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Asymmetric synthesis of the 4-hydroxymethyl-2-oxazolidinone from the serinol derivative and chloroformates

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Abstract

Asymmetric desymmetrization of 2-[(α*R*)-α-methylbenzyl]amino-1,3-propanediol (**1**) with 2-chloroethyl chloroformate and DBU at room temperature gave optically active (4*S*)-4-hydroxymethyl-*N*-[(α*R*)-α-methylbenzyl]-2-oxazolidinone [(4*S*)-**2**] (up to 94% de). This reaction involves kinetic resolution and [1,3]-alkoxyacyl migration of 2-chloroethyl (2*S*)- and 2-chloroethyl (2*R*)-3-hydroxy-2-[(α*R*)-α-methylbenzyl]aminopropyl carbonates [(2*S*)-**4** and (2*R*)-**4**].

Keywords: diastereoselection; oxazolidinones; amino alcohols; cyclization.

Asymmetric desymmetrization of prochiral 2-substituted-1,3-propanediols is successfully achieved using enzymes. For example, 2-methyl-1,3-propanediol and its diester are acylated and hydrolyzed to their corresponding optically active monoesters by *Pseudomonas fluorescens* lipase.[1] Other 2-substituted-1,3-propanediols are also converted to optically active alcohols by chemical methods.[2] In these reactions, however, serinol derivatives have not been investigated. On the other hand, optically active 4-hydroxymethyl-2-oxazolidinone derivatives are used as important intermediates for organic syntheses.[3] The oxazolidinones are prepared from optically active serine,[3a,i] mono-*O*-substituted serinol,[3i,4] and glycidol.[3h] In these cases the chirality of the 4-position of the oxazolidinone ring is derived from the chirality of the starting material. Here we describe a new methodology for the asymmetric synthesis of 4-hydroxymethyl-2-oxazolidinones from a serinol derivative involving asymmetric desymmetrization. We focused on a starting material, prochiral serinol **1**, possessing a chiral α-methylbenzyl group on its nitrogen. Serinol **1** would react with chloroformates, and optically active oxazolidinones (4*S*)-**2** or (4*R*)-**2** would be given by diastereoselective intramolecular cyclization (Scheme 1).

Serinol **1** was prepared by amination of diethyl bromomalonate with (*R*)-(+)-α-methylbenzylamine, following reduction of the ester groups with sodium borohydride[5] (Scheme 2). Serinol **1** was treated with alkyl, haloalkyl, benzyl, or phenyl chloroformates in $CDCl_3$ in the presence of Py-d_5 (base-1) and triphenylmethane as an internal standard for ^1H NMR analysis. After standing for 24 h at room

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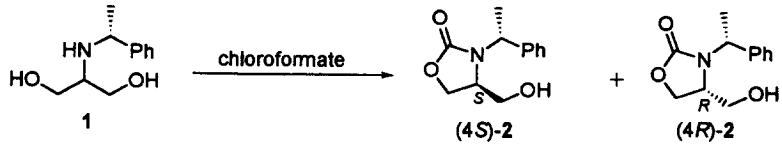
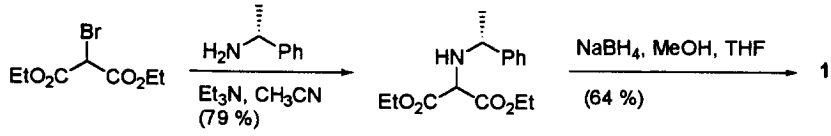


Scheme 1.

temperature, the mixture was treated with DBU (base-2). The resulting mixture was kept at room temperature for 48 h, affording (4*S*)-**2** and (4*R*)-**2**. The results are summarized in Table 1. The absolute configurations of (4*S*)-**2** and (4*R*)-**2** were determined by comparison with the spectral data of the samples obtained from (*R*)-(+)-α-methylbenzyl isocyanate and (*S*)-(−)-glycidol and from the isocyanate and (*R*)-(+)-glycidol, respectively.[6,7]



Scheme 2.

For the synthesis of the oxazolidinones from **1**, chloroalkyl and benzyl chloroformates were good reagents (entries 3, 5 and 6). Methyl and ethyl chloroformates were less reactive among them (entries 1 and 2). In these reactions, the major product was (4*S*)-**2** and the diastereomeric excess was high (92–84% de) except 2,2,2,1-tetrachloroethyl chloroformate (8% de, entry 5). DBU was needed for cyclization to give the oxazolidinone ring. Pyridine and triethylamine did not work at all for cyclization. In both yield and diastereoselectivity, 2-chloroethyl chloroformate was the most effective for the purpose.

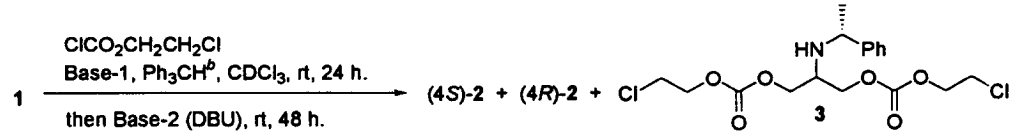
Table 1
Synthesis of 2-oxazolidinones **2** from **1** with chloroformates ($ClCO_2R$)[a]

1 + $ClCO_2R$ (1.0 equiv.) → (4*S*)-**2** + (4*R*)-**2**
Py-d_5 (1 equiv.), Ph_3CH [b] (0.25 equiv.), $CDCl_3$ (0.04 mol/L), rt, 24 h.
then DBU (3 equiv.), rt, 48 h.

Entry	Chloroformates	Oxazolidinones **2**	
	R	Yield (%)[c]	(4*S*) : (4*R*) (de, %)[d]
1	CH_3	47	96 : 4 (92)
2	CH_2CH_3	18	94 : 6 (88)
3	CH_2CH_2Cl	62	96 : 4 (92)
4	CH_2CCl_3	51	93 : 7 (86)
5	$CHClCCl_3$	60	54 : 46 (8)
6	CH_2Ph	59	96 : 4 (92)
7	Ph	51	92 : 8 (84)

[a] The reactions were carried out in NMR tubes. [b] Internal standard. [c] The yields were calibrated with the internal standard by ^{1}H-NMR integration. Characteristic signals ($CDCl_3$): δ[(4*S*)-**2**] = 5.30 ppm, δ[(4*R*)-**2**] = 5.15 ppm, δ(Ph_3CH) = 5.55 ppm. [d] The ratio of the products was obtained by the comparison of their HPLC area. HPLC conditions, column; LiChroCART/LiChrospher Si 60, 5 μm (Merck), solvent; *n*-hexane : AcOEt = 3 : 7, flow rate; 0.5 mL/min, detection; UV (254 nm). Retention time, (4*S*)-**2**; 35.0 min, (4*R*)-**2**; 33.0 min. The ratio of (4*S*)-**2** and (4*R*)-**2** was estimated with their area. The ratio of the HPLC area for (4*S*)-**2** and (4*R*)-**2** is in good agreement with that of the ^{1}H-NMR integration.

Table 2
Synthesis of (4*S*)-**2** and (4*R*)-**2** with 2-chloroethyl chloroformate[a]



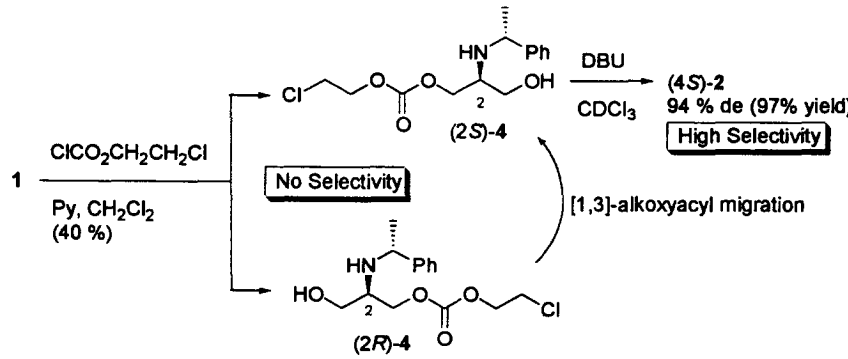
Entry	Chloroformate (equiv.)	Base-1 Py-d_5 (equiv.)	Base-1 DBU (equiv.)	Base-2 DBU (equiv.)	Oxazolidinones **2** Yield (%)[c]	Oxazolidinones **2** (4*S*) : (4*R*) (de, %)[d]
1[e]	1	1	-	3	62	96 : 4 (92)
2	1.2	1.2	-	3	45	95 : 5 (90)
3	1.4	1.4	-	3	44	95 : 5 (90)
4	1.6	1.6	-	3	44	95 : 5 (90)
5	1	1	-	1	0	-
6	1	1	-	2	56	96 : 4 (92)
7	1	-	-	3	61	89 : 11 (78)
8	1	1	3	-	43	72 : 28 (44)
9	1	-	1	2	52	96 : 4 (92)
10	1	-	2	1	34	81 : 19 (62)
11	1	-	3	-	37	77 : 23 (54)

[a–d] See the corresponding footnotes in Table 1. [e] Data taken from Table 1.

We studied the reactions of **1** containing various concentrations of 2-chloroethyl chloroformate and bases (Py-d_5 and DBU). The results are summarized in Table 2. When we used more than 1 equivalent of the chloroformate, the yield of oxazolidinones decreased, whereas the yield of biscarbonate **3** increased (11, 12, 16 and 35% in entries 1–4, respectively). The yield was not changed without pyridine; however, diastereomeric excess was found to be lower (entries 1 and 7). Use of less than 3 equivalents of DBU as base-2 (entries 5 and 6) and use of DBU as base-1 instead of pyridine (entries 9–11) gave poor yields and selectivities.

The best reaction conditions are shown in entry 1 on Table 2. According to the conditions, the preparative synthesis of (4*S*)-**2** from **1** (25.6 mmol) was performed. The best yield (68%) and diastereoselectivity (94% de, HPLC analysis) for (4*S*)-**2** were achieved.[8] The optical pure (4*S*)-**2** was prepared by recrystallization from *tert*-butyl methyl ether. This new procedure will be a convenient and efficient method for preparation of optically active 4-hydroxymethyl-2-oxazolidinones.

In order to clear the reaction paths, we tried to trap the intermediate of this one-pot reaction. A diastereomixture of monocarbonates (2*S*)-**4** and (2*R*)-**4** (1:1) could be obtained (40%) from a reaction of **1**, 2-chloroethyl chloroformate and pyridine in methylene chloride (Scheme 3). The mixture of (2*S*)-**4** and (2*R*)-**4** was treated with DBU in $CDCl_3$ at room temperature affording (4*S*)-**2** in excellent yield (97%) and in high diastereoselectivity (94% de). The selectivity was identical with that of the one-pot reaction from **1**. These facts indicate that the cyclization to (4*S*)-**2** involves kinetic resolution of monocarbonate (2*S*)-**4** and (2*R*)-**4** accompanied with [1,3]-alkoxyacyl migration from (2*R*)-**4** to (2*S*)-**4**.



Scheme 3.

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7. Recently antipodes of these oxazolidinones were synthesized from optically active aziridines.[4]
8. The procedure is as follows. Serinol **1** (5.00 g, 25.6 mmol) was dissolved in methylene chloride (640 mL, 0.04 mol/L) at 40°C (bath temperature). Pyridine (2.16 g, 25.6 mmol) was added, and then 2-chloroethyl chloroformate (3.66 g, 25.6 mmol) was added by one shot to the mixture at room temperature. After being stirred for 24 h at room temperature, the mixture was cooled to 1°C (internal temperature) with an ice bath and treated with DBU (11.85 g, 76.8 mmol). The resulting mixture was stirred for 4 h with warming to room temperature. The reaction mixture was washed twice with 5% HCl aq. (60 mL) and once with water (60 mL). It was then dried, filtered and concentrated in vacuo to give a yellow oil (5.92 g) which was chromatographed on silica gel (hexane:AcOEt 1:2, column 7 cm $\phi \times 22$ cm) to afford biscarbonate **3** (503 mg, 5%) as a colorless oil and a mixture of oxazolidinones (4*S*)-**2** and (4*R*)-**2** (3.85 g, 68% yield, 97: 3, 94% de) as colorless crystals. The crystals (3.84 g) were recrystallized from *tert*-butyl methyl ether (30 mL) to give pure (4*S*)-**2** as colorless plates (2.19 g).