Synthesis of Optically Active α-Amino Esters via Dynamic Kinetic Resolution: A Mechanistic Study

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Synthesis of N-protected optically active α-amino esters from racemic α-halo esters via dynamic kinetic resolution (DKR) will be described. This methodology is general in nature and provides the desired optically active N-protected amino esters in 70−95% yield with diastereomeric excesses in the range of 85 to >98%. Applications and mechanistic aspects will be discussed.

Introduction

Kinetic resolutions have been known and utilized by synthetic organic chemists for many decades and have found widespread use in the separation of enantiomeric mixtures.[1] While many variations of kinetic resolutions have been reported, they all have one feature in common. In order for such a reaction to be effective, there must exist a significant difference in the rate of reaction of one isomer over the other. Even under such conditions, the maximum yield of the desired isomer (starting from a racemate) is 50%. This aspect tends to make kinetic resolution a costly process since half of the starting material must be discarded or recycled.

In contrast to the above, a dynamic kinetic resolution (DKR) is potentially much more efficient. In a DKR process the slower reacting isomer is converted into the faster one *in situ*. As a result, it is possible in ideal situations to obtain the desired isomer in yields approaching 100%. Reactions of this type are relatively rare in the literature. Several examples have been reported which utilize enzymes.[2] A classic example of DKR not involving enzymes is Noyori's catalytic hydrogenation of 2-substituted-3-keto esters.[3] Classic resolutions under conditions in which one of the diastereomers is converted to the other while one of the diastereomeric salts crystallizes preferentially have also been described.[4]

Several years ago we described a DKR process which was the basis for a synthesis of highly enantiomerically enriched α-amino esters starting from racemic α-halo esters.[5] Since that time, some insight has been gained with respect to the scope, generality and mechanism of this useful reaction through a number of studies. In this paper we describe these findings.

Results and Mechanistic Aspects

Our serendipitous discovery of this DKR process occurred while we were developing a synthesis of *N*-benzylproline derivatives from optically active α-halo-(*R*)-pantolactone esters. As shown, it was anticipated that reaction of **1** with benzylamine would preferentially furnish the desired *N*-benzyl-(*R*)-proline derivative, **3**. In the event, the product, obtained in 78% yield, was a 7:1 mixture of diastereomers in which the major product was **2** possessing the (*S*,*R*) configuration instead of the expected (*R*,*R*) configuration.[6]

There are two possible explanations to account for this unexpected result: (i) the products (**2** and **3**) are not configurationally stable under the reaction conditions, and **2** is significantly more stable than **3**, or (ii) the starting materials are interconverted under the reaction conditions. Since it was shown that **2** and **3** are configurationally stable, the major isomer, **2**, must therefore result from a sequence of two inversion reactions. The first is an inversion of the (*S*,*R*)-diastereomer of **1** into the (*R*,*R*)-diastereomer by bromide released after a small amount of displacement reaction with benzylamine has taken place.[7] The second S_N2 involves reaction of the (*R*,*R*)-diastereomer of **1** with benzylamine to give the major observed product. This displacement reaction is necessarily slower than epimerization of the (*S*,*R*)-**1** to (*R*,*R*)-**1** but more rapid than the conversion of (*S*,*R*)-**1** to **3** with benzylamine (Scheme 1). It should be noted that epimerization of **1** might be catalyzed by triethylamine instead of bromide or iodide ion, but subsequent experiments have shown that **1** is configurationally stable in the presence of triethylamine. The practical consequence of Scheme 1 is that a 1:1 mixture of the diastereomers **1** can lead to enantiomerically pure product **2** in greater than 50% chemical yield. Several examples of this process resulting in the formation of both bicyclic and acyclic α-amino esters in >60% yield and with >98% enantiomeric purity have been reported by us.[5]

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(1) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(2) Meijer, E. M.; Boestan, W. H. J.; Schoemaker, H. E.; Van Blaken, J. A. M. In *Biocatalysis in Organic Synthesis*; Tramper, J., Van der Plas, H. C., Linko, P., Eds.; Elsevier Publishing: Amsterdam, 1985; p 135.

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(5) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.* **1993**, *34*, 4473.

(6) Durst, T.; Koh, K. *Tetrahedron Lett.* **1992**, *33*, 6799.

(7) It has been proposed that the oxygen of the lactone carbonyl may participate in displacement of the bromide. The resulting bicyclic oxonium ion could then undergo reaction with benzylamine to furnish products **2** and **3**. This reaction pathway is not likely since diastereomerically enriched mixtures of products would not be expected or obtained.

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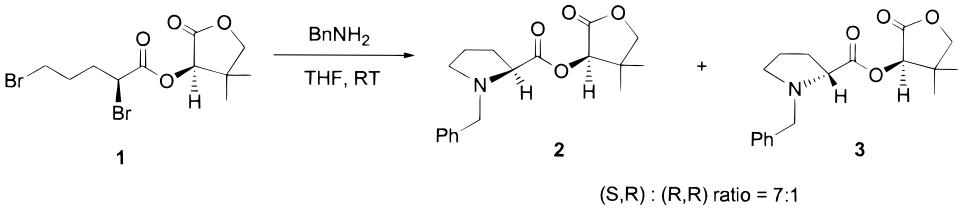
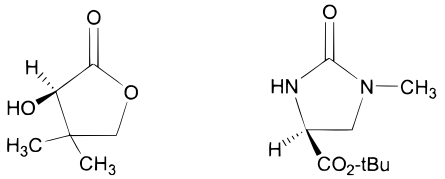
Scheme 1



(A) The Effect of Other Chiral Auxiliaries on Diastereoselectivity. A survey of alternate chiral auxiliaries was undertaken to gain insight into the mechanism of this reaction, to improve product diastereoselectivities, and to increase yields such that this process might become synthetically more useful. The initial auxiliary, (*R*)-pantolactone **4**, has thus far given the best results among all of the alcohol auxiliaries tested. (4*S*)-*tert*-Butyl-1-methyl-2-oxoimidazolidine-4-carboxylate, **5**,

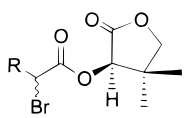


4 **5**

is a superior chiral auxiliary for the S_N2-DKR process involving α-halo acids, giving generally higher ee's than (*R*)-pantolactone. The induced chirality is opposite for these two auxiliaries, and the dynamic aspect of the DKR process using **5** as described by Nunami[8] involves a base-catalyzed isomerization rather than the halide ion induced epimerization described by us. In addition, the preferred conformation of these imides is quite different from that of the (*R*)-pantolactone esters. As a consequence, this system will not be discussed in this paper.

(*R*)-Pantolactone was initially chosen by us because it showed superior diastereofacial selectivity in additions to unsymmetrically substituted ketenes.[9] It is also known to be an efficient chiral auxiliary in a variety of reaction types including the rhodium-catalyzed cyclopropanations[10] and metal-coordinated Lewis acid catalyzed Diels−Alder reactions.[11]

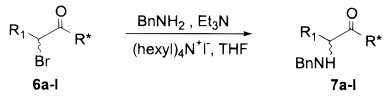
A number of other auxiliaries having the α-hydroxy motif found in (*R*)-pantolactone with the 2-bromobutyrate **6h** or α-bromophenylacetic ester **6i** as probes gave



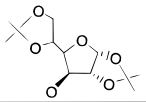
6h R = CH_2CH_3
6i R = Ph

inferior results, Table 1. For example, replacement of the *gem*-dimethyl groups in **4** by either hydrogen or phenyl

Table 1. Effects of Various Chiral Auxiliaries and Side Chain R_1 on Diastereoselectivity[a]



6a-l **7a-l**

entry	R_1	R*	Yield (%)	Diastereomeric Ratio of 7
1	ethyl (**6a**)		60	2:1[b]
2	ethyl (**6b**)		92	2:1[c]
3	ethyl (**6c**)		83	2:1[b]
4	ethyl (**6d**)		75	2:1
5	ethyl (**6e**)		72	1.5:1[c]
6	ethyl (**6f**)		93	3:1
7	phenyl (**6g**)		97	3.5:1
8	ethyl (**6h**)		70	7:1[c]
9	phenyl (**6i**)		85	10:1[c]
10	naphthyl (**6j**)		55	>12:1[c]
11	benzyl (**6k**)		trace	-
12	phenyl (**6l**)		85	5:1

[a] Products **7a**−**l** were shown to be configurationally stable under these reaction conditions. [b] *SR*/*RS* ratio. [c] *SR*/*RR* ratio.

decreased the product diastereoselectivity (entries 5−7). The use of an open chain auxiliary such as methyl-(*S*)-mandelate (entry 1) or a bicycloketo alcohol (entry 4) afforded only a 2:1 product ratio. Chiral alcohols having non-α-carbonyl substituents such as *trans*-2-phenylcyclohexanol (entry 2) or D-glucose diacetonide (entry 3) gave excellent displacement yields but only a 2:1 diastereomeric ratio. Evans' auxiliary, (4*R*)-isopropyl-1,3-oxazolidin-2-one (entry 12), gave a 5:1 diastereomeric ratio when tested with α-bromophenylacetic acid.

(B) Effect of Size Changes in the Nucleophile and the Substrate on the DKR Process. As anticipated for an S_N2 process, an increase in the size of the nucleophile decreased the rate of reaction and also increased the selectivity (Table 2). For example, reaction of the α-bromo ester **6i** (R_1 = phenyl) with dibenzylamine or benzhydrylamine afforded the (*S*)-α-amino-substituted products **8a** and **8c** in 70% and 74% yields, respectively, with greater than 96% de (entries 1 and 3). In contrast, anisidine

(8) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. *J. Org. Chem.* **1997**, *62*, 5830. Kubota, H.; Kubo, A.; Nunami, K. *Tetrahedron Lett.* **1994**, *35*, 3107. Nunami, K.; Kubota, H.; Kubo, A. *Tetrahedron Lett.* **1994**, *35*, 8639. Kubota, H.; Kubo, A.; Takahashi, M.; Shimizu, R.; Date, T.; Okamura, K.; Nunami, K. *J. Org. Chem.* **1995**, *60*, 6776.

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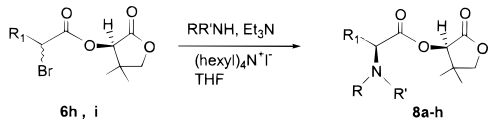
(10) Davies, H. M. L.; Cantrell, W. R. *Tetrahedron Lett.* **1991**, *32*, 6509.

(11) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095.

Table 2. Effect of Different Nitrogen Nucleophiles[d]



6h , i **8a-h**

entry	R_1	Amine	Yield (%)	Diastereomeric Ratio [a]
1	Phenyl	$(PhCH_2)_2NH$	70 (**8a**)	>98:2
2	Ethyl	$(PhCH_2)_2NH$	30 (**8b**)[b]	12:1
3	Phenyl	Ph_2CHNH_2	74 (**8c**)	>98:2
4	Phenyl	Ph_3CNH_2	N.R.[c]	-
5	Phenyl	(S)-$PhCH(CH_3)NH_2$	84 (**8d**)	>98:2
6	Phenyl	(R)-$PhCH(CH_3)NH_2$	84 (**8e**)	>98:2
7	Phenyl	4-CH_3O-Ph-NH_2	75 (**8f**)	>98:2
8	Phenyl	4-HO-Ph-NH_2	75 (**8g**)	12:1
9	Phenyl		87 (**8h**)	4:1

[a] Diastereomeric ratios of **8** (*SR*/*RR*) were determined using 500 MHz ^{1}H NMR. [b] Significant amounts of elimination product were also obtained under these reaction conditions. [c] No reaction. [d] Products **8a**−**h** were shown to be configurationally stable under these reaction conditions.

(4-methoxyaniline), 4-aminophenol, and pyrrolidine gave diastereomer ratios of 98:2, 12:1, and 4:1, respectively (entries 7−9), demonstrating that the relative nucleophilicity of the amine may have a profound effect upon stereoselectivity. Similar results were observed in the reaction of **6h** (R_1 = ethyl); the diastereomer ratio increased from 7:1 to 12:1 when the nucleophile was changed from benzyl- to dibenzylamine (entry 2). Interestingly, both (*S*)- and (*R*)-1-phenylethylamine gave the same chirality at the α-carbon, showing that the stereochemistry of the major product is dominated by the asymmetry of the chiral auxiliary and not that of the incoming nucleophile (entries 5 and 6).

Limited results indicate that the size and nature of the R_1 group attached to the reacting center also affect both the rate of reaction and product formation. For example, the product diastereomer ratio with $PhCH_2NH_2$ increases from 7:1 to 10:1 in going from **6h** to **6i** (Table 1, entries 8 and 9). In this case, the rate of reaction is also accelerated since reaction is occurring at a benzylic carbon as opposed to an aliphatic carbon.

(C) Solvent Effects. Highest chemical yields and product diastereomer ratios were observed with solvents such as THF (Table 3). n-Hexylammonium bromide or iodide has significant solubility in this solvent and, thus, allows Br^- or I^- to epimerize the starting materials. The more polar solvent DMF resulted in a diminished product diastereomer ratio. Methanol or ethanol was an unsuitable solvent from the points of view of both chemical yields and diastereoselectivities.

Origin of the Selectivity. On the basis of the results described above and others introduced during this discussion, we propose that the scheme and free energy diagram shown in Figure 1 is operative. Isomerization experiments show that the diastereomeric starting esters have approximately the same free energies. Thus, reac-

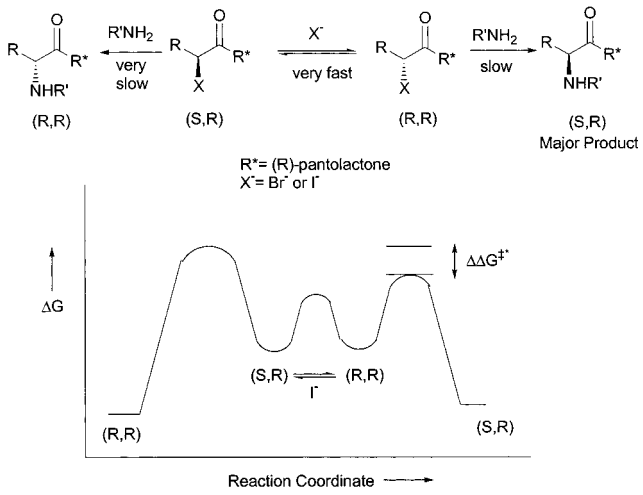
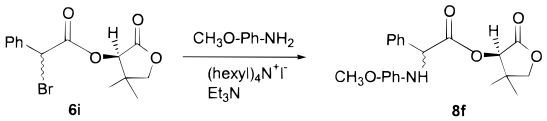


Figure 1. A qualitative free energy diagram for the DKR process.

Table 3. Solvent Effect on the Formation of 8



6i **8f**

Solvent	Diastereomeric Ratio (SR/RR)
THF	**>98:2**
Et_2O	14:1
DMF	3:1
Toluene (reflux)	2:1

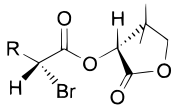
tion of a 10:1 mixture of *SR*:*RR* of the ester **6h** with $Bu_4N^+I^-$ in THF at rt gave a 1.1:1 mixture within 1 h. Similarly, 1:1 mixtures of a number of other α-halo-(*R*)-pantolactone esters when stirred with the corresponding halide for one day in THF showed only slight changes in composition as determined by NMR. The diastereomeric products, as reported earlier, are not interconverted under our reaction conditions. Finally, the observed product ratios which are typically about 7:1 in the reaction with benzylamine at 20 °C translate to a free energy difference of about 1 kcal/mol in the transition states for the reaction of the two diastereomers. In the case of the more hindered nucleophiles such as dibenzylamine the difference in the $G^{\ddagger}$* value must exceed 3 kcal/mol to account for the >96% diastereomeric excesses.

The probable structure of the two transition states must be addressed to understand why one of the diastereomers reacts significantly faster than the other. To begin this process, we have examined the preferred conformations of the two α-bromo-(*R*)-pantolactone esters.

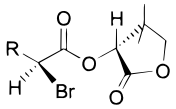
X-ray structure determination of several α-amino products and the α-bromo esters showed consistently that the ester function exists in the *cisoid* conformation.[12] Theoretical calculations by Houk *et al.*[13] confirmed this

(12) Ben, R. N.; Durst, T. Unpublished results.
(13) Loncharich, R. T.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14. Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935.

and indicate a 7 kcal/mol preference for this arrangement. The two carbonyl groups in all relevant X-ray structures were nearly perpendicular to each other. This leads to a dihedral angle of near 0° between the pantolactone methine C—H bond and the plane of the O—C=O group. Semiempirical molecular modeling using PC-Model confirmed this observed small dihedral angle. When such calculations were carried out on the α-keto ester **6d** (Table 1, entry 4), the relevant dihedral angle was found to be nearly 60°. Reaction of **6d** with benzylamine under the usual DKR reaction conditions gave poor diastereoselectivity, thus indicating the importance of this angle. These results suggested that the structures of the pantolactone esters are quite rigid and only conformational changes due to rotation about the C1—C2 bond are allowed. Taken together, these data point to ground-state structures such as **9** and **10** for the (*R*,*R*)- and the (*S*,*R*)-diastereomers.



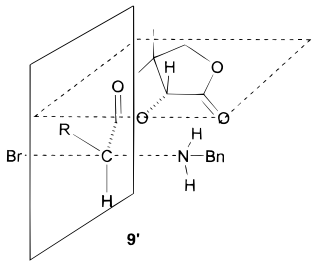
9
(R,R)



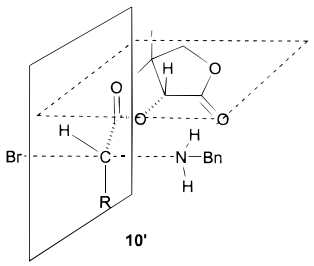
10
(S,R)

In the transition states leading to displacement of bromide ion, it is assumed that the Br atom is perpendicular to the ester carbonyl group since it has been shown experimentally that a halogen fixed in this conformation is displaced much more rapidly than one which cannot attain perpedicularity.[14] This effect has been called the "neighboring orbital overlap" effect.

We assume that the geminal dimethyl group on the lactone ring effectively blocks attack by the nucleophile from the rear. In contrast, delivery of the nucleophile from the front side can be aided by hydrogen bonding to the lactone carbonyl group (see below). Thus, the relevant transition states shown in **9′** and **10′** can be considered.



9'



10'

The transition state **9′** which leads to the (*S*,*R*)-product has two eclipsing interactions. One involves the R group and the carbonyl oxygen, and in the other, the H atom eclipses the alkyl oxygen. This situation is more favorable than the alternate arrangement found in **10′**. Support for this comes from *ab initio* calculation on 2-butanone by Allinger *et al.*[15] who demonstrated that the conformation in which the methyl group partially eclipses the carbonyl oxygen is favored by 2.8 kcal/mol over that in which hydrogen eclipses the carbonyl group. Our own calculations using AM1 on the faster reacting (*RR*)-

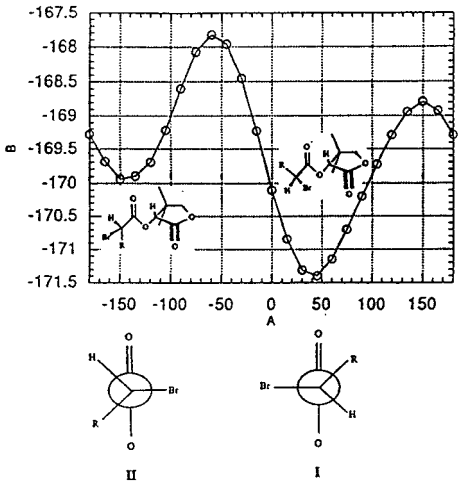


Figure 2. Energy minima for the faster reacting diastereomer **9**.

diastereomer where R = methyl were also in agreement with this precedent. Figure 2 depicts the energy profile as the dihedral angle between the methyl group and carbonyl group of the ester function is rotated through 360°. As shown, conformation **I** that begins to approximate **9′** is at an energy minimum while **II**, (approximately **10′**) is about 1.5 kcal/mol higher in energy.

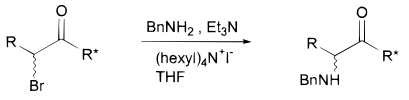
We therefore propose that the origin of the diastereoselectivity is due essentially to the fixed conformation of the pantolactone ester. It is because of this that a strong preference for attack of the nucleophile from the same side as the lactone carbonyl group (anti to the *gem*-dimethyl group) exists. In addition, the preferential eclipsing of the R group compared to hydrogen with the acyl rather than the alkyl oxygen of the ester in the transition state facilitates formation of the (*S*,*R*)-diastereomer as a major product. Our experimental results reviewed in the previous sections are in agreement with this conclusion.

As predicted, more sterically demanding amines show a greater diastereoselectivity (Table 2). Thus, the (*SR*/*RR*)-product ratio increases from 4:1 to >98:2 when the nucleophile is pyrrolidine and dibenzylamine, respectively, with the α-bromophenylacetate as probe. A similar trend is observed with the α-bromobutyrate esters (R_1 = ethyl). The large nucleophiles are likely blocked from attacking the same side as the *gem*-dimethyl groups in **9′** or **10′**, thereby allowing attack only as shown in **9′** and **10′**. Interestingly, both (*R*)- and (*S*)-α-methylbenzylamine give the same (*S*)-stereochemistry at the α-carbon in the product, both with >98:2 selectivity. Not surprisingly, the rate of the S_N2 reaction decreases with the increasing size of the nucleophile. Small nucleophiles such as azide gave only modest selectivity (1.5:1). Good diastereoselectivities have been observed with sodium phenoxides[16] and with the stabilized carbanions derived from dimethyl malonate and malononitrile.[17]

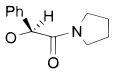
An increase in the size of the R group on the α-carbon increases the observed product diastereoselectivity (Table 1). However, elimination reactions may dominate (i.e., R_1 = CH_2Ph). Thus, this route is not practical for the preparation of phenylalanine or analogues.

(14) Streitwieser, A. *Solvolytic Displacement Reactions*; McGraw-Hill Book Company Inc.: New York, 1962; p 26.
(15) Allinger, K. B.; Kuchsiang, C.; Rahman, M.; Pathiaseril, A. *J. Am. Chem. Soc.* **1991**, *113*, 4505.
(16) Koh, K.; Durst, T. *J. Org. Chem.* **1994**, *59*, 4683.
(17) Koh, K.; Durst, T. Unpublished results.

Table 4. Effect of Amide-Derived Chiral Auxiliaries

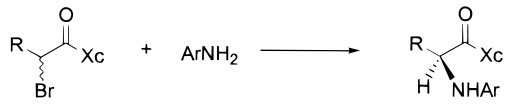


11a-e 12a-e

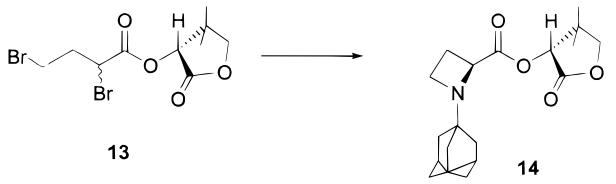
entry	R	R*	Yield (%)	Diastereomeric Ratio (SR/RR) of 12
1	ethyl **(11a)**		82	4:1
2	phenyl **(11b)**		80	10:1

It was suggested above that hydrogen bonding between the nucleophile and the lactone carbonyl group should favor the attack as shown in **9′** or **10′**. To verify this hypothesis, the ester of (*S*)-mandelate was converted to an amide (Table 4). It was anticipated that the increased basicity of the amide versus ester carbonyl oxygen would enhance hydrogen bonding. Indeed, an increase in diastereoselectivity was observed for the open chain amide vs the corresponding ester (Tables 1 and 4).

Synthetic Applications. A number of applications of our DKR of (*R*)-pantolactone ester of α-bromo acids have been described in preliminary form. These include the synthesis of a number of (*S*)-*N*-benzyl-α-amino acids,[5] *N*-carboxylalkylamino acids, and (*S*,*S*)-pyrrolidine-2,5-dicarboxylic acids.[18] The DKR approach is particularly useful for the preparation of N-substituted α-amino acids. For example, a variety of *N*-aryl-α-amino acid derivatives were obtained in good to excellent yields according to eq 1.



The formation of the N-substituted azetidine-2-carboxylates as a 15:1 *SR* to *RR* mixture in 75% isolated yield starting from the 2,4-dibromobutanoate ester **13** also illustrates the versatility of the DKR approach. Compounds such as **14** have been patented as possible anti-Parkinson's agents.



13 **14**

Experimental Section

Microanalyses were performed at the University of Ottawa or by M-H-W Laboratories, Phoenix, AZ.

Chromatographic separations were performed using 230−400 mesh SiO_2 from Terochem Laboratories in the solvent systems specified. All solvents were dried and distilled prior to utilization; THF was distilled over sodium−benzophenone, and methylene chloride was distilled over P_2O_5.

General Procedures for the Preparation of α-Bromo Esters. Procedure A. A solution of the appropriate α-bromoacyl halide (obtained commercially or prepared via literature procedure[19]) in dry THF was added dropwise to a solution of triethylamine and the desired alcohol (2.0 equiv each) in THF at 0 °C over a 1 h period. The reaction mixture was then quenched with H_2O and subjected to extractive workup. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Crude products were then purified by column chromatography using the appropriate solvent system and fully characterized.

Procedure B. The appropriate alcohol, α-bromo carboxylic acid (1.0 equiv), DCC (1.0 equiv), and DMAP (0.1 equiv) were dissolved in dry CH_2Cl_2 and stirred at room temperature under a nitrogen atmosphere until TLC verified that the alcohol had been consumed. The precipitate was filtered off, and the organic phase was washed with 3 × 20 mL of H_2O and 1 × 20 mL of 10% HCl. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to furnish the crude product that was purified via column chromatography.

General Procedure for the Dynamic Kinetic Resolution. The appropriate α-halo ester was dissolved in 5−10 mL of dry THF. Triethylamine (2.0 equiv), tetrahexylammonium iodide (0.2 equiv), and the desired amine (1.05 equiv) were added to the solution. The reaction mixture was stirred under a nitrogen atmosphere until TLC verified that all of the starting materials had been consumed. After addition of 20−30 mL of ether, the precipitate was filtered off and the filtrate was evaporated under reduced pressure to furnish the crude product. At this point, a proton NMR was taken of the crude mixture to determine the diastereomeric ratio, and the crude product was then purified via column chromatography.

Methyl-(*S*)-*O*-(2-bromobutyryl)mandelate (6a). Compound **6a** was prepared using procedure A. The crude product was purified via column chromatography using hexane−EtOAc (10:1) as elutant to furnish **6a** in 91% yield as a colorless oil: IR (CH_2Cl_2) 2948, 1750, 1748, 1497, 1145, 1033 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (m, 3H), 2.10 (m, 2H), 3.70 (s, 3H), 4.30 (m, 1H), 5.94 (s, 1H), 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 28.4, 52.3, 75.2, 75.4, 127.5, 128.8, 129.4, 133.0, 133.1, 168.5, 168.8; CIMS (ether) *m*/*e* (relative intensity) 389 (0.6), 317 (17), 315, (17), 297 (100).

(1*R*,2*S*)-2-Bromobutyryloxy-1-phenylcyclohexane (6b). Compound **6b** was prepared via procedure A. The crude product was obtained as a colorless oil in 60% yield after column chromatography using hexane−EtOAc (5:1): IR (CH_2Cl_2) 2980, 1720, 1328, 1032, 852 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.60 (m, 3H), 1.30−2.20 (m, 10H), 3.85 (m, 1H), 4.80 (m, 1H), 5.00 (m, 1H), 7.20 (m, 5H); CIMS (ether) *m*/*e* (relative intensity) 327 (4), 325 (4), 249 (11), 171 (14.2). Anal. Calcd for $C_{16}H_{21}O_2Br$: C, 59.26; H, 6.52. Found: C, 59.14; H, 6.54.

3-(2-Bromobutyryl)-1,2,5,6-diisopropylidene-*O*-glucose (6c). α-Bromo ester **6c** was prepared via procedure A, and the crude product was purified via column chromatography on silica using hexane−EtOAc (5:1). Compound **9c** was isolated in 63% yield as a yellow oil: IR (CH_2Cl_2) 3479, 2913, 1743, 1206, 1156, 1080, 1026 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 8.2 Hz), 1.27 (s, 3H), 1.28 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H), 2.0 (m, 2H), 3.90−4.20 (m, 5H), 4.45 (t, 1H, J = 4.2 Hz), 5.31 (br s, 1H), 5.87, 5.89 (both s, total 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.6, 11.7, 25.1, 26.1, 26.5, 26.6, 28.1, 49.5, 47.0, 60.1, 67.3, 67.4, 71.9, 72.1, 76.5, 79.8, 79.9, 82.7, 82.8, 167.8, 168.1; CIMS (ether) *m*/*e* (relative intensity) 411 (38), 409 (39), 393 (12), 351 (100), 293 (20).

2-(2-Bromobutyryloxy)-3,3-diphenyl-γ-butyrolactone (6f). Compound **6f** was prepared using procedure B and was purified via column chromatography on silica using hexane−EtOAc (3:1). The desired product was obtained in 52% yield as a colorless oil: IR (CH_2Cl_2) 2930, 1802, 1752, 1498, 1074, 1016 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (m, 3H), 1.50−2.20 (m, 2H), 4.10 (m, 1H), 4.50, 4.60 (both d, total 1H, J = 9.6 Hz), 5.15 (d, 1H, J = 9.6 Hz), 6.39, 6.41 (both s, total 1H), 7.25 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 11.3, 27.4, 27.8, 54.9 (2), 55.4, 55.5, 73.7, 126.1, 127.4, 127.6, 128.1 (2),

(18) O'Meara, J. A.; Gardee, N.; Jung, M.; Ben, R. N.; Durst, T. *J. Org. Chem.* **1998**, *63*, 3117. Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.* **1994**, *35*, 375.

(19) Harpp, D. W.; Black, C. J.; Gleason, J. G.; Smith, R. A. *J. Org. Chem.* **1975**, *40*, 3420.

128.9, 137.8, 140.6, 167.5, 168.2, 170.0, 170.1; EIMS *m/e* (relative intensity) 404 (4), 402 (4), 291 (3), 236 (4), 211 (39); HRMS calcd for $C_{20}H_{19}O_4Br$ (M^+) 402.0466, found 402.0461.

2-(2-Bromo-2-phenylacetoxy)-3,3-diphenyl-γ-butyrolactone (6g). Compound **6g** was prepared using procedure B and was obtained in 56% yield after purification by column chromatography using hexane−EtOAc (3:1): IR (CH_2Cl_2) 2930, 1802, 1752, 1498, 1136, 1073 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.50, 4.54 (both d, total 1H, J = 9.6 Hz), 5.10, 5.40 (both d, total 1H, J = 9.6 Hz), 5.30, 5.35 (both s, total 1H), 6.35, 6.40 (both s, 1H), 6.80−7.50 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.5, 46.5, 73.3, 73.8, 126.0, 126.2, 127.4, 127.5, 128.0, 128.1, 128.3, 128.5, 128.6, 128.9, 129.0, 129.1, 166.3, 169.8, 169.9; EIMS *m/e* (relative intensity) 452 (2), 450 (2), 371 (25), 325 (21); HRMS calcd for $C_{24}H_{19}O_4Br$ (M^+) 450.0466, found 450.0452.

(*R*)-*O*-(2-Bromo-2-phenyl)acetylpantolactone (6i). Compound **6i** was prepared using procedure B and was purified via column chromatography using hexane−EtOAc (3:1). The desired product was obtained in 72% yield as a colorless oil which solidified on standing in a freezer: mp 143−144 °C; IR (CH_2Cl_2) 3014, 1800, 1762, 1076, 1136 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88, 1.10, 1.15, 1.23 (all s, total 6H), 3.98, 4.05 (both s, total 2H), 5.34, 5.36 (both s, total 1H), 5.48, 5.51 (both s, total 1H), 7.25−7.60 (m, 5H); ^{13}C NMR (75MHz, $CDCl_3$) δ 20.1, 20.3, 23.2, 23.4, 40.2 (2), 45.6 (2), 47.3 (2), 77.8 (2), 78.4 (2), 128.5, 128.7, 129.1, 129.6, 130.1, 135.3, 136.1, 167.8, 168.3, 172.1; CIMS (ether) *m/e* (relative intensity) 329 (34), 327 (34), 283 (9), 247 (100). Anal. Calcd for $C_{14}H_{15}O_4Br$: C, 51.40; H, 4.62. Found: C, 51.61; H, 4.70.

(4*S*)-(2-Bromo-2-phenylacetyl)-4-isopropyl-2-oxazolidinone (6l). Compound **6l** was obtained as a yellow oil in 75% yield after purification by column chromatography using hexane−EtOAc (5:1): IR (CH_2Cl_2) 2946, 1780, 1706, 1379, 1197, 1101, 972 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.50−1.40 (m, 6H), 2.10−2.60 (m, ^1H), 4.00−4.50 (m, 3H), 6.82, 6.90 (both s, total 1H), 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.4, 17.5, 44.1, 45.8, 58.5, 63.1, 63.2, 128.3, 128.5, 128.9, 129.0, 129.2, 129.3, 134.7, 135.2, 152.9, 166.8, 167.2; EIMS *m/e* (relative intensity) 327 (75), 325 (75), 246 (100), 196 (100), 198 (100), 170 (100); HRMS calcd for $C_{14}H_{16}NO_3Br$ (M^+) 325.0310, found 325.0333.

Methyl-(*S*)-*O*-(2-aminobutyryl)mandelate (7a). Ester **7a** was prepared according to the general procedure. The crude product was obtained as a 2:1 mixture (*SS*/*RS*) of diastereomers and was purified via column chromatography using toluene−acetone (17:1) in 60% yield as a colorless oil: IR (CH_2Cl_2) 3527, 2945, 1739, 1680, 1495, 1092, 1067 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.95, 1.05 (both t, total 3H, J = 7.8 Hz), 1.60−1.92 (m, 2H), 3.40 (m, 1H), 3.60−3.92 (m, 5H), 6.00, 6.01 (both s, total 1H), 7.10−7.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7, 9.8, 26.1, 26.2, 51.5, 51.6, 52.3, 52.4, 61.4, 74.2, 74.3, 126.8, 127.4, 128.1, 128.2, 128.5, 128.6, 128.7, 129.0, 133.4, 139.2, 168.9, 174.4; CIMS (isobutylene) *m/e* (relative intensity) 342 (100), 194 (11), 148 (100), 106 (12). Anal. Calcd for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79. Found: C, 70.52; H, 6.83.

(1*R*,2*S*)-(2-Phenylmethylamino)butyryloxy-1-phenylcyclohexane (7b). The general procedure using **6b** with benzylamine produced compound **7b** in a diastereomeric ratio of 2:1, which was isolated in 92% yield as a pale yellow oil: IR (CH_2Cl_2) 2936, 1725, 1494, 1188, 1013 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.50, 0.70 (both t, total 3H, J = 8.1 Hz), 1.10−2.40 (m, 11H), 2.60−3.52 (m, 4H), 5.10 (m, 1H), 7.20 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 10.0, 24.7, 25.8, 26.2, 26.6, 32.4, 32.6, 34.1, 34.3, 49.8, 49.9, 51.4, 51.2, 61.8, 62.1, 75.9, 76.2, 126.5, 126.7, 127.4, 127.6, 128.2 (2), 128.3, 139.8, 143.1, 174.7, 174.8; CIMS 17 (isobutylene) *m/e* (relative intensity) 352 (100), 194 (18), 159 (40), 148 (94), 106 (14). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32. Found: C, 78.25; H, 8.09.

3-(2-Phenylmethylamino)butyryloxy-1,2:5,6-diisopropylidene-*O*-glucose (7c). Compound **7c** was prepared according to the general procedure. The crude product was obtained as a 2:1 mixture of diastereomers and was isolated as such in 83% yield as a yellow oil: IR (CH_2Cl_2) 2917, 1740, 1378, 1164, 1076, 1024, 848 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.8 Hz), 1.23 (s, 3H), 1.24 (s, 3H), 1.40 (s, 3H), 1.50 (s, 3H), 1.75 (m, 1H), 3.20 (m, 1H), 3.60 (d, 1H, J = 12.3 Hz), 3.80 (d, 1H, J = 12.3 Hz), 3.95 (m, 6H), 4.35, 4.36 (both d, total 1H, J = 3.5 Hz), 5.29, 5.35 (both d, total 1H, J = 3 Hz), 5.80, 5.82 (both d, total 1H, J = 4 Hz), 7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 25.0, 25.1, 25.2, 26.1, 26.4, 26.6, 26.7, 26.8, 51.2, 52.0, 61.8, 67.4, 67.7, 72.1, 72.3, 75.9, 80.0, 81.2, 83.2, 83.4, 85.0, 105.0, 105.2, 127.1, 128.2, 128.3, 139.5, 173.9. Anal. Calcd for $C_{23}H_{32}NO_7$: C, 63.57; H, 7.42. Found: C, 63.72; H, 7.60.

2-(2-Phenylmethylamino)butyryloxy-3,3-diphenyl-γ-butyrolactone (7f). Compound **7f** was synthesized according to the general procedure. The crude product showed a 3:1 mixture of diastereomers which were isolated together via column chromatography using hexane−EtOAc (3:1) in 93% yield: IR (CH_2Cl_2) 2912, 1799, 1746, 1376, 1073, 1015, 870 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (m, 3H), 1.60 (m, 2H), 1.90 (br s, 1H), 3.20 (m, 1H), 3.50, 3.60 (both d, total 1H, J = 10.2 Hz), 3.80 (d, 1H, J = 10.2 Hz), 4.46, 4.52, (both d, total 1H, J = 9.6 Hz), 5.15 (d, 1H, J = 9.6 Hz), 6.48, 6.52 (both s, total 1H), 7.2 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.9, 10.0, 25.9, 26.3, 51.6, 55.2, 61.6, 62.0, 71.7, 71.9, 74.3, 74.5, 126.5, 126.8, 127.1, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.7, 129.3, 138.8, 141.1, 170.9, 173.7; CIMS (isobutylene) *m/e* (relative intensity) 430 (100), 237 (42), 194 (81), 148 (100). Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.33. Found: C, 75.61; H, 6.35.

2-[(2-Phenylmethylamino)-2-phenyl]acetoxy-3,3-diphenyl-γ-butyrolactone (7g). Compound **7g** was obtained according to the general procedure. Analysis of the reaction mixture by proton NMR revealed that the crude product contained a mixture of diastereomers in a 3.5:1 ratio and was purified as a white solid in 97% yield via column chromatography using hexane−EtOAc (2:1) which was recrystallized from ether−hexanes to furnish the major diastereomer: mp 101 °C; IR (CH_2Cl_2) 3450, 2840, 1800, 1751, 1496, 1132, 1074, 869 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (br s, 1H), 3.70 (s, 2H), 4.36 (s, 1H), 4.45 (d, 1H, J = 9.6 Hz), 5.08 (d, 1H, J = 9.6 Hz), 6.32 (s, 1H), 6.70 (m, 4H), 7.20 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.8, 54.5, 63.8, 72.3, 73.2, 73.3, 125.8, 126.5, 126.7, 127.1, 127.4, 127.6, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 136.9, 137.7, 138.8, 140.5, 170.3, 171.4; CIMS (isobutylene) *m/e* (relative intensity) 478 (100), 237 (5), 196 (50), 106 (21).

(*R*)-*O*-[(2-Phenylmethylamino)-2-phenyl]acetylpantolactone (7i). A proton NMR of the crude reaction mixture revealed that **7i** was formed as a 10:1 mixture of diastereomers. After purification by column chromatography using hexane−EtOAc (3:1) the mixture of diastereomers was obtained in 85% yield as a colorless oil: IR (CH_2Cl_2) 2949, 1784, 1780, 1109, 1007 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.40, 0.92, 1.00, 1.18 (all s, total 6H), 2.40 (br s, 1H), 3.75, 3.90, 3.92, 4.00 (all s, total 4H), 4.55, 4.56 (both s, total 1H), 5.46, 5.47 (both s, total 1H), 7.20−7.50 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.9, 22.4, 40.1, 50.9, 63.7, 74.9, 75.8, 126.9, 127.4, 128.1, 128.2, 128.4, 128.5, 137.5, 138.9, 171.8, 171.9; CIMS (isobutylene) *m/e* (relative intensity) 260 (70), 247 (90), 226 (10), 131 (100). Anal. Calcd for $C_{21}H_{23}O_4N$: C, 71.36; H, 6.55. Found: C, 71.21; H, 6.45.

(*R*)-*O*-[(2-Bisphenylmethylamino)-2-phenyl]acetylpantolactone (8a). Compound **8a** which was obtained as a single diastereomer was purified on silica using hexane−EtOAc (3:1) and was obtained in 70% yield as a pale orange solid: mp 83 °C; IR (CH_2Cl_2) 2931, 1794, 1748, 1127, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.27 (s, 3H), 3.78 (ABq, 4H, J = 9.6 Hz), 4.05 (s, 2H), 4.70 (s, 1H), 5.60 (s, 1H), 7.20−7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 22.7, 39.8, 53.7, 65.2, 74.7, 75.9, 127.7, 128.0, 128.1, 128.3, 128.4, 128.7, 135.9, 138.9, 170.5, 171.7; CIMS (isobutylene) *m/e* (relative intensity) 444 (1), 443 (1), 288 (2), 286 (55), 91 (100). Anal. Calcd for $C_{28}H_{29}O_4N$: C, 75.82; H, 6.59. Found: C, 75.42; H, 6.58.

(*R*)-*O*-2-(Bisphenylmethylamino)butyrylpantolactone (8b). Compound **8b** which was obtained as a 12:1 mixture of diastereomers was purified via column chromatography using hexane−EtOAc (3:1) and isolated in 30% yield as a colorless oil: IR (CH_2Cl_2) 2810, 1782, 1740, 1325, 1072, 1010, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 8.0 Hz), 1.10, 1.11, 1.20, 1.22 (all s, total 6H), 1.80 (m, 2H), 3.35 (t, 1H, J =

8.2 Hz), 3.60, 3.62 (both d, 2H, $J = 12$ Hz), 3.95, 3.98 (both d, total 2H, $J = 12$ Hz), 4.05 (s, 2H), 5.45, 5.50 (both s, total 1H), 7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 20.2, 22.8, 22.9, 40.1, 54.2, 62.1, 74.8, 76.2, 126.9, 128.2, 128.9, 139.5, 171.6, 172.1; CIMS (isobutylene) *m/e* (relative intensity) 396 (100), 304 (2), 238 (84), 234 (8). Anal. Calcd for $C_{24}H_{29}O_4N$: C, 72.88; H, 7.39. Found: C, 72.92; H, 7.32.

(*R*)-*O*-[(2-Diphenylmethylamino)-2-phenyl]acetylpantolactone (8c). Compound **8c** was obtained as a single diastereomer and was isolated by column chromatography using hexane−EtOAc (3:1) in 74% yield as a colorless oil: IR (CH_2Cl_2) 2915, 1793, 1749, 1352, 1075, 1019, 850 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.60 (s, 3H), 0.95 (s, 3H), 2.70 (br s, 1H), 3.90 (s, 2H), 4.50 (s, 1H), 5.40 (s, 1H), 7.30 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 22.5, 40.1, 62.2, 64.2, 75.3, 75.8, 127.2, 127.4, 127.6, 128.3, 128.4, 128.5, 128.7, 128.9, 129.0, 132.1, 140.1, 141.2, 171.2, 172.0, 172.3; EIMS *m/e* (relative intensity) 429 (3), 352 (14), 316 (9), 272 (99), 182 (100); HRMS calcd for $C_{27}H_{27}O_4N$ (M^+) 429.1941, found 429.1932.

(*R*)-*O*-[2-((1*S*)-Phenyl(ethylamino))-2-phenyl]acetylpantolactone (8d). Compound **8d** was isolated as a single diastereomer by column chromatography using hexane−EtOAc (3:1) in 84% yield as a colorless oil: IR (CH_2Cl_2) 2914, 1793, 1748, 1371, 1144, 1077, 1012 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70 (s, 3H), 0.95 (s, 3H), 1.40 (d, 3H, $J = 8.1$ Hz), 2.30 (br s, 1H), 3.90 (q, 1H, $J = 8.1$ Hz), 3.95 (s, 2H), 4.35 (s, 1H), 5.40 (s, 1H), 7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 22.7, 24.5, 40.2, 56.4, 62.8, 75.2, 76.0, 127.0, 127.1, 128.1, 128.2, 128.4, 128.7, 138.1, 144.4, 171.8, 173.0; CIMS (isobutylene) *m/e* (relative intensity) 368 (100), 320 (16), 264 (80), 249 (10), 210 (67). Anal. Calcd for $C_{22}H_{25}O_4N$: C, 71.91; H, 6.83. Found: C, 71.52; H, 6.80.

(*R*)-*O*-[2-(4-Methoxyphenylamino)phenyl]acetylpantolactone (8f). Compound **8f** which was obtained as a single diastereomer was purified by column chromatography using hexane−EtOAc (3:1) and isolated in 75% yield as needle-like crystals: mp 118−120 °C; IR (CH_2Cl_2) 2929, 1795, 1753, 1514, 1161, 1075 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 22.6, 40.4, 55.6, 62.0, 75.7, 76.0, 115.0, 121.1, 127.4, 127.6, 128.1, 128.5, 128.8, 128.9, 129.0, 129.1, 130.4, 131.8; EIMS *m/e* (relative intensity) 369 (10), 212 (100), 210 (13), 196 (4), 77 (9); HRMS calcd for $C_{21}H_{23}O_5N$ (M^+) 369.1570, found 369.1595.

(*R*)-*O*-[2-(4-Hydroxyphenylamino)phenyl]acetylpantolactone (8g). Compound **8g** was obtained as a 12:1 mixture of diastereomers and isolated by column chromatography using hexane−EtOAc (1:1) in 75% yield as a colorless oil: IR (CH_2Cl_2) 3586, 2900, 1794, 1749, 1515, 1376, 1165, 1075, 1007, 822 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70, 0.80, 0.90, 1.10 (all s, total 6H), 3.95, 4.00 (both s, total 2H), 4.55, 4.60 (both d, total 1H, $J = 6.3$ Hz), 5.20, 5.25 (both d, total 1H, $J = 6.3$ Hz), 5.40, 5.45 (both s, total 1H), 6.50 (d, 2H, $J = 7.0$ Hz), 6.80 (d, 2H, $J = 7.0$ Hz), 7.30−7.60 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 18.8, 19.4, 22.2, 22.5, 30.5, 40.1, 61.3, 61.5, 75.3, 75.4, 75.7, 75.9, 114.0, 115.0, 115.8, 126.7, 127.1, 128.1, 128.3, 128.5, 128.6, 137.2, 139.5, 147.9, 171.1; EIMS *m/e* (relative intensity) 355 (7), 198 (100), 196 (12); HRMS calcd for $C_{20}H_{21}O_5N$ (M^+) 355.1420, found 355.1430.

(*R*)-*O*-[2-(1-Pyrrolidyl)-2-phenylacetyl]pantolactone (8h). Compound **8h** which was obtained as a 4:1 mixture of diastereomers was purified using column chromatography with hexane−EtOAc (3:1) to furnish a colorless oil in 87% yield: IR (CH_2Cl_2) 2907, 1787, 1756, 1471, 1131, 1010, 856 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.60, 0.90, 1.00, 1.10 (all s, total 6H), 2.80 (br s, 4H), 2.30−2.70 (m, 4H), 3.80−4.10 (m, 3H), 5.25, 5.35 (both s, total 1H), 7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 19.7, 22.3, 22.7, 22.9, 23.0, 29.8, 40.1, 51.2, 52.1, 72.5, 73.1, 74.4, 74.8, 75.6, 75.7, 128.0, 128.1, 128.3, 136.2, 170.4, 171.3; CIMS (isobutylene) *m/e* (relative intensity) 318 (100), 316 (9), 160 (92). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11; H, 7.30. Found: C, 68.32; H, 7.41.

(1*S*)-[Phenyl(pyrrolidinecarbonyl)methyl]-2-bromobutanoate (11a). Compound **11a** which was synthesized using procedure B was purified by column chromatography using hexane−EtOAc (1:1) to furnish the desired compound in 70% yield as a white solid: IR (CH_2Cl_2) 2865, 1743, 1712, 1363, 1221, 1099, 844 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (q, 3H, $J = 7.2$ Hz), 1.60−2.20 (m, 6H), 3.00 (m, 1H), 3.30 (m, 1H), 3.50 (m, 2H), 4.20 (q, 1H, $J = 7.2$ Hz), 5.92, 5.95 (both s, total 1H), 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 23.7, 25.9, 28.4, 28.5, 45.8, 45.9, 46.2, 47.5, 47.6, 128.5, 128.6, 128.7 (2), 128.8, 128.9, 129.3, 129.4, 133.0, 133.2, 165.5, 165.6, 169.1, 169.6; EIMS *m/e* (relative intensity) 355 (1), 353 (1), 317 (2), 274 (2), 187 (6); HRMS calcd for $C_{16}H_{20}NO_3Br$ (M^+) 353.0627, found 353.0599.

(1*S*)-[Phenyl(pyrrolidinecarbonyl)methyl]-2-bromo-2-phenylacetate (11b). Compound **11b** which was synthesized using procedure B was purified by column chromatography using hexane−EtOAc (1:1) to furnish the desired compound in 40% yield as a colorless oil: IR (CH_2Cl_2) 2896, 1748, 1711, 1356, 1137, 1024, 849 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70 (m, 4H), 3.05 (m, 1H), 3.20−3.60 (m, 3H), 5.40 (s, 1H), 5.95, 6.00 (both s, total 1H), 7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 24.9, 26.0, 33.8, 45.9, 46.3, 75.8, 75.9, 128.4, 128.5, 128.7 (2), 128.8, 128.9, 129.0, 129.2, 129.4, 129.5, 131.1, 135.3, 135.6, 165.5, 167.9, 168.2; CIMS (isobutylene) *m/e* (relative intensity) 404 (20), 402 (20), 352 (11), 324 (79).

(1*S*)-[Phenyl(pyrrolidinecarbonyl)methyl]-2-(phenylmethylamino)butanoate (12a). Compound **12a** was obtained as a 4:1 mixture of diastereomers and was purified via column chromatography using hexane−EtOAc (1:1) to furnish the desired product as a pale yellow oil in 82% yield: IR (CH_2Cl_2) 2908, 1747, 1656, 1492, 1170, 1031 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80, 0.90 (both t, total 3H, $J = 8.0$ Hz), 1.50−2.00 (m, 8H), 3.00 (m, 1H), 3.20−3.80 (m, 5H), 5.92, 5.98 (both s, total 1H), 7.10−7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0, 10.2, 23.7, 26.0, 26.3, 45.8, 46.2, 51.8, 51.9, 61.7, 61.8, 74.3, 74.4, 126.7, 126.8, 128.2, 128.3 (2), 128.4, 128.6, 128.9, 129.2, 133.8, 139.9, 166.0, 175.1; CIMS (isobutylene) *m/e* (relative intensity) 381 (100), 275 (13), 190 (50).

(1*S*)-[Phenyl(pyrrolidinecarbonyl)methyl]-2-(phenylmethylamino)butanoate (12b). Compound **12b** which was obtained as a 10:1 diastereomeric mixture was purified by column chromatography using hexane−EtOAc (1:1) to furnish the desired product as a colorless oil in 80% yield: IR (CH_2Cl_2) 2901, 1747, 1656, 1497, 1176, 1032 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70 (m, 4H), 2.15 (br s, 1H), 3.05 (m, 1H), 3.30 (m, 1H), 3.50 (m, 2H), 3.70, 3.76 (both s, total 1H), 4.45, 4.50 (both s, total 1H), 5.92, 5.98 (both s, total 1H), 7.25 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 25.7, 45.6, 46.0, 51.1, 63.8, 74.6, 126.7, 127.3, 127.7, 128.0, 128.3, 128.4, 128.9, 133.2, 137.3, 139.2, 165.8, 172.6; CIMS (isobutylene) *m/e* (relative intensity) 429 (44), 323 (9), 242 (18), 196 (72), 188 (21), 160 (31), 106 (34). Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.67; H, 6.58. Found: C, 75.82; H, 6.62.

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