Pergamon

Tetrahedron 56 (2000) 341–350

TETRAHEDRON

Synthesis of Diacetal Trioxa-cage Compounds via Reaction of Bicyclo[2.2.1]heptenes and Bicyclo[2.2.2]octenes with Dimethyldioxirane

Hui-Chang Lin and Hsien-Jen Wu*

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

Received 20 September 1999; accepted 2 November 1999

Abstract—A new entry for the synthesis of diacetal trioxa-cage compounds via oxirane-induced sequential cyclization reaction of 2,3-bis-*endo*-diacylbicyclo[2.2.1]-5-heptenes and 2,3-bis-*endo*-diacylbicyclo[2.2.2]-5-octenes is reported. In the case of bicyclo[2.2.2]octenes, sequential cyclization reaction induced by iodine as electrophile failed. We have also demonstrated that dimethyldioxirane can selectively oxidize hemiacetals to give lactones with the secondary hydroxy group intact.

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. These cage compounds have played a key role in theoretical organic chemistry by providing rigid and often symmetric frameworks for evaluating theories put forth on the physico-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. Heterocyclic cage compounds have also received attention in recent years from synthetic as well as mechanistic consideration. The main purpose for the studies was the desire to compare the reactivity pattern of carbon cage compounds with their heterologues. We envision that studies on the synthesis and chemistry of heterocyclic cage compounds can greatly expand the scope and utilities of cage compounds.

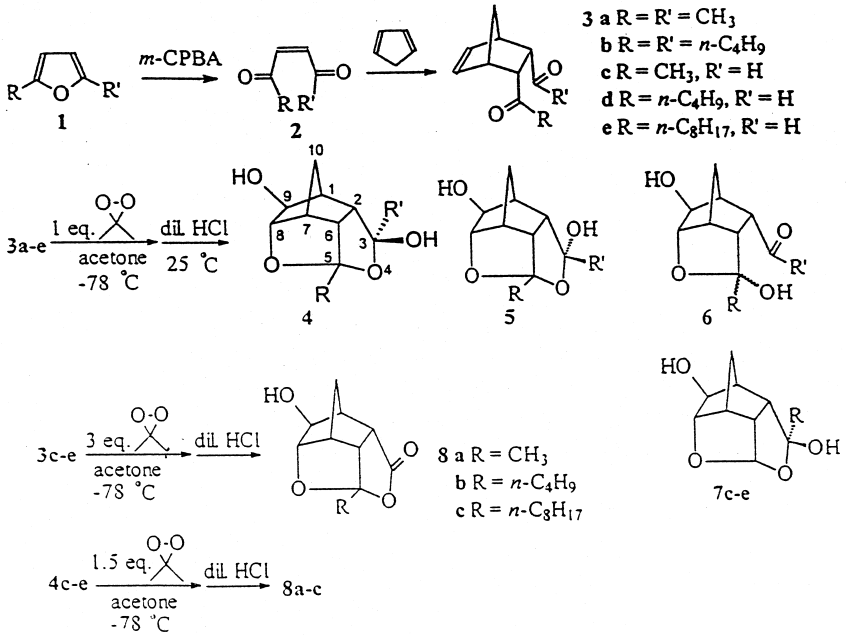
There are some reports regarding the chemistry[2] and synthesis[3–8] of oxa-cage compounds in the literature. This class of heterocyclic cage compounds is synthesized by intramolecular alkene–oxirane ($2\sigma-2\pi$) photocycloaddition,[3] by transannular cyclization of suitable compounds,[4] by tandem 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] Recently, we utilized ozonolysis reaction for the synthesis of a series of oxa-cage compounds, such as diacetal trioxa-cages,[9] triacetal trioxa-cages,[10] tetraacetal tetraoxa-cages,[11] tetraacetal pentaoxa-cages,[12] and pentaacetal pentaoxa-cages (the pentaoxa[5]-peristylanes).[13] Later on, we investigated the chemical nature of the acetal group of tetraoxa-cages and discovered a hydride rearrangement and a one-pot conversion from oxa-cages to aza-cages.[14] We also developed a method for the synthesis of dioxa-cages[15] and diacetal trioxa-cages[16] via the iodine-induced cyclization reaction of norbornene derivatives. As part of a program that involves the synthesis, chemistry, and applications of new heterocyclic cages, we report here the synthesis of diacetal trioxa-cage compounds via dimethyldioxirane-induced sequential cyclization reaction of 2,3-bis-*endo*-diacylbicyclo[2.2.1]-5-heptenes and 2,3-bis-*endo*-diacylbicyclo[2.2.2]-5-octenes. The synthesis of diacetal trioxa-cages via transannular cyclization of dilactones based on bicyclo[2.2.1]heptanes was also accomplished by Pillai et al.[17]

Results and Discussion

Oxidation of alkylfurans **1a**–**e** with *m*-chloroperoxybenzoic acid (*m*-CPBA)[18] in dichloromethane at 0°C gave the *cis*-enediones **2a**–**e**. Diels–Alder reaction of **2a**–**e** with cyclopentadiene at room temperature gave the *endo* adducts **3a**–**e** as the major products in 80–86% yields.[11] Reaction of **3a**–**e** with one equivalent of dimethyldioxirane[19] in acetone at −78°C, followed by addition of dilute HCl at room temperature, gave the sequential cyclization products **4a**–**e** in 75–86% yields (Scheme 1). The stereochemistry of the hemiacetal hydroxy group of **4** was determined on the basis of NOE experiments of **4a**. Irradiation of the C_9 proton (δ 4.08) gave 7.8% enhancement for the angular methyl proton absorptions on C_3, 2.0% enhancement for the C_8

Keywords: dimethyldioxirane; diacetal trioxa-cage compounds; lactones.
* Corresponding author.

0040–4020/00/$ - see front matter
PII: S0040-4020(99)00997-7

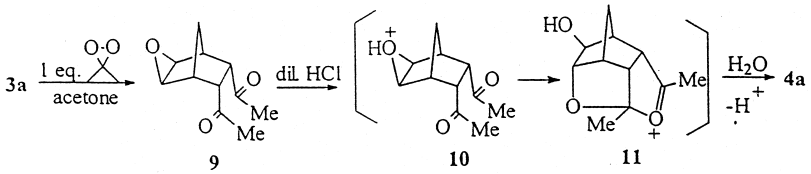


Scheme 1.

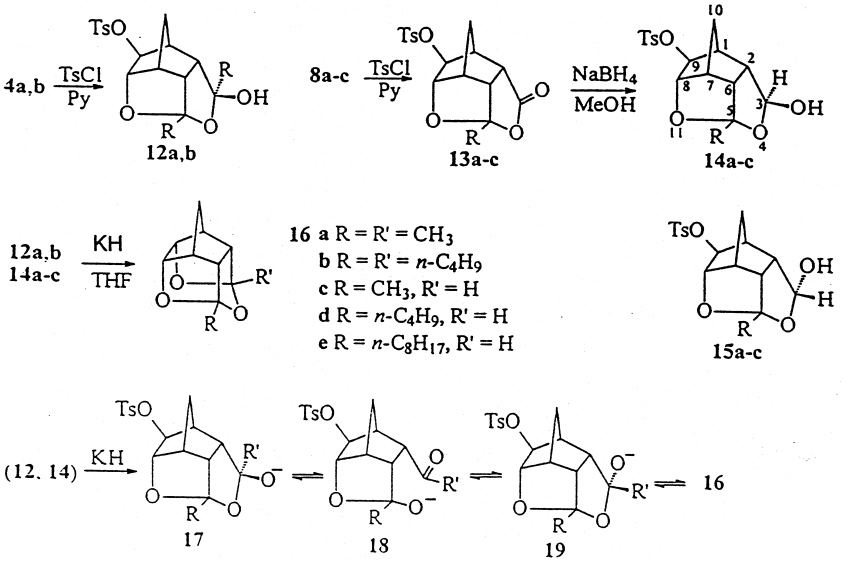
proton peak, and 3.0% enhancement for the C_1 proton absorptions. The ^{1}H NMR spectrum of **4c** revealed one singlet at δ 5.44 for the hemiacetal proton on C_3. The coupling constant (J=0 Hz) implies that the proton on C_3 is *trans* to the C_2 proton. Quantities of the other stereoisomers **5a**–**e** were too small to be isolated. No detectable amount of the monocyclization product **6** was obtained. For the cases of reaction of **3c**–**e**, the other regioisomers **7c**–**e** were formed in too small amounts to be isolated. Reaction of **3c**–**e** with 3 equiv. of dimethyldioxirane under the same reaction conditions gave the lactones **8a**–**c** in 84–86% yields. Treatment of the hemiacetals **4c**–**e** with 1.5 equiv. of dimethyldioxirane in acetone gave **8a**–**c** in 86–90% yields. Therefore, we have demonstrated that dimethyldioxirane can selectively oxidize hemiacetals to give lactones with secondary hydroxy group intact. Curci et al. and Adam et al. have recently reported[20] the oxidation of cyclic ethers into lactones in the absence of hydroxy group, presumably via the corresponding hemiacetals.

Treatment of **4a** with 1 equiv. of dimethyldioxirane in acetone at −78°C, without addition of dilute HCl, gave the epoxide **9** in 90% yield. Reaction of **9** with dilute HCl in acetone at room temperature gave compound **4a** in 95% yield. A mechanism is proposed for the formation of **4a**–**e** from **3a**–**e** (Scheme 2). Electrophilic attack of dimethyldioxirane at the alkene bond of **3a** gave the epoxide **9**. Protonation of the oxygen atom of the oxirane ring of **9**, followed by sequential intramolecular nucleophilic addition of the *endo* acyl groups to the protonated oxirane **10**, gave the oxonium ion **11** as the reaction intermediate. Nucleophilic addition of a water molecule to the oxonium ion **11** from the less hindered *exo* face, followed by loss of a proton, gave the product **4a**.

The synthesis of diacetal trioxa-cage compounds was accomplished from **4** and **8** by a two-step and a three-step sequence. Reaction of **4a**,**b** and **8a**–**c** with *p*-toluenesulfonyl chloride in pyridine at room temperature gave the tosylation products **12a**,**b** and **13a**–**c** in 88–92% yields, respectively. Reduction of **13a**–**c** with sodium borohydride in methanol at 0°C gave the hemiacetals **14a**–**c** in 80–85% yields (Scheme 3). The ^{1}H NMR spectrum of **14a** revealed one singlet at δ 5.35 for the hemiacetal proton on C_3. The coupling constant (J=0 Hz) implies that the proton on C_3 is *trans* to the proton on C_2. The stereochemistry of the hydroxy group of **14a**–**c** was also determined by NOE experiments of **14a**. Irradiating the acetal proton on C_3 of **14a** (δ 5.35) gives 10.8% enhancement for the C_9 proton absorptions and 5.2% enhancement for the C_1 proton absorptions. Irradiating the C_9 proton (δ 4.62) gives 8.8% enhancement for the acetal proton peak, 4.0% enhancement for the C_1 proton peak, and 2.8% enhancement for the C_8 proton peak. Nucleophilic addition of $NaBH_4$ to the lactone carbonyl group of **8a**–**c** may take place from the less hindered *exo* face, leading to formation of the stereoisomers **15a**–**c**, which, followed by anomerization, gave the thermodynamically more stable products **14a**–**c**. Treatment of



Scheme 2.

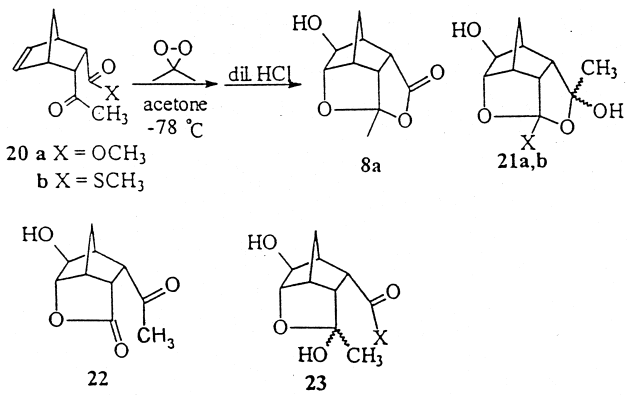


Scheme 3.

12a,**b** and **14a**–**c** with KH in dry THF at 0°C gave the diacetal trioxa-cage compounds **16a**–**e** in 86–90% yields, respectively. Trioxa-cages **16a**–**e** were also synthesized by iodine-induced cyclization reaction. A mechanism is proposed for the conversion of **12a**,**b** and **14a**–**c** to the trioxa-cages **16a**–**e** via the base-promoted anomerization intermediates **17**–**19**.

To compare the ability of the nucleophilic cyclization of an ester group and a thioester group with that of an acetyl group to the protonated oxirane ring of **10**, compounds **20a**[11b] and **20b**[11h] were prepared. Reaction of **20a** and **20b** with dimethyldioxirane in acetone at −78°C, followed by addition of dilute HCl at room temperature, gave the same product **8a** in 85% yield (Scheme 4). No detectable amount of the other regioisomers **21a** or **21b** was obtained. Also, no detectable amount of the monocyclization products **22** or **23** was obtained.

To extend the oxirane-induced sequential cyclization and the synthesis of diacetal trioxa-cage compounds, the bis-*endo*-diacylbicyclo[2.2.2]octanes **24a**,**b** were prepared.[11g] Reaction of **24a** with 1 equiv. of dimethyldioxirane in

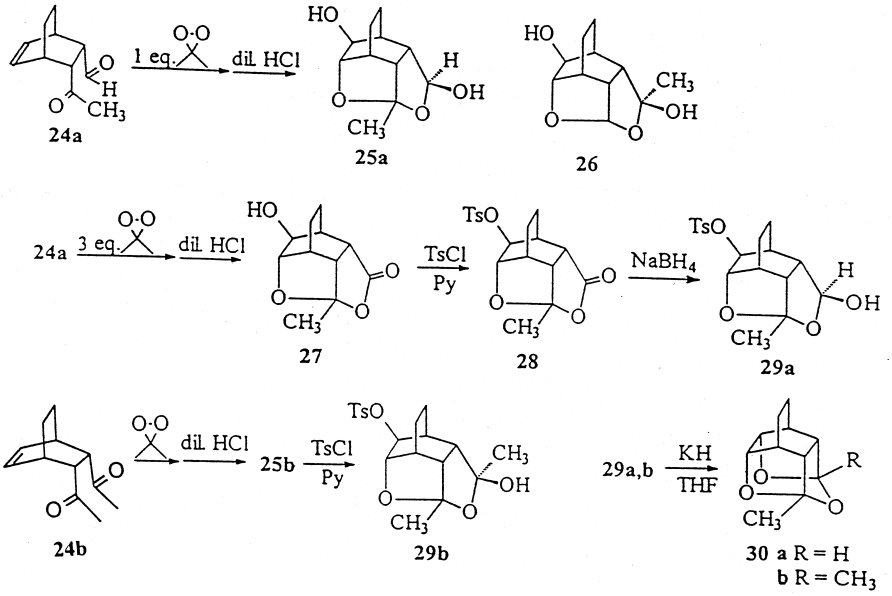


Scheme 4.

acetone at −78°C, followed by addition of dilute HCl at room temperature, gave the sequential cyclization products **25a** in 84% yield (Scheme 5). The amount of the other regioisomer **26** was too small to be isolated. The stereochemistry of the hemiacetal hydroxy group of **25a** was determined on the basis of NOE experiments. Irradiating the hemiacetal proton on C_3 gave 8.2% enhancement for the C_9 proton absorptions and 2.4% enhancement for the C_1 proton absorptions. Treatment of **24a** with 3 equiv. of dimethyldioxirane in acetone at −78°C followed by addition of dilute HCl at 25°C, gave the lactone **27** in 80% yield. Reaction of the hemiacetal **25a** with 1.5 equiv. of dimethyldioxirane in acetone gave the lactone **27** in 86% yield. Again, dimethyldioxirane oxidizes the hemiacetal hydroxy group, not the secondary alcohol. Tosylation of **27** in pyridine at room temperature gave the tosylate **28**. Reduction of **28** with sodium borohydride in methanol at 0°C gave the hemiacetal **29a** in 82% yield. Treatment of **24b** with 1 equiv. of dimethyldioxirane, followed by addition of dilute HCl at 25°C, gave the sequential cyclization product **25b**, which, without purification, was converted to the tosylate **29b**. Treatment of **29a**,**b** with KH in dry THF at 0°C gave the trioxa-cages **30a**,**b** in 80–82% yields. Thus, we have accomplished the synthesis of trioxa-cages **30a**,**b**, starting with bicyclo[2.2.2]octenes.

To understand the ability of the iodine-induced sequential cyclization[16] in bicyclo[2.2.2]octenes, the following experiments were performed. Treatment of **24a**,**b** with I_2 in aqueous THF in the presence of KI at 25°C for 8 h did not give the sequential cyclization products **31a**,**b**. The starting compounds **24a**,**b** remained unchanged. On the other hand, treatment of norbornene derivative **32** with I_2 under the same reaction conditions gave the sequential cyclization products **33**[16] (Scheme 6).

To explain the different reactivity between **24** and **32**, we may attribute it to the iodonium ion **34** being much more reactive to the cyclization than **35**, presumably the strain energy of **34** is higher than that of **35**. Another possible



Scheme 5.

factor to affect the cyclization of the transition states **34** and **35** is the different distance between the partially positive carbon C_2 and the carbonyl oxygen. Based on molecular modelling, the distance in **34** is shorter than that in **35**. Since coordination of an iodine molecule to the alkene bond is a reversible reaction, dissociation of iodine from the alkene bond of **35** took place. No sequential cyclization product **31** was observed. In the reaction of **24** with dimethyldioxirane, formation of the epoxide **36** is an irreversible reaction and the protonated oxirane **37** forces the sequential cyclization to take place to give the product **25**. Thus in reaction with bicyclo[2.2.2]octenes, the protonated oxirane ring affects the sequential cyclization whereas the iodine electrophile does not.

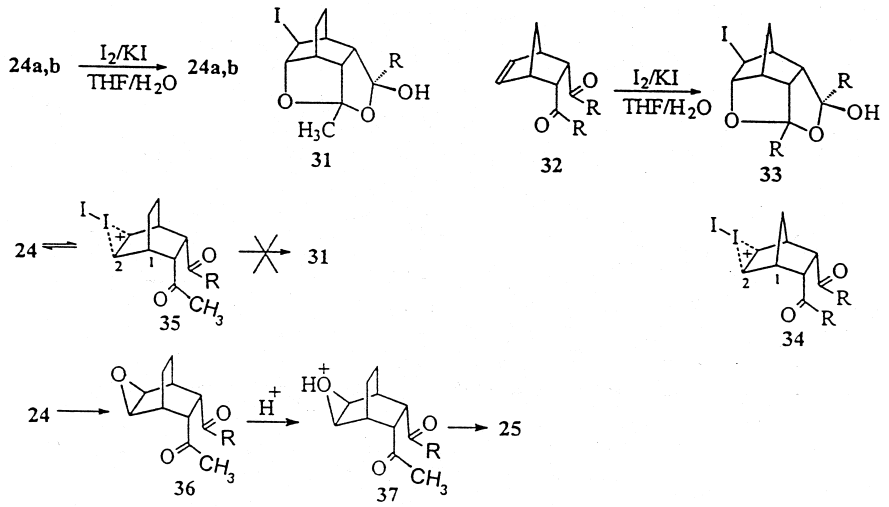
Conclusion

We have accomplished a new entry for the synthesis of diacetal trioxa-cage compounds via oxirane-induced sequential cyclization reaction of 2,3-bis-*endo*-diacylbicyclo[2.2.1]-5-heptenes and 2,3-bis-*endo*-diacylbicyclo-[2.2.2]-5-octenes. We have also demonstrated that dimethyldioxirane can selectively oxidize hemiacetals to give lactones with the secondary hydroxy group intact. In the reaction of bicyclo[2.2.2]octenes with iodine, a weak electrophile, reversible reaction back to starting compounds took place. No sequential cyclization products were obtained.

Experimental

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



Scheme 6.

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. Elemental analyses were performed at the microanalysis laboratory of this department. For thin-layer chromatography (TCL) 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.

Preparation of dimethyldioxirane solution

A 250 mL, three-necked, round-bottomed flask, containing a mixture of water (20 mL), acetone (13 mL, 0.177 mol), sodium bicarbonate (12 g), and a magnetic stirring bar, was equipped with an addition funnel for solids containing potassium monoperoxy sulfate (25 g, 0.041 mol) and an air condenser which was connected to a receiving flask, cooled by means of liquid nitrogen–acetone. While applying a slight vacuum (ca. 180 Torr, water aspirator), the solid potassium monoperoxy sulfate was added in one portion, stirring vigorously at room temperature. The yellow dioxirane–acetone solution (11 mL, 0.11 M) was collected in the receiving flask.

Titration of dimethyldioxirane solution

A solution of dimethyldioxirane in acetone (1.00 mL) was added to a 3:2 mixture of acetic acid–acetone solution (2 mL). Saturated aqueous KI solution (2 mL) was then added together with some dry ice to deaerate and the resulting mixture was stored in the dark at room temperature for 10 min. The sample was diluted with water (5 mL) and three aliquots (1.00 mL) were titrated with aqueous $Na_2S_2O_3$ (0.001N) solution, affording a dioxirane concentration of 0.11 M.

General procedure for the reaction of 3a–e with dimethyldioxirane. Formation of the hemiacetals 4a–e. To a yellow dioxirane–acetone solution (11 mL, 0.11 M), which was collected in a cooled receiving flask, was added a solution of **3a** (0.194 g, 1.09 mmol) in acetone (10 mL) at −78°C. The reaction mixture was stirred at room temperature for 30 min. To this solution was added 1 M HCl (5 mL) and the reaction mixture was stirred at room temperature for 10 min. Saturated sodium carbonate solution (10 mL) was slowly added to neutralize the reaction solution. The reaction mixture was extracted with dichloromethane (4×30 mL) and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography to give **4a** (0.198 g, 0.93 mmol) in a 86% yield.

3α,5-Dimethyl-3β,9β-dihydroxy-4,11-dioxatetracyclo-[5.2.1.1^{5,8}.0^{2,6}]undecane 4a. White solid; mp 148–149°C; 86% yield; IR ($CHCl_3$) 3600–3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (s, 1H), 4.08 (brs, 1H), 3.92 (d, J=4.8 Hz, 1H), 3.78 (brs, 1H), 2.88–2.70 (m, 2H), 2.40–2.35 (m, 1H), 2.24–2.22 (m, 1H), 2.12–2.06 (m, 2H), 1.45 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.16 (C), 104.11(C), 89.72 (CH), 74.44 (CH), 56.36 (CH), 54.08 (CH), 48.54 (CH), 45.26 (CH), 35.86 (CH_2), 26.67 (CH_3), 24.24 (CH_3); LRMS m/z (rel int) 212 (M^+, 2), 151 (100); HRMS (EI) calcd for $C_{11}H_{16}O_4$ 212.1048, found 212.1043; Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 62.18; H, 7.64.

3α,5-Di-*n*-butyl-3β,9β-dihydroxy-4,11-dioxatetracyclo-[5.2.1.1^{5,8}.0^{2,6}]undecane 4b. White solid; mp 121–122°C; 84% yield; IR ($CHCl_3$) 3600–3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (s, 1H), 4.09 (d, J=4.8 Hz, 1H), 2.98–2.91 (m, 1H), 2.83–2.77 (m, 2H), 2.50–2.44 (m, 1H), 2.28 (brs, 2H), 2.12–2.06 (m, 1H), 1.83–1.74 (m, 4H), 1.52–1.48 (m, 1H), 1.40–1.31 (m, 8H), 0.95–0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 119.09 (C), 105.70 (C), 89.05 (CH), 74.62 (CH), 53.36 (CH), 51.07 (CH), 47.87 (CH), 43.65 (CH), 39.10 (CH_2), 37.23 (CH_2), 35.51 (CH_2), 26.47 (CH_2), 26.28 (CH_2), 22.97 (CH_2), 22.84 (CH_2), 14.04 (CH_3), 14.01 (CH_3); LRMS m/z (rel int) 296 (M^+, 9), 151 (100); HRMS (EI) calcd for $C_{17}H_{28}O_4$ 296.1987, found 296.1981; Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.87; H, 9.53. Found: C, 68.81; H, 9.59.

5-Methyl-3β,9β-dihydroxy-4,11-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}]undecane 4c. White solid; mp 110–111°C; 75% yield; IR ($CHCl_3$) 3600–3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 1H), 4.08 (d, J=3.3 Hz, 1H), 4.03 (s, 1H), 2.90–2.84 (m, 2H), 2.76 (brs, 1H), 2.62–2.58 (m, 1H), 2.34 (brs, 1H), 2.12–2.08 (m, 1H), 1.81 (brs, 1H), 1.59–1.56 (m, 1H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 118.80 (C), 99.58 (CH), 90.13 (CH), 74.88 (CH), 54.74 (CH), 52.87 (CH), 49.22 (CH), 45.62 (CH), 36.42 (CH_2), 25.89 (CH_3); LRMS m/z (rel int) 198 (M^+, 5), 79 (100); HRMS (EI) calcd for $C_{10}H_{14}O_4$ 198.0892, found 198.0896.

5-*n*-Butyl-3β,9β-dihydroxy-4,11-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}]undecane 4d. White solid; mp 89–90°C; 78% yield; IR ($CHCl_3$) 3600–3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.52 (s, 1H), 4.07 (d, J=3.6 Hz, 1H), 4.02 (s, 1H), 3.92 (brs, 1H), 3.18 (brs, 1H), 2.90–2.78 (m, 2H), 2.60–2.40 (m, 2H), 2.12–2.06 (m, 1H), 1.80–1.68 (m, 2H), 1.58–1.52 (m, 1H), 1.40–1.21 (m, 4H), 0.87 (t, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 120.28 (C), 98.36 (CH), 88.93 (CH), 74.26 (CH), 52.63 (CH), 49.80 (CH), 48.30 (CH), 43.86 (CH), 37.90 (CH_2), 35.59 (CH_2), 26.64 (CH_2), 22.57 (CH_2), 13.98 (CH_3); LRMS m/z (rel int) 240 (M^+, 6), 85 (100); HRMS (EI) calcd for $C_{13}H_{20}O_4$ 240.1361, found 240.1366.

5-*n*-Octyl-3β,9β-dihydroxy-4,11-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}]undecane 4e. White solid; mp 47–48°C; 80% yield; IR ($CHCl_3$) 3600–3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (s, 1H), 4.08 (d, J=4.5 Hz, 1H), 4.02 (s, 1H), 2.90–2.83 (m, 2H), 2.59–2.52 (m, 1H), 2.40–2.37 (m, 1H), 2.12–2.06 (m, 1H), 1.84–1.72 (m, 4H), 1.58–1.53 (m, 1H), 1.40–1.25 (m, 12H), 0.87 (t, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 120.33 (C), 98.38 (CH), 88.98 (CH), 74.34 (CH), 52.73 (CH), 49.75 (CH), 48.21 (CH), 44.19 (CH), 38.44 (CH_2), 35.54 (CH_2), 31.85 (CH_2), 29.74

(CH_2), 29.50 (CH_2), 29.24 (CH_2), 24.48 (CH_2), 22.65 (CH_2), 14.11 (CH_3); LRMS *m*/*z* (rel int) 296 (M^+, 2), 141 (100); HRMS (EI) calcd for $C_{17}H_{28}O_4$ 296.1987, found 296.1981.

General procedure for the reaction of 3c–e with excess dimethyldioxirane. Formation of the lactones 8a–c. The same reaction conditions and procedure as for the preparation of **4a–e**, except with excess dimethyldioxirane (3 equiv.), were applied for the formation of **8a–c**.

5-Methyl-9β-hydroxy-3-oxo-4,11-dioxatetracyclo[5.2.1.$1^{5,8}$.$0^{2,6}$]undecane 8a. White waxy solid; mp 55–56°C; 80% yield; IR ($CHCl_3$) 3500–3400, 1775, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, *J*=4.5 Hz, 1H), 3.86 (s, 1H), 3.07–2.96 (m, 3H), 2.66–2.62 (m, 2H), 2.25 (d, *J*=12.3 Hz, 1H), 1.74 (d, *J*=12.3 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 175.72 (CO), 117.08 (C), 89.53 (CH), 75.01 (CH), 51.54 (CH), 47.31 (CH), 46.84 (CH), 45.76 (CH), 36.56 (CH_2), 23.73 (CH_3); LRMS *m*/*z* (rel int) 196 (M^+, 4), 97 (100); HRMS (EI) calcd for $C_{10}H_{12}O_4$ 196.0735, found 196.0739; Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.20; H, 6.17. Found: C, 61.15; H, 6.20.

5-*n*-Butyl-9β-hydroxy-3-oxo-4,11-dioxatetracyclo[5.2.1.$1^{5,8}$.$0^{2,6}$]undecane 8b. White waxy solid; mp 45–46°C; 84% yield; IR ($CHCl_3$) 3500–3400, 1775, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, *J*=4.8 Hz, 1H), 3.90 (s, 1H), 3.05–2.93 (m, 3H), 2.66–2.60 (m, 2H), 2.24 (d, *J*=11.1 Hz, 1H), 1.89–1.80 (m, 2H), 1.73 (d, *J*=11.1 Hz, 1H), 1.40–1.26 (m, 4H), 0.91 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 175.48 (CO), 119.07 (C), 89.36 (CH), 75.32 (CH), 49.96 (CH), 47.08 (CH), 46.99 (CH), 45.87 (CH), 36.59 (CH_2), 36.41 (CH_2), 25.68 (CH_2), 22.55 (CH_2), 13.89 (CH_3); LRMS *m*/*z* (rel int) 238 (M^+, 8), 119 (100); HRMS (EI) calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1209; Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.51; H, 7.62. Found: C, 65.59; H, 7.68.

5-*n*-Octyl-9β-hydroxy-3-oxo-4,11-dioxatetracyclo[5.2.1.$1^{5,8}$.$0^{2,6}$]undecane 8c. White waxy solid; mp 40–41°C; 83% yield; IR ($CHCl_3$) 3500–3400, 1775, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (d, *J*=4.8 Hz, 1H), 3.88 (s, 1H), 3.05–2.93 (m, 3H), 2.66–2.60 (m, 2H), 2.24 (d, *J*=11.4 Hz, 1H), 1.90–1.81 (m, 2H), 1.73 (d, *J*=11.4 Hz, 1H), 1.39–1.25 (m, 12H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 175.71 (CO), 119.15 (C), 89.34 (CH), 75.20 (CH), 49.93 (CH), 47.05 (CH), 46.99 (CH), 45.82 (CH), 36.67 (CH_2), 36.59 (CH_2), 31.77 (CH_2), 29.41 (CH_2), 29.35 (CH_2), 29.12 (CH_2), 23.54 (CH_2), 22.60 (CH_2), 14.08 (CH_3); LRMS *m*/*z* (rel int) 294 (M^+, 3), 181 (100); HRMS (EI) calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1837; Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.34; H, 8.91. Found: C, 69.27; H, 8.96.

Reaction of 4c–e with dimethyldioxirane in acetone. The same reaction conditions and procedure as for the reaction of **3a–e** with dimethyldioxirane were applied for the reaction of **4c–e** with dimethyldioxirane to give the lactones **8a–c** in 86–90% yields.

Reaction of 3a with dimethyldioxirane without addition of dilute HCl. Formation of the epoxide 9. To a yellow dioxirane–acetone solution (11 mL, 0.11 M), which was collected in a cooled receiving flask, was added a solution of **3a** (0.194 g, 1.09 mmol) in acetone (15 mL) at −78°C. The reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated and the crude product was purified by column chromatography to give the epoxide **9** in a 90% yield.

Spectral data for **9**: white solid; mp 112–113°C; IR ($CHCl_3$) 1710, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.41 (s, 2H), 3.22–3.20 (m, 2H), 2.90–2.88 (m, 2H), 2.18 (s, 6H), 1.57–1.53 (m, 1H), 0.83–0.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 206.68 (2CO), 56.05 (2CH), 49.24 (2CH), 41.22 (2CH), 29.80 ($2CH_3$), 26.20 (CH_2); LRMS *m*/*z* (rel int) 194 (M^+, 3), 79 (100); HRMS (EI) calcd for $C_{11}H_{14}O_3$ 194.0942, found 194.0948.

Reaction of the epoxide 9 with dilute HCl in acetone. To a solution of **9** (0.19 g, 1.0 mmol) in acetone (20 mL) was added 1 M HCl (1 mL) at room temperature. The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was neutralized with saturated $NaHCO_3$ (5 mL) and the solvent was evaporated. After extraction with ether (5×30 mL), the combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography to give the sequential cyclization product **4a** in 95% yield.

General procedure for the tosylation of compounds 4a,b and 8a–c. To a solution of compound **4a** (0.10 g, 0.48 mmol) in pyridine (20 mL) was added *p*-toluenesulfonyl chloride (0.10 g, 0.52 mmol) at 25°C. The reaction mixture was stirred at 25°C for 24 h. To the reaction mixture was slowly added 2 M HCl (15 mL) and then saturated Na_2CO_3 (10 mL). After extraction with ether (5×30 mL), the combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography to give the tosylate **12a** in 90% yield.

3α,5-Dimethyl-3β-hydroxy-9β-tosyl-4,11-dioxatetracyclo-[5.2.1.$1^{5,8}$.$0^{2,6}$]undecane 12a. Highly viscous liquid; 90% yield; IR ($CHCl_3$) 3400, 1610, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.1 Hz, 2H), 7.32 (d, *J*=8.1 Hz, 2H), 4.77 (s, 1H), 4.20 (d, *J*=4.8 Hz, 1H), 2.97–2.93 (m, 1H), 2.89–2.85 (m, 1H), 2.53–2.48 (m, 2H), 2.44 (s, 3H), 2.04 (d, *J*=11.1 Hz, 1H), 1.65 (brs, 1H), 1.54 (d, *J*=11.1 Hz, 1H), 1.50 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 144.88 (C), 133.87 (C), 129.97 (2CH), 127.72 (2CH), 117.41 (C), 103.80 (C), 86.43 (CH), 84.27 (CH), 54.83 (CH), 52.62 (CH), 48.00 (CH), 42.67 (CH), 35.30 (CH_2), 25.85 (CH_3), 24.12 (CH_3), 21.65 (CH_3); LRMS *m*/*z* (rel int) 366 (M^+, 7), 211 (100); HRMS (EI) calcd for $C_{18}H_{22}O_6S$ 366.1137, found 366.1131.

3α,5-Di-*n*-butyl-3β-hydroxy-9β-tosyl-4,11-dioxatetracyclo[5.2.1.$1^{5,8}$.$0^{2,6}$]undecane 12b. Highly viscous liquid; 92% yield; IR ($CHCl_3$) 3400, 1610, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 4.76 (s, 1H), 4.25 (d, *J*=5.1 Hz, 1H), 2.90–2.87 (m, 1H), 2.80–2.76 (m, 1H), 2.48–2.44 (m, 2H), 2.42 (s, 3H), 2.10–1.88 (m, 2H), 1.80–1.68 (m, 2H), 1.62–1.20 (m, 11H), 0.93–0.84 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 144.72 (C), 133.86 (C), 129.96 (2CH), 127.77

(2CH), 119.06 (C), 103.14 (C), 86.35 (CH), 84.99 (CH), 53.34 (CH), 50.91 (CH), 47.92 (CH), 42.33 (CH), 38.08 (CH_2), 35.35 (CH_2), 31.29 (CH_2), 26.82 (CH_2), 25.98 (CH_2), 22.79 (CH_2), 22.77 (CH_2), 21.60 (CH_3), 15.19 (CH_3), 13.93 (CH_3); LRMS *m/z* (rel int) 450 (M^+, 8), 295 (100); HRMS (EI) calcd for $C_{24}H_{34}O_6S$ 450.2076, found 450.2071.

5-Methyl-9β-tosyl-3-oxo-4,11-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}] undecane 13a. Highly viscous liquid; 88% yield; IR ($CHCl_3$) 1775, 1610, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J=8.1 Hz, 2H), 7.36 (d, J=8.1 Hz, 2H), 4.46–4.45 (m, 1H), 4.32 (s, 1H), 3.06–3.00 (m, 3H), 2.74–2.72 (m, 1H), 2.46 (s, 3H), 2.17 (d, J=11.4 Hz, 1H), 1.78 (d, J=11.4 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 173.58 (CO), 145.37 (C), 132.85 (C), 130.14 (2CH), 127.88 (2CH), 116.80 (C), 87.19 (CH), 83.25 (CH), 51.20 (CH), 46.94 (2CH), 43.94 (CH), 36.87 (CH_2), 23.57 (CH_3), 21.68 (CH_3); LRMS *m/z* (rel int) 350 (M^+, 3), 195 (100); HRMS (EI) calcd for $C_{17}H_{18}O_6S$ 350.0824, found 350.0828.

5-*n*-Butyl-9β-tosyl-3-oxo-4,11-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}] undecane 13b. Highly viscous liquid; 90% yield; IR ($CHCl_3$) 1775, 1610, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J=8.1 Hz, 2H), 7.37 (d, J=8.1 Hz, 2H), 4.48–4.46 (m, 1H), 4.32 (s, 1H), 3.04–2.94 (m, 3H), 2.73–2.71 (m, 1H), 2.46 (s, 3H), 2.17 (d, J=11.7 Hz, 1H), 1.85–1.66 (m, 3H), 1.36–1.30 (m, 4H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 173.70 (CO), 145.34 (C), 132.85 (C), 130.13 (2CH), 127.87 (2CH), 118.91 (C), 87.02 (CH), 83.85 (CH), 49.57 (CH), 47.14 (CH), 46.63 (CH), 43.95 (CH), 36.87 (CH_2), 36.10 (CH_2), 25.56 (CH_2), 22.45 (CH_2), 21.67 (CH_3),13.84 (CH_3); LRMS *m/z* (rel int) 392 (M^+, 4), 237 (100); HRMS (EI) calcd for $C_{20}H_{24}O_6S$ 392.1293, found 392.1298.

5-*n*-Octyl-9β-tosyl-3-oxo-4,11-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}] undecane 13c. Highly viscous liquid; 92% yield; IR ($CHCl_3$) 1775, 1610, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J=8.1 Hz, 2H), 7.36 (d, J=8.1 Hz, 2H), 4.48–4.46 (m, 1H), 4.32 (s, 1H), 3.03–2.94 (m, 3H), 2.74–2.72 (m, 1H), 2.45 (s, 3H), 2.17 (d, J=11.4 Hz, 1H), 1.85–1.74 (m, 3H), 1.40–1.22 (m, 12H), 0.87 (t, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 173.73 (CO), 145.35 (C), 132.85 (C), 130.13 (2CH), 127.87 (2CH), 118.91 (C), 87.02 (CH), 83.36 (CH), 49.56 (CH), 47.13 (CH), 46.62 (CH), 43.94 (CH), 36.87 (CH_2), 36.40 (CH_2), 31.75 (CH_2), 29.51 (CH_2), 29.31 (CH_2), 29.09 (CH_2), 23.46 (CH_2), 22.59 (CH_2), 21.68 (CH_3), 14.07 (CH_3); LRMS *m/z* (rel int) 448 (M^+, 5), 293 (100); HRMS (EI) calcd for $C_{24}H_{32}O_6S$ 448.1919, found 448.1912.

General procedure for the reduction of 13a–c with sodium borohydride in methanol. To a solution of **13a** (0.070 g, 0.20 mmol) in methanol (20 mL) was added sodium borohydride (0.038 g, 1.0 mmol) at 0°C. The reaction mixture was stirred at 25°C for 1 h. After addition of saturated NH_4Cl (20 mL) and 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 hemiacetal **14a** in 80% yield.

5-Methyl-3β-hydroxy-9β-tosyl-4,11-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}]undecane 14a. Highly viscous oil; IR ($CHCl_3$) 3500–3300, 1610, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H), 5.35 (s, 1H), 4.61 (s, 1H), 4.20 (d, J=4.5 Hz, 1H), 2.89–2.87 (m, 2H), 2.60–2.54 (m, 3H), 2.44 (s, 3H), 2.02 (d, J=11.1 Hz, 1H), 1.59 (d, J=11.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 144.92 (C), 133.79 (C), 129.97 (2CH), 127.69 (2CH), 118.22 (C), 98.04 (CH), 86.48 (CH), 83.70 (CH), 52.83 (CH), 51.14 (CH), 48.02 (CH), 42.78 (CH), 35.53 (CH_2), 25.45 (CH_3), 21.65 (CH_3); LRMS *m/z* (rel int) 352 (M^+, 4), 197 (100); HRMS (EI) calcd for $C_{17}H_{20}O_6S$ 352.0980, found 352.0987.

5-*n*-Butyl-3β-hydroxy-9β-tosyl-4,11-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}]undecane 14b. Highly viscous oil; 83% yield; IR ($CHCl_3$) 3500–3300, 1610, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H), 5.36 (s, 1H), 4.60 (s, 1H), 4.21 (d, J=4.8 Hz, 1H), 2.95-2.77 (m, 3H), 2.58–2.54 (m, 2H), 2.44 (s, 3H), 2.02 (d, J=11.4 Hz, 1H), 1.90–1.62 (m, 2H), 1.59 (d, J=11.4 Hz, 1H), 1.35–1.23 (m, 4H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 144.88 (C), 133.81 (C), 129.97 (2CH), 127.70 (2CH), 120.57 (C), 97.92 (CH), 86.25 (CH), 83.85 (CH), 52.60 (CH), 49.37 (CH), 48.24 (CH), 42.84 (CH), 37.18 (CH_2), 35.59 (CH_2), 26.51 (CH_2), 22.71 (CH_2), 21.66 (CH_3), 13.95 (CH_3); LRMS *m/z* (rel int) 394 (M^+, 6), 239 (100); HRMS (EI) calcd for $C_{20}H_{26}O_6S$ 394.1450, found 394.1456.

5-*n*-Octyl-3β-hydroxy-9β-tosyl-4,11-dioxatetracyclo-[5.2.1.1^{5,8}.0^{2,6}]undecane 14c. Highly viscous oil; 85% yield; IR ($CHCl_3$) 3500–3300, 1610, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H), 5.36 (s, 1H), 4.60 (s, 1H), 4.21 (d, J=4.8 Hz, 1H), 2.90–2.82 (m, 3H), 2.58–2.55 (m, 2H), 2.45 (s, 3H), 2.02 (d, J=11.4 Hz, 1H), 1.78–1.70 (m, 2H), 1.59 (d, J=11.4 Hz, 1H), 1.40–1.18 (m, 12H), 0.87 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 144.89 (C), 133.77 (C), 129.96 (2CH), 127.69 (2CH), 120.56 (C), 97.90 (CH), 86.24 (CH), 83.84 (CH), 52.57 (CH), 49.35 (CH), 48.24 (CH), 42.82 (CH), 38.13 (CH_2), 35.59 (CH_2), 31.81 (CH_2), 29.63 (CH_2), 29.44 (CH_2), 29.19 (CH_2), 24.37 (CH_2), 22.62 (CH_2), 21.66 (CH_3), 14.09 (CH_3); LRMS *m/z* (rel int) 450 (M^+, 2), 175 (100); HRMS (EI) calcd for $C_{24}H_{34}O_6S$ 450.2076, found 450.2071.

General procedure for the reaction of 12a,b and 14a–c with potassium hydride in dry THF. Formation of trioxa-cages 16a–e. To a solution of **12b** (0.090 g, 0.20 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 destroy the unreacted KH. After addition of saturated NH_4Cl (10 mL) and 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 diacetal trioxa-cage compound **16b** in 86% yield. Compounds **16a** and **16c–e** have been prepared with a different method.[16a]

4,6-Di-*n*-butyl-3,5,7-trioxapentacyclo[7.2.1.0^{2,8}.0^{4,11}.0^{6,10}]-dodecane 16b. White solid; mp 116–117°C; IR ($CHCl_3$)

2990, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (brs, 2H), 2.79 (brs, 2H), 2.68 (brs, 2H), 1.88–1.75 (m, 6H), 1.46–1.31 (m, 8H), 0.91 (d, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.56 (2C), 79.74 (2CH), 53.44 (2CH), 46.93 (2CH), 35.01 ($2CH_2$), 31.37 (CH_2), 26.42 ($2CH_2$), 22.54 ($2CH_2$), 13.66 ($2CH_3$); LRMS *m*/*z* (rel int) 278 (M^+, 20), 85 (100); HRMS (EI) calcd for $C_{17}H_{26}O_3$ 278.3950, found 278.3955; Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.33; H, 9.42. Found: C, 73.24; H, 9.48.

Reaction of compounds 20a,b with dimethyldioxirane. Followed by treatment with dilute HCl. The same reaction conditions as for the reaction of **3a**–**e** with 1 equiv. of dimethyldioxirane at −78°C, followed by treatment with dilute HCl, were applied for the reaction of compounds **20a**,**b** with dimethyldioxirane to give the same product **8c** in 85% yield. No detectable amount of the other regioisomers **21a** or **21b** or the monocyclization products **22** and **23** was obtained.

Reaction of compound 24a with 1 equiv. of dimethyldioxirane. The same reaction conditions and procedure as for the reaction of **3a**–**e** with 1 equiv. of dimethyldioxirane at −78°C, followed by treatment with dilute HCl, were applied for the reaction of compound **24a** with dimethyldioxirane to give the lactol **25a** in 84% yield.

5-Methyl-3β,9β-dihydroxy-4,12-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}]dodecane 25a. White solid; mp 166–170°C; IR ($CHCl_3$) 3600–3400, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.58 (brs, 1H), 3.91 (d, J=3.9 Hz, 1H), 3.74 (d, J=4.8 Hz, 1H), 3.54 (brs, 1H), 2.74–2.60 (m, 2H), 2.36–2.28 (m, 2H), 2.08–1.92 (m, 2H), 1.78–1.62 (m, 2H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 117.50 (C), 102.55 (CH), 83.82 (CH), 70.62 (CH), 48.07 (CH), 46.41 (CH), 36.76 (CH), 31.55 (CH), 25.49 (CH_3), 17.88 (CH_2), 14.85 (CH_2); LRMS *m*/*z* (rel int) 212 (M^+, 6.5), 166 (100); HRMS (EI) calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1041; Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 62.18; H, 7.66.

Reaction of compound 24a with 3 equiv. of dimethyldioxirane. The same reaction conditions and procedure as for the reaction of **3c**–**e** with 3 equiv. of dimethyldioxirane at −78°C, followed by treatment with dilute HCl, were applied for the reaction of compound **24a** to give the lactone **27** in 80% yield.

5-Methyl-9β-hydroxy-3-oxo-4,11-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}]dodecane 27. White solid; mp 118–121°C; IR ($CHCl_3$) 3600–3400, 1775, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (d, J=5.4 Hz, 1H), 3.87 (d, J=4.2 Hz, 1H), 2.80–2.68 (m, 2H), 2.50–2.36 (m, 2H), 2.21–2.00 (m, 2H), 1.80–1.64 (m, 3H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 177.90 (CO), 116.04 (C), 85.01 (CH), 71.00 (CH), 45.56 (CH), 42.74 (CH), 35.01 (CH), 32.77 (CH), 23.62 (CH_3), 17.24 (CH_2), 14.50 (CH_2); LRMS *m*/*z* (rel int) 210 (M^+, 7.6), 166 (100); HRMS (EI) calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0897.

Tosylation of compound 27. The same reaction conditions and procedure as for the tosylation of compounds **4a**,**b** and **8a**–**c** were applied for the tosylation of **27** to give the tosylate **28** in 92% yield.

5-Methyl-9β-tosyl-3-oxo-4,12-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}]-dodecane 28. Highly viscous oil; IR ($CHCl_3$) 1775, 1610, 1380, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=8.4 Hz, 2H), 7.36 (d, J=8.4 Hz, 2H), 4.34 (d, J=4.2 Hz, 1H), 4.05 (d, J=5.1 Hz, 1H), 2.74–2.67 (m, 2H), 2.45 (s, 3H), 2.46–2.38 (m, 2H), 2.02–1.70 (m, 4H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 176.36 (CO), 145.30 (C), 133.00 (C), 130.12 (2CH), 127.90 (2CH), 115.87 (C), 82.13 (CH), 79.65 (CH), 45.13 (CH), 42.15 (CH), 34.55 (CH), 30.88 (CH), 23.30 (CH_3), 21.67 (CH_3), 17.82 (CH_2), 14.21 (CH_2); LRMS *m*/*z* (rel int) 364 (M^+, 2), 166 (100); HRMS (EI) calcd for $C_{18}H_{20}O_6S$ 364.0981, found 364.0989.

Reaction of compound 28 with sodium borohydride in methanol. The same reaction conditions and procedure as for the reduction of **13a**–**c** were applied for the reduction of **28** to give the hemiacetal **29a** in 82% yield.

5-Methyl-3β-hydroxy-9β-tosyl-4,12-dioxatetracyclo[5.2.1.1^{5,8}.0^{2,6}]dodecane 29a. Highly viscous oil; IR ($CHCl_3$) 3600–3400, 1610, 1380, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 5.31 (s, 1H), 4.59 (d, J=4.8 Hz, 1H), 3.80 (d, J=4.8 Hz, 1H), 2.65–2.60 (m, 1H), 2.45 (s, 3H), 2.35–2.28 (m, 2H), 2.14 (brs, 1H), 2.00–1.88 (m, 1H), 1.78–1.64 (m, 4H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 144.86 (C), 133.79 (C), 130.06 (2CH), 127.67 (2CH), 117.68 (C), 102.15 (CH), 81.17 (CH), 80.67 (CH), 47.89 (CH), 46.03 (CH), 36.41 (CH), 30.41 (CH), 25.37 (CH_3), 21.64 (CH_3), 18.35 (CH_2), 14.56 (CH_2); LRMS *m*/*z* (rel int) 366 (M^+, 5), 166 (100); HRMS (EI) calcd for $C_{18}H_{22}O_6S$ 366.1137, found 366.1128.

Preparation of compound 29b from 24b. The same reaction conditions and procedure as for the reaction of **3a**–**e** with 1 equiv. of dimethyldioxirane were applied for the reaction of **24b** with dimethyldioxirane to give the crude product **25b**, which was run for the tosylation without purification. The same reaction conditions and procedure as for the tosylation of **27** were applied for the reaction of the crude compound **25b** to give compound **29b** in 68% overall yield.

3α,5-Dimethyl-3β-hydroxy-9β-tosyl-4,12-dioxatetracyclo-[5.2.1.1^{5,8}.0^{2,6}]dodecane 29b. Highly viscous oil; IR ($CHCl_3$) 3600–3400, 1610, 1380, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J=8.4 Hz, 2H), 7.34 (d, J=8.4 Hz, 2H), 4.67 (d, J=4.8 Hz, 1H), 3.82 (d, J=4.5 Hz, 1H), 2.82–2.79 (m, 1H), 2.44 (s, 3H), 2.32–2.15 (m, 5H), 2.08–1.99 (m, 2H), 1.69 (brs, 1H), 1.50 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 144.85 (C), 133.71 (C), 129.94 (2CH), 127.71 (2CH), 116.71 (C), 106.50 (C), 81.03 (CH), 80.95 (CH), 49.52 (CH), 48.04 (CH), 36.64 (CH), 29.37 (CH), 25.92 (CH_3), 24.23 (CH_3), 21.65 (CH_3), 18.43 (CH_2), 14.45 (CH_2); LRMS *m*/*z* (rel int) 380 (M^+, 5), 226 (100); HRMS (EI) calcd for $C_{19}H_{24}O_6S$ 380.1294, found 380.1299.

General procedure for the reaction of compounds 29a,b with potassium hydride. Formation of diacetal trioxa-cages 30a,b. The same reaction conditions and procedure as for the synthesis of the trioxa-cages **16a**–**e** were applied for the synthesis of the diacetal trioxa-cages **30a**,**b** in 80–82% yields.

4-Methyl-3,5,7-trioxapentacyclo[7.2.2.0^{2,8}.0^{4,11}.0^{6,10}]tridecane 30a. Highly viscous oil; IR ($CHCl_3$) 2980, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (d, J=3.9 Hz, 1H), 4.16–4.11 (m, 2H), 2.66–2.61 (m, 1H), 2.26–2.08 (m, 3H), 1.73–1.66 (m, 4H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 116.60 (C), 107.86 (CH), 78.31 (CH), 77.96 (CH), 46.44 (CH), 44.37 (CH), 36.94 (CH), 36.27 (CH), 21.84 (CH_3), 15.73 (CH_2), 15.58 (CH_2); LRMS *m*/*z* (rel int) 194 (M^+, 10), 95 (100); HRMS (EI) calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0949; Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.01; H, 7.27. Found: C, 68.10; H, 7.30.

4,6-Dimethyl-3,5,7-trioxapentacyclo[7.2.2.0^{2,8}.0^{4,11}.0^{6,10}]-tridecane 30b. Highly viscous oil; IR ($CHCl_3$) 2980, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (brs, 2H), 2.35 (brs, 2H), 2.14 (brs, 2H), 1.70–1.64 (m, 4H), 1.60 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 115.73 (2C), 78.54 (2CH), 48.19 (2CH), 36.49 (2CH), 22.03 ($2CH_3$), 15.72 ($2CH_2$); LRMS *m*/*z* (rel int) 208 (M^+, 6), 123 (100); HRMS (EI) calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1092; Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.19; H, 7.75. Found: C, 69.27; H, 7.80.

General procedure for the reaction of 24a,b with iodine in the presence of KI in aqueous THF. To a solution of **24a** (0.36 g, 2.0 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 (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 starting compound **24a**. No detectable amount of the sequential cyclization product **31a** was obtained. In the case of **24b**, the same result was observed.

Acknowledgements

We thank the National Science Council of the Republic of China for financial support (Grant No. NSC86-2113-M009-001).

References

1. For review, see: (a) Eaton, P. E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1421. (b) Griffin, G. W.; Marchand, A. P. *Chem. Rev.* **1989**, *89*, 997. (c) Marchand, A. P. *Chem. Rev.* **1989**, *89*, 1011. (d) Paquett, L. A. *Chem. Rev.* **1989**, *89*, 1051. (e) Klunder, A. J. H.; Zwanenburg, B. *Chem. Rev.* **1989**, *89*, 1035. (f) Osawa, E.; Yonemitsu, O. *Carbocyclic Cage Compounds;* VCH: New York, 1992. (g) Olah, G. A. *Cage Hydrocarbons*; Wiley: New York, 1990.

2. (a) Meta, G.; Nair, M. S. *J. Chem. Soc., Chem. Commun.* **1983**, 439. (b) Shen, K. W. *J. Am. Chem. Soc.* **1971**, *93*, 3064. (c) Allred, E. L.; Beck, B. R. *Tetrahedron Lett.* **1974**, 437. (d) Barborak, J. C.; Khoury, D.; Maier, W. F.; Schleyer, P. V. R.; Smith, E. C.; Smith Jr., W. F.; Wyrick, C. *J. Org. Chem.* **1974**, *44*, 4761.

3. (a) Prinzbach, H.; Klaus, M. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 276. (b) Marchand, A. P.; Reddy, G. M.; Watson, W. H.; Kashyap, R. *Tetrahedron* **1990**, *46*, 3409.

4. (a) Sasaki, T.; Eguchi, S.; Kiriyama, T.; Hiroaki, O. *Tetrahedron* **1974**, *30*, 2707. (b) Singh, P. *J. Org. Chem.* **1979**, *44*, 843. (c) Coxon, J. M.; Fong, S. T.; McDonald, D. Q.; O'Connell, M. J.; Steel, P. J. *Tetrahedron Lett.* **1991**, *32*, 7115. (d) Klaus, R. O.; Tobler, H.; Ganter, C. *Helv. Chim. Acta* **1974**, *57*, 2517. (e) Ganter, C.; Portmann, R. E. *Helv. Chim. Acta* **1971**, *54*, 2069. (f) Stetter, H.; Meissner, H. J.; Last, W. D. *Chem. Ber.* **1968**, *101*, 2889. (g) Chow, T. J.; Hon, Y. S.; Jen, C. C.; Liu, S. S.; Chern, J. H.; Lin. K. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1095. (h) Speckamp, W. N.; Dijkink, J.; Huisman, H. O. *J. Chem. Soc., Chem. Commun.* **1970**, 197. (i) Deslongchamps, P.; Ruest, L.; Dube, S. *Can. J. Chem.* **1975**, *53*, 3613.

5. Suri, S. C. *J. Org. Chem.* **1993**, *58*, 4153.

6. (a) Metha, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543. (b) Metha, G.; Nair, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 7519. (c) Marchand, A. P.; LaRoe, W. D.; Sharma, G. V. M.; Suri, S. C.; Reddy, D. S. *J. Org. Chem.* **1986**, *51*, 1622. (d) Fessner, W. D.; Prinzbach, H. *Tetrahedron* **1986**, *42*, 1797. (e) Smith, E. C.; Barborak, J. C. *J. Org. Chem.* **1976**, *41*, 1433.

7. (a) Marchand, A. P.; Chou, T. C. *Tetrahedron* **1975**, *31*, 2655. (b) Metha, G.; Reddy, K. R. *J. Org. Chem.* **1987**, *52*, 460.

8. (a) Metha, G.; Rao, H. S. P. *J. Chem. Soc., Chem. Commun.* **1986**, 472. (b) Metha, G.; Rao, H. S. P.; Reddy, K. R. *J. Chem. Soc., Chem. Commun.* **1987**, 78.

9. Wu, H. J.; Chao, C. S.; Lin, C. C. *J. Org. Chem.* **1998**, *63*, 7687.

10. (a) Wu, C. Y.; Lin, C. C.; Lai, M. C.; Wu, H. J. *J. Chin. Chem. Soc.* **1996**, *43*, 187. (b) Wu, H. J.; Wu, C. Y.; Lin, C. C. *Chin. Chem. Lett.* **1996**, *7*, 15.

11. (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) Wu, H. J.; Chern, J. H.; Wu, C. Y. *Tetrahedron* **1997**, *53*, 2401. (d) Wu, H. J.; Chern, J. H. *Tetrahedron* **1997**, *53*, 17 653. (e) Lin, C. C.; Wu, H. J. *Tetrahedron Lett.* **1995**, *36*, 9353. (f) Wu, H. J.; Huang, F. J.; Lin, C. C. *J. Chem. Soc., Chem. Commun.* **1991**, 770. (g) Lin, C. C.; Wu, H. J. *J. Chin. Chem. Soc.* **1995**, *42*, 815. (h) Lin, C. C.; Huang, F. J.; Lin, J. C.; Wu, H. J. *J. Chin. Chem. Soc.* **1996**, *43*, 177. (i) Lin, R. L.; Wu, C. Y.; Chern, J. H.; Wu, H. J. *J. Chin. Chem. Soc.* **1996**, *43*, 289. (j) Chern, J. H.; Wu, H. J.; Wang, S. L.; Liao, F. L. *J. Chin. Chem. Soc.* **1998**, *45*, 139.

12. Lin, C. C.; Wu, H. J. *Synthesis* **1996**, 715.

13. (a) Wu, H. J.; Wu, C. Y. *Tetrahedron Lett.* **1997**, *38*, 2493. (b) Wu, H. J.; Wu, C. Y. *J. Org. Chem.* **1999**, *64*, 1576. (c) Mehta, G.; Vidya, R. *Tetrahedron Lett.* **1997**, *38*, 4173.

14. (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. (c) Wu, H. J.; Chern, J. H. *Tetrahedron Lett.* **1997**, *38*, 2887. (d) Chern, J. H.; Wu, H. J. *J. Chin. Chem. Soc.* **1997**, *44*, 71. (e) Chern, J. H.; Wu, H. J. *Tetrahedron* **1998**, *54*, 5967.

15. (a) Lin, H. C.; Wu, C. Y.; Wu, H. J. *J. Chin. Chem. Soc.* **1997**, *44*, 609. (b) Yen, C. H.; Tsai, S. H.; Wu, H. J. *J. Chin. Chem. Soc.* **1998**, *45*, 799.

16. (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. Chin. Chem. Soc.* **1996**, *43*, 445.
17. Murthy, Y. V. S. N.; Pillai, C. N. *Synth. Commun.* **1996**, *26*, 2363.
18. (a) Williams, P. D.; LeGoff, E. *J. Org. Chem.* **1981**, *46*, 4143. (b) Williams, P. D.; LeGoff, E. *Tetrahedron Lett.* **1985**, *26*, 1367.
19. (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.
20. Curci, R.; D'Accolti, L.; Fiorentino, M.; Fusco, C.; Adam, W.; Gonzalez-Nunez, M. E.; Mello, R. *Tetrahedron Lett.* **1992**, *33*, 4225.