4.9% enhancement for the intensity of the *endo* proton Ha on C_9 and 2.3% enhancement for the C_1 proton peak. Irradiating the C_1 proton of **28a** (δ 2.27) gives 3.8% enhancement for the intensity of the angular methyl protons on R′. Alkoxymercuration of **15a** with $Hg(OAc)_2$ in methanol at 25 °C followed by reduction with $NaBH_4$ gave **31** in 75% yield. Reaction of **15a** with $Hg(OAc)_2$ in acetonitrile at 25 °C, followed by reduction with $NaBH_4$, gave **32** in 70% yield. Oxymercuration of **2a**−**c** with $Hg(OAc)_2$ in aqueous THF at 25 °C followed by reduction with $NaBH_4$, gave the lactones **30b**,**c** and **30d**. Thus, the sequential cyclization was also effective with $Hg(OAc)_2$ as the electrophile.

Conclusions

In summary, we have demonstrated a sequential cyclization reaction of norbornene derivatives induced by electrophiles, and we have accomplished for the first time the synthesis of diacetal trioxa-cage compounds in a short sequence via this sequential cyclization reaction. In each case of the sequential cyclization, no detectable amount of monocyclization products was obtained. For unsymmetric norbornenes, the sequential cyclization was found to be highly regioselective. We found that the exclusive regioselective cleavage of the partial carbon−iodine bond of the iodonium ion **7** may be preferentially affected through space by the acyl group rather than by the thioester group or the ester group. For the diacylnorbornenes **15a**−**d**, the stereochemistry of the hydroxy group of **16a**−**d** was found to be highly stereoselective. The structure of the diacetal trioxa-cases **14a**−**e** and **24a**−**d** was proven by X-ray analysis of the crystalline compound **14e**. Other electrophiles, such as bromine, *m*-CPBA, and $Hg(OAc)_2$, were found to be also effective for the sequential cyclization reaction. Oxymercuration of **2** and **15** with $Hg(OAc)_2$ followed by reduction with $NaBH_4$ gave the corresponding dioxa-cages **30** and **28**.

Experimental Section

General. Melting points were determined in capillary tubes with a Laboratory Devices melting point apparatus and are uncorrected. Infrared spectra were recorded in $CHCl_3$ solutions or on neat thin films between NaCl disks. ^{1}H NMR spectra were determined at 300 MHz, and ^{13}C NMR spectra were determined at 75 MHz on Fourier transform spectrometers. Chemical shifts are reported in ppm relative to TMS in the solvents specified. The multiplicities of ^{13}C signals were determined by DEPT techniques. High-resolution mass values were obtained with a high resolution mass spectrometer at the Department of Chemistry, National Tsing Hua University. Elemental analyses were performed at the microanalysis laboratory of National Taiwan University. X-ray analysis were carried out on a diffractometer at the Department of Chemistry, National Sun Yat Sen University.[16] 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 Sequential Cyclization Reactions of Norbornene Derivatives 2a−**d.** To a solution of **2a** (0.50 g, 2.4 mmol) in THF (2 mL) and H_2O (20 mL) were added I_2 (3.0 g, 11.8 mmol) and KI (2.0 g, 12 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 6 h. To this solution was added saturated $Na_2S_2O_3$ (30 mL) for reducing unreacted iodine and the mixture was extracted with ether (3 × 30 mL). The organic layer was washed with brine, drived over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the iodo-lactone cage compound **3a** (0.59 g, 80%).

Spectral data for 3a: white solid; mp 107−108 °C; IR ($CHCl_3$) 2990, 1770, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (d, J = 4.8 Hz, 1H), 4.01 (d, J = 3.0 Hz, 1H), 3.19 (dd, J = 9.9 Hz, J = 4.5 Hz, 1H), 3.11 (dd, J = 9.9 Hz, J = 5.1 Hz, 1H), 3.04−3.02 (m, 1H), 2.94−2.92 (m, 1H), 2.50−2.46 (m, 1H), 2.05−2.01 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 174.26 (C=O), 116.10 (C), 91.31 (CH), 51.04 (CH), 49.61 (CH), 48.56 (CH), 48.33 (CH), 40.49 (CH_2), 27.88 (CH),

(16) The author has deposited atomic coordinates for **14e** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

23.45 (CH_3); LRMS *m/z* (rel inten) 306 (M^+, 9), 179 (100), 135 (41); HRMS (EI) calcd for $C_{10}H_{11}O_3I$ 305.9753, found 305.9759.

General Procedure for the Sequential Cyclization Reactions of the Esters 10a,b. The same reaction conditions and procedure for the iodine-induced sequential cyclization of **2a**−**d** were applied to the cyclization reaction of **10a**,**b** to give compounds **3a** and **11**.

Spectral data for 11: yield 80%; white solid; mp 112−113 °C; IR ($CHCl_3$) 2990, 1776, 1605, 1100, 755, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.36 (m, 5H), 5.19 (d, J = 4.8 Hz, 1H), 4.18 (d, J = 2.4 Hz, 1H), 3.31−3.25 (m, 2H), 3.13−3.10 (m, 1H), 3.02−3.00 (m, 1H), 2.56−2.52 (m, 1H), 2.07−2.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 174.29 (C═O), 137.75 (C), 129.18 (2CH), 128.40 (2CH), 125.16 (CH), 116.22 (C), 91.98 (CH), 53.98 (CH), 49.41 (CH), 48.88 (CH), 48.56 (CH), 40.75 (CH_2), 27.67 (CH); LRMS *m/z* (rel inten) 368 (M^+, 26), 241 (100), 164 (53); HRMS (EI) calcd for $C_{15}H_{13}O_3I$ 367.9909, found 367.9917.

General Procedure for Reduction of 3a−d and 11 with $NaBH_4$. To a solution of **3a** (0.50 g, 1.6 mmol) in methanol (30 mL) was added $NaBH_4$ (0.30 g, 7.9 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h. After addition of saturated NH_4Cl (30 mL) and extraction with ether (4 × 50 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 hemiacetal **12a** (0.41 g, 80%).

Spectral data for 12a: highly viscous liquid; IR ($CHCl_3$) 3400, 2990, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (d, J = 2.4 Hz, 1H), 4.81 (d, J = 4.2 Hz, 1H), 4.32 (s, 1H), 4.23 (d, J = 2.4 Hz, 1H), 2.98−2.86 (m, 2H), 2.70−2.65 (m, 2H), 2.35−2.31 (m, 1H), 1.87−1.83 (m, 1H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.38 (C), 98.36 (CH), 90.93 (CH), 54.97 (CH), 50.92 (CH), 49.58 (CH), 47.28 (CH), 39.62 (CH_2), 29.71 (CH), 25.22 (CH_3); LRMS *m/z* (rel inten) 308 (M^+, 1), 181 (100), 135 (43); HRMS (EI) calcd for $C_{10}H_{13}O_3I$ 307.9909, found 307.9914.

Spectral data for 12b: yield 70%; highly viscous liquid; IR ($CHCl_3$) 3400, 2990, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (d, J = 3.0 Hz, 1H), 4.84 (d, J = 5.1 Hz, 1H), 4.22 (d, J = 2.4 Hz, 1H), 3.72 (d, J = 3.0 Hz, 1H), 2.97−2.92 (m, 1H), 2.78−2.75 (m, 1H), 2.72−2.61 (m, 2H), 2.35−2.32 (m, 1H), 2.01−1.96 (m, 1H), 1.88−1.84 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 122.05 (C), 98.15 (CH), 90.37 (CH), 54.54 (CH), 49.73 (CH), 47.40 (CH), 47.22 (CH), 39.62 (CH_2), 34.32 (CH), 29.97 (CH), 17.36 (CH_3), 17.12 (CH_3); LRMS *m/z* (rel inten) 336 (M^+, 24), 209 (100), 191 (48); HRMS (EI) calcd for $C_{12}H_{17}O_3I$ 336.0222, found 336.0226.

General Procedure for the Synthesis of Diacetal Trioxa-Cage Compounds 14a−e. To a solution of **12a** (0.31 g, 1.0 mmol) in dry THF (20 mL) was added KH (0.10 g, 2.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. To this reaction mixture was dropwise added H_2O (5 mL) at 0 °C to destory the unreacted KH. After addition of saturated NH_4Cl (10 mL) and extraction with ether (3 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the diacetal trioxa-cage compound **14a** (028 g, 90%).

4-Methyl-3,5,7-trioxapentacyclo[7.2.1.$0^{2,8}$.$0^{4,11}$.$0^{6,10}$]-dodecane (14a): highly viscous liquid; IR ($CHCl_3$) 2990, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (d, J = 4.5 Hz, 1H), 4.28−4.23 (m, 2H), 3.10−3.07 (m, 1H), 2.76−2.69 (m, 3H), 1.88−1.77 (m, 2H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 116.31 (C), 107.83 (CH), 80.32 (CH), 79.65 (CH), 55.06 (CH), 53.20 (CH), 47.25 (CH), 46.70 (CH), 31.69 (CH_2), 21.96 (CH_3); LRMS *m/z* (rel inten) 180 (M^+, 72), 124 (100), 95 (30); HRMS (EI) calcd for $C_{10}H_{12}O_3$ 180.0786, found 180.0791. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72, found: C, 66.69; H, 6.68.

Sequential Cyclization Reactions of Bis-*endo*-diacylnorbornenes 15a−d. The same reaction conditions and procedure for the iodine-induced sequential cyclization of **2a**−**d** were applied to the sequential cyclization reactions of bis-*endo*-diacylnorbornenes **15a**−**d** to give the iodo-cage compounds **16a**−**d** in 80−90% yields.

Spectral data for 16a: yield 80%; highly viscous liquid; IR ($CHCl_3$) 3450, 2990, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, J = 4.8 Hz, 1H), 4.42 (d, J = 1.5 Hz, 1H), 3.02−2.98 (m, 1H), 2.88−2.83 (m, 2H), 2.62−2.58 (m, 2H), 2.35−2.31 (m, 1H), 1.81−1.79 (m, 1H), 1.55 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 116.83 (C), 103.98 (C), 90.93 (CH), 56.81 (CH), 52.26 (CH), 49.61 (CH), 47.14 (CH), 39.56 (CH_2), 30.35 (CH), 25.75 (CH_3), 24.32 (CH_3); LRMS *m/z* (rel inten) 322 (M^+, 6), 177 (100); HRMS (EI) calcd for $C_{11}H_{15}O_3I$ 322.0066, found 322.0072.

Sequential Cyclization Reaction of Bis-*endo*-diacylnorbornene 15g. The same reaction conditions and procedure for the iodine-induced sequential cyclization of **2a**−**d** were applied to the sequential cyclization reaction of **15g** to give the dehydration iodo-cage **20**. Spectral data for **20**: yield 75%; white solid; mp 104−105 °C; IR ($CHCl_3$) 3050, 1640, 1600, 1100, 745, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58−7.55 (m, 2H), 7.31−7.12 (m, 8H), 5.26 (s, 1H), 4.78 (d, J = 4.5 Hz, 1H), 4.02 (d, J = 2.1 Hz, 1H), 3.28, 3.10 (ABq, J = 13.5 Hz, 2H), 3.34−3.28 (m, 1H), 2.83−2.77 (m, 1H), 2.63−2.60 (m, 1H), 2.33−2.29 (m, 1H), 2.26−2.23 (m, 1H), 1.82−1.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 154.05 (C), 135.80 (C), 135.45 (C), 130.29 (2CH), 128.16 (2CH), 128.05 (2CH), 127.61 (2CH), 126.77 (CH), 125.31 (CH), 119.95 (C), 100.51 (CH), 90.67 (CH), 51.86 (CH), 50.98 (CH), 49.50 (CH), 48.91 (CH), 42.59 (CH_2), 39.62 (CH_2), 30.82 (CH); LRMS *m/z* (rel inten) 456 (M^+, 5), 329 (45), 197 (42), 105 (100); HRMS (EI) calcd for $C_{23}H_{21}O_2I$ 456.0586, found 456.0578.

Sequential Cyclization Reactions of Bis-*endo*-diacylnorbornenes 15e,f. The same reaction conditions and procedure for the iodine=induced sequential cyclization of **2a**−**d** were applied to the sequential cyclization reactions of **15e**,**f** to give the iodo-cages **12a**,**c** in 80% yields.

General Procedure for the Oxidation of 12a,c and 16d with Pyridinium Chlorochromate. To a solution of **12a** (0.31 g, 1.0 mmol) in dichloromethane (30 mL) was added PCC (0.42 g, 2.0 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 3 h. To this reaction mixture, Celite (3.0 g) was added. The reaction mixture was filtered and the solvent was evaporated. The residue was purified by column chromatography to give the iodo-lactone **3a** in 80% yield. The same reaction conditions and procedure were applied for the oxidation of **16d** to give **21** in 80% yield.

Spectral data for 21: white waxy solid; mp 55−56 °C; IR ($CHCl_3$) 2980, 1770, 1240, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.95 (d, J = 5.4 Hz, 1H), 4.04 (d, J = 2.6 Hz, 1H), 3.18−3.04 (m, 2H), 2.95−2.91 (m, 2H), 2.48 (d, J = 11.7 Hz, 1H), 2.00 (d, J = 11.7 Hz, 1H), 1.88−1.80 (m, 2H), 1.40−1.20 (m, 12H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 174.49 (C═O), 118.30 (C), 91.31 (CH), 49.68 (CH), 49.42 (CH), 48.86 (CH), 48.50 (CH), 40.67 (CH_2), 36.50 (CH_2), 31.75 (CH_2), 29.35 (CH_2), 29.32 (CH_2), 29.08 (CH_2), 28.00 (CH), 23.46 (CH_2), 22.58 (CH_2), 14.06 (CH_3); LRMS *m/z* (rel inten) 404 (M^+, 6), 233 (100); HRMS (EI) calcd for $C_{17}H_{25}O_3I$ 404.0848, found 404.0845.

General Procedure for the Synthesis of Diacetal Trioxa-Cage Compounds 24a−d. The same reaction conditions and procedure for the preparation of trioxa-cages **14a**−**e** were applied for the synthesis of diacetal trioxa-cage compounds **24a**−**d**.

4,6-Dimethyl-3,5,7-trioxapentacyclo[7.2.1.$0^{2,8}$.$0^{4,11}$.$0^{6,10}$]-dodecane (24a): yield 80%; white waxy solid; 70−71 °C; IR ($CHCl_3$) 2990, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (brs, 2H), 2.83 (brs, 2H), 2.76 (brs, 2H), 1.83−1.73 (m, 2H), 1.60 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 115.81 (2C), 80.29 (2CH), 56.66 (2CH), 46.99 (2CH), 31.61 (CH_2), 22.19 ($2CH_3$); LRMS *m/z* (rel inten) 194 (M^+, 27), 138 (100); HRMS (EI) calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0948. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.01; H, 7.27, found: C, 68.12; H, 7.30.

Reaction of Bis-*endo*-diacetylnorbornene 15a with Bromine or *N*-Bromosuccinimide. To a solution of bis-*endo*-diacetylnorbornene **15a** (0.36 g, 2.0 mmol) in THF (2 mL) and H_2O (20 mL) was added Br_2 (0.64 g, 4.0 mmol) or *N*-bromosuccinimide (0.72 g, 4.0 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. To this solution was added saturated $Na_2S_2O_3$ (30 mL) for reducing unreacted Br_2

and the mixture was extracted with ether (4 × 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the bromo-cage compound **25** (0.88 g, 80%): highly viscous liquid; IR ($CHCl_3$) 3400, 2995, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.64 (d, J = 4.5 Hz, 1H), 4.37 (d, J = 2.4 Hz, 1H), 3.05−3.00 (m, 1H), 2.96−2.91 (m, 1H), 2.67−2.62 (m, 1H), 2.56 (brs, 1H), 2.33−2.30 (m, 1H), 1.72−1.68 (m, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.46−1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.09 (C), 103.92 (C), 89.88 (CH), 56.60 (CH), 53.34 (CH), 52.47 (CH), 48.97 (CH), 45.94 (CH), 37.67 (CH_2), 25.87 (CH_3), 24.35 (CH_3); LRMS *m/z* (rel inten) 274 (M^+, 18), 195 (46), 177 (65), 151 (100).

Reaction of 25 with KH. The same reaction conditions and procedure for the preparation of **24a** from **16a** were applied for the reaction of **25** with KH to give **24a** in 90% yield.

Sequential Cyclization of Bis-*endo*-diacylnorbornenes 15a,b Mediated by *m*-Chloroperoxybenzoic Acid (*m*-CPBA). To a solution of **15a** (0.18 g, 1.00 mmol) in dichloromethane (20 mL) was added *m*-CPBA (0.43 g, 2.5 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 4 h. After addition of saturated $NaHCO_3$ (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 the sequential cyclization product **26a** (0.28 g, 80%).

Spectral data for 26a: highly viscous liquid; IR ($CHCl_3$) 3500−3300, 2970, 1725, 1600, 1050, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95−7.93 (m, 1H), 7.87−7.83 (m, 1H), 7.59−7.56 (m, 1H), 7.42 (dd, J = 6.0 Hz, J = 6.0 Hz, 1H), 4.21 (s, 1H), 4.15 (d, J = 4.8 Hz, 1H), 3.01−2.93 (m, 2H), 2.69−2.65 (m, 1H), 2.42 (brs, 1H), 2.18 (d, J = 10.8 Hz, 1H), 1.74 (s, 3H), 1.57 (s, 3H), 1.55−1.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 163.12 (C═O), 134.84 (C), 133.66 (CH), 130.01 (CH), 129.26 (CH), 128.90 (C), 127.33 (CH), 118.83 (C), 113.41 (C), 89.15 (CH), 74.33 (CH), 52.52 (CH), 51.76 (CH), 47.82 (CH), 44.01 (CH), 35.31 (CH_2), 24.83 (CH_3), 19.15 (CH_3); LRMS *m/z* (rel inten) 352, 350 (M^+, 5), 195 (100).

Tosylation of 26a,b. To a solution of **26a** (0.25 g, 0.71 mmol) in pyridine (10 mL) was added *p*-toluenesulfonyl chloride (0.16 g, 0.85 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. After addition of 1 M HCl (10 mL) and extraction with ether (3 × 30 mL), the organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the tosylate **27a** (0.32 g, 90%).

Spectral data for 27a: highly viscous liquid; IR ($CHCl_3$) 2970, 1720, 1600, 1380, 1200, 1070, 850, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92−7.79 (m, 4H), 7.57−7.35 (m, 4H), 4.76 (d, J = 1.2 Hz, 1H), 4.24 (d, J = 4.8 Hz, 1H), 2.98−2.92 (m, 2H), 2.70−2.62 (m, 2H), 2.44 (s, 3H), 2.11−2.05 (m, 1H), 1.65 (s, 3H), 1.62−1.58 (m, 1H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 162.79 (C═O), 144.98 (C), 134.76 (C), 133.62 (C), 133.54 (CH), 129.98 (2CH), 129.85 (CH), 129.10 (CH), 128.70 (C), 127.60 (2CH), 127.22 (CH), 118.91 (C), 112.86 (C), 86.31 (CH), 83.66 (CH), 52.14 (CH), 51.74 (CH), 47.91 (CH), 42.71 (CH), 35.14 (CH_2), 24.49 (CH_3), 21.53 (CH_3), 18.80 (CH_3); LRMS *m/z* (rel inten) 506, 504 (M^+, 2), 349 (100).

Conversion of the Tosylates 27a,b to the Trioxa-Cages 24a,c. To a solution of **27a** (0.59 g, 1.00 mmol) in dry THF (40 mL) was added KH (0.080 g, 2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h. To this reaction mixture was dropwise added H_2O (10 mL) at 0 °C to destroy the excess KH. After addition of saturated NH_4Cl (10 mL) and extraction with ether (3 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the trioxa-cage **24a** in 70% yield.

General Procedure for Oxymercuration−Demercuration of Bis-*endo*-diacylnorbornenes 15a−f. To a solution of **15a** (0.18 g, 1.0 mmol) in aqueous THF (20 mL, THF/H_2O = 4:1) was added $Hg(OAc)_2$ (0.35 g, 1.1 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. To this solution was added $NaBH_4$ (0.060 g, 1.5 mmol) and the reaction mixture was stirred at 25 °C for another 2 h. After addition of saturated NH_4Cl (10 mL) and extraction with ether (3 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the sequential cyclization product **28a** (0.16 g, 80%).

Spectral data for 28a: pale yellow oil; IR ($CHCl_3$) 3500−3300, 2970, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.46 (dd, J = 8.1 Hz, J = 4.5 Hz, 1H), 3.00−2.80 (m, 3H), 2.55−2.50 (m, 1H), 2.27 (brs, 1H), 1.90 (dd, J = 14.1 Hz, J = 3.6 Hz, 1H), 1.60−1.45 (m, 3H), 1.56 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 116.69 (C), 104.51 (C), 81.21 (CH), 56.23 (CH), 53.79 (CH), 49.37 (CH), 39.60 (CH_2), 36.60 (CH), 33.82 (CH_2), 26.36 (CH_3), 23.99 (CH_3); LRMS *m/z* (rel inten) 196 (M^+, 42), 179 (100); HRMS (EI) calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1091. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.31; H, 8.22, found: C, 67.19; H, 8.28.

General Procedure for Oxidation of 28d−f with PCC. To a solution of **28e** (0.18 g, 1.00 mmol) in dichloromethane (30 mL) was added PCC (0.54 g, 2.5 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. To this mixture, Celite (2.0 g) was added. The reaction mixture was filtered through Celite and the solvent ws evaporated. The residue was purified by column chromatography to give the lactone **30b** (0.14 g, 80%).

Spectral data for 30b: yield 80%; pale yellow oil; IR ($CHCl_3$) 2970, 1765, 1250, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H), 3.09−2.98 (m, 3H), 2.69 (brs, 1H), 1.82−1.66 (m, 4H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 176.12 (C═O), 116.32 (C), 81.86 (CH), 52.51 (CH), 50.19 (CH), 48.56 (CH), 40.76 (CH_2), 39.25 (CH), 35.67 (CH_2), 24.03 (CH_3); LRMS *m/z* (rel inten) 180 (M^+, 13), 136 (100); HRMS (EI) calcd for $C_{10}H_{12}O_3$ 180.0786, found 180.0782. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72, found: C, 66.48; H, 6.80.

Alkoxymercuration−Demercuration of Bis-*endo*-diacetylnorbornene 15a. To a solution of **15a** (0.18 g, 1.00 mmol) in methanol (20 mL) was added $Hg(OAc)_2$ (0.35 g, 1.1 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 h. To this solution was then added $NaBH_4$ (0.060 g, 1.5 mmol) and the reaction mixture was stirred at 25 °C for another 2 h. The solvent was evaporated and saturated NH_4Cl (20 mL) was added. After extraction with ether (4 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the sequential cyclization product **31** (0.16 g, 75%): pale yellow oil; IR ($CHCl_3$) 2980, 2880, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (dd, J = 8.1 Hz, J = 4.5 Hz, 1H), 3.24 (s, 3H), 2.93−2.80 (m, 2H), 2.49−2.44 (m, 1H), 2.27 (brs, 1H), 1.92 (dd, J = 14.1 Hz, J = 3.0 Hz, 1H), 1.57−1.43 (m, 3H), 1.50 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 116.73 (C), 106.86 (C), 81.32 (CH), 56.92 (CH), 53.65 (CH), 49.32 (CH), 47.46 (CH_3), 39.50 (CH_2), 36.66 (CH), 33.99 (CH_2), 25.29 (CH_3), 17.85 (CH_3); LRMS *m/z* (rel inten) 210 (M^+, 56), 195 (100); HRMS (EI) calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1260. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.53; H, 8.63, found: C, 68.40; H, 8.70.

Mercuration−Demercuration of 15a in Acetonitrile. To a solution of **15a** (0.18 g, 1.00 mmol) in acetonitrile (30 mL) was added $Hg(OAc)_2$ (0.35 g, 1.1 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 3 h. To this solution was then added $NaBH_4$ (0.060 g, 1.5 mmol) and the reaction mixture was stirred at 25 °C for 2 h. After addition of saturated NH_4Cl (20 mL) and extraction with ether (3 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the dioxa-cage compound **32** (0.13 g, 70%): pale yellow oil; IR ($CHCl_3$) 2980, 2880, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.44 (dd, J = 8.7 Hz, J = 5.1 Hz, 1H), 4.26−4.18 (m, 1H), 2.88−2.74 (m, 2H), 2.42−2.38 (m, 1H), 2.25 (brs, 1H), 2.07 (dd, J = 14.1 Hz, J = 3.6 Hz, 1H), 1.58−1.42 (m, 3H), 1.48 (s, 3H), 1.34 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 115.53 (C), 81.22 (CH), 75.70 (CH), 55.52 (CH), 51.57 (CH), 49.45 (CH), 39.51 (CH_2), 35.68 (CH), 34.61 (CH_2), 24.60 (CH_3), 16.28 (CH_3); LRMS *m/z* (rel inten) 180 (M^+, 100), 165 (32); HRMS (EI) calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1145. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95, found: C, 73.18; H, 8.99.

General Procedure for Oxymercuration−Demercuration of 2a−c. The same reaction conditions and procedure for the oxymercuration of **15a−f** were applied for oxymercuration−demercuration of **2a−c** to give the sequential cyclization product **30b−d** in 70−80% yields.

Spectral data for 30d: yield 75%; pale yellow oil; IR ($CHCl_3$) 2970, 1767, 1250, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (dd, J = 6.6 Hz, J = 6.6 Hz, 1H), 3.10−3.03 (m, 2H), 2.90−2.86 (m, 1H), 2.69 (brs, 1H), 2.12−2.05 (m, 1H), 1.83−1.66 (m, 4H), 1.01 (d, J = 7.2 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 176.34 (C=O), 120.73 (C), 81.52 (CH), 49.75 (CH), 48.98 (CH), 48.77 (CH), 40.80 (CH_2), 39.31 (CH), 35.85 (CH_2), 34.04 (CH), 16.70 (CH_3), 16.60 (CH_3); LRMS *m*/*z* (rel inten) 208 (M^+, 12), 164 (100); HRMS (EI) calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1094. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.19; H, 7.75, found: C, 69.10; H, 7.81.

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Supporting Information Available: ^1H and ^{13}C NMR spectra data of **3b−d**, **12c−e**, **14b−e**, **16b−d**, **24b−d**, **26b**, **27b**, **28b−f**, and **30a−c** (23 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.

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