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Non-enzymatic diastereoselective asymmetric desymmetrization of 2-benzylserinols giving optically active 4-benzyl-4-hydroxymethyl-2-oxazolidinones: asymmetric syntheses of α-(hydroxymethyl)phenylalanine, *N*-Boc-α-methylphenylalanine, cericlamine and BIRT-377

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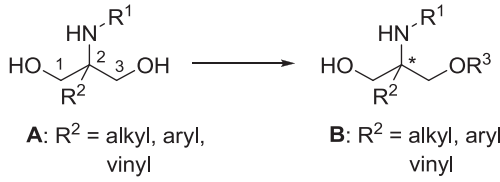
ABSTRACT

A reaction of (*S*)-2-benzyl-2-(α-methylbenzyl)amino-1,3-propanediol (*S*)-**4a** and 2-chloroethyl chloroformate, and the subsequent addition of DBU gave (4*R*,α*S*)-4-benzyl-4-hydroxymethyl-3-(α-methylbenzyl)-2-oxazolidinone (4*R*)-**5a** (92% de) via a diastereoselective asymmetric desymmetrization process. Debenzylation of (4*R*)-**5a** using trifluoromethanesulfonic acid and anisole in $MeNO_2$ gave (*R*)-4-benzyl-4-hydroxymethyl-2-oxazolidinone (*R*)-**15a**, which was converted into (*R*)-(α-hydroxymethyl) phenylalanine (**7**) in two steps. *N*-Boc-α-methylphenylalanine (**8**), cericlami0ne (**9**) and BIRT-377 (**10**) were also synthesized using these asymmetric desymmetrization and debenzylation.

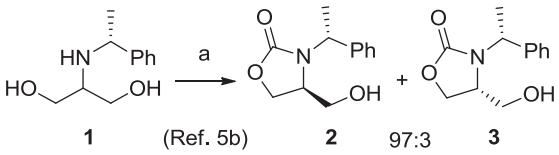
1. Introduction

Stereoselective construction of quaternary carbon stereocenters is one of the most important techniques for organic synthesis. Many methods have been developed to construct asymmetric centers of quaternary carbon, especially for the synthesis of optically active quaternary α-amino acids.[1] For example, optically active 4,4-disubstituted-2-oxazolidinones have been synthesized asymmetrically and then converted to 2,2-disubstituted 2-aminoethanols[2] and α,α-disubstituted amino acids.[3] Enzymatic asymmetric desymmetrization of prochiral compounds are frequently used for this purpose. Desymmetrization of 2-substituted serinols **A** giving optically active monoacyl 2-substituted serinols **B** (R^3=acyl group) has been reported (Scheme 1).[4]

We are investigating new synthetic methods of optically active 2-oxazolidinones and their related reactions.[5] In the previous paper we reported asymmetric desymmetrization of *N*-(α-methylbenzyl) serinol **1** using 2-chloroethyl chloroformate (CCF) and DBU to give 4-hydroxymethyl-2-oxazolidinone **2** in 94% de (Scheme 2).[5b] We considered that this reaction would be applied to 2-substituted serinol derivatives to give the corresponding 2-oxazolidinones diastereoselectively. We selected benzyl groups for the substituent at 2-position of serinol **1** and investigated the diastereoselective asymmetric desymmetrization of serinol (*S*)-**4a** to afford 2-oxazolidinone (4*R*)-**5a** (Scheme 3), because few enzymatic[6] or chemical[7] desymmetrizations of 2-benzylserinol



Scheme 1. Desymmetrization of serinol derivatives **A** (*: chiral center).



Scheme 2. Reported diastereoselective asymmetric desymmetrization of serinol **1**. Reaction conditions: (a) CCF, Py, CH_2Cl_2, rt, then DBU, 1 °C to rt.

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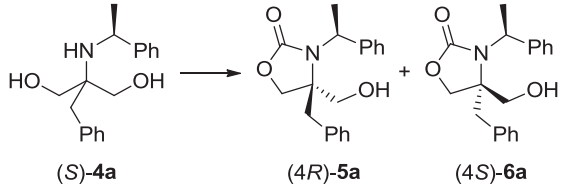
derivatives have been reported. This type of compounds would be a key intermediate for the asymmetric synthesis of α-substituted phenylalanines (e.g., **7**[8] and **8**[8d,9]), as well as of pharmaceuticals, such as the selective 5-HT uptake inhibitor cericlamine (**9**)[10] and lymphocyte function-associated antigen-1 (LFA-1) antagonist BIRT-377 (**10**)[11] (Fig. 1).



Scheme 3. Diastereoselective asymmetric desymmetrization in this study.

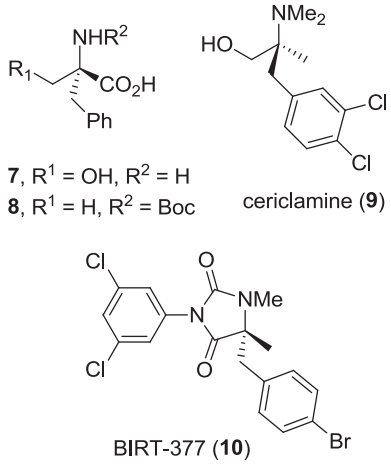


Fig. 1. Synthetic targets.

In this paper, we report a new synthetic method of obtaining optically active 4-benzyl-4-hydroxymethyl-2-oxazolidinones (4*R*)-**5a** using the asymmetric desymmetrization of 2-benzylserinols (*S*)-**4a** (Scheme 3). This methodology was applied for other 2-benzylserinols possessing 3,4-dichlorobenzyl and 4-bromobenzyl groups instead of benzyl group to synthesize corresponding optically active 4-benzyl-4-hydroxymethyl-2-oxazolidinones. We also investigated the synthesis of α-(hydroxymethyl)phenylalanine **7**,[8] cericlamine (**9**),[10] BIRT-377 (**10**)[11] and *N*-Boc-(α-methyl)phenylalanine (**8**)[8d,9] from the oxazolidinones. In the synthesis of **9** and **10**, debenzylation of the *N*-α-methylbenzyl groups without dehalogenation of the halogenated phenyl groups were also focused on.

2. Results and discussion

2.1. Synthesis of 2-benzylserinols

Benzylserinol (*S*)-**4a** was synthesized as follows (Table 1). Aminomalonate (*S*)-**11**[12] was benzylated with benzyl bromide and potassium *tert*-butoxide in DMF (entry 1). Although desired *C*-benzyl aminomalonate (*S*)-**12a** was obtained by this method, undesired *N*-benzyl aminomalonate **13** (Fig. 2) was also formed. A reaction using 2 equiv of potassium *tert*-butoxide and benzyl bromide gave no *N*,*C*-dibenzyl compound **14**.[†] The ratio of (*S*)-**12a**/**13** was ca. 1:1 as confirmed by ^{1}H NMR analysis of the crude material, and was not changed by the use of toluene or THF as a reaction solvent or benzyl chloride instead of benzyl bromide (entry 2).

C-Benzylation of *N*-acylaminomalonates[7a,13] and *N*,*N*-dialkylaminomalonate[14] has been performed successfully. However, the selective C-benzylation of (*S*)-**11** was found to be difficult because the α-methylbenzylamino group of (*S*)-**11** is also active as a nucleophilic group. Moreover, *C*-benzyl aminomalonate (*S*)-**12a** could not be separated from *N*-benzyl aminomalonate **13** with silica gel column chromatography. We investigated another isolation method and found that the desired compound (*S*)-**12a** was easy to isolate by fractional crystallization. After the mixture of (*S*)-**12a** and **13** was dissolved in Et_2O and treated with a solution of 4 mol/L HCl in dioxane, fortunately *C*-alkyl aminomalonate hydrogen chloride (*S*)-**12a**-**HCl** was precipitated selectively in 45% yield from (*S*)-**11** (entry 1). After a $NaHCO_3$ aq/$CHCl_3$ partition to give free amine (*S*)-**12a** (97%), the ester groups were reduced with $LiAlH_4$ to afford 2-benzylserinol (*S*)-**4a** (89%, entry 1). Benzylserinol (*R*)-**4a** was also synthesized from diethyl bromomalonate according to this procedure using crude aminomalonate (*R*)-**11** (entry 3).

According to this procedure, 2-benzylserinols (*S*)-**4b** and (*R*)-**4c** were synthesized from aminomalonates (*S*)-**11** and (*R*)-**11** using 3,4-dichlorobenzyl bromide and 4-bromobenzyl bromide, respectively (entries 4–7). Aminomalonate (*S*)-**11** was benzylated with 3,4-dichlorobenzyl bromide (entry 4) and chloride (entries 5 and 6) in the presence of potassium *tert*-butoxide in DMF to afford 2-amino-2-benzylmalonate (*S*)-**12b**. The crude (*S*)-**12b** was converted to (*S*)-**12b**-**HCl** to be purified by fractional crystallization. After recovery of pure free amine (*S*)-**12b** from (*S*)-**12b**-**HCl**, the malonate (*S*)-**12b** was converted to 2-benzylserinol (*S*)-**4b** (entry 6). Benzylserinol (*R*)-**4c** was also obtained by this method from aminomalonate (*R*)-**11** using 4-bromobenzyl bromide (entry 7). Thus, 2-benzylserinols **4** were synthesized easily via C-benzylation of aminomalonates **11**, fractional crystallization of **12**-**HCl**, and reduction of the ester groups (Table 1). This method is an easily handled and low-cost method for a large scale synthesis of 2-benzylserinols **4**.

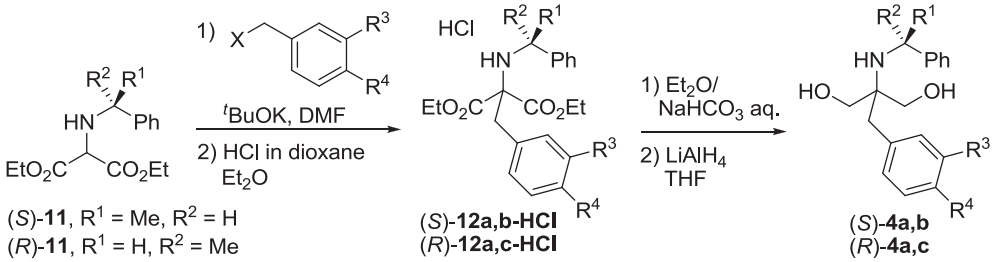
2.2. Asymmetric desymmetrization of 2-benzylserinols

Next, we investigated the formation of 4-benzyl-4-hydroxymethyl-2-oxazolidinone (4*R*)-**5a** from 2-benzylserinol (*S*)-**4a** (Table 2). In the previous paper, we used CCF in CH_2Cl_2 to give a diastereomeric mixture of two monocarbonates (ca. 1:1) of serinol **1**, and then this mixture was treated with DBU to form an optically active 2-oxazolidinone **2** in 94% de (Scheme 2).[5b] First, these reaction conditions were examined using 2-benzylserinol (*S*)-**4a**, and the desired 2-oxazolidinone (4*R*)-**5a** was given in 40% yield and 88% de (entry 1). Reactions of (*S*)-**4a** in THF (entry 2) and Et_2O (entry 3) were also tested; however, the yields (28 and 20%) and diastereoselectivities (78 and 82% de) were lower than those of the reaction in CH_2Cl_2. Identical results to entry 1 were given using a 5-g scale of 2-benzylserinol (*S*)-**4a** and CCF in CH_2Cl_2. The diastereoselectivity of (4*R*)-**5a** before recrystallization was 88% de, and (4*R*)-**5a** was given in 47% yield after recrystallization of the crude material (entry 4). The reaction using DMAP and Et_3N instead of pyridine[5c] gave (4*R*)-**5a** in 69% yield and 92% de (entry 7).

The oxazolidinones (4*R*)-**5b** and (4*S*)-**5c** were also synthesized by means of CCF with pyridine (entries 5 and 6) or with DMAP and Et_3N (entries 8 and 9). The yields of (4*R*)-**5b** and (4*S*)-**5c** using DMAP and Et_3N were better than those using pyridine. The reaction of (*R*)-**4a** with 1,1′-carbonylbis-1*H*-imidazole (CDI)[5a] gave (4*S*)-**5a** and (4*R*)-**6a** in 84% yield and in 40% de (entry 10). The reaction of **4a**–**c** with *N*,*N*′-disuccinimidyl carbonate (DSC)[5b] gave the products **5a**–**c** and **6a**–**c** in 84–53% yield and 0–24% de (entries 11–13).

[†] Although we synthesized diethyl *N*-Boc-(α-methylbenzyl)aminomalonate from **11** and $(Boc)_2O$ in 71% yield and investigated its C-benzylation using BnBr with bases (*t*-BuOK and NaH) in DMF at room temperature, no *C*-benzyl product was obtained. Thus, reactivity of the C-2 carbon of *N*-protected diethyl (α-methylbenzyl) aminomalonates was decreased extremely by the *N*-protective groups.

Table 1
Synthesis of serinols (*S*)-**4a**,**b** and (*R*)-**4a**,**c**



Entry	Aminomalonate **11**	Benzyl halide			Benzylation and fractional crystallization		Partition and reduction	
		X	R^3	R^4	**12**-HCl	Yield (%)	**4**	Yield[a] (%)
1	(*S*)-**11**	Br	H	H	(*S*)-**12a**-**HCl**	45	(*S*)-**4a**	84
2	(*S*)-**11**	Cl	H	H	(*S*)-**12a**-**HCl**	39	—	—
3	(*R*)-**11**	Br	H	H	(*R*)-**12a**-**HCl**	31[b]	(*R*)-**4a**	89
4	(*S*)-**11**	Br	Cl	Cl	(*S*)-**12b**-**HCl**	30	—	—
5	(*S*)-**11**[c]	Cl	Cl	Cl	(*S*)-**12b**-**HCl**	27	—	—
6	(*S*)-**11**[d]	Cl	Cl	Cl	(*S*)-**12b**-**HCl**	35	(*S*)-**4b**	77
7	(*R*)-**11**	Br	H	Br	(*R*)-**12c**-**HCl**	47	(*R*)-**4c**	55

[a] The yield was calculated from aminomalonate HCl salt **12**-**HCl**.
[b] This yield was calculated from diethyl bromomalonate (see Experimental 4.1.4).
[c] (*S*)-**11** (2 mmol) was used.
[d] (*S*)-**11** (111 mmol) was used.

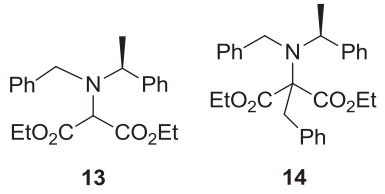


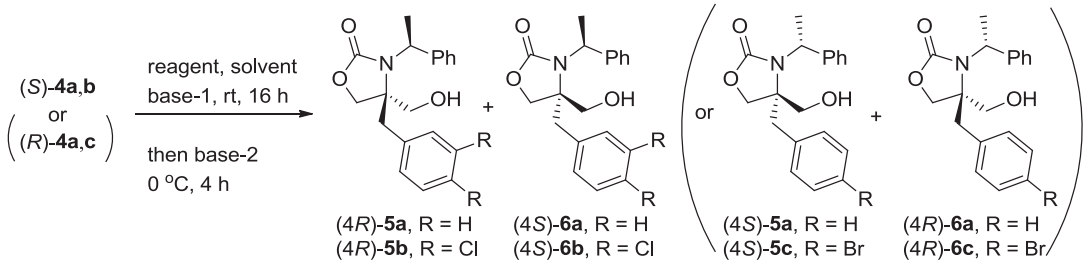
Fig. 2. *N*-Benzyl and *N*,*C*-dibenzyl compounds **13** and **14**. (Compound **14** have not been obtained.)

As shown here, optically active 4-benzyl-4-hydroxymethyl-2-oxazolidinones **5a**–**c** were synthesized from diethyl bromomalonate (**11**) by the four-step synthesis without tedious purifications.

2.3. Synthesis of (*R*)-α-(hydroxymethyl)phenylalanine, (*S*)-*N*-Boc-α-methylphenylalanine, cericlamine and BIRT-377

We found that oxazolidinones **5a**–**c** were easy to synthesize diastereoselectively and easy to separate from side products **6a**–**c** with recrystallization or silica gel column chromatography. To show

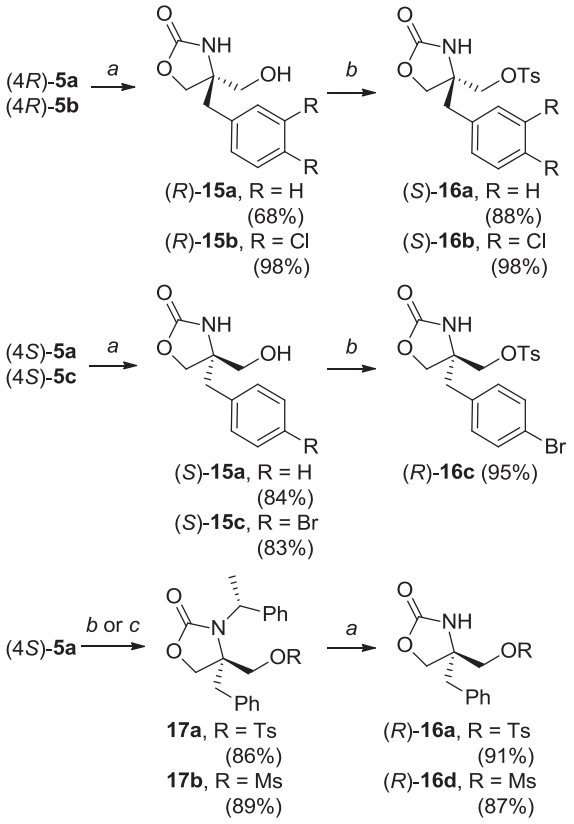
Table 2
Formation of 2-oxazolidinones **5a**–**c** and **6a**–**c** from 2-benzylserinols **4a**–**c**



Entry	Material[a]	Conditions				Results		
		Reagent	Solvent	Base-1	Base-2	Product	Yield[b] (%)	Ratio (de, %)[b]
1	(*S*)-**4a**	CCF	CH_2Cl_2	Py	DBU	(4*R*)-**5a**, (4*S*)-**6a**	40[c]	94:6 (88)[d]
2	(*S*)-**4a**	CCF	THF	Py	DBU	(4*R*)-**5a**, (4*S*)-**6a**	28[c]	89:11 (78)[d]
3	(*S*)-**4a**	CCF	Et_2O	Py	DBU	(4*R*)-**5a**, (4*S*)-**6a**	20[c]	91:9 (82)[d]
4	(*S*)-**4a**	CCF	CH_2Cl_2	Py	DBU	(4*R*)-**5a**, (4*S*)-**6a**	47[e]	94:6 (88)[d]
5	(*S*)-**4b**	CCF	CH_2Cl_2	Py	DBU	(4*R*)-**5b**, (4*S*)-**6b**	45	96:4 (92)
6	(*R*)-**4c**	CCF	CH_2Cl_2	Py	DBU	(4*S*)-**5c**, (4*R*)-**6c**	40	94:6 (88)
7	(*S*)-**4a**	CCF	CH_2Cl_2	DMAP, Et_3N	DBU	(4*R*)-**5a**, (4*S*)-**6a**	69	96:4 (92)
8	(*S*)-**4b**	CCF	CH_2Cl_2	DMAP, Et_3N	DBU	(4*R*)-**5b**, (4*S*)-**6b**	68	95:5 (90)
9	(*R*)-**4c**	CCF	CH_2Cl_2	DMAP, Et_3N	DBU	(4*S*)-**5c**, (4*R*)-**6c**	71	95:5 (90)
10	(*R*)-**4a**	CDI	THF	Et_3N	DBU	(4*S*)-**5a**, (4*R*)-**6a**	84	70:30 (40)
11	(*S*)-**4a**	DSC	MeCN	—	—	(4*R*)-**5a**, (4*S*)-**6a**	86	51:49 (2)
12	(*S*)-**4b**	DSC	MeCN	—	—	(4*R*)-**5b**, (4*S*)-**6b**	87	62:38 (24)
13	(*R*)-**4c**	DSC	MeCN	—	—	(4*S*)-**5c**, (4*R*)-**6c**	53	50:50 (0)

[a] The reactions were carried out using 7.9 mg of (*S*)-**4a** in entries 1–3. (See Experimental for other entries.).
[b] Estimated from the isolated products of **5a**–**c** and **6a**–**c** otherwise noted.
[c] The yields were calibrated with the internal standard (triphenylmethane) by ^{1}H NMR integration.
[d] The ratio of the products was estimated by the integral values of their ^{1}H NMR spectra before purification.
[e] Isolated yield of (4*R*)-**5a** only.

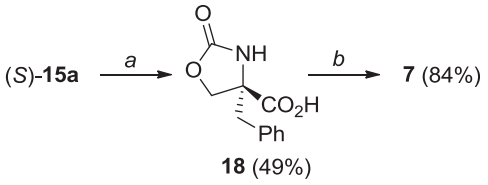
the utility of 2-oxazolidinones **5a**–**c** as intermediates for the syntheses of bioactive compounds, we first remove the α-methylbenzyl group from 2-oxazolidinones (Scheme 4). Debenzylations of (4*R*)- and (4*S*)-**5a** by the use of trifluoromethanesulfonic acid (TfOH) and anisole in $MeNO_2$[15] gave oxazolidinones (*R*)- and (*S*)-**15a** in high yield, respectively. Debenzylation of (4*R*)-**5b** and (4*S*)-**5c** possessing halogens on their *C*-benzyl groups were also proceeded smoothly without dehalogenation to give (*R*)-**15b** and (*S*)-**15c**, respectively (Scheme 4). After the debenzylation, the hydroxyl groups were tosylated using TsCl in pyridine to afford corresponding tosylates (*S*)-**16a**, (*S*)-**16b** and (*R*)-**16c**. Tosylate (*R*)-**16a** and mesylate (*R*)-**16d** were synthesized via another route from (4*S*)-**5a**. Tosylation and mesylation of oxazolidinone (4*S*)-**5a** were proceeded slowly but smoothly to give the corresponding tosylate **17a** and mesylate **17b**, respectively. Their debenzylation gave (*R*)-**16a** and (*R*)-**16d** in good yield.



Scheme 4. Synthesis of sulfonates. Reagents and conditions: (a) TfOH [1.0 equiv for (4*R*)-**5a** and **17a**,**b**, 1.5 equiv for the other **5a**–**c**], anisole, $MeNO_2$, 50 or 100 °C; (b) TsCl, Py, rt; (c) MsCl, Py, rt.

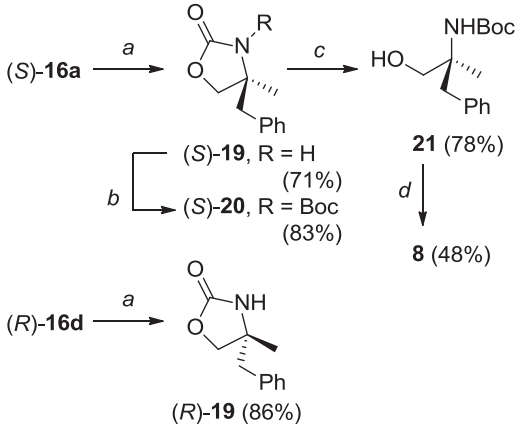
To determine the stereochemistry of (4*S*)-**5a**, we synthesized (*R*)-α-(hydroxymethyl)phenylalanine (**7**) from (*S*)-**15a**. Oxidation[16] of the hydroxymethyl group of 2-oxazolidinone (*S*)-**15a** followed by acidic hydrolysis of the 2-oxazolidinone ring of **18** gave the desired (*R*)-amino acid **7** (Scheme 5). The absolute configuration of the (*R*)-amino acid **7** was determined by comparison of the specific rotation, $[\alpha]_D^{21}$ −16.4 (*c* 1.0, H_2O), with the reported value, $[\alpha]_D^{20}$ +16.4 (*c* 0.89, H_2O), of the corresponding (*S*)-amino acid.[9b] Therefore, the stereochemistry of (4*S*)-**5a** was determined to be 4*S*,α*R*.

(*S*)-*N*-Boc-α-Methylphenylalanine (**8**) was synthesized from the oxazolidinone (*S*)-**16a** as follows (Scheme 6); tosylate (*S*)-**16a** was treated with $NaBH_4$ in DMSO in 100 °C[17] to afford (*S*)-4-benzyl-4-methyl-2-oxazolidinone [(*S*)-**19**]. Demesylation of **16b** also gave (*R*)-**19** in good yield. Oxazolidinone (*S*)-**19** was converted to *N*-Boc-2-oxazolidinone (*S*)-**20**, and the oxazolidinone ring of (*S*)-**20** was cleaved with Cs_2CO_3 in MeOH[19] to afford *N*-Boc-aminoalcohol



Scheme 5. Synthesis of (*R*)-α-(hydroxymethyl)phenylalanine (**7**). Reagents and conditions: (a) $RuCl_3$, $NaIO_4$, MeCN, CCl_4, H_2O, rt; (b) 6 mol/L HCl aq, reflux.

21. Oxidation of the hydroxymethyl group of **21** gave *N*-Boc-α-methylphenylalanine (**8**) as an optically pure form (>99% ee checked by HPLC analysis).



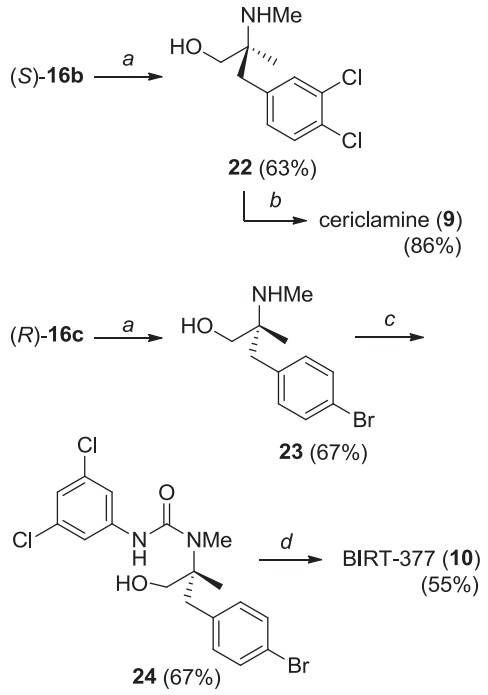
Scheme 6. Reduction of sulfonates and synthesis of *N*-Boc-(α-methyl)phenylalanine (**8**). Reagents and conditions: (a) $NaBH_4$, DMSO, 100 °C; (b) $(Boc)_2O$, Et_3N, DMAP, THF, rt; (c) Cs_2CO_3, MeOH, rt; (d) $RuCl_3$, $NaIO_4$, MeCN, CCl_4, H_2O, rt.

Finally, tosylate (*S*)-**16b** and (*R*)-**16c** were converted to *N*-methyl-3-phenyl-2-aminopropanols **22** and **23**, respectively, by treatment of $LiAlH_4$ in Et_2O.[17] Cericlamine (**9**) was obtained after N-methylation[20] of **22**, and BIRT-377 (**10**) was obtained after reaction of **23** with 3,5-dichlorophenylisocyanate and then oxidation of the hydroxymethyl group of **24** (Scheme 7). In this Ru-oxidation, we realized that AcOEt/H_2O[21] was a good solvent system to prevent the formation of 4-bromobenzoic acid, which was formed from **24** during the oxidation in CCl_4/MeCN/H_2O.[16]

The reaction of 2-benzylserinols **4** and CCF using DBU gave oxazolidinones **5** with high diastereoselectivities (Table 2, entries 4–9). These reaction pathways from **4** to **5** would be identical to those from serinol **1** to oxazolidinone **2** (Scheme 2) via cyclic carbonate **25a** and then proposed bicyclic intermediate **26a** (Fig. 3).[5b] Therefore, **25b** would be formed from serinols **4** and CCF, and then converted to bicyclic intermediate **26b**. The benzyl group of **26b** was located at the opposite site of the reaction site and would have no effect on the diastereoselectivities. On the other hand, the reaction of 2-benzylserinols **4** and DSC gave oxazolidinones **5** and **6** with poor diastereoselectivities (Table 2, entries 11–13). The serinols **4** reacted with DSC and then would give oxazolidinones directly without forming cyclic carbonate **25b** and bicyclic intermediate **26b** as we had shown the reaction of **1** and DSC.[5b] Cyclic carbonate **25a** is also formed form serinol **1** using CDI.[5a] The reaction of serinol **4** and CDI would give oxazolidinones **5** and **6** via **25b** and **26b**, and direct cyclization.[15]

3. Conclusion

In conclusion, we report a simple and practical route to enantioenriched 4-benzyl-2-oxazolidinones (*R*)- and (*S*)-**15a** possessing a quaternary carbon through the non-enzymatic diastereoselective



Scheme 7. Syntheses of cericlamine (**9**) and BIRT-377 (**10**). Reagents and conditions: (a) $LiAlH_4$, solvent (Et_2O for **16b** and THF for **16c**), reflux; (b) HCHO, $NaBH_4$, TFA, THF, rt; (c) 3,5-dichlorophenylisocyanate, NaH, THF, rt; (d) $RuCl_3$, $NaIO_4$, AcOEt, H_2O, rt.

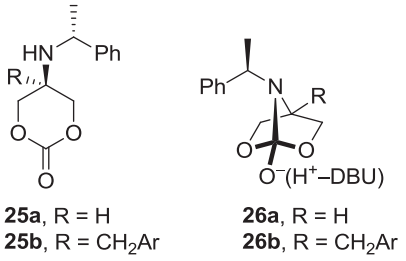


Fig. 3. The first and second intermediates **25** and **26** for the reaction in Table 2.

desymmetrization of readily available 2-benzylserinols (*S*)- and (*R*)-**4a** and the debenzylation of 3-α-methylbenzyl-2-oxazolidinones (4*R*)- and (4*S*)-**5a** using TfOH and anisole in $MeNO_2$. 2-Benzylserinols (*S*)-**4b** and (*R*)-**4c** possessing halogenated phenyl groups were also applied for the diastereoselective desymmetrization to give oxazolidinones (4*R*)-**5b** and (4*S*)-**5c**, respectively. Debenzylation using TfOH and anisole in $MeNO_2$ was also useful for 3-(α-methylbenzyl)-2-oxazolidinones (4*R*)-**5b** and (4*S*)-**5c** possessing 3,4-dichlorobenzyl and 4-bromobenzyl groups. Optically active α-(hydroxymethyl)phenylalanine (**7**), *N*-Boc-α-methylphenylalanine (**8**), cericlamine (**9**), and BIRT-377 (**10**) were synthesized from the corresponding oxazolidinones (*S*)- and (*R*)-**15a**, (*R*)-**15b**, and (*S*)-**15c**, respectively. Application of other 2-substituted serinols instead of 2-benzylserinols **4** in the diastereoselective asymmetric desymmetrization giving 2-substituted 2-oxazolidinones is underway, and will be reported in due course.

4. Experimental

Melting points were measured with Yanaco MP-3 apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-140 polarimeter. NMR spectra were obtained a JEOL JNM-GSX400 (^1H NMR: 400 MHz and ^{13}C NMR: 100 MHz) spectrometers using tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi 215 spectrophotometer. MS and high-resolution MS (HRMS) were taken on a JEOL JMS-DX302 spectrometer using glycerol as a matrix of positive FABMS otherwise noted. Column chromatography was performed with silica gel 60 (spherical, 40–50 μm, Kanto Chemical). Analytical TLC was performed on plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} (Merck) or on those of RP-18 F_{254}s (Merck).

4.1. Synthesis of aminomalonate hydrochlorides 12a–c-HCl (Table 1)

*4.1.1. Synthesis of (S)-**12a-HCl** using benzyl bromide (entry 1).* Aminomalonate (*S*)-**11**[12] (17.0 g, 60.9 mmol) was dissolved in DMF (152 mL), and *t*-BuOK (13.7 g, 122 mmol) was added portionwise to the DMF solution at room temperature. After being stirred for 30 min, the mixture was cooled using an ice bath, and benzyl bromide (20.8 g, 122 mmol) was added dropwise to the mixture. After the resulting mixture was stirred for 18 h at room temperature, the reaction mixture was diluted with H_2O (170 mL) and extracted with Et_2O (170 mL, three times). The extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo.

This oil was dissolved in Et_2O (500 mL) again, and 4 mol/L solution of hydrogen chloride in dioxane (16.7 mL) was added to the ether solution with vigorously stirring. Crystalline material was precipitated in the mixture, and the resulting mixture was filtered through a glass filter to give (*S*)-**12a-HCl** as white-ivory powder (11.0 g, 45%). (The filtrate containing **13-HCl** was used in 4.2.3 to afford **13**.)

For spectral analysis, pure (*S*)-**12a-HCl** was prepared by following procedure; benzylmalonate (*S*)-**12a** (296 mg), which was obtained from (*S*)-**12a-HCl** described in 4.2.1 was dissolved in Et_2O (5 mL) and the solution was extracted with 10% HCl aq (10 mL). After the aqueous layer was separated and allowed to stand for 30 min at room temperature, colorless crystalline material was precipitated, and the material was collected by filtration to give pure (*S*)-**12a-HCl** (165 mg).

*4.1.2. Diethyl 2-benzyl-N-(S)-(α-methylbenzyl)aminomalonate hydrochloride [(S)-**12a-HCl**].* Colorless powder; mp 111–113 °C. $[\alpha]_D^{26}$ −40.2 (*c* 0.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70 (2H, d, *J*=7.1 Hz, Ar), 7.31–7.40 (6H, m, Ar), 7.21–7.25 (2H, m, Ar), 4.67 (1H, q, *J*=6.8 Hz, PhCH), 4.20 (2H, q, *J*=7.1 Hz, OCH_2), 4.13 (1H, d, *J*=14.2 Hz, PhC*H*H), 3.90 (1H, dq, *J*=10.8, 7.2 Hz, OC*H*H), 3.85 (1H, d, *J*=14.2 Hz, PhCH*H*), 3.68 (1H, dq, *J*=10.8, 7.6 Hz, OCH*H*), 1.96 (3H, d, *J*=6.3 Hz, Me), 1.28 (3H, t, *J*=7.1 Hz, OCH_2Me), 1.09 (3H, t, *J*=7.1 Hz, OCH_2Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5 (C=O ×2), 145.9 (Ar, C), 132.4 (Ar, C), 130.3 (Ar, CH ×2), 129.1 (Ar, CH), 128.8 (Ar, CH ×2) 128.6 (Ar, CH ×2), 128.2 (Ar, CH ×2), 127.9 (Ar, CH), 71.4 (NCBn), 63.5 (CH_2O), 63.3 (CH_2O), 59.7 (PhCHN), 39.3 ($PhCH_2$), 22.4 (PhCH*Me*), 13.9 (Me), 13.7 (Me). IR (KBr) cm^{-1}: 1750. MS (FAB) *m*/*z*: 370 [(M+1−HCl)$^+$]. Anal. Calcd for $C_{22}H_{28}ClNO_4$: C, 65.01; H, 6.95; N, 3.45. Found: C, 64.87; H, 6.96; N, 3.25.

*4.1.3. Synthesis of (S)-**12a-HCl** using benzyl chloride (entry 2).* Aminomalonate hydrochloride (*S*)-**12a-HCl** (9.50 g, 39%) was also synthesized from aminomalonate (*S*)-**11** (17.0 g, 60,9 mmol) using benzyl chloride (15.4 g, 122 mmol) according to the procedure described in 4.1.1.

*4.1.4. Synthesis of (R)-**12a-HCl** from a crude (R)-11 (entry 3).* A mixture of triethylamine (7.91 g, 78.2 mmol) and (*R*)-(+)-α-methylbenzylamine (9.48 g, 78.2 mmol) was added to a mixture of diethyl bromomalonate (92% purity, Aldrich, 20.3 g, 78.1 mmol as 92% purity) in MeCN (78 mL) at room temperature, and the resulting mixture was stirred for 18 h at room temperature. After the reaction mixture was filtered, the filtrate was concentrated in vacuo. The residue was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo to

give a crude (*R*)-**11**[12] (22.3 g) as brown oil, which was used without further extraction for the synthesis of (*R*)-**12a**-**HCl** using *t*-BuOK (17.6 g, 15.7 mmol), DMF (200 mL) and benzyl bromide (26.8 g, 157 mmol) according to the procedure described in 4.1.1 to afford (*R*)-**12a**-**HCl** as white-ivory powder (9.77 g, 31% from diethyl bromomalonate). $[\alpha]_D^{23}$ +40.3 (*c* 1.0, $CHCl_3$). ^1H NMR spectrum was good agreement with that of (*S*)-**12a**-**HCl**.

*4.1.5. Synthesis of (S)-**12b**-**HCl** (entries 4–6).* According to the procedure described in 4.1.1, (*S*)-**12b**-**HCl** (215 mg, 27%) was obtained from (*S*)-**11** (500 mg, 1.79 mmol) and 3,4-dichlorobenzyl chloride (700 mg, 3.58 mmol) (entry 4). (*S*)-**12b**-**HCl** (240 mg, 31%) was also obtained from (*S*)-**11** (500 mg, 1.79 mmol) and 3,4-dichlorobenzyl bromide (859 mg, 3.58 mmol) (entry 5) or from (*S*)-**11** (30.7 g, 110 mmol) and 3,4-dichlorobenzyl chloride (43.0 g, 220 mmol) (entry 6).

*4.1.6. Diethyl (S)-2-(3,4-dichlorobenzyl)-2-(α-methylbenzyl)aminomalonate hydrochloride [(S)-**12b**-**HCl**].* White-ivory powder, mp 82–84 °C. $[\alpha]_D^{28}$ −38.7 (*c* 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.74 (2H, d, *J*=7.1 Hz, Ar), 7.31–7.40 (4H, m, Ar), 7.26 (1H, d, *J*=8.3 Hz, Ar), 7.17 (1H, dd, *J*=8.3, 2.0 Hz, Ar), 4.79 (1H, q, *J*=6.8 Hz, PhC*H*), 4.10–4.16 (2H, m, OCH_2), 4.10 (1H, d, *J*=14.6 Hz, PhC*H*H), 3.97 (1H, d, *J*=13.9 Hz, PhCH*H*), 3.62–3.70 (1H, m, OC*H*H), 3.51–3.40 (1H, m, OCH*H*), 2.03 (3H, d, *J*=6.8 Hz, Me), 1.20 (3H, t, *J*=7.1 Hz, OCH_2*Me*), 1.02 (3H, t, *J*=7.1 Hz, OCH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5 (C=O), 163.5 (C=O), 136.6 (Ar, C), 133.6 (Ar, C), 132.5 (Ar, CH), 131.9 (Ar, C), 131.6 (Ar, C), 130.1 (Ar, CH), 129.8 (Ar, CH), 129.1 (Ar, CH) 128.7 (Ar, CH ×2), 128.6 (Ar, CH ×2), 70.9 (NCBn), 63.3 (CH_2O), 63.2 (CH_2O), 59.6 (PhC*H*N), 38.7 (PhCH_2), 23.0 (PhCH*Me*), 13.8 (Me), 13.6 (Me). IR (KBr) cm^{-1}: 1740. MS (FAB) *m*/*z*: 438 [(M−HCl+1)$^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{22}H_{26}Cl_2NO_4$: 438.1239. Found: 438.1246. Anal. Calcd for $C_{22}H_{26}Cl_3NO_4$: C, 55.60; H, 5.52; N, 2.95. Found: C, 56.05; H, 5.54; N, 2.81.

*4.1.7. Synthesis of (R)-**12c**-**HCl** (entry 7).* Aminomalonate hydrochloride (*R*)-**12c**-**HCl** (11.0 g, 47%) was synthesized from (*R*)-**11** (13.6 g, 48.6 mmol) and 4-bromobenzyl bromide (24.3 g, 97.2 mmol) (entry 7) according to the procedure described in 4.1.1.

*4.1.8. Diethyl (R)-2-(4-bromobenzyl)-2-(α-methylbenzyl)aminomalonate hydrochloride [(R)-**12c**-**HCl**].* White-ivory powder, mp 94–96 °C. $[\alpha]_D^{25}$ +40.7 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.67 (2H, d, *J*=6.8 Hz, Ar), 7.33–7.59 (5H, m, Ar), 7.22 (2H, d, *J*=8.0 Hz, Ar), 4.62 (1H, q, *J*=6.8 Hz, PhC*H*), 4.05 (1H, d, *J*=6.8 Hz, OC*H*H), 4.03 (1H, d, *J*=6.8 Hz, OCH*H*), 3.96 (1H, d, *J*=14.0 Hz, ArC*H*H), 3.80–3.88 (1H, m, OC*H*H), 3.77 (1H, d, *J*=14.0 Hz, ArCH*H*), 3.59–3.67 (1H, m, OCH*H*), 1.95 (3H, d, *J*=6.8 Hz, Me), 1.20 (3H, t, *J*=6.8 Hz, OCH_2*Me*), 1.04 (3H, t, *J*=6.8 Hz, OCH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6 (C=O), 164.5 (C=O), 137.5 (Ar, C), 132.20 (Ar, C), 132.17 (Ar, CH ×2), 131.4 (Ar, CH ×2), 129.0 (Ar, CH), 128.7 (Ar, CH ×2), 128.4 (Ar, CH ×2), 121.8 (Ar, C), 71.0 (NCCH_2Ar), 63.2 (CH_2O), 63.1 (CH_2O), 59.0 (PhC*H*N), 38.3 (ArCH_2), 22.8 (PhCH*Me*), 13.8 (Me), 13.7 (Me). IR (KBr) cm^{-1}: 1750. MS (FAB) *m*/*z*: 448 [(M−HCl+1)$^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{22}H_{27}BrNO_4$: 448.1123. Found: 448.1121.

4.2. *C*-Benzylaminomalonates 12a–c and *N*-benzyl aminomalonate (Table 1)

*4.2.1. Diethyl 2-benzyl-N-(S)-(α-methylbenzyl)aminomalonate [(S)-**12a**] (entry 1).* HCl salt (*S*)-**12a**-**HCl** (11.6 g, 28.6 mmol) was treated with saturated aqueous $NaHCO_3$ (200 mL), and the mixture was extracted with Et_2O (once with 100 mL and twice with 50 mL). The extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give (*S*)-**12a** as brown viscous oil (10.2 g, 97%). This material was used at the next reaction without further purification. For spectral analysis, (*R*)-**12a** was prepared by following procedure; the pure salt (*S*)-**12a**-**HCl** (68.6 mg, 169 μmol), which was obtained for the spectrum analysis in 4.1.1, was dissolved in $CHCl_3$ and the solution was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give pure (*S*)-**12a** (62.4 mg, quant.) as colorless oil. R_f value; 0.32 (RP-18, MeOH/H_2O, 9:1). $[\alpha]_D^{20}$ −1.9 (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.15–7.33 (10H, m, Ar), 4.02 (1H, q, *J*=6.8 Hz, PhCH), 3.960 (1H, q, *J*=7.1 Hz, OC*H*H), 3.959 (1H, q, *J*=7.1 Hz, OCH*H*), 3.84 (1H, dq, *J*=10.7, 7.1 Hz, OC*H*H), 3.56 (1H, dq, *J*=10.7, 7.1 Hz, OCH*H*), 3.40 (1H, d, *J*=14.4 Hz, PhC*H*H), 3.19 (1H, d, *J*=14.4 Hz, PhCH*H*), 1.35 (3H, d, *J*=6.8 Hz, Me), 1.15 (3H, t, *J*=7.1 Hz, OCH_2*Me*), 1.05 (3H, t, *J*=7.1 Hz, OCH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0 (C=O), 169.6 (C=O), 145.6 (Ar, C), 135.5 (Ar, C), 129.9 (Ar, CH ×2), 127.9 (Ar, CH ×2), 127.8 (Ar, CH ×2) 126.7 (Ar, CH ×2), 126.6 (Ar, CH ×2), 126.5 (Ar, CH), 70.1 (NCBn), 61.4 (CH_2O), 61.1 (CH_2O), 53.2 (PhC*H*N), 38.6 (PhCH_2), 26.4 (PhCH*Me*), 14.0 (Me), 13.8 (Me). IR (film) cm^{-1}: 1740. MS (FAB) *m*/*z*: 370 [(M+1)$^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{22}H_{28}NO_4$, 370.2019; found, 370.2019.

*4.2.2. Diethyl 2-benzyl-N-(R)-(α-methylbenzyl)aminomalonate [(R)-**12a**] (entry 3).* Aminomalonate (*R*)-**12a** (8.47 g, 97%) was also synthesized according to the procedure described in 4.2.1 from (*R*)-**12a**-**HCl** (9.62 g). $[\alpha]_D^{27}$ +1.9 (*c* 1.0, $CHCl_3$). ^1H NMR spectrum was good agreement with that of (*S*)-**12a**.

*4.2.3. Diethyl N-benzyl-N-(S)-(α-methylbenzyl)aminomalonate (**13**).* The filtrate containing **13**-**HCl** in Et_2O, which had been given from the mixture of (*S*)-**12** and **13** in Et_2O as described in 4.1.1, was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil (20.5 g). A small amount of the oil (601 mg) was chromatographed on silica gel (hexane/AcOEt, 9:1) to give a pure **13** (248 mg) as a colorless oil. Thus, the brown oil (20.5 g) had been containing 8.45 g (38%) of **13**. R_f value; 0.34 (RP-18, MeOH/H_2O, 9:1). $[\alpha]_D^{27}$ −10.5 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.53 (2H, d, *J*=7.6 Hz, Ar), 7.46 (2H, d, *J*=8.0 Hz, Ar), 7.41–7.20 (6H, m, Ar), 4.25–4.05 (8H, m, OCH_2 ×2, $PhCH_2$, PhCH–NCH), 1.29 (3H, d, *J*=6.8 Hz, Me), 1.25 (3H, t, *J*=7.2 Hz, OCH_2*Me*), 1.21 (3H, t, *J*=7.19 Hz, OCH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4 (C=O), 168.8 (C=O), 143.0 (Ar, C), 140.6 (Ar, C), 128.3 (Ar, CH ×2), 128.1 (Ar, CH ×2), 128.0 (Ar, CH ×2), 127.5 (Ar, CH ×2), 126.9 (Ar, CH), 126.7 (Ar, CH), 64.4 (CH), 61.3 (CH_2), 61.2 (CH_2), 58.0 (CH), 53.2 (CH_2), 16.9 (Me), 14.2 (Me ×2). IR (film) cm^{-1}: 1730. MS (EI) *m*/*z*: 370 (M+1)$^+$. HRMS (EI) *m*/*z*: calcd for $C_{22}H_{27}NO_4$, 369.1941; found, 369.1936.

*4.2.4. Diethyl (S)-2-(3,4-dichlorobenzyl)-2-(α-methylbenzyl)aminomalonate [(S)-**12b**] (entry 6).* Aminomalonate (*S*)-**12b** (14.9 g, 89%) was obtained from aminomalonate hydrochloride (*S*)-**12b**-**HCl** (18.0 g). This material was used at the next reaction without further purification; a colorless oil. $[\alpha]_D^{26}$ +21.3 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29 (5H, d-like m, Ar), 7.18–7.23 (2H, m, Ar), 6.97 (1H, dd, *J*=8.4, 2.0 Hz, Ar), 4.08 (2H, q-like m, PhCH+OC*H*H), 3.87 (2H, m, OCH_2), 3.59 (1H, m, OCH*H*), 3.29 (1H, d, *J*=14.7 Hz, PhC*H*H), 3.06 (1H, d, *J*=14.7 Hz, PhCH*H*), 2.56 (1H, br s, NH), 1.38 (3H, d, *J*=6.8 Hz, Me), 1.21 (3H, t, *J*=7.1 Hz, OCH_2*Me*), 1.06 (3H, t, *J*=7.1 Hz, OCH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4 (C=O ×2), 145.3 (Ar, C), 136.0 (Ar, C), 132.0 (Ar, CH), 131.6 (Ar, C), 130.6 (Ar, C), 129.6 (Ar, CH), 129.3 (Ar, CH), 128.0 (Ar, CH ×2), 126.8 (Ar, CH) 126.5 (Ar, CH ×2), 70.1 (NCCH_2Ar), 61.8 (CH_2O), 61.4 (CH_2O), 53.3 (PhC*H*N), 37.2 (ArCH_2), 26.4 (PhCH*Me*), 14.1 (Me), 13.9 (Me). IR ($CHCl_3$) cm^{-1}: 1760, 1200, 1040. MS (FAB) *m*/*z*: 438 [(M+1)$^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{22}H_{26}Cl_2NO_4$: 438.1239. Found: 438.1245.

*4.2.5. Diethyl (R)-2-(4-bromobenzyl)-2-(α-methylbenzyl)aminomalonate [(R)-**12c**] (entry 7).* Aminomalonate (*R*)-**12c** (8.40 g, 82%)

was obtained from aminomalonate hydrochloride (*R*)-**12c**-**HCl** (11.0 g). This material was used at the next reaction without further purification; an yellow oil. $[\alpha]_D^{22}$ −3.7 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33 (2H, d, *J*=9.2 Hz, Ar), 7.17–7.31 (5H, m, Ar), 7.02 (2H, d, *J*=8.4 Hz, Ar), 4.03 (1H, d, *J*=6.8 Hz, OC*H*H), 3.99 (1H, d, *J*=7.2 Hz, OCH*H*), 3.95 (1H, q, *J*=7.2 Hz, PhCH), 3.80–3.88 (1H, m, OC*H*H), 3.53–3.61 (1H, m, OCH*H*), 3.32 (1H, d, *J*=14.4 Hz, ArC*H*H), 3.10 (1H, d, *J*=14.4 Hz, ArCH*H*), 1.36 (3H, d, *J*=6.4 Hz, Me), 1.17 (3H, t, *J*=7.2 Hz, OCH_2*Me*), 1.05 (3H, t, *J*=7.2 Hz, OCH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8 (C=O), 169.6 (Ar, C=O), 145.5 (Ar, C), 134.7 (Ar, C), 131.6 (Ar, CH ×2), 130.9 (Ar, CH ×2), 128.0 (Ar, CH ×2), 126.7 (Ar, CH), 126.6 (Ar, CH ×2), 120.7 (Ar, C), 70.1 ($NCCH_2Ar$), 61.7 (CH_2O), 61.3 (CH_2O), 53.3 (PhC*H*N), 37.8 ($ArCH_2$), 26.5 (PhCH*Me*), 14.1 (Me), 13.9 (Me). IR (neat) cm^{-1}: 2970, 1730, 1490. MS (FAB) *m*/*z*: 448 [$(M+1)^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{22}H_{27}BrNO_4$: 448.1123. Found: 448.1131.

4.3. Synthesis of 2-benzylserinols 4a–c (Table 1)

*4.3.1. (S)-2-Benzyl-2-(α-methylbenzyl)amino-1,3-propanediol [(S)-**4a**].* $LiAlH_4$ (5.07 g, 134 mmol) was added slowly to a solution of *C*-benzyl aminomalonate (*S*)-**12a** (9.85 g, 26.7 mmol) in Et_2O (134 mL, 0.2 mol/L) with cooling by use of an ice bath. The mixture was stirred for 2.5 h with cooling. H_2O/THF (1:1, 10.2 mL) was added dropwise carefully, and 15% NaOH aq (5.1 mL) and then H_2O (5.1 mL) were added to the mixture. The resulting mixture was stirred for 2 h at room temperature and filtered through a glass filter. The solid was washed with Et_2O. The filtrate was extracted with 10% HCl aq three times (40 mL×1 and 20 mL×2). The aqueous layer was alkalined (ca. pH 11) with NaOH and extracted with Et_2O three times (40 mL×1 and 20 mL×2). The organic extracts were combined, washed with H_2O twice (40 mL×2), dried over $MgSO_4$ and evaporated in vacuo to afford benzylserinol (*S*)-**4a** (6.42 g, 84%) as brown viscous oil. This oil was used at the next reaction without further purification. For spectral analysis, the benzylserinol (*S*)-**4a** (99.9 mg) was purified with silica gel column chromatography (hexane/AcOEt, 3:7) to give a pure (*S*)-**4a** (73.9 mg) as colorless oil. $[\alpha]_D^{27}$ −73.6 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.19–7.42 (10H, m, Ar), 4.10 (1H, q, *J*=11.2 Hz, PhC*H*), 3.24 (1H, d, *J*=11.2 Hz, OC*H*H), 3.30 (1H, d, *J*=11.2 Hz, OCH*H*), 3.25 (1H, d, *J*=11.2 Hz, OC*H*H), 3.23 (1H, d, *J*=11.2 Hz, OCH*H*), 2.80 (1H, d, *J*=13.3 Hz, PhC*H*H), 2.71 (1H, d, *J*=13.3 Hz, PhCH*H*), 1.37 (3H, d, *J*=6.6 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.7 (Ar, C), 136.7 (Ar, C), 130.3 (Ar, CH ×2), 128.7 (Ar, CH ×2), 128.1 (Ar, CH ×2), 127.0 (Ar, CH), 126.3 (Ar, CH), 125.8 (Ar, CH ×2), 63.7 (OCH_2), 63.3 (OCH_2), 61.4 (NCBn), 51.6 (PhCHN), 38.2 ($PhCH_2$), 27.0 (Me). IR (film) cm^{-1}: 3400, 3330, 2925, 1455, 1040. MS (FAB) *m*/*z*: 286 [$(M+1)^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{18}H_{24}NO_2$, 286.1808; found, 286.1810.

*4.3.2. (R)-2-Benzyl-2-(α-methylbenzyl)amino-1,3-propanediol [(R)-**4a**].* Benzylserinol (*R*)-**4a** (5.37 g, 89%) was also synthesized via (*R*)-**12a** (8.18 g, 22.1 mmol) according to the procedure described in 4.3.1. $[\alpha]_D^{26}$ +70.1 (*c* 1.0, $CHCl_3$). ^1H NMR spectrum data was good agreement with those of (*S*)-**4a**.

*4.3.3. (S)-2-(3,4-Dichlorobenzyl)-2-(α-methylbenzyl)amino-1,3-propanediol [(S)-**4b**].* Benzylserinol **4b** (10.4 g, 87%) was obtained from *C*-benzyl aminomalonate (*S*)-**12b** (14.9 g, 33.9 mmol) as a brown viscous oil according to the procedure described in 4.3.1. This oil was used at the next reaction without further purification.

For spectral analysis, the benzylserinol (*S*)-**4b** (182 mg) was purified with silica gel column chromatography (hexane/AcOEt, 1:1) to give a pure (*S*)-**4b** (106 mg); an yellow oil. $[\alpha]_D^{28}$ −59.6 (*c* 2.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.08–7.30 (8H, m, Ar), 3.95 (1H, q, *J*=6.4 Hz, PhC*H*), 3.18 (1H, d, *J*=11.2 Hz, OC*H*H), 3.16 (1H, d, *J*=10.8 Hz, OCH*H*), 3.08 (1H, d, *J*=11.2 Hz, OC*H*H), 3.03 (1H, d, *J*=10.8 Hz, OCH*H*), 2.63 (1H, d, *J*=13.6 Hz, PhC*H*H), 2.57 (1H, d, *J*=13.6 Hz, PhCH*H*), 1.26 (3H, d, *J*=6.4 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.5 (Ar, C), 137.1 (Ar, C), 132.1 (Ar, CH), 131.8 (Ar, C), 130.2 (Ar, C), 129.8 (Ar, CH ×2), 128.7 (Ar, CH ×2), 127.1 (Ar, CH), 125.7 (Ar, CH ×2), 62.9 (OCH_2), 62.7 (OCH_2), 61.3 ($NCCH_2Ar$), 51.5 (PhCHN), 36.9 ($ArCH_2$), 26.9 (Me). IR (neat) cm^{-1}: 3450, 3380, 1480, 1410, 1150, 1050. MS (FAB) *m*/*z*: 354 [$(M+1)^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{18}H_{22}Cl_2NO_2$: 354.1028. Found: 354.1033.

*4.3.4. (R)-2-(4-Bromobenzyl)-2-(α-methylbenzyl)amino-1,3-propanediol [(R)-**4c**].* Crude benzylserinol (*R*)-**4c** (6.4 g) was obtained from *C*-benzyl aminomalonate (*R*)-**12c** (8.34 g, 18.6 mmol) as a dark brown solid according to the procedure described in 4.3.1. This solid was recrystallized from EtOH to give a pure (*R*)-**4c** (3.12 g, 46%). The residue was purified with silica gel column chromatography (hexane/AcOEt, 3:7) to give a pure (*R*)-**4c** (1.41 g, total 4.53 g, 67%); colorless powder, mp 127–128 °C. $[\alpha]_D^{18}$ +74.5 (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.40 (7H, m, Ar), 7.08 (2H, d, *J*=8.3 Hz, Ar), 4.05 (1H, q, *J*=6.6 Hz, PhC*H*), 3.15–3.30 (4H, m, OCH_2 ×2), 2.74 (1H, d, *J*=13.2 Hz, ArC*H*H), 2.67 (1H, d, *J*=13.2 Hz, ArCH*H*), 1.36 (3H, d, *J*=6.6 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.7 (Ar, C), 135.8 (Ar, C), 132.1 (Ar, CH ×2), 131.1 (Ar, CH ×2), 128.8 (Ar, CH ×2), 127.2 (Ar, CH), 125.7 (Ar, CH ×2), 120.3 (Ar, C), 63.3 (OCH_2), 62.9 (OCH_2), 61.4 ($NCCH_2Ar$), 51.6 (PhCHN), 37.6 ($PhCH_2$), 27.1 (Me). IR ($CHCl_3$) cm^{-1}: 1635. MS (FAB) *m*/*z*: 364 [$(M+1)^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{18}H_{23}BrNO_2$: 364.0912. Found: 364.0921.

4.4. Synthesis of 2-oxazolidinones 5 and 6 (Table 2)

4.4.1. Test of the solvents (entries 1–3). CCF (3.0 μL, 29 μmol) was added to a solution of (*S*)-**4a** (7.9 mg, 29 μmol), pyridine (2.3 μL, 29 μmol) and triphenylmethane (1.3 mg, an internal standard) in CH_2Cl_2, THF, or Et_2O (0.29 mL) at room temperature. After being stirred for 16 h at room temperature, DBU (13 μL, 87 μmol) was added to the mixture, and the resulting mixture was stirred for 4 h at room temperature. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The extracts were combined, dried over $MgSO_4$, filtered and, concentrated in vacuo. The yields and ratios were estimated with the internal standard (triphenylmethane) by ^1H NMR integration in $CDCl_3$. Characteristic signals ($CDCl_3$): $\delta_{\mathbf{5a}}$=4.82 ppm, $\delta_{\mathbf{6a}}$=4.44 ppm, and δ_{Ph3CH}=5.55 ppm.

*4.4.2. Synthesis of **5a–c** using CCF and pyridine (entries 4–6).* Entry 4; CCF (2.70 g, 18.9 mmol) was added to a mixture of benzylserinol (*S*)-**4a** (5.13 g, 18.0 mmol) and pyridine (1.49 g, 18.9 mmol) in CH_2Cl_2 (180 mL) at room temperature. After being stirred for 15 h at room temperature, the mixture was cooled to 2 °C (internal temperature) by use of an ice bath. DBU (8.63 g, 56.7 mmol) was added dropwise to the mixture, and the resulting mixture was stirred for 6 h at this temperature. The reaction mixture was washed twice with 10% HCl aq (40 mL and 20 mL) and once with saturated aqueous $NaHCO_3$ (40 mL), dried, filtered, and concentrated in vacuo to give a dark brown solid. This solid was recrystallized from AcOEt (70 mL) to give (4*R*)-**5a** (2.31 g) as colorless needles. The filtrate was concentrated in vacuo to give a mixture of dark brown viscous oil and solid. This mixture was suspended with Et_2O (10 mL), and the solid was collected with filtration and then recrystallized from AcOEt (11 mL) to give (4*R*)-**5a** as colorless needles (0.31 g, total 2.62 g, 47%).

Entry 5; a crude dark brown solid containing (4*R*)-**5b** was obtained from benzylserinol (*S*)-**4b** (10.0 g, 28.2 mmol) according to the procedure described in 4.4.2. This solid was recrystallized from AcOEt (70 mL) to give (4*R*)-**5b** as colorless needles (2.51 g). The filtrate was concentrated in vacuo to give a mixture of dark brown viscous oil and solid. This mixture was suspended with Et_2O (10 mL), and the solid was collected with by filtration and

recrystallized from AcOEt (11 mL) to give (4*R*)-**5b** as colorless needles (1.59 g). The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give (4*R*)-**5b** (0.45 g, total 4.55 g, 43%) and (4*S*)-**6b** (202 mg, 2%).

Entry 6; a crude dark brown solid containing (4*S*)-**5c** was obtained from benzylserinol (*R*)-**4c** (300 mg, 0.82 mmol) according to the procedure described in 4.4.2. This solid was recrystallized from EtOH to give (4*S*)-**5c** as colorless needles (52.6 mg). The filtrate was concentrated in vacuo to give a mixture of dark brown viscous oil and solid. The residue (390 mg) was purified with silica gel column chromatography ($CHCl_3$/MeOH, 9:1) to give (4*S*)-**5c** (76.3 mg, total 129 mg, 40%).

*4.4.3. Reactions of **4a**–**c** using CCF, DMAP, and Et_3N (entries **7**–**9**).* Entry 7; CCF (322 μL, 3.11 mmol) was added to a mixture of benzylserinol (*S*)-**4a** (888 mg, 3.11 mmol), DMAP (19.1 mg, 156 μmol) and Et_3N (431 μL, 3.11 mmol) in CH_2Cl_2 (31 mL) at room temperature. After being stirred for 15 h at room temperature, the mixture was cooled by use of an ice bath. DBU (1.40 mL, 9.33 mmol) was added dropwise to the mixture, and the resulting mixture was stirred for 6 h at this temperature. The reaction mixture was washed with 10% HCl aq and saturated aqueous $NaHCO_3$, dried, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel to give (4*R*)-**5a** (636 mg, 66%) and (4*S*)-**6a** (27.0 mg, 2.8%).

Entry 8; reaction conditions in entry 8 were identical with those in entry 7 and used for serinol (*S*)-**4b** (286 mg).

Entry 9; a crude dark brown solid containing (4*S*)-**5c** was obtained from benzylserinol (*R*)-**4c** (1.94 g, 5.34 mmol) according to the procedure described in 4.4.3. This solid was recrystallized from AcOEt to give (4*S*)-**5c** as colorless needles (1.14 g). The filtrate was concentrated in vacuo to give a mixture of dark brown viscous oil and solid. The residue (1.14 g) was purified with silica gel column chromatography ($CHCl_3$/MeOH, 9:1) to give (4*S*)-**5c** (276 mg, total 1.41 g, 68%) and (4*R*)-**6c** (56.5 mg, 3.4%).

*4.4.4. Reaction of **4a** with CDI (entry 10).* CDI (85 mg, 0.52 mmol) was added to a solution of benzylserinol (*S*)-**4a** (149 mg, 0.522 mmol) in THF (13 mL) at room temperature. After the mixture was stirred for 6 h at room temperature, DBU (233 μL, 1.56 mmol) was added to the mixture. The resulting mixture was stirred for 15 h at room temperature. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt. The extracts were combined, dried, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt, 3:7) to give (4*S*)-**5a** (96.1 mg, 59%) and (4*R*)-**6a** (41.2 mg, 25%).

*4.4.5. Reaction of **4a**–**c** with DSC (entries 11–13).* DSC (500 mg, 1.97 mmol) was added to a solution of benzylserinol (*S*)-**4a** (563 mg, 1.97 mmol) in MeCN (20 mL) at room temperature. After being stirred for 15 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt, 1:4) to give (4*S*)-**6a** (274 mg, 45%) and (4*R*)-**5a** (249 mg, 41%). This reaction conditions were used for the reaction of serinol (*S*)-**4b** (1.01 g) and (*R*)-**4c** (89 mg) (entries 12 and 13).

*4.4.6. (4S,αR)-4-Benzyl-4-hydroxymethyl-3-(α-methylbenzyl)-2-oxazolidinone [(4S)-**5a**].* Colorless needles, mp 186–188 °C (AcOEt). R_f value; 0.27 (silica gel, hexane/AcOEt, 1:1). $[\alpha]_D^{28}$ −59.7 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.58–7.60 (2H, m, Ar), 7.35–7.39 (2H, m, Ar), 7.23–7.31 (4H, m, Ar), 7.02–7.04 (2H, m, Ar), 4.82 (1H, q, *J*=7.3 Hz, PhC*H*), 4.23 (1H, d, *J*=9.0 Hz, COC*H*H), 3.88 (1H, d, *J*=8.8 Hz, COCH*H*), 3.70 (1H, dd, *J*=11.7, 4.2 Hz, HOC*H*H), 3.57 (1H, dd, *J*=11.7, 6.6 Hz, HOCH*H*), 3.09 (1H, d, *J*=13.7 Hz, PhC*H*H), 2.79 (1H, d, *J*=13.7 Hz, PhCH*H*), 1.91 (3H, d, *J*=7.3 Hz, Me), 1.64 (1H, m, OH). ^1H NMR (400 MHz, $CDCl_3$ with D_2O) *δ*: 7.57–7.59 (2H, m, Ar), 7.35–7.38 (2H, m, Ar), 7.23–7.31 (4H, m, Ar), 7.02–7.04 (2H, m, Ar), 4.80 (1H, q, *J*=7.3 Hz, PhC*H*), 4.23 (1H, d, *J*=8.8 Hz, COC*H*H), 3.88 (1H, d, *J*=8.8 Hz, COCH*H*), 3.69 (1H, d, *J*=11.7 Hz, DOC*H*H), 3.57 (1H, d, *J*=11.8 Hz, DOCH*H*), 3.08 (1H, d, *J*=13.7 Hz, PhC*H*H), 2.79 (1H, d, *J*=13.4 Hz, PhCH*H*), 1.90 (3H, d, *J*=7.3 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 157.2 (C=O), 142.3 (Ar, C), 134.3 (Ar, C), 129.9 (Ar, CH ×2), 128.6 (Ar, CH ×2), 128.5 (Ar, CH ×2), 127.5 (Ar, CH), 127.2 (Ar, CH ×3), 67.9 (CH_2), 65.9 (C), 64.4 (CH_2), 52.6 (CH), 40.9 (CH_2), 19.9 (Me). IR ($CHCl_3$) cm^{-1}: 1735. MS (EI) *m*/*z*: 280 [$(M-CH_2OH)^+$, 4%], 220 [$(M-Bn)^+$, 45], 176 (11), 116 (14), 105 (100). MS (FAB) *m*/*z*: 312 [$(M+1)^+$]. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.45; H, 6.89; N, 4.37.

*4.4.7. (4R,αS)-4-Benzyl-4-hydroxymethyl-3-(α-methylbenzyl)-2-oxazolidinone [(4R)-**5a**].* Oxazolidinone (4*R*)-**5a** was synthesized according to the method described in 4.4.3. $[\alpha]_D^{30}$ +55.0 (*c* 0.3, $CHCl_3$).

*4.4.8. (4R,αR)-4-Benzyl-4-hydroxymethyl-3-(α-methylbenzyl)-2-oxazolidinone [(4R)-**6a**].* Colorless needles, mp 173–175 °C (AcOEt). R_f value; 0.49 (silica gel, hexane/AcOEt, 1:1). $[\alpha]_D^{22}$ −12.1 (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.59–7.61 (2H, m, Ar), 7.28–7.39 (6H, m, Ar), 7.21–7.23 (2H, m, Ar), 4.44 (1H, q, *J*=7.3 Hz, PhC*H*), 4.25 (1H, d, *J*=8.8 Hz, COC*H*H), 4.05 (1H, d, *J*=8.8 Hz, COCH*H*), 3.60 (1H, dd, *J*=12.5, 4.2 Hz, HOC*H*H), 3.32 (1H, dd, *J*=12.5, 9.5 Hz, HOCH*H*), 3.03 (1H, d, *J*=14.2 Hz, PhC*H*H), 2.94 (1H, d, *J*=13.7 Hz, PhCH*H*), 1.87 (3H, d, *J*=7.3 Hz, Me), 1.01 (1H, dd, *J*=9.5, 4.2 Hz, OH). ^1H NMR (400 MHz, $CDCl_3$ with D_2O) *δ*: 7.59 (2H, d, *J*=7.1 Hz, Ar), 7.30–7.39 (6H, m, Ar), 7.21–7.23 (2H, m, Ar), 4.45 (1H, q, *J*=7.3 Hz, PhC*H*), 4.25 (1H, d, *J*=8.5 Hz, COC*H*H), 4.05 (1H, d, *J*=8.8 Hz, COCH*H*), 3.59 (1H, d, *J*=12.5 Hz, DOC*H*H), 3.31 (1H, d, *J*=12.5 Hz, DOCH*H*), 3.03 (1H, d, *J*=13.9 Hz, PhC*H*H), 2.94 (1H, d, *J*=13.9 Hz, PhCH*H*), 1.87 (3H, d, *J*=7.3 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 157.3 (C=O), 143.3 (Ar, C), 134.1 (Ar, C), 130.0 (Ar, CH ×2), 129.2 (Ar, CH ×2), 128.7 (Ar, CH ×2), 128.0 (Ar, CH), 127.4 (Ar, CH), 126.5 (Ar, CH ×2), 67.2 (CH_2), 66.4 (C), 64.2 (CH_2), 52.9 (CH), 39.7 (CH_2), 21.0 (Me). IR ($CHCl_3$) cm^{-1}: 1740. MS (FAB) *m*/*z*: 312 [$(M+1)^+$]. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.96; H, 6.74; N, 4.24.

*4.4.9. (4R,αS)-4-(3,4-Dichlorobenzyl)-4-hydroxymethyl-3-(α-methylbenzyl)-2-oxazolidinone [(4R)-**5b**].* Colorless needle, mp 159–160 °C (AcOEt). $[\alpha]_D^{21}$ −108 (*c* 0.9, MeOH). ^1H NMR (400 MHz, CD_3OD) *δ*: 7.56 (2H, d, *J*=7.2 Hz, Ar), 7.26–7.83 (4H, m, Ar), 7.06 (1H, d, *J*=2.0 Hz, Ar), 6.81 (1H, dd, *J*=8.0, 2.0 Hz, Ar), 4.75 (1H, q, *J*=7.2 Hz, PhC*H*), 4.10 (1H, d, *J*=8.8 Hz, COC*H*H), 3.89 (1H, d, *J*=8.8 Hz, COCH*H*), 3.70 (1H, dd, *J*=7.2, 4.0 Hz, HOC*H*H), 3.62 (1H, dd, *J*=7.2, 4.0 Hz, HOCH*H*), 3.00 (1H, d, *J*=9.6 Hz, PhC*H*H), 2.74 (1H, d, *J*=9.6 Hz, PhCH*H*), 2.10 (1H, t, *J*=4.0 Hz, OH), 1.88 (3H, d, *J*=7.2 Hz, Me). ^{13}C NMR (100 MHz, CD_3OD) *δ*: 157.1 (C=O), 142.2 (Ar, C), 134.6 (Ar, C), 132.5 (Ar, C), 131.8 (Ar, CH), 131.5 (Ar, C), 130.3 (Ar, CH), 129.2 (Ar, CH), 128.7 (Ar, CH ×2), 127.6 (Ar, CH), 127.2 (Ar, CH ×2), 67.7 (NCBn), 65.7 (OCH_2C), 64.5 ($HOCH_2C$), 52.9 (PhCHN), 39.3 ($PhCH_2$), 20.1 (Me). IR ($CHCl_3$) cm^{-1}: 1700. MS (FAB) (Magic bullet) *m*/*z*: 380 [$(M+1)^+$]. HRMS (FAB) (Magic bullet) calcd for $C_{19}H_{20}NO_3Cl_2$: 380.0822. Found: 380.0828. Anal. Calcd for $C_{19}H_{19}Cl_2NO_3$: C, 60.01; H, 5.04; N, 3.68. Found: C, 59.96; H, 5.13; N, 3.49.

*4.4.10. (4S,αS)-4-(3,4-Dichlorobenzyl)-4-hydroxymethyl-3-(α-methylbenzyl)-2-oxazolidinone [(4S)-**6b**].* Colorless needle, mp 127–128 °C. $[\alpha]_D^{22}$ −23.5 (*c* 0.8, MeOH). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.57 (2H, d, *J*=7.2 Hz, Ar), 7.29–7.43 (5H, m, Ar), 7.08 (1H, dd, *J*=8.0, 2.0 Hz, Ar), 4.46 (1H, q, *J*=6.8 Hz, PhC*H*), 4.15 (1H, d, *J*=8.8 Hz, COC*H*H), 4.02 (1H, d, *J*=8.8 Hz, COCH*H*), 3.54 (1H, d, *J*=12.0 Hz, HOC*H*H), 3.33 (1H, d, *J*=12.0 Hz, HOCH*H*), 3.00 (1H, d, *J*=14.0 Hz, PhC*H*H), 2.89 (1H, d, *J*=14.0 Hz, PhCH*H*), 1.89 (3H, d,

J=6.8 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.0 (C=O), 143.1 (Ar, C), 134.4 (Ar, C), 132.8 (Ar, C), 131.9 (Ar, CH), 131.8 (Ar, C), 130.6 (Ar, CH), 129.2 (Ar, CH ×3), 128.0 (Ar, CH), 126.5 (Ar, CH ×2), 67.0 (OCH_2), 66.1 (N*C*CH_2Ar), 64.3 (OCH_2), 53.1 (N*C*HPh), 38.4 (*C*H_2Ar), 21.1 (Me). IR ($CHCl_3$) cm^{-1}: 1740, 1205, 1060. MS (FAB) m/z: 380 [(M+1)$^+$]. HRMS (FAB) m/z: calcd for $C_{19}H_{20}NO_3$ (M+1): 380.0820. Found: 380.0817.

*4.4.11. (4S,αR)-4-(4-Bromobenzyl)-4-hydroxymethyl-3-(α-methylbenzyl)-2-oxazolidinone [(4S)-**5c**].* Colorless needles, mp 197–198 °C. $[\alpha]_D^{24}$ −85.9 (c 0.3, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.56 (2H, d, J=7.6 Hz, Ar), 7.32–7.36 (3H, m, Ar), 7.28 (2H, d, J=8.0 Hz, Ar), 6.85 (2H, d, J=8.0 Hz, Ar), 4.70 (1H, q, J=6.8 Hz, PhC*H*), 4.23 (1H, d, J=8.8 Hz, COC*H*H), 4.02 (1H, d, J=8.8 Hz, COCH*H*), 3.82 (1H, d, J=11.2 Hz, HOC*H*H), 3.55 (1H, d, J=11.2 Hz, HOCH*H*), 2.89 (1H, d, J=13.9 Hz, ArC*H*H), 2.78 (1H, d, J=13.9 Hz, ArCH*H*), 1.84 (3H, d, J=6.8 Hz, Me). ^{13}C NMR (100 MHz, CD_3OD) δ: 159.7 (C=O), 144.1 (Ar, C), 135.3 (Ar, C), 133.0 (Ar, CH ×2), 132.2 (Ar, CH ×2), 129.3 (Ar, CH ×2), 128.5 (Ar, CH ×2), 128.2 (Ar, CH), 121.8 (Ar, C), 69.4 (OCH_2), 67.5 (N*C*H_2Ar), 64.6 (HO*C*H_2), 53.5 (Ph*C*HN), 40.0 (Ar*C*H_2), 20.2 (Me). IR (KBr) cm^{-1}: 1700. MS (FAB) m/z: 390 [(M+1)$^+$]. HRMS (FAB) m/z: calcd for $C_{19}H_{21}BrNO_3$: 390.0705. Found: 390.0706.

*4.4.12. (4R,αR)-4-(4-Bromobenzyl)-4-hydroxymethyl-3-(α-methylbenzyl)-2-oxazolidinone [(4R)-**6c**].* Colorless crystals, mp 128–130 °C. $[\alpha]_D^{21}$ −1.4 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (2H, d, J=7.1 Hz, Ar), 7.48 (2H, dt, J=6.6, 1.7 Hz, Ar), 7.37 (2H, m, Ar), 7.28–7.33 (1H, m, Ar), 7.11 (2H, dt, J=8.3, 1.7 Hz, Ar), 4.45 (1H, q, J=7.1 Hz, PhC*H*), 4.17 (1H, d, J=8.8 Hz, OC*H*H), 4.02 (1H, d, J=8.8 Hz, OCH*H*), 3.56 (1H, dd, J=12.2, 4.2 Hz, HOC*H*H), 3.31 (1H, dd, J=12.2, 8.8 Hz, HOCH*H*), 3.00 (1H, d, J=13.9, ArC*H*H), 2.89 (1H, d, J=14.2 Hz, ArCH*H*), 1.87 (3H, d, J=7.1 Hz, Me), 1.15 (1H, dd, J=8.8, 4.2 Hz, OH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 157.1 (C=O), 143.1 (C, Ar), 133.2 (C, Ar), 131.8 (CH ×2, Ar), 131.6 (CH ×2, Ar), 129.1 (CH_2 ×2, Ar), 128.0 (CH, Ar), 126.5 (CH_2 ×2), 121.5 (C, Ar), 67.0 (OCH_2), 66.1 (C), 64.2 (OCH_2), 53.0 (CH), 38.9 (CH_2), 21.1 (Me). IR (KBr) cm^{-1}: 3438, 1721. MS (FAB) m/z: 390 [(M+1)$^+$]. HRMS (FAB) m/z: calcd for $C_{19}H_{21}BrNO_3$ (M+1): 390.0705. Found: 390.0703.

4.5. Debenzylation of 5a–c

*4.5.1. (S)-4-Benzyl-4-hydroxymethyl-2-oxazolidinone [(S)-**15a**].* Trifluoromethanesulfonic acid (462 mg, 3.08 mmol) was added to a mixture of 2-oxazolidinone (4*S*)-**5a** (640 mg 2.06 mmol) and anisole (1.15 g, 10.3 mmol) in $MeNO_2$ (20.5 mL). After the mixture was stirred for 6 h at 50 °C, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2. The extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue (1.1 g) was purified with silica gel column chromatography (AcOEt) to give (*S*)-**15a** (358 mg, 84%, >99% ee detected by HPLC). Colorless needles, mp 118–121 °C. $[\alpha]_D^{26}$ −24.3 (c 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23–7.33 (4H, m, Ar), 7.18–7.20 (2H, m, Ar), 6.40 (1H, s, NH), 4.25 (1H, d, J=8.8 Hz, COC*H*H), 4.20 (1H, d, J=8.8 Hz, COCH*H*), 3.56 (1H, d, J=11.5 Hz, HOC*H*H), 3.47 (1H, d, J=11.7 Hz, HOCH*H*), 2.93 (1H, d, J=13.9 Hz, PhC*H*H), 2.84 (1H, d, J=13.7 Hz, PhCH*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7 (C=O), 134.5 (Ar, C), 130.1 (Ar, CH ×2), 128.6 (Ar, CH ×2), 127.2 (Ar, CH), 71.0 (OCH_2), 65.7 (OCH_2), 62.2 (N*C*Bn), 41.3 (Ph*C*H_2). IR (KBr) cm^{-1}: 1750. MS (FAB) m/z: 208 [(M+1)$^+$]. HRMS (FAB) m/z: calcd for $C_{11}H_{14}NO_3$: 208.0974. Found: 208.0969. HPLC conditions: Chiralcel OD-H column eluted with hexane/2-propanol (7:3) at 0.5 mL/min using UV detector at 254 nm. Retention time: t_R=13.1 min and t_S=15.1 min.

*4.5.2. (R)-4-Benzyl-4-hydroxymethyl-2-oxazolidinone [(R)-**15a**].* Oxazolidinone (*R*)-**15a** (226 mg, 68%, >99% ee detected by HPLC) was synthesized from (4*R*)-**5a** (500 mg, 1.60 mmol) using trifluoromethanesulfonic acid (240 mg, 1.60 mmol) and anisole (894 mg, 8.00 mmol) in $MeNO_2$ (8.0 mL) according to the method described in 4.5.1. $[\alpha]_D^{30}$ +25.4 (c 0.7, $CHCl_3$).

*4.5.3. (R)-4-(3,4-Dichlorobenzyl)-4-hydroxymethyl-2-oxazolidinone [(R)-**15b**].* Oxazolidinone (*R*)-**15b** (213 mg, 98%) was obtained from (4*R*)-**5b** (300 mg 0.79 mmol) according to the procedure described in 4.5.1; colorless powder, mp 128–130 °C. $[\alpha]_D^{25}$ +30.5 (c 0.7, EtOH). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.43–7.46 (2H, m, Ar), 7.19–7.21 (1H, m, Ar), 4.26 (1H, d, J=9.2 Hz, COC*H*H), 4.15 (1H, d, J=9.2 Hz, COCH*H*), 3.54 (1H, d, J=11.2 Hz, HOC*H*H), 3.50 (1H, d, J=11.2 Hz, HOCH*H*), 2.89 (1H, d, J=14.0 Hz, ArC*H*H), 2.80 (1H, d, J=14.0 Hz, ArCH*H*). ^{13}C NMR (100 MHz, CD_3OD) δ: 161.2 (C=O), 137.4 (Ar, C), 133.3 (Ar, CH), 132.9 (Ar, C), 131.8 (Ar, C), 131.2 (Ar, CH), 131.1 (Ar, CH), 71.4 (OCH_2), 66.8 (OCH_2), 63.1 (N*C*CH_2Ar), 40.5 (Ar*C*H_2). IR ($CHCl_3$) cm^{-1}: 1720. MS (FAB) m/z: 276 [(M+1)$^+$]. HRMS (FAB) m/z: calcd for $C_{11}H_{12}Cl_2NO_3$: 276.0194. Found: 276.0195.

*4.5.4. (S)-4-(4-Bromobenzyl)-4-hydroxymethyl-2-oxazolidinone [(S)-**15c**].* Oxazolidinone (*S*)-**15c** (0.89 g, 83%) was obtained from (4*S*)-**5c** (1.48 g, 3.79 mmol) according to the procedure described in 4.5.1; colorless powder, mp 149–151 °C. $[\alpha]_D^{26}$ −36.1 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.46 (2H, d, J=8.4 Hz, Ar), 7.19 (2H, d, J=8.4 Hz, Ar), 4.24 (1H, d, J=11.2 Hz, COC*H*H), 4.15 (1H, d, J=11.2 Hz, COCH*H*), 3.54 (1H, d, J=7.2 Hz, HOC*H*H), 3.49 (1H, d, J=7.2 Hz, HOCH*H*), 2.87 (1H, d, J=14.0 Hz, ArC*H*H), 2.79 (1H, d, J=14.0 Hz, ArCH*H*). ^{13}C NMR (100 MHz, CD_3OD) δ: 161.3 (C=O), 135.8 (Ar, C), 133.3 (Ar, CH ×2), 132.3 (Ar, CH ×2), 121.8 (Ar, C), 71.4 (OCH_2), 66.9 (OCH_2), 63.2 (N*C*CH_2Ar), 40.9 (Ar*C*H_2). IR (KBr) cm^{-1}: 1760. MS (FAB) m/z: 276 [(M+1)$^+$]. HRMS (FAB) m/z: calcd for $C_{11}H_{13}BrNO_3$: 286.0079. Found: 286.0075.

4.6. Tosylation of 15a–c

*4.6.1. (S)-(4-Benzyl-2-oxazolidinon-4-yl)methyl p-toluenesulfonate [(S)-**16a**].* *p*-Toluenesulfonyl chloride (400 mg, 2.10 mmol) was added to a solution of 2-oxazolidinone (*R*)-**15a** (175 mg, 0.84 mmol) in pyridine (2.1 mL) at 0 °C. The reaction mixture was stirred for 6 h at room temperature. Pyridine was removed in vacuo. The residue was dissolved in CH_2Cl_2, and washed with 10% HCl aq. The aqueous layer was extracted twice with CH_2Cl_2. The extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt, 1:1) to give (*S*)-**16a** (268 mg, 88%). Colorless amorphous foam. $[\alpha]_D^{22}$ +29.3 (c 0.2, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (2H, d, J=8.2 Hz, Ar), 7.38 (2H, d, J=8.2 Hz, Ar), 7.28 (3H, m, Ar), 7.09 (2H, m, Ar), 5.50 (1H, s, NH), 4.20 (1H, d, J=9.2 Hz, CO_2C*H*H), 4.15 (1H, d, J=9.2 Hz, CO_2CH*H*), 3.91 (1H, d, J=9.8 Hz, *C*HHOTs), 3.71 (1H, d, J=9.8 Hz, CH*H*OTs), 3.00 (1H, d, J=13.7 Hz, PhC*H*H), 2.89 (1H, d, J=14.0 Hz, PhCH*H*), 2.48 (3H, s, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.7 (C=O), 145.7 (C), 133.4 (C), 132.0 (C), 130.2 (CH ×2), 130.0 (CH ×2), 129.0 (CH ×2), 128.0 (CH ×2), 127.8 (CH), 71.1 (CH_2), 70.3 (CH_2), 59.6 (C), 41.0 (CH_2), 21.7 (Me). IR (film) cm^{-1}: 1770. MS (FAB) m/z: 362 [(M+1)$^+$]. HRMS (FAB) m/z: calcd for $C_{18}H_{20}NO_5S$, 362.1063; found, 362.1061.

*4.6.2. (S)-[4-(3,4-Dichlorobenzyl)-2-oxazolidinon-4-yl]methyl p-toluenesulfonate [(S)-**16b**].* *p*-Toluenesulfonate (*S*)-**16b** (306 mg, 98%) was obtained from (*R*)-**15b** (200 mg, 0.72 mmol) according to the procedure described in 4.6.1; colorless amorphous foam. $[\alpha]_D^{25}$ +2.3 (c 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (2H, d, J=8.4 Hz, Ar), 7.24–7.37 (3H, m, Ar), 6.99 (1H, dd, J=8.4, 1.6 Hz, Ar), 6.82 (1H, d, J=14.4 Hz, Ar), 4.17 (1H, d, J=9.2 Hz, COC*H*H), 4.12 (1H, d, J=9.2 Hz, COCH*H*), 3.96 (1H, d, J=10.0 Hz, TsOC*H*H), 3.88 (1H, d, J=10.0 Hz, TsOCH*H*), 2.94 (1H, d, J=14.0 Hz, ArC*H*H), 2.92 (1H, d, J=14.0 Hz,

ArCH*H*), 2.45 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1 (C=O), 145.5 (Ar, C), 133.7 (Ar, C), 132.5 (Ar, C), 131.9 (Ar, CH), 131.7 (Ar, C), 131.5 (Ar, C), 130.5 (Ar, CH ×2), 130.0 (Ar, CH), 129.4 (Ar, CH), 127.7 (Ar, CH ×2), 70.8 (OCH_2), 70.4 (OCH_2), 59.7 ($NCCH_2Ar$), 39.8 ($ArCH_2$) 21.8 (Me). IR ($CHCl_3$) cm^{-1}: 1800, 1720, 1680, 1600. MS (FAB) *m*/*z*: 430 [(M+1)$^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{18}H_{18}NO_5Cl_2S$: 430.0283. Found: 430.0283.

*4.6.3. (R)-[4-(4-Bromobenzyl)-2-oxazolydinon-4-yl]methyl p-toluenesulfonate [(R)-**16c**].* *p*-Toluenesulfonate (*R*)-**16c** (1.16 g, 95%) was obtained from (*S*)-**15c** (793 mg, 2.77 mmol) according to the procedure described in 4.6.1; colorless amorphous form. $[\alpha]_D^{25}$ +6.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (2H, d, *J*=8.3 Hz, Ar), 7.38–7.41 (4H, m, Ar), 6.98 (1H, d, *J*=8.3 Hz, Ar), 4.16 (1H, d, *J*=9.2 Hz, COC*H*H), 4.14 (1H, d, *J*=9.2 Hz, COCH*H*), 3.89 (1H, d, *J*=14.0 Hz, TsOC*H*H), 3.84 (1H, d, *J*=14.0 Hz, TsOCH*H*), 2.96 (1H, d, *J*=13.9 Hz, ArC*H*H), 2.85 (1H, d, *J*=13.9 Hz, ArCH*H*), 2.48 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4 (C=O), 145.7 (Ar, C), 132.2 (Ar, C), 132.0 (Ar, CH ×2), 131.7 (Ar, C), 131.5 (Ar, CH ×2), 130.1 (Ar, CH ×2), 127.9 (Ar, CH ×2), 121.1 (Ar, C), 70.9 (OCH_2), 70.2 (OCH_2), 59.5 ($NCCH_2Ar$), 40.5 ($ArCH_2$) 21.9 (Me). IR (neat) cm^{-1}: 1760, 1370, 1180, 1040. MS (FAB) *m*/*z*: 440 [(M+1)$^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{18}H_{18}BrNO_3$: 440.0167. Found: 440.0181.

*4.6.4. (4R,αR)-4-Benzyl-3-(α-methylbenzyl)-2-oxo-oxazolidin-4-ylmethyl p-toluene-4-sulfonate (**17a**).* *p*-Tolunenesulfonyl chloride (TsCl) (367 mg, 1.93 mmol) was added to a solution of (4*S*)-**5a** (200 mg, 0.644 mol) in pyridine (1.5 mL). The reaction mixture was stirred for four days. After the work up described in 4.6.1, the crude product was purified with silica gel chromatography (hexane/AcOEt, 7:3 then 3:7) to afford **17a** (256 mg, 86%) as colorless solid, mp 118–120 °C. $[\alpha]_D^{19}$ −10.6 (*c* 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (2H, d, *J*=8.3 Hz, Ar), 7.51 (2H, d, *J*=7.1 Hz, Ar), 7.39 (2H, d, *J*=7.8 Hz, Ar), 7.34 (2H, t, *J*=7.3 Hz, Ar), 7.27–7.29 (1H, m, Ar), 7.18–7.24 (3H, m, Ar), 6.93–6.95 (2H, m, Ar), 4.53 (1H, q, *J*=7.1 Hz, PhC*H*), 4.21 (1H, d, *J*=9.3 Hz, OC*H*H), 4.11 (1H, d, *J*=10.3 Hz, OC*H*H), 3.98 (1H, d, *J*=10.3 Hz, OCH*H*), 3.69 (1H, d, *J*=9.3 Hz, OCH*H*), 3.09 (1H, d, *J*=13.7 Hz, PhC*H*H), 2.75 (1H, d, *J*=PhCH*H*), 2.48 (3H, s, Me), 1.78 (3H, d, *J*=7.1 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.2 (C=O), 145.6 (C, Ar), 142.1 (C, Ar), 133.0 (C, Ar), 131.8 (C, Ar), 130.0 (CH ×2), 129.7 (CH ×2), 128.8 (CH ×2), 128.5 (CH ×2), 127.8 (CH ×2), 127.6 (CH, Ar), 127.5 (CH, Ar), 127.1 (CH ×2, Ar), 69.5 (OCH_2), 67.8 (OCH_2), 63.9 (C), 53.1 (CH), 40.5 (CH_2), 21.9 (Me), 20.0 (Me). IR (KBr) cm^{-1}: 2360, 1761, 1446, 1413, 1371, 1270, 1189, 1096. MS (FAB) *m*/*z*: 466 [(M+1)$^+$], 312, 208, 105. HRMS (FAB) *m*/*z*: calcd for $C_{26}H_{27}NO_5S$: 466.1689. Found: 466.1679. Anal. Calcd for $C_{26}H_{27}NO_5S$: C, 67.08; H, 5.85; N, 3.01. Found: C, 67.06; H, 6.03; N, 2.97.

*4.6.5. (4S,αR)-4-Benzyl-3-(α-methylbenzyl)-2-oxo-oxazolidin-4-ylmethyl methanesulfonate (**17b**).* Methanesulfonyl chloride (MsCl) (1.93 mmol, 221 mg) was added to a solution of oxazolidinone (4*S*)-**5a** (200 mg, 0.644 mmol) in pyridine (1.5 mL) at 0 °C. After being stirred 15 h at room temperature, the reaction mixture was diluted with AcOEt and washed with water, 10% hydrochloric acid, saturated aqueous $NaHCO_3$, and brine, consequently. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt, 3:7) to afford **17b** (223 mg, 89%). Colorless solid, mp 137–142 °C. $[\alpha]_D^{19}$ −11.4 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (2H, d, *J*=7.8 Hz, Ar), 7.36 (2H, t, *J*=7.1 Hz, Ar), 7.25–7.31 (4H, m, Ar), 6.98–7.31 (4H, m, Ar), 4.57 (1H, q, *J*=7.1 Hz, PhC*H*), 4.32 (d, *J*=10.7 Hz, OC*H*H), 4.30 (1H, d, *J*=10.7 Hz, OC*H*H), 4.13 (d, *J*=10.5 Hz, OCH*H*), 3.96 (d, *J*=9.3 Hz, OCH*H*), 3.08 (3H, s, SO_2Me), 3.04 (1H, d, *J*=13.7 Hz, PhC*H*H), 2.85 (1H, d, *J*=13.9 Hz, PhCH*H*), 1.91 (3H, d, *J*=7.1 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.5 (C=O), 141.9 (C, Ar), 132.8 (C, Ar), 129.6 (CH ×2, Ar), 128.9 (CH ×2, Ar), 128.6 (CH ×2, Ar), 127.8 (CH, Ar), 127.6 (CH, Ar), 127.0 (CH ×2, Ar), 68.1 (OCH_2), 67.7 (OCH_2), 64.1 (C), 52.9 (CH), 41.2 (CH_2), 38.0 (Me), 20.1 (Me). IR (KBr) cm^{-1}: 2360, 1749, 1456, 1419. MS (FAB) *m*/*z*: 390 [(M+1)$^+$], 286, 105. HRMS (FAB) *m*/*z*: calcd for $C_{20}H_{23}NO_5S$: 390.1376. Found 390.1383. Anal. Calcd for $C_{20}H_{23}NO_5S$: C, 61.68; H, 5.95; N, 3.60. Found: C, 61.12; H, 5.88; N, 3.50.

*4.6.6. (4S)-4-Benzyl-2-oxo-oxazolidin-4-ylmethyl p-toluene-4-sulfonate [(R)-**16a**].* TfOH (31 μL, 0.35 mmol) was added to a mixture of tosylate **17a** (163 mg, 0.351 mmol) and anisole (190 mg, 1.76 mmol) in $MeNO_2$ (1.8 mL) at room temperature. The resulting mixture was stirred for 1 h at 100 °C. After being cooled to room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. 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 (*R*)-**16a** as a colorless amorphous foam (115 mg, 91%). $[\alpha]_D^{21}$ −32.6 (*c* 0.8, MeOH).

*4.6.7. (4S)-4-Benzyl-2-oxo-oxazolidin-4-ylmethyl methanesulfonate [(R)-**16d**].* Mesylate (*R*)-**16d** (84.2 mg, 87%) was synthesized from mesylate **17b** (132 mg, 0.34 mmol) according to the procedure from **17a** to (*R*)-**16a**. Colorless solid, mp 170–175 °C. $[\alpha]_D^{24}$ −31.8 (*c* 0.2, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.32–7.35 (2H, m, Ar), 7.26–7.29 (3H, m, Ar), 4.27 (1H, d, *J*=9.3 Hz, OC*H*H), 4.25 (1H, d, *J*=10.5 Hz, OC*H*H), 4.24 (1H, d, *J*=9.3 Hz, OCH*H*), 4.22 (1H, d, *J*=10.5 Hz, OCH*H*), 3.15 (3H, s, Me), 2.99 (1H, d, *J*=13.9 Hz, PhC*H*H), 2.89 (1H, d, *J*=13.9 Hz, PhCH*H*). ^{13}C NMR (100 MHz, CD_3OD) δ: 135.4 (C, Ar), 131.4 (CH ×2, Ar), 129.4 (CH ×2, Ar), 128.2 (CH, Ar), 73.1 (OCH_2), 70.8 (OCH_2), 61.5 (C), 41.4 (CH_2), 37.3 (Me). IR (KBr) cm^{-1}: 3354, 3026, 2936, 1752, 1351, 1179, 1036, 999. MS (FAB) *m*/*z*: 286 [(M+1)$^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{12}H_{16}NO_5S$: 286.0750. Found: 286.0753. Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91. Found: C, 50.63; H, 5.59; N, 4.64.

4.7. Synthesis of (*R*)-α-(hydroxymethyl)phenylalanine (7)

*4.7.1. (R)-(4-Benzyl-2-oxo-4-oxazolidine)carboxylic acid (**18**).* $RuCl_3 \cdot nH_2O$ (9.9 mg) and $NaIO_4$ (1.52 g, 7.09 mmol) were added to a stirred mixture of 2-oxazolidinone (*S*)-**15a** (358 mg, 1.73 mmol) in CCl_4/MeCN/H_2O[16] (2:2:3, 17 mL). The mixture was stirred vigorously at room temperature for 5 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue (372 mg) was purified with silica gel column chromatography (AcOEt) to give **18** (187 mg, 49%). Colorless needles, mp 201–203 °C. $[\alpha]_D^{17}$ −14.1 (*c* 0.4, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.30 (5H, m, Ar), 4.55 (1H, d, *J*=9.3 Hz, OC*H*H), 4.31 (1H, d, *J*=9.0 Hz, OCH*H*), 3.20 (1H, d, *J*=13.7 Hz, PhC*H*H), 13.9 (1H, d, *J*=13.9 Hz, PhCH*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.8 (C=O), 151.0 (C=O), 125.9 (Ar, C), 121.7 (Ar, CH ×2), 119.8 (Ar, CH ×2), 118.7 (Ar, CH), 64.2 (OCH_2), 56.5 (NCBn), 33.7 ($PhCH_2$). IR ($CHCl_3$) cm^{-1}: 1750, 1600. MS (EI) *m*/*z*: 221 (M$^+$, 4.8%), 175 (3.4), 130 (4.4), 91 (100). HRMS (EI) *m*/*z*: calcd for $C_{11}H_{11}NO_4$: 221.0688. Found: 221.0693.

*4.7.2. (R)-2-Amino-3-hydroxy-2-benzylpropionic acid [(R)-α-(hydroxymethyl)phenylalanine] (**7**).* A solution of 2-oxazolidinone **18** (101 mg, 0.46 mmol) in 6 mol/L HCl aq (4.6 mL) was refluxed for 12 h. The reaction mixture was concentrated. The residue was diluted with H_2O and washed three times with CH_2Cl_2. The aqueous layer was concentrated in vacuo to give a residue (100 mg). The residue (77.0 mg) was purified through a DOWEX 50 W–X8 (100–200 mesh) column eluting with 5% aqueous ammonia to give a pure **7** (65.0 mg, 84%). Colorless powder, mp 261–263 °C (decompose). $[\alpha]_D^{21}$ −16.4 (*c* 1.0, H_2O) {(S)-form,[9b] $[\alpha]_D^{20}$ +16.4 (*c* 0.89,

H_2O)}. ^1H NMR (400 MHz, D_2O) δ: 7.37–7.42 (3H, m, Ar), 7.27 (2H, d, J=6.8 Hz, Ar), 4.05 (1H, d, J=12.0 Hz, OC*H*H), 3.78 (1H, d, J=12.0 Hz, OCH*H*), 3.26 (1H, d, J=14.2 Hz, C*H*HPh), 2.97 (1H, d, J=14.4 Hz, CH*H*Ph). ^{13}C NMR (100 MHz, D_2O) δ: 173.6 (C=O), 133.8 (Ar, C), 130.2 (Ar, CH), 129.2 (Ar, CH ×2), 128.1 (Ar, CH ×2), 67.4 (NCPh) 64.5 (OCH_2), 38.3 (CH_2Ph). MS (FAB) m/z: 196 [$(M+1)^+$]. HRMS (FAB) m/z: calcd for $C_{10}H_{14}NO_3$: 196.0974. Found: 196.0966.

4.8. Synthesis of *N*-Boc-α-methylphenylalanine (8)

*4.8.1. (S)-4-Benzyl-4-methyl-2-oxazolidinone [(S)-**19**].* $NaBH_4$ (40.9 mg, 1.08 mmol) was added to a solution of oxazolidinone (*S*)-**16a** (196 mg, 0.54 mmol) in DMSO (1.4 mL), and the mixture was stirred for 3 h at 100 °C.[17] After cooling to rt, the reaction mixture was diluted with Et_2O and washed with 10% HCl aq. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt, 1:1) to give (*S*)-**19** (74.1 mg, 71%). Colorless plate, mp 82–86 °C. $[\alpha]_D^{26}$ +28.2 (*c* 0.3, EtOH). {(*R*)-form,[18] $[\alpha]_D^{25}$ −28.8 (*c* 1.548, EtOH)}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.92–7.37 (3H, m, Ar), 7.17–7.24 (2H, m, Ar), 5.66 (1H, br s, NH), 4.28 (1H, d, J=8.4 Hz, COC*H*H), 4.07 (1H, d, J=8.4 Hz, COCH*H*), 2.90 (1H, d, J=13.4 Hz, PhC*H*H), 2.83 (1H, d, J=13.4 Hz, PhCH*H*), 1.32 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5 (C=O), 135.1 (Ar, C), 130.0 (Ar, CH ×2), 128.5 (Ar, CH ×2), 127.1 (Ar, CH), 75.3 (OCH2), 58.1 (NCPh), 46.3 ($PhCH_2$), 27.9 (Me). IR ($CHCl_3$) cm^{-1}: 1720, 1695, 1390. MS (EI) m/z: 191 (M^+, 0.5%), 100 [$(M-Bn)^+$, 100], 91 (16), 56 (28). HRMS (EI) m/z: calcd for $C_{11}H_{13}NO_2$, 191.0947; found, 191.0951.

*4.8.2. (R)-4-Benzyl-4-methyl-2-oxazolidinone [(R)-**19**].* Reductive demesylation of (*R*)-**16d** (61.3 mg, 0.215 mmol) was carried out according to the procedure described in 4.8.1 to afford (*R*)-**19** (35.3 mg, 86%). $[\alpha]_D^{26}$ −22.7 (*c* 0.7, EtOH).

*4.8.3. (S)-4-Benzyl-3-tert-butoxycarbonyl-4-methyl-2-oxazolidinone [(S)-**20**].* A mixture of oxazolidinone (*S*)-**19** (74.1 mg, 0.39 mmol), Boc_2O (0.77 g, 3.51 mmol), triethylamine (118 mg, 1.17 mmol) and DMAP (24.4 mg, 0.20 mmol) in THF (0.78 mL) was stirred for 3.5 h at room temperature. The reaction mixture was diluted with water and extracted with AcOEt twice. The extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt, 3:2) to give (*S*)-**20** (94.0 mg, 83%). Colorless oil. $[\alpha]_D^{28}$ +65.2 (*c* 1.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.33–7.26 (3H, m, Ar), 7.16–7.14 (2H, m, Ar), 4.27 (1H, d, J=8.6 Hz, OC*H*H), 3.77 (1H, d, J=8.9 Hz, OCH*H*), 3.32 (1H, d, J=13.7 Hz, PhC*H*H), 2.96 (1H, d, J=13.7 Hz, PhCH*H*), 1.61 (9H, s, ^{t}Bu), 1.59 (3H, s, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.4 (C=O), 149.8 (C=O), 135.0 (C), 130.0 (CH ×2), 128.8 (CH ×2), 127.5 (CH), 83.9 (C), 71.1 (CH_2), 62.3 (C), 42.8 (CH_2), 28.2 (Me ×3), 24.7 (Me). IR ($CHCl_3$) cm^{-1}: 1810, 1730, 1350, 1330, 1170, 1090. MS (FAB) m/z: 292 [$(M+1)^+$]. HRMS (FAB) m/z: calcd for $C_{16}H_{22}NO_4$, 292.1550; found, 292.1540.

*4.8.4. (S)-2-(tert-Butoxycarbonyl)amino-2-methyl-3-phenylpropan-1-ol (**21**).* To a solution of *N*-Boc-oxazolidinone **20** (82.5 mg, 0.28 mmol) in MeOH (2.8 mL) was added Cs_2CO_3 (45.6 mg, 0.14 mmol) at room temperature,[19] and the resulting mixture was stirred for 4 h. After the neutralization with saturated aqueous citric acid, the product was extracted with AcOEt three times. The extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with silica gel column chromatography (hexane/AcOEt, 4:1) to give **21** (58.4 mg, 78%). Colorless needle, mp 65–67 °C. $[\alpha]_D^{28}$ −72.4 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.21–7.19 (5H, m, Ar), 4.20 (1H, br s, NH), 3.69 (2H, s, CH_2O), 3.18 (1H, d, J=13.4 Hz, PhC*H*H), 2.80 (1H, d, J=13.6 Hz, PhCH*H*), 1.47 (9H, s, ^{t}Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 156.0 (C=O), 136.8 (C), 130.5 (CH ×2), 128.0 (CH ×2), 126.4 (CH), 79.9 (C), 69.8 (CH_2), 57.3 (C), 41.1 (CH_2), 28.5 (Me ×3), 23.3 (Me). IR ($CHCl_3$) cm^{-1}: 1700, 1500, 1370, 1160. MS (FAB) m/z: 266 [$(M+1)^+$]. HRMS (FAB) m/z: calcd for $C_{15}H_{24}NO_3$, 266.1757; found, 266.1756.

*4.8.5. (S)-N-Boc-α-methylphenylalanine (**8**).* To a solution of *N*-Boc-aminoalcohol **21** (47.8 mg, 0.18 mmol) in CCl_4/MeCN/H_2O (2:2:3, 0.91 mL) was added $NaIO_4$ (158 mg, 0.74 mmol) and $RuCl_3 \cdot nH_2O$ (1.1 mg) under stirring vigorously at room temperature for 8 h. The reaction mixture was diluted with AcOEt, washed with water. The aqueous layer was extracted with AcOEt twice. The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with silica gel column chromatography ($CHCl_3$) to give **8** (24.3 mg, 48%, >99% ee detected by HPLC). Colorless powder, mp 119–121 °C, $[\alpha]_D^{27}$ +12.6 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.24–7.27 (3H, m, Ar), 7.14 (2H, d, J=6.79 Hz, Ar), 5.08 (1H, br, s, NH), 3.30 (2H, s, $ArCH_2$), 1.56 (3H, s, Me), 1.47 (9H, s, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2 (C=O), 154.7 (C=O), 135.9 (Ar, C), 130.1 (Ar, CH ×2), 128.1 (Ar, CH ×2), 126.8 (Ar, CH), 71.9 (*t*-Bu, C), 60.3 (NCBn), 41.4 ($PhCH_2$), 28.5 (*t*-Bu, Me ×3), 23.7 (Me). IR ($CHCl_3$) cm^{-1}: 3440, 2950, 1720, 1500, 1460, 1380, 1180. MS (FAB) m/z: 280 [$(M+1)^+$]. HRMS (FAB) m/z: calcd for $C_{15}H_{21}NO_4$: 280.1549. found: 280.1540. HPLC conditions: Chiralcel OD-H column eluted with hexane/2-propanol/trifluoroacetic acid (90:10:0.1) at 0.5 mL/min using UV detector at 254 nm. Retention time: t_R=8.1 min and t_S=9.3 min. (*RS*)-*N*-Boc-α-methylphenylalanine was synthesized from (*RS*)-α-methylphenylalanine (Aldrich) and used for the HPLC analysis.

4.9. Synthesis of cericlamine (9)

*4.9.1. (S)-3-(3,4-Dichlorophenyl)-2-methyl-2-methylamino-1-propanol (**22**).* $LiAlH_4$ (71.1 mg, 1.78 mmol) was added carefully to a solution of the oxazolidinone (*S*)-**16b** (255 mg, 0.59 mmol) in Et_2O (3.0 mL, 0.2 mol/L) with cooling by use of an ice bath.[18] The mixture was refluxed for 3 h. After cooling, H_2O/THF (1:1, 142 μL) was added dropwise carefully, and 15% NaOH aq (70 μL) and then water (105 μL) were added to the mixture successively. The resulting mixture was stirred for 2 h at room temperature and filtered through a glass filter. The solid was washed with Et_2O. The filtrate was extracted three times with 10% HCl aq. The aqueous layers were combined, made basic (pH=ca. 11) with sodium hydroxide and extracted three times with Et_2O. The organic extracts were combined, washed twice with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$/MeOH, 7:3) to give a pure **22** (92.8 mg, 63%); colorless powder, mp 111–112 °C. $[\alpha]_D^{22}$ +3.5 (*c* 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35 (1H, d, J=8.3 Hz, Ar), 7.28 (1H, d, J=2.0 Hz, Ar), 7.03 (1H, dd, J=8.3, 2.0 Hz, Ar), 3.30 (1H, d, J=10.7 Hz, C*H*HOH), 3.24 (1H, d, J=10.7 Hz, CH*H*OH), 2.69 (1H, d, J=13.2 Hz, C*H*HAr), 2.63 (1H, d, J=13.2 Hz, CH*H*Ar), 2.36 (3H, s, NMe), 0.98 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.7 (Ar, C), 132.0 (Ar, CH), 131.9 (Ar, C), 130.3 (Ar, C), 129.9 (Ar, CH), 129.7 (Ar, CH), 65.0 ($HOCH_2$), 56.8 ($NCCH_2Ar$), 41.2 ($ArCH_2$), 28.2 (NMe), 20.3 (Me). IR ($CHCl_3$) cm^{-1}: 2930, 1475, 1135, 1040. MS (FAB) m/z: 248 [$(M+1)^+$]. HRMS (FAB) m/z: calcd for $C_{11}H_{16}Cl_2NO$: 248.0609. Found: 248.0604.

*4.9.2. (S)-3-(3,4-Dichlorophenyl)-2-dimethylamino-2-methyl-1-propanol (cericlamine) (**9**).* To a solution of propanol **22** (68.0 mg, 0.27 mmol) in THF (2.2 mL) were added paraformaldehyde (81.1 mg, 2.70 mmol) and $NaBH_4$ (102 mg, 2.7 mmol).[20] Then a solution of TFA (1.10 mL, 14.3 mmol) in THF (6.5 mL) was added dropwise (10 drops/min) under stirring vigorously at room temperature over 30 min, and the resulting mixture was stirred for 18 h at room temperature. The reaction mixture was diluted with H_2O and made basic with sodium hydroxide. The basic mixture was extracted three times with AcOEt. The extracts were combined, dried over $MgSO_4$, and

concentrated in vacuo. The residue (71.8 mg) was purified with silica gel column chromatography ($CHCl_3$/MeOH, 9:1) to give a pure **9** (62.1 mg, 86%). Colorless powder, mp 65–67 °C. $[\alpha]_D^{16}$ +6.4 (*c* 0.6, EtOH) {Ref., $[\alpha]_D^{22}$ +6.3 (*c* 1.0, EtOH)[10a]}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (1H, d, *J*=8.3 Hz, Ar), 7.27 (1H, d, *J*=2.0 Hz, Ar), 7.05 (1H, dd, *J*=8.3, 2.0 Hz, Ar), 3.28 (1H, d, *J*=10.8 Hz, C*H*HOH), 3.22 (1H, d, *J*=10.8 Hz, CH*H*OH), 2.74 (1H, d, *J*=12.8 Hz, C*H*HAr), 2.64 (1H, d, *J*=12.8 Hz, CH*H*Ar), 2.35 (6H, s, NMe_2), 0.89 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.2 (Ar, C), 132.1 (Ar, CH), 131.8 (Ar, C), 130.3 (Ar, C), 129.9 (Ar, CH), 129.8 (Ar, CH), 63.9 ($HOCH_2$), 60.5 ($NCCH_2Ar$), 38.4 ($ArCH_2$), 38.1 (NMe_2), 15.8 (Me). IR ($CHCl_3$) cm^{-1}: 2950, 1480, 1140, 1050. MS (FAB) *m*/*z*: 262 [$(M+1)^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{12}H_{18}Cl_2NO$: 262.0765. Found: 262.0760.

4.10. Synthesis of BIRT-377 (10)

*4.10.1. (R)-3-(4-Bromophenyl)-2-methyl-2-methylamino-1-propanol (**23**).* $LiAlH_4$ (297 mg, 7.44 mmol) was added carefully to a solution of the oxazolidinone (*R*)-**16c** (1.09 g, 2.48 mmol) in THF (12.4 mL) with cooling by use of an ice bath.[18] The mixture was refluxed for 3 h. After cooling, H_2O/THF (1:1, 600 μL) was added dropwise carefully, and 15% NaOH aq (300 μL) and then water (450 μL) were added to the mixture successively. The resulting mixture was stirred for 19 h at room temperature and filtered through a glass filter. The solid was washed with AcOEt. The filtrate was washed twice with water. The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue (498 mg) was chromatographed on silica gel ($CHCl_3$/MeOH, 7:3) to give a pure **23** (428 mg, 67%); colorless powder, mp 144–146 °C. $[\alpha]_D^{27}$ −1.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (1H, d, *J*=8.3 Hz, Ar), 7.28 (1H, d, *J*=2.0 Hz, Ar), 7.03 (1H, dd, *J*=8.3, 2.0 Hz, Ar), 3.30 (1H, d, *J*=10.7 Hz, C*H*HOH), 3.24 (1H, d, *J*=10.7 Hz, CH*H*OH), 2.69 (1H, d, *J*=13.2 Hz, C*H*HAr), 2.63 (1H, d, *J*=13.2 Hz, CH*H*Ar), 2.36 (3H, s, NMe), 0.98 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.7 (Ar, C), 132.0 (Ar, CH), 131.9 (Ar, C), 130.3 (Ar, C), 129.9 (Ar, CH), 129.7 (Ar, CH), 65.0 ($HOCH_2$), 56.8 ($NCCH_2Ar$), 41.2 ($ArCH_2$), 28.2 (NMe), 20.3 (Me). IR (neat) cm^{-1}: 2940, 1500, 1420. MS (FAB) *m*/*z*: 258 [$(M+1)^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{11}H_{17}BrNO$: 258.0494. Found: 258.0503.

*4.10.2. (R)-1-(1-(4-Bromophenyl)-3-hydroxy-2-methylpropan-2-yl)-3-(3,5-dichlorophenyl)-1-methylurea (**24**).* Propanol **23** (157 mg, 0.61 mmol) was added portionwise to a stirred solution of sodium hydride (ca. 60% oil suspension, 48.8 mg, ca. 1.22 mmol) in THF (6.1 mL), followed by an addition of 3,5-dichlorophenylisocyanate (239 mg, 1.22 mmol). The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with AcOEt, washed with saturated aqueous NaCl. The aqueous layer was extracted three times with AcOEt. The extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue (290 mg) was chromatographed on silica gel (hexane/AcOEt, 9:1) to give a pure **24** (183 mg, 67%); colorless powder, mp 163–165 °C. $[\alpha]_D^{22}$ +12.2 (*c* 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (1H, d, *J*=8.4 Hz, Ar), 7.25–7.28 (3H, m, Ar), 6.95–6.99 (3H, m, Ar), 3.59 (1H, d, *J*=8.8 Hz, C*H*HOH), 3.31 (1H, d, *J*=9.2 Hz, CH*H*OH), 2.90 (3H, s, *N*-Me), 2.88 (1H, d, *J*=15.2 Hz, C*H*HAr), 2.73 (1H, d, *J*=13.6 Hz, CH*H*Ar), 1.40 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.8 (C=O), 141.7 (Ar, C), 134.8 (Ar, C ×2), 134.2 (Ar, C), 131.6 (Ar, CH ×2), 131.3 (Ar, CH ×2), 121.8 (Ar, CH), 121.3 (Ar, C), 115.2 (Ar, CH ×2), 57.6 ($NCCH_2Ar$), 53.3 ($HOCH_2$), 42.6 ($ArCH_2$), 25.3 (NMe), 24.2 (Me). IR (neat) cm^{-1}: 2940, 1500, 1420. MS (FAB) *m*/*z*: 427 [$(M-H_2O+1)^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{18}H_{18}BrCl_2N_2O$ ($M-H_2O+1$): 426.9980. Found: 426.9979.

*4.10.3. (R)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethylimidazolidine-2,4-dione (BIRT-377) (**10**).* $RuCl_3 \cdot nH_2O$ (1.8 mg) and $NaIO_4$ (62.0 mg, 0.29 mmol) were added to a stirred solution of urea **24** (30.5 mg, 0.07 mmol) in AcOEt/H_2O[21] (5:1, 1.2 mL). The mixture was stirred vigorously at room temperature for 20 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue (32.0 mg) was purified with silica gel column chromatography (hexane/AcOEt, 1:1) to give a pure **12** (16.5 mg, 55%); colorless powder. $[\alpha]_D^{17}$ −133.5 (*c* 0.2, EtOH) {Ref., $[\alpha]_D^{25}$ −134.3 (*c* 1.0, EtOH)[11d]}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (2H, d, *J*=6.4 Hz, Ar), 7.26–7.29 (1H, m, Ar), 6.94 (2H, d, *J*=8.8 Hz, Ar), 6.85 (2H, d, *J*=1.6 Hz, Ar), 3.09 (1H, d, *J*=16.4 Hz, ArC*H*H), 3.07 (3H, s, NMe), 2.97 (1H, d, *J*=14.0 Hz, ArCH*H*), 1.62 (3H, s, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1 (C=O), 153.3 (C=O), 134.9 (Ar, C ×2), 132.9 (Ar, C), 132.7 (Ar, C), 131.7 (Ar CH ×2), 131.0 (Ar, CH ×2), 128.2 (Ar, CH), 124.4 (Ar, CH ×2), 121.9 (Ar, C), 65.7 (*N*CMe), 40.9 (CH_2Ar), 25.5 (NMe), 21.2 (Me). IR ($CHCl_3$) cm^{-1}: 1720. MS (FAB) *m*/*z*: 441 [$(M+1)^+$]. HRMS (FAB) *m*/*z*: calcd for $C_{18}H_{16}BrCl_2N_2O_2$: 440.9772. Found: 440.9780.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.090. These data include MOL files and InChiKeys of the most important compounds described in this article.

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