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Synthesis of 3,11-Dioxatetracyclo[6.3.0.0^{2,6}.0^{5,9}]undecanes and 3,5,7-Trioxapentacyclo[7.2.1.0^{2,8}.0^{4,11}.0^{6,10}]dodecane

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The synthesis of 3,11-dioxatetracyclo[6.3.0.0^{2,6}.0^{5,9}]undecanes has been accomplished from furans in a short sequence by iodine-induced cyclization reaction. The application of iodine-induced cyclization reaction for the synthesis of 3,5,7-trioxapentacyclo[7.2.1.0^{2,8}.0^{4,11}.0^{6,10}]dodecane itself was also demonstrated.

INTRODUCTION

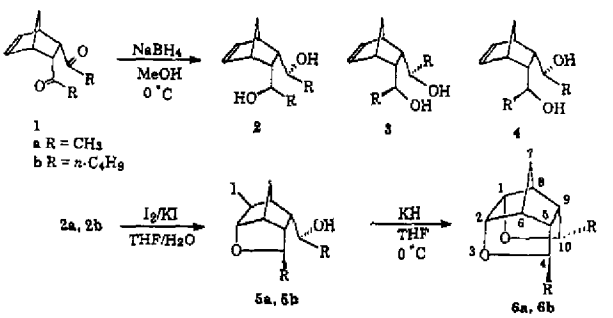
Considerable attention has been paid to the synthesis and chemistry of polycyclic cage compounds,[1] but much less to the heterocyclic analogs. However, there are some reports of the chemistry[2] and synthesis[3-8] of oxa-cage compounds. Heterocyclic cage compounds of this class are synthesized with intramolecular alkene-oxirane (2σ-2π) photocycloaddition,[3] transannular cyclization of suitable compounds,[4] tandem cyclization,[5] dehydration of diols having the proper stereochemistry,[6] base-promoted rearrangement,[7] and intramolecular etherification of the alkene bond with an organoselenium reagent.[8]

Recently, we developed new methods 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] We also investigated the chemical nature of the acetal group of tetraoxa-cages and discovered a novel hydride rearrangement and a one-pot conversion from oxa-cages to aza-cages.[14] As part of a program that involves the synthesis, chemistry, and applications of new heterocyclic cages, we report here the synthesis of dioxa-cages and the unsubstituted (parent) compound of diacetal trioxa-cages by iodine-induced cyclization reaction.

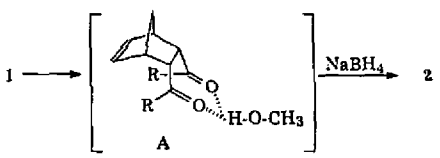
RESULTS AND DISCUSSION

Reduction of the bis-*endo*-diacylnorbornenes **1a** and **1b**[9a] with sodium borohydride in methanol at 0 °C gave the diols **2a** and **2b** as major product in 80-82% yields. The other two stereoisomers **3** and **4** were obtained in amounts too small to be obtained in a pure compound. The stereochemistry of the hydroxy groups of **2a** and **2b** was difficult to assign at this stage and was determined by the following chemical transformation. Treatment of **2a** and **2b** with iodine in the presence of potassium iodide in aqueous THF at 0 °C for 6 h gave the iodo-alcohols **5a** and **5b** in 80-83% yields (Scheme I). Reaction of **5a** and **5b** with KH in dry THF at 0 °C for 3 h gave the dioxa-cages **6a** and **6b** in 82-85% yields. The stereochemistry of the alkyl groups of **6** was determined on the basis of NOE experiments of **6a**. Irradiating the methyl protons of **6a** (δ 1.08) gives 2.3% enhancement for the C_4 and C_{10} proton absorptions, 1.7% enhancement for the C_6 and C_8 proton absorptions, and 1.6% enhancement for the C_5 and C_9 proton absorptions. Irradiating the methine protons on C_4 and C_{10} of **6a** (δ 4.40) gives 5.3% enhancement for the methyl proton absorptions and 2.4% enhancement for the C_5 and C_9 proton absorptions and no enhancement for the C_6 and C_8 proton absorptions.

Scheme I

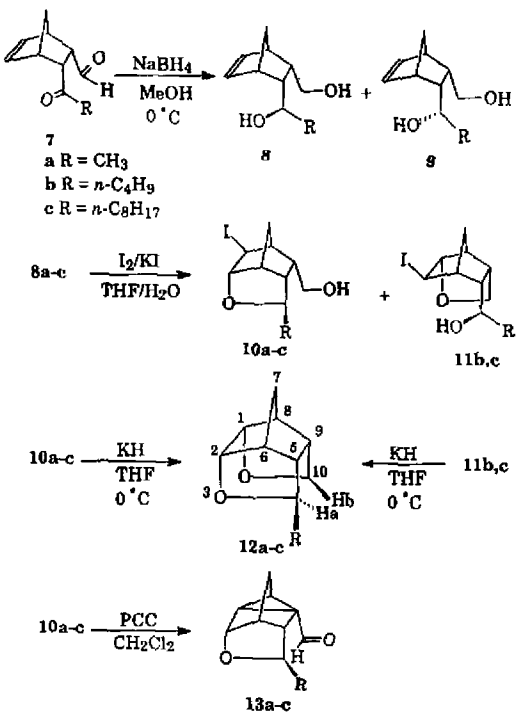


To account for the high stereoselectivity of the reduction reaction of **1a** and **1b** with $NaBH_4$ in MeOH, we propose that compounds **1a** and **1b** may adopt conformation **A** in the protic solvent by virtue of double hydrogen bonding. Nucleophilic attack of $NaBH_4$ to the carbonyl groups of **A** from the sterically less hindered outside face gives the major products **2**.



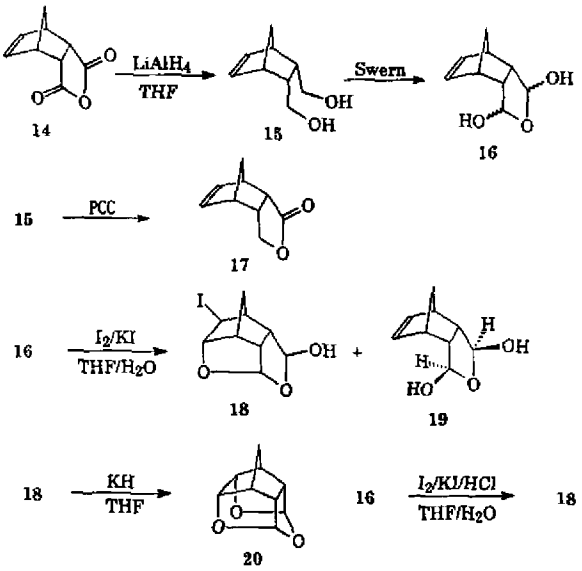
Reduction of compounds **7a-c**[11b] with sodium borohydride in methanol at 0 °C gave the diols **8a-c** in 75-78% yields and the other stereoisomers **9a-c** in 12-15% yields. The stereochemistry of the hydroxy group of **8** was determined by the following chemical transformation. Treatment of **8a-c** with iodine in the presence of KI in aqueous THF at 0 °C for 6 h gave compounds **10a-c** and **11b-c** in ratios of 3-4:1 in 90% yields (Scheme II). Reaction of **10a-c** with KH in dry THF at 0 °C gave the dioxa-cages **12a-c** in 83-86% yields. Reaction of **11b** and **11c** with KH under the same reaction conditions gave **12b** and **12c**. To differentiate compounds **10** and **11**, compounds **10a-c** were oxidized with PCC (pyridinium chlorochromate) to give the aldehydes **13a-c**. The stereochemistry of the alkyl group of the dioxa-cages **12a-c** was determined on the basis of NOE experiments of **12a**. Irradiating the methine proton H_a on C_4 of **12a** (δ 4.32) gives 8.0% enhancement for the proton H_b on C_{10}, 1.6% enhancement for the proton on C_5, and 5.3% enhancement for the methyl proton absorptions. Thus, we have developed a general method for the synthesis of dioxa-cages.

Scheme II



We have also applied the iodine-induced cyclization reaction for the synthesis of the unsubstituted (parent) compound of diacetal trioxa-cages. Reduction of maleic anhydride-cyclopentadiene adduct **14** with $LiAlH_4$ in dry THF gave the diol **15**. Swern oxidation[15] of **15** gave the dihemiacetal **16**, which is a mixture of stereoisomers. On the other hand, oxidation of **15** with pyridinium chlorochromate (PCC) gave the lactone **17**. Treatment of the stereoisomeric mixture **16** with iodine in the presence of potassium iodide in aqueous THF gave the iodo-hemiacetal **18** and left the unreacted dihemiacetal **19** in a pure isomer. The stereochemistry of the hydroxy groups of the dihemiacetal **19** was determined on the basis of NOE experiments. Irradiating the alkene protons (δ 6.10) gives 3.8% enhancement for the hemiacetal proton absorptions and 4.0% enhancement for the bridgehead proton absorptions. Irradiating the hemiacetal protons (δ 4.97) gives 4.7% enhancement for the alkene proton absorptions and 4.8% enhancement for the bridgehead proton absorptions. Reaction of **18** with KH in dry THF at 0 °C gave the unsubstituted (parent) compound **20** (Scheme III). Treatment of the mixture **16** with iodine in the presence of KI and HCl in aqueous THF at 25 °C gave **18** quantitatively, and no detectable amount of **19** was left. Thus, the mixture **16** can be converted to the trioxa-cage **20** in a high yield.

Scheme III



CONCLUSION

We have accomplished the general synthesis of the title compounds by iodine-induced cyclization reaction. The stereochemistry of the alkyl group of the dioxa-cages **6** and **12** was determined by NOE experiments. We have also applied the iodine-induced cyclization reaction for the synthesis of the unsubstituted (parent) compound **20** of diacetal trioxa-cages.

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. ^1H NMR spectra were determined at 300 MHz, and ^{13}C NMR were determined at 75 MHz on Fourier transform spectrometers. Chemical shifts were 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. For thin-layer chromatography (TLC) analysis, precoated TLC plates (Kieselgel 60 F_{254}) were used, and column chromatography was done 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 Reduction of Compounds 1a and 1b with Sodium Borohydride

To a solution of compound **1a**[21a] (0.50 g, 2.8 mmol) in methanol (10 mL) was added sodium borohydride (0.11 g, 2.8 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The solvent was evaporated, and saturated NH_4Cl (20 mL) was added. After exaction with ether (5 × 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 diol **2a** (0.40 g, 80%) and a mixture of stereoisomers (0.05 g, 10%).

2,3-Bis-*endo*-(1'β,1'β-diethanolyl)bicyclo[2.2.1]-5-heptene 2a

White solid; mp 148-149 °C; IR ($CHCl_3$) 3500-3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (brs, 2H), 4.17 (q, J = 6.6 Hz, 2H), 3.79 (brs, 2H), 2.98 (brs, 2H), 2.27 (brs, 2H), 1.28 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 134.06 (2CH), 66.07 (2CH), 50.44 (2CH), 50.30 (CH_2), 43.46 (2CH), 23.32 ($2CH_3$); MS *m/z* (rel int) 182 (M^+, 5), 131 (100).

2,3-Bis-*endo*-(1'β,1'β-di-*n*-pentanolyl)bicyclo[2.2.1]-5-heptene 2b

White solid; mp 121-122 °C; yield 82%; IR ($CHCl_3$) 3500-3300, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (brs, 2H), 3.93-3.89 (m, 2H), 2.94 (brs, 2H), 2.36 (brs, 2H), 1.61-1.25 (m, 14H), 0.94-0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 134.42 (2CH), 70.49 (2CH), 50.82 (CH_2), 49.25 (2CH), 43.89 (2CH), 37.38 ($2CH_2$), 28.86 ($2CH_2$), 22.71 ($2CH_2$), 14.05 ($2CH_3$); MS *m/z* (rel int) 266 (M^+, 3), 215 (100).

General Procedure for the Iodine-Induced Cyclization of 2a,b

To a solution of **2a** (0.55 g, 3.1 mmol) in THF (4 mL) and H_2O (20 mL) were added I_2 (1.55 g, 6.1 mmol) and KI (1.0 g, 6.0 mmol) at 0 °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. After 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 iodo-alcohol **5a** (0.76 g, 80%).

2β-Ethanolyl-4β-methyl-9-*anti*-iodo-5-oxatricyclo-[4.2.1.0^{3,7}]nonane 5a

Pale yellow oil; IR ($CHCl_3$) 3500-3300, 2990, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (d, J = 4.8 Hz, 1H), 4.00 (q, J = 6.3 Hz, 1H), 3.93 (d, J = 2.4 Hz, 1H), 3.81-3.75 (m, 1H), 2.85 (brs, 1H), 2.66 (brs, 1H), 2.32 (s, 1H), 2.18 (d, J = 10.8 Hz, 1H), 2.11-2.05 (m, 1H), 1.95-1.85 (m, 1H), 1.68 (d, J = 10.8 Hz, 1H), 1.25 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 90.02 (CH), 74.64 (CH), 65.04 (CH), 51.33 (CH), 46.60 (CH), 46.36 (CH), 43.99 (CH), 36.34 (CH_2), 33.74 (CH), 22.99 (CH_3), 22.61 (CH_3); MS *m/z* (rel int) 308 (M^+, 5), 181 (100); HRMS (EI) calcd for $C_{11}H_{17}O_2I$ 308.0273, found 308.0277.

2β-Pentanolyl-4β-*n*-butyl-9-*anti*-iodo-5-oxatricyclo-[4.2.1.0^{3,7}]nonane 5b

Pale yellow oil; yield 83%; IR ($CHCl_3$) 3500-3300, 2990, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (d, J = 4.8 Hz, 1H), 3.93 (d, J = 2.4 Hz, 1H), 3.72-3.68 (m, 1H), 3.60-3.50 (m, 1H), 2.80-2.71 (m, 1H), 2.65 (brs, 1H), 2.18 (d, J = 10.8 Hz, 1H), 2.14-2.08 (m, 1H), 1.99-1.80 (m, 2H), 1.78 (d, J = 10.8 Hz, 1H), 1.61-1.49 (m, 2H), 1.35-1.26 (m, 10H), 0.95-0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 89.87 (CH), 78.92 (CH), 69.21 (CH), 49.76 (CH), 46.86 (CH), 46.41 (CH), 42.45 (CH), 36.37 (CH_2), 36.27 (CH_2), 33.78 (CH), 28.44 (CH_2), 27.90 (CH_2), 22.64 ($2CH_2$), 22.53 (CH_2), 14.02 (CH_3), 13.96 (CH_3); MS *m/z* (rel int) 392 (M^+, 10), 265 (100); HRMS (EI) calcd for $C_{17}H_{29}O_2I$ 392.1212, found 392.1217.

General Procedure for the Synthesis of Dioxa-Cages 6a and 6b

To a solution of **5a** (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 destroy 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 dioxa-cage compound **6a** (0.15 g, 85%).

4β,10β-Di-methyl-3,11-dioxatetracyclo[6.3.0.0^{2,6}.0^{5,9}]-undecane 6a

Pale yellow oil; IR ($CHCl_3$) 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (q, J = 6.3 Hz, 2H), 3.90 (d, J = 2.1 Hz, 2H), 2.71 (brs, 2H), 2.10 (brs, 2H), 1.57 (d, J = 11.7 Hz, 1H), 1.48 (d, J = 11.7 Hz, 1H), 1.08 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 78.01 (2CH), 75.63 (2CH), 47.17 (2CH), 43.23 (2CH), 24.50 (CH_2), 22.71 ($2CH_3$); MS *m/z* (rel int) 180 (M^+, 6), 83 (100); HRMS (EI) calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1154.

4β,10β-Di-*n*-butyl-3,11-dioxatetracyclo[6.3.0.0^{2,6}.0^{5,9}]-undecane 6b

Pale yellow oil; yield 82%; IR ($CHCl_3$) 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16-4.12 (m, 2H), 3.88 (brs, 2H), 2.64 (brs, 2H), 2.14 (brs, 2H), 1.70 (brs, 2H), 1.54-1.26 (m, 12H), 0.92-0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 79.99 (2CH), 77.77 (2CH), 45.74 (2CH), 43.51 (2CH), 36.67 ($2CH_2$), 28.70 ($2CH_2$), 24.66 (CH_2), 22.73 ($2CH_2$), 14.05 ($2CH_3$); MS *m/z* (rel int) 264 (M^+, 10), 207 (100); HRMS (EI) calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2084.

General Procedure for the Reduction of Compounds 7a-c with Sodium Borohydride

The same reaction conditions and procedure as for the reduction of **1a** and **1b** were applied for the reduction of **7a-c** to give the diols **8a-c** as major products and **9a-c** as minor products.

2-*endo*-(1'β-ethanolyl)-3-*endo*-(methanolyl)bicyclo[2.2.1]-5-heptene 8a

White waxy solid; mp 114-115 °C; yield 76%; IR ($CHCl_3$) 3500-3300, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27-6.19 (m, 2H), 3.73-3.56 (m, 2H), 3.44 (dd, J = 10.8 Hz, J = 8.4 Hz, 1H), 3.05 (brs, 1H), 2.99 (brs, 1H), 2.44-2.38 (m, 1H), 2.28-2.21 (m, 1H), 1.71 (brs, 2H), 1.47 (d, J = 8.1 Hz, 1H), 1.30 (d, J = 8.1 Hz, 1H), 1.26 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 135.43 (CH), 135.30 (CH), 67.46 (CH), 62.95 (CH_2), 50.47 (CH), 49.15 (CH_2), 45.56 (CH), 45.16 (CH), 44.82 (CH), 24.38 (CH_3); MS *m/z* (rel int) 168 (M^+, 1), 117 (100).

2-*endo*-(1'β-*n*-pentanolyl)-3-*endo*-(methanolyl)bicyclo-[2.2.1]-5-heptene 8b

White waxy solid; mp 85-86 °C; yield 77%; IR ($CHCl_3$) 3500-3300, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26-6.19 (m, 2H), 3.71-3.66 (m, 1H), 3.48-3.35 (m, 2H), 3.02-2.99 (m, 2H), 2.44-2.40 (m, 1H), 2.32-2.26 (m, 1H), 1.74 (brs, 2H), 1.60-1.21 (m, 8H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 135.43 (CH), 135.39 (CH), 71.47 (CH), 63.10 (CH_2), 49.31 (CH_2), 48.87 (CH), 45.52 (CH), 45.10 (CH), 45.02 (CH), 38.15 (CH_2), 28.59 (CH_2), 22.69 (CH_2), 14.08 (CH_3); MS *m/z* (rel int) 210 (M^+, 3), 159 (100).

2-*endo*-(1'β-*n*-nonanolyl)-3-*endo*-(methanolyl)bicyclo-[2.2.1]-5-heptene 8c

White waxy solid; mp 75-76 °C; yield 78%; IR ($CHCl_3$) 3500-3300, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24-6.20 (m, 2H), 3.69-3.65 (m, 1H), 3.49-3.34 (m, 2H), 3.02-2.98 (m, 2H), 2.45-2.40 (m, 1H), 2.32-2.25 (m, 1H), 1.90 (brs, 2H), 1.60-1.20 (m, 16H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 135.32 (2CH), 71.39 (CH), 62.85 (CH_2), 49.18 (CH_2), 48.84 (CH), 45.48 (CH), 45.08 (CH), 44.91 (CH), 38.40 (CH_2), 31.81 (CH_2), 29.62 (CH_2), 29.57 (CH_2), 29.22 (CH_2), 26.39 (CH_2), 22.59 (CH_2), 14.03 (CH_3); MS *m/z* (rel int) 266 (M^+, 2), 215 (100).

General Procedure for the Iodine-Induced Cyclization of 8a-c

The same reaction conditions and procedure as for the iodine-induced cyclization of **2a** and **2b** were applied for the cyclization of **8a-c**. In the cases of **8b** and **8c**, the iodo-cages **10b** and **10c** were obtained as major products (75%) and **11b** and **11c** were obtained as minor products (15%). In the case of **8a**, the iodo-cage **10a** was obtained in 75% yield. The other isomer **11a** was obtained in an amount too small for taking spectra.

2-Methanolyl-4β-methyl-9-*anti*-iodo-5-oxatricyclo-[4.2.1.0^{3,7}]nonane 10a

Pale yellow oil; IR ($CHCl_3$) 3500-3300, 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76 (d, J = 5.1 Hz, 1H), 4.04 (q, J = 6.3 Hz, 1H), 3.92 (d, J = 2.1 Hz, 1H), 3.70-3.68 (m, 2H), 2.87 (brs, 1H), 2.49 (brs, 1H), 2.25-2.16 (m, 3H), 1.75 (d, J = 11.1 Hz, 1H), 1.24 (d, J = 11.1 Hz, 1H), 1.08 (d, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 89.35 (CH), 74.63 (CH), 59.91 (CH_2), 46.05 (2CH), 44.80 (CH), 43.76 (CH), 36.81 (CH_2), 33.65 (CH), 22.35 (CH_3). MS *m/z*

(rel int) 294 (M^+, 4), 79 (100); HRMS (EI) calcd for $C_{10}H_{15}O_2I$ 294.0116, found 294.0112.

2-Methanolyl-4β-*n*-butyl-9-*anti*-iodo-5-oxatricyclo-[4.2.1.0^{3,7}]nonane 10b

Pale yellow oil; yield 75%; IR ($CHCl_3$) 3500-3300, 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, J = 4.8 Hz, 1H), 3.84-3.71 (m, 4H), 2.79 (brs, 1H), 2.48 (brs, 1H), 2.24-2.18 (m, 3H), 1.73 (d, J = 11.1 Hz, 1H), 1.63 (brs, 1H), 1.36-1.24 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 89.36 (CH), 78.88 (CH), 60.48 (CH_2), 46.47 (CH), 46.20 (CH), 45.11 (CH), 42.41 (CH), 37.05 (CH_2), 36.20 (CH_2), 33.71 (CH), 28.49 (CH_2), 22.61 (CH_2), 14.04 (CH_3). MS *m/z* (rel int) 336 (M^+, 5), 231 (100); HRMS (EI) calcd for $C_{13}H_{21}O_2I$ 336.0586, found 336.0580.

2-Methanolyl-4β-*n*-octyl-9-*anti*-iodo-5-oxatricyclo-[4.2.1.0^{3,7}]nonane 10c

Pale yellow oil; yield 75%; IR ($CHCl_3$) 3500-3300, 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, J = 4.8 Hz, 1H), 3.85-3.69 (m, 4H), 2.78 (brs, 1H), 2.49 (s, 1H), 2.26-2.18 (m, 3H), 2.06 (s, 1H), 1.73 (d, J = 10.8 Hz, 1H), 1.34-1.21 (m, 14H), 0.85 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 89.33 (CH), 78.90 (CH), 60.30 (CH_2), 46.45 (CH), 46.16 (CH), 45.03 (CH), 42.39 (CH), 36.99 (CH_2), 36.49 (CH_2), 33.67 (CH), 31.79 (CH_2), 29.53 (CH_2), 29.50 (CH_2), 29.17 (CH_2), 26.29 (CH_2), 22.58 (CH_2), 14.06 (CH_3); MS *m/z* (rel int) 392 (M^+, 4), 287 (100); HRMS (EI) calcd for $C_{17}H_{29}O_2I$ 392.1212, found 392.1218.

2β-*n*-Pentanolyl-9-*anti*-iodo-5-oxatricyclo[4.2.1.0^{3,7}]-nonane 11b

Pale yellow oil; yield 15%; IR ($CHCl_3$) 3500-3300, 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (d, J = 4.8 Hz, 1H), 3.93 (d, J = 2.4 Hz, 1H), 3.65-3.48 (m, 3H), 2.72-2.63 (m, 2H), 2.39-2.33 (m, 1H), 2.18 (d, J = 11.1 Hz, 1H), 1.99-1.91 (m, 1H), 1.75-1.22 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 89.91 (CH), 69.15 (CH), 68.36 (CH_2), 48.85 (CH), 48.43 (CH), 46.00 (CH), 38.41 (CH), 36.70 (CH_2), 36.48 (CH_2), 33.81 (CH), 27.93 (CH_2), 22.70 (CH_2), 14.08 (CH_3); MS *m/z* (rel int) 336 (M^+, 7), 231 (100).

2β-*n*-Nonanolyl-9-*anti*-iodo-5-oxatricyclo[4.2.1.0^{3,7}]-nonane 11c

Pale yellow oil; yield 15%; IR ($CHCl_3$) 3500-3300, 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (d, J = 5.1 Hz, 1H), 3.93 (d, J = 2.4 Hz, 1H), 3.64-3.51 (m, 3H), 2.72-2.69 (m, 1H), 2.63 (s, 1H), 2.38-2.34 (m, 1H), 2.18 (d, J = 10.8 Hz, 1H), 2.01-1.94 (m, 1H), 1.73 (d, J = 11.1 Hz, 1H), 1.67 (s, 1H), 1.54-1.52 (m, 2H), 1.34-1.27 (m, 12H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 89.92 (CH), 69.16 (CH), 68.38 (CH_2), 48.86 (CH), 48.44 (CH), 46.02 (CH), 38.42 (CH), 36.78 (CH_2), 36.70 (CH_2), 33.81 (CH), 31.82 (CH_2), 29.62 (CH_2), 29.57 (CH_2), 29.22 (CH_2), 25.76 (CH_2), 22.63 (CH_2), 14.09 (CH_3); MS *m/z* (rel int) 392 (M^+, 5), 287 (100).

General Procedure for the Synthesis of Dioxa-cages 12a-c

The same reaction conditions and procedure as for the synthesis of dioxa-cages **6b** and **6c** were applied for the synthesis of dioxa-cages **12a-c** from **10a-c** and **11b** and **11c**.

4β-Methyl-3,11-dioxatetracyclo[6.3.0.0^{2,6}.0^{5,9}]undecane 12a

Pale yellow oil; yield 85%; IR ($CHCl_3$) 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (q, J = 6.3 Hz, 1H), 4.09 (d, J = 11.4 Hz, 1H), 3.93-3.91 (m, 2H), 3.77 (dd, J = 11.4 Hz, J = 3.9 Hz, 1H), 2.68 (brs, 1H), 2.59 (brs, 1H), 2.44-2.40 (m, 1H), 2.14-2.09 (m, 1H), 1.63 (d, J = 12.9 Hz, 1H), 1.49 (d, J = 12.9 Hz, 1H), 1.16 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 78.15 (CH), 77.72 (CH), 75.66 (CH), 69.09 (CH_2), 46.41 (CH), 45.41 (CH), 42.57 (CH), 41.87 (CH), 24.57 (CH_2), 22.80 (CH_3); MS *m/z* (rel int) 166 (M^+, 5), 71 (100); HRMS (EI) calcd for $C_{10}H_{14}O_2$ 166.0993, found 166.0997.

4β-*n*-Butyl-3,11-dioxatetracyclo[6.3.0.0^{2,6}.0^{5,9}]undecane 12b

Pale yellow oil; yield 83%; IR ($CHCl_3$) 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10-4.05 (m, 2H), 3.91-3.89 (m, 2H), 3.79-3.75 (m, 1H), 2.61-2.58 (m, 2H), 2.44-2.38 (m, 1H), 2.18-2.13 (m, 1H), 1.71-1.25 (m, 8H), 0.85 (t, J = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 79.96 (CH), 77.89 (CH), 77.78 (CH), 69.17 (CH_2), 45.40 (CH), 44.97 (CH), 42.90 (CH), 41.92 (CH), 36.76 (CH_2), 28.65 (CH_2), 24.68 (CH_2), 22.70 (CH_2), 14.04 (CH_3); MS *m/z* (rel int) 208 (M^+, 6), 151 (100); HRMS (EI) calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1468.

4β-*n*-octyl-3,11-dioxatetracyclo[6.3.0.0^{2,6}.0^{5,9}]undecane 12c

White waxy solid; mp 40-41 °C; yielel 86%; IR ($CHCl_3$) 2990, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10-4.05 (m, 2H), 3.90 (brs, 2H), 3.76 (dd, J = 11.4 Hz, J = 3.9 Hz, 1H), 2.61-2.58 (m, 2H), 2.44-2.38 (m, 1H), 2.17-2.13 (m, 1H), 1.62 (d, J = 11.4 Hz, 1H), 1.48 (d, J = 11.4 Hz,

1H), 1.40-1.24 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 79.89 (CH), 77.81 (CH), 77.70 (CH), 69.08 (CH_2), 45.32 (CH), 44.90 (CH), 42.83 (CH), 41.85 (CH), 37.00 (CH_2), 31.77 (CH_2), 29.57 (CH_2), 29.47 (CH_2), 29.15 (CH_2), 26.42 (CH_2), 24.59 (CH_2), 22.55 (CH_2), 14.00 (CH_3); MS *m/z* (rel int) 264 (M^+, 10), 152 (100); HRMS (EI) calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2083.

General Procedure for Oxidation of Compounds 10a-c with Pyridinium Chlorochromate (PCC)

To a solution of **10a** (0.38 g, 1.3 mmol) in dichloromethane (30 mL) were added PCC (0.57 g, 2.6 mmol) and Celite (2 g). The reaction mixture was stirred at room temperature for 4 h. Then, the reaction mixture was filtered through Celite. The solvent was evaporated, and the crude product was purified by column chromatography to give **13a** (0.17 g, 80%).

2-Formyl-4β-methyl-5-oxatetracyclo[4.2.1.0^{2,9}.0^{3,7}]-nonane 13a

Pale yellow oil; IR ($CHCl_3$) 2990, 1725, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 4.43-4.41 (m, 1H), 4.16 (q, J = 6.6 Hz, 1H), 2.50 (d, J = 2.1 Hz, 1H), 2.28-2.16 (m, 3H), 1.85-1.75 (m, 2H), 1.45 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.14 (CHO), 82.30 (CH), 74.91 (CH), 46.98 (CH), 41.23 (C), 38.38 (CH), 28.79 (CH_2), 28.03 (CH), 26.30 (CH), 21.48 (CH_3); MS *m/z* (rel int) 164 (M^+, 4), 91 (100); HRMS (EI) calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0832.

2-Formyl-4β-*n*-butyl-5-oxatetracyclo[4.2.1.0^{2,9}.0^{3,7}]-nonane 13b

Pale yellow oil; yield 84%; IR ($CHCl_3$) 2990, 1725, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 4.41 (s, 1H), 3.98-3.94 (m, 1H), 2.55 (d, J = 1.8 Hz, 1H), 2.23-2.16 (m, 3H), 1.84-1.74 (m, 2H), 1.41-1.25 (m, 6H), 0.90 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.19 (CHO), 82.19 (CH), 79.33 (CH), 45.85 (CH), 41.37 (C), 38.77 (CH), 35.63 (CH_2), 28.93 (CH_2), 28.20 (CH), 27.82 (CH_2), 26.27 (CH), 22.63 (CH_2), 13.98 (CH_3); MS *m/z* (rel int) 206 (M^+, 6), 91 (100); HRMS (EI) calcd for $C_{13}H_{18}O_2$ 206.1306, found 206.1309.

2-Formyl-4β-*n*-octyl-5-oxatetracyclo[4.2.1.0^{2,9}.0^{3,7}]-nonane 13c

Pale yellow oil; yield 85%; IR ($CHCl_3$) 2990, 1725, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 4.42-4.40 (m, 1H), 3.97-3.95 (m, 1H), 2.54 (d, J = 2.1 Hz, 1H), 2.23-2.16 (m, 3H), 1.84-1.74 (m, 3H), 1.40-1.27 (m, 13H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.19 (CHO), 82.19 (CH), 79.35 (CH), 45.89 (CH), 41.36 (C), 38.79 (CH), 35.97 (CH_2), 31.82 (CH_2), 29.58 (CH_2), 29.49 (CH_2), 29.20 (CH_2), 28.94 (CH_2), 28.21 (CH), 26.28 (CH), 25.67 (CH_2), 22.61 (CH_2), 14.07 (CH_3); MS *m/z* (rel int) 262 (M^+, 5), 91 (100); HRMS (EI) calcd for $C_{17}H_{26}O_2$ 262.1932, found 262.1938.

Swern Oxidation[15] of Compound 15

A mixture of DMSO (2.5 mL, 35 mmol) and CH_2Cl_2 (6 mL) was added to a solution of oxalyl chloride (2.6 g, 20 mmol) in 20 mL of CH_2Cl_2 at -55 °C. After the mixture was stirred for 30 min, a solution of **15** (0.50 g, 3.3 mmol) in CH_2Cl_2 (13 mL)/DMSO (12 mL) was added at -55 °C. The solution was stirred at -55 °C for 2 h. Triethylamine (9.3 mL, 49 mmol) was then added, and the reaction mixture was allowed to warm to 25 °C for 30 min. Water (25 mL) was then added, and the CH_2Cl_2 layer was separated. Concentrated HCl (4 mL) was added to the aqueous part, followed by extraction of the aqueous solution with CH_2Cl_2 (3 × 20 mL). The combined organic solutions were washed once with 1N HCl (10 mL) and once with a saturated NaCl solution (20 mL). The organic layer was dried over $MgSO_4$ and evaporated, and the residue was purified by column chromatography to give the dihemiacetal **16** (0.44 g, 80%), which is a mixture of stereoisomers.

3,5-Dihydroxy-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene 16

Pale yellow oil; IR ($CHCl_3$) 3500-3300, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30-6.00 (m, 2H), 5.10-4.80 (m, 2H), 4.00 (brs, 2H), 3.20-2.70 (m, 4H), 1.50-1.30 (m, 2H); MS *m/z* (rel int) 168 (M^+, 2), 151 (100).

Oxidation of Compound 15 with Pyridinium Chlorochromate (PCC)

To a solution of **15** (0.15 g, 1.0 mmol) in dichloromethane (20 mL) were added PCC (0.86 g, 4.0 mmol) and Celite (4 g). The reaction mixture was stirred at room temperature for 8 h. After filtration through Celite, the solvent was evaporated, and the crude product was purified by column chloromatography to give **17** (0.12 g, 80%), which is a known compound.[9d]

Iodine-Induced Cyclization of the Diastereoisomeric Mixture 16

The same reaction conditions and procedure as for the iodine-induced cyclization of **2a** and **2b** were applied for the reaction of the diastereoisomeric mixture **16** to give the iodo-cage **18** (30%) and to leave the unreacted dihemiacetal **19** in a pure isomer (56%). The iodo-cage **18** is a known compound.[9d]

3β,5β-Dihydroxy-4-oxatricyclo[5.2.1.0^{2,6}]-8-decene 19

Pale yellow oil; IR ($CHCl_3$) 3500-3300, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (brs, 2H), 4.97 (brs, 2H), 3.96 (brs, 2H), 3.05 (brs, 2H), 2.99 (brs, 2H), 1.45-1.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 134.40 (2CH), 102.20 (2CH), 54.83 (2CH), 51.30 (CH_2), 44.80 (2CH); MS *m/z* (rel int) 168 (M^+, 2), 151 (100).

Iodine-Induced Cyclization of the Mixture 16 in the Presence of HCl

To a solution of **16** (0.44 g, 2.6 mmol) in THF (10 mL) and H_2O (10 mL) were added I_2 (1.32 g, 5.2 mmol) and KI (1.0 g, 6.0 mmol) at 0 °C. To this reaction mixture was then added concentrated HCl (3 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 60 h. To this solution was added saturated $Na_2S_2O_3$ (30 mL) for reducing unreacted iodine. After extraction with ether (3 × 30 mL), the organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaported, and the residue was purified by column chloromatography to give the iodo-cage **18** (0.65 g, 96%).

Synthesis of 3,5,7-Trioxapentacyclo[7.2.1.0^{2,8}.0^{4,11}.0^{6,10}]-dodecane 20

The same reaction conditions and procedure as for the synthesis of dioxa-cages **6a** and **6b** were applied for the synthesis of diacetal trioxa-cage **20** from **18** in 84% yield. The unsubstituted diacetal trioxa-cage compound **20** has been synthesized by a different route.[9d]

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3,11-Dioxatetracyclo[6.3.0.0^{2,6}.0^{5,9}]undecanes; 3,5,7-Trioxapentacyclo[7.2.1.0^{2,8}.0^{4,11}.0^{6,10}]dodecane; Iodine-induced cyclization.

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