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The Overman Rearrangement on a Diacetone-D-Glucose Template: Kinetic and Theoretical Studies on the Chirality Transcription[1]

Tadashi Eguchi, Takashi Koudate, and Katsumi Kakinuma*

Department of Chemistry, Tokyo Institute of Technology
O-okayama, Meguro-ku, Tokyo 152, Japan

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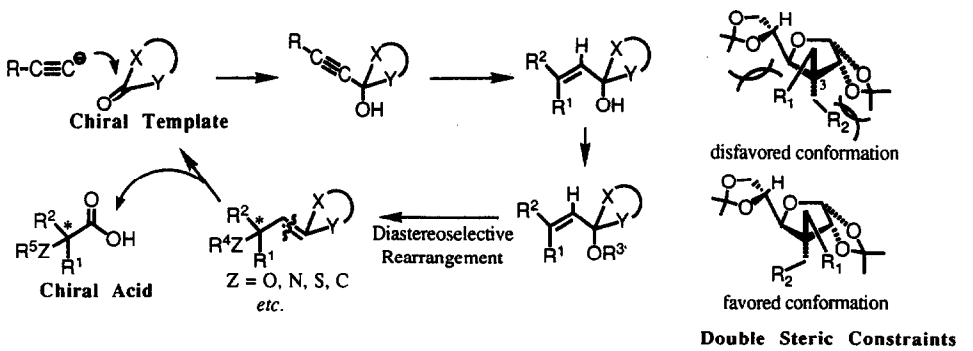
***Abstract**: A divergent and highly enantioselective synthetic methodology for both enantiomers of α-amino acids and chirally deuterated glycine was developed based upon the chirality transcription approach using a versatile chiral template, diacetone-D-glucos-3-ulose **1**. An acetylenic C_3 starting unit was introduced into the chiral template **1** and was transformed into (E)-allylic trichloroacetimidate **5a** and (Z)-counterpart **5b** via stereospecific reduction and condensation with trichloroacetonitrile. The Overman's thermal rearrangement of **5a** and **5b** underwent with high diastereoselectivity to afford (Z)-allylic trichloroacetamide **6a** and **6b**, which in turn were converted to L- and D-alanine, respectively, by oxidative cleavage of the double bond and acid hydrolysis. The effectiveness of the present approach was assessed by using the simplest allylic alcohol system, i.e. (Z)- and (E)-monodeuterated allylic trichloroacetimidates **10a** and **10b**. Both enantiomers of chirally deuterated glycine were prepared stereoselectively in a similar sequence of reactions. Kinetic analyses of the template-based diastereoselective rearrangement of **5a** and **5b** were carried out along with theoretical studies of the transition states using the semi-empirical molecular orbital calculations, PM3-MNDO, which allowed us to deduce the mechanism of chirality transcription on the versatile chiral template **1**.*

INTRODUCTION

Carbohydrates are important sources of chirality in organic synthesis, especially for the synthesis of physiologically significant natural products.[2] Most of these synthetic approaches utilize the individual chiral centers of carbohydrate chirons as the source of stereogenic centers of the target molecules. During the first synthesis of D-(6*R*)- and (6*S*)-(6-$^2H_1$)glucose,[3] we became aware of possible stereochemical control element to be exploited, that is, the intrinsic molecular architecture of the carbohydrates and the derivatives thereof may affect an important function as a template for chirality transcription irrespective of the individual stereogenic centers. An alkynyl carbanion is added to a chiral template, 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexos-3-ulose (**1**). The derived alkynyl carbinol can be stereoselectively reduced to either an (*E*)- and a (*Z*)-allylic alcohol system. An appropriate reaction of the olefinic carbons may give rise to chirality transcription, by which new chiral centers are created. This concept was successfully utilized recently in the synthesis of chirally monodeuterated glycerols and chiral glycines,[1,4] in which the concept materialized in combination with *inter*molecular oxidations of the allylic alcohol to diastereoisomeric products and chromatographic separation thereof. This methodology was based upon single steric constraint and was suffered from inevitable chromatographic separation. Further improvement of this first generation of the chirality transcription approach has now allowed to develop the second generation, which involves highly diastereoselective *intra*molecular rearrangement due to double steric constraints. Chromatographic separation of diastereomers is unnecessary. The present concept of the chirality transcription is illustrated in Scheme 1.



Scheme 1

The α- and β-substituents introduced onto the C-3 position of **1** must sterically interact with an α-oriented bulky 1,2-*O*-isopropylidene protecting group and a β-oriented bulky substituent at C-4 on the five-membered furanose ring so that the β-substituent at C-3 tends to depart from the bulky C-4 substituent and the α-substituent at C-3 tends to depart from the 1,2-*O*-isopropylidene group. In other words, these dual repulsive constraints may well force the two substituents on the C-3 position of **1** into a unique orientation so that the stereochemical outcome of the intramolecular reaction between the substituents at C-3 can be predictable. Successful demonstrations of this concept have recently been published in a preliminary form.[5]

In this paper, we describe a full account of the divergent and highly enantioselective synthesis of both enantiomers of optically active α-amino acids and chirally deuterated glycine based upon the aforementioned chirality transcription approach using a versatile chiral template **1**. The Overman's thermal rearrangement of trichloroacetimidates was employed as the key reaction,[6] and the transition states of the rearrangement were deduced from the semi-empirical molecular orbital calculations. Also described are the features and mechanism of the present chirality transcription elucidated from the kinetic analyses and the theoretical calculations.

RESULTS AND DISCUSSION

Synthesis of both enantiomers of alanine and chirally deuterated glycines

With the anticipation described above, we first attempted a novel method of stereochemical control for the synthesis of chiral α-amino acids. The target selected were D- and L-alanine, because alanine is by any means the smallest chiral α-amino acid so that the capability of the present approach for the stereochemical control may be appropriately evaluated. Required manipulations included: 1) transformation of an acetylenic C_3 starting unit linked to the chiral template **1** to an (*E*)- or (*Z*)-allylic alcohol *via* stereospecific reduction, 2) the Overman's thermal rearrangement of the derived imidates to diastereoselectively introduce a nitrogen atom,[6] and 3) the oxidative cleavage of the resulting double bond. The Overman's rearrangement was applied previously to the synthesis of racemic α-amino acids by Takano *et al.*[7]

A versatile synthon in the present approach is crystalline 3-*C*-ethynyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose **2a**, which was prepared in good yield and with high stereoselectivity from **1** as described previously.[4] The starting material for alanine, 3-*C*-(propyn-1-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose **3b** was prepared from **2** *via*: 1) trimethylsilylation of the OH group, 2) methylation of the acetylene, and 3) desilylation, in 70 % overall yield. Stereospecific reduction of **3b** with $LiAlH_4$ in THF at room temperature

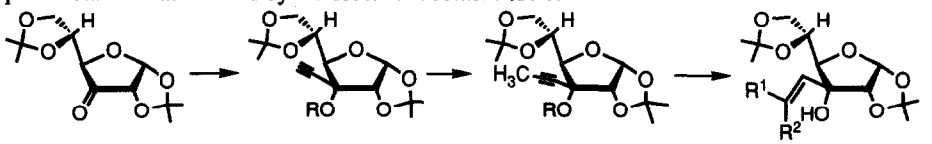
afforded the (*E*)-olefin **4a**, which in turn was transformed to a crystalline imidate **5a** by a method adopted from the Overman's protocol in 76 % yield. The rearrangement of **5a** was carried out in xylene under reflux for 36 hr to give a trichloroacetamide **6a** in 90 % yield. The stereoselectivity of the reaction turned out to be as high as 94:6 as determined by ^{1}H-NMR analysis after removal of the solvent from the reaction mixture. Minor signals were assumed to be due to a product formed by a reaction on the opposite face of the double bond, but were not rigorously assigned. The stereochemistry of **6a** was assigned by the ^{1}H-NMR differential NOE experiments, in which the irradiation of the olefinic proton signal at 5.88 ppm clearly affected mutual signal enhancement of the H-4 signal at 4.63 ppm of the furanose ring but not of the H-2 signal at 5.17 ppm, thereby suggesting the *Z*-geometry for the resulting double bond. This suggested that the nitrogen attack took place to the *re*-face of the double bond of **5a**. Based on these results, the absolute configuration of the crucial methine group attached to the amide group was assigned as *R*. This was ultimately confirmed by the following transformations of **6a** into D-alanine. Thus, ruthenium oxidation of **6a** under the Sharpless conditions[8] afforded trichloroacetyl alanine **7a** in 36 % yield. Acid hydrolysis of **7a** finally provided D-alanine **8a** in 69 % yield.

As to the enantioisomeric L-alanine, the (*Z*)-allyl alcohol **4b**, obtained in 78 % yield by hydrogenation of **3b** over Pd/$CaCO_3$, was similarly converted in 68 % yield to the corresponding imidate **5b**, which was then subjected similarly as above to the rearrangement. Solvent was removed from the reaction mixture by evaporation and the residue was directly analyzed by ^{1}H-NMR, which suggested almost quantitative formation of **6b**. Essentially no trace of signals due to the isomeric products was observed. In other words, the reaction proceeded almost stereospecifically. The *Z*-geometry for the double bond in **6b** was confirmed again by the ^{1}H-NMR NOE experiments, in which the irradiation of the vinylic proton signal at 5.70 ppm enhanced the H-4 signal at 4.77 ppm *vice versa*. Consequently, the *si*-face attack of the nitrogen atom on the double bond of **5b** proved to be taken place during the rearrangement and the *S*-configuration was strongly implied for the amide-carrying methine group. The rearranged product **6b** was converted to L-alanine **8b** through the same treatment as described above.

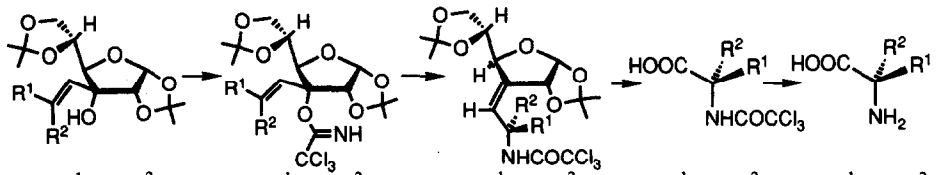
Attempts were then directed to assess the effectiveness of the present approach with the simplest allylic alcohol system, *i.e.* (*Z*)- and (*E*)-monodeuterated allyl alcohols **9a** and **9b**, the potential precursors of chirally deuterated glycines. Chirally deuterated glycines are important in bioorganic research. The synthetic methods so far developed for chiral glycine are not flexible but rather specific in terms of the starting materials and the chemical manipulations involved.[9,10] Little is known as to the synthetically divergent methodology in which a common starting material and common manipulations can be employed to generally prepare chiral α-amino acids and chiral glycines.[10]

Reduction of **2a** with $LiAl^2H_4$ gave regio- and stereoselectively a deuterated allyl alcohol **9a** in good yield as already described.[11] The deuterium was introduced into the γ-position relative to the OH group and less than 5 % of the product was β-deuterated as judged by ^{1}H-NMR spectroscopy. The allylic alcohol **9a** was then transformed to an oily imidate **10a**, in 89 % yield. The rearrangement of **10a** was carried out in xylene under reflux for 36 hr to afford in 97 % yield a trichloroacetamide **11a**. The stereochemistry was assigned as described above by the ^{1}H-NMR differential NOE experiments, which again demonstrated clearly mutual signal enhancement between the H-4 signal at 4.65 ppm and the olefinic proton signal at 6.03 ppm. No NOE was observed between H-2 at 5.24 ppm and the olefinic proton. Thus, the *Z*-geometry was assigned to the resulting double bond. The content of the (*E*)-isomer was estimated to be 9 % (*Z* : *E* = 10 : 1). This isomer ratio was a key determinant of the chiral purity of the deuterated glycine product. Subsequent transformations involving

RuO_4 oxidation and acid hydrolysis were carried out to afford (2*S*)-[2-$^2H_1$]glycine **12a**, $[\alpha]_{230}$ -49.0° (*c* 2.1, H_2O), in 32 % yield. The absolute configuration of **12a** implied that the imidate attack took place to the *si*-face of the deuterated double bond of **10a** and this stereochemical feature was completely identical with that of the methylated cases. Complementary results were obtained, as anticipated, using the regioisomerically deuterated olefin **9b** as a starting material, where (2*R*)-[2-$^2H_1$]glycine **12b**, $[\alpha]_{230}$ +42.6° (*c* 0.85, H_2O), was produced. The optical rotation was affected by the deuterium content of **9b**.



1 **2a**: R=H, **2b**: R=TMS **3a**: R=TMS, **3b**: R=H **4a**: R^1=Me, R^2=H, **4b**: R^1=H, R^2=Me



4a: R^1=Me, R^2=H **5a**: R^1=Me, R^2=H **6a**: R^1=Me, R^2=H **7a**: R^1=Me, R^2=H **8a**: R^1=Me, R^2=H
4b: R^1=H, R^2=Me **5b**: R^1=H, R^2=Me **6b**: R^1=H, R^2=Me **7b**: R^1=H, R^2=Me **8b**: R^1=H, R^2=Me
9a: R^1=H, R^2=^2H **10a**: R^1=H, R^2=^2H **11a**: R^1=H, R^2=^2H **12a**: R^1=H, R^2=^2H
9b: R^1=^2H, R^2=H **10b**: R^1=^2H, R^2=H **11b**: R^1=^2H, R^2=H **12b**: R^1=^2H, R^2=H

Scheme 2

The results described above demonstrated that: 1) irrespective of the geometry of the starting olefins, the same face of the double bond was attacked in the rearrangement to afford the products with (*Z*)-geometry in both methylated and non-methylated cases: and 2) even in the simplest allyl alcohol system, efficient stereoselection was achieved. In other word, our prediction of the stereochemical control on the carbohydrate template was clearly verified. It remained to be understood, however, why the *Z*-imidate **5b** showed higher diastereofacial selectivity than the corresponding *E*-isomer **5a** in the thermal rearrangement. Critical analyses of this statistical results and of the mechanistic bases of this chirality transcription methodology should be important in order to broaden its scope and limitation. We therefore undertook extensive studies on the mechanism of the key reaction, the thermal rearrangement of the imidates on the diacetone-D-glucose template.

The mechanism of chirality transcription

Kinetic studies. The thermal rearrangement of the allylic imidates was reported to follow the first order kinetics, thereby suggesting the reaction to be intramolecular. Previously, Overman proposed that the rearrangement reaction under the thermal conditions proceeds *via* the concerted [3,3]sigmatropic mechanism.[6] However, a detailed mechanism of the thermal rearrangemnt of allylic imidates has yet to be elucidated. A prerequisite to understand the mechanism of the chirality transcription is therefore a detailed knowledge of the reaction surface as well as the geometric features of the transition states during the rearrangement reaction. To tackle these, use was made of the semi-empirical molecular orbital methodology as well as the kinetic analysis.

Firstly, the reaction kinetics of the thermal rearrangement of imidates **5a** and **5b** were analyzed. The reactions were conveniently followed under the conditions of various temperatures by monitoring the disappearance of olefinic methyl group signal of the starting imidates on the ^{1}H NMR spectroscopy. First-order kinetics were clearly observed over the two half-lives periods. This demonstrated that the thermal rearrangement of the imidates **5a** and **5b** proceeds intramolecularly. The resulting rate constants (k) are summarized in Table 1 and the graphical plots are shown Figure 1. The plots demonstrated well-fitted linearity, and the activation enthalpies were estimated to be 25.6 kcal/mol for the *E*-isomer **5a** and 28.3 kcal/mol for the *Z*-counterpart **5b**. These values are slightly higher than the value of the geranyl imidate (23.8 kcal/mol) reported previously by Overman.[6] This may be due to the severe steric constraint of the sugar template in the present cases.

With these statistical results of stereoselectivity and kinetic parameters in hands, we then took advantage of recent advances in theoretical chemistry to evaluate our system. The MNDO-PM3 semi-empirical molecular orbital method was used to estimate the geometries of the transition-state and ground-state of the imidate rearrangement.[12]

Table 1. Kinetics of the Thermal Rearrangement of the Imidates **5a** and **5b**.

Compound	Temp (°C)	10^5k (S^{-1})	$\Delta H^{\neq}$ (kcal/mol)
5a	120.0	2.72 ± 0.3	25.6 ± 0.4
	123.0	3.39 ± 0.3	
	127.0	4.97 ± 0.5	
	132.0	7.92 ± 0.8	
5b	125.0	1.62 ± 0.2	28.3 ± 0.5
	127.0	1.97 ± 0.2	
	133.0	4.14 ± 0.4	
	137.0	4.58 ± 0.8	

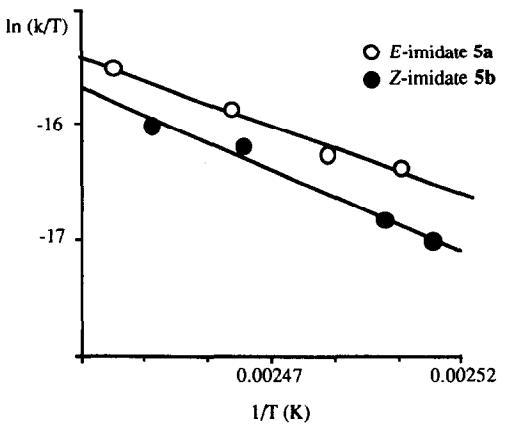


Figure 1. Temperature dependence of the reaction rate constants for **5a** and **5b**.

Computational studies. The MOPAC (version 6.0) molecular orbital package utilizing the MNDO-PM3 Hamiltonian was used for the semi-empirical MO calculations.[12,13] The transition-states for the imidate rearrangement of the model compounds **13-15** were located using the SADDLE routine[13] implemented in MOPAC. No arbitrary assumption was imposed on to find the most likely geometry for the transition-state. Further refinements of the transition-states were carried out by minimizing the norm of energy[14] with the use of

keyword NLLSQ. The starting geometries for the transition-states from the imidates of **5a** and **5b** were generated by incorporating both enantiomeric forms of each transition-state of the model compounds **14** and **15** separately into the sugar moiety so that the favored and disfavored conformations could be calculated. Each structure was then minimized by multitortional optimization dihedral analysis in the MM2 force field[16] with the fixed geometry of the transition-state structure of the reaction site. The resulting global minima were used for the next calculation. Further refinements for each transition-state for the imidate rearrangement of **5a** and **5b** were carried out by the Baker's eigenvector following method[17] with the use of the keyword TS implemented in the MOPAC. All the transition-states were characterized by the presence of one and only one negative force constant in the Hessian matrix of a force calculation.[15] Calculations were carried out on Stardent TITAN or Sun Microsystems SUN4 work stations at the Computer Center of Tokyo Institute of Technology.

The transition-state structure of the rearrangement of 3-propenyl trichloroacetimidate **13** was first deduced as a model. Two structures were obtained as possible transition-states depending upon the geometry of the imine moiety. As can be seen in Figure 2, the one is the transition-state of an allylic rearrangement type through an ion-pair like mechanism and the other is a [3,3]-sigmatropic transition-state. The calculated enthalpies of formation indicated that the transition-state of the ion-pair mechanism is remarkably more stable than the [3,3]-sigmatropic transition-state. Additional evidences were that the imine proton of the *E*-imidate **5a** was exchangeable with D_2O and that the crystallographical structure of **5a** clearly included *E*-geometry in the imine moiety.[18] Thus, the thermal rearrangement of allylic imidates appears to proceed through the ion-pair mechanism of allylic rearrangement. These results were coincided with the previous reports of catalytic rearrangement of allylic imidates by mercury (II) salts,[6] Pd (0) and Pd (II) species.[19] Furthermore, the mechanism of these catalytic reactions can be rationalized with stabilization of the ionic nature of the transition-state in the allylic rearrangement by the metallic species. The transition-states of (*E*)- and (*Z*)-2-butenyl trichloroacetimidates were also calculated in the same manner (data not shown).

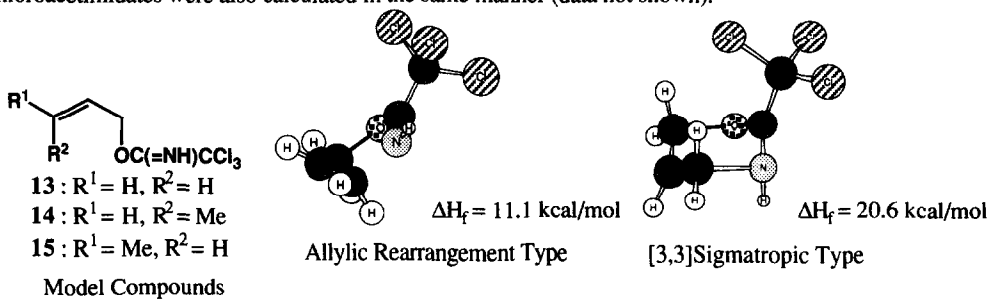


Figure 2. Structures of the model compounds **13-15** and the transition-states of **13** for the rearrangement.

Inclusion of the transition-state structure into the sugar moiety represents a crucial test for our mechanistic proposal of chirality transcription on the diacetone-D-glucose template. Calculation with the sugar moiety did not essentially cause drastic changes in the transition-states in comparison with the model studies mentioned above. The resulting transition-state structures for the rearrangement of the imidates **5a** and **5b** are shown in Figure 3. The calculated values of the heat of formation at 415 K for each transition-states are also included in Figure 3, which clearly indicated the preferred reaction pathway. The ground-state energies at 298 K for the favored transition-states were also calculated by the intrinsic reaction coordinate method.[20] The activation enthalpies for the reactions of both (*E*)- and (*Z*)-imidates were estimated first by recalculating the corresponding ΔH_f (298 K)

and then by substracting the ΔH_f (ground-state, 298 K) from ΔH_f (transition-state, 298 K). The results were compared with the experimental data. The structures for each ground-states are shown in Figure 4.

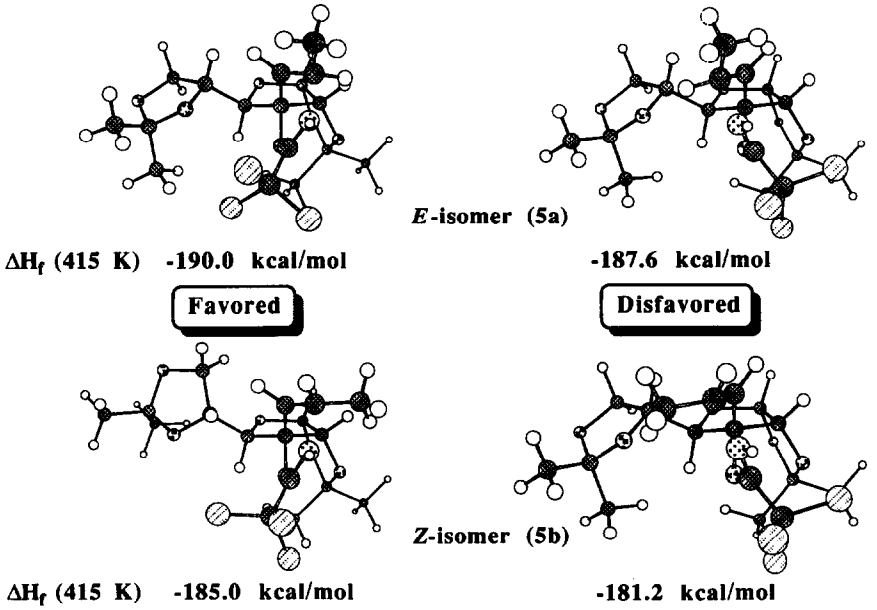


Figure 3. Possible transition-states of the imidate rearrangement of **5a** and **5b** calculated with the MNDO-PM3 method.

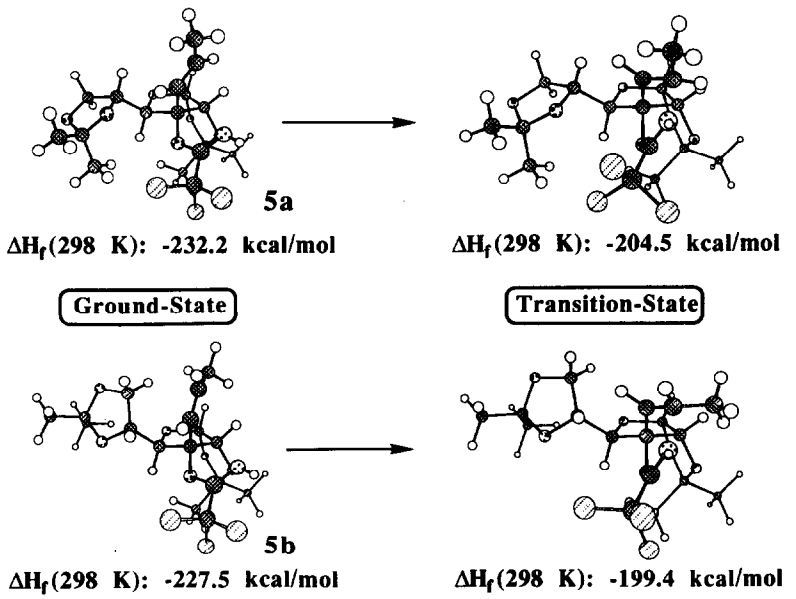


Figure 4. The transition-state and ground-state structures of the imidate rearrangement of **5a** and **5b** calculated with MNDO-PM3 method.

Table 2 shows the comparison of the estimated and experimental $\Delta H^{\neq}$s and stereoselectivities at 415 K for the rearrangement of the imidates **5a** and **5b** deduced from the heat of formation for the favored and disfavored cases as described above. At a glance, extremely good agreement can be notified between the theoretical values and the experimental data. In other words, these results further reinforced that the thermal rearrangement of allylic imidates proceeds *via* the allylic rearrangement mechanism rather than the [3,3]sigmatropic fashion.

Table 2. Theoretical and Experimental Kinetic Parameters.

Compound	$\Delta H^{\neq}$ (kcal/mol) calcd/exptl	Selectivity calcd (415 K)/exptl
5a	27.7 / 25.6	95 : 5 / 94 : 6
5b	28.1 / 28.3	99.2 : 0.8 / >99.5 : <0.5

The high diastereofacial selectivity in the thermal rearrangement of the imidates **5a** and **5b** can be interpreted by the calculated favored transition-states. The bulky trichloroacetimidic group sterically interacts not only with 1,2-*O*-isopropylidene protecting group as anticipated, but also with the substituent at C-4 of the furanose ring. Thus, the conformational flexibility of trichloroacetimidic group is greatly reduced in the transition-state. As to the 3β-alkenyl group is concerned, severe steric contact between the C-4 substituent and the 3β-alkenyl group might be encountered in the disfavored transition-states. In other word, this transition-state would almost be forbidden. Conversely, rotational flexibility between the 3β-vinyl group and the C-3 carbon allows only the favored transition-states to form. Consequently, the thermal rearrangement of the allylic imidates **5a** and **5b** proceeds with high diastereofacial selectivity through the preferred transition-states. The higher diastereofacial selectivity for the *Z*-imidate **5b** than for the *E*-counterpart **5a** seemed reasonable, since the *Z*-imidate **5b** involves lager steric interaction between the C-4 substituent and the 3β-alkenyl group. Apparently, the 3α-bulky substituent is a crucial determinant for the high diastereofacial selectivity.

CONCLUSION

Since the alkylation of **2** is operationally quite simple and varieties of the alkyl substituent can be introduced, the potential usefulness of the present method for the chiral synthesis of a wide variety of α-amino acids may well be anticipated. Although the present chemical transformations have not yet been optimized, the present study appears to be of significance in demonstrating a new way to utilize the chirality of the carbohydrate derivatives. In addition, the kinetic and theoretical analyses of the present intramolecular diastereoselection may allow further rational design of more efficient chiral templates. Furthermore, the present results clearly illustrates the high potential of combined use of the experimental and semi-empirical computational approaches to analyse the intriguing chemical reactions. Currently, further extension of our chirality transcription methodology based on diacetone-D-glucose template are in progress.

EXPERIMENTAL

Melting points were measured with a Yanagimoto BY-1 micromelting point apparatus and are uncorrected. IR spectra were taken on a JASCO IR-810 or a Hitachi 285 infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on JEOL FX-200, JEOL GSX-270, and/or JEOL GSX-500 spectrometers. Deuteriochloroform (99.75 % atom enriched, Merck) was used for the NMR solvent, unless otherwise stated. ^1H NMR chemical shifts were reported in ppm relative to the signal of internal tetramethylsilane. Column chromatography was carried out with a Kieselgel 60 (70-230 mesh, Merck). All reactions were carried out in an inert (Ar or N_2) atmosphere.

3-*C*-Ethynyl-3-*O*-trimethylsilyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (2b). Chlorotrimethylsilane (4.0 ml, 30.1 mmol) was added to a solution of **2a**[7] (8.0 g, 28.1 mmol) in pyridine (20 ml) at 0°C. After 10 min of stirring at room temperature, sat. aqueous NH_4Cl solution was added and the mixture was extracted with ether. The organic phase was washed with 1N HCl and brine, successively, dried over Na_2SO_4, filtered, and concentrated to give colorless crystalline **2b** (9.69 g, 97 %). mp 83-84°C. ^1H NMR: δ 0.22 (9H, s), 1.35 (3H, s), 1.36 (3H, s), 1.43 (3H, s), 1.54 (3H, s), 2.62 (1H, s), 4.06 (1H, d, *J*=5.4 Hz), 4.07 (1H, dd, *J*=6.4, 8.8 Hz), 4.11 (1H, dd, *J*=5.4, 8.8 Hz), 4.37 (1H, dt, *J*=6.4, 5.2 Hz), 4.44 (1H, d, *J*=3.9 Hz), 5.79 (1H, d, *J*=3.9 Hz). ^{13}C NMR: δ 1.4, 25.5, 26.7, 26.8, 27.0, 65.7, 74.7, 76.0, 77.3, 82.1, 82.6, 84.5, 104.2, 108.8, 113.2. IR ($CHCl_3$): 3300 (≡C-H), 2100 (C≡C) cm^{-1}. *Anal.* calcd for $C_{17}H_{28}O_6Si$: C; 57.28, H; 7.92. Found: C; 57.56, H; 8.21.

3-*C*-(1-propynyl)-3-*O*-trimethylsilyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (3a). A solution of n-butyllitium in hexane (6.4 ml, 1.66 M) was added dropwise to a solution of **2b** (3.14 g, 8.8 mmol) in THF (15 ml) at -78°C. The mixture was stirred for 20 min at the same temperature, and then iodomethane (0.8 ml, 13.2 mmol) was added. Stirring was continued at -78°C for an additional 2 h. The reaction was quenched by addition of sat. aqueous NH_4Cl solution and the mixture was extracted with ether. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed over silica gel with hexane-ethyl acetate (3:1) to give **3a** (2.80 g, 89 %). mp 85-87°C. ^1H NMR: δ 0.20 (9H, s), 1.33 (3H, s), 1.37 (3H, s), 1.43 (3H, s), 1.54 (3H, s), 1.86 (3H, s), 4.04 (1H, dd, *J*=6.8, 8.3 Hz), 4.07 (1H, d, *J*=4.4 Hz), 4.10 (1H, dd, *J*=5.9, 8.2 Hz), 4.34 (1H, m), 4.36 (1H, d, *J*=3.4 Hz), 5.76 (1H, d, *J*=3.4 Hz). ^{13}C NMR: δ 1.4, 3.6, 25.5, 26.6, 26.8, 26.9, 65.3, 74.7, 75.9, 77.9, 82.0, 84.6, 85.4, 104.2, 108.5, 113.0. IR ($CHCl_3$): 2100 (C≡C) cm^{-1}. *Anal.* calcd for $C_{18}H_{30}O_6Si$: C; 58.35, H; 8.16. Found: C; 58.09, H; 8.36.

3-*C*-(1-propynyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (3b). A mixture of **3a** (3.42 g, 9.6 mmol) and K_2CO_3 (110 mg) in methanol (20 ml) was stirred for 3 h at room temperature. The reaction was quenched by addtion of sat. aqueous NH_4Cl solution and the mixture was extracted with ether. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residual solid was recrystallized from ethyl acetate-hexane to give **3b** (2.40 g, 84 %). mp 103°C. ^1H NMR: δ 1.36 (3H, s), 1.38 (3H, s), 1.46 (3H, s), 1.59 (3H, s), 1.90 (3H, s), 2.97 (1H, s), 3.86 (1H, d, *J*=7.3 Hz), 4.04 (1H, dd, *J*=4.9, 8.8 Hz), 4.12 (1H, dd, *J*=6.3, 8.8 Hz), 4.41 (1H, m), 4.55 (1H, d, *J*=3.4 Hz), 5.80 (1H, d, *J*=3.4 Hz). ^{13}C

NMR: δ 3.6, 25.2, 26.6, 26.7, 26.8, 66.9, 74.9, 75.9, 76.0, 81.1, 84.3, 85.6, 104.1, 109.5, 113.6. IR ($CHCl_3$): 3540 (OH), 2100 (C≡C) cm^{-1}. *Anal.* calcd for $C_{15}H_{22}O_6$: C; 60.39, H; 7.43. Found: C; 60.11, H; 7.70.

3-*C*-[(*E*)-1-propenyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (4a). A mixture of **3a** (2.01 g, 6.78 mmol) and $LiAlH_4$ (551 mg, 13.5 mmol) in THF (20 ml) was stirred for 1h at room temperature. Water was carefully added to destroy an excess reagent. The mixture was diluted with ether and was dried over Na_2SO_4. The insoluble materials were filtered off and washed with ether. The filtrate and washings were combined and concentrated to dryness. The residual solid was recrystallized from ethyl acetate-hexane to afford **4a** (1.73 g, 85 %). mp 111°C. ^1H NMR: δ 1.33 (3H, s), 1.35 (3H, s), 1.44 (3H, s), 1.61 (3H, s), 1.70 (3H, dd, *J*=1.7, 6.6 Hz), 2.74 (1H, s), 3.91 (1H, d, *J*=6.8 Hz), 3.92 (1H, dd, *J*=6.1, 8.3 Hz), 4.00 (1H, dd, *J*=6.1, 8.6 Hz), 4.12 (1H, m), 4.26 (1H, d, *J*=3.4 Hz), 5.44 (1H, dd, *J*=1.7, 15.6 Hz), 5.76 (1H, d, *J*=3.4 Hz), 5.95 (1H, dq, 15.6, 6.6 Hz). ^{13}C NMR: δ 18.2, 25.3, 26.4, 26.6, 26.7, 66.8, 73.9, 79.7, 81.5, 83.9, 103.8, 109.2, 113.0, 127.6, 127.7. IR ($CHCl_3$): 3450 (OH), 1670 (C=C) cm^{-1}. *Anal.* calcd for $C_{15}H_{24}O_6$: C; 59.98, H; 8.05. Found: C; 60.04, H; 8.26.

3-*C*-[(*Z*)-1-propenyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (4b). A mixture of **3b** (2.40 g, 8.04 mmol), Pd-$CaCO_3$ (376 mg), and quinoline (1.8 ml) in ethyl acetate (60 ml) was vigorously stirred for 15 min under hydrogen atmosphere. The mixture was filtered through a pad of Celite. The filtrate was successively washed with 2N HCl and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure. The residual solid was purified by flash chromatography with ethyl acetate-hexane (3:1) and recrystallization from ethyl acetate-hexane to give **4b** (1.90 g, 79 %). mp 97°C. ^1H NMR: δ 1.35 (3H, s), 1.36 (3H, s), 1.44 (3H, s), 1.55 (3H, s), 1.96 (3H, dd, *J*=1.7, 7.3 Hz), 2.73 (1H, s), 3.87 (1H, d, *J*=7.6 Hz), 3.94 (1H, dd, *J*=5.6, 8.3 Hz), 4.08 (1H, dd, *J*=6.1, 8.5 Hz), 4.24 (1H, m), 4.34 (1H, d, *J*=3.4 Hz), 5.32 (1H, dd, *J*=1.7, 11.7 Hz), 5.70 (1H, d, *J*=3.4 Hz), 5.83 (1H, dq, 11.7, 7.3 Hz). ^{13}C NMR: δ 15.0, 25.3, 26.5, 26.6, 26.7, 67.3, 73.8, 80.7, 82.1, 84.1, 103.9, 109.4, 113.2, 125.7, 132.1. IR ($CHCl_3$): 3450 (OH), 1650 (C=C) cm^{-1}. *Anal.* calcd for $C_{15}H_{24}O_6$: C; 59.98, H; 8.05. Found: C; 60.06, H; 8.11.

3-*C*-[(*E*)-1-propenyl)]-3-*O*-trichloroacetimidyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (5a). A solution of **4a** (1.85 g, 6.14 mmol) in THF (20 ml) was added to a suspension of pre-washed KH (90 mg, 2.2 mmol) in hexane (1.0 ml). The mixture was stirred for 15 min at room temperature, and then cooled with an ice-bath. A solution of trichloroacetonitrile (1.0 ml) in ether (7 ml) was added dropwise over 4 min. The resulting mixture was stirred for 2 h at 0°C. The reaction was quenched by addtion of sat. aqueous NH_4Cl solution and the mixture was extracted with ether. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The residual solid was purified by flash chromatography with ethyl acetate-hexane (5:1) and recrystallization from ethyl acetate-pet. ether to give **5a** (2.07 g, 76 %). mp 115-116°C. ^1H NMR: δ 1.34 (6H, s), 1.47 (3H, s), 1.54 (3H, s), 1.79 (3H, dd, *J*=0.9, 6.8 Hz), 3.96 (2H, m), 4.14 (1H, m), 4.25 (1H, d, *J*=7.8 Hz), 5.07 (1H, d, *J*=3.9 Hz), 5.50 (1H, d, *J*=16.6 Hz), 5.63 (1H, dq, 16.1, 6.1 Hz), 5.83 (1H, d, *J*=3.9 Hz). ^{13}C NMR: δ 18.3, 25.4, 26.6, 26.8, 26.9, 66.5, 73.8, 81.3, 81.9, 86.6, 91.5, 104.4, 109.2, 112.8, 125.9, 128.2, 159.2. IR ($CHCl_3$): 3340 (NH), 1665 (C=N) cm^{-1}. *Anal.* calcd for $C_{17}H_{24}NO_6Cl_3$: C; 45.91, H; 5.44, N; 3.15. Found: C; 45.62, H; 5.40, N; 3.38.

3-*C*-[(*Z*)-1-propenyl)]-3-*O*-trichloroacetimidyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (5b). Compound **4b** (1.67 g, 5.62 mmol) was treated in the same manner as described for the preparation of **5a** to give oily **5b** (1.70 g, 68 %). ^{1}H NMR: δ 1.33 (6H, s), 1.46 (3H, s), 1.53 (3H, s), 1.84 (3H, dd, *J*=1.5, 7.3 Hz), 4.03 (2H, m), 4.24 (2H, m), 5.06 (1H, d, *J*=3.9 Hz), 5.15 (1H, dd, *J*=1.5, 12.2 Hz), 5.85 (2H, m). ^{13}C NMR: δ 14.7, 25.5, 26.7, 26.9, 27.0, 66.8, 73.9, 82.0, 82.2, 88.0, 91.5, 104.4, 109.3, 113.0, 123.2, 130.6, 159.5. IR ($CHCl_3$): 3340 (NH), 1665 (C=N) cm^{-1}. *Anal.* calcd for $C_{17}H_{24}NO_6Cl_3$: C; 45.91, H; 5.44, N; 3.15. Found: C; 45.71, H; 5.24, N; 3.22.

3-Deoxy-3-[(*Z*,2*S*)-2-tricholoroacetylaminopropylidene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (6a). A solution of **5a** (1.50 g, 3.38 mmol) in xylene (15 ml) was refluxed for 36 h. The solvent was removed by evaporation and the residue was purified by flash chromatography with hexane-ethyl acetate (5:1) to afford **6a** (1.35 g, 90 %) as an oil. ^{1}H NMR: δ 1.35 (3H, s), 1.37 (3H, s), 1.42 (3H, s), 1.42 (3H, d, *J*=6.8 Hz), 1.49 (3H, s), 3.89 (1H, dd, *J*=5.4, 7.8 Hz), 3.99 (1H, m), 4.07 (1H, dd, *J*=6.4, 7.3 Hz), 4.63 (1H, dd, *J*=1.5, 6.4 Hz), 4.85 (1H, sextet, *J*=6.8 Hz), 5.17 (1H, br. d, *J*=4.4 Hz), 5.86 (1H, d, *J*=4.4 Hz), 5.88 (1H, dt, *J*=5.9, 1.5 Hz), 7.39 (1H, br. d, *J*=7.0 Hz). ^{13}C NMR: δ 21.4, 25.4, 26.6, 27.4, 27.6, 47.3, 66.7, 73.6, 78.3, 81.0, 92.7, 105.2, 110.0, 112.8, 128.1, 140.1, 160.9. IR ($CHCl_3$): 3425 (NH), 1710 (C=O) cm^{-1}. *Anal.* calcd for $C_{17}H_{24}NO_6Cl_3$: C; 45.91, H; 5.44, N; 3.15. Found: C; 46.02, H; 5.23, N; 3.01.

3-Deoxy-3-[(*Z*,2*R*)-2-tricholoroacetylaminopropylidene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (6b). Compound **5b** (1.42 g, 3.19 mmol) was treated in the same manner as described for the preparation of **6a** to give oily **6b** (1.32 g, 93 %). ^{1}H NMR: δ 1.33 (3H, s), 1.38 (3H, s), 1.42 (3H, s), 1.44 (3H, d, *J*=6.8 Hz), 1.48 (3H, s), 3.96 (3H, m), 4.64 (1H, d, *J*=4.8 Hz), 4.77 (1H, ddq, *J*=9.8, 6.8, 6.8 Hz), 5.46 (1H, dt, *J*=4.0, 1.5 Hz), 5.70 (1H, dt, *J*=9.8, 1.9 Hz), 5.85 (1H, d, *J*=4.4 Hz), 6.77 (1H, br. d, *J*=6.8 Hz). ^{13}C NMR: δ 19.9, 25.2, 26.3, 27.1x2, 46.9, 76.5, 77.3, 78.3, 79.3, 92.3, 104.7, 109.5, 112.0, 126.8, 141.3, 160.8. IR ($CHCl_3$): 3430 (NH), 1710 (C=O) cm^{-1}. *Anal.* calcd for $C_{17}H_{24}NO_6Cl_3$: C; 45.91, H; 5.44, N; 3.15. Found: C; 45.71, H; 5.22, N; 3.42.

***N*-Trichloroacetyl-D-alanine (7a).** A mixture of **6a** (1.78 g, 4.00 mmol), $NaIO_4$ (3.51 g, 16.4 mmol), $RuCl_3 \cdot nH_2O$ (93 mg), water (12 ml), carbon tetrachloride (8 ml), and acetonitrile (8 ml) was stirred for 15 h at room temperature. Sodium periodate (1.81 g, 8.4 mmol) was further added and stirring was continued for 5 h. The mixture was filtered through a pad of Celite and the residue was washed with ethyl acetate. The organic layer of the filtrate was separated and extracted with 1N NaOH solution. The aqueous layer was acidified with 2N HCl and was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residual solid was recrystallized from methyl isobutyl ketone-pet. ether gave **7a** (340 mg, 36 %). mp 125-127°C. ^{1}H NMR: δ 1.59 (3H, d, *J*=7.0 Hz), 4.62 (1H, q, *J*=7.0 Hz), 7.78 (1H, br. s). IR ($CHCl_3$): 1705 (C=O) cm^{-1}. *Anal.* calcd for $C_5H_6NO_3Cl_3$: C; 25.61, H; 2.58, N; 5.97. Found: C; 25.89, H; 2.49, N; 5.77.

***N*-Trichloroacetyl-L-alanine (7b).** Compound **6b** (1.09 g, 2.46 mmol) was treated in the same manner as described for the preparation of **7a** to give **7b** (409 mg, 71 %). mp 124-125°C. ^{1}H NMR: δ 1.59 (3H, d, *J*=7.0 Hz), 4.62 (1H, q, *J*=7.0 Hz), 7.78 (1H, br. s). IR ($CHCl_3$): 1705 (C=O) cm^{-1}. *Anal.* calcd for $C_5H_6NO_3Cl_3$: C; 25.61, H; 2.58, N; 5.97. Found: C; 25.99, H; 2.76, N; 5.63.

D-Alanine (8a). A mixture of **7a** (300 mg, 1.28 mmol) and 2N HCl (25 ml) was heated for 5 h in a sealed tube at 120°C. After being cooled to room temperature, the mixture was diluted with water (25 ml). The solution was subjected to a Dowex 50 WX2 column (H^+ form, 100 ml) and the column was eluted with 5% pyridine in water to give **8a** (78 mg, 69 %). mp 285°C (dec.). $[\alpha]_D$ -12.7° (c 0.51, 5N HCl), lit.[21] for L-isomer: +14.6°. ^{1}H NMR (D_2O): δ 1.40 (3H, d, *J*=6.8 Hz), 3.71 (1H, q, *J*=6.8 Hz). ^{13}C NMR (D_2O): δ 16.4, 50.8, 176.0. *Anal.* calcd for $C_3H_7NO_2$: C; 40.44, H; 7.92, N; 15.72. Found: C; 40.60, H; 7.93, N; 15.53.

L-Alanine (8b). Compound **7b** (300 g, 1.28 mmol) was treated in the same manner as described for the preparation of **8a** to give **8b** (79 g, 69 %). mp 290°C (dec.). $[\alpha]_D$ +15.7° (c 0.44, 5N HCl). ^{1}H NMR (D_2O): δ 1.40 (3H, d, *J*=6.8 Hz), 3.71 (1H, q, *J*=6.8 Hz). ^{13}C NMR (D_2O): δ 16.4, 50.8, 176.0. *Anal.* calcd for $C_3H_7NO_2$: C; 40.44, H; 7.92, N; 15.72. Found: C; 40.67, H; 7.63, N; 16.02.

3-*C*-[(*Z*)-(2-^{2}H)Ethenyl]-3-*O*-trichloroacetimidyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (10a). Compound **9a**[5,11] (1.62 g, 21.1 mmol) was treated in the same manner as described for the preparation of **5a** to give oily **10a** (2.17 g, 89 %). ^{1}H NMR: δ 1.33 (3H, s), 1.35 (3H, s), 1.47 (3H, s), 1.55 (3H, s), 4.02 (2H, m), 4.14 (1H, m), 4.25 (1H, d, *J*=7.5 Hz), 5.12 (1H, d, *J*=3.9 Hz), 5.40 (1H, d, *J*=11.8 Hz), 5.85 (1H, d, *J*=3.9 Hz), 5.92 (1H, d, *J*=11.5 Hz), 8.42 (1H, br. s). ^{13}C NMR: δ 25.3, 26.6, 26.8, 26.9, 66.8, 73.7, 81.1, 82.0, 87.1, 91.3, 104.4, 109.3, 112.7, 116.4 (t, *J*=23 Hz), 133.4, 159.3. IR ($CHCl_3$): 3340 (NH), 1670 (C=N) cm^{-1}. *Anal.* calcd for $C_{16}H_{21}{}^2H_1NO_6Cl_3$: C; 44.53, H+^{2}H; 5.14, N; 3.25. Found: C; 44.32, H+^{2}H; 5.26, N; 3.04.

3-*C*-[(*E*)-(2-^{2}H)Ethenyl]-3-*O*-trichloroacetimidyl-1,2:5,6-di-*O*-isopropylidene-α-D-allo-furanose (10b). Compound **9b**[5,11] (6.05 g, 21.1 mmol) was treated in the same manner as described for the preparation of **5a** to give oily **10b** (7.83 g, 86 %). ^{1}H NMR: δ 1.33 (3H, s), 1.35 (3H, s), 1.48 (3H, s), 1.55 (3H, s), 4.02 (2H, m), 4.14 (1H, m), 4.25 (1H, d, *J*=7.5 Hz), 5.12 (1H, d, *J*=3.8 Hz), 5.20 (1H, d, *J*=17.8 Hz), 5.85 (1H, d, *J*=4.1 Hz), 5.93 (1H, br. d, *J*=17.8 Hz), 8.42 (1H, br. s). ^{13}C NMR: δ 25.4, 26.7, 26.9, 27.0, 66.9, 73.8, 81.2, 82.0, 87.1, 91.4, 104.5, 109.4, 112.8, 116.6 (t, *J*=25 Hz), 133.5, 159.5. IR ($CHCl_3$): 3320 (NH), 1665 (C=N) cm^{-1}. *Anal.* calcd for $C_{16}H_{21}{}^2H_1NO_6Cl_3$: C; 44.53, H+^{2}H; 5.14, N; 3.25. Found: C; 44.72, H+^{2}H; 5.30, N; 3.14.

3-Deoxy-3-[(*Z*,2*S*)-(2-^{2}H)-2-tricholoroacetylaminoethylidene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (11a). Compound **10a** (1.94 g, 4.48 mmol) was treated in the same manner as described for the preparation of **6a** to give oily **11a** (1.87 g, 96 %). ^{1}H NMR: δ 1.35 (3H, s), 1.39 (3H, s), 1.43 (3H, s), 1.49 (3H, s), 3.92 (1H, dd, *J*=5.0, 7.3 Hz), 3.98 (1H, m), 4.07 (1H, dd, *J*=5.0, 7.3 Hz), 4.29 (1H, t, *J*=7.5 Hz), 4.65 (1H, d, *J*=6.5 Hz), 5.24 (1H, d, *J*=4.5 Hz), 5.89 (1H, d, *J*=4.5 Hz), 6.03 (1H, d,

J=7.3 Hz), 7.23 (1H, br. s). ^{13}C NMR: δ 25.3, 26.5, 27.3, 27.4, 39.4 (t, *J*=21 Hz), 66.6, 77.4, 78.5, 80.1, 92.4, 105.0, 109.8, 112.6, 122.3, 144.0, 161.7. IR ($CHCl_3$): 3420 (NH), 1690 (C=O) cm^{-1}. *Anal.* Calcd for $C_{16}H_{21}{}^2H_1NO_6Cl_3$: C; 44.53, H+^{2}H; 5.14, N; 3.25. Found: C; 44.23, H+^{2}H; 5.43, N; 3.14.

3-Deoxy-3-[(*Z*,2*R*)-(2-^{2}H)-2-tricholoroacetylaminoethylidene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (11b). Compound **10b** (7.83 g, 18.2 mmol) was treated in the same manner as described for the preparation of **6a** to give oily **11b** (6.49 g, 83 %). ^1H NMR: δ 1.35 (3H, s), 1.39 (3H, s), 1.43 (3H, s), 1.49 (3H, s), 3.92 (1H, dd, *J*=5.2, 7.3 Hz), 3.97 (2H, m), 4.07 (1H, dd, *J*=5.4, 7.3 Hz), 4.65 (1H, d, *J*=7.5 Hz), 5.24 (1H, d, *J*=4.5 Hz), 5.89 (1H, d, *J*=4.4 Hz), 6.04 (1H, d, *J*=7.1 Hz), 7.23 (1H, br. s). ^{13}C NMR: δ 25.4, 26.7, 27.4, 27.5, 39.5 (t, *J*=21 Hz), 66.8, 77.5, 78.7, 80.3, 92.5, 105.0, 110.0, 112.9, 122.5, 144.0, 161.7. IR ($CHCl_3$): 3420 (NH), 1690 (C=O) cm^{-1}. $C_{16}H_{21}{}^2H_1NO_6Cl_3$: C; 44.53, H+^{2}H; 5.14, N; 3.25. Found: C; 44.70, H+^{2}H; 5.00, N; 3.43.

(*S*)-(2-^{2}H)Glycine (12a). Ozone was bubbled into a solution of **11a** (1.60 g, 3.69 mmol) in CH_2Cl_2 (10 ml) at -78°C until the starting material disappeared (ca. 1 h). Nitrogen was introduced to purge the remaining ozone and the mixture was warmed to room temperature. After the solvent was almost removed by a stream of nitrogen, acetic acid (9 ml) and 30% H_2O_2 (6 ml) were added. The mixture was heated with stirring for 4 h at 65°C. After being cooled, the mixture was concentrated under reduced pressure. The residue was dissolved in 2N HCl (10 ml) and the mixture was heated for 22 h in a sealed tube at 120°C. After cooling to room temperature, the mixture was diluted with water (10 ml). The solution was subjected to a Dowex 50 WX2 column (H^+ form, 100 ml) and the column was eluted with 5% pyridine in water to give **12a** (151 mg, 54 %). mp 234°C (dec.). $[\alpha]_{230}$ -49.0° (c 2.1, H_2O), lit.[22]: -54.8°. ^1H NMR (D_2O): δ 3.80 (s). ^{13}C NMR (D_2O): δ 43.9 (t, *J*=22 Hz), 175.2. *Anal.* calcd for $C_2H_4{}^2H_1NO_2$: C; 31.54, H+^{2}H; 6.57, N; 18.42. Found: C; 31.57, H+^{2}H; 6.58, N; 18.39.

(*R*)-(2-^{2}H)Glycine (12b). Compound **11a** (841 mg, 1.95 mmol) was treated in the same manner as described for the preparation of **12a** to give **12b** (91 mg, 61 %). mp 230°C (dec.). $[\alpha]_{230}$ 42.6° (c 0.85, H_2O). ^1H NMR (D_2O): δ 3.80 (s). ^{13}C NMR (D_2O): δ 43.9 (t, *J*=22 Hz), 175.2. Anal. calcd for $C_2H_4{}^2H_1NO_2$: C; 31.54, H+^{2}H; 6.57, N; 18.42. Found: C; 31.57, H+^{2}H; 6.53, N; 18.39.

Kinetics of the Thermal Rearrangement of the Imidates 5a and 5b. The reactions were carried out with a sealed NMR tubes in xylene-d_{10} at concentrations of 5-7 mg in 0.6 ml. The reactions were followed by monitoring the disappearance of the signals of the olefinic methyl group of the starting imidates and were studied over at least 2-harf lives. All NMR analyses were repeated three times and activation parameters were calculated from the least squares slope of plots of ln *k* (S^{-1}) versus 1/*T*.

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