Hydride-Transfer Domino Rearrangement of Glycine-Containing Dioxa-azawurtzitane

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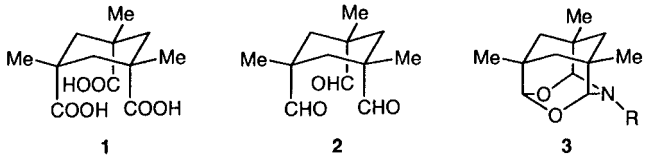
Received November 19, 2001

The novel synthetic method for dioxa-azawurtzitanes to selectively cap amino groups in amino acids or peptides is described. Mixing the CH_3CN solution of *cis,cis*-1,3,5-triformyl-1,3,5-trimethylcyclohexane (**2**) with the aqueous solution of the equimolar amounts of glycine and $NaHCO_3$ yields glycine-containing dioxa-azawurtzitane **7-Na**. Dioxa-azawurtzitane **7-Na** almost quantitatively isomerizes to lactone-imine **9-Na** through the hydride-transfer rearrangement in CH_3CN/H_2O. Lactone-imine **9-Na** also isomerizes to lactam-aldehyde **12-Na** in DMSO.

Introduction

Protein mimics have been shown to play a critical role in resolving an interrelation between structure and activity.[1] These structures have been also attracting considerable interest from the pharmaceutical point of view.[2] For efficient target screening and optimization of lead structures, flexible synthetic concepts have been needed. Kazmaier and co-workers have indicated that a stereoselective Claisen rearrangement of achiral glycine subunits is available for the peptide backbone modifications.[3]

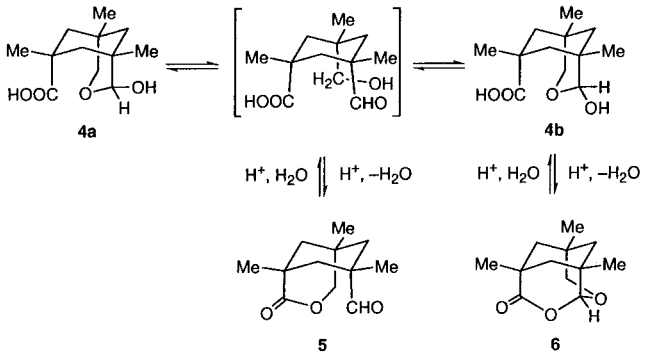
In nature, various enzymes use synergistic effects to cooperatively catalyze the hydrolysis of their substrates.[4] A synergistic effect is also useful for an organic synthesis of antimicrobial agents.[5] Derivatives of *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid (Kemp's triacid) (**1**)[6] have been used as a versatile molecule for molecular recognition studies.[7] We have synthesized trialdehyde **2**[8,9] and mixed heteroatom wurtzitanes (tetracyclo[5.3.1.1.^{2,6}0^{4,9}]dodecanes) **3**[10] as unique scaffolds



1 **2** **3**

to utilize the synergistic effect of numerous functional groups upon the reactions of other neighboring groups. However, the synthetic method for wurtzitanes **3** using chloroform is not applied to the synthesis of amino acid- or peptide-containing wurtzitanes because of the low solubility. We have also reported the interaction of adjacent hydroxymethyl, formyl, and carboxyl groups.[8] Hemiacetal **4a** undergoes solvent-dependent conversions to hemiacetal **4b**, lactone **5**, or 1,7,9-trimethyl-2-oxo-3,5-dioxatricyclo[5.3.1.0^{4,9}]undecane (**6**) via 5-formyl-*cis,cis*-1,3,5-trimethyl-3-hydroxymethylcyclohexane-1-carboxylic acid (Scheme 1).[8] This interaction has a great potential

Scheme 1



for the utilization of the synergistic effect. In this paper, we report the new synthetic method for glycine- or peptide-containing dioxa-azawurtzitanes and the novel hydride-transfer rearrangement of glycine-containing dioxa-azawurtzitanes. We also discuss the mechanism for the hydride-transfer rearrangement of mixed heteroatom wurtzitanes and trialdehyde **2**.

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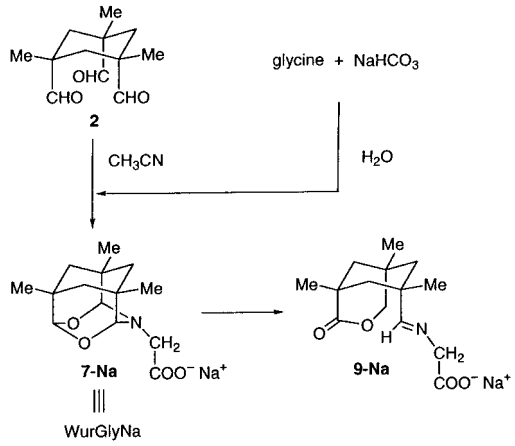
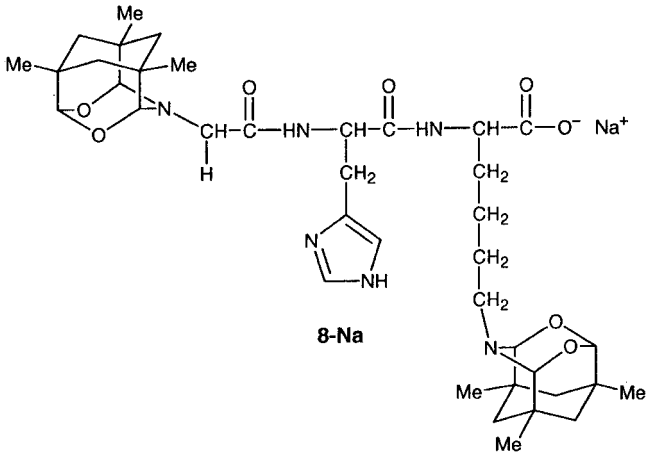
Published on Web 02/12/2002

Scheme 2

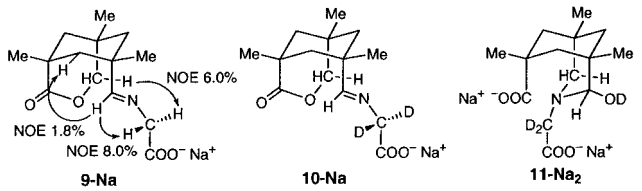


Results and Discussion

Synthesis of Dioxa-azawurtzitanes. As shown in Scheme 2, mixing an acetonitrile solution (8 mL) of trialdehyde **2** with an aqueous solution (5 mL) of equimolar amounts of glycine and $NaHCO_3$ at room temperature for 2 h gave glycine-containing dioxa-azawurtzitane WurGlyNa (**7-Na**) in 78% yield. In this reaction, the addition of $NaHCO_3$ is necessary. Dioxa-azawurtzitane **7-Na** could not be detected without $NaHCO_3$. The ^1H and ^{13}C NMR spectra of **7-Na** indicated the characteristic signals of wurtzite methines (δ_H 4.14 and δ_C 89.17 for OCHN; δ_H 4.71 and δ_C 100.11 for OCHO). The ESI mass spectrum of **7-Na** supported the form of sodium salt (*m*/*z* 555 [28, $2M^- - Na$]). This synthetic method was also available for the synthesis of a peptide-containing dioxa-azawurtzitane. The reaction of trialdehyde **2** (2 equiv) with a sodium salt of Gly-His-Lys using this method yielded WurGly-His-WurLysNa (**8-Na**) containing two wurtzite rings. This finding suggests that trialdehyde **2** can selectively cap more than one amino group in peptides.



Hydride-Transfer Rearrangement of Dioxa-azawurtzitane 7-Na. Dioxa-azawurtzitane **7-Na** was not stable in the presence of water. Storage of the CH_3CN/H_2O (8 mL/5 mL) solution of **7-Na** at room temperature for 5 days yielded lactone-imine **9-Na** almost quantitatively (Scheme 2). Lactone-imine **9-Na** was purified by HPLC (TSK-GEL Amide-80), using CH_3CN/H_2O (3:1) as an eluent. The structure of **9-Na** was confirmed by the NMR techniques and the deuterium labeling experiment.[11] The reaction using glycine-d_5 also afforded the deuterated compound **10-Na**. The methylene signals of the lactone part were easily characterized by the ^1H NMR spectrum of **10-Na**.[11] The NOE differential spectra of lactone-imine **9-Na** indicated a similarity to the structure of lactone **5**.[8,12] The imino proton of **9-Na** correlated with the two adjacent methylene protons. The ab initio energy calculation (HF/6-31G*) for **9-H**[11,13] also supported the structure of **9-Na**. An optimized geometry (−896.304 904 5 hartree) corresponded to the above NOE result.[11] WurGly-His-WurLysNa (**8-Na**) also decomposed under the similar conditions to form many unidentified products.[14] The formation of lactone-imine **9-Na** from dioxa-azawurtzitane **7-Na** suggests the isomerization of **7-Na**. The methylene hydrogens of lactone part of **10-Na** were not deuterated by using glycine-d_5 or deuterated solvents.[11] The imino hydrogen was not deuterated either.[11] These findings suggest that the wurtzite methine hydrogens of dioxa-azawurtzitane **7-Na** intramolecularly shift to the methylene hydrogens of lactone part or the imino hydrogen of lactone-imine **9-Na**. The framework of lactone-imine **9-Na** was stable in the presence of acids but not bases. Lactone-imine **9-Na** did not decompose in the presence of dilute HCl under 100 °C for 1 day. However, the reaction of lactone-imine **10-Na** with NaOH in CD_3CN/D_2O (4:5) immediately gave dicarboxylate **11-Na$_2$**. The ^1H NMR and NOE differential spectra of dicarboxylate **11-Na$_2$** indicated a similarity to the structure of hemiacetal **4a**. The doublet signals (δ_H 2.07 and 2.59) of **11-Na$_2$** were characterized as CH_2N (**4a**, δ_H 3.15 and 3.39 for CH_2O; **4b**, δ_H 3.22 and 3.63 for CH_2O; **5**, δ_H 3.92 and 4.04 for CH_2O; **9-Na**, δ_H 3.47 and 3.57 for CH_2O; **12-Na**, δ_H 2.46 and 3.40 for CH_2N). The ^{13}C NMR spectrum of **11-Na$_2$** also supported the characterization. It is proposed that deuterioxide attacks the imino carbon, followed by the reaction of the produced amide with the lactone to yield **11-Na$_2$**. The ^1H NMR signals of **11-Na$_2$** gradually disappeared, but further products were not detected.[11] It is suggested that the structure of nitrogen-displaced hemiacetal in **11-Na$_2$** is not stable.



The DMSO-d_6 solution of lactone-imine **9-Na** at room temperature for 3 months yielded lactam-aldehyde **12-Na** quantitatively (Scheme 3).[11] The determination of the NOE and w-shape long-range couplings for lactam-

(11) See Supporting Information.

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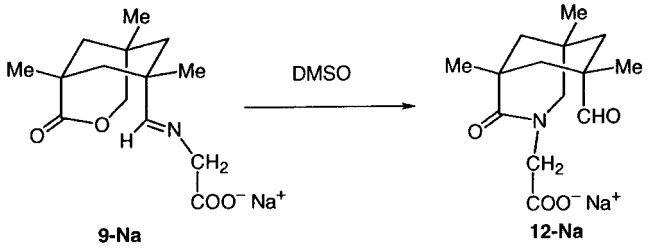
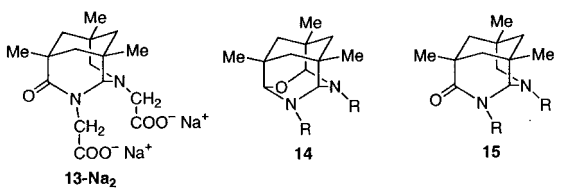
Scheme 3



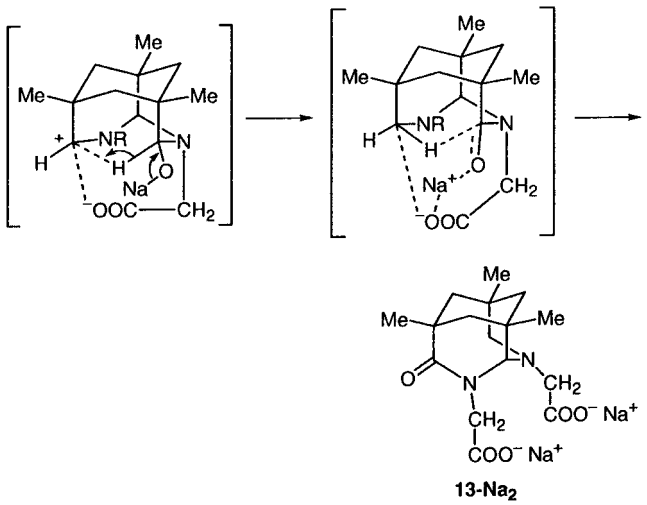
aldehyde **12-Na** supported the structure of **12-Na**.[11] The CD_3CN/D_2O (8:5) solution of purified lactone-imine **9-H** at room temperature for 6 months also afforded lactam-aldehyde **12-D** (**9-D**:**12-D** = 1:1).[11] The isomerization of lactone-imine **9-Na** to lactam-aldehyde **12-Na** in CD_3OD was also slow. The CD_3OD solution of **9-Na** at room temperature for 1 week yielded only a small amount of **12-Na** (**9-Na**:**12-Na** = 100:1). The CD_3CN/D_2O (8:5) solution of lactam-aldehyde **12-Na** at 50 °C for 3 weeks did not give lactone-imine **9-Na** at all. It is suggested that lactam-aldehyde **12-Na** is not in equilibrium with lactone-imine **9-Na** under this condition.

Carboxylate Function of Glycine Moiety on the Rearrangement. Mixing an acetonitrile solution (4 mL) of trialdehyde **2** with an aqueous solution (2 mL) of equimolar amounts of glycine and $KHCO_3$ at room temperature for 1 h also gave glycine-containing dioxa-azawurtzitane WurGlyK (**7-K**). Storage of the CH_3CN/H_2O (4 mL/2 mL) solution of **7-K** at room temperature for 3 days yielded lactone-imine **9-K** almost quantitatively. The DMSO-d_6 solution of lactone-imine **9-K** at room temperature for 10 days yielded lactam-aldehyde **12-K** quantitatively. The potassium ion catalyzes these isomerizations more effectively than the sodium ion. However, dioxa-azawurtzitane $WurGlyNH_4$ (**7-NH$_4$**) was not isolated by the reaction using NH_4HCO_3 instead of $NaHCO_3$. Storage of the solution of the reaction mixture at room temperature for 5 days afforded small amounts of lactone-imine **9-NH$_4$** and lactam-aldehyde **12-NH$_4$**. The CD_3CN/D_2O (8:5) solution of esterified dioxa-azawurtzitane **7-Me** with $NaHCO_3$ at 50 °C for 6 days gave lactone-imine **9-Na**.[11] A small amount of lactam-aldehyde **12-Na** was also detected. However, the amount of **12-Na** hardly increased at room temperature after 2 months. On the other hand, dioxa-azawurtzitane **7-Me** was hydrolyzed without $NaHCO_3$ at room temperature for 2 months to yield lactone-imine **9-D** and lactam-aldehyde **12-D** (**9-D**:**12-D** = 5:3).[11] These findings suggest that the carboxylate of the glycine moiety has a great influence on the rearrangement, and the alkali metal ions accelerate the reactions. It is also suggested that the sodium ion stabilizes the lactone-imine structure in acetonitrile and delays the isomerization of **9-Na** to **12-Na**.

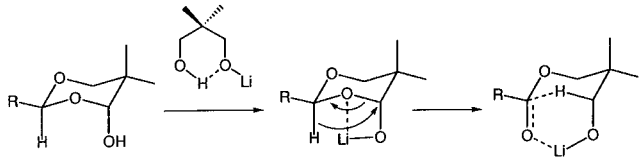
Hydride-Transfer Mechanism of Mixed Heteroatom Wurtzitanes and Trialdehyde 2. The reaction of trialdehyde **2** with excesses of glycine and $NaHCO_3$ in CH_3CN/H_2O (8:5) gave tricycle **13-Na$_2$** as a byproduct.



Scheme 4



Scheme 5



We have already shown that oxadiazawurtzitanes **14** easily isomerize to tricycles **15** through a hydride-transfer.[10] Nielsen and co-workers also suggested the hydride-transfer mechanism for the formation of tricycles.[15] We could not detect the lactam-imine structure at all. This finding suggests that a nonacid-catalyzed hydride-transfer occurs, and the hydride-transfer is not to a carbon−nitrogen double bond in an imino group. Scheme 4 shows a proposed mechanism for the formation of **13-Na$_2$**.

For the hydride-transfer rearrangement of dioxa-azawurtzitane **7-Na** to lactone-imine **9-Na**, two possible mechanisms are depicted. One is the mechanism for the direct formation of **9-Na**. In the Tishchenko reaction,[16] two aldehydes are converted to a monofunctional simple ester in the presence of a Lewis acid catalyst.[17] Recently, Koskinen and co-workers reported a Tishchenko reaction, in which the hydride-transfer is not to a carbon−oxygen double bond (Scheme 5).[18] Scheme 6 shows a possible mechanism for the hydride-transfer rearrangement of **7-Na**. The other is the mechanism via the tricycle structure as described above (Scheme 7). The intermediate tricycle **A** has the distorted structure of nitrogen-displaced acetal, and such distorted structure has not been reported much. Oxadiazawurtzitanes **14** containing

(14) The wurtzitanes containing 3-methyl-L-histidine or Gly-Gly-His residues were also hydrolyzed. The decomposition of the wurtzitane containing Gly-Gly residue was extremely slow. Further study on these reactions is in progress.

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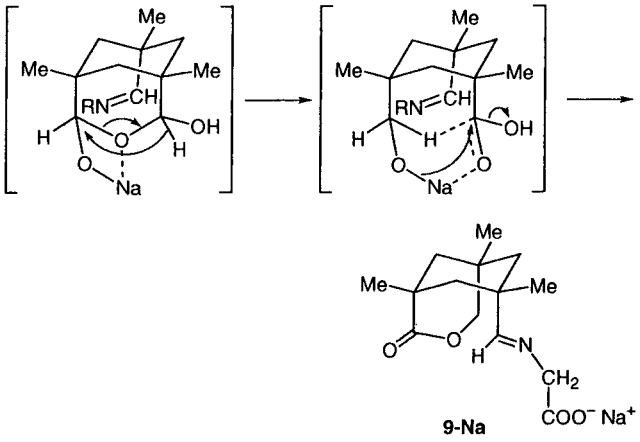
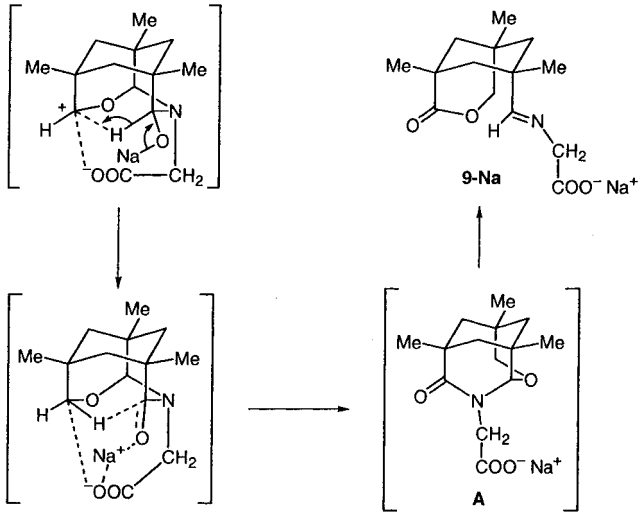
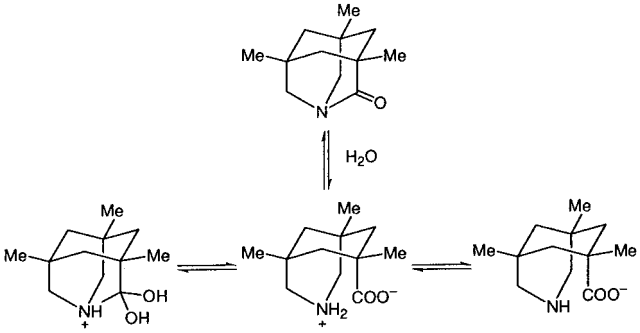
Scheme 6



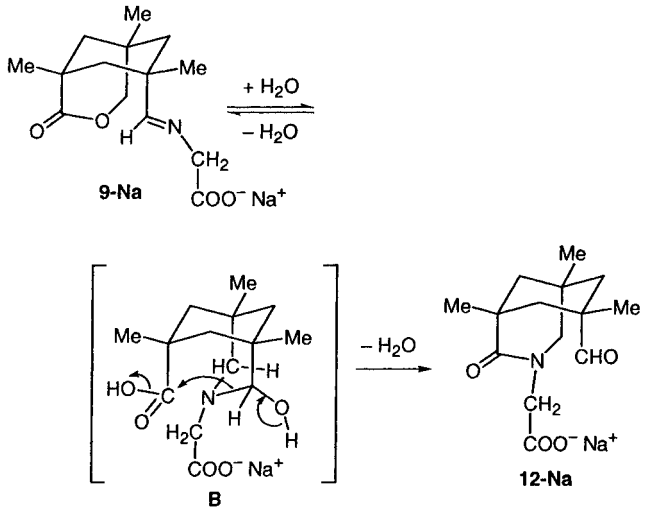
Scheme 7



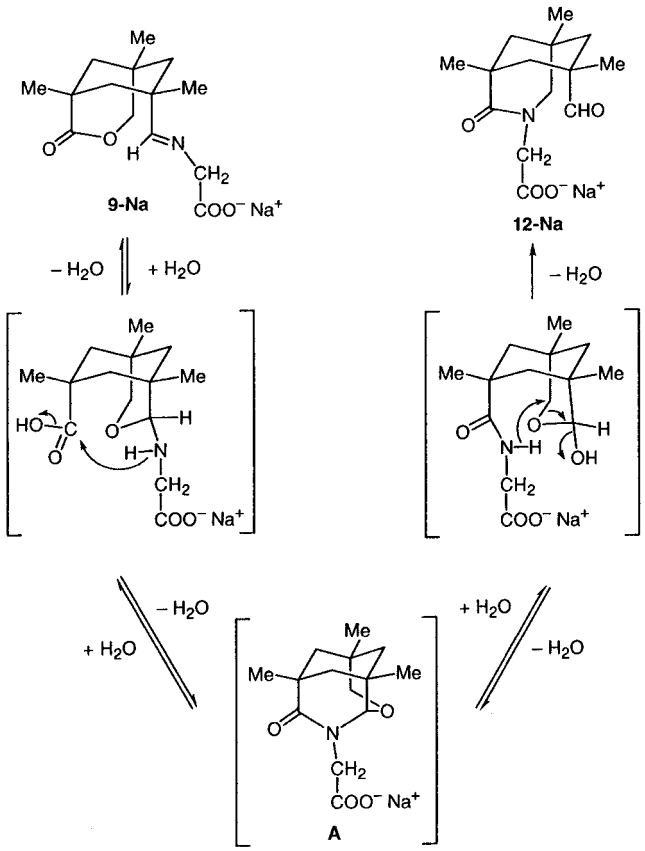
Scheme 8



Scheme 9



Scheme 10



such frames are extremely unstable.[10] Kirby and coworkers have reported that highly twisted amides are rapidly hydrolyzed when dissolved in water (Scheme 8).[19] In addition, the similar structure of tricycle **6** is not stable in the presence of water.[8] It is suggested that tricycle **A** is also unstable in the presence of water because of the two boat rings. We detected a weak characteristic signal (4.68 ppm) in the hydride-transfer rearrangement of dioxa-azawurtzitane **7-Na** in DMSO-d_6. As described above, lactone-imine **9-D** and lactam-aldehyde **12-D** were formed from dioxa-azawurtzitane **7-Me** without $NaHCO_3$.

This finding suggests that the hydride-transfer rearrangement occurs without the sodium ion and is not a simple Tishchenko reaction.

For the isomerization of lactone-imine **9-Na** to lactam-aldehyde **12-Na**, two possible mechanisms are also depicted. One is the mechanism via intermediate **B** (Scheme 9). The other is the mechanism via tricycle **A** (Scheme 10). In the isomerization of lactone-imine **9-D** to lactam-aldehyde **12-D**, a weak characteristic signal of methine (OCHN, 4.66 ppm) in the ^{1}H NMR spectra was observed. This signal did not accord with the methine one in dicarboxylate **11-Na$_2$** (OCHN, 3.99 ppm). In the CD_3CN/D_2O (8:5) solution of purified lactone-imine **9-Na**, lactam-aldehyde **12-Na** was not detected at room tem-

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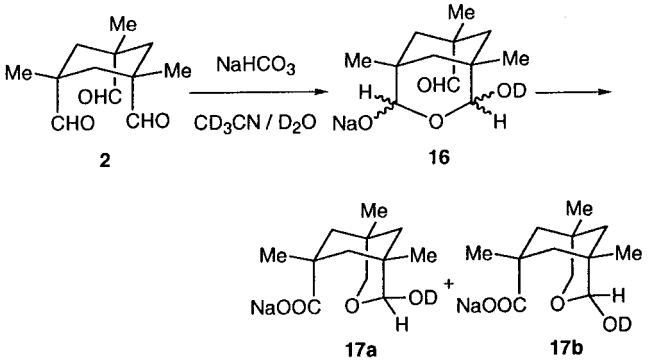
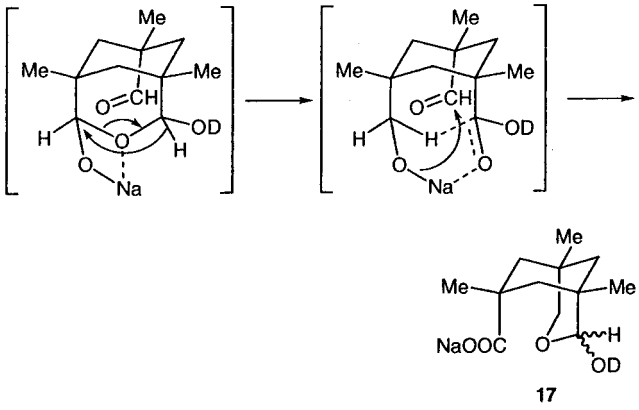
Scheme 11



Scheme 12

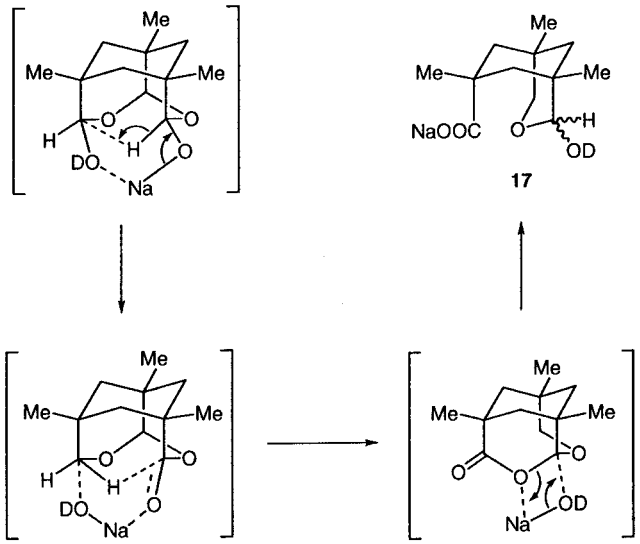


perature for 1 day. However, a small amount of lactam-aldehyde **12-Na** along with lactone-imine **9-Na** was detected at room temperature for 1.5 h in the hydride-transfer rearrangement of dioxa-azawurtzitane **7-Na.** These findings suggest the existence of the other pathway to lactam-aldehyde **12-Na** not via lactone-imine **9-Na**. This supports the possibility of the mechanism for the hydride-transfer rearrangement via tricycle **A**.

To clarify the mechanism for the hydride-transfer rearrangement, we also examined the reactivity of trialdehyde **2** in the presence of $NaHCO_3$ and water. The CD_3CN/D_2O (8:5) solution of **2** with $NaHCO_3$ yielded hydrolyzed compounds **16** at room temperature for 4 h, followed by the gradual build-up of hemiacetals **17a**[8] and **17b**[8] (2 months, **17a**:**17b** = 1:6) (Scheme 11).[11] Lactone-aldehyde **5** was not detected at all. We reported that the hydrolysis of lactone-aldehyde **5** was slower than that of tricycle **6**.[8] These findings suggest that hemiacetals **17** are produced directly not via lactone-aldehyde **5** (Scheme 12) or via tricycle **6** (Scheme 13). In this reaction, a weak characteristic signal of methine (OCHO, 5.41 ppm) in the ^{1}H NMR spectra was observed. This supports the existence of a form of tricycle ring and the possibility of the mechanism via tricycle **6**.

From these results, we propose the possible mechanism for the hydride-transfer rearrangement of dioxa-azawurtzitane **7-Na** (Scheme 14). Dioxa-azawurtzitane **7-Na** is in equilibrium with the ring-opening forms in the presence of water. In the tricycle structure, the hydride can be easily transferred to give tricycle **A**. The hydride-transfer is followed by the rapid domino reaction to yield the kinetic product **9-Na**. The thermodynamic product **12-Na** is also formed via tricycle **A**. Lactam-aldehyde **12-Na** is also available as a scaffold because of the stability.

Scheme 13



Conclusions

In summary, we have described the new synthetic method for dioxa-azawurtzitanes to selectively cap amino groups in amino acids or peptides. Dioxa-azawurtzitane **7-Na** almost quantitatively isomerizes to lactone-imine **9-Na** through the hydride-transfer rearrangement. Lactone-imine **9-Na** also isomerizes to lactam-aldehyde **12-Na** in DMSO. The alkali metal ions accelerate the rearrangement reactions and stabilize the lactone-imine structures in acetonitrile. From the NMR evidence, it is suggested that the different route not via lactone-imine **9-Na** for the formation of lactam-aldehyde **12-Na** exists. The formation of lactone-imine **9-D** and lactam-aldehyde **12-D** from dioxa-azawurtzitane **7-Me** without $NaHCO_3$ suggests that the rearrangement is not a simple Tishchenko reaction. The formation of tricycle **13-Na$_2$** supports the possibility of the mechanism via tricycle rings for the hydride-transfer rearrangements.

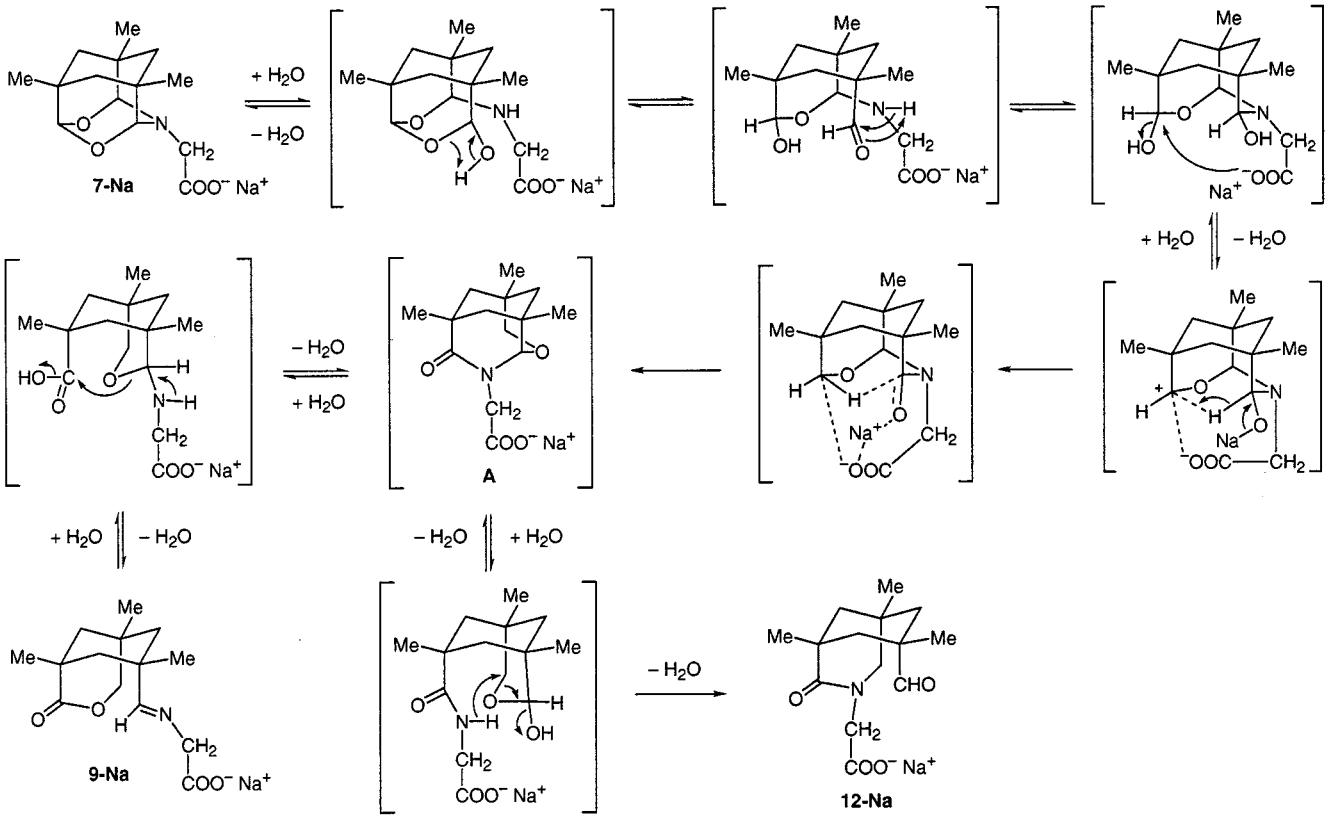
The dioxa-azawurtzitane ring has a potential for such transformation due to the synergistic effect. The derivatives of dioxa-azawurtzitane **7-Na** sustain acids and bases not to yield free glycine. Further study on exploring the utilization of peptide-containing dioxa-azawurtzitanes as scaffolds is in progress.

Experimental Section

General Methods. All reactions were performed in oven-dried glassware equipped with a magnetic stirring bar under argon atmosphere using standard syringe techniques. *cis,cis*-1,3,5-Triformyl-1,3,5-trimethylcyclohexane (**2**) was prepared by the similar procedures previously reported.[8] All other reagents were of commercial grade.

Sodium (1,7,9-Trimethyl-3,5-dioxa-12-azawurtzitano)-acetate (7-Na). An acetonitrile solution (8 mL) of trialdehyde **2** (40.4 mg, 0.19 mmol) was mixed with an aqueous solution (5 mL) of glycine (16.2 mg, 0.22 mmol) and $NaHCO_3$ (16.8 mg, 0.20 mmol). After the mixture had been reacted at room temperature for 2 h with stirring, volatiles were removed under reduced pressure. Dioxa-azawurtzitane **7-Na** was purified by washing with acetonitrile (43.2 mg, 0.15 mmol, 78%). Dioxa-azawurtzitane **7-K** was afforded by the similar procedure with $KHCO_3$. **7-Na:** colorless solids; ^{1}H NMR (acetonitrile-d_3:D_2O = 12:5, 500 MHz) δ 0.71 (1H, d, $^2J_{HH}$ = 11.9 Hz, CH_aH_e), 0.83 (2H, d, $^2J_{HH}$ = 12.2 Hz, CH_aH_e), 0.93 (3H, s, CH_3), 0.97 (6H, s, CH_3), 1.27 (2H, d, $^2J_{HH}$ = 12.2 Hz, CH_aH_e), 1.55 (1H, d, $^2J_{HH}$ = 11.9 Hz, CH_aH_e), 3.55 (2H, s, NCH_2CO), 4.14

Scheme 14



(2H, s, OCHN), 4.71 (1H, s, OCHO); ^{13}C NMR (acetonitrile-d_3:D_2O = 12:5, 125.7 MHz) δ 28.35 (CH_3), 28.79 (CH_3), 35.86 [$(CH_2)_2CCH_3$], 35.91 [$(CH_2)_2CCH_3$], 42.79 (CCH_2C), 43.79 (CCH_2C), 54.53 (CH_2N), 89.17 (OCHN), 100.11 (OCHO), 178.17 (COO); MS (ESI) *m*/*z* 555 [28, $2M^- - Na$], 284 [100, $M^- - Na + H_2O$], 266 [48, $M^- - Na$].

The similar manner that was employed in the preparation of dioxa-azawurtzitane **7-Na** was used with trialdehyde **2** (30.9 mg, 0.15 mmol), Gly-His-Lys·AcOH·H_2O (32.5 mg, 0.078 mmol), and $NaHCO_3$ (13.0 mg, 0.16 mmol). Dioxa-azawurtzitanes **8-Na** was afforded in 86% yield (49.6 mg, 0.066 mmol). **8-Na**: colorless solids; ^{1}H NMR (acetone-d_6:D_2O = 8:5, 500 MHz) δ 0.86 (CH_3), 0.87 (CH_3), 0.88 (CH_3), 3.99 (OCHN), 4.01 (OCHN), 4.03 (OCHN), 4.65 (OCHO), 4.68 (OCHO); MS (ESI) *m*/*z* 723 [100, $M^- - Na$].

Methyl (1,7,9-Trimethyl-3,5-dioxa-12-azawurtzitano)-acetate (7-Me). An acetonitrile solution (4 mL) of trialdehyde **2** (46.1 mg, 0.22 mmol) was mixed with an aqueous solution (2.5 mL) of glycine methyl ester hydrochloride (26.5 mg, 0.21 mmol) and $NaHCO_3$ (17.9 mg, 0.21 mmol). After the mixture had been reacted at room temperature for 1.5 h with stirring, volatiles were removed under reduced pressure. After being extracted with CH_2Cl_2, the solvent was removed under reduced pressure. Dioxa-azawurtzitane **7-Me** was purified by molecular distillation (56.9 mg, 0.20 mmol, 96%). **7-Me:** colorless solids; ^{1}H NMR (acetonitrile-d_3, 500 MHz) δ 0.80 (1H, d, $^2J_{HH}$ = 11.6 Hz, CH_aH_e), 0.88 (2H, d, $^2J_{HH}$ = 12.2 Hz, CH_aH_e), 0.98 (3H, s, CH_3), 1.00 (6H, s, CH_3), 1.32 (2H, d, $^2J_{HH}$ = 12.2 Hz, CH_aH_e), 1.47 (1H, d, $^2J_{HH}$ = 11.6 Hz, CH_aH_e), 3.65 (3H, s, CH_3OCO), 3.84 (2H, s, NCH_2CO), 4.12 (2H, s, OCHN), 4.70 (1H, s, OCHO); ^{13}C NMR (acetonitrile-d_3, 125.7 MHz) δ 28.40 (CH_3), 28.95 (CH_3), 35.88 [$(CH_2)_2CCH_3$], 36.05 [$(CH_2)_2CCH_3$], 42.76 (CCH_2C), 44.25 (CCH_2C), 51.77 (CH_2N), 52.09 (CH_3O), 88.90 (OCHN), 99.99 (OCHO), 172.24 (COO). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.42; H, 8.24; N, 4.91.

Sodium [(1,5,7-Trimethyl-2-oxo-3-oxa-bicyclo[3.3.1]-non-7-ylmethylene)amino]acetate (9-Na). An acetonitrile solution (8 mL) of trialdehyde **2** (51.8 mg, 0.25 mmol) was mixed with an aqueous solution (5 mL) of glycine (17.7 mg, 0.24 mmol) and $NaHCO_3$ (20.7 mg, 0.25 mmol). After the mixture had been reacted at room temperature for 5 days with stirring, volatiles were removed under reduced pressure. Lactone-imine **9-Na** was obtained by washing with acetonitrile (68.6 mg, 0.24 mmol, 96%). Further purification was carried out by HPLC (TSK-GEL Amide-80), using CH_3CN/H_2O (3:1) as an eluent. **9-Na**: colorless solids; ^{1}H NMR (acetonitrile-d_3:D_2O = 12:5, 500 MHz) δ 0.97 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.05 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH_aH_e), 1.23 (1H, d, $^2J_{HH}$ = 13.7 Hz, CH_aH_e), 1.26 (3H, s, CH_3), 1.30 (1H, d, $^2J_{HH}$ = 12.8 Hz, CH_aH_e), 1.55 (1H, d, $^2J_{HH}$ = 12.8 Hz, CH_aH_e), 2.34 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH_aH_e), 2.51 (1H, d, $^2J_{HH}$ = 13.7 Hz, CH_aH_e), 3.47 (1H, d, $^2J_{HH}$ = 15.9 Hz, CH_2O), 3.57 (1H, d, $^2J_{HH}$ = 15.9 Hz, CH_2O), 4.02 (1H, d, $^2J_{HH}$ = 16.2 Hz, NCH_2CO), 4.35 (1H, d, $^2J_{HH}$ = 16.2 Hz, NCH_2CO), 8.15 (1H, s, $CH{=}NCH_2$); ^{13}C NMR (acetonitrile-d_3:D_2O = 12:5, 125.7 MHz) δ 24.78 (CH_3), 28.09 (CH_3), 30.21 (CH_3), 32.03 [$(CH_2)_2CCH_3$], 39.38 [$(CH_2)_2CCH_3$], 40.68 (CCH_2C), 43.93 [$(CH_2)_2CCH_3$], 47.69 (CCH_2C), 47.83 (CCH_2C), 62.62 (CH_2O), 63.87 (NCH_2CO), 170.01 (COO), 183.83 (COO), 187.32 ($CH{=}NCH_2$); MS (ESI) *m*/*z* 555 [35, $2M^- - Na$], 266 [100, $M^- - Na$]. Anal. Calcd for $C_{14}H_{20}NNaO_4 \cdot 1.5H_2O$: C, 53.16; H, 7.33; N, 4.43. Found: C, 53.32; H, 7.72; N, 4.74.

The similar manner using excesses of glycine and $NaHCO_3$ gave tricycle **13-Na$_2$**[10] as a byproduct. Tricycle **13-Na$_2$**[10] was recrystallized from CH_3OH/CH_3CN. **13-Na$_2$**: colorless solids; ^{1}H NMR (acetonitrile-d_3:D_2O = 12:5, 500 MHz) δ 0.76 (1H, d, $^2J_{HH}$ = 11.9 Hz, CH_aH_e), 0.89 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.03 (1H, d, $^2J_{HH}$ = 12.3 Hz, CH_aH_e), 1.09 (3H, s, CH_3), 1.11 (1H, d, $^2J_{HH}$ = 13.7 Hz, CH_aH_e), 1.47 (1H, d, $^2J_{HH}$ = 13.7 Hz, CH_aH_e), 1.71 (1H, d, $^2J_{HH}$ = 11.9 Hz, CH_aH_e), 1.81 (1H, d, $^2J_{HH}$ = 12.2 Hz, CH_aH_e), 1.94 (1H, d, $^2J_{HH}$ = 12.1 Hz, CH_2N), 2.37 (1H, d, $^2J_{HH}$ = 12.1 Hz, CH_2N), 2.96 (1H, d, $^2J_{HH}$ = 15.7 Hz, NCH_2CO), 3.11 (1H, d, $^2J_{HH}$ = 15.7 Hz, NCH_2CO), 3.28 (1H, d, $^2J_{HH}$ = 16.5 Hz, NCH_2CO), 4.16 (1H, d, $^2J_{HH}$ = 16.5 Hz, NCH_2CO), 4.23 (1H, s, NCHN);^{13}C NMR (acetonitrile-d_3:D_2O = 12:5, 125.7 MHz) δ 26.84 (CH_3), 29.45 (CH_3), 31.83 (CH_3), 32.33 [$(CH_2)_2CCH_3$], 35.45 [$(CH_2)_2CCH_3$], 40.45 [$(CH_2)_2$-

CCH_3], 44.61 (C*C*H_2C), 46.98 (C*C*H_2C), 50.28 (C*C*H_2C), 53.57 (CH_2N), 57.12 (CH_2N), 59.83 (CH_2N), 82.60 (NCHN), 176.67 (CO), 178.18 (CO), 182.10 (CO).

NMR Monitoring Experiments. Lactone-imine **9-Na** (6.2 mg, 0.02 mmol) was added to DMSO-d_6 (0.8 mL) in an NMR tube. Storage of the solution at room temperature for 3 months gave lactam-aldehyde **12-Na** quantitatively. **12-Na**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.79 (3H, s, CH_3), 0.88 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.09 (1H, dt, $^2J_{HH}$ = 13.6 Hz, $^4J_{HH}$ = 1.7 Hz, $^4J_{HH}$ = 1.0 Hz, CH_aH$_e$), 1.20 (1H, d, $^2J_{HH}$ = 13.7 Hz, CH_aH$_e$), 1.27 (1H, dd, $^2J_{HH}$ = 12.5 Hz, $^4J_{HH}$ = 2.1 Hz, CH_aH$_e$), 1.64 (1H, d, $^2J_{HH}$ = 12.5 Hz, CH$_a$$H_e$), 2.10 (1H, d, $^2J_{HH}$ = 13.6 Hz, CH$_a$$H_e$), 2.16 (1H, d, $^2J_{HH}$ = 13.7 Hz, CH$_a$$H_e$), 2.27 (1H, d, $^2J_{HH}$ = 15.9 Hz, NCH_2CO), 2.46 (1H, dd, $^2J_{HH}$ = 11.8 Hz, $^4J_{HH}$ = 2.1 Hz, CH_2N), 3.40 (1H, dd, $^2J_{HH}$ = 11.8 Hz, $^4J_{HH}$ = 1.7 Hz, CH_2N), 4.05 (1H, d, $^2J_{HH}$ = 15.9 Hz, NCH_2CO), 9.00 (1H, d, $^4J_{HH}$ = 1.0 Hz, CHO); ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 25.41 (CH_3), 26.12 (CH_3), 28.42 (CH_3), 29.79 [(CH$_2$)$_2$*C*CH_3], 38.04 [(CH$_2$)$_2$-*C*CH_3], 43.18 (C*C*H_2C), 44.26 (C*C*H_2C), 45.41 [(CH$_2$)$_2$*C*CH_3], 45.51 (C*C*H_2C), 50.75 (N*C*H_2CO), 58.76 (CH_2N), 170.59 (CO), 171.76 (CO), 203.03 (CHO).

Lactone-imine **10-Na** (3.8 mg, 0.01 mmol) was added to CD_3-CN/D_2O (0.8 mL/0.5 mL) in an NMR tube. A D_2O solution (0.5 mL) of NaOH (9.7 mg, 0.24 mmol) was added to this solution. The ^{1}H NMR signals of **10-Na** immediately disappeared, and the formation of dicarboxylate **11-Na$_2$** was detected. The signals of **11-Na$_2$** gradually disappeared, but further products were not detected. **11-Na$_2$**: ^{1}H NMR (acetonitrile-d_3:D_2O = 4:5, 500 MHz) δ 0.63 (1H, d, $^2J_{HH}$ = 12.0 Hz, CH_aH$_e$), 0.69 (3H, s, CH_3), 0.72 (3H, s, CH_3), 0.75 (2H, d, $^2J_{HH}$ = 14.1 Hz, CH_aH$_e$), 0.85 (3H, s, CH_3), 1.48 (1H, d, $^2J_{HH}$ = 12.0 Hz, CH$_a$$H_e$), 2.07 (1H, d, $^2J_{HH}$ = 10.4 Hz, CH_2N), 2.21 (1H, d, $^2J_{HH}$ = 14.1 Hz, CH$_a$$H_e$), 2.25 (1H, d, $^2J_{HH}$ = 14.3 Hz, CH$_a$$H_e$), 2.59 (1H, d, $^2J_{HH}$ = 10.4 Hz, CH_2N), 3.99 (1H, s, NCHOD); ^{13}C NMR (acetonitrile-d_3:D_2O = 4:5, 125.7 MHz) δ 21.54 (CD_2), 27.19, 28.84, 31.87, 33.73, 36.86, 41.94, 44.53, 47.67, 48.05, 54.01, 90.54, 177.31, 184.03.

Dioxa-azawurtzitane **7-Me** (7.0 mg, 0.03 mmol) was added to CD_3CN (0.8 mL) in an NMR tube. A D_2O solution (0.5 mL) of $NaHCO_3$ (2.3 mg, 0.03 mmol) was added to this solution. Storage of the solution at 50 °C for 6 days yielded lactone-imine **9-Na** almost quantitatively. A small amount of lactam-aldehyde **12-Na** was also detected. However, the amount of **12-Na** hardly increased at room temperature after 2 months.

Dioxa-azawurtzitane **7-Me** (5.5 mg, 0.02 mmol) was added to CD_3CN (0.8 mL) in an NMR tube. D_2O (0.5 mL) was added to this solution. Storage of the solution at room temperature for 2 weeks gave free MeOD. Broad signals were also observed. After 2 months, lactone-imine **9-D** and lactam-aldehyde **12-D** (**9-D**:**12-D** = 5:3) were mainly formed.

Trialdehyde **2** (6.8 mg, 0.03 mmol) was added to CD_3CN (0.8 mL) in an NMR tube. A D_2O solution (0.5 mL) of $NaHCO_3$ (2.8 mg, 0.03 mmol) was added to this solution. After 4 h, the broad signals of hydrolyzed compounds **16** were observed. Storage of the solution at room temperature for 2 months yielded hemiacetals **17a**[8] and **17b**[8] (**17a**:**17b** = 1:6).

Computational Methods. All geometry optimizations and conformer searches were performed using the Gaussian 98 program.[13]

Acknowledgment. We thank Professor Masahiro Hirama and referees for their helpful suggestions relating to the hydride-transfer rearrangement mechanism. This work was supported by Industrial Technology Research Grant Program in '01 from the New Energy and Industrial Technology Development Organization of Japan (00A43007a).

Supporting Information Available: Spectroscopic data and optimized geometry data for representative products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO011088H