Intramolecular Interaction of Adjacent Hydroxymethyl, Formyl, and Carboxyl Groups: Proximity Effect in the Swern Oxidation of *cis,cis*-1,3,5-Tris(hydroxymethyl)-1,3,5-trimethylcyclohexane

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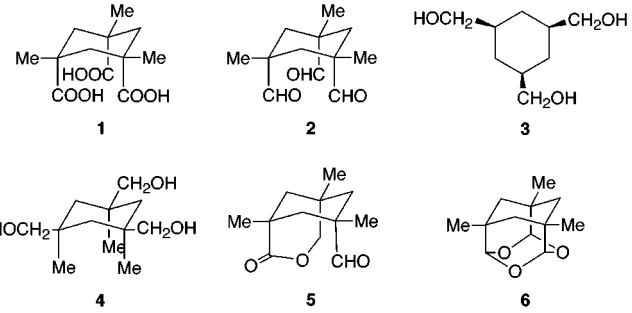
The proximity effect in the Swern oxidation of *cis,cis*-1,3,5-tris(hydroxymethyl)-1,3,5-trimethylcyclohexane (**4**) with TFAA was examined. The oxidation reaction of triol **4** with DMSO, TFAA, and relatively small amounts of triethylamine gave 5-formyl-*cis,cis*-1,3,5-trimethyl-3-hydroxymethylcyclohexane-1-carboxylic acid hemiacetal (**7a**) as well as 1,7,9-trimethyl-3,5,12-trioxawurtzitane (**6**), 5-formyl-*cis,cis*-1,3,5-trimethyl-3-hydroxymethylcyclohexane-1-carboxylic acid lactone (**5**), and polymers of *cis,cis*-1,3,5-triformyl-1,3,5-trimethylcyclohexane (**2**). Hemiacetal **7a** underwent novel solvent-dependent conversions to hemiacetal **7b**, lactone **5**, or 1,7,9-trimethyl-2-oxo-3,5-dioxatricyclo-[5.3.1.$0^{4,9}$]undecane (**8**) via 5-formyl-*cis,cis*-1,3,5-trimethyl-3-hydroxymethylcyclohexane-1-carboxylic acid. In the cases of relatively large amounts of triethylamine, trialdehyde **2** was given in moderate yield.

Introduction

cis,cis-1,3,5-Trimethylcyclohexane-1,3,5-tricarboxylic acid (Kemp's triacid) (**1**)[1] has been used as a versatile molecule for molecular recognition studies.[2] Derivatives of triacid **1** have been also applied as a molecular cleft,[3] self-replicating system,[4] chiral auxiliary,[5] and sodium saccharide cotransporter.[6] Recently, Lippard and co-workers indicated that the dianion of *m*-xylylenediamine bis-(Kemp's triacid imide) is available for a methane monooxygenase model system[7] and a molecular 18-wheeler.[8] On the other hand, trisubstituted cyclohexanes have been used as ligands to model metal-containing enzymes[9,10] or phosphate receptors.[11] These ligands were synthesized by using triamines, not trialdehydes, as the starting materials. Aldehydes are good reagents for a variety of reactions, and *cis,cis*-1,3,5-triformyl-1,3,5-trimethylcyclohexane (**2**)[12] may also be utilized for new types of ligands.[13,14]



Hydroxymethyl, formyl, and carboxyl groups have different oxidation states, respectively. Intermolecular and intramolecular reactions of alcohols with carboxylic acids[15,16] or aldehydes[17,18] have been well-known, and uronic acids[19] have been known as compounds containing hydroxymethyl, formyl, and carboxyl groups. However, these derivatives have received little attention, and the interaction among the adjacent three groups has not clarified much.

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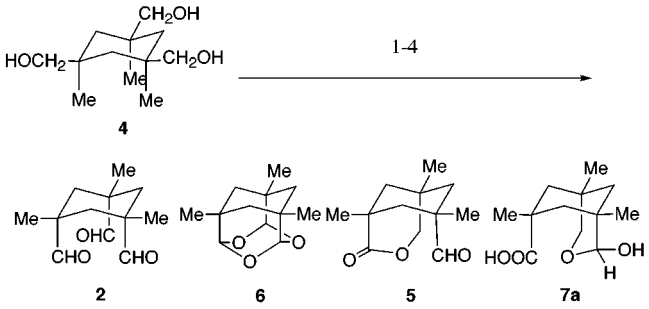
Table 1. Swern Oxidation Reactions of Triol 4 with DMSO, TFAA, and NEt_3



entry	products (% yield)
1[a]	**7a** (9%), **6** (6%), **5** (trace amounts)
2[b]	**2** (43%), **5** (4%)
3[c]	**6** (26%), **5** (trace amounts), **7a** (trace amounts)
4[d]	**2** (53%), **5** (1%)

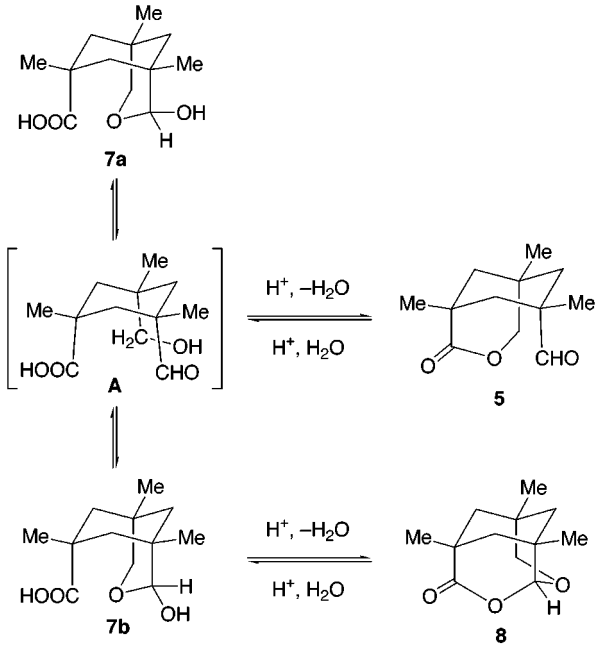
[a] (i) TFAA (7 mol equiv), DMSO/CH_2Cl_2, −55 °C; (ii) NEt_3 (22 mol equiv); (iii) acidic workup. [b] (i) TFAA (4 mol equiv), DMSO/CH_2Cl_2, −55 °C; (ii) NEt_3 (29 mol equiv); (iii) acidic workup. [c] (i) TFAA (4 mol equiv), DMSO/CH_2Cl_2, −55 °C; (ii) NEt_3 (8 mol equiv); (iii) acidic workup. [d] (i) TFAA (4 mol equiv), DMSO/CH_2Cl_2, −55 °C; (ii) NEt_3 (8 mol equiv).

Swern oxidation is one of the most efficient methods to selectively oxidize primary and secondary alcohols.[20] This oxidation is usually conducted below −50 °C. At room temperature (rt), however, methylthiomethyl ethers are given as byproducts, not carboxylic acids or hemiacetals. Swern oxidation is also useful for the oxidation of *cis*,*cis*-1,3,5-tris(hydroxymethyl)cyclohexane (**3**).[21] The oxidation of **3** with DMSO and oxalyl chloride gives the corresponding trialdehyde in 70% yield. However, the oxidation of triol **4**[22] containing *ipso* methyl groups yields only small amounts of trialdehyde **2**.[12] The main byproduct is lactone **5**.[1,12] The contrast between these reactions may be ascribed to the conformational preference of the corresponding species. On the other hand, the oxidation of **4** with TFAA instead of oxalyl chloride affords 1,7,9-trimethyl-3,5,12-trioxawurtzitane (1,7,9-trimethyl-3,5,-12-trioxatetracyclo[5.3.1.1.^{2,6}0^{4,9}]dodecane) (**6**).[12] In this paper, we report the proximity effect in the Swern oxidation of triols **4** and **3** with DMSO, TFAA, and triethylamine. We also present the first evidence for the existence of 5-formyl-*cis*,*cis*-1,3,5-trimethyl-3-hydroxymethylcyclohexane-1-carboxylic acid.

Results and Discussion

As shown in Table 1, a Swern oxidation reaction of **4** with TFAA (7 mol equiv), triethylamine (22 mol equiv), and acidic workup gave 5-formyl-*cis*,*cis*-1,3,5-trimethyl-3-hydroxymethylcyclohexane-1-carboxylic acid hemiacetal (**7a**) (9%) as well as trioxawurtzitane **6** (6%),[12] lactone **5** (trace amounts),[1,12] and polymers of trialdehyde **2**.[12] The formation of **5** and **6** was confirmed in comparison with ^{1}H NMR data of authentic samples previously isolated.[12] The ^{1}H NMR spectrum of polymers of **2** indicated many complicated broad signals.[12] The ^{1}H and ^{13}C NMR (DEPT) spectra of **7a** (DMSO-d_6) indicated the signals of a carboxyl group and a hemiacetal methine. The conformation of **7a** was decided by its NOE differential spectra (DMSO-d_6). The hemiacetal methine proton correlated with one methylene proton. The NOE differential spectra of **7a** (DMSO-d_6) also indicated the exchange between the carboxyl proton and the hydroxyl proton.[23] On the other hand, a Swern oxidation reaction of **4** with TFAA (4 mol equiv), triethylamine (29 mol equiv), and acidic workup gave trialdehyde **2**[12] in 43% yield (Table 1). We also detected lactone **5** (4%) but not hemiacetal **7a**.

Scheme 1



This oxidation reaction of **4** with TFAA was sensitive to the amounts of reagents. A Swern oxidation reaction of **4** with TFAA (4 mol equiv), triethylamine (8 mol equiv), and acidic workup gave trioxawurtzitane **6** in 26% yield (Table 1). Trace amounts of lactone **5** and hemiacetal **7a** were also detected. In this reaction, the ^{1}H NMR spectrum of sample **I** before acidic workup indicated the signals of trialdehyde **2** and lactone **5** (**2**:**5** = 25:2).[23] However, the ^{1}H NMR spectrum of sample **II** after acidic workup mainly showed the signals of trioxawurtzitane **6** and polymers of **2**.[23] This finding suggests that trialdehyde **2** decomposed to give trioxawurtzitane **6** and polymers by the acidic workup. A Swern oxidation reaction of **4** with TFAA (4 mol equiv) and triethylamine (8 mol equiv) without acidic workup afforded trialdehyde **2** (53%) and lactone **5** (1%) (Table 1).

The conformer **7a** was relatively stable in DMSO-d_6. However, **7a** in acetone-d_6 and $CDCl_3$ showed a different behavior. The acetone-d_6 solution of **7a** gave an equilibrium mixture of **7a** and **7b** (rt, 5.5 h; **7a**:**7b** = 5:4) (Scheme 1). The structure of **7b** was supported by the NOE differential spectra of the mixture of **7a** and **7b** (acetone-d_6). The hemiacetal methine proton of **7b** correlated with the two adjacent methylene protons. Allowing the DMSO-d_6 solution of this mixture to stand at room temperature for 3 days increased the ratio of **7a** (**7a**:**7b** = 20:3). It is well-known that D-glucose is a stable hemiacetal, and the α-form is in equilibrium with the β-form via aldehyde form.[18] It is analogously suggested

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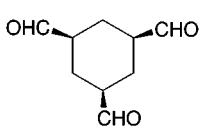
that **7a** is in equilibrium with **7b** via intermediate **A**. On the other hand, the $CDCl_3$ solution of **7a** mainly yielded 1,7,9-trimethyl-2-oxo-3,5-dioxatricyclo[5.3.1.$0^{4,9}$]-undecane (**8**) and lactone **5** (rt, 20 h; **8**:**5** = 5:3) (Scheme 1). Allowing the DMSO-d_6 solution of the mixture to stand at room temperature also gradually increased **7a** concentration with the decrease in those of **8** and **5**.[23] We have already described that acid catalysis works in chloroform,[12,13] and hemiacetal **7a** itself contains the carboxyl group. It is suggested that acid-catalyzed dehydration reactions of **7a** give **8** and **5** in $CDCl_3$. The formation of **5** supports the existence of **A** containing hydroxymethyl, formyl, and carboxyl groups. These findings indicate that the stabilities of **7a**, **7b**, **8**, and **5** differ, depending on solvents.

As described above, the different amounts of triethylamine caused the difference of products from the oxidation reactions of triol **4**. Triethylamine has two roles in Swern oxidation. One is the proton abstraction from dimethylalkoxysulfonium salts,[24] and the other is the trap for TFA. In the cases of relatively large amounts of triethylamine, it is suggested that the formation of a dialdehyde occurs first, followed by an oxidation of the last hydroxymethyl group to produce trialdehyde **2** and, as a byproduct, lactone **5**. We have already shown that trialdehyde **2** easily cyclizes to trioxawurtzitane **6** in acidic conditions.[12] The formation of **6** suggests that the reaction condition was acidic because of relatively small amounts of triethylamine. We conducted NMR monitoring experiments to understand the mechanism for the formation of hemiacetal **7a**. The $CDCl_3$ (0.9 mL) solution of lactone **5** containing water (0.1 mL) gave hemiacetal **7a** and tricycle **8** (rt, 9 days; **5**:**7a**:**8** = 14:2:1), but the $CDCl_3$ (0.8 mL) solution of **5** not containing water afforded neither **7a** nor **8**. The acetone-d_6 (0.9 mL) solution of **5** containing water (0.1 mL) gave hemiacetals **7a** and **7b** (rt, 9 days; **5**:**7a**:**7b** = 10:2:1). These findings suggest that **7a** is produced from **5** in the presence of water and acid.

To clarify the effect of *ipso* methyl groups further, we also examined the Swern oxidation of triol **3** with TFAA. A Swern oxidation reaction of **3** with TFAA (4 mol equiv) and triethylamine (34 mol equiv) without acidic workup gave trialdehyde **9**[21] (26%) and polymeric material. The formation of the corresponding lactone could not be confirmed. The ^{1}H NMR spectrum of **9** supported the triequatorial conformation of the formyl groups. A Swern oxidation reaction of **3** with TFAA (7 mol equiv), triethylamine (21 mol equiv), and acidic workup afforded polymeric material. The formation of the corresponding trioxawurtzitane, lactone, and hemiacetal could not be confirmed. It has been known that the reaction of Kemp's triacid **1** with $SOCl_2$ gives anhydride acid chloride **10**,[1] but the reaction between the corresponding triacid without *ipso* methyl groups and $SOCl_2$ yields triacid chloride **11**.[25] We have already shown that the steric repulsion of *ipso* methyl groups stabilizes the triaxial conformation of the formyl groups in trialdehyde **2**.[12] It is suggested that the introduction of *ipso* methyl groups makes the intramolecular reaction into lactone **5** predominant.



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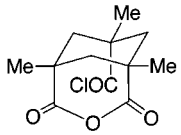

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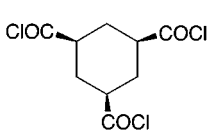

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Conclusion

We have described the proximity effect in the Swern oxidation of triols **4** and **3** with DMSO, TFAA, and triethylamine. The intramolecular reaction is predominant in the oxidation of **4**. In the cases of relatively small amounts of triethylamine added, hemiacetal **7a**, trioxawurtzitane **6**, and lactone **5** were given. Hemiacetal **7a** can be changed into hemiacetal **7b**, lactone **5**, or tricycle **8** via **A**, depending on the solvents used.

Experimental Section

General Methods. All reactions were performed in oven-dried glassware equipped with a magnetic stirring bar under an argon atmosphere, using standard syringe techniques. DMSO and CH_2Cl_2 were distilled from CaH_2 and stored over molecular sieves. All other solvents were of anhydrous grade. *cis,cis*-1,3,5-Tris(hydroxymethyl)-1,3,5-trimethylcyclohexane (**4**)[12] and *cis,cis*-1,3,5-tris(hydroxymethyl)cyclohexane (**3**)[21] were prepared by the similar procedures previously reported. All other reagents were of commercial grade. ^{1}H (500 MHz) and ^{13}C (125.7 MHz) NMR spectra were recorded in DMSO-d_6, acetone-d_6, $CDCl_3$, or C_6D_6.

5-Formyl-*cis,cis*-1,3,5-trimethyl-3-hydroxymethylcyclohexane-1-carboxylic acid hemiacetal (2-hydroxy-1,5,7-trimethyl-*endo*-3-oxabicyclo[3.3.1]nonane-7-carboxylic acid) (7a). A mixture of dry DMSO (4 mL) and dry CH_2Cl_2 (10 mL) was added to a dry CH_2Cl_2 solution (40 mL) of TFAA (7.26 g, 34.6 mmol) at −55 °C. After the mixture was stirred for 30 min, a solution of 1.04 g (4.8 mmol) of triol **4** in dry CH_2Cl_2 (25 mL)/DMSO (20 mL) was added at −55 °C. The solution was allowed to stir at −55 °C for 2 h. NEt_3 (15 mL, 0.11 mol) was added slowly, and the reaction mixture was allowed to warm to room temperature. Water (50 mL) was then added, and the CH_2Cl_2 layer was separated. Concentrated HCl (3 mL) was added to the aqueous phase, followed by extraction with CH_2Cl_2. The combined CH_2Cl_2 solutions were washed once with dilute HCl and once with saturated aqueous NaCl. After being dried with $MgSO_4$ for 30 min, followed by filtration, the filtrate was concentrated to remove volatiles. The mixture of **6** (0.060 g, 6%) and **5** (trace amounts) was separated first by flash chromatography on silica gel, using CH_2Cl_2/acetone (500 mL/10 mL) as an eluent. Hemiacetal **7a** and polymers were then separated by using acetone as an eluent. Attempts to recrystallize **7a** were in vain. **7a** was purified by washing with hexane (0.102 g, 9%). **7a**: colorless solids; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.67 (3H, s, CH_3), 0.73 (3H, s, CH_3), 0.75 (1H, d, $^2J_{HH}$ = 12.3 Hz, CH_aH$_e$), 0.89 (2H, d, $^2J_{HH}$ = 13.4 Hz, CH_aH$_e$), 1.01 (3H, s, CH_3), 1.59 (1H, d, $^2J_{HH}$ = 12.3 Hz, CH$_a$$H_e$), 2.27 (2H, d, $^2J_{HH}$ = 13.4 Hz, CH$_a$$H_e$), 3.15 (1H, d, $^2J_{HH}$ = 10.2 Hz, CH_2O), 3.39 (1H, d, $^2J_{HH}$ = 10.2 Hz, CH_2O), 4.51 (1H, d, $^3J_{HH}$ = 3.7 Hz, OC*H*OH), 5.82 (1H, d, $^3J_{HH}$ = 3.7 Hz, OH), 11.43 (1H, br. s, COOH); ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 25.79 (CH_3), 26.06 (CH_3), 30.86 [$(CH_2)_2C$CH$_3$], 31.98 (CH_3), 34.94 [$(CH_2)_2C$CH$_3$], 40.59 (CCH$_2$C), 41.75 [$(CH_2)_2C$CH$_3$], 45.04 (CCH$_2$C), 45.15 (CCH$_2$C), 67.46 (CH_2O), 95.06 (OCHOH), 177.62 (COOH); IR (KBr) ν_{CO} 1692 cm^{-1}; MS (EI) *m*/*z* 228 (8, M^+); HRMS calcd for $C_{12}H_{20}O_4$ 228.1362, found 228.1343. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.37; H, 8.78.

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***cis,cis*-1,3,5-Triformyl-1,3,5-trimethylcyclohexane (2).**[12] A mixture of dry DMSO (5 mL) and dry CH_2Cl_2 (15 mL) was added to a dry CH_2Cl_2 solution (40 mL) of TFAA (4.93 g, 23.5 mmol) at −55 °C. After the mixture was stirred for 30 min, a solution of 1.28 g (5.9 mmol) of triol **4** in dry CH_2Cl_2 (15 mL)/DMSO (15 mL) was added at −55 °C. The solution was allowed to stir at −55 °C for 2 h. NEt_3 (6.5 mL, 47 mmol) was added, and the reaction mixture was allowed to warm to room temperature. Water (50 mL) was then added, and the CH_2Cl_2 layer was separated. The aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with saturated aqueous NaCl. After being dried with $MgSO_4$ for 30 min, followed by filtration, the filtrate was concentrated to remove volatiles. The residual solid was subjected to a silica gel column and eluted with CH_2Cl_2/acetone (500 mL/10 mL). Trialdehyde **2** (0.662 g, 53%) and lactone **5** (11 mg, 1%) were obtained as the first and second fractions, respectively.

A Swern oxidation reaction of **4** (1.32 g, 6.1 mmol) with TFAA (5.25 g, 25.0 mmol), triethylamine (25 mL, 0.18 mol), and acidic workup that was employed in the preparation of **7a** also gave trialdehyde **2** (0.548 g, 43%) and lactone **5** (56 mg, 4%).

A Swern oxidation reaction of **4** (1.32 g, 6.1 mmol) with TFAA (5.25 g, 25.0 mmol), triethylamine (7 mL, 0.05 mol), and acidic workup that was employed in the preparation of **7a** afforded trioxawurtzitane **6** (0.335 g, 26%). Trace amounts of lactone **5** and hemiacetal **7a** were also detected.

***cis,cis*-1,3,5-Triformylcyclohexane (9).**[21] The similar manner that was employed in the preparation of trialdehyde **2** was used with triol **3** (0.910 g, 5.2 mmol), TFAA (4.28 g, 20.4 mmol), and triethylamine (25 mL, 0.18 mol). This oxidation reaction gave trialdehyde **9** (0.230 g, 26%) and polymeric material. The formation of the corresponding lactone could not be confirmed. **9**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18 (3H, dt, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 12.6 Hz, CH_aH$_e$), 2.33 (3H, br. d, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 3.2 Hz, CH$_a$$H_e$), 2.40 (3H, tt, $^3J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 3.2 Hz, CH), 9.65 (3H, s, CHO); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 25.20 (C*C*H$_2$C), 47.94 [(CH$_2$)$_2$*C*H], 201.69 (CHO).

A Swern oxidation reaction of **3** (0.909 g, 5.2 mmol) with TFAA (7.67 g, 36.5 mmol), triethylamine (15 mL, 0.11 mol), and acidic workup that was employed in the preparation of **7a** gave polymeric material. The formation of the corresponding trioxawurtzitane, lactone, and hemiacetal could not be confirmed.

1,7,9-Trimethyl-2-oxo-3,5-dioxatricyclo[5.3.1.0^{4,9}]-undecane (8). Hemiacetal **7a** (46 mg, 0.20 mmol) was added to $CDCl_3$ (6 mL). After the solution was stirred for 3 days, volatiles were removed under reduced pressure. It was very difficult to separate tricycle **8** from lactone **5**. The residue was heated at 170 °C for 30 min and cooled to room temperature. After being extracted with hexane, the solvent was removed under reduced pressure. Tricycle **8** was separated by molecular distillation (6.4 mg, 15%).

Heating lactone **5** (86 mg, 0.41 mmol) at 170 °C for 40 min gave decomposition products. Tricycle **8** was not detected. **8**: ^{1}H NMR (C_6D_6, 500 MHz) δ 0.33 (1H, d, $^2J_{HH}$ = 12.1 Hz, CH_aH$_e$), 0.43 (3H, s, CH$_3$), 0.45 (1H, d, $^2J_{HH}$ = 12.5 Hz, CH_aH$_e$), 0.61 (3H, s, CH$_3$), 0.62 (1H, d, $^2J_{HH}$ = 13.6 Hz, CH_aH$_e$), 1.09 (3H, s, CH$_3$), 1.16 (1H, d, $^2J_{HH}$ = 12.1 Hz, CH$_a$$H_e$), 1.19 (1H, d, $^2J_{HH}$ = 12.5 Hz, CH$_a$$H_e$), 1.32 (1H, d, $^2J_{HH}$ = 13.6 Hz, CH$_a$$H_e$), 3.14 (1H, d, $^2J_{HH}$ = 11.8 Hz, CH$_2$O), 3.35 (1H, d, $^2J_{HH}$ = 11.8 Hz, CH$_2$O), 5.23 (1H, s, OCHO); ^{13}C NMR (C_6D_6, 125.7 MHz) δ 26.43 (CH$_3$), 27.86 (CH$_3$), 29.17 (CH$_3$), 31.47 [(CH$_2$)$_2$*C*CH$_3$], 33.24 [(CH$_2$)$_2$*C*CH$_3$], 39.58 [(CH$_2$)$_2$*C*CH$_3$], 42.00 (C*C*H$_2$C), 43.44 (C*C*H$_2$C), 48.96 (C*C*H$_2$C), 69.42 (CH$_2$O), 104.29 (OCHO), 176.54 (COO); MS (EI) *m*/*z* 210 (3, M$^+$); HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1267.

NMR Monitoring Experiments. Hemiacetal **7a** (7.5 mg, 0.033 mmol) was added to acetone-d_6 (0.8 mL) in an NMR tube. Allowing the solution to stand at room temperature for 3 days gave an equilibrium mixture of **7a** and **7b** (**7a**:**7b** = 5:4). After acetone-d_6 was removed under reduced pressure, allowing the DMSO-d_6 (0.8 mL) solution of the residue to stand at room temperature for 3 days increased the ratio of **7a** (**7a**:**7b** = 20:3). **7b**: ^{1}H NMR (acetone-d_6, 500 MHz) δ 0.74 (3H, s, CH$_3$), 0.81 (3H, s, CH$_3$), 0.88 (1H, d, $^2J_{HH}$ = 14.5 Hz, CH_aH$_e$), 1.12 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH_aH$_e$), 1.14 (3H, s, CH$_3$), 1.19 (1H, d, $^2J_{HH}$ = 12.8 Hz, CH_aH$_e$), 1.32 (1H, d, $^2J_{HH}$ = 12.8 Hz, CH$_a$$H_e$), 2.39 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH$_a$$H_e$), 2.52 (1H, d, $^2J_{HH}$ = 14.4 Hz, CH$_a$$H_e$), 3.22 (1H, d, $^2J_{HH}$ = 10.9 Hz, CH$_2$O), 3.63 (1H, d, $^2J_{HH}$ = 10.9 Hz, CH$_2$O), 3.99 (1H, d, $^3J_{HH}$ = 11.4 Hz, OH), 4.20 (1H, d, $^3J_{HH}$ = 11.4 Hz, OC*H*OH).

Hemiacetal **7a** (7.5 mg, 0.033 mmol) was added to $CDCl_3$ (0.8 mL) in an NMR tube. Allowing the solution to stand at room temperature for 20 h mainly yielded tricycle **8** and lactone **5** (**8**:**5** = 5:3). After $CDCl_3$ was removed under reduced pressure, allowing the DMSO-d_6 (0.8 mL) solution of the residue to stand at room temperature gradually increased **7a** concentration with the decrease in those of **8** and **5**.[23]

Water (0.1 mL) was added to a solution of lactone **5** (4.6 mg, 0.022 mmol) in $CDCl_3$ (0.9 mL). Allowing the solution to stand at room temperature for 9 days gave hemiacetal **7a** and tricycle **8** (**5**:**7a**:**8** = 14:2:1). The $CDCl_3$ (0.8 mL) solution of **5** (4.6 mg, 0.022 mmol) not containing water afforded neither **7a** nor **8**.

Water (0.1 mL) was added to a solution of lactone **5** (5.4 mg, 0.026 mmol) in acetone-d_6 (0.9 mL). Allowing the solution to stand at room temperature for 9 days gave hemiacetals **7a** and **7b** (**5**:**7a**:**7b** = 10:2:1).

Supporting Information Available: ^{1}H NMR spectra of samples **I** and **II**; ^{1}H NMR and NOE differential spectra of hemiacetal **7a** in DMSO-d_6, acetone-d_6, and $CDCl_3$; the spectral changes upon the equilibration of a mixture of **8**, **5**, and **7a** in DMSO-d_6; ^{1}H NMR spectra of **5**, **8**, and **9**; NOE values for **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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