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Diastereoselective intramolecular acyl transfer of 5-(α-methylbenzyl)amino-1,3-dioxan-2-one to 4-hydroxymethyl-2-oxazolidinones

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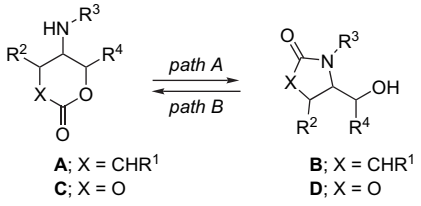
Abstract—Intramolecular acyl transfer of (*R*)-5-(α-methylbenzyl)amino-1,3-dioxan-2-one (**2**) by treatment with DBU in CD_2Cl_2, $CDCl_3$, C_6D_6, CD_3CN, CD_3NO_2, DMSO-d_6, DMF, THF-d_8, ^{i}PrOH, and ^{t}BuOH at room temperature afforded (4*S*,α*R*)-4-hydroxymethyl-3-α-methylbenzyl-2-oxazolidinone [(4*S*)-**3**] in moderate to quantitative yields with 58–94% de via an asymmetric desymmetrization process. Treatment of **2** with DBU and Cs_2CO_3 in MeOH and EtOH gave (4*S*)-**3** and (4*R*)-**3** without diastereoselectivities. Acidic treatment of **2** using HCO_2H, AcOH, $EtCO_2H$, ^{i}PrCO$_2$H, ^{t}BuCO$_2$H, and C_6F_5OH in $CDCl_3$ gave (4*S*)-**3** in moderate diastereoselectivities (26–52% de). First-order kinetics were observed in the reaction of **2** to (4*S*)-**3** with DBU in $CDCl_3$ and THF-d_8.

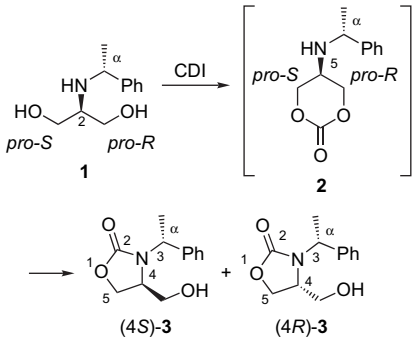
1. Introduction

The intramolecular acyl transfer between six- and five-membered rings has been used to exchange ring sizes and types. For example, the acyl transfer of 4-amino-5-pentanolides **A** (R^3=H) exchanges the ring sizes from six to five to afford γ-lactams **B** (R^3=H, Scheme 1, *path A*).[1,2] The intramolecular acyl transfer from five- to six-membered rings has also been reported; *N*-Ts- and *N*-Boc-γ-lactams **B** (R^3=Ts and Boc) are converted to the corresponding 4-amino-5-pentanolide derivatives **A** (Scheme 1, *path B*).[3] Oxazolidinones **D** (R^3=9-phenylfluoren-9-yl[4] and allyl,[5] R^2=H) have also been converted to the corresponding 5-amino-1,3-dioxan-2-ones **C** (Scheme 1, *path B*).[4,6] However, the acyl transfer from 5-amino-1,3-dioxan-2-ones **C** to 2-oxazolidinones **D** has not been reported (Scheme 1, *path A*).



Scheme 1. Intramolecular acyl transfers of 4-amino-5-pentanolides **A** to γ-lactams **B** and 5-amino-1,3-dioxan-2-ones **C** to 2-oxazolidinones **D** (*path A*) and their reverse reactions (*path B*).

We are investigating new methods for the asymmetric synthesis of optically active 2-oxazolidinones via asymmetric desymmetrization processes.[7,8] While investigating to synthesize 2-oxazolidinones (4*S*)-**3** and (4*R*)-**3** from serinol **1**[7] by means of 1,1′-carbonyl diimidazole (CDI), we observed that the ^{1}H NMR spectrum of the reaction mixture in $CDCl_3$ indicated the presence of an unknown intermediate in the reaction mixture after 15 h. Oxazolidinones (4*S*)-**3** and (4*R*)-**3** were also formed in 55% after 7 days and in 74% after 15 days. We assumed that the intermediate for producing (4*S*)-**3** and (4*R*)-**3** was 5-amino-1,3-dioxan-2-one (cyclic carbonate) **2** (Scheme 2).[9] Therefore, we were interested in the structure of cyclic carbonate **2** and anticipated that treatment of **2** possessing a σ-symmetric moiety with a base would give (4*S*)-**3** or (4*R*)-**3**[7] diastereoselectively. We here report the novel and highly diastereoselective intramolecular acyl transfer of cyclic carbonate **2** to oxazolidinone (4*S*)-**3** via *path A* in Scheme 1.[10]



Scheme 2. Intermediate for the reaction from **1** to **3**.

Keywords: Acyl transfer; Asymmetric desymmetrization; Oxazolidinone; Serinol.
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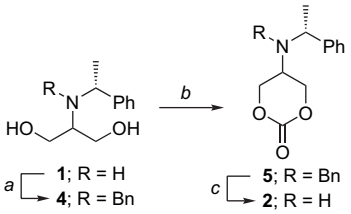
2. Results and discussion

2.1. Preparation of cyclic carbonate 2

We first tried to synthesize cyclic carbonate **2** from serinol **1**[7] directly as shown in Scheme 2. ^{1}H NMR spectrum showed that cyclic carbonate **2** and oxazolidinones (4*S*)-**3** and (4*R*)-**3** existed in the crude material after work-up. We also observed that **2** was converted to (4*S*)-**3** and (4*R*)-**3** during the purification using silica gel column chromatography.[11] Therefore, we need a crude material of **2** without (4*S*)-**3** and (4*R*)-**3** to isolate **2** as soon as possible. Actually, cyclic carbonate **2** was synthesized from serinol **1** as follows. Benzylation of the (α-methylbenzyl)amine group of **1** with benzyl bromide gave serinol **4**, which was converted to cyclic carbonate **5** using CDI. Selective debenzylation of **5** was achieved using ceric ammonium nitrate (CAN) in MeCN.[12] The ^{1}H NMR spectrum of the crude product after debenzylation revealed that no oxazolidinones (4*S*)-**3** and (4*R*)-**3** were formed. The crude cyclic carbonate **2** was purified with silica gel column chromatography; however, **2** was partially converted to oxazolidinones (4*S*)-**3** and (4*R*)-**3** during the purification. The yield of pure **2** was 53%, and a mixture of **2**/(4*S*)-**3**/(4*R*)-**3** (71:25:4, 17%) was also obtained (Scheme 3).[11]



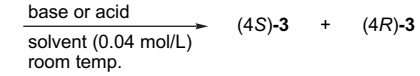
Scheme 3. Reagents and conditions: (a) BnBr, ^{i}Pr$_2$EtN, $CHCl_3$, reflux, 16 h. (b) CDI, CH_2Cl_2, room temperature, 13 h. (c) CAN, MeCN, H_2O, room temperature, 30 min.

2.2. Intramolecular acyl transfer of cyclic carbonate 2

The diastereoselective intramolecular acyl transfer of **2** was investigated using various bases and acids in various solvents at room temperature, and the results are summarized in Table 1. Cyclic carbonate **2** was essentially stable in CD_2Cl_2 regardless of the presence or absence of triethylamine (entries 1 and 2). Pyridine and DMAP were not as effective as for the acyl transfer (entries 3 and 4). The acyl transfer of **2** went smoothly in CD_2Cl_2 and $CDCl_3$ by treatment of 3 or 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give (4*S*)-**3** within 1.5 h in quantitative yield and excellent diastereoselectivities (entries 5–7). Treatment with imidazole gave (4*S*)-**3** in good yield and diastereoselectivity within 21 h (entry 8).

In other aprotic solvents such as C_6D_6, CD_3CN, CD_3NO_2, DMSO-d_6, and DMF, cyclic carbonate **2** underwent the acyl transfer smoothly within 3 h in high to excellent diastereoselectivities (entries 9–13). In THF-d_8, (4*S*)-**3** was slowly formed in excellent yield and diastereoselectivity (entry 14).

Table 1. Diastereoselective intramolecular acyl transfer of cyclic carbonate **2**



Entry	Additive (equiv)	Solvent	Time (h)	Oxazolidinones (4*S*)-**3**/(4*R*)-**3**		Recovery of **2** (%)
				Yield (%)	(4*S*)-**3**:(4*R*)-**3**	
1	—	CD_2Cl_2	21	Trace[a]	—	>95
2	Et_3N (3)	CD_2Cl_2	21	Trace[a]	—	>95
3	Py-d_5 (3)	CD_2Cl_2	21	4[a]	—	82
4	DMAP (3)	CD_2Cl_2	21	28[a]	87:13	70
5	DBU (3)	CD_2Cl_2	1.5	Quant.[b]	97:3	0
6	DBU (1)	CD_2Cl_2	1.5	Quant.[b]	97:3	0
7	DBU (3)	$CDCl_3$	1.5	Quant.[b]	97:3	0
8	imidazole (2)	CD_2Cl_2	21	88[b]	92:8	4
9	DBU (3)	C_6D_6	2	Quant.[b]	96:4	0
10	DBU (3)	CD_3CN	1.5	Quant.[a,b]	96:4	0
11	DBU (3)	CD_3NO_2	2	Quant.[b]	96:4	0
12	DBU (3)	DMSO-d_6	3	Quant.[a,b]	93:7	0
13	DBU (3)	DMF	3	97[b]	79:21	0
14	DBU (3)	THF-d_8	30	96[a,b]	96:4	0
15	TBAF (3)	THF	3	83[b]	93:7	0
16	DBU (3)	MeOH	3	31[b]	1:1	0
17	DBU (3)	EtOH	3	29[b]	2:3	0
18	DBU (3)	^{i}PrOH	3	61[b]	96:4	0
19	DBU (3)	^{t}BuOH	3	80[b]	92:8	0
20	Cs_2CO_3 (3)	MeOH	3	15[b]	1:1	0
21	—	CD_3OD	1.3	—	—	34
22	HCO_2H (3)	$CDCl_3$	21	74[a]	63:37	0
23	AcOH (3)	$CDCl_3$	21	97[a,b]	74:26	0
24	$EtCO_2H$ (3)	$CDCl_3$	21	94[a]	70:30	0
25	^{i}PrCO$_2$H (3)	$CDCl_3$	21	Quant.[a]	71:29	0
26	^{t}BuCO$_2$H (3)	$CDCl_3$	21	86[a]	76:24	0
27	C_6F_5OH (3)	$CDCl_3$	32	74[b]	62:38	14
28	MsOH (3)	$CDCl_3$	21	5[b]	3:2	0

[a] The yield, ratio of (4*S*)-**3**/(4*R*)-**3**, and the recovery of **2** were calibrated with an internal standard (Ph_3CH) by ^{1}H NMR integration before work-up.
[b] The yield, ratio of (4*S*)-**3**/(4*R*)-**3**, and the recovery of **2** were calibrated with the internal standard (Ph_3CH) by ^{1}H NMR integration after work-up.

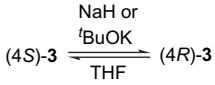
Tetrabutylammonium fluoride (TBAF) in THF was also effective for this reaction (entry 15). The reaction with TBAF went apparently faster than that with DBU in THF, and (4*S*)-**3** was obtained within 3 h in 83% yield. In this case, fluoride ion acted as a base.[13] Treatments of **2** with DBU in MeOH and EtOH gave mixtures of (4*S*)-**3**/(4*R*)-**3** (1:1 and 2:3, respectively) in poor yields (entries 16 and 17). On the other hand, the reactions in ^{i}PrOH and ^{t}BuOH gave the products in 61 and 80% yields with excellent diastereoselectivities (entries 18 and 19). Treatment of **2** with Cs_2CO_3 in MeOH gave a mixture of (4*S*)-**3**/(4*R*)-**3** (1:1) in 15% yields (entry 20). We confirmed that **2** decomposed partially within 1.3 h in CD_3OD without additives (entry 21) and completely within 15 h. Thus, cyclic carbonate **2** partially undergoes methanolysis before the acyl transfer; the low diastereoselectivity is discussed later in this paper. We also observed that addition of DBU (3 equiv) to the mixture of decomposed products in CD_3OD gave serinol **1** quantitatively within 10 min at room temperature.

The reactions in acidic conditions were also investigated. Treatment of **2** with formic acid (HCO_2H) in $CDCl_3$ gave a mixture of (4*S*)-**3** and (4*R*)-**3** (63:37) in 74% (entry 22). Acetic acid (AcOH), propionic acid ($EtCO_2H$), isobutyric acid ($^{i}PrCO_2H$), pivalic acid ($^{t}BuCO_2H$), and pentafluorophenol (C_6F_5OH) were also effective for this reaction, which gave the mixture in high to excellent yields, however, with less diastereoselectivities than those in basic media (entries 23–27). The reactions with methanesulfonic acid (MsOH) in $CDCl_3$ gave the products in poor yields (entry 28).

2.3. Proposed intermediates of the acyl transfer from 2 to 3

Since the highly diastereoselective formation of 2-oxazolidinone (4*S*)-**3** from cyclic carbonate **2** in the presence of DBU was observed, we considered the mechanism of the acyl transfer from **2** to (4*S*)-**3**. The amino group of **2** was initially envisaged to participate in a facile intramolecular nucleophilic substitution reaction with the carbonyl group, which would result in the formation of anions of 7-aza-2,6-dioxabicyclo[2.2.1]heptane intermediates **6** and **7**. At this point, two tentative *N*-invertomers $\mathbf{6}^-$ and $\mathbf{7}^-$ are proposed as intermediates (Fig. 1).

On the other hand, we have reported that a metal-cation-mediated intramolecular acyl transfer between 2-oxazolidinone (4*S*)-**3** and (4*R*)-**3** by sodium hydride or potassium *tert*-butoxide in THF at room temperature gives an approximate equimolar diastereomixture of (4*S*)-**3** and (4*R*)-**3** (Scheme 4).[7b,14,15] The acyl transfer in the presence of 18-crown-6 in THF-d_8 also gave a 1:1 mixture of (4*S*)-**3** and (4*R*)-**3**. These results may suggest that the acyl transfer between (4*S*)-**3** and (4*R*)-**3** proceeds via intramolecular nucleophilic substitution reactions of the hydroxyl groups with the carbonyl groups forming the same oxyanions $\mathbf{6}^-$ and $\mathbf{7}^-$ (Fig. 1) and the chiral center of the α-methylbenzyl group does not influence the diastereoselectivity in this case.



Scheme 4. Intramolecular acyl transfer between (4*S*)-**3** and (4*R*)-**3**.

We tried to determine a difference in diastereoselectivities between the reaction of **2** to **3** and the acyl transfer between (4*S*)-**3** and (4*R*)-**3**. The difference could be rationalized in terms of the difference of the solvation property of the counter cations, protonated DBU (DBU-H$^+$),[16,17] and metal cations (Na^+ and K^+, Scheme 4). The DBU-H$^+$ cation would form contact ion pairs at the oxyanion in the aprotic solvents shown in Table 1. The contact ion pair $\mathbf{6}^-$**(DBU-H$^+$)** (Fig. 2) might be presumably the most favorable model producing (4*S*)-**3** as the major product (entries 5–7 and 9–14 in Table 1). Namely, the DBU-H$^+$ cations may coordinate with $\mathbf{6}^-$ at the O(2) side, and then activate the C(1)–O(2) bond cleavage. This process would be involved in the hydrogen-bonded delivery of the proton from protonated DBU[16] to the O(2). In spite of using DBU, the reactions of **2** in MeOH and EtOH gave (4*S*)-**3** and (4*R*)-**3** without diastereoselectivity (entries 16 and 17 in Table 1). In these cases, the free oxyanions $\mathbf{6}^-$ and $\mathbf{7}^-$ or alcohols **6** and **7** might be favorably in the polar and protic medias such as MeOH and EtOH producing both (4*S*)-**3** and (4*R*)-**3**. In the cases of reactions in ^{i}PrOH and ^{t}BuOH, the contact ion pairs might exist stably because ^{i}PrOH and ^{t}BuOH are less polar solvents compared with MeOH and EtOH (entries 18 and 19 in Table 1).

The diastereoselectivity of the reaction must be induced by the chirality of the α-methylbenzyl group in cyclic carbonate **2**. In order to study the role of the group, we first investigated the orientation of the group in a stable *N*-rotamer of **2**. A comparison with the δ-values of the methylenic protons of **2** on the ^{1}H NMR spectra indicated that one of them was apparently shielded to δ 4.07 and signals of other methylenic protons appeared at δ 4.27–4.32.[18] This indicated that the phenyl group located near the shielding methylenic proton; however, we were not able to assign the shielding protons because of the σ-symmetry.

To analyze the stable *N*-rotamer of cyclic carbonate **2** by ^{1}H NMR analysis, we synthesized two dideuteriocyclic carbonates (5*R*)-**2**-d_2 and (5*S*)-**2**-d_2, in which two deuteriums were incorporated at the *pro-R* and *pro-S* methylenic positions, respectively (Scheme 5). The reduction of the aziridine

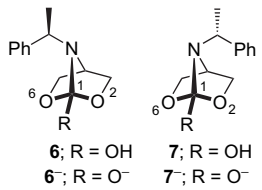


Figure 1. Intermediate models of the acyl transfer in the basic conditions.

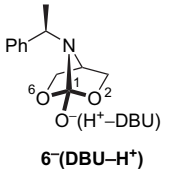
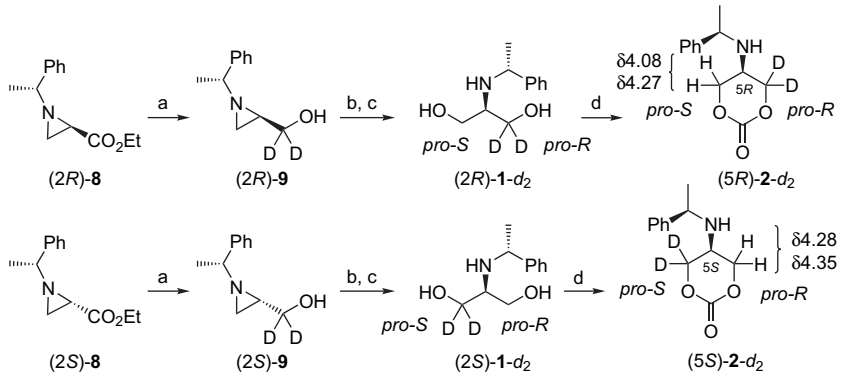
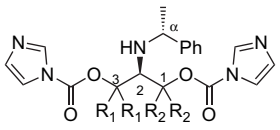


Figure 2. The most favorable contact ion pair model.



Scheme 5. Reagents and conditions: (a) $LiAlD_4$, Et_2O, 0 °C, 1.5 h. (b) AcOH, $CHCl_3$, reflux, 8 h. (c) KOH, EtOH, reflux, 3 h. (d) CDI, $CDCl_3$, room temperature, 15 h.



(2*R*)-**10**-d_2; R_1 = H, R_2 = D
(2*S*)-**10**-d_2; R_1 = D, R_2 = H
10; R_1 = R_2 = H

Figure 3. Diimidazolylcarbonyl serinols as side products.

(2*R*)-**8**[19] with lithium aluminum deuteride and the ring-opening reaction of the aziridine ring with acetic acid[20] following alkaline hydrolysis gave dideuterioserinol (2*R*)-**1**-d_2. The other dideuterioserinol (2*S*)-**1**-d_2 was also synthesized from (2*S*)-**8** according to the same procedure. The ^{1}H NMR spectra of (2*R*)-**1**-d_2 and (2*S*)-**1**-d_2 are shown in Figure 4b and c, respectively. Dideuterioserinols (2*R*)-**1**-d_2 and (2*S*)-**1**-d_2 reacted separately with CDI in $CDCl_3$ at room temperature for 15 h to give dideuteriocyclic

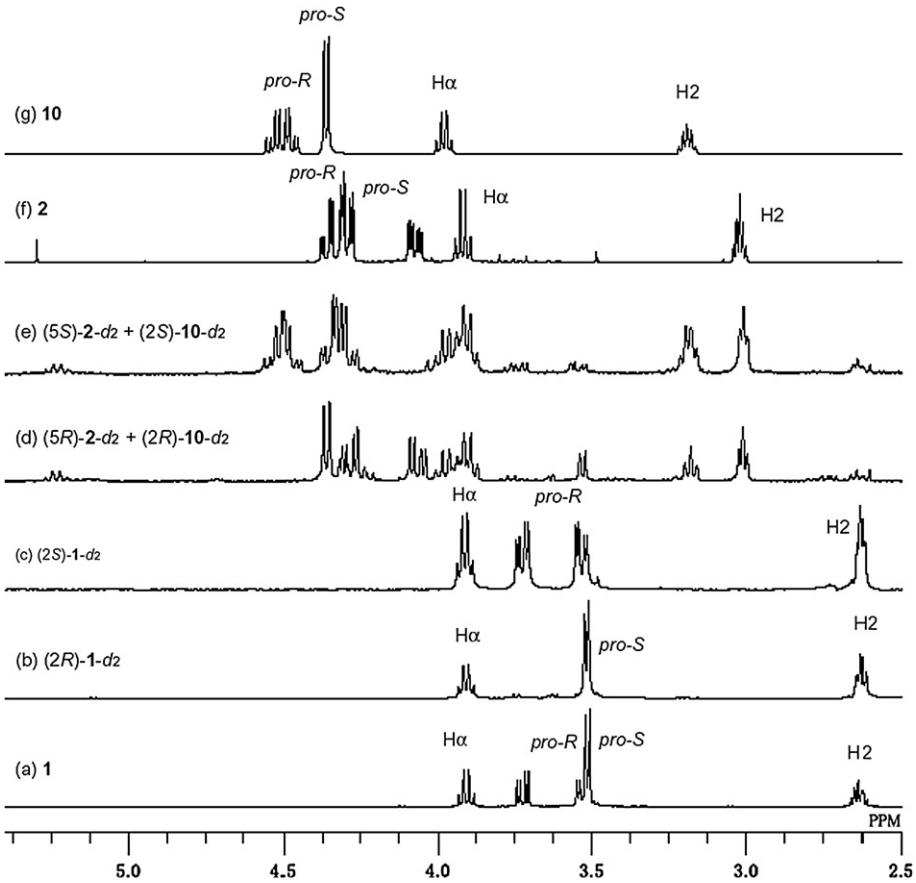
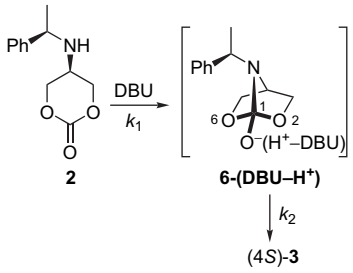


Figure 4. ^{1}H NMR spectra in $CDCl_3$: (a) serinol **1**, (b) dideuterioserinol (2*R*)-**1**-d_2, (c) dideuterioserinol (2*S*)-**1**-d_2, (d) a reaction mixture of (2*R*)-**1** and CDI in $CDCl_3$ including dideuteriocyclic carbonate (5*R*)-**2**-d_2 and dideuterio diimidazolylcarbonyl serinol (2*R*)-**10**-d_2 (62:38); small amounts of the oxazolidinone and the starting material were also present, (e) a reaction mixture of (2*S*)-**1**-d_2 and CDI in $CDCl_3$ including dideuteriocyclic carbonate (5*S*)-**2**-d_2 and dideuterio diimidazolylcarbonyl serinol (2*S*)-**10**-d_2 (61:39); small amounts of the oxazolidinone and the starting material were also present, (f) cyclic carbonate **2**, and (g) diimidazolylcarbonyl serinol **10** [400 MHz for (a)–(c) and (f)–(g); 300 MHz for (d) and (e)].

carbonates (5*R*)-**2**-d_2 and (5*S*)-**2**-d_2, respectively, and we measured their ^{1}H NMR spectra without work-up (Fig. 4d and e). Small amount of the starting materials and oxazolidinones were also observed in the respective reaction mixtures in $CDCl_3$. Diimidazolylcarbonyl compounds (2*R*)-**10**-d_2 and (2*S*)-**10**-d_2 (Fig. 3) were also obtained as side products, and we confirmed the structures by comparison of the ^{1}H NMR spectrum of **10**, which was obtained quantitatively from serinol **1** and CDI (3 equiv) in CH_2Cl_2 (Fig. 4g). In this case, **2** was not obtained. We suppose that the reaction of the second hydroxyl group with CDI was faster than the intramolecular cyclization giving **2** after the first hydroxyl group of **1** reacted with CDI.

The methylenic protons of *pro-R* of (5*R*)-**2**-d_2 and those of *pro-S* of (5*S*)-**2**-d_2 were not observed on the ^{1}H NMR spectra (Fig. 4d and e). The chemical shifts of the methylenic protons of *pro-S* of (5*R*)-**2**-d_2 were δ 4.08 and δ 4.27, and those of *pro-R* of (5*S*)-**2**-d_2 were δ 4.28 and δ 4.35 (Scheme 5). We recognized the shielding methylenic proton at δ 4.08 belongs to one of the *pro-S* methylenic protons. Thus, the phenyl group located in the *pro-S* side of cyclic carbonate **2**, as shown in Scheme 5.

From the study of the stable *N*-rotamer, we assumed that intermediate **6$^-$(DBU-H$^+$)** would be smoothly formed from the stable *N*-rotamer of **2** by keeping the steric factors concerning nitrogen (Scheme 6). Thus, the chirality of the α-methylbenzyl group should be also effective to form **6$^-$(DBU-H$^+$)**.



Scheme 6. Synthesis of (4*S*)-**3** from the stable *N*-rotamer of **2** via **6$^-$(DBU-H$^+$)**.

2.4. Kinetic studies

The intramolecular acyl transfer of **2** to (4*S*)-**3** is a consecutive reaction; the first step is the formation of the intermediate **6$^-$(DBU-H$^+$)**, and the second one is its diastereoselective ring-opening reaction to give (4*S*)-**3** (Scheme 6). To analyze the existence of an intermediate in the reaction mixture, we attempted to observe the consecutive reaction of cyclic carbonate **2** in the presence of DBU (3 equiv) by analyzing the ^{1}H NMR spectra (Figs. 5 and 6). The experiments were

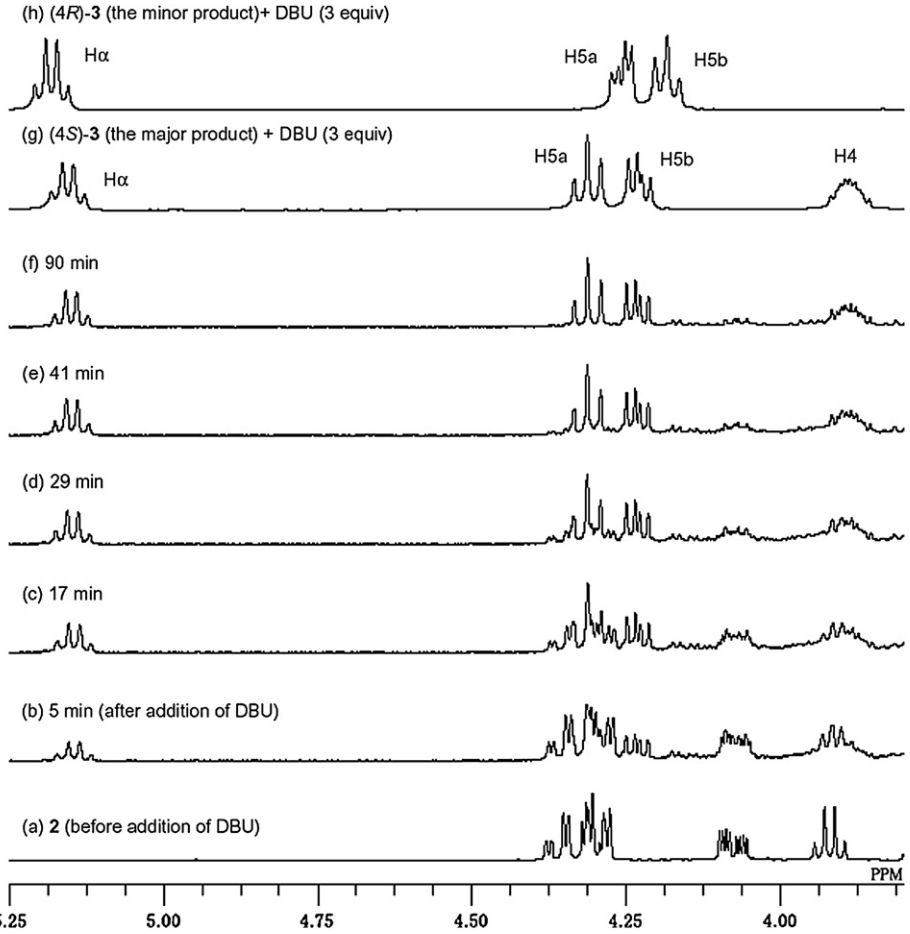


Figure 5. ^{1}H NMR spectra (400 MHz) of the reaction of cyclic carbonate **2** to oxazolidinones (4*S*)-**3** and (4*R*)-**3** by treatment of DBU (3 equiv) in $CDCl_3$ (0.04 mol/L) at 25 °C: (a) before addition of DBU, (b) 5 min after addition of DBU, (c) 17 min, (d) 29 min, (e) 41 min, (f) 90 min, (g) a mixture of (4*S*)-**3** (the major product) and DBU (3 equiv) in $CDCl_3$, and (h) a mixture of (4*R*)-**3** (the minor product) and DBU (3 equiv) in $CDCl_3$.

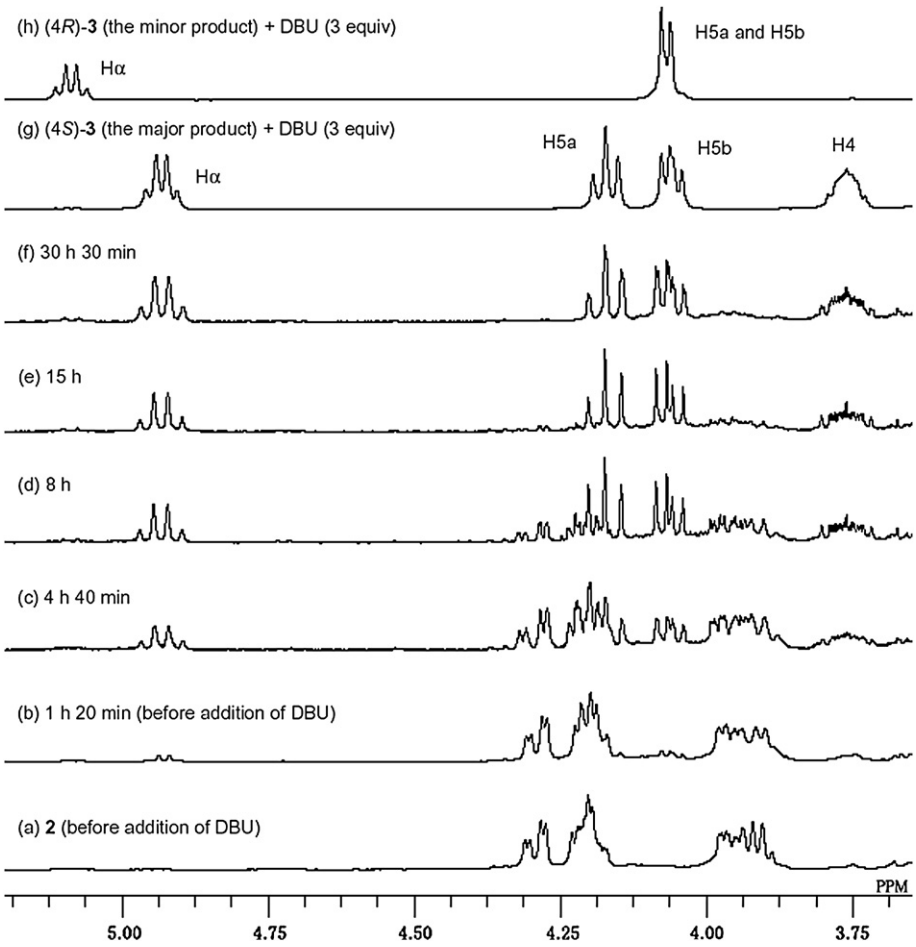


Figure 6. ^{1}H NMR spectra of the reaction of cyclic carbonate **2** to oxazolidinones (4*S*)-**3** and (4*R*)-**3** by treatment of DBU (3 equiv) in THF-d_8 (0.04 mol/L) at 25 °C: (a) before addition of DBU, (b) 1 h 20 min after addition of DBU, (c) 4 h 40 min, (d) 8 h, (e) 15 h, (f) 30 h 30 min, (g) a mixture of (4*S*)-**3** (the major product) and DBU (3 equiv) in THF-d_8, and (h) a mixture of (4*R*)-**3** (the minor product) and DBU (3 equiv) in THF-d_8 [400 MHz for (a), (b), (g), (h) and 300 MHz for (c)–(f)].

conducted in $CDCl_3$ and THF-d_8 (0.04 mol/L) at a probe temperature of 25 °C. Immediately after the start of the reaction, new signals began to appear; however, they did not correspond to those of the intermediates. The signals were the benzylic protons of (4*S*)-**3** and (4*R*)-**3**, and these oxazolidinones were products of the second reaction. These signals appeared at δ 5.16 [1H, q, J=7.1 Hz, PhC*H* of (4*S*)-**3**] and 5.18 [1H, q, J=7.3 Hz, PhC*H* of (4*R*)-**3**] in $CDCl_3$ and δ 4.93 [1H, q, J=7.2 Hz, PhC*H* of (4*S*)-**3**] and 5.09 [1H, q, J=7.2 Hz, PhC*H* of (4*R*)-**3**] in THF-d_8. We realized that the signals of (4*S*)-**3** and (4*R*)-**3** were useful to measure the concentration of (4*S*)-**3** and (4*R*)-**3** by comparison with an integral value of triphenylmethane as an internal standard and analyzed the kinetics. The signals of (4*S*)-**3** and (4*R*)-**3** (δ 5.16 and 5.18, respectively) in $CDCl_3$ with DBU were partially overlapped on the ^{1}H NMR spectrum; therefore, the ratio of (4*S*)-**3**/(4*R*)-**3** in the reaction mixture could not be estimated. Although those protons in THF-d_8 (δ 4.93 and 5.09) were separated and the ratio of (4*S*)-**3**/(4*R*)-**3** was estimated as 96:4 during the reaction, we used the concentration of 2-oxazolidinones **3** as a sum of the products (4*S*)-**3** and (4*R*)-**3** in these studies.

Neither **6**$^-$**(DBU-H**$^+$**)** nor the other intermediates were observed during ^{1}H NMR experiments for the kinetic studies (Figs. 5 and 6); therefore, the relation of two rate constants (k_1 and k_2) for the reactions should be $k_1 \ll k_2$, and the first reaction would be a rate-determining step (Scheme 6). On

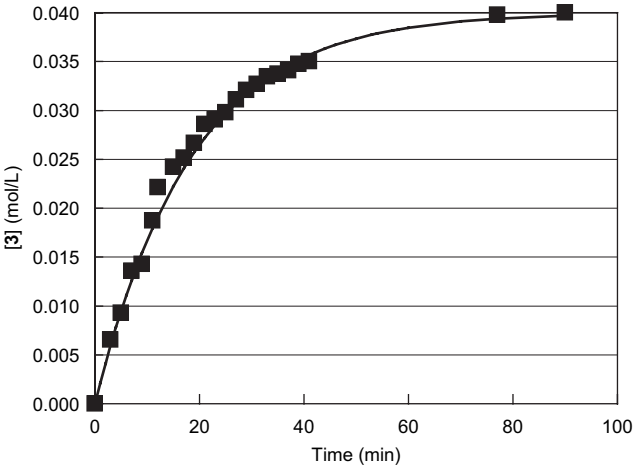


Figure 7. Concentration of the sum of 2-oxazolidinones (4*S*)-**3** and (4*R*)-**3** (■) of the DBU-catalyzed acyl transfer of **2** in $CDCl_3$ plotted against time. The line is the concentration calculated by the kinetic simulation using the rate constant k_{CDCl_3} shown in Figure 8. The equation is as follows: $[\mathbf{3}]=[\mathbf{2}]_0-[\mathbf{2}]_0(\exp(-k_{CDCl_3}t))$.

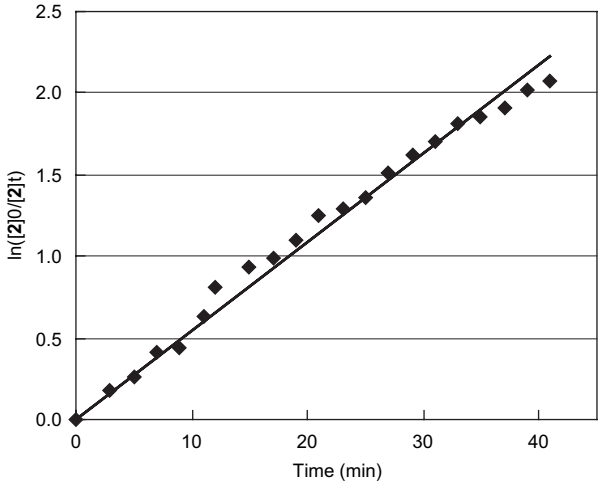


Figure 8. Linear correlation of plot of $\ln([\mathbf{2}]_0/[\mathbf{2}]_t)$ versus the reaction time (in $CDCl_3$, $k_{CDCl_3} = 5.4 \times 10^{-2}\text{min}^{-1}$).

the other hand, the intramolecular acyl transfer of cyclic carbonate **2** required DBU as a base, and we expected the base not to lose its activity because no acidic compound was released during the reaction. Thus, the concentration of DBU was constant during the intramolecular reaction. According to this consideration, a first-order formation of **3**, expressed as $d[\mathbf{3}]/dt=-d[\mathbf{2}]/dt=k[\mathbf{2}]=k([\mathbf{2}]_0-[\mathbf{3}]_t)$, was expected. Transformation of the rate equation into the integrated form gave $\ln([\mathbf{2}]_0/[\mathbf{2}]_t)=\ln([\mathbf{2}]_0/([\mathbf{2}]_0-[\mathbf{3}]_t))=kt$, in which $[\mathbf{2}]_0$, $[\mathbf{2}]_t$, and $[\mathbf{3}]_t$ are the concentration of **2** at times equal to 0 min and t min and that of **3** at t min, respectively. Both of the reactions in $CDCl_3$ and THF-d_8 proceeded according to the first-order kinetics in **2**, as shown in Figures 7 and 9, and the prediction was consistent with the linear correlation in the plot of $\ln([\mathbf{2}]_0/[\mathbf{2}]_t)=\ln([\mathbf{2}]_0/([\mathbf{2}]_0-[\mathbf{3}]_t))$ versus the reaction time shown in Figures 8 and 10. The rate constants of the reactions in $CDCl_3$ and THF-d_8 estimated from the slopes of linear first-order plots (Figs. 8 and 10) were $5.4\times10^{-2}\,\text{min}^{-1}$ and $1.7\times10^{-3}\,\text{min}^{-1}$, respectively.

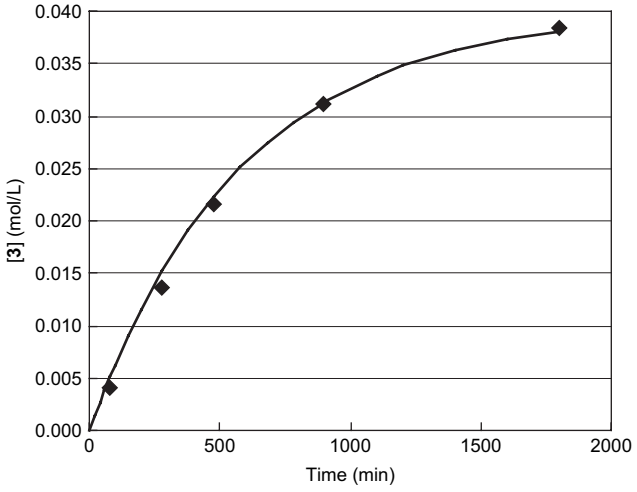


Figure 9. Concentration of the sum of 2-oxazolidinones (4*S*)-**3** and (4*R*)-**3** (■) of the DBU-catalyzed acyl transfer of **2** in THF plotted against time. The line is the concentration calculated by the kinetic simulation using the rate constant k_{THF-d_8} shown in Figure 10. The equation is as follows: $[\mathbf{3}]=[\mathbf{2}]_0-[\mathbf{2}]_0(\exp(-k_{THF-d_8}t))$.

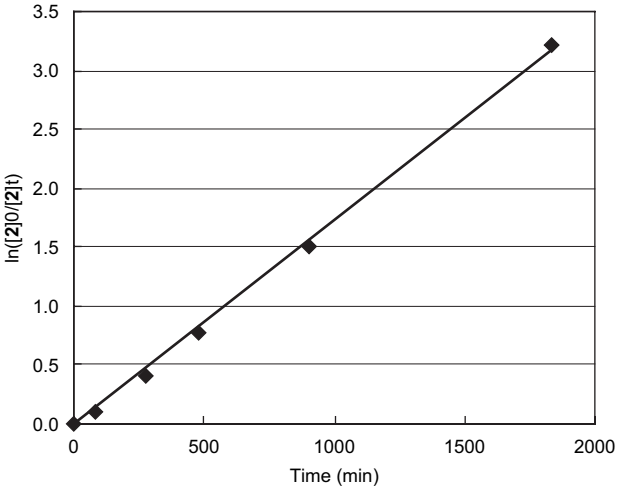


Figure 10. Linear correlation of the plot of $\ln([\mathbf{2}]_0/[\mathbf{2}]_t)$ versus the reaction time (in THF-d_8, $k_{THF-d_8} = 1.7 \times 10^{-3}\text{min}^{-1}$).

3. Conclusion

In summary, the results obtained from these studies furnished a novel approach to the diastereoselective synthesis of 2-oxazolidinone (4*S*)-**3** from cyclic carbonate **2** via the intramolecular acyl transfer. The developed novel reaction showed quantitative yields and high diastereoselectivities (up to 94% de) and proceeded according to the first-order kinetics to give (4*S*)-**3**; the best results were obtained when the reactions were carried out using DBU in CD_2Cl_2 or $CDCl_3$. The proposed intermediate of this diastereoselective reaction appears to be the contact ion pair **6**$^-$**(DBU-H**$^+$**)**, which would be easily formed from the stable *N*-rotamer of **2**. This is the first example of an intramolecular acyl transfer from a 5-amino-1,3-dioxan-2-one **C** to a 2-oxazolidinone **D** (Scheme 1). The carbonate **2** possesses a σ-symmetric moiety; therefore, this diastereoselective reaction would be an asymmetric desymmetrization.

4. Experimental

4.1. General

All commercially available materials were used without further purification. Melting points were measured with Yanaco MP-3 apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-140 polarimeter. IR spectra were recorded on a Hitachi 215 spectrophotometer. NMR spectra were obtained with JEOL JNM-GSX400 (^{1}H NMR: 400 MHz and ^{13}C NMR: 100 MHz) and JEOL JNM-AL300 (^{1}H NMR: 300 MHz) spectrometers using tetramethylsilane as an internal standard. MS and high-resolution MS (HRMS) were taken on a JEOL JMS-DX302 spectrometer. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). Analytical TLC was performed on plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} (Merck).

4.2. Synthesis of cyclic carbonate 2 (Scheme 3)

4.2.1. (*R*)-*N*-Benzyl-*N*-(α-methyl)benzyl-2-amino-1,3-propanediol (4). A mixture of **1**[7] (809 mg, 4.14 mmol),

diisopropylethylamine (1.61 g, 12.4 mmol), and benzyl bromide (1.42 g, 8.28 mmol) in $CHCl_3$ (10 mL) was refluxed for 22 h. After the reaction mixture was cooled to room temperature, water was added and the resulting mixture was extracted with chloroform. The extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt 3:7) to afford **4** (757 mg, 64%). Colorless plates, mp 91–92 °C. $[\alpha]_D^{28}$ +40.3 (*c* 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24–7.34 (10H, m, Ar), 4.02 (1H, q, *J*=6.8 Hz, PhC*H*), 3.83 (1H, d, *J*=14.1 Hz, PhC*H*H), 3.77 (1H, d, *J*=13.9 Hz, PhCH*H*), 3.72 (1H, d, *J*=11.2 Hz, C*H*HOH), 3.67 (1H, d, *J*=11.2 Hz, CH*H*OH), 3.37 (1H, dd, *J*=10.7, 6.6 Hz, C*H*HOH), 3.30 (1H, dd, *J*=10.7, 6.6 Hz, CH*H*OH), 3.08 (1H, quint, *J*=6.6 Hz, NCH), 1.44 (3H, d, *J*=6.8 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.8 (C), 140.2 (C), 128.41 (CH×2), 128.39 (CH×2), 128.3 (CH×2), 127.6 (CH×2), 127.2 (CH), 127.0 (CH), 61.6 (CH_2OH), 61.2 (CH_2OH), 59.0 (CH), 56.6 (CH), 50.1 (PhCH), 17.4 (Me). IR ($CHCl_3$) cm^{-1}: 3445, 2950, 1465, 1395, 1140, 1030. HRMS (positive FAB) *m*/*z*: 286.1812 (calcd for $C_{18}H_{24}NO_2$: 286.1808). MS (positive FAB) *m*/*z*: 286 [(M+1)$^+$]. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.79; H, 8.04; N, 4.99.

4.2.2. (*R*)-*N*-Benzyl-*N*-(α-methyl)benzyl-5-amino-1,3-dioxan-2-one (5). A mixture of **4** (733 mg, 2.57 mmol) and CDI (500 mg, 3.08 mmol) in CH_2Cl_2 (13 mL) was stirred for 13 h at room temperature. The reaction mixture was poured into water and extracted with dichloromethane. The extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to afford **5** (399 mg, 50%). Colorless viscous oil. $[\alpha]_D^{26}$ +31.8 (*c* 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.35 (10H, m, Ar), 4.38 (1H, ddd, *J*=11.0, 5.6, 1.5 Hz, OC*H*H), 4.32 (1H, dd, *J*=11.0, 9.0 Hz, OCH*H*), 4.05 (1H, dd, *J*=11.0, 9.0 Hz, C*H*H), 3.98 (1H, q, *J*=7.1 Hz, PhCH), 3.93 (1H, ddd, *J*=11.0, 5.6, 1,5 Hz, OCH*H*), 3.84 (2H, s, PhCH_2), 3.48 (1H, m, NCH), 1.43 (3H, d, *J*=7.1 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.9 (C=O), 141.8 (C), 139.2 (C), 128.5 (CH×2), 128.4 (CH×2), 127.8 (CH×2), 127.4 (CH), 127.3 (CH), 127.2 (CH×2), 69.1 (CH_2O), 68.8 (CH_2O), 57.1 (CH), 50.8 (CH_2), 48.5 (CH), 16.2 (Me). IR (film) cm^{-1}: 1760, 1180, 1125. HRMS (EI) *m*/*z*: 311.1525 (calcd for $C_{19}H_{21}NO_3$: 311.1522). MS (EI) *m*/*z*: 311 (M$^+$, 20%), 296 (13), 224 (61), 120 (37), 105 (100), 91 (84).

4.2.3. (*R*)-5-(α-Methyl)benzylamino-1,3-dioxan-2-one (2). Ceric ammonium nitrate (CAN, 349 mg, 637 μmol) was added to a solution of **5** (94.5 mg, 303 μmol) in acetonitrile–water (5:1, 1.0 mL) with cooling by use of an ice bath. After being stirred for 45 min with cooling, the acidic reaction mixture was diluted with water and neutralized with satd aq $NaHCO_3$ and the mixture was extracted with Et_2O three times. The extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual mixture of the desired product **2** and benzaldehyde was chromatographed on silica gel ($CHCl_3$/MeOH 98:2, 1.5 cm Φ×6.0 cm) using a glass-filter-column within ca. 5 min to afford the cyclic carbonate **2** (35.5 mg, 53%) as a light-yellow viscous oil and a mixture of **2**/(4*S*)-**3**/(4*R*)-**3** (71:25:4, 11.2 mg, 17%).[11] The oil was crystallized in a freezer. Colorless crystals, mp 47–50 °C. $[\alpha]_D^{27}$ +52.6 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24–7.39 (5H, m, Ar), 4.36 (1H, dd, *J*=11.0, 3.4 Hz, OC*H*H), 4.27–4.32 (2H, m, OCH*H*, OC*H*H), 4.07 (1H, ddd, *J*=11.0, 4.6, 2.2 Hz, OCH*H*), 3.91 (1H, q, *J*=6.6 Hz, PhCH), 3.02 (1H, m, NCH), 1.38 (3H, d, *J*=6.6 Hz, Me). (CD_2Cl_2) δ: 7.26–7.41 (5H, m, Ar), 4.38 (1H, ddd, *J*=11.2, 3.3, 0.8 Hz, OC*H*H), 4.27–4.33 (2H, m, OCH*H*, OC*H*H), 4.07 (1H, ddd, *J*=11.0, 4.4, 2.4 Hz, OCH*H*), 3.95 (1H, q, *J*=6.6 Hz, PhC*H*), 3.04 (1H, m, NCH), 1.40 (3H, d, *J*=6.6 Hz, Me). (THF-d_8) δ: 7.33 (2H, d, *J*=7.6 Hz, Ar), 7.27 (2H, t, *J*=7.3 Hz, Ar), 7.17 (1H, t, *J*=7.3 Hz, Ar), 4.29 (1H, dd, *J*=10.7, 3.4 Hz, OC*H*H), 4.18–4.23 (2H, m, OCH*H*, OC*H*H), 3.94–3.97 (1H, m, OCH*H*), 3.91 (1H, q, *J*=6.6 Hz, PhC*H*), 2.91 (1H, m, NCH), 1.31 (3H, d, *J*=6.6 Hz, Me). (C_6D_6) δ: 7.03–7.13 (3H, m, Ar), 6.94 (2H, d, *J*=6.8 Hz, Ar), 3.50 (1H, dq, *J*=6.6, 2.2 Hz, OC*H*H), 3.27–3.36 (4H, m, OCH_2, OC*H*H, PhC*H*), 2.08 (1H, quint, NCH), 0.95 (3H, d, *J*=6.6 Hz, Me). (CD_3CN) δ: 7.32–7.33 (4H, m, Ar), 7.25 (1H, m, Ar), 4.33 (1H, dd, *J*=11.2, 2.9 Hz, OC*H*H), 4.23–4.29 (2H, m, OCH*H*, OC*H*H), 4.01 (1H, dt, *J*=7.8, 3.2 Hz, OCH*H*), 3.90 (1H, q, *J*=6.6 Hz, PhC*H*), 2.93 (1H, quint, *J*=6.6 Hz, NCH), 1.30 (3H, d, *J*=6.6 Hz, Me). (CD_3NO_2) δ: 7.32–7.39 (4H, m, Ar), 7.26–7.28 (1H, m, Ar), 4.42 (1H, dd, *J*=11.2, 2.9 Hz, OC*H*H), 4.09 (1H, ddd, *J*=11.2, 3.9, 2.6 Hz, OCH*H*), 3.99 (1H, q, *J*=6.6 Hz, PhC*H*), 3.07 (1H, quint, *J*=3.5 Hz, NCH), 1.37 (3H, d, *J*=6.6 Hz, Me). Some signals of **2** were overlapped with the solvent residual peak. (DMSO-d_6) δ: 7.28–7.36 (4H, m, Ar), 7.20 (1H, t-like m, Ar), 4.24–4.34 (3H, m, OCH_2, OC*H*H), 4.04 (1H, dt, *J*=7.6, 3.2 Hz, OCH*H*), 3.85 (1H, q, *J*=6.3 Hz, PhC*H*), 2.79 (1H, m, NCH), 1.25 (3H, d, *J*=6.6 Hz, Me). (CD_3OD) δ: 7.28–7.36 (4H, m, Ar), 7.21–7.25 (1H, m, Ar), 4.40 (1H, dd, *J*=11.0, 2.9 Hz, OC*H*H), 4.29–4.36 (2H, m, OCH*H*, OC*H*H), 4.07 (1H, ddd, *J*=11.0, 4.0, 2.3 Hz, OCH*H*), 3.91 (1H, q, *J*=6.6 Hz, PhC*H*), 2.97 (1H, quint, *J*=3.5 Hz, NCH), 1.36 (3H, d, *J*=6.6 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.9 (C=O), 144.0 (C), 128.7 (CH×2), 127.5 (CH), 126.3 (CH×2), 72.1 (CH_2), 69.9 (CH_2), 55.7 (CH), 46.1 (CH), 24.9 (Me). IR (film) cm^{-1}: 1745, 1175, 1120, 770, 710. HRMS (positive FAB) *m*/*z*: 222.1117 (calcd for $C_{12}H_{16}NO_3$: 222.1131). MS (positive FAB) *m*/*z*: 222 [(M+1)$^+$].

4.3. General procedure for the acyl transfer (Table 1)

4.3.1. For entries 1–12, 14, and 21–28. A typical procedure for the reaction in NMR tubes is as follows: the additive (0–3 equiv) was added to a mixture of **2** (6.5 mg, 29 μmol) and triphenylmethane (an internal standard, 2.2 mg, 8.8 μmol) in the solvent in an NMR tube. After the tube was shaken vigorously for a few seconds, the reaction was carried out with spinning at a probe temperature of 25 °C or allowed to stand at room temperature. For entries 5–20, the reaction mixture was poured into satd aq NH_4Cl and extracted with $CHCl_3$. The extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. For entries 22 and 26–28, the reaction mixture was poured into satd aq $NaHCO_3$ and extracted with $CHCl_3$. The extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. For entries 1–4, 10, 12, 14, and 21–26, the reactions were estimated directly with ^{1}H NMR analysis.

4.3.2. For entries 13 and 15–20. According to the procedure described in Section 4.3.1, the reactions for entries 13 and 15–20 were carried out with stirring at room temperature in small flasks instead of NMR tubes.

4.4. ^{1}H NMR shift values in the presence of DBU

^{1}H NMR spectra were measured in the solvents with 3 equiv of the additives (DBU or the acids). Characteristic signals not being overlapped with those of the additives were as follows.

4.4.1. (*R*)-*N*-(α-Methyl)benzyl-5-amino-1,3-dioxan-2-one (2). ^{1}H NMR (400 MHz, $CDCl_3$ with DBU) δ: 4.36 (1H, dd, J=11.0, 3.2 Hz, OC*H*H). (CD_2Cl_2 with DBU) δ: 4.35 (1H, dd, J=11.0, 2.9 Hz, OC*H*H). (THF-d_8 with DBU) δ: 4.30 (1H, dd, J=10.7, 3.2 Hz, OC*H*H).

4.4.2. (4*S*,α*R*)-4-Hydroxymethyl-3-α-methylbenzyl-2-oxazolidinone [(4*S*)-3]. ^{1}H NMR (400 MHz, $CDCl_3$ with DBU) δ: 5.16 (1H, q, J=7.1 Hz, PhC*H*), 4.31 (1H, t, J=8.5 Hz, OC*H*H), 4.23 (1H, dd, J=8.5, 5.9 Hz, OCH*H*), 3.89 (1H, m, NCH), 3.10 (1H, dd, J=11.2, 6.8 Hz, HOC*H*H), 1.70 (3H, d, J=7.1 Hz, Me). (THF-d_8 with DBU) δ: 4.93 (1H, q, J=7.2 Hz, PhC*H*). (CD_3OD with DBU) δ: 4.95 (1H, q, J=7.1 Hz, PhC*H*), 4.34 (1H, t, J=8.8 Hz, OC*H*H), 4.22 (1H, dd, J=8.5, 4.9 Hz, OCH*H*), 3.93 (1H, m, NCH). (C_6D_6, DBU) δ: 5.11 (1H, q, J=7.1 Hz). (CD_3CN) δ: 4.90 (1H, q, J=7.1 Hz). (CD_3NO_2, DBU) δ: 4.97 (1H, q, J=7.1 Hz). (DMSO-d_6, DBU) δ: 4.80 (1H, q, J=7.1 Hz). ($CDCl_3$, the carboxylic acids) δ: 5.30 (1H, q, J=7.1 Hz).

4.4.3. (4*R*,α*R*)-4-Hydroxymethyl-3-α-methylbenzyl-2-oxazolidinone [(4*R*)-3]. ^{1}H NMR (400 MHz, $CDCl_3$ with DBU) δ: 5.18 (1H, q, J=7.3 Hz, PhC*H*), 4.26 (1H, dd, J=8.5, 4.4 Hz, OC*H*H), 4.18 (1H, t, J=8.1 Hz, OCH*H*), 3.63 (1H, dd, J=8.1 Hz, HOC*H*H), 3.46–3.50 (2H, m, NCH, HOCH*H*). (THF-d_8 with DBU) δ: 5.09 (1H, q, J=7.2 Hz, PhC*H*). (CD_3OD with DBU) δ: 5.08 (1H, q, J=7.1 Hz, PhC*H*), 4.19–4.26 (2H, m, OCH_2), 3.56 (3H, m, OCH_2, NCH). (CD_3CN) δ: 4.99 (1H, q, J=7.3 Hz). (DMSO-d_6, DBU) δ: 4.93 (1H, q, J=7.1 Hz). ($CDCl_3$, the carboxylic acids) δ: 5.16 (1H, q, J=7.1 Hz).

4.5. Preparation of dideuteriocyclic carbonates (5*R*)-2-d_2 and (5*S*)-2-d_2 (Scheme 5)

4.5.1. (2*R*,α*R*)-2-(*N*-α-Methylbenzyl)amino-1,1-dideuterio-1,3-propanediol [(2*R*)-1-d_2]. This compound was synthesized from the aziridine (2*R*)-**8**[19] according to the reported procedure.[20] Lithium aluminum deuteride (0.26 g, 6.5 mmol) was added to a solution of (2*R*)-**8** (1.05 g, 4.79 mmol) in diethyl ether (15.5 mL) at 0 °C. After being stirred for 1.5 h, the reaction mixture was treated with water (0.26 mL), 15% aq sodium hydroxide (0.26 mL), and water (0.78 mL) with stirring. The mixture was stirred for 2 h at room temperature, and filtered though a glass filter. The filtrate was concentrated in vacuo. The residue [crude (2*R*)-**9**-d_2] was dissolved in a mixture of acetic acid (0.64 mL) and chloroform (12 mL), and the mixture was refluxed for 8 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in a mixture of potassium hydroxide (0.61 mg) and ethanol (18 mL) and the mixture was refluxed for 3 h. After the reaction mixture was cooled to room temperature and concentrated in vacuo, the residue was diluted with water (35 mL) and acidified with 10% hydrochloric acid (ca. pH 2). The mixture was washed with ethyl acetate (35 mL×3), then alkalized with 10% aq sodium hydroxide (ca. pH 12), and extracted with ethyl acetate (35 mL×3). The extracts were combined, washed with water (35 mL), dried with magnesium sulfate, filtered, and concentrated in vacuo to afford (2*R*)-**1**-d_2 [680 mg, 72% yield from (2*R*)-**8**]. Colorless plates, mp 117–118 °C (ethyl acetate). $[\alpha]_D^{20}$ +60.9 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23–7.35 (5H, m, Ar), 3.91 (1H, q, J=6.6 Hz, PhC*H*), 3.52 (2H, d, J=5.1 Hz, OCH_2), 2.63 (1H, t, J=5.1 Hz, NC*H*CH_2O), 1.39 (3H, d, J=6.6 Hz, Me) (Fig. 4b). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.2, 128.5 (×2), 127.0, 126.3 (×2), 63.5, 56.8, 55.7, 24.9. IR (KBr) cm^{-1}: 3350, 3240, 1100, 970. MS (positive FAB) *m*/*z*: 198 [(M+1)$^+$]. Anal. Calcd for $C_{11}H_{15}D_2NO_2$: C, 66.97; N, 7.10. Found: C, 66.81; N, 7.03.

4.5.2. (2*S*,α*R*)-2-(*N*-α-Methylbenzyl)amino-1,1-dideuterio-1,3-propanediol [(2*S*)-1-d_2]. According to the synthetic procedure of (2*R*)-**1**-d_2, (2*S*)-**1**-d_2 was prepared from (2*S*)-**8**.[17] Colorless plates, mp 117–118 °C (ethyl acetate). $[\alpha]_D^{20}$ +58.0 (*c* 0.6, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23–7.36 (5H, m, Ar), 3.92 (1H, q, J=6.6 Hz, PhC*H*), 3.73 (1H, dd, J=11.0, 4.4 Hz, OC*H*H), 3.54 (1H, dd, J=11.0, 4.0 Hz, OCH*H*), 2.62 (1H, dd, J=4.4, 4.0 Hz, NC*H*CH_2O), 1.39 (3H, d, J=6.6 Hz, Me) (Fig. 4c). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.2, 128.5 (×2), 127.1, 126.4 (×2), 61.8, 56.8, 55.7, 24.9. IR (KBr) cm^{-1}: 3350, 3250, 1055, 965. MS (positive FAB) *m*/*z*: 198 [(M+1)$^+$]. Anal. Calcd for $C_{11}H_{15}D_2NO_2$: C, 66.97; N, 7.10. Found: C, 66.81; N, 7.03.

4.5.3. (5*R*,α*R*)-*N*-(α-Methyl)benzyl-5-amino-4,4-dideuterio-1,3-dioxan-2-one [(5*R*)-2-d_2]. CDI (3.4 mg, 21 μmol) was added to a mixture of serinol (2*R*)-**1** (3.5 mg, 18 μmol) in $CDCl_3$ (0.45 mL) in an NMR tube. After the tube was shaken vigorously for a few seconds, the tube was allowed to stand for 15 h at room temperature to afford a mixture of (5*R*)-**2** and diimidazolylcarbonayl serinol (2*R*)-**10** (61:39). Small amounts of the starting material (2*R*)-**1** and the oxazolidinone also existed in the mixture (Fig. 4e). ^{1}H NMR spectrum was measured without work-up. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta_{(5R)\text{-}\mathbf{2}\text{-}d_2}$: 4.29 (1H, dd, J=11.0, 3.7 Hz, OC*H*H), 4.07 (1H, dd, J=11.0, 4.4 Hz, OCH*H*), 3.91 (1H, q, J=6.6 Hz, PhC*H*), 3.02 (1H, t, J=4.0 Hz, NCH), 1.38 (3H, d, J=6.6 Hz, Me). $\delta_{(2R)\text{-}\mathbf{10}}$: 4.54 (1H, dd, J=11.7, 5.9 Hz, OC*H*H), 4.48 (1H, dd, J=11.6 Hz, OCH*H*), 3.98 (1H, q, J=6.7 Hz, PhC*H*), 3.20 (1H, q, J=5.3 Hz, CH), 1.37 (3H, d, J=6.4 Hz, Me).

4.5.4. (5*S*,α*R*)-*N*-(α-Methyl)benzyl-5-amino-4,4-dideuterio-1,3-dioxan-2-one [(5*S*)-2-d_2]. According to the synthetic procedure of (5*R*)-**2**, a mixture of (5*S*)-**2** and (2*S*)-**10** (62:38) was prepared from (2*S*)-**1**-d_2. Small amounts of the starting material (2*S*)-**1**-d_2 and the oxazolidinone also existed in the mixture (Fig. 4f). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta_{(5R)\text{-}\mathbf{2}\text{-}d_2}$: 4.36 (1H, dd, J=11.2, 3.5 Hz, OC*H*H), 4.30 (1H, J=11.2, 4.4 Hz, OCH*H*), 3.92 (1H, q, J=6.6 Hz,

PhC*H*), 3.02 (1H, t, *J*=3.8 Hz, NCH), 1.38 (3H, d, *J*=6.6 Hz, Me). $\delta_{(2S)-\mathbf{10}-d_2}$: 4.37 (2H, d, *J*=5.9 Hz, OCH2), 3.98 (1H, q, *J*=6.7 Hz, PhC*H*), 3.02 (1H, t, *J*=4.0 Hz, NCH), 1.37 (3H, d, *J*=6.4 Hz, Me).

4.6. Preparation of side product 10

4.6.1. (*R*)-1,3-Di[(1-imidazolyl)carbonyl]oxy-2-(*N*-α-methylbenzyl)aminopropane (10). CDI (4.96 g, 30.6 mmol) was added to a solution of **1** (2.00 g, 10.3 mmol) in CH_2Cl_2 (51 mL) at 0 °C. After being stirred for 2 h, the reaction mixture was washed with satd aq NH_4Cl (51 mL) twice, dried, filtered, and concentrated in vacuo to give colorless solid (3.92 g, 100%). For spectral analysis the solid **10** (1.00 g) was recrystallized from THF (10 mL) to afford pure **10** (105 mg) as colorless needles. Mp 130–133 °C; $[\alpha]_D^{24}$ +30.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.41 (1H, s, imidazole), 8.06 (1H, s, imidazole), 7.41 (1H, imidazole), 7.36 (1H, s, imidazole), 7.29–7.23 (5H, m, Ph), 7.10 (1H, s-like m, imidazole), 7.09 (1H, s-like m, imidazole), 4.54 (1H, dd, *J*=11.2, 5.9 Hz, OC*H*H), 4.48 (1H, dd, *J*=11.5, 4.2 Hz, OCH*H*), 4.37 (2H, d, *J*=5.9 Hz, OCH_2), 3.99 (1H, q, *J*=6.6 Hz, MeC*H*), 3.20 (1H, m, NC*H*CH_2), 1.37 (3H, d, *J*=6.6 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 148.3, 148.2, 144.3, 136.9 (×2), 130.9, 130.8, 128.6 (×2), 127.5, 126.3 (×2), 116.9 (×2), 67.6, 66.0, 56.0, 52.8, 24.9. IR ($CHCl_3$) cm^{-1}: 1762. HRMS *m*/*z*: 383.1599 (calcd for $C_{19}H_{21}N_5O_4$: 383.1595). MS (EI) *m*/*z*: 383 (M^+, 0.5%), 271 (18), 256 (17), 204 (34), 173 (22), 166 (14), 160 (14), 105 (100).

4.7. Acyl transfer in the presence of 18-crown-6

4.7.1. With sodium hydride. Sodium hydride (60% oil suspension, 2.0 mg, 50 μmol) was added to a mixture of 2-oxazolidinone (2*R*)-**3** (5.5 mg, 25 μmol) in THF-d_8. The mixture was allowed to stand for 8 h at room temperature to afford a 57:43 mixture of the oxazolidinones (2*R*)-**3** and (2*S*)-**3**. To this mixture was added 18-crown-6 (27.3 mg, 103 μmol) and the resulting mixture was allowed to stand for 13 h to give a 50:50 mixture.

4.7.2. With potassium *tert*-butoxide. Potassium *tert*-butoxide (5.5 mg, 49 μmol) was added to a mixture of 2-oxazolidinone (2*R*)-**3** (5.4 mg, 24 μmol) in THF-d_8. The mixture was allowed to stand for 8 h at room temperature to afford a 56:44 mixture of the oxazolidinones (2*R*)-**3** and (2*S*)-**3**. To this mixture was added 18-crown-6 (30.7 mg, 116 μmol) and the resulting mixture was allowed to stand for 13 h to give a 49:51 mixture.

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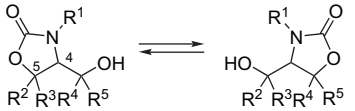

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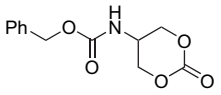

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