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One-pot acylation and fractional crystallization: preparation of optically active serinol monobenzoates

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Abstract—Mono-*O*-acylation of (*R*)-2-(α-methylbenzyl)amino-1,3-propanediol **1** with 4-nitrobenzoyl chloride and DMAP in dichloromethane at room temperature gave crystals of optically active (2*S*,α*R*)-3-hydroxy-2-(α-methylbenzyl)aminopropyl 4-nitrobenzoate hydrochloride [(2*S*)-**2a**·HCl] in 33% yield by fractional crystallization. Optically active oxazolidinones, aziridines, and serinol derivatives were synthesized from the benzoate (2*S*)-**2a**.

1. Introduction

Optically active mono-*O*-substituted serinol derivatives have been used as important intermediates for organic syntheses; the serinols are converted to useful synthetic building blocks such as serinals,[1] 2-oxazolidinones,[2,3] aziridines,[4] oxazolines,[5] and a 3-iodo-2-amino-1-propanol derivative.[6] In general, the mono-*O*-substituted serinols are synthesized from (*S*)- or (*R*)-serines[1,3b–c,4–7] and aziridines.[2] Enzymatic preparations of optically active mono-*O*-acyl serinols B from serinol derivatives A have also been reported;[3a,8] however, non-enzymatic preparations of mono-*O*-acyl serinols B from serinol derivatives A have not been studied thoroughly (Fig. 1).[9] On the other hand, two diastereomeric 2-(*N*-α-methylbenzyl)amino-1-ethanol derivatives can be prepared by ring-opening reactions of *cis*-epoxides with optically active α-methylbenzylamines, and the fractional crystallization of some of the diastereomeric mixtures gives enantiomerically pure aminoalcohols[10] (Fig. 2).

We investigated the potential of the prochiral serinol **1** by conversion to a number of optically active compounds.[11] We considered that the two diastereomeric amino alcohols, (2*S*)-**2** and (2*R*)-**2**, would be prepared from **1** by mono-*O*-acylation, and that the products would possess 2-(*N*-α-methylbenzyl)amino-1-ethanol moieties. We also expected that one of them would be isolated by fractional crystallization. Herein, we report the one-pot procedure of the acylation of **1** and the fractional crystallization of optically active serinol monobenzoates (2*S*)-**2a**,**b**·HX (X = Cl, Br) salts (Scheme 1). We have also investigated the efficiency of the intramolecular transesterification of optically active monobenzoate (2*S*)-**2a** in various basic media.

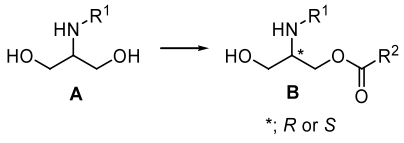

Figure 1. Mono-*O*-acyl serinol **B** from serinol derivative **A**.

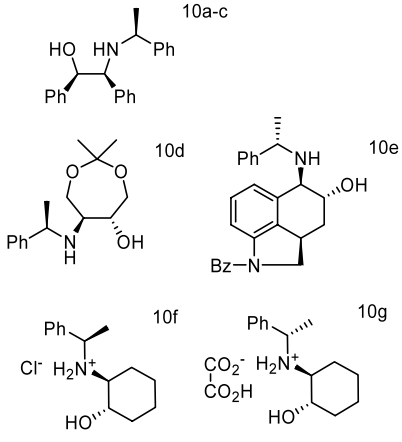

Figure 2. Amino alcohols purified by fractional crystallization.

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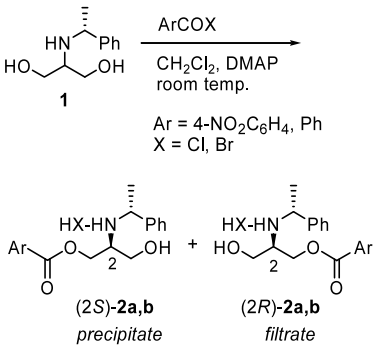


Scheme 1. One-pot acylation and fractional crystallization.

2. Results and discussion

2.1. Preparation of the monoesters

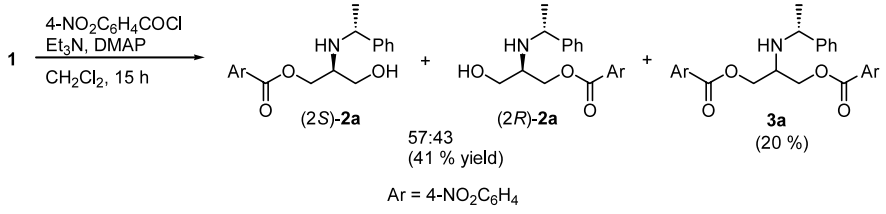
For the preparation of the mono-*O*-acyl compounds (2*S*)-**2** and (2*R*)-**2**, 4-nitrobenzoyl chloride (1.0 mol equiv.) was added to a saturated dichloromethane solution of serinol **1**[11] (0.04 mol/L) in the presence of triethylamine, which was used for trapping hydrogen chloride generated from acyl chloride (Scheme 2). The desired diastereomeric mixture of monoesters (2*S*)-**2a** and (2*R*)-**2a** was obtained in 41% yield (diastereomeric ratio; (2*S*)-**2a**:(2*R*)-**2a** = 57:43; ^{1}H NMR analysis); however, these monoesters were shown to give the same R_f value on TLC, and an undesired diester **3a** was also formed in 20% yield.

2.2. One-pot acylation and fractional crystallization

To increase the yield of (2*S*)-**2a** and (2*R*)-**2a**, the formation of **3a** from (2*S*)-**2a** and (2*R*)-**2a** must be prevented. We examined the reaction of serinol **1** and the acylating reagent without triethylamine and as a result found that the monoester hydrochloride salts (2*S*)-**2a**·HCl and (2*R*)-**2a**·HCl formed as soon as serinol **1** reacted. Also if the HCl salts precipitated, the yield of diester **3a** was seen to decrease. While the reaction was being carried out with a catalytic amount (0.2 mol equiv.) of DMAP, a crystalline material appeared in the reaction mixture. The crystals were collected by filtration, and a free amine was obtained by treatment of the crystals in ethyl acetate with saturated aqueous sodium hydrogen carbonate. After ^{1}H NMR analysis, we found that the free amine was not a mixture of (2*S*)-**2a** and (2*R*)-**2a** but a single isomer of (2*S*)-**2a** (33% yield). We also found another diastereomer, (2*R*)-**2a**·HCl (25% yield), and a dibenzoate **3a**·HCl (4% yield), in the filtrate. A resolution of (2*S*)-**2a**·HCl was achieved directly by fractional crystallization from the reaction mixture.

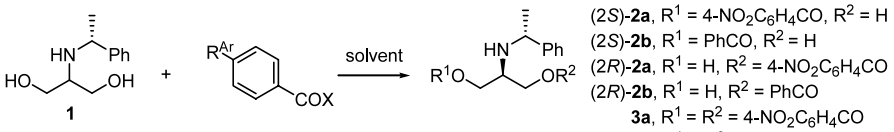
Next, we optimized the reaction conditions (one-pot acylation and fractional crystallization; Method A). The results are summarized in Table 1. The yields of crystallized (2*S*)-**2**·HCl, afforded by filtration, are shown in square brackets [HX salt] at the column of (2*S*)-**2**. The salt (2*S*)-**2a**·HCl was given by the reaction catalyzed with DMAP (0.2 mol equiv.) and crystallized directly from the reaction mixture as described previously in this text (entry 1). The reaction proceeded with 0.05 mol equiv. of DMAP (entry 2) or without DMAP (entry 3), and (2*S*)-**2a**·HCl was obtained in each case; however, the reaction proceeded slowly. In the case of a concentrated reaction mixture (0.1 mol/L) without DMAP, the reaction proceeded slowly even at the reflux temperature, and the precipitation of (2*S*)-**2a**·HCl was accompanied by (2*R*)-**2a**·HCl (entry 4). The mixture of crystallized (2*S*)-**2a**·HCl and (2*R*)-**2a**·HCl was also given from the reaction mixtures in *tert*-butyl methyl ether (entry 5), benzene (entry 6), and toluene (entry 7). Dichloromethane and THF were the best solvents to afford the crystalline (2*S*)-**2a**·HCl (33%, entries 1 and 8). Monobenzoate (2*S*)-**2b** was yielded by the reaction with benzoyl chloride and benzoyl bromide (entries 9 and 10). The yield of (2*S*)-**2b** with benzoyl bromide (36%, entry 10) was better than that of (2*S*)-**2b** with benzoyl chloride (34%, entry 9). However, the (2*S*)-**2b**·HCl salt (25%, entry 9) was obtained by fractional crystallization in better yield than that of (2*S*)-**2b**·HBr salt (19%, entry 10).

Other acylating reagents were also examined. In the case of the reaction of **1** with benzoic anhydride or 4-nitrobenzoic anhydride, no crystalline materials were found in the reaction mixtures (entries 11 and 13), and an additional procedure for fractional crystallization was required (entries 12 and 14). After work-up, the residue was dissolved in dichloromethane, and to this a solution of hydrogen chloride in dioxane (4 mol/L; commercially available) was added to form the HCl salts (Method B). Monobenzoates (2*S*)-**2a** and (2*S*)-**2b** were also obtained by this method in low and moderate yields (10% and 32%, entries 12 and 14, respectively). Other reagents, such as pivaloyl chloride, phenylacetyl chloride, cyclohexylcarbonyl chloride, and dimethylphenylsilyl chloride, were also tested using Method A in dichloromethane (0.04 mol/L) with DMAP (0.2 mol equiv.), but no crystalline material were obtained from the reaction mixtures. Free amines



Scheme 2.

Table 1. One-pot procedure of acylation and fractional crystallization[a]



Entry	Acylating reagent		Method	Equiv. of DMAP	Solvent	Yield of the products (%)[b]		
	R^{Ar}	X				(2*S*)-**2** [HX salt][c]	(2*R*)-**2** [HX salt][c]	**3**[b]
1	NO_2	Cl	A[d]	0.2	CH_2Cl_2	36 [33]	25 [0]	4
2[e]	NO_2	Cl	A	0.05	CH_2Cl_2	34 [28]	19 [0]	12
3[e]	NO_2	Cl	A	None	CH_2Cl_2	31 [23]	18 [0]	4
4[f]	NO_2	Cl	A	None	CH_2Cl_2	27 [27]	4 [4]	3
5	NO_2	Cl	A	0.2	^{t}BuOMe	34 [32]	22 [20]	14
6	NO_2	Cl	A	0.2	Benzene	45 [45]	28 [22]	9
7	NO_2	Cl	A	0.2	Toluene	38 [38]	30 [4]	6
8	NO_2	Cl	A	0.2	THF	38 [33]	24 [0]	4
9	H	Cl	A	0.2	CH_2Cl_2	34 [25]	17 [0]	24
10	H	Br	A	0.2	CH_2Cl_2	36 [19]	30 [0]	17
11	NO_2	$NPCO_2$[g]	A	0.2	CH_2Cl_2	16 [0]	22 [0]	<1
12	NO_2	$NPCO_2$	B[h]	0.2	CH_2Cl_2	16 [10]	22 [0]	<1
13	H	$PhCO_2$	A	0.2	CH_2Cl_2	48 [0]	26 [0]	4
14	H	$PhCO_2$	B	0.2	CH_2Cl_2	48 [32]	26 [0]	4

[a] The reactions were carried out with **1** (400 mg), the acylating reagents (1.0 mol equiv.), and DMAP in a solvent (51 mL), shown in Table 1, for 15 h at room temperature unless otherwise noted.
[b] Yields are total yields of the HX salts and the monoesters from the filtrate.
[c] Yields in square brackets; yields of the corresponding salts which were collected by filtration.
[d] Method A: The salts were collected by filtration of the reaction mixture.
[e] The reaction was carried out for 4 days.
[f] The mixture in dichloromethane (20 mL) was refluxed for 4 days and allowed to stand for 15 h at room temperature.
[g] NP: 4-nitrophenyl.
[h] Method B: After work-up, a solution of the crude materials in dichloromethane (51 mL) was treated with 4 mol/L HCl (1.0 mol equiv.) in dioxane. The HCl salt was collected by filtration.

(2*S*)-**2a** and (2*S*)-**2b** were obtained quantitatively from the salts (2*S*)-**2a**·HCl [or (2*S*)-**2a**·HBr] and (2*S*)-**2b**·HCl, respectively, by extraction.

2.3. Isolation of (2*R*)-2a

Another diastereomer, (2*R*)-**2a**, was isolated as follows: After work-up of the filtrate obtained from the reaction mixture (entry 1 in Table 1), the residue was chromatographed on silica gel to afford **3a** and a 9:1 mixture of (2*R*)-**2a** and (2*S*)-**2a**. This mixture was then recrystallized from a solution of hexane and *tert*-butyl methyl ether (1:1) to give pure (2*R*)-**2a** (13% yield from **1**). The monoester (2*R*)-**2b** was not obtained in its pure form via this method because (2*R*)-**2b** would not crystallize.

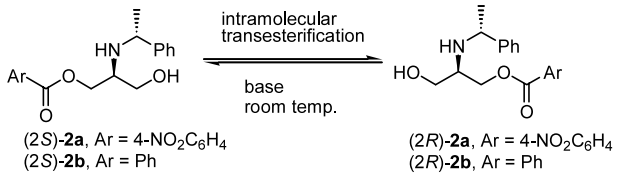
2.4. Recovery of serinol 1 and DMAP from the filtrate

A mixture of serinol **1** and DMAP was recovered from the filtrate after hydrolysis of the monoesters and the diester. After the filtrate of entry 1 in Table 1 was concentrated in vacuo, the residue was treated with an aqueous ethanol solution of potassium hydroxide for hydrolysis of the ester groups in (2*R*)-**2a**, (2*S*)-**2a**, and diester **3**. After work-up, serinol **1** was recovered in 67% yield accompanied with DMAP (97% recovery). Thus, serinol **1** was recovered completely, except **1**, which was consumed by the crystallized (2*S*)-**2a**·HCl. The recovered mixture of **1** and DMAP was then used again for one-pot acylation and fractional crystallization. The ratio of **1** versus DMAP for the reaction was 5:1; and so, we adjusted the ratio of **1** to DMAP to 5:1 by the addition of **1** to the recovered mixture. This adjusted mixture was used for the one-pot acylation and fractional crystallization (Method A), and (2*S*)-**2a**·HCl was obtained with a 20% yield.

2.5. Intramolecular transesterification in basic media

To clarify the stability and usefulness of monobenzoates (2*S*)-**2a**,**b** and (2*R*)-**2a** as synthetic intermediates, we exposed them to various basic media. The results are summarized in Table 2. Monoesters (2*S*)-**2a**,**b** were stable in pyridine-d_5 and with triethylamine in $CDCl_3$ at room temperature. However, transesterification proceeded with DBU in $CDCl_3$ (entries 5–7). The transesterification from (2*S*)-**2a** proceeded faster than that from (2*S*)-**2b**. Thus, the ratio of (2*S*)-**2a** versus (2*R*)-**2a** was 55:45 after exposure of (2*S*)-**2a** to DBU for 10 min (entry 5); however, the ratios of (2*S*)-**2b** versus (2*R*)-**2b** were 77:23 and 65:35 after exposure of (2*S*)-**2b** to DBU for 2 h and 25 h, respectively (entries 6–7). Monoben-

Table 2. Intramolecular transesterification of (2*S*)-**2a**–**c** and (2*R*)-**2a**[a]



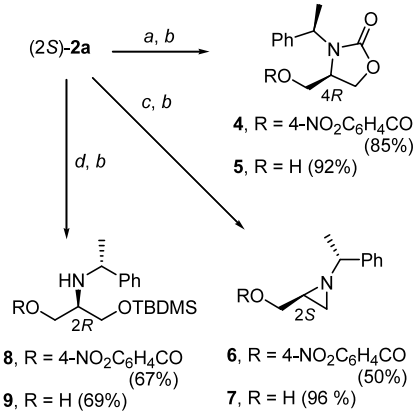
Entry	Material	Solvent[b]	Base[c]	Reaction time	(2*S*)-**2**/(2*R*)-**2**[d]
1	(2*S*)-**2a**	Py-d_5	Py-d_5	25 h	100/0
2	(2*S*)-**2b**	Py-d_5	Py-d_5	25 h	100/0
3	(2*S*)-**2a**	$CDCl_3$	Et_3N	25 h	100/0
4	(2*S*)-**2b**	$CDCl_3$	Et_3N	25 h	100/0
5	(2*S*)-**2a**	$CDCl_3$	DBU	10 min	55/45
6	(2*S*)-**2b**	$CDCl_3$	DBU	2 h	77/23
7	(2*S*)-**2b**	$CDCl_3$	DBU	25 h	65/35
8	(2*R*)-**2a**	$CDCl_3$	Et_3N	25 h	0/100
9	(2*R*)-**2a**	$CDCl_3$	DBU	10 min	48/52

[a] The reactions were carried out at room temperature in NMR tubes.
[b] 0.04 mol/L.
[c] One molar equivalent of Et_3N and DBU was used.
[d] The ratios of (2*S*)-**2** and (2*R*)-**2** were obtained by the comparison of their ^1H NMR integrations.

zoate (2*R*)-**2a** was also stabilized with triethylamine (entry 8) and epimerized with DBU (entry 9). Therefore, monobenzoates (2*S*)-**2a**,b and (2*R*)-**2a** were used as synthetic intermediates in the reaction using triethylamine and pyridine.

2.6. Utility of monobenzoate (2*S*)-2a as a synthetic intermediate

As described in the introduction, optically active mono-*O*-acyl serinol derivatives are useful as synthetic intermediates. We converted (2*S*)-**2a** to oxazolidinone **5**[11a,b] and aziridine **7** (Scheme 3).[12] Oxazolidinone **5** was prepared from (2*S*)-**2a** with *N*,*N*′-disuccinimidyl carbonate (DSC) following alkaline hydrolysis. Aziridine **7** was prepared from (2*S*)-**2a** with *p*-toluenesulfonyl chloride (TsCl) following hydrolysis of the ester group. The spectrum data of **5** and **7** were good in agreement with the reported data.[11b,12] The absolute configuration of (2*S*)-**2b** was determined by the comparison of the ^1H NMR spectrum of (2*S*)-**2a**. Serinol derivative **9** was also prepared from (2*S*)-**2a**. Silylation of (2*S*)-**2a** with *tert*-butyldimethylsilyl chloride (TBDMSCl) following hydrolysis of the ester group gave (2*R*)-mono-*O*-silylserinol **9**.



Scheme 3. *Reaction conditions*: (a) DSC, MeCN, rt; (b) KOH, EtOH, H_2O, rt; (c) TsCl, CH_2Cl_2, Et_3N, rt; (d) TBDMSCl, imidazole, THF, rt.

3. Conclusions

We have developed a new method to prepare the optically active mono-*O*-benzoyl serinol derivatives (2*S*)-**2a** and (2*S*)-**2b**. This method involves the one-pot acylation of serinol **1** and fractional crystallization of the hydrogen halide salts of (2*S*)-**2a**,**b**. From the filtrate containing serinol **1**, the monoesters, and the diester, **1** can be recovered in a quantitative yield after hydrolysis of the ester groups. We also demonstrated the usefulness of (2*S*)-**2a** as a synthetic intermediate.

4. Experimental

4.1. General

Melting points were measured with Yanaco MP-3 apparatus and uncorrected. Optical rotations were determined on a JASCO DIP-140 polarimeter. IR spectra were recorded on a Hitachi 215 spectro photometer. NMR spectra were obtained with a JEOL JNM-GX400 (400 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution MS (HRMS) were taken on a JEOL JMS-DX302 spectrometer. Column chromatography was performed with Merck silica gel (230–400

mesh). All reagents and solvents were reagent grade and used without any purification. Hydrogen chloride in dioxane (4 mol/L) was purchased from Kokusan Chemical.

4.2. General procedure of the one-pot acylation and fractional crystallization (2.2, Table 1)

4.2.1. Method A (the one-pot acylation and fractional crystallization). An acylating reagent (2.05 mmol) was added to a mixture of **1** (400 mg, 2.05 mmol) and DMAP (52.5 mg, 0.41 mmol) in dichloromethane (51 mL) at room temperature. The resulting mixture was then stirred for 15 h at room temperature, after which crystallized (2*S*)-**2**·HX (X = Cl, Br) was collected by filtration. The salt (2*S*)-**2**·HX (X = Cl, Br) was treated with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo to give (2*S*)-**2**.

The filtrate from the fractional crystallization was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:ethyl acetate = 1:1) to give the diester **3** and a mixture of (2*R*)-**2** and (2*S*)-**2**. The ratio of (2*R*)-**2** versus (2*S*)-**2** in this mixture was determined by the comparison of their integral value on ^{1}H NMR spectrum.

4.2.2. Method B (after work-up, addition of HCl). An acid anhydride (2.05 mmol) was added to a mixture of **1** (400 mg, 2.05 mmol) and DMAP (53 mg, 0.41 mmol) in dichloromethane (51 mL) at room temperature. After the resulting mixture was stirred for 15 h at room temperature, the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in dichloromethane (51 mL), and hydrogen chloride in dioxane (4 mol/L, 0.58 mL) was added to the mixture. After the mixture was stirred for 1 h, (2*S*)-**2**·HCl as a crystalline material was collected by filtration. The salt (2*S*)-**2**·HCl was treated with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo to give (2*S*)-**2**.

The filtrate from the fractional crystallization was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:ethyl acetate = 1:1) to give the diester **3**, and a mixture of (2*R*)-**2** and (2*S*)-**2**. The ratio of this mixture was determined by the comparison of their integral values in the ^{1}H NMR spectrum.

4.2.3. (2*S*,α*R*)-3-Hydroxy-2-(α-methylbenzyl)aminopropyl 4-nitrobenzoate hydrochloride (2*S*)-2a·HCl. White solid, mp 207–208°C (dichloromethane). $[\alpha]_D^{21} = -15.4$ (*c* 1.0, DMSO). ^{1}H NMR (400 MHz, Py-d_5) δ 1.80 (d, $J = 6.4$ Hz, 3H, Me), 3.55 (m, 1H, C2-H), 4.32 (m, 2H, CH_2), 4.75 (q, $J = 6.4$ Hz, 1H, PhC*H*), 4.91 (dd, $J = 11$, 5.4 Hz, 1H, C*H*H), 5.00 (dd, $J = 11$, 5.4 Hz, 1H, CH*H*), 7.26–7.42 (m, 3H, Ph), 7.93 (d, $J = 7.4$ Hz, 2H, Ph), 8.19 (d, $J = 8.6$ Hz, 2H, nitrobenzoyl), 8.25 (d, $J = 8.6$ Hz, 2H, nitrobenzoyl). IR (KBr) 1728 cm^{-1}. EI-MS *m*/*z* (%) 344 [(M−HCl)$^+$, 0.2%], 329 (11), 313 (72), 209 (10), 164 (26), 150 (12), 105 (100). Anal. calcd for $C_{18}H_{21}ClN_2O_5$: C, 56.77; H, 5.56; N, 7.36. Found: C, 55.91; H, 5.54; N, 7.17.

4.2.4. (2*S*,α*R*)-3-Hydroxy-2-(α-methylbenzyl)aminopropyl 4-nitrobenzoate (2*S*)-2a. White solid, mp 103–104°C (ethyl acetate). $[\alpha]_D^{21} = -14.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, $J = 6.6$ Hz, 3H, Me), 2.97 (m, 1H, C2-H), 3.52 (dd, $J = 11$, 4.0 Hz, 1H, C*H*H), 3.76 (dd, $J = 11$, 4.4 Hz, 1H, CH*H*), 3.93 (q, $J = 6.6$ Hz, 1H, PhC*H*), 4.30 (dd, $J = 11$, 5.8 Hz, 1H, C*H*H), 4.34 (dd, $J = 11$, 5.1 Hz, 1H, CH*H*), 7.23–7.28 (m, 5H, Ph), 8.12 (d, $J = 8.8$ Hz, 2H, nitrobenzoyl), 8.29 (d, $J = 8.8$ Hz, 2H, nitrobenzoyl). IR (KBr) 1720 cm^{-1}. FAB-MS *m*/*z* 345 [(M+1)$^+$]. Anal. calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.57; H, 5.89; N, 8.18.

4.2.5. (2*S*,α*R*)-3-Hydroxy-2-(α-methylbenzyl)aminopropyl benzoate hydrochloride (2*S*)-2b·HCl. White solid, mp 195–197°C (dichloromethane). $[\alpha]_D^{21} = -12.1$ (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, Py-d_5) δ 1.83 (d, $J = 6.6$ Hz, 3H, Me), 3.61 (m, 1H, C2-H), 4.30 (dd, $J = 12$, 4.2 Hz, 1H, C*H*H), 4.36 (dd, $J = 12$, 4.3 Hz, 1H, CH*H*), 4.79 (q, $J = 6.6$ Hz, 1H, PhC*H*), 4.90 (dd, $J = 11$, 5.9 Hz, 1H, C*H*H), 5.03 (dd, $J = 11$, 5.6 Hz, 1H, CH*H*), 7.30–7.41 (m, 5H, Ph), 7.50 (m, 1H, Ph), 7.94 (d, $J = 7.3$ Hz, 2H, Ph), 8.05 (d, $J = 7.3$ Hz, 2H, Ph). IR (KBr) 1720 cm^{-1}. EI-MS *m*/*z* (%) 299 [(M−HCl)$^+$, 0.4%], 268 (46), 164 (33), 105 (100), 77 (18). Anal. calcd for $C_{18}H_{22}ClNO_3$: C, 64.38; H, 6.60; N, 4.17. Found: C, 63.92; H, 6.46; N, 4.15.

4.2.6. (2*S*,α*R*)-3-Hydroxy-2-(α-methylbenzyl)aminopropyl benzoate hydrobromide (2*S*)-2b·HBr. White solid, mp 205–206°C (dichloromethane). $[\alpha]_D^{21} = -6.5$ (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, Py-d_5) δ 1.87 (d, $J = 6.8$ Hz, 3H, Me), 3.68 (m, 1H, C2-H), 4.34 (dd, $J = 12$, 4.6 Hz, 1H, C*H*H), 4.39 (dd, $J = 12$, 4.8 Hz, 1H, CH*H*), 4.95 (q, $J = 6.8$ Hz, 1H, PhC*H*), 4.97 (dd, $J = 12$, 5.9 Hz, 1H, C*H*H), 5.11 (dd, $J = 12$, 5.2 Hz, 1H, CH*H*), 7.33–7.45 (m, 5H, Ph), 7.52 (m, 1H, Ph), 8.06 (d, $J = 7.5$ Hz, 2H, Ph), 8.16 (d, $J = 7.5$ Hz, 2H, Ph). IR (KBr) 1720 cm^{-1}. EI-MS *m*/*z* (%) 299 [(M−HBr)$^+$, 0.3%], 268 (45), 164 (33), 105 (100), 77 (19). Anal. calcd for $C_{18}H_{22}BrNO_3$: C, 56.85; H, 5.83; N, 3.68. Found: C, 55.73; H, 5.69; N, 3.63.

4.2.7. (2*S*,α*R*)-3-Hydroxy-2-(α-methylbenzyl)aminopropyl benzoate (2*S*)-2b. Colorless oil. $[\alpha]_D^{21} = -11.3$ (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, $J = 6.6$ Hz, 3H, Me), 2.95 (m, 1H, C2-H), 3.49 (dd, $J = 11$, 4.2 Hz, 1H, C*H*H), 3.73 (dd, $J = 11$, 4.9 Hz, 1H,

CH*H*), 3.94 (q, $J=6.6$ Hz, 1H, PhC*H*), 4.25 (dd, $J=11$, 6.4 Hz, 1H, C*H*H), 4.31 (dd, $J=11$, 5.9 Hz, 1H, CH*H*), 7.22–7.34 (m, 5H, Ph), 7.44 (m, 2H), 7.58 (m, 1H), 7.97–7.99 (m, 2H). IR ($CHCl_3$) 1710 cm^{-1}. EI-MS m/z (%) 299 (M^+, 0.5%), 268 (63), 164 (38), 105 (100), 77 (14). HRMS calcd for $C_{18}H_{21}NO_3$: 299.1522. Found: 299.1520.

4.2.8. (α*R*)-2-(α-Methylbenzyl)amino-1,3-propyl di-4-nitrobenzoate 3a. White solid, mp 144–145°C (ethyl acetate). $[\alpha]_D^{21}=-3.2$ (*c* 0.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, $J=6.4$ Hz, 3H, Me), 3.23 (m, 1H, C2-H), 4.04 (q, $J=6.4$ Hz, 1H, PhC*H*), 4.42 (m, 2H, CH_2), 4.52 (m, 2H, CH_2), 7.22–7.35 (m, 5H, Ph), 8.14 (d, $J=8.5$ Hz, 2H, nitrobenzoyl), 8.20 (d, $J=8.5$ Hz, 2H, nitrobenzoyl), 8.29 (d, $J=8.5$ Hz, 2H, nitrobenzoyl), 8.30 (d, $J=8.5$ Hz, 2H, nitrobenzoyl). IR ($CHCl_3$) 1725 cm^{-1}. EI-MS m/z 493 (M^+, 0.6%), 478 (39), 326 (12), 313 (100), 209 (12), 157 (17), 150 (14), 105 (88). Anal. calcd for $C_{25}H_{23}N_3O_8$: C, 60.85; H, 4.70; N, 8.52. Found: C, 60.70; H, 5.00; N, 7.80.

4.2.9. (α*R*)-2-(α-Methylbenzyl)amino-1,3-propyl dibenzoate 3b. Colorless oil, $[\alpha]_D^{21}=-18.6$ (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, $J=6.6$ Hz, 3H, Me), 3.18 (m, 1H, C2-H), 4.07 (q, $J=6.6$ Hz, 1H, PhC*H*), 4.37 (m, 2H, CH_2), 4.45 (dd, $J=11$, 4.0 Hz, 1H, C*H*H), 4.51 (dd, $J=11$, 5.7 Hz, 1H, CH*H*), 7.21–7.45 (9H, m), 7.56 (2H, m), 7.98–8.04 (4H, m). IR ($CHCl_3$) 1718 cm^{-1}. EI-MS m/z 403 (M^+, 0.9), 269 (13), 268 (61), 164 (20), 159 (15), 105 (100), 77 (18). Anal. calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.12; H, 6.20; N, 3.47.

4.2.10. (2*R*,α*R*)-3-Hydroxy-2-(α-methylbenzyl)aminopropyl 4-nitrobenzoate (2*R*)-2a. A mixture of (2*R*)-**2a** and (2*S*)-**2a** (9:1, 197 mg) that was obtained from Method A using serinol **1** (400 mg, 2.05 mmol) was recrystallized from a solution of hexane and *tert*-butyl methyl ether (1:1) to give (2*R*)-**2a** (92 mg, 13% from serinol **1**). Yellowish crystal, mp 95–96°C (solvent; see above). $[\alpha]_D^{21}=+46.6$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, $J=6.6$ Hz, 3H, Me), 2.95 (m, 1H, C2-H), 3.48 (dd, $J=11$, 6.6 Hz, 1H, C*H*H), 3.56 (dd, $J=11$, 4.6 Hz, 1H, CH*H*), 4.03 (q, $J=6.6$ Hz, 1H, PhC*H*), 4.40 (dd, $J=11$, 4.4 Hz, 1H, C*H*H), 4.47 (dd, $J=11$, 5.6 Hz, 1H, CH*H*), 7.22–7.35 (m, 5H, Ph), 8.20 (d, $J=9.0$ Hz, 2H, nitrobenzoyl), 8.32 (d, $J=9.0$ Hz, 2H, nitrobenzoyl). IR (KBr) 1718 cm^{-1}. EI-MS m/z (%) 345 [$(M+1)^+$, 23], 155 (72), 137 (11), 135 (33), 119 (100). Anal. calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.52; H, 5.88; N, 8.26.

4.3. Recovery of the serinol 1 and DMAP from the filtrate

The filtrate from the one-pot acylation and fractional crystallization of **1** and nitrobenzoyl chloride in dichloromethane (Table 1, entry 1, the yield of the crystallized (2*S*)-**2a**·HCl; 33%) was concentrated in vacuo. The residue was dissolved in a solution of potassium hydroxide (75 mg) in 75% aqueous ethanol (6.7 mL). The reaction mixture was stirred for 1 h at room temperature and concentrated in vacuo. The residue was dissolved in ethyl acetate, and the mixture was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and concentrated in vacuo to give a mixture of serinol **1** (268 mg, 67% recovery) and DMAP (50 mg, 96% recovery). After addition of **1** (116 mg) to adjust the ratio of **1** versus DMAP (5:1), the mixture of **1** (384 mg) and DMAP (50 mg) could be used for the one-pot acylation and fractional crystallization (Method A), and (2*S*)-**2a**·HCl (85 mg) was obtained in 20% yield.

4.4. Synthesis of the heterocyclic compounds and the serinol derivatives

4.4.1. (4*S*,α*R*)-(3-α-Methylbenzyl-2-oxazolidinon-4-yl)methyl 4-nitrobenzoate 4. A solution of DSC (2.46 g, 9.58 mmol) in acetonitrile (5.3 mL) was added to a mixture of (2*S*)-**2a** (3.30 g, 9.58 mmol) in acetonitrile (240 mL) at room temperature, and the resulting mixture was stirred for 23 h at room temperature. After the reaction mixture was concentrated in vacuo, the residue was chromatographed on silica gel (hexane:ethyl acetate = 1:1) to give the oxazolidinone **4** (1.71 g, 85%). White solid, mp 128–129°C (cyclohexane:ethyl acetate = 2:1). $[\alpha]_D^{26}=-51.5$ (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.69 (d, $J=7.2$, 3H, Me), 3.80 (m, 1H, C4-H), 4.23 (dd, $J=8.9$, 4.0 Hz, 1H, $ArCO_2HH$), 4.33–4.37 (m, 3H, C5-H_2 and $ArCO_2HH$), 5.22 (q, $J=7.2$ Hz, 1H, PhC*H*), 7.26–7.39 (m, 5H, Ph), 8.15 (d, $J=9.0$ Hz, 2H, nitrobenzoyl), 8.30 (d, $J=9.0$ Hz, 2H, nitrobenzoyl). IR ($CHCl_3$) 1730 cm^{-1}. EI-MS m/z (%) 370 (M^+, 12), 190 (13), 150 (13), 105 (100). Anal. calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.46; H, 4.90; N, 7.55.

4.4.2. (4*S*,α*R*)-4-Hydroxymethyl-3-α-methylbenzyl-2-oxazolidinone 5. A solution of potassium hydroxide (79 mg, 1.4 mmol) in water (1.2 mL) was added to a solution of **4** (261 mg, 0.71 mmol) in ethanol (7.1 mL), and the resulting mixture was stirred for 30 min at room temperature. The reaction mixture was neutralized with 10% hydrochloric acid and concentrated in vacuo. The residue was diluted with ethyl acetate (40 mL), washed once with 4% aqueous sodium hydroxide (5 mL), three times with water (10 mL×3), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:ethyl acetate = 1:4) to give **5** (144 mg, 92%). For analysis, the oxazolidinone **5** was recrystallized from a solution of hexane and ethyl acetate (1:1). The spectral data were good in agreement with the reported data.[11b]

4.4.3. (2*S*,α*R*)-1-α-Methylbenzyl-2-aziridinyl)methyl 4-nitrobenzoate 6. Methanesulfonyl chloride (50 μL, 0.64 mmol) was added dropwise to a mixture of (2*S*)-**2a** (200 mg, 0.58 mmol), triethylamine (0.17 mL, 1.28 mmol) and a catalytic amount of DMAP (0.6 mg) in dichloromethane (2.9 mL) at −20°C. The resulting mixture was stirred for 15 h while allowing it to warm to room temperature. The reaction mixture was diluted with dichloromethane (30 mL), washed twice with saturated aqueous ammonium chloride (30 mL), twice with

saturated aqueous sodium carbonate (30 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:ethyl acetate = 1:1) to give **6** (95 mg, 50%). Yellowish oil. $[\alpha]_D^{28} = +31.4$ (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.46 (d, $J = 6.6$ Hz, 3H, Me), 1.62 (d, $J = 6.4$ Hz, 1H, NC*H*H), 1.90–1.97 (m, 2H, C2-H and NCH*H*), 2.49 (q, $J = 6.6$ Hz, 1H, PhC*H*), 3.79 (dd, $J = 12$, 3.5 Hz, 1H, OC*H*H), 4.56 (dd, $J = 12$, 8.5 Hz, 1H, OCH*H*), 7.15–7.26 (m, 3H, Ph), 7.35 (m, 2H, Ph), 7.77 (d, $J = 9.2$ Hz, 2H, nitrobenzoyl), 8.17 (d, $J = 9.2$ Hz, 2H, nitrobenzoyl). IR ($CHCl_3$) 1715 cm^{-1}. EI-MS *m*/*z* (%) 326 (M^+, 9), 221 (15), 150 (46), 105 (100). HRMS calcd for $C_{18}H_{18}N_2O_4$: 326.1266. Found: 326.1263.

4.4.4. (2*S*,α*R*)-1-(α-Methylbenzyl)aziridinylmethanol 7. According to the procedure for hydrolysis of **4**, the aziridine **7** (26 mg, 96%) was prepared from **6**. The spectrum data of **7** were good in agreement with the reported data.[12]

4.4.5. (2*R*,α*R*)-3-(*tert*-Butyldimethylsilyl)oxy-2-(*N*-α-methylbenzyl)aminopropyl 4-nitrobenzoate 8. A solution of *tert*-butyldimethylsilyl chloride (105 mg, 0.70 mmol) in DMF (0.5 mL) was added dropwise to a mixture of (*S*)-**2a** (100 mg, 0.29 mmol) and imidazole (78 mg, 0.87 mmol) in DMF (0.5 mL) at room temperature. After being stirred for 1 h, the reaction mixture was poured into saturated aqueous ammonium chloride and extracted with diethyl ether. The extracts were combined, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:ethyl acetate = 4:1) to give **8** (89 mg, 67%). Yellowish oil. $[\alpha]_D^{26} = -0.8$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.05 (s, 3H, MeSi), 0.08 (s, 3H, MeSi), 0.91 (s, 9H, ^{t}Bu), 1.34 (d, $J = 6.6$ Hz, 3H, PhCH*Me*), 2.86 (m, 1H, C2-H), 3.65 (dd, $J = 10$, 3.4 Hz, 1H, OC*H*H), 3.78 (dd, $J = 10$, 4.9 Hz, 1H, OCH*H*), 3.94 (q, $J = 6.6$ Hz, 1H, PhC*H*), 4.24 (dd, $J = 15$, 4.2 Hz, 1H, OC*H*H), 4.28 (dd, $J = 15$, 4.6 Hz, 1H, OCH*H*), 7.21–7.70 (m, 5H, Ph), 8.13 (d, $J = 8.9$ Hz, 2H, nitrobenzoyl), 8.28 (d, $J = 8.9$ Hz, 2H, nitrobenzoyl). IR ($CHCl_3$) 1723 cm^{-1}. MS (EI) *m*/*z*: (%) 458 (M^+, 0.7), 443 (5), 313 (75), 278 (14), 209 (10), 105 (100). HRMS calcd for $C_{24}H_{34}N_2O_5Si$: 458.2237. Found: 458.2238.

4.4.6. (2*R*,α*R*)-3-(*tert*-Butyldimethylsilyl)oxy-2-(*N*-α-methylbenzyl)amino-1-propanol 9. A mixture of **8** (50 mg, 0.11 mmol) and potassium hydroxide (11.2 mg, 0.20 mmol) in 85% aqueous methanol (5.8 mL) was stirred for 30 min at room temperature. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The extracts were combined, dried and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:ethyl acetate = 1:1) to give **9** (23 mg, 69%). Yellowish oil. $[\alpha]_D^{26} = -0.3$ (*c* 0.46, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 3H, MeSi), 0.08 (s, 3H, MeSi), 0.91 (s, 9H, ^{t}Bu), 1.36 (d, $J = 6.6$ Hz, 3H, Me), 2.60 (m, 1H, C2-H), 3.38 (d, $J = 5.6$ Hz, 2H, OCH_2), 3.53 (dd, $J = 10$, 4.2 Hz, 1H, OC*H*H), 3.74 (dd, $J = 10$, 4.6 Hz, 1H, OCH*H*), 3.91 (q, $J = 6.6$ Hz, 1H, PhC*H*), 7.21–7.52 (m, 5H, Ph). IR ($CHCl_3$) 2920, 2850, 1100 cm^{-1}. MS (EI) *m*/*z*: 309 (M^+, 0.5), 279 (13), 278 (54), 174 (14), 164 (90), 105 (100). HRMS calcd for $C_{17}H_{31}NO_2Si$: 309.2124. Found: 309.2122.

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