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Synthesis of 3,5,7-Trioxapentacyclo[7.2.1.$0^{2,8}$.$0^{4,11}$.$0^{6,10}$]dodecane. A Novel Diacetal Trioxa-Cage

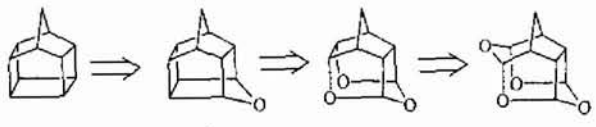
Shih-Hwa Tsai (蔡世華), Hsien-Jen Wu* (吳獻仁) and Wen-Sheng Chung (鍾文聖)
Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, R.O.C.

3,5,7-Trioxapentacyclo[7.2.1.$0^{2,8}$.$0^{4,11}$.$0^{6,10}$]dodecane, the parent compound of novel diacetal trioxa-cages, was synthesized from maleic anhydride cyclopentadiene adduct **1** by a four-step sequence. Attempts for the synthesis of monoaza dioxa-cage **12** failed. Ozonolysis of compound **9** in CH_2Cl_2-EtOH (1:1) at -78 °C followed by reduction with Me_2S gave **13** in 65% yield.

INTRODUCTION

The design of molecular assemblies with chemically distinct surfaces has received a great deal of attention in recent years because of their role in complexation chemistry, ion-transport phenomena, surfactant chemistry, and in enzyme mimicry. Recently, we conceived[1] that some heterocyclic cage systems might be viewed as novel classes of cage-backboned coronands (crown ethers) and might exhibit interesting cation-binding properties. We also 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 (Scheme I). Recently, we have accomplished the synthesis of tetraacetal tetraoxa-cages (type **D**),[1,2] tetraacetal pentaoxa-cages,[3] and triacetal trioxa-cages.[4] As part of a program that involves the synthesis and chemistry of new heterocyclic cage compounds, we report here the synthesis of 3,5,7-trioxapentacyclo-[7.2.1.$0^{2,8}$.$0^{4,11}$.$0^{6,10}$]dodecane, a novel diacetal trioxa-cage (type **C**), via iodine-induced cyclization reaction and an attempt to synthesize diacetal monoazadioxa-cage compounds.

Scheme I

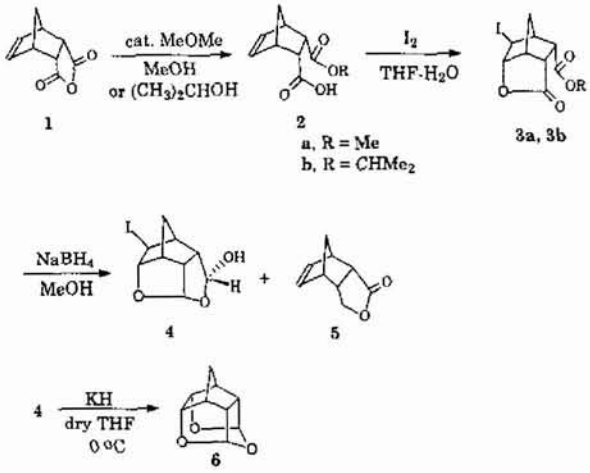


A B C D

RESULTS AND DISCUSSION

Treatment of compound **1** with a catalytic amount of sodium methoxide in alcoholic solvents at 0 °C gave the ester-acids **2a** and **2b**. Reaction of **2a** and **2b** with iodine in aqueous THF in the presence of KI at 25 °C gave the iodo-lactones **3a** and **3b** in 81% and 83% yields, respectively (Scheme II). Reduction of **3a** and **3b** with $NaBH_4$ in methanol at 0 °C gave the same products **4** (35%) and **5** (45%). The stereochemistry of the hydroxy group of the novel iodo-cage **4** was confirmed by the transformation of **4** to the diacetal trioxa-cage compound **6**. Treatment of **4** with KH in dry THF at 0 °C for 5 h gave the novel oxa-cage **6** in 82% yield. Thus, we have accomplished the synthesis of the unsubstituted compound of diacetal trioxa-cages (type **C**) by a short sequence.

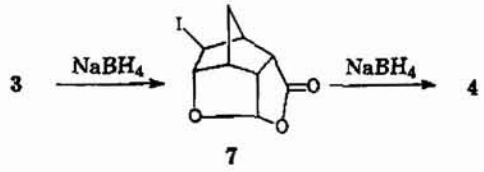
Scheme II



1 2 a, R = Me b, R = CHMe2 3a, 3b 4 5 6

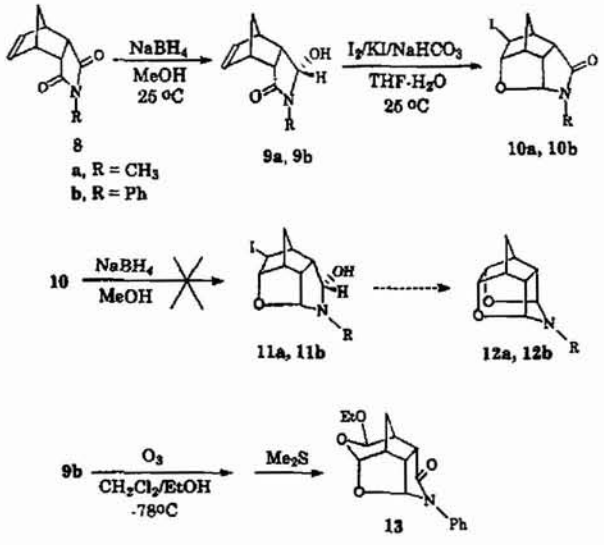
A mechanism is proposed for the transformation of **3a** and **3b** to **4**. Reduction of the lactone carbonyl group of **3** from the sterically less hindered side followed by lactonization gives the iodo-lactone **7** as intermediate. Further reduction of **7** from the convex surface gives the product **4** (Scheme III). On the other hand, the mechanism of the formation of **5** from **3** is unclear.

Scheme III



We also attempted to synthesize monoaza analogue of compound **6** by using a similar approach. Reduction of the *endo* adducts **8a** and **8b** with $NaBH_4$ in methanol at 25 °C gave compounds **9a** and **9b** in 75% and 83% yields. Nucleophilic addition of $NaBH_4$ on the imide carbonyl group of **8a** and **8b** from the sterically less hindered side gives **9**. The stereochemistry of the hydroxy group of **9a** and **9b** was confirmed by an iodo cyclization reaction. Treatment of **9a** and **9b** with iodine in the presence of KI and $NaHCO_3$ in aqueous THF at 25 °C gave the iodo-cage compounds **10a** and **10b** in 78% and 82% yields respectively (Scheme IV). No reaction was observed when **10a** and **10b** were treated with $NaBH_4$ in methanol at 25 °C. Reaction of **10a** and **10b** with $LiAlH_4$ in dry THF gave a messy mixture. Thus, attempts for the synthesis of monoaza dioxa-cage compounds **12a** and **12b** failed. Ozonolysis of **9b** in a mixture of dichloromethane and ethanol at -78 °C followed by reduction with dimethyl sulfide gave compound **13** in 65% yield.

Scheme IV



CONCLUSION

We have accomplished the synthesis of 3,5,7-trioxapentacyclo[7.2.1.$0^{2,8}$.$0^{4,11}$.$0^{6,10}$]dodecane, the unsubstituted (parent) compound of novel diacetal trioxa-cages, via iodine-induced cyclization reaction. Attempts for the synthesis of monoaza dioxa-cage **12** by a similar sequence were unsuccessful.

EXPERIMENTAL SECTION

General Procedure

Proton nuclear magnetic resonance spectra were taken on 300 MHz unless otherwise specified. Natural abundance ^{13}C NMR spectra were taken by means of pulsed Fourier transform, on a Verian Unity-300 MHz, high resolution NMR spectrometer, operating at 75.4 MHz where Broad-Band decoupling was used to simplify spectra and aid peak identification. Chemical shift are reported in parts per million and coupling constants in Hz for both nuclei with the solvent (usually $CDCl_3$) peak as an internal standard, were AB_q represents an AB quartet. The reference peak for ^{13}C is δ 77.00, with is set at the center peak $CDCl_3$, and for ^1H it is δ 0.00 for TMS. Infrared spectra were recorded in $CHCl_3$ solutions determined by Nicolet 520 spectrometer. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm) were used, and column chromatography was done by using Merck Kieselgel 60 (70-230 mesh) silica gel as the stationary phase.

General Procedure for the Alcoholysis of Maleic Anhydridecyclopentadiene Adduct 1

To a solution of compound **1** (5.00 g, 30.5 mmol) in methanol (75 mL) was added sodium methoxide (2.50 g, 46.3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 12 h. After addition of saturated NH_4Cl (50 mL) and extraction with ether (3 × 75 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography with ethyl acetate *n*-hexane (1:2) as eluent to give **2a** (5.7 g, 90%). Both **2a** and **2b** are known compounds.[5]

General Procedure for the Iodolactonization of 2a and 2b

To a solution of compound **2a** (2.00 g, 10.2 mmol) in THF (5 mL) and H_2O (50 mL) was added I_2 (6.50 g, 25.6 mmol) and KI (3.70 g, 23.7 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 18 h. After addition of saturated $Na_2S_2O_3$ (50 mL) and extraction with ether (3 × 75 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by col-

umn chromatography with ethyl acetate *n*-hexane (1:4) as eluent to give the iodo-lactone **3a** (2.62 g, 81%).

Methyl (2-oxa-3-oxo-9β-iodo)tricyclo[4.2.1.0^{4,8}]nonane-5α-carboxylate 3a

White solid; mp 102-103 °C; IR (KBr) 2990, 1733, 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (d, J = 5.1 Hz, 1H), 4.64 (d, J = 3.0 Hz, 1H), 3.73 (s, 3H), 3.31-3.41 (m, 1H), 3.13 (dd, J = 3.3, 10.7 Hz, 1H), 2.93 (bs, 1H), 2.82 (dd, J = 4.8, 10.7 Hz, 1H), 2.45-2.49 (m, 1H), 1.89-1.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.18 (C=O), 170.50 (C=O), 88.51 (CH), 52.18 (CH_3), 49.12 (CH), 48.39 (CH), 48.18 (CH), 40.03 (CH), 37.35 (CH_2), 24.88 (CH); Ms *m/z* (rel int.) 322 (M^+, 22), 195 (100), 151 (49), 136 (60); HRMS (EI) *m/z* calcd 322.0992, obsd 322.1002, $C_{10}H_{11}O_4I$.

Isopropyl (2-oxa-3-oxo-9β-iodo)tricyclo[4.2.1.0^{4,8}]-nonane-5α-carboxylate 3b

White solid; mp 117-117.5 °C; IR (KBr) 2990, 1733, 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (d, J = 5.1 Hz, 1H), 4.99-5.07 (m, 1H), 4.67 (d, J = 2.1 Hz, 1H), 3.29-3.33 (m, 1H), 3.06 (dd, J = 3.3, 10.5 Hz, 1H), 2.92 (bs, 1H), 2.81 (dd, J = 4.7, 10.7 Hz, 1H), 2.43-2.47 (m, 1H), 1.87-1.91 (m, 1H), 1.26 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.01 (C=O), 169.57 (C=O), 88.48 (CH), 69.10 (CH), 49.20 (CH), 48.65 (CH), 48.27 (CH), 39.97 (CH), 37.29 (CH_2), 25.05 (CH), 21.55 (CH_3), 21.50 (CH_3); Ms *m/z* (rel int.) 350 (M^+, 17), 223 (100), 179 (38), 164 (52); HRMS (EI) *m/z* calcd 350.1532, obsd 350.1540, $C_{12}H_{15}O_4I$.

General Procedure for the Reduction of 3a and 3b with Sodium Borohydride

To a solution of **3a** (2.00 g, 6.21 mmol) in methanol (30 mL) was added sodium borohydride (0.25 g, 6.58 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After addition of saturated NH_4Cl (30 mL) and extraction with ether (3 × 75 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography with ethyl acetate *n*-hexane (1:5) as eluent to give compounds **4** (0.64 g, 35%) and **5** (0.42 g, 45%).

(4β-Iodo-7α-hydroxy-2,8-dioxa)tetracyclo[3.3.3.0^{3,10}.0^{6,9}]-undecane 4

White solid; mp 105-106 °C; IR (KBr) 3300, 2985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J = 5.1 Hz, 1H), 5.44 (s, 1H), 4.81 (d, J = 4.5 Hz, 1H), 4.79 (s, 1H), 4.13 (d, J = 2.4 Hz, 1H), 3.19-3.26 (m, 1H), 2.82-2.86 (m, 1H), 2.68-2.69 (m, 1H), 2.60-2.65 (m, 1H), 2.33-2.36 (m, 1H), 1.89-1.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.79 (CH), 98.74 (CH), 90.37 (CH), 53.60 (CH), 49.50 (CH), 47.40 (CH), 46.05 (CH), 39.73 (CH_2), 29.45 (CH); Ms *m/z* (rel int.) 294 (M^+, 19), 192 (28), 167 (98), 85 (100); HRMS (EI) *m/z* calcd 294.0889, obsd 294.0881, $C_9H_{11}O_3I$.

3-Oxo-4-oxa-tricyclo[5.2.1.0^{2,6}]-8-decene 5

Pale yellow oil; IR (neat) 3010, 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (dd, J = 1.5, 2.1 Hz, 2H), 4.29 (dd, J = 8.6, 9.5 Hz, 1H), 3.80 (dd, J = 3.3, 9.9 Hz, 1H), 3.32-3.34 (m, 1H), 3.23-3.28 (m, 1H), 3.09-3.16 (m, 2H), 1.65-1.66 (m, 1H), 1.46-1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.93 (C=O), 136.53 (CH), 134.28 (CH), 70.10 (CH_2), 51.56 (CH_2), 47.40 (CH), 45.88 (CH), 45.53 (CH), 40.00 (CH); Ms *m/z* (rel int.) 150 (M^+, 51), 106 (100), 84 (43); HRMS (EI) *m/z* calcd 150.1775, obsd 150.1781, $C_9H_{10}O_2$.

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

To a solution of **4** (0.50 g, 1.70 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 half an hour. After destroying the excess KH by slow addition of H_2O (10 mL) at 0 °C and extraction with ether (3 × 50 mL), the organic layer was washed with brine, dride over $MgSO_4$, and evaporated, and the residue was purified by column chromatography with ethyl acetate *n*-hexane (1:1) as eluent to give the diacetal trioxa-cage **6** (0.23 g, 82%), 3,5,7-trioxapentacyclo-[7.2.1.0^{2,8}.0^{4,11}.0^{6,10}]dodecane.

Pale yellow oil; IR (neat) 2985, 1105 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (br s, 2H), 4.33 (br s, 2H), 3.00 (br s, 2H), 2.72 (br s, 2H), 1.94-1.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.06 (2C), 79.62 (2CH), 51.56 (2CH), 46.87 (2CH), 31.75 (CH_2); Ms *m/z* (rel int.) 166 (M^+, 38), 118 (100); HRMS (EI) *m/z* calcd 166.1769, obsd 166.1775, $C_9H_{10}O_3$.

General Procedure for the Preparation of 9a and 9b

To a solution of compound **8a** (2.00 g, 11.3 mmol) in methanol (30 mL) was added sodium borohydride (0.500 g, 13.1 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 18 h. After addition of saturated NH_4Cl (50 mL) and extraction with ether (3 × 50 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography with ethyl acetate *n*-hexane (1:1) as eluent to give compound **9a** (1.53 g, 75%).

(N-Methyl-5α-hydroxy-3-oxo-4-aza)tricyclo[5.2.1.0^{2,6}]-8-decene 9a

White solid; mp 154-155 °C; IR (neat) 3310, 3015,

1685 cm^{-1}; ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 6.09-6.14 (m, 2H), 5.78-5.80 (m, 1H), 4.99 (d, J = 5.4 Hz, 1H), 3.41-3.43 (m, 2H), 2.90-3.00 (m, 2H), 2.65 (s, 3H), 1.56-1.57 (m, 1H), 1.34-1.36 (m, 1H); ^{13}C NMR (75 MHz, CD_3SOCD_3) δ 172.31 (C=O), 136.50 (CH), 131.46 (CH), 79.21 (CH), 50.46 (CH_2), 48.82 (CH), 44.69 (CH), 44.16 (CH), 42.18 (CH), 25.78 (CH_3); Ms m/z (rel int.) 179 (M^+, 17), 162 (48), 164 (100); HRMS (EI) m/z calcd 179.2191, obsd 179.2188, $C_{10}H_{13}O_2N$.

(N-Phenyl-5α-hydroxy-3-oxo-4-aza)tricyclo[5.2.1.0^{2,6}]-8-decene 9b

White solid; mp 123-124 °C; IR (neat) 3310, 3015, 1685, 1600 cm^{-1}; ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 7.42-7.45 (m, 2H), 7.30-7.35 (m, 2H), 7.14-7.19 (m, 1H), 6.28-6.31 (m, 1H), 6.19-6.20 (m, 1H), 6.06-6.07 (m, 1H), 4.91 (d, J = 8.4 Hz, 1H), 3.23-3.27 (m, 1H), 3.16 (br s, 1H), 2.63-2.67 (m, 1H), 2.50 (br s, 1H), 1.41-1.46 (m, 1H), 1.36-1.38 (m, 1H); ^{13}C NMR (75 MHz, CD_3SOCD_3) δ 174.08 (C=O), 138.01 (C), 135.45 (CH), 133.99 (CH), 128.48 (2CH), 125.25 (2CH), 123.53 (CH), 85.62 (CH), 50.66 (CH_2), 49.23 (CH), 46.14 (CH), 45.27 (CH), 44.69 (CH); Ms m/z (rel int.) 241 (M^+, 13), 223 (8), 175 (100), 146 (17); HRMS (EI) m/z calcd 241.2901, obsd 241.2907, $C_{15}H_{15}O_2N$.

General Procedure for the Iodocyclization of 9a and 9b

To a solution of compound **9a** (1.00 g, 5.59 mmol) in THF (5 mL) and H_2O (30 mL) was added I_2 (2.00 g, 7.87 mmol), KI (1.00 g, 6.02 mmol) and $NaHCO_3$ (0.50 g, 5.95 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. After addition of saturated $Na_2S_2O_3$ (30 mL) and extraction with ether (3 × 50 mL), the organic layer was washed with brine, dried over $MgSO_4$ and evaporated, and the residue was purified by column chromatography with ethyl acetate n-hexane (1:4) as eluent to give the iodo-lactam **10a** (1.34 g, 78%).

(N-Methyl-4β-iodo-2-oxa-7-oxo-8-aza)tetracyclo-[3.3.3.0^{3,10}.0^{6,9}]undecane 10a

White solid; mp 110-111 °C; IR (KBr) 2990, 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (d, J = 5.4 Hz, 1H), 4.89 (d, J = 4.8 Hz, 1H), 3.75 (d, J = 2.7 Hz, 1H), 3.10-3.14 (m, 1H), 2.88 (s, 3H), 2.81-2.89 (m, 3H), 2.42-2.46 (m, 1H), 1.97-2.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.24 (CH), 94.13 (CH), 90.75 (CH), 48.77 (CH), 48.48 (CH), 47.60 (CH), 43.32 (CH), 39.94 (CH_2), 29.62 (CH), 27.79 (CH_3); Ms m/z (rel int.) 305 (M^+, 19), 192 (29), 276 (22), 178 (100), 150 (39), 138 (45); HRMS (EI) m/z calcd 305.1151, obsd 305.1146, $C_{10}H_{12}O_2NI$.

(N-Phenyl-4β-iodo-2-oxa-7-oxo-8-aza)tetracyclo-[3.3.3.0^{3,10}.0^{6,9}]undecane 10b

White solid; mp 137-138 °C; IR (KBr) 2995, 1685, 1600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.63 (m, 2H), 7.36-7.41 (m, 2H), 7.22-7.25 (m, 1H), 5.67 (d, J = 5.4 Hz, 1H), 4.99 (d, J = 4.8 Hz, 1H), 3.98 (d, J = 2.4 Hz, 1H), 3.23-3.26 (m, 1H), 3.08-3.11 (m, 1H), 2.97-2.98 (m, 1H), 2.90-2.93 (m, 1H), 2.49-2.52 (m, 1H), 2.04-2.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.07 (C=O), 137.49 (C), 128.89 (2CH), 125.89 (CH), 121.96 (2CH), 94.51 (CH), 90.99 (CH), 50.05 (CH), 48.56 (CH), 47.92 (CH), 43.38 (CH), 40.11 (CH_2), 29.33 (CH); Ms m/z (rel int.) 367 (M^+, 100), 338 (9), 240 (14), 212 (37); HRMS (EI) m/z calcd 367.1861, obsd 367.1855, $C_{15}H_{14}O_2NI$.

Ozonolysis of 9b

A solution of **9b** (0.50 g, 2.07 mmol) in dichloromethane (30 mL) was cooled to -78 °C, and ozone was bubbled through it at -78 °C until the solution turned light blue. To this solution was added dimethyl sulfide (1.00 g, 16.1 mmol) at -78 °C. Then, the reaction mixture was stirred at room temperature for 5 h. The solvent was evaporater, and the crude product was purified by column chromatography with ethyl acetate n-hexane (2:1) as eluent to give compound **13** (0.43 g, 65%), (N-phenyl-5-ethoxy-2,4-dioxa-8-oxo-9-aza)tetracyclo[4.3.3.0^{3,11}.0^{7,10}]dodecane.

Pale yellow oil; IR (neat) 2990, 1685, 1600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.67 (m, 2H), 7.35-7.40 (m, 2H), 7.19-7.24 (m, 1H), 5.73 (d, J = 6.6 Hz, 1H), 5.65 (d, J = 5.7 Hz, 1H), 4.77 (s, 1H), 3.78-3.81 (m, 1H), 3.34-3.48 (m, 2H), 3.20 (dd, J = 7.8, 9.9 Hz, 1H), 2.85-2.89 (m, 1H), 2.68-2.72 (m, 1H), 2.28-2.32 (m, 1H), 1.70-1.75 (m, 1H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.74 (C=O), 137.58 (C), 128.72 (2CH), 125.83 (CH), 122.37 (2CH), 102.23 (CH), 99.41 (CH), 94.19 (CH), 64.09 (CH_2), 48.07 (CH_2), 45.59 (CH), 44.71 (CH), 43.06 (CH), 27.85 (CH_2), 15.03 (CH_3); Ms m/z (rel int.) 301 (M^+, 26), 244 (80), 227 (47), 198 (100); HRMS (EI) m/z calcd 301.3427, obsd 301.3432, $C_{17}H_{19}NO_4$.

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Unsubstituted diacetal trioxa-cage.

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