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Reaction of (R)-pantolactone esters of alpha-bromoacids with amines A remarkable synthesis of optically active alpha-amino esters

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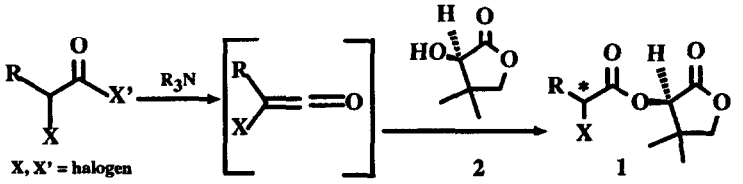
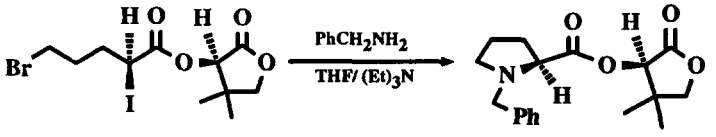
Abstract: *(R)-Pantolactone esters of racemic α-bromo acids react with amines to give α-amino esters having the (S)-configuration at the α-carbon in yields which are considerably greater than the 50% expected on the basis of a simple S_N2 displacement reaction.*

Recently we reported the syntheses of optically active α-halo esters **1** via trapping of α-halogenated ketenes with (R)-pantolactone **2**.[1] We have also shown that the halide atom could be displaced with the expected inversion of configuration using nucleophiles such as N_3^- [1] and $PhCOS^-$.[2]



We envisaged that the reaction of α-iodo ester **3** (obtained in a 6:1 diastereomeric ratio via the above method) with benzylamine would lead mainly to the (R)-pantolactone ester of (R)-N-benzylproline via an S_N2 displacement of both the α-iodo and ω-bromine atom.



3 **4**

In the event, reaction of **3** (dr=6:1) with benzylamine in THF for 2 days afforded in about 70% yield, a 5:1 mixture of proline esters in which the (S,R) diastereomer **4** and not the expected (R,R) diastereomer predominated.[3] Similar treatment of a 1:1 diastereomeric mixture of **3** [4] also gave predominantly **4** but with a better diastereomeric ratio of 7:1. Recrystallization of the crude product from the latter reaction gave diastereomerically pure **4** (300 MHz ^{1}H NMR) in 61% ioslated yield.[5]

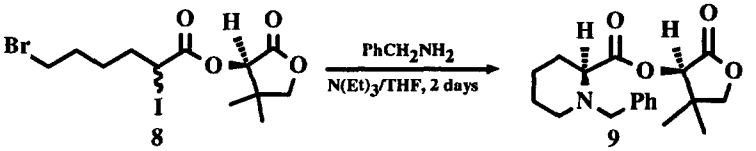
Since the product **4** was configurationally stable under the reaction conditions[6], epimerization of **3** at the α-position must occur prior to the displacement of iodide by the amino group. The surprising aspect of

this reaction is that the (R)-2-iodo isomer of **3** must react significantly faster than the 2-(S)-isomer. The greater than 50% yield of the (S)-proline ester **4** is made possible by replenishing the faster reacting isomer via bromide or iodide ion catalysis. The following equation is operative.

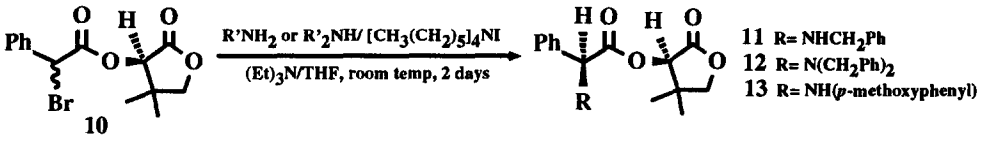
The predominant 2-(S)-stereochemistry was verified by reducing pure **4** ($LiAlH_4$ in THF at rt for 12 hrs) to the known (S)-1-benzyl-2- pyrrolidinemethanol **5** (80% yield, $[\alpha]^{22}_D$ -54.3° (c 0.78, $CHCl_3$), lit.[7] $[\alpha]^{22}_D$ -59.5°).

The above ring closure reaction is not restricted to benzylamine as the amine source. For example, reaction of **3** (dr 1:1) with 1-aminohexane resulted in a 51% isolated yield of a 7:1 mixture of the N-hexylproline analog **6**. Reduction of the mixture gave the known (S)-1-hexyl-2-pyrrolidinemethanol **7** (83% yield, $[\alpha]^{22}_D$ -37.9° (c 0.78, $ClCH_2CH_2Cl$), lit.[7] $[\alpha]^{22}_D$ -53.5°).

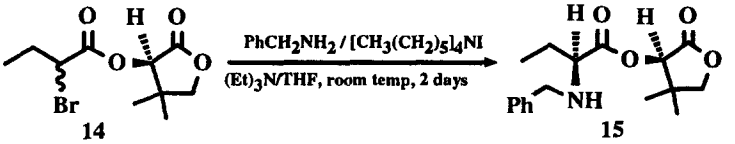
Cyclisation of the 2-iodo-6-bromo derivative **8** (dr = 1:1) with benzylamine gave the (R)-pantolactone ester of (S)-pipecolinic acid **9** in a diastereomeric ratio of 10:1. The minor isomer was removed by chromatography of the crude reaction mixture (15% ethyl acetate/hexanes as eluent), giving pure **9** in 60% isolated yield.



Displacement of bromide from the pantolactone esters of racemic α-bromophenylacetic acid gave even more impressive results. Thus reaction of **10** and benzylamine afforded a 10:1 mixture of diastereomers **11** in 77% isolated yield. Use of the sterically more demanding dibenzylamine and p-methoxyaniline gave **12** and **13** as single diastereomers[8] in 70 and 75% isolated yields.

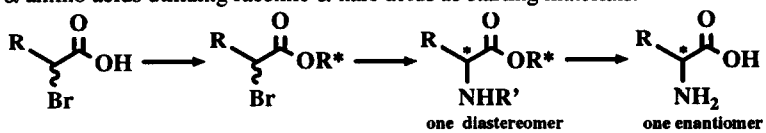


Other non-cyclic α-amino esters could also be prepared with good diastereoselectivities. For example, reaction of the diastereomeric mixture (4:5) of the bromide **14** afforded in 70% isolated yield, a 7:1 mixture of the 2-N-benzylaminobutanoic esters **15**.



The diastereomeric ratio of product **15** was also found to be dependent on the starting ratio in the bromide **14**. In the absence of tetra-*n*-hexylammonium iodide, an 11:1 (SR/RR) mixture of **14** gave a 1:2 (SR/RR) ratio of **15** while a 4:5 (SR:RR) mixture of **14** gave a 7:1 (SR:RR) mixture of **15**. These results suggested that the rate of epimerization of **14** at C-2, catalysed by the Br^- which is released as the amino ester formation progresses, is comparable to the amino ester formation. The epimerization at C-2 can be facilitated by the addition of catalytic amounts (usually 0.2 molar equivalent) of tetraalkylammonium iodide to the reaction mixture.[9] This serves to convert the slower reacting 2-(S)-bromo isomer into the faster reacting 2-(R)-isomer. The predominant (S)-stereochemistry of the acyclic amino esters were verified by first reducing **15** (7:1 mixtures) to (S)-2-(N-benzylamino)-1-butanol **16** ($LiAlH_4$ in THF at room temp for 12 hrs, 90% yield, $[\alpha]^{22}_D$ +21.5° (c 0.83, CH_2Cl_2). The N-benzyl group of **16** was then removed under standard conditions (H_2/Pd/C, MeOH/AcOH (98:2) at room temp for 24 hrs) giving the known (S)-2-amino-1-butanol **17** (54%, $[\alpha]^{22}_D$ +6.1° (c 0.88, MeOH).[10]

The above results indicate considerable potential for efficient syntheses of both common and unusual optically active α-amino acids utilizing racemic α-halo acids as starting materials.

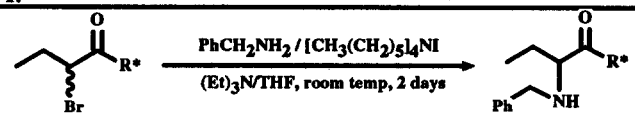


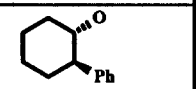
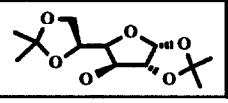
There exist a variety of excellent routes to optically active α-amino acids ranging from resolution of racemic α-amino acids, enzymatic resolution of α-amino esters, asymmetric hydrogenations, a variety of methods for introduction of electrophilic nitrogen via chiral ester enolates, reaction of the same enolates with halogens followed by nucleophilic displacement with N_3^-, and alkylation of chiral α-amino- and imino ester enolates.[11] The present methodology is conceptually different. It makes use of the significant differences in the rate of displacement of bromine or iodine from diastereomeric α-halo esters. The advantages this method has over the other conceptually similar methodologies, (i.e. the kinetic resolution of racemic α-amino- or α-halo esters by enzymes) is that the slower reacting diastereomer is converted into the faster reacting isomer under the reaction conditions.[12] Thus, the maximum yield of the optically pure α-amino esters obtainable by the present methodology starting from a racemic precursor is a 100% rather than 50%.

A comparison with four other optically active alcohols as chiral auxiliaries indicated that the pantolactone auxiliary has unique properties which gave the best diastereoseletivities in the formation of both cyclic and acylic α-amino esters. Thus, replacement of the (R)-pantolactone moiety in **14** by (S)-methyl lactate, (R)-methyl mandelate, diacetone glucose or (R,R)-trans-2-phenylcyclohexanol resulted in the formation of the expected 2-N-benzylaminobutanoic esters, but with lower diastereoselectivities than that observed with **14** (see table 1).

At this stage, we feel that speculations concerning the reasons for the remarkable rate differences with the various diastereomeric pantolactone esters are premature. We are continuing to study this aspect by examining other auxiliaries and applying this methodology to the synthesis of interesting and important optically active α-amino acids.

Table 1.



Auxiliary used (R*)	Diastereomeric ratio of product	Chemical yield(%)
	4 : 1	50
	2 : 1	60
	2 : 1	95
	2 : 1	80

Acknowledgments

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References and Notes

φ - NSERC (Canada) PGS Fellow 1992-1994

1. Durst, T.; Koh, K. *Tetrahedron Lett.*, **1992**, *33*, 6799.
2. K. Koh; unpublished observations.
3. The diastereomeric ratio was readily determined by integrating the signals for the hydrogen α- to the lactone group near δ = 5.4 ppm (in the 5.3-5.5 ppm region).
4. Diastereomeric esters **3** and **8** were prepared by refluxing the corresponding acid chloride with (R)-pantolactone in the presence of 4Å molecular sieves. See Banks, A.R.; Fibiger, R.F.; Jones, T. *J. Org. Chem.*, **1977**, *42*, 3965.
5. All new products described in this article were isolated by chromatography on silica gel (EtOAc/hexanes as eluent) or recrystallization, and show satisfactory analytical data (IR, NMR, MS and HRMS). All the diastereomeric ratios of the products were determined by examination of the crude reaction mixtures in $CDCl_3$ using ^1H NMR (200 MHz or 300 MHz).
6. Isolated pure **4** showed no configurational alteration when it was stirred in THF with triethylamine or tetra-*n*-hexylammonium iodide for 2 days.
7. Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 2887.
8. Identified as the (S) isomer by reduction to the known (S)-N-benzylglycinol. Ref: Kaseda, T.; Kikuchi, T.; Kibayashi, C. *Tetrahedron Lett.*, **1989**, *30*, 4539.
9. An 11:1 (SR:RR) mixture of the α-bromoester **11** show complete epimerization at C-2 after stirring in THF with 0.2 molar equivalents of tetra-*n*-hexylammonium iodide for 8 hours.
10. A sample of (S)-2-amino-1-butanol obtained from Aldrich has the following specific rotation: $[\alpha]^{22}_D$ +8.6° (c 2.3, MeOH).
11. Williams, R.M.; Im, M.N. *J. Am. Chem. Soc.*, **1991**, *113*, 9276.
12. An exception is the preparation of D-*p*-hydroxyphenylglycine starting with racemic *p*-hydroxyphenyl hydantoin. This substrate is selectively hydrolyzed to D-N-carbamoyl-*p*-hydroxyphenylglycine by a D-specific hydantoinase from *Bacillus brevis*. The unreacted L-isomer spontaneously racemizes under the conditions of the enzymatic reaction. Ref: Meijer, E.M.; Boestan, W.H.J.; Schoemaker, H.E.; Van Balken, J.A.M. *In Biocatalysts in organic synthesis*, Elsevier Pub., Amsterdam Tramper, J.; Van der Plas, H.C.; Linko, P., Eds., **1985**, 135.

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