ation and chemical shifts in determining 1s ionization energies. Improved means of correlating gas and metal-adsorbed  $\sigma^*$  resonance positions with bond lengths are detailed.

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**Registry No.**  $Mn_2(CO)_{10}$ , 10170-69-1;  $Mn(CO)_5Br$ , 14516-54-2;  $Mn(CO)_5H$ , 16972-33-1.

## Stereoselective Alkylation of Glycine Units in Dipeptide Derivatives: "Chirality Transfer" via a Pivalaldehyde N,N-Acetal Center<sup>1</sup>

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Abstract: Dipeptide esters (of glycylglycine, glycylalanine, alanylglycine) and aldehydes (isobutyraldehyde, pivalaldehyde, benzaldehyde) are condensed to (4-oxoimidazolidin-3-yl)acetates and -propionates (1-3). Lithium enolates of these derivatives are generated (deprotonation of the ring and/or side-chain  $\alpha$ -carbonyl positions) with LDA, LDA/LiBr, or LHMDS and alkylated with high diastereoselectivity (products 4, 6, 7). Dipeptides of either *R*,*R* or *S*,*S* configuration can be prepared from the glycine-containing precursors. Surprising proton-transfer effects (Schemes VI-IX, XII) are interpreted as a consequence of "intimate complexation" among LDA, LiBr, lithium enolates, and diisopropylamine.

A major challenge for chemists is the successful alkylation of enantiomerically pure compounds without loss of optical activity and the stereoselective introduction of new stereogenic centers. Recently, many synthetic procedures which use chiral auxiliaries to achieve overall enantioselective alkylations have emerged.<sup>2</sup> A major disadvantage in all of these procedures is the necessary recovery and/or the cost of the chiral auxiliaries. Where possible, it is preferable to incorporate chiral building blocks into the product itself. One possibility of manipulating bonds on the one and only stereogenic center of simple chiral compounds without generating achiral intermediates and thus producing racemic mixtures is the reaction with an achiral auxiliary, creating a new temporary stereogenic center (Scheme I). We have been interested in stereoselective alkylations of functionalized enolates. Previously, we have shown that cyclic S,O-, O,O-, O,N-, and N,N-acetals are useful as protecting groups to preserve both the functionality and the chirality of  $\alpha$ - and  $\beta$ -heterosubstituted carboxylic acid derivatives during enolization and alkylation ("self-reproduction of chirality", or better, "self-regeneration of stereogenic centers").3

Reactions on increasingly complex compounds with more sensitive functionality have been another important goal for many research groups in synthesis. One of our goals has been the use of intact peptides as substrates in enolate reactions. New work with imidazolidinones derived from dipeptide esters has resulted in the discovery of a novel type of "chirality transfer" in which the original stereogenic center can be either retained or inverted during enolization/alkylation with the stereoselectivity induced via an N,N-acetal carbon atom to the newly created stereogenic center. In synthetic terms, this means that stereogenic centers may be generated along a peptide backbone.<sup>1</sup> This represents a fundamentally new approach to peptide synthesis.<sup>4</sup>

## **Results and Discussion**

**Preparation of Imidazolidinones.** We have shown previously that simple imines of glycine amides can be cyclized with anhydrous HCl in MeOH.<sup>3a,b,e</sup> Similar methodology worked well

with the pivalaldehyde imine of glycylglycine methyl ester. The resulting imidazolidinone hydrochloride crystallized in high yield and proved to be surprisingly stable, possessing a half-life of ca. 1-2 days in  $D_2O$  solution at room temperature. The NH group of the imidazolidinone was protected with Z (Cbz) to give 1 (benzyl chloroformate in  $CH_2Cl_2/NEt_3$ ) (Scheme II).<sup>5</sup>

D. Helv. Chem. Acta 1987, 70, 1930.
(2) (a) Evans, D. A. In Asymmetric Synthesis; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 1-110. (b) Lutomski, K. A.; Meyers, A. I. Ibid. pp 213-274. (c) Enders, D. Ibid. pp 275-339. (d) Bergbreiter, D. E.; Newcomb, M. Ibid. 1983; Vol. 2, pp 243-273. (e) McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chadha, R. J. Org. Chem. 1986, 53, 1947. (f) Oppolzer, W.; Pedrosa, R.; Moretti, R. Tetrahedron Lett. 1986, 27, 831. (g) Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. Tetrahedron Lett. 1986, 27, 3403. (h) Sinclair, P. J.; Zhair, D.; Reibenzpies, J.; Williams, R. M. J. Am. Chem. Soc. 1986, 108, 1103. (i) Brown, S. L.; Davies, S. G.; Foster, D. F.; Seeman, J. I.; Warner, P. Tetrahedron Lett. 1985, 26, 3567. (k) Belokon, Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryapkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. J. Am. Chem. Soc. 1985, 107, 4252. (l) Schmierer, R.; Grotemeir, G.; Helmchen, G.; Selim, A. Angew. Chem., Int. Ed. Engl. 1981, 20, 207. (m) Schöllkopf, U.; Groth, U.; Deng, C. Angew. Chem., Int. Ed. Engl. 1981, 20, 798.

(3) (a) Seebach, D.; Naef, R. Helv. Chim. Acta 1981, 64, 2704. (b)
Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. J. Am. Chem. Soc. 1983, 105, 5390. (c) Seebach, D.; Naef, R.; Calderari, G. Tetrahedron 1984, 40, 1313. (d) Seebach, D.; Roggo, S.; Zimmermann, J. Stereochemistry of Organic and Bioorganic Transformations; Bartmann, W., Sharpless, K. B., Eds.; VCH: New York, 1985; pp 85-126. (e) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. Helv. Chem. Acta 1987, 70, 237. (f) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. J. Am. Chem. Soc. 1988, 110, 4763-4778. (g) Seebach, D.; Fitzi, R. Tetrahedron 1988, 44, 5277.

(4) Ojima and co-workers have used asymmetric [2 + 2] cycloaddition reactions of chiral ketenes and amino ester derived imines to synthesize  $\beta$ -lactams which were opened to produce dipeptides stereoselectively. Although their system uses a chiral auxiliary and a chiral imine, the overall "chirality transfer" is similar: (a) Ojima, I.; Chen, H.-J. C. J. Chem. Soc., Chem. Commun. 1987, 625. Additionally, their  $\beta$ -lactam esters can be enolized and alkylated: (b) Ojima, I.; Qiu, X. J. Am. Chem. Soc. 1987, 109, 6537.

(5) The *t*-BOC-protected analogue was also prepared (87% yield from the imidazolidinone hydrochloride, mp 73.0-73.5 °C) and was methylated in the same manner as **1a** to give an analogous product (**4b**, BOC instead of Z, 75% yield, mp 81.5-82.5 °C) with comparable stereoselectivity.

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<sup>(1)</sup> A preliminary account of this work has appeared: Polt, R.; Seebach, D. Helv. Chem. Acta 1987, 70, 1930.





Scheme II. Synthesis of Imidazolidinone Dipeptide and Tripeptide Derivatives



i - Me3CCHO/CH2Cb/NEt3/MgSO4 ii - AcCI/EtOH or MeOH iii - Z-CI/DMAP/NEt3/CH2C2



By the incorporation of an L-alanine into the dipeptide we hoped that the stereogenic center would influence the cyclization reaction, providing diastereoselective formation of imidazolidinones 2 and 3. In practice, additional substitution retards the cyclization and it is not highly diastereoselective.<sup>6</sup> Nevertheless, the cyclization reaction gave acceptable yields of crystalline, enantiomerically pure (+)-2a and (-)-3a. The configuration of (-)-3a was determined to be trans from the observation of nuclear Overhauser effects (NOE), and the configuration of (+)-2a was determined by single-crystal X-ray diffraction on the corresponding ethyl ester.<sup>7</sup> Similar dipeptide-derived imines (for example, imines derived from isobutyraldehyde, benzaldehyde, or 2-methoxy-2methylpropanal) underwent cyclization under the same reaction conditions. None of these imidazolidinones showed any appreciable increase in diastereoselectivity either during cyclization or upon alkylation. The imidazolidinone derived from the pivalaldehyde imine of the tripeptide glycylglycylglycine methyl ester was also prepared but could not be alkylated selectively.<sup>8c,d</sup>

Alkylations. The imidazolidinones 1-3 have two enolizable carbonyls of roughly equal acidity, and the serious problem of achieving selective enolization at one site was foreseen. Since it was not clear to us which position would be deprotonated preferably,<sup>8a,9</sup> the simplest case, the racemic glycylglycine derivative

<sup>(6)</sup> Cyclization experiments with the pivalaldehyde imines from glycine benzylamide and glycine (S)-2-phenethylamide showed that it is possible to obtain high diastereoselectivity in the cyclization reaction, but the yield drops dramatically from 60% to 5%, respectively. This pattern of increasing diastereoselectivity and decreasing yields with increasing steric bulk was observed with dipeptide derivatives also. For example: the imine derived from glycylglycine ethyl ester cyclized in good yield (>80%); glycyl-L-alanine methyl ester cyclized with moderate diastereoselectivity (~2:1) and in moderate yield (~50%); glycyl-L-leucine methyl ester cyclized with good diastereoselectivity (>5:1) but in poor yield (<10%); the imine from glycyl-L-valine methyl ester diastereoselectivity but lower yields as well. The reaction was very slow at temperatures below -15 °C.

<sup>(7)</sup> The  $\dot{X}$ -ray analysis was carried out by Dr. M. Egli of the ETH. This work will be published elsewhere (*Chimia*, in press).

<sup>(8)</sup> See the large  $pK_a$  difference between dimethyl malonate ( $pK_a = 15.9$ ) and Meldrum's acid ( $pK_a = 7.3$ ): (a) Wang, X.; Houk, K. N. J. Am. Chem. Soc. **1988**, 110, 1870. (b) Wiberg, K. B.; Laidig, K. E. J. Am. Chem. Soc. **1988**, 110, 1872. The  $pK_a$  difference between CH<sub>3</sub>CONH<sub>2</sub> protons ( $pK_a = 25.5$ ) and CH<sub>3</sub>COOCH<sub>3</sub> protons ( $pK_a = 26.5$ ) is very small. See, for example: (c) Bordwell, F. G.; Algrim, D. J. J. Org. Chem. **1976**, 41, 2507. (d) Krapcho, A. P.; Dundulis, E. A. Tetrahedron Lett. **1976**, 2205. (e) Hoye, T. R.; Duff, S. R.; King, R. S. Tetrahedron Lett. **1985**, 26, 3433.

<sup>(9) (</sup>a) Bilyard, K. G.; Garratt, P. J.; Hunter, R.; Lee, E. J. Org. Chem. **1982**, 47, 4731. (b) Furuta, K.; Misumi, A.; Mori, A.; Ikeda, N.; Yamamoto, H. Tetrahedron Lett. **1984**, 25, 669. (c) Beak, P.; Musick, T. J.; Chen, C. J. Am. Chem. Soc. **1988**, 110, 3538. It is quite conceivable that the second pK<sub>a</sub> of a diacid (monoenolate  $\rightarrow$  bis-enolate) can actually be lower than the first pK<sub>a</sub> ( $\alpha$ -ester CH<sub>2</sub>  $\rightarrow$  ester enolate) under conditions of appropriate solvation. In situations where solvation energies can dominate the intrinsic acidities (e.g. carbanions), this is reasonably common: (d) Bachrach, S. M. J. Am. Chem. Soc. **1986**, 108, 6406 and references therein. For reviews of dianions in synthesis: (e) Harris, T. M.; Harris, C. M. Org. React. **1969**, 17, 155. (f) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. Synthesis **1977**, 509.





Scheme IV. Enolization Occurs Preferentially at the Ester



Scheme V. Monoalkylation of Ester Enolate



i-LiHMDS/THF/-78°C ii - 3 LiBr/LDA/THF/-78°C iii - 5 Mel/-78°C

1a, was examined first with the hope that it would be easy to analyze the results. We were surprised to find that bis-enolization of this substrate was facile. Thus addition of 1 equiv of LDA to 1a in THF at -78 °C, followed by an excess of MeI, gave ca. 50% starting material and ca. 50% dimethylated product 4b. More surprising was that, of the six possible dimethylated products (four diastereomeric pairs of enantiomers + two geminally dimethylated enantiomeric pairs), only 4b was formed in appreciable amounts. Bis-enolization was best achieved by adding *slightly less than* 2 equiv of LDA to 1a; use of *more than* 2 equiv of base resulted in reduced stereoselectivity and lower yields of 4b upon methylation.

Experimentation showed that high yields of the monoalkylated product **4a** could be obtained from the bis-enolate derived from **1a** with excellent diastereoselectivity (% ds) by adding only 1 equiv of MeI. In the dialkylation of the bis-enolate the second alkyl group was introduced much more slowly than the first one, thus, it seemed feasible to attempt sequential alkylations with different electrophiles. By monitoring the progress of the first alkylation by TLC and adding a second alkylating agent it was possible to alkylate first the imidazolidinone moiety and then the pendant ester sequentially. Several examples are shown in Scheme III. From these results it was clear that the most reactive position and presumably the site of the second deprotonation<sup>9d-f,10</sup> was the endocyclic imidazolidinone methylene group. As shown by NOE on 4b, the first alkyl group was introduced trans to the *tert*-butyl moiety as expected.<sup>3</sup> In fact, no cis isomer was detected in any of the experiments. The configuration at the  $\alpha$ -ester carbonyl position showed some variation with selectivities ranging from 7:1 to greater than 50:1. Since the rotamer populations of the pendant ester group were not known, NOE was of no help in determining the configuration of the stereogenic center in the side chain. Since HPLC methods were available to distinguish the diastereoisomers of alanylalanine,<sup>11</sup> it was possible to degrade the imidazolidinone to the free dipeptide (see the section on Deprotection and Further Transformations, below) to determine the relative configuration. Upon deprotection of 4b, the resulting diastereomerically pure but racemic dipeptide had the same retention time as L-alanyl-L-alanine,<sup>11,12</sup> thus proving the relative configuration to be as shown in Scheme III.

We thought that the use of a less reactive base such as LiHMDS (lithium hexamethyldisilazide)<sup>13a</sup> would allow us to enolize the more acidic ester position selectively without competing bis-enolate formation. Although experiments showed this to be true, *geminal* bis-alkylation to give 5 became a problem (Scheme IV). With the use of 2 equiv of LiHMDS and an excess of MeI, product 5 predominated. LiHMDS was capable of enolizing the

<sup>(10)</sup> Multiply lithiated substrates are quite common in synthesis. Generally, the site of the last deprotonation is the most reactive anionic site in alkylation reactions (cf. "Hauser's rule"): (a) Hauser, C. R.; Harris, T. M. J. Am. Chem. Soc. **1958**, 80, 6360. For recent review articles on the use of polylithiated ketones and nitroalkanes, see: (b) Seebach, D.; Pohmakotr, M. Tetrahedron **1981**, 37, 4047. (c) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. Chimia **1979**, 33, 1. For polylithiated sulfur derivatives, see: (d) Geiss, K.; Seebach, D.; Seuring, B. Chem. Ber. **1977**, 110, 1833. (e) Pohmakotr, M.; Geiss, K.; Seebach, D. Chem. Ber. **1979**, 112, 1420. (f) Widler, L.; Weber, T.; Seebach, D. Chem. Ber. **1985**, 118, 1329.

<sup>(11)</sup> Kroeff, E. P.; Pietrzyk, D. J. Anal. Chem. 1978, 50, 1353.

<sup>(12)</sup> The two samples also displayed identical TLC behavior (visualization with ninhydrin).

<sup>(13)</sup> Conditions for generation of ester enolates typically involve the addition of the substrate to an excess of LDA at -78 °C, for example: (a) Rathke, M. W. J. Am. Chem. Soc. 1970, 92, 3222. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. J. Am. Chem. Soc. 1976, 98, 2868. (c) Wissner, A. J. Org. Chem. 1979, 44, 4617. (d) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. J. Am. Chem. Soc. 1980, 102, 3959. (e) Garst, M. E.; Bonfiglio, D. A.; Grundoski, J.; Marks, J. J. Org. Chem. 1980, 45, 4617. (f) Evans, D. A. Asymmetric Synthesis; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 1-110. (g) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. J. Am. Chem. Soc. 1986, 108, 4943. (h) d'Angelo, J. Tetrahedron 1976, 32, 2979.





Scheme VII. Monoalkylation of Imidazolidinone Enolate



i-3LiBr/LDA/THF/-78°C

ii - 5 Mel / -78°C

imidazolidinone, resulting in product 6 upon alkylation but only after the more acidic ester position was completely blocked.

With this experience in hand, we turned our attention to the monoalkylation of the nonracemic substrates (+)-2a and (-)-3a. Alkylation of the ester position of (-)-3a was straightforward with less than 1 equiv of LiHMDS at -78 °C. The crystalline product (-)-7a was obtained in excellent yield with a stereoselectivity of 20:1, and we could detect no epimerization of the original centers by <sup>1</sup>H NMR of the crude reaction mixture (Scheme V). Attempts to perform this same alkylation using LDA as the base, either with normal addition or inverse addition,<sup>13</sup> gave mixtures of the desired product, its epimer, geminally dialkylated product, starting material, and other unidentified products. Hence, enolization at the ester position and even bis-enolization probably occurred. Other workers9 have noted that certain bis-enolates are remarkably stable species and are alkylated with good regio- and stereocontrol, whereas the corresponding mono-enolates give product mixtures. Proton-exchange processes have been claimed to be the root cause of these problems and are certainly quite fast relative to alkylation.9,14 In spite of these facts, we found that the bis-enolate generated from 1a with 2 equiv of LDA could be alkylated twice in high yield, even when the second alkylation was quite slow. The second alkylation must have proceded via a mono-enolate of the required type.

It seemed plausible to us that the crucial difference between the mono-enolate formed by monoalkylation of the LDA-generated bis-enolate of 1a on the one hand and the desired enolate derived from deprotonation of (-)-3a by 1 equiv of LDA on the other hand was the presence of 1 equiv of LiBr or LiI formed in the first alkylation of the bis-enolate (Scheme VI). The presence of additional lithium halide salts, as Jackman has pointed out,<sup>15</sup> should lead to the formation of mixed LiX-(enolate) aggregates. An attempt was made to enolize **3a** in the presence of LiBr. Thus, the addition of 3 equiv of LiBr to (-)-**3a** followed by dropwise addition of less than 1 equiv of LDA at -78 °C produced an enolate which was methylated to give a high yield of the expected product (-)-**7a** with a diastereoselectivity of 7:1 or higher (Scheme V, ii). Once again we could detect no epimerization of the original stereogenic center.

Imidazolidinone (+)-2a was subjected to the same LDA/LiBr enolization conditions used above, followed by methylation. We expected to see either methylation  $\alpha$  to the ester group to give (2R)-5 (see Scheme IV) or, less likely, alkylation to proceed at the ring position to give the (2R, 5R, 1'S)-imidazolidinone. In fact, we obtained the (2R,5R,1'R)-(+)-7a, i.e. the enantiomer of (-)-7a. Thus, not only has inversion of the original stereogenic center occurred during the reaction but the regioselectivity of alkylation has changed with the base (Scheme VII). When the epimeric starting material (-)-2b was alkylated in the same fashion, it gave a product with the same NMR spectrum as the minor product from (+)-2a, which is epimeric at the side-chain stereogenic center. Thus the stereoisomer of 7b must have been formed from (-)-2b, again with inversion of the original stereogenic center. Note that the "stereochemical information" contained in the different configurations of 2a and 2b is "preserved" in the derived enolate structures and is "regenerated" with inversion of configuration in the side chain during the alkylation process-otherwise, the ester enolates from 2a and 2b would be enantiomeric and would give enantiomeric and not diastereoisomeric products.

Since the enolate of (+)-2a was generated under "thermodynamic conditions" (e.g. less than 1 equiv of base and normal addition),<sup>13</sup> it seemed likely that either the starting material

<sup>(14)</sup> For example, Wakefield has shown that PhCH<sub>2</sub>CN does *not* form a dianion upon treatment with 2 equiv of *n*-BuLi but rather a complex of the monoanion and *n*-BuLi is formed, which behaves as a dianion due to fast *intraaggregate* proton transfer. Thus, proton transfer within an aggregate can be much faster than alkylation and is even faster than  $D^+$  transfer from an external source: Crowley, P. J.; Leach, M. R.; Meth-Cohn, O.; Wakefield, B. J. Tetrahedron Lett. **1986**, 25, 2909.

<sup>(15) (</sup>a) Jackman, L. M.; Hadden, R. C. J. Am. Chem. Soc. 1973, 95,
3687. (b) Jackman, L. M.; Lange, B. C. Tetrahedron 1977, 33, 2737. (c)
Jackman, L. M.; Dunne, T. S. J. Am. Chem. Soc. 1985, 107, 2805. (d)
Jackman, L. M.; Smith, D. B. J. Am. Chem. Soc. 1988, 110, 3829.

Scheme VIII. No Deuterium Incorporation or Inversion



Scheme IX. Deuterium Returns with Inversion



or the initial alkylation product was undergoing base-catalyzed equilibration to give the observed final product.<sup>16</sup> Subsequent experiments showed that this was *not* the case. Neither **2a** nor **2b** underwent significant equilibration under the same conditions used for alkylation (0.05–0.2 equiv of LDA·3LiBr, THF, -78 °C, 24 h). Treatment of the product imidazolidinone (+)-7a with 0.9 equiv of LDA·3LiBr, followed by quenching with HOAc, resulted in the formation of a ca. 1:1 mixture of 7a and its side-chain epimer **7b**. Thus, there appears to be no intrinsic stereochemical preference for protonation of the enolate from **7a**. Attempts to epimerize this mixture with LDA·3LiBr again resulted in ca. 1:1 mixtures of the same two products. These results imply that *the epimerization of* (+)-**2a**/(+)-**7a** occurs during the alkylation and is not the result of base-catalyzed thermodynamic equilibration of the starting material or product.

**Deuterium Labeling Studies.** In an effort to clear up this mechanistic intrigue, some deuterium labeling studies were performed. Attempts to epimerize and/or label (+)-2a kinetically by treatment with 0.9 equiv of LDA-3LiBr followed by quenching with CD<sub>3</sub>COOD failed (Scheme VIII). In each attempt unlabeled (+)-2a was recovered with the configuration essentially unchanged ( $\leq 5\%$  change). The fact that no D was incorporated was not surprising to us, since we had shown previously that enolates generated with LDA can be tightly complexed with iPr<sub>2</sub>NH and show poor D incorporation due to competitive reprotonation<sup>3b,17</sup> by iPr<sub>2</sub>NH upon the addition of D<sup>+</sup> ("internal return"<sup>18</sup> or "conducted tour"<sup>19</sup>). Generally, however, there is some D incorporation in such cases. In the present case we could detect *no* D incorporation, even by mass spectroscopy. We have also

shown previously<sup>17a</sup> that alkylation of the normally nonnucleophilic LDA can be effected in the presence of the appropriate enolate.

There remained the possibility that the enolate was being protonated by some other proton source which had escaped our attention. Thus, labeled *rac*-**2a** was synthesized de novo from racemic deuterium-labeled alanine methyl ester<sup>20</sup> and the deuterium-labeled imidazolidinone was subjected to both the quenching experiment (this time with H<sup>+</sup>) and to alkylation. In both cases the D was returned to the ester position. Upon *protonation* of the enolate (we assume that the ester position must have enolized upon addition of LDA-3LiBr) the D was returned to give the *original configuration* of the starting material, e.g. *rac*-**2a**. Upon *alkylation* of the enolate, *rac*-**7a** was obtained, once again with the *inverted configuration* at the  $\alpha$ -position of the ester group (Scheme IX).

The same procedure (0.9 equiv of LDA·3LiBr then CD<sub>3</sub>COOD) was applied to (+)-7a. This gave, very cleanly, a mixture of three compounds: starting material 7a, epimerized material 7b, and epimerized, labeled material 7b-d in a ratio of ca. 2:1:1. Only the epimerized material contained D. Thus, the Si face was ca. 50% deuterated by the CD<sub>3</sub>COOD and the Re face was not deuterated at all. Apparently, only one face of the enolate (the Si face) is accessible to the CD<sub>3</sub>COOD. From this result it is again clear that there is no intrinsic preference for the enolate of 7a to protonate stereoselectively.<sup>21</sup> Again, attempts to equilibrate this mixture back to the original configuration using 0.05–0.20 equiv of LDA·3LiBr failed (Scheme X).

Thus, we were unable to epimerize the starting material 2a and unable to reepimerize the epimeric product 7b with LDA-3LiBr. Apparently, the epimerization occurs kinetically during the alkylation step. Duhamel and others have shown that the choice of base can critically affect the stereoselectivity of protonation of  $\alpha$ -amino ester enolates.<sup>22</sup> Clearly, the base used in the enolization is critical in the present case, since LiHMDS gives alkylation  $\alpha$  to the ester group and LDA·3LiBr results in epimerization of the ester and alkylation at the imidazolidinone. A tightly complexed HN(iPr)<sub>2</sub> molecule could affect the reactivity of the ester enolate in two ways: (1) by shielding the enolate from alkylation<sup>23</sup> and (2) by acting as a proton donor in the reprotonation<sup>17,22</sup> of the ester enolate and a proton acceptor in the enolization<sup>16</sup> of the imidazolidinone. Both solid-state X-ray structures<sup>17</sup> and solution studies<sup>22,25</sup> of lithium enolates indicate that  $HN(iPr)_2$  and other secondary amines are complexed to the lithium. The base  $HN(SiMe_3)_2$  is known to be a poor ligand for lithium, a fact that is reflected by its lower basicity relative to diisopropylamine; the lower basicity of the Li derivative, relative to LDA; its lower aggregation state in solution,  $^{26}$  and in the solid state structures of its lithium salts.  $^{27}$  In a definitive study,  $^{26c}$ 

<sup>(16)</sup> In fact, 2b was never observed in crude alkylation mixtures of 2a. One possible implication is that 2b does not equilibrate under the reaction conditions.

<sup>(17) (</sup>a) Laube, T.; Dunitz, J. D.; Seebach, D. Helv. Chim. Acta 1985, 68, 1373.
(b) Aebi, J. D.; Seebach, D. Helv. Chim. Acta 1985, 68, 1507.
(c) Dietrich, H.; Mahdi, W.; Knorr, R. J. Am. Chem. Soc. 1986, 108, 2462.
(d) Wanat, R. A.; Collum, D. B.; Van Duyne, G.; Clardy, J.; DePue, R. T. J. Am. Chem. Soc. 1986, 108, 3415.
It should be pointed out, however, that HN(iPr)<sub>2</sub> need not be present [(e) Seebach, D.; Bauer, W.; Hansen, J.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. J. Chem. Soc., Chem. Commun. 1984, 853] and can be exchanged with THF as a ligand [(f) Bauer, W.; Laube, T.; Seebach, D. Chem. Ber. 1985, 118, 764].
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<sup>(18)</sup> Winstein, E. J. Am. Chem. Soc. 1965, 87, 376.

<sup>(19)</sup> Cram, D. J. Fundamentals of Carbanion Chemistry, Academic Press: New York, 1965; p 101.

<sup>(20)</sup> Synthesized by phase-transfer alkylation of the benzophenone Schiff base using KOD/D<sub>2</sub>O generated by carefully adding small pieces of K metal to D<sub>2</sub>O under argon at 0 °C: (a) O'Donnell, M. J.; Polt, R. L. J. Org. Chem. **1982**, 47, 2663. (b) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. Tetrahedron Lett. **1978**, 2641.

<sup>(21)</sup> Stereoselective protonation of steroid butenolides is known: Takano, S.; Yamada, S.; Numata, H.; Ogasawara, K. J. Chem. Soc., Chem. Commun. **1983**, 760.

<sup>(22) (</sup>a) Eleveld, M. B.; Hogeveen, H. Tetrahedron Lett. 1986, 27, 631.
(b) Duhamel, L.; Fouquay, S.; Plaquevent, J.-C. Tetrahedron Lett. 1986, 27, 4975.

<sup>(23)</sup> Amine complexes of enolates and other anionic species are known to be less reactive in alkylation reactions. For examples, see: (a) Amupitan, J.; Sutherland, J. K. J. Chem. Soc., Perkin Trans. I 1983, 747. (b) Sutherland, J. K. J. Chem. Soc., Chem. Commun. 1978, 852. (c) Midland, M. M. J. Org. Chem. 1975, 40, 2250.

<sup>(24)</sup> Reprotonation of the ester enolate would necessarily regenerate a molecule of LDA which would still be in close proximity or complexed to the acidic imidazolidinone proton.

<sup>(25)</sup> Kallman, N.; Collum, D. B. J. Am. Chem. Soc. 1987, 109, 7644 and references therein.

<sup>(26) (</sup>a)  $pK_a$ 's, LDA = 35.7; LiHMDS = 29.5: Fraser, R. R.; Mansour, T. S. J. Org. Chem. 1984, 49, 3442. (b) Dimers were proposed for LiHMDS on the basis of molecular weight determinations: Wannagat, U. Adv. Inorg. Chem. Radiochem. 1964, 6, 237. (c) Kimura, B. Y.; Brown, T. L. J. Organomet. Chem. 1971, 26, 57.

Scheme X. Deuterium Quenching of Deprotonated (+)-7a



Scheme XI. H<sub>2</sub>O Molecule Allows Favorable Geometry for H<sup>+</sup> Transfer<sup>29c</sup>



LiHMDS was shown to be a mixture of dimers and monomers in THF:  $(LiHMDS)_2 \rightarrow 2LiHMDS$ ,  $\Delta H^\circ = -4.0 \text{ kcal/mol}$ ,  $\Delta S^\circ = -17 \text{ cal/}^\circ \text{C} \cdot \text{mol}$ . Clearly, HN(SiMe<sub>3</sub>)<sub>2</sub> would not complex to the Li ester enolate strongly enough to shield the enolate from alkylation (cf. Scheme IV).

We may regard the initially formed ester enolate (Scheme VII) as an enolate with an internal proton source (the imidazolidinone methylene). A number of similar ambident systems have been studied in great detail by using kinetic methods.<sup>28</sup> In aqueous systems, intervening H<sub>2</sub>O molecules are often invoked to explain intramolecular proton transfers.<sup>29</sup> Bernasconi has presented evidence based on proton-inventory studies that an H<sub>2</sub>O molecule acts as a bridge in the intramolecular protonation ("intramolecular proton switch") of enolates derived from Meldrum's acid<sup>29c</sup> (Scheme XI). The complexed HN(iPr)<sub>2</sub> in the imidazolidinone dipeptide system can act in an analogous fashion, functioning as a proton donor/acceptor in a concerted fashion, just as H<sub>2</sub>O does in the less basic systems.<sup>30</sup>

Three types of enolates studied, enolates generated from 2a, 3a, and the bis-enolate from 1a all showed similar behavior. Since literature examples indicate that both alkylation and protonation of ester enolates occur from the same diastereotopic face,<sup>31</sup> it is likely that the observed configurational preference in the side chain is a result of the bulky *tert*-butyl group occluding one face of the enolate. Regardless of the mechanism, the overall steric course

<sup>(27)</sup> LiN(SiR<sub>3</sub>)<sub>2</sub> X-ray structures show a lower tendency to aggregate than LiNR<sub>2</sub>. For example: (a) Mootz, D.; Zinnius, A.; Böttcher, B. Angew. Chem., Int. Ed. Engl. 1969, 8, 378. (b) Lappert, M. F.; Slade, M. J.; Singh, J.; Atwood, J. L.; Rogers, R. D.; Shakir, R. J. J. Am. Chem. Soc. 1983, 105, 302. (c) Engelhardt, L. M.; May, A. S.; Raston, C. L.; White, A. L. J. Chem. Soc., Dalton Trans. 1983, 1671. (d) Power, P. P.; Xiaojie, X. J. Chem. Soc., Chem. Commun. 1984, 358. (e) Bartlett, R. A.; Power, P. P. J. Am. Chem. Soc., 1987, 109, 6509. (f) Barr, D.; Clegg, W.; Mulvey, R. E.; Snaith, R. J. Chem. Soc., Chem. Commun. 1984, 285. (g) Barr, D.; Clegg, W.; Mulvey, R. E.; Snaith, R. J. Chem. Soc., Chem. Soc., Chem. Commun. 1984, 287. (h) Armstrong, D. R.; Barr, D.; Clegg, W.; Mulvey, R. E.; Snaith, R.; Wade, K. J. Chem. Soc., Chem. Commun. 1986, 869. (i) Barr, D.; Clegg, W.; Mulvey, R. E.; Snaith, R.; Wright, D. S. J. Chem. Soc., Chem. Commun. 1987, 716. (j) For a gas phase e<sup>-</sup> diffraction study of LiN(TMS)<sub>2</sub>: Fjeldberg, T.; Hitchcock, P. B.; Lappert, M. F.; Thorne, A. J. J. Chem. Soc., Chem. Commun. 1984, 822.

<sup>mun. 1984, 622.
(28) (a) Bernasconi, C. F.; Carrè, D. J. J. Am. Chem. Soc. 1979, 101, 2698. (b) Bernasconi, C. F.; Fornarini, S. J. Am. Chem. Soc. 1980, 102, 5329.
(c) Tapuhi, E.; Jencks, W. P. J. Am. Chem. Soc. 1982, 104, 5758. (d) Bernasconi, C. F.; Murray, C. J. J. Am. Chem. Soc. 1984, 106, 3257. (e) Bernasconi, C. F.; Fox, J. P.; Kanavarioti, A.; Panda, M. J. Am. Chem. Soc. 1986, 108, 2372. (f) Bernasconi, C. F.; Murray, C. J. J. Am. Chem. Soc. 1986, 108, 5257. (g) A study using LDA/2-methyl-3-pentanone in THF shows that proton transfer is not the slow step in kinetic enolate formation: Miller, D. J.; Saunders, W. H., Jr. J. Org. Chem. 1982, 47, 5039.</sup> 

<sup>(29) (</sup>a) Gandour, R. D. Tetrahedron Lett. 1974, 295. (b) Kirby, A. L.;
Lloyd, G. J. J. Chem. Soc., Perkin Trans. 2 1976, 1762. (c) Bernasconi, C.
F.; Fairchild, D. E.; Murray, C. J. J. Am. Chem. Soc. 1987, 109, 3409.
(30) (a) Stein, R. L.; Strimper, A. M. J. Am. Chem. Soc. 1987, 109, 4387.
(b) Craik, C. S.; Roczniak, S.; Largman, C.; Rutter, W. J. Science 1987, 237,
909. (c) Sprang, S.; Standing, T.; Fletterick, R. J.; Stroud, R. M.; Finer-Moore, J.; Xuong, N. H.; Hamlin, R.; Rutter, W. J.; Craik, C. S. Science 1987, 237, 905. (d) Bachovchin, W. W. Biochemistry 1986, 25, 7751. (e) Kossiakoff, A. A.; Spencer, S. A. Biochemistry 1981, 20, 6462.

<sup>(31)</sup> Literature examples indicate that both protonation and alkylation of ester enolates generally occur from the same face of the enolate: (a) Bernard, W.; Fleming, I.; Waterson, D. J. Chem. Soc., Chem. Commun. 1984, 28. (b) Yamamoto, Y.; Maruyama, K. J. Chem. Soc., Chem. Commun. 1984, 904. (c) Fleming, I.; Lewis, J. J.; J. Chem. Soc., Chem. Commun. 1985, 149. (d) Tomioka, K.; Yasuda, K.; Kawasaki, H.; Koga, K. Tetrahedron Lett. 1986, 27, 3247.

Scheme XII. Lithium Enolate-Secondary Amine Interactions<sup>17</sup>



of the reactions studied here seems to be subject to the two following rules: (a) as in simple cases,<sup>3</sup> the new substituent in the  $\alpha$ -carbonyl position of the imidazolidinone ring is attached trans to the *tert*-butyl group (relative configuration *like*) and (b) the new stereogenic center in the side-chain  $\alpha$ -ester carbonyl position and the *tert*-butyl-substituted acetal center also have a *like* relative configuration (**2b**  $\rightarrow$  **7b** is an exception).

The surprising effects observed upon the addition of alkyl halides (and of other electrophiles) to solutions of lithium enolate-secondary amine complexes (see, for instance, eq 1 in Scheme XII)<sup>17a,b,f</sup> are now expanded by an especially striking case (eq 2 in Scheme XII).

The Role of LiBr. Quite some time ago Morton<sup>32</sup> observed a striking change in the reactivity of allylsodium upon the addition of small amounts of NaCl. Since then Wittig<sup>33</sup> has pointed out the importance of added halide salts in numerous anionic reactions. In spite of this knowledge, the effects of added LiBr, etc. on enolate reactions have only recently begun to be studied.<sup>15,34</sup> X-ray diffraction studies<sup>35</sup> of lithium aggregates can provide structural clues as to the precise mechanistic role of added salts on lithium aggregates. While it is not possible to state categorically that the aggregate structures of enolates observed in the solid state are always mechanistically important, ample evidence from solution studies suggests that they are the appropriate starting point for any mechanistic discussion of enolate behavior.<sup>35</sup> Clearly, judging from known X-ray structures,<sup>36</sup> when LiBr is incorporated into an aggregate, the net effect is to replace anionic species within the aggregate. Since Br and Cl are small ligands, they can readily replace bulkier anions such as  $N(iPr)_2$  within an aggregate.

(32) (a) Morton, A. A.; Finnegan, R. A. J. Polym. Sci. 1959, 38, 19. (b)
 Morton, A. A.; Cluff, E. F. J. Am. Chem. Soc. 1952, 74, 4056. (c) Morton,
 A. A.; Magat, E. E.; Letsinger, R. L. J. Am. Chem. Soc. 1947, 69, 950.
 (32) (a) Witting G. Q. Paro, Chem. Soc. 1966, 20, 101

(33) (a) Wittig, G. Q. Rev. Chem. Soc. 1966, 20, 191. For more recent work, see: (b) Soderquist, J. A.; Anderson, C. L. Tetrahedron Lett. 1988, 29, 2425 and references therein.

(34) (a) Guibe, F.; Sarthou, P.; Bram, G. *Tetrahedron* **1974**, *30*, 3139. (b) Galiano-Roth, A. S.; Michaelides, E. M.; Collum, D. B. J. Am. Chem. Soc. **1988**, *110*, 2658–2660. (c) DePue, J. S.; Collum, D. B., personal communication.

(35) Seebach, D. Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research XXVII. Stereospecificity in Chemistry and Biochemistry, 1983; pp 93-145 (published 1984). While the overall aggregation state may not change due to the addition of LiX, the net effect is "deaggregation", in terms of the reactive species.

Solution studies<sup>34</sup> as well reflect this "deaggregating" effect of lithium halides, with corresponding changes in reactivity of the aggregates. While it is quite possible that the LiBr forms a complex with the enolate, <sup>15,36</sup> thereby slowing intraaggregate proton-exchange processes,<sup>14</sup> the results of alkylation using LiHMDS clearly show that the LiBr is not necessary for the overall stereochemical result. A far more likely explanation of the effect of LiBr is that it deaggregates the LDA, thereby preventing the formation of an LDA-enolate complex<sup>37</sup> which could undergo fast intraaggregate proton transfer<sup>14</sup> resulting in the formation of a bis-enolate in the present case. This bis-enolate would be expected to be alkylated very quickly, giving an enolate of **7a**, which has already been shown (see the section on Deuterium Labeling Studies, above) to be protonated *without* any stereoselectivity.

Deprotection and Tripeptide Synthesis. The alkylated products (e.g. 7a) can be saponified in nearly quantitative yield with KO-SiMe<sub>3</sub> in THF at room temperature. Acidification with ca. 1.1 equiv of 0.1 N HCl, followed by extraction with EtOAc, drying, and solvent removal, gave the corresponding imidazolidinyl-substituted acid 8 (Scheme XIII). The Z group was removed with  $H_2/Pd-C$  in EtOAc, which gave rise to the " $\delta$ -amino acid" 9, again in high yield. Alternatively, the imidazolidinyl acid was coupled with an amino ester to yield a tripeptide derivative 10. When the Z group was removed first, the resulting amino ester underwent facile cyclization<sup>38</sup> to the cyclic dipeptide (diketopiperazine). The imidazolidinyl amino acids (acetals) were surprisingly stable, especially in acidic solution. In deionized water (pH  $\sim$  5), however, 9 underwent ring opening at 80 °C in less than 20 min to give pure D-alanyl-D-alanine in excellent yield. Tripeptide Dalanyl-D-alanyl-L-alanine was obtained from 10 in an analogous fashion.

## **Experimental Section**

General. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F-254 analytical plates. Flash chromatography was per-

<sup>Biochemistry, 1983; pp 93-145 (published 1984).
(36) (a) For a review of alkyllithium structures which have been determined by X-ray diffraction, see: Setzer, W.; Schleyer, P. R. Adv. Organomet. Chem. 1985, 24, 353. (b) For specific examples of the deaggregating effects of LiBr on anions, see: Hope, H.; Power, P. P. J. Am. Chem. Soc. 1983, 105, 5320. (c) Schmidbauer, H.; Schier, A.; Schubert, U. Chem. Ber. 1983, 116, 1938. (d) Amstutz, R.; Dunitz, J. D.; Laube, T.; Schweizer, W. B.; Seebach, D. Chem. Ber. 1986, 119, 434. (e) Bauer, W.; Seebach, D. Helv. Chim. Acta 1984, 67, 1972. (f) Seebach, D.; Amstutz, R.; Dunitz, J. D. Helv. Chim. Acta 1981, 64, 2622.</sup> 

<sup>(37) (</sup>a) Eleveld, M. B.; Hogeveen, H. Tetrahedron Lett. 1986, 27, 631.
(b) Williard, P. G.; Carpenter, G. B. J. Am. Chem. Soc. 1986, 108, 462. (c) Williard, P. G.; Hintze, M. J. J. Am. Chem. Soc. 1987, 109, 5539 and references therein. For a study of lithium salts of aromatic amines in polar aprotic solvents, see: (d) Jackman, L. M.; Scarmoutzos, L. M. J. Am. Chem. Soc. 1987, 109, 5348.

<sup>(38) (</sup>a) Preu, J. Justus Liebigs Ann. Chem. 1865, 134, 372. (b) Fischer, E. Chem. Ber. 1906, 39, 467. (c) Pickenhagen, W.; Dietrich, P.; Borivoij, K.; Polonsky, J.; Nouaille, F.; Lederer, E. Helv. Chim. Acta 1975, 58, 1078.





i-KOSi(Me)<sub>3</sub>/THF ii-H<sub>2</sub>/Pd-C/EtOAc iii-H<sub>2</sub>O/80°C iv-L-ala-OMe/DCC/HOBT/EtOAc v-PhOH/150°C

formed as described by Still et al.<sup>39</sup> using Merck silica gel 60 (230–400 mesh). THF was freshly distilled from potassium benzophenone ketyl under argon. All alkylations and reactions with LDA were carried out under a positive (ca. 50 mmHg) pressure of argon in glassware flamedried (T > 450 °C) under a stream of argon. <sup>1</sup>H NMR were measured at 300 MHz and <sup>13</sup>C NMR were measured at 75 MHz on a Bruker WM-300 instrument. Infrared spectra were measured on a Perkin-Elmer 782 spectrophotometer. Optical rotations were recorded with a 10-cm, 1-mL cell on a Perkin-Elmer 241 polarimeter. Elemental analyses were generally correct to within  $\pm 0.3\%$  and are listed in detail for poorer cases. High-pressure liquid chromatography was performed as described in the literature<sup>11</sup> on a 4 × 25 mm, 7- $\mu$ m LiChrosorb RP-8 column (commercially available from Dr. Herbert Knauer, KG, P.O.B 1322, Oberursel, D6370, Federal Republic of Germany).

*rac*-1-(Benzyloxycarbonyl)-2-*tert*-butyl-3-[(ethoxycarbonyl)methyl]imidazolidin-4-one (1a). Glycylglycine ethyl ester hydrochloride (20.00 g, 0.102 M) was suspended in 200 mL of  $CH_2Cl_2$ . Pivalaldehyde (12 mL, 0.11 M) and MgSO<sub>4</sub> (20 g) were added, and the reaction mixture was cooled to 0 °C. Triethylamine (17 mL, 0.12 M) was added dropwise and the reaction vessel was fitted with a drying tube and the mixture was allowed to stir overnight as the bath melted. After 24 h the reaction was diluted with 200 mL of Et<sub>2</sub>O, filtered, and evaporated to a colorless oil and the residual solvent removed in vacuo. The crude yield was 20.7 g (89%).

The crude oil was dissolved in 100 mL of dry EtOH under argon and chilled to -10 °C (ice/MeOH) and AcCl (7.1 mL, 0.14 M) was added dropwise. The reaction was allowed to warm to room temperature and stir overnight. The resulting suspension of white crystals was diluted with 100 mL of dry Et<sub>2</sub>O, collected on a frit, and washed with Et<sub>2</sub>O. Drying in vacuo yielded 19.19 g of pure imidazolidinone hydrochloride, mp 147-149 °C. A second crop yielded an additional 2.70 g of white crystals (91%).

The imidazolidinone hydrochloride (14.00 g, 52.8 mmol) was dissolved in 200 mL of CH<sub>2</sub>Cl<sub>2</sub> and benzyl chloroformate (8.3 mL, 58 mmol) added. The reaction was chilled to 0 °C and NEt<sub>3</sub> (20 mL, 140 mmol) added dropwise. After addition was complete, the reaction was allowed to stand at 4 °C overnight under a drying tube. After 12 h the reaction was diluted with 200 mL of dry  $Et_2O$ , filtered and, evaporated to a solid material. Recrystallization from EtOH yielded 17.30 g of Z-protected imidazolidinone peptide ester 1a (90%, overall yield from dipeptide ester was 72%): mp 69-70 °C; IR (KBr) 3020-2860, 1758, 1705 (br), 1410, 1399, 1275, 1200 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.35 (distorted s, 5 H, aromatic), 5.18 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 5.17 (s, 1 H, HC acetal), 4.52 (A of AX system, 1 H, J = 17 Hz, HCHCOOEt), 4.28 (br A of AB system, 1 H, J = 14 Hz, HC(5)), 4.17 (q, 2 H, J = 7.1, CH<sub>3</sub>CH<sub>2</sub>O), 3.84 (br B of AB + X of AX, 2 H, HC(5), HCHCOOEt), 1.23 (t, J = 7.1 Hz, 3 H, CH<sub>3</sub>CH<sub>2</sub>), 0.97 (s, 9 H, (CH<sub>3</sub>)<sub>3</sub>C); <sup>13</sup>C NMR δ 171.4, 167.7, 155.4 135.8, 128.6, 128.4, 128.1, 81.3, 68.0, 61.9, 49.6, 45.7, 39.8, 25.9, 14.3. Anal. (C19H26N2O5) C, H, N.

rac-1-(Benzyloxycarbonyl)-2-(1'-methoxy-1'-methyleth-1'-yl)-3-[(methoxycarbonyl)methyl]imidazolidin-4-one (1b). Methoxyisobutyronitrile<sup>40</sup> (18.16 g, 0.183 M) was added to 220 mL of CH<sub>2</sub>Cl<sub>2</sub> under argon and chilled to -78 °C with stirring. Diisobutylaluminum hydride (36 mL, 0.20 M) was added dropwise and allowed to stir for 20 h at -78 °C and then for 1 h at 0  $^{\circ}C.^{41}$  The reaction was quenched with 5 mL of ethyl formate and then with 400 mL of 25% NH<sub>4</sub>Cl at 0 °C. The organic layer was filtered, washed with H<sub>2</sub>O, and dried (MgSO<sub>4</sub>). The resulting aldimine [<sup>1</sup>H NMR (90 MHz)  $\delta$  7.5 (s, 1 H, HC=NH), 4.3-3.5 (br s, 1 H, HC=NH), 3.2 (s, 3 H, CH<sub>3</sub>O), 1.3 (s, 6 H,  $(CH_3)_2C(OCH_3))$ ] could be isolated by solvent removal and distillation (~150 °C/10 mmHg), but it was used and conveniently stored at -20 °C as a CH<sub>2</sub>Cl<sub>2</sub> solution. Glycylglycine ethyl ester hydrochloride (500 mg, 2.54 mmol) was added to 10 mL of the above aldimine solution at room temperature and stirred for 4 h. The reaction was diluted with 30 mL of EtOAc and filtered, and the solvent was removed in vacuo to give 597 mg of pure dipeptide imine (96%) [IR (film) 3440-3200, 3000-2820, 1747, 1685, 1517, 1378, 1196, 1070 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 7.67 (s, 1 H, HC==N), 7.34 (br s, 1 H, CONH), 4.22 (q, J = 7.1 Hz, 2 H,  $CH_3CH_2OOC$ ), 4.13 (s, 2 H, C=NCH<sub>2</sub>CONH), 4.09 (d, J = 5.3 Hz, CONHCH<sub>2</sub>COOCH<sub>2</sub>CH<sub>3</sub>), 3.23 (s, 3 H, CH<sub>3</sub>OC(CH<sub>3</sub>)<sub>2</sub>), 1.35 (s, 6 H,  $(CH_3)_2C(OCH_3)$ , 1.29 (t, J = 7.1 Hz, 3 H,  $CH_3CH_2OOC$ )]. The imine (500 mg, 2.0 mmol) was dissolved in 5 mL of EtOH and chilled to 0 °C, and AcCl (0.2 mL, 2.8 mmol) was added dropwise. The reaction was stirred overnight at room temperature and pumped to a solid mass. The crude imidazolidinone hydrochloride was dissolved in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and chilled to 0 °C, and benzyl chloroformate (0.30 mL, 2.1 mmol) added, followed by dropwise addition of NEt<sub>3</sub> (1.0 mL, 7.2 mmol). The reaction was stirred for 7 h at room temperature, filtered, washed with 10% citric acid and saturated NaHCO<sub>3</sub>, and dried (MgSO<sub>4</sub>). Filtration, solvent removal, and chromatography (flash) on a 90  $\times$  30 mm SiO<sub>2</sub> column with a 25-50% EtOAc/hexane gradient yielded 456 mg of crystalline 1b, (60% overall): mp 51-54 °C; IR (KBr) 3090-2860, 2835, 1725, 1708, 1458, 1440, 1410, 1360, 1305, 1272, 1212, 1195, 1177, 1155, 1125, 1070, 1032, 738 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 7.36 (s, 5 H, aromatic), 5.35 (br s, 1 H, CH acetal), 5.17 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 4.37 (A of AB system, J = 17.4 Hz, 1 H, unassigned), 4.40-4.15 (br m, 2 H, unassigned), 4.18 (q, J = 7.1 Hz, 2 H, CH<sub>3</sub>CH<sub>2</sub>OOC), 3.84 (B of AB system, 1 H, unassigned), 3.15 (s, 3 H, CH<sub>3</sub>O), 1.25 (t, J = 7.1 Hz, 3 H, CH<sub>3</sub>CH<sub>2</sub>OOC), 1.21 (br s, 3 H, CH<sub>3</sub>C(OCH<sub>3</sub>)CH<sub>3</sub>), 1.08 (s, 3 H, CH<sub>3</sub>C(OCH<sub>3</sub>)CH<sub>3</sub>); <sup>13</sup>C NMR δ 169.8, 168.2, 155.3, 135.7, 128.7, 128.4, 128.3, 80.8, 78.1, 68.1, 61.2, 49.3, 49.0, 44.8, 21.5, 17.6, 14.2. Anal. (C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>) C, H, N

*rac*-1-(Benzyloxycarbonyl)-2-phenyl-3-[(methoxycarbonyl)methyl]imidazolidin-4-one (1c). Glycylglycine ethyl ester hydrochloride (10.00 g, 50.86 mmol) was suspended in 100 mL of  $CH_2Cl_2$  and stirred with

<sup>(40)</sup> Navovokina, R. A.; Zil'berman, E. N. Zh. Org. Khim. 1980, 16, 1629-1633.

<sup>(41)</sup> Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. J. Org. Chem. 1970, 35, 858.

PhCHO (5.40 g, 50.88 mmol), MgSO<sub>4</sub> (10 g), and NEt<sub>3</sub> (8.0 mL, 57 mmol) under a drying tube. After 36 h the reaction mixture was diluted with 100 mL of EtOAc, filtered, and evaporated to yield the crude imine. The imine was dissolved in 30 mL of MeOH, chilled to -10 °C, treated with AcCl (4.5 mL, 52 mmol), and stirred at room temperature for 16 h. Solvent removal resulted in a foamy, yellow, transesterified solid. The imidazolidinone hydrochloride was dissolved in 100 mL of CH<sub>2</sub>Cl<sub>2</sub> and chilled to 0 °C. DMAP (250 mg) was added, and NEt<sub>1</sub> was added dropwise. The reaction was stirred overnight at room temperature, diluted with EtOAc, filtered, washed with 10% citric acid and saturated NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), filtered, and evaporated to an oil. Chromatography (flash) on a 100  $\times$  50 mm SiO<sub>2</sub> column with 30% EtOAc/ hexane gave a crystalline material, which was recrystallized from acetone to give 5.04 g of pure 1c (27%): mp 94-95 °C; IR (KBr) 3100-2840, 1770, 1711, 1703, 1459, 1432, 1421, 1403, 1360, 1320, 1312, 1284, 1210, 1136, 747 cm<sup>-1</sup>; <sup>1</sup>H NMR (70 °C/CDCl<sub>3</sub>)  $\delta$  7.37–7.12 (m, 10 H, aromatic), 6.11 (s, 1 H, CH acetal), 5.06 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 4.46 (A of AX system, J = 17.7 Hz, 1 H, CH<sub>3</sub>COOHCH), 4.26 (A(BX) system,  $J_2 = 16.2-17.1$  Hz,  $J_3 = 0.8$  Hz, only B shows coupling to X,  $H_2C(5)$ , 3.70 (s, 3 H, COOCH<sub>3</sub>), 3.20 (X of AX system, J = 17.7 Hz, 1 H, CH<sub>3</sub>COOHCH); <sup>13</sup>C NMR δ 168.2 (d), 167.6 (d), 153.1, 136.6 (d), 135.6 (d), 129.8, 129.0, 128.7, 128.6, 128.3, 128.1, 127.8, 127.3, 75.4 (d), 67.6, 52.4, 48.15 (d), 40.8. Anal. (C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>) C, H, N.

rac-1-(Benzyloxycarbonyl)-2-tert-butyl-3-(methoxyglycylglycyl)imidazolidin-4-one (1d). Glycylglycylglycine methyl ester hydro-chloride,<sup>42</sup> mp 197-198 °C, (8.00 g, 33.4 mmol) was suspended in 200 mL of CH<sub>3</sub>CN, and MgSO<sub>4</sub> (10 g), pivalaldehyde (3.8 mL, 35 mmol), and NEt<sub>3</sub> (6.0 mL, 43 mmol) were added at room temperature and stirred overnight under a drying tube. After 24 h the reaction was diluted with 100 mL of EtOAc, filtered, and evaporated to yield 8.76 g of the crude imine. The imine was dissolved in 130 mL of MeOH under argon, chilled to -10 °C (ice/MeOH), and AcCl (3.0 mL, 42 mmol) was added dropwise. The reaction was allowed to come to room temperature and stir overnight at room temperature under a drying tube. After 24 h the reaction mixture was evaporated to give 8.90 g of the imidazolidinone hydrochloride as a sticky mass. The imidazolidinone salt was dissolved in 150 mL of  $CH_2Cl_2$  and chilled to 0 °C, and benzyl chloroformate (4.9 mL, 35 mmol) and NEt<sub>3</sub> (10 mL, 72 mmol) were added. The reaction was stirred overnight at room temperature, washed with 10% citric acid and then with saturated NaHCO<sub>3</sub>, and dried (MgSO<sub>4</sub>). Filtration through a 50  $\times$  50 mm SiO<sub>2</sub> column (wash with EtOAc) and solvent removal gave 8.87 g of 1d as a colorless oil (65%): <sup>1</sup>H NMR  $\delta$  7.37 (s, 5 H, aromatic), 7.08 (distorted t,  $J = \sim 5$  Hz, HNCO), 5.18 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 5.17 (s, 1 H, CH acetal), 4.33 (A of AX system, J = 16.6 Hz, 1 H, HNCOHCHN(1)), 4.11 (m, 2 H, H<sub>2</sub>C(5)), 4.04 (ABX system,  $J_2 = 18$  Hz,  $J_3 = 5$  Hz, 2 H, CH<sub>3</sub>COOH<sub>2</sub>CNH), 3.89 (X of AX system, J = 16.6 Hz, 1 H, HNCOHCHN(1)), 3.74 (s, 3 H, COOCH<sub>3</sub>), 1.00 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR δ 172.1, 169.7, 167.6, 155.1, 135.6, 128.6, 82.7, 68.1, 52.5, 49.8, 48.7, 41.3, 39.5, 25.8. Anal. (C<sub>20</sub>H<sub>27</sub>N<sub>3</sub>O<sub>6</sub>) C, H, N.

(+)-1-(Benzyloxycarbonyl)-2(R)-tert-butyl-3-[(S)-methyl(methoxycarbonyl)methyl]imidazolidin-4-one ((+)-2a) and (-)-1-(Benzyloxycarbonyl)-2(S)-tert-butyl-3-[(S)-methyl(methoxycarbonyl)methyl]imidazolidin-4-one ((-)-2b). Glycyl-(S)-alanine methyl ester hydrochloride (50.0 g, 0.254 M) was suspended in 500 mL of CH<sub>2</sub>Cl<sub>2</sub> and chilled to 0 °C. Pivalaldehyde (30 mL, 0.27 M) and MgSO<sub>4</sub> (60 g) were added, and NEt<sub>3</sub> (60 mL, 0.43 M) in 100 mL of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise at 0 °C. The reaction was stirred for 24 h at room temperature under a drying tube and was filtered. The solvent was evaporated and the residue was taken up in EtOAc and refiltered. Solvent removal yielded a colorless oil.

The crude imine was dissolved in 300 mL of MeOH and chilled to -10 °C (ice/MeOH), and AcCl (20 mL, 0.28 M) was added dropwise. After 16 h at room temperature the reaction mixture was evaporated in vacuo (0.5 mmHg) to a foamy solid.

The crude salt was dissolved in 300 mL of CH<sub>2</sub>Cl<sub>2</sub>, and benzyl chloroformate (43 mL, 0.30 M) and 300 mg of (dimethylamino)pyridine (DMAP) were added. The reaction was chilled to 0 °C and NEt<sub>3</sub> (125 mL, 0.90 M) in 125 mL of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise. The reaction was stirred overnight at room temperature under a drying tube, washed with 10% citric acid and saturated NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), and evaporated to a yellow oil. Chromatography (flash) on a 110 × 80 mm SiO<sub>2</sub> column with 1 L of 20% EtOAc/hexane and then 1 L of 30% EtOAc/hexane, followed by 1 L of 50% EtOAc/hexane (6 × 500 mL fractions), yielded a crystallization from EtOAc/hexane yielded 24.23 g (26%) of pure **2a**. The mother liquors were rechromatographed to yield

(42) Fischer, E. Chem. Ber. 1906, 39, 469.

20.97 g (22%) of pure 2b as a colorless oil.

(+)-2a: mp 123-124 °C;  $[\alpha]_D = +14.0^\circ$  (c = 2.37, EtOAc); IR (KBr) 3020-2860, 1744, 1708, 1698, 1430, 1400, 1306, 1270, 1212, 1206, 1199 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.36 (distorted s, 5 H, aromatic); 5.17 (s, 2 H, CH<sub>2</sub> benzyloxy), 5.07 (br s, 1 H, HC acetal), 4.19 (A of AX system, J = 16.2 Hz, 1 H, HC(5)H), 4.04 (q, J = 7.0 Hz, 1 H, CH<sub>3</sub>CHCOOCH<sub>3</sub>), 3.80 (X of AX system, J = 16 Hz, 1 H, HC(5)H), 3.77 (s, 3 H, CH<sub>3</sub>O), 1.49 (d, J = 7.0 Hz, 3 H, CH<sub>3</sub>CHCOOCH<sub>3</sub>), 1.04 (s, 9 H, (CH<sub>3</sub>)<sub>3</sub>C); <sup>13</sup>C NMR  $\delta$  170.4, 169.6, 155.2, 135.7, 128.6, 128.4, 128.3, 128.2, 81.0, 68.0, 54.0, 52.5, 49.8, 40.2, 25.6, 14.7. Anal. (C<sub>19</sub>-H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>) C, H, N.

(-)-2b:  $[\alpha]_D = -43.4^\circ$  (c = 1.50, EtOAc); IR (film) 3040–2860, 1744, 1710, 1399, 1360, 1296, 1272, 1100 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.36 (br s, 5 H, aromatic), 5.23 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 5.08 (br s, 1 H, HC acetal), 4.26–4.20 (br d, J = 17 Hz, 1 H, HC(5)), 4.01 (m, 1 H, CH<sub>3</sub>CHCOOCH<sub>3</sub>), 3.86–3.80 (br d, J = 17 Hz, 1 H, C(5)H), 3.65 (s, 3 H, COOCH<sub>3</sub>), 1.77 (d, J = 7.3 Hz, 3 H, CH<sub>3</sub>CHCOOCH<sub>3</sub>), 1.00 (br s, 9 H, (CH<sub>3</sub>)<sub>3</sub>C); <sup>13</sup>C NMR  $\delta$  172.3, 170.6, 155.5, 135.9, 128.6, 128.3, 128.1, 83.0, 67.8, 55.4, 52.7, 50.3, 39.5, 25.5, 15.1.

(-)-1-(Benzyloxycarbonyl)-2(R)-isopropyl-3-[(S)-methyl(methoxycarbonyl)methyl]imidazolidin-4-one ((+)-2c). Glycyl-(S)-alanine methyl ester hydrochloride (2.42 g, 12.3 mmol) was suspended in 30 mL of CH<sub>2</sub>Cl<sub>2</sub> under argon and chilled to 0 °C. Isobutyraldehyde (1.3 mL, 14 mmol) and MgSO<sub>4</sub> (3 g) were added, and NEt<sub>3</sub> (2.0 mL, 14 mmol) in 10 mL of CH2Cl2 was added dropwise at 0 °C. The reaction was stirred for 4.5 h at 0 °C under argon, diluted with 100 mL of EtOAc, and filtered. Solvent removal gave 2.59 g of colorless oil. The crude product was dissolved in 15 mL of MeOH at -15 °C (ice/MeOH) under argon and AcCl (1.2 mL, 17 mmol) was added dropwise. The reaction was allowed to warm to room temperature, stirred overnight, and pumped down to a foamy solid. The crude product was dissolved in 30 mL of CH<sub>2</sub>Cl<sub>2</sub>, chilled to 0 °C, and benzyl chloroformate (1.75 mL, 12.3 mmol) was added. Triethylamine (5.0 mL, 36 mmol) was added and the reaction was allowed to come to room temperature and was stirred for 6 h. Chromatography (flash) on a  $130 \times 50 \text{ mm SiO}_2$  column with 35%EtOAc/hexane gave 3.0 g (70%) of the two epimers as an inseparable 56:44 mixture. The mixture was separated by preparative HPLC on a LiChroprep column using 35% EtOAc/hexane. The major isomer 2c crystallized: mp 109.0–109.5 °C;  $[\alpha_D] = -0.577^\circ$  (c = 2.12, EtOAc); IR (KBr) 3060–2860, 1750, 1742, 1708, 1440, 1413, 1362, 1300, 1271, 1220, 1214, 1190, 1120, 1108, 980, 955, 754, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.36 (s, 5 H, aromatic), 5.32 (br s, 1 H, (CH<sub>3</sub>)<sub>2</sub>CHCH acetal), 5.17 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 4.35-4.15 (br m, 2 H, CH<sub>3</sub>CHCOOCH<sub>3</sub> + HC(5)H, 3.81 (B of AB system, J = 16.3 Hz, 1 H, HC(5)H), 3.74 (s, 3 H, COOCH<sub>3</sub>), 2.13 (br m, 1 H, (CH<sub>3</sub>)<sub>2</sub>CHCH), 1.51 (d, J = 7.2, 3 H, CH<sub>3</sub>CHCOOCH<sub>3</sub>), 1.04 (br s, 3 H, CH<sub>3</sub>CHCH<sub>3</sub>), 0.94 (d, J = 6.7 Hz, 3 H, CH<sub>3</sub>CHCOOCH<sub>3</sub>); <sup>13</sup>C NMR  $\delta$  170.5, 168.6, 154.8, 135.8, 128.1, 77.5, 67.8, 52.6, 51.2, 49.6, 33.8, 18.4, 15.2, 15.1. Anal. (C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>) C. H. N

(-)-1-(Benzyloxycarbonyl)-2(S)-tert-butyl-3-[(methoxycarbonyl)methyl]-5(S)-methylimidazolidin-4-one ((-)-3a). (S)-Alanyl-glycine methyl ester hydrochloride (5.08 g, 34.7 mmol) was suspended in 70 mL of CH<sub>2</sub>Cl<sub>2</sub>. MgSO<sub>4</sub> (5 g) and pivalaldehyde (4.2 mL, 39 mmol) were added, and the mixture was chilled to 0 °C. Triethylamine (10 mL, 72 mmol) was added dropwise and the reaction mixture was stirred overnight under a drying tube. After 24 h at room temperature the mixture was filtered, evaporated, taken up in EtOAc, and refiltered (NH<sub>4</sub>Cl). Solvent removal resulted in a colorless, clear oil.

The crude imine was dissolved in 20 mL of MeOH under argon and chilled to -10 °C (ice/MeOH). AcCl (4.0 mL, 56 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h and evaporated to a foamy solid and excess HCl was removed in vacuo.

The crude imidazolidinone dipeptide was dissolved in 50 mL of CH<sub>2</sub>Cl<sub>2</sub>, and DMAP (50 mg) and benzyl chloroformate (5.0 mL, 35 mmol) were added, and triethylamine (15.0 mL, 108 mmol) was added dropwise at room temperature. The mixture was refluxed overnight under argon. After cooling, the reaction mixture was diluted with 50 mL of Et<sub>2</sub>O, filtered, and evaporated to an oil. Chromatography (flash) on a 50  $\times$  130 mm SiO<sub>2</sub> column yielded 4.80 g of a mixture of stereoisomers as a colorless oil (38% from dipeptide). The ratio was  $\sim$ 2:1 by NMR. The major isomer 3a crystallized from the mixture was colorless prisms: mp 62–70 °C  $[\alpha]_{D}$  = -22.6° (c = 2.44, EtOAc); IR (KBr) 3040–2860, 1757, 1711, 1695, 1436, 1406, 1214 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 7.36 (distorted s, 5 H, aromatic), 5.21–5.09 (AB,  $J = \sim 14$  Hz, 2 H, CH<sub>2</sub> benzyloxy), 5.18 (s, 1 H, HC acetal), 4.58 (A of AX system, J = 17.7 Hz, 1 H,  $HCHCOOCH_3$ ), 4.16–4.04 (br q, J = 6.7 Hz, 1 H, HC(5)), 3.85 (X of AX system, J = 17.7 Hz, 1 H, HCHCOOCH<sub>3</sub>), 3.74 (s, 3 H, COOCH<sub>3</sub>), 1.60-1.59 (br d + H<sub>2</sub>O,  $J = \sim 6$  Hz, 3 H, CH<sub>3</sub>HC(5)), 0.93 (s, 9 H, (CH<sub>3</sub>)<sub>3</sub>C); <sup>13</sup>C NMR δ 174.0, 167.9, 155 (br), 135.5, 128.3, 128.1, 79.2,

67.4, 55.6, 52.4, 45.6, 40.6, 26.1, 17.9 (br). Anal.  $(C_{19}H_{26}N_2O_5)$  C, H, N.

1-1-(Benzyloxycarbonyl)-2-tert-butyl-3-[(ethoxycarbonyl)methyl]-5methylimidazolidin-4-one (4a). Imidazolidinone 1a (500 mg, 1.38 mmol) was dissolved in 10 mL of THF in a flame-dried flask under argon. The mixture was chilled to -78 °C and LDA-2Et<sub>2</sub>O (2.8 mL, 1.0 M/hexane) was added dropwise via a syringe. After 1 hour at -78 °C, the reaction was distinctly green. MeI (0.086 mL, 1.4 mmol) was added and the green color disappeared. The reaction was warmed to -30 °C for 1 h and quenched with 0.1 mL of HOAc. A normal workup with EtOAc, 10% citric acid, NaHCO<sub>3</sub>, and drying (MgSO<sub>4</sub>) yielded a colorless oil after solvent removal. Chromatography (flash) on a  $90 \times 30$  mm column of SiO<sub>2</sub> with 30% EtOAc/hexane yielded 400 mg of crystalline product (77%): mp 64-67 °C; IR (KBr) 3040-2860, 1752, 1714, 1699, 1410, 1360. 1225, 1187 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.36 (distorted s, 5 H, aromatic), 5.21-5.10 (AB, J = 12 Hz, 2 H, benzyloxy CH<sub>2</sub>), 5.17 (s, 1 H, HC acetal), 4.61-4.55 (d, J = 17.7 Hz, 1 H, HCHCOOEt), 4.21 (q, J = 7.1 Hz, 2 H,  $CH_2CH_3$ ), 4.08 (br q, J = 6.5 Hz, 1 H, HC(5)), 3.85-3.79 (d, J = 17.7 Hz, 1 H, HCHCOOEt), 1.68–1.48 (br dd, J = 6.5-4.7 Hz, HC(5), 1.24 (t, J = 7.1 Hz, 3 H,  $CH_3C(5)$ ), 0.94 (s, 9 H,  $(CH_3)_3C$ ); <sup>13</sup>C NMR δ 174.3, 167.7, 154 (br), 135.9, 128.6, 128.4, 79.5, 67.6, 61.7, 55.9, 46.0, 40.8, 26.3, 17.7 (br), 14.2. Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>) C, H, N.

1,1-1-(Benzyloxycarbonyl)-2-tert-butyl-3-[methyl(ethoxycarbonyl)methyl]-5-methylimidazolidin-4-one (4b). Imidazolidinone 1a (500 mg, 1.38 mmol) was enolized as before (see the procedure for 4a) and MeI (0.22 mL, 3.5 mmol) was added and the reaction warmed to -30 °C. After 1 h at -30 °C the reaction was warmed to 0 °C for an additional hour and worked up as before. Chromatography (flash) on a 90 × 30 mm column of SiO<sub>2</sub> with 30% EtOAc/hexane yielded 436 mg of a waxy solid (81%): IR (KBr) 3090–2840, 1739, 1708, 1692, 1411, 1359, 1282, 1270, 1227, 1120, 1042, 757, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.37 (br s, 1 H, aromatic), 5.14 (AB system, 2 H, PhCH<sub>2</sub>O), 5.08 (s, 1 H, acetal H), 4.24 (ABX<sub>3</sub> system, 10 lines, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 4.03 (br q, J = 6.7 Hz, 1 H,  $C(\alpha)CH_3$ ), 1.45 (d, J = 6.9 Hz, 1 H,  $C(\alpha)$ H), 1.50 (d, J = 6.7 Hz, 3 H,  $C(\alpha)CH_3$ ), 1.45 (d, J = 6.9 Hz, 7 (28.5, 79.2, 67.6, 61.6, 55.8, 54.4, 41.3, 25.9, 17.5-6 (br), 14.6, 14.1. Anal. (C<sub>21</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>) C, H, N.

I-1-(Benzyloxycarbonyl)-2-tert-butyl-3-[(ethoxycarbonyl)methyl]-5ethylimidazolidin-4-one (4c). Imidazolidinone 1a (500 mg, 1.38 mmol) was enolized as before (see the procedure for 4a). After 40 min, EtI (0.111 mL, 1.37 mmol) was added and the reaction was stirred at -78 °C for 16 h. The reaction was quenched and worked up as before. Chromatography (flash) on a  $100 \times 30 \text{ mm SiO}_2$  column with a 20-30%EtOAc/hexane gradient and solvent removal yielded 328 mg of colorless oil (61%); IR (film) 3020-2860, 1750, 1713, 1445, 1400, 1360, 1263, 1199, 1125 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 7.39-7.32 (m, 5 H, aromatic), 5.30-5.06 (AB, J = 12 Hz, 2 H, CH<sub>2</sub> benzyloxy), 5.25 (s, 1 H, HC acetal), 4.67-4.62 (d, J = 17.6 Hz, 1 H,  $HCHCOOCH_2CH_3$ ), 4.19 (dq, J = 2.8, 7.1 Hz, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 4.18-4.12 (m, 1 H, HC(5)), 3.87-3.81 (d, J = 17.6 Hz, 1 H, HCHCOOCH<sub>2</sub>CH<sub>3</sub>), 2.66-2.30 (br m, 1 H, HCHC-(5)), 2.14-1.81 (m, 15 lines, 1 H, HCHC(5)), 1.25 (t, J = 7.1 Hz, 3 H,  $OCH_2CH_3$ , 0.95 (s, 9 H, (CH<sub>3</sub>)<sub>3</sub>C), 0.65 (br t, J = 6.2 Hz, 3 H,  $CH_3CH_2C(5)$ ; <sup>13</sup>C NMR  $\delta$  172.7, 167.6, 154 (br), 135.7, 128.7, 128.6, 128.4, 79.1, 67.6, 61.6, 60.0, 45.2, 40.8, 26.4, 14.1, 6.9. Anal. ( $C_{21}$ . H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>) C, H, N.

1,1-1-(Benzyloxycarbonyl)-2-tert-butyl-3-[ethyl(ethoxycarbonyl)methyl]-5-ethylimidazolidin-4-one (4d). Imidazolidinone 1a (500 mg, 1.38 mmol) was enolized as before. After 40 min EtI (0.36 mL, 4.5 mmol) was added and the reaction stirred for 16 h at -78 °C. TLC still showed some starting material in the reaction. The reaction was warmed to -30 °C for 3 h and then to 0 °C for 2 h and worked up as before. Chromatography (flash) on a  $100 \times 30 \text{ mm SiO}_2$  column with a 20-30% EtOAc/hexane gradient and solvent removal gave 272 mg of colorless oil (47%): IR (film) 3020-2860, 1743, 1710, 1440, 1403, 1361, 1270, 1247, 1210 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 7.36 (distorted s, 5 H, aromatic), 5.26-5.04  $(AB, J = 12 Hz, 2 H, CH_2 benzyloxy), 5.13 (s, 1 H, HC acetal), 4.24$  $(dq, J = 3.8, 7.1 Hz, 2 H, OCH_2CH_3), 4.14-4.08 (m, 1 H, HC(5)),$ 3.84-3.79 (dd, J = 5.0, 9.4 Hz, 1 H, HCCOOEt, 2.65-2.34 (br m, 1 H, HCHC(5)), 2.19-2.10 (m, 1 H, HCHC(5)), 2.00-1.89 (m, 2 H,  $CH_3CH_2CHCOOEt$ ), 1.28 (t, J = 7.1 Hz, 3 H,  $CH_3CH_2O$ ), 1.03 (s, 9 H,  $(CH_3)_3C$ , 0.99 (t, J = 7.6, 3 H,  $CH_3CH_2CHCOOEt$ ), 0.58 (br t, J = 7 Hz, 3 H,  $CH_3CH_2C(5)$ ; <sup>13</sup>C NMR  $\delta$  171.2, 169.5, 154 (br), 135.7, 128.7, 128.4, 81.0, 67.6, 61.5, 60.9, 60.1, 41.6, 25.9, 22.9, 22 (br), 14.1, 7.0. Anal. (C<sub>23</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>) C, H, N.

1,1-1-(Benzyloxycarbonyl)-2-tert-butyl-3-[methyl](ethoxycarbonyl)methyl]-5-benzylimidazolidin-4-one (4e). Imidazolidinone 1a (500 mg, 1.38 mmol) was enolized as before (see the procedure for 4a). After 1 h benzyl bromide (0.164 mL, 1.38 mmol) was added and the reaction was stirred for 6 h at -78 °C. The reaction was monitored by TLC. The reaction was warmed to -40 °C, and after 1 h only traces of starting material were visible. MeI (0.086 mL, 1.4 mmol) was added and the reaction was stirred for 2 more h at -40 °C. Quenching and workup as before gave a semicrystalline material. Chromatography (flash) on a 100 × 30 mm SiO<sub>2</sub> column with 20% EtOAc/hexane gave 483 mg of crystalline **4e** (75%): mp 115–116 °C IR (KBr) 3020–2860, 1748, 1700, 1440, 1405, 1362, 1257, 1216, 1104 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.43–7.35 (m, 5 H, aromatic), 7.12–7.04 (m, 5 H, aromatic), 5.37–5.33 (d, J = 12 Hz, 1 H, HCH benzyloxy), 5.06–5.03 (br d, J = 12 Hz, 1 H, HCH benzyloxy), 4.79 (br s, 1 H, HC acetal), 4.36–4.34 (m, 1 H, HC(5)), 4.21 (q, J = 7.1 Hz, 2 H, CH<sub>3</sub>CH<sub>2</sub>O), 3.91–3.80 (br d, J = 14 Hz, 1 H, HCHC(5)), 3.78 (q, J = 7.0 Hz, 1 H, HC(3)CHDOCH<sub>2</sub>CH<sub>3</sub>), 3.14–3.08 (dd, J = 2.8, 14.2 Hz, 1 H, HC(5)CHH), 1.26 (t, J = 7.1 Hz, 3 H, CH<sub>3</sub>CHCOOCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR  $\delta$  1700, 169.7, 153.7, 135.6, 135.2, 130.8, 128.9, 128.6, 128.5, 127.9, 126.6, 79.5, 67.5, 61.5, 60.4, 54.3, 41.8, 33.8 (br), 26.1, 14.3, 14.1. Anal. (C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub>) C, H, N.

1,1-1-(Benzyloxycarbonyl)-2-tert-butyl-3-[benzyl(ethoxycarbonyl)methyl]-5-benzylimidazolidin-4-one (4f). Imidazolidinone 1a (510 mg, 1.41 mmol) was enolized as before (see the procedure for 4a). After 1 h benzyl bromide (0.35 mL, 2.9 mmol) was added and the reaction was stirred for 17 h at -78 °C. The reaction was quenched and worked up as before. Chromatography (flash) on a  $80 \times 30$  mm SiO<sub>2</sub> column with 15% EtOAc/hexane yielded 668 mg of crystalline product (87%): mp 101-103 °C; IR (KBr) 3020-2860, 1737, 1709, 1693, 1453, 1440, 1410, 1359, 1331, 1275, 1220, 1128 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.46–7.14 (m, 10 H, aromatic), 6.93 (br s, 3 H, aromatic), 6.26 (br s, 2 H, aromatic), 5.32-5.28 (d, J = 12 Hz, 1 H, HCH benzyloxy), 4.87 (br s, 1 H, HC(2)), 4.39-4.34 (m, 1 H, HC(5)), 4.30 (q, J = 7 Hz, 2 H, CH<sub>3</sub>CH<sub>2</sub>O), 4.06-3.78 (m, 2 H, HCHPh, HCHC(5)), 4.00-3.95 (dd, J = 4, 11 Hz, 1 H, PhCH<sub>2</sub>CHCOOEt), 3.29-3.22 (dd, J = 3, 11 Hz, 1 H, PhHCHCHCOOEt), 3.24-3.18 (dd, J = 4, 13 Hz, 1 H, PhHCHHC(5)), 2.47 (distorted t, J = 11 Hz, 1 H, PhHCHCHCOOEt), 1.28 (t, J = 7Hz, 3 H, CH<sub>3</sub>CH<sub>2</sub>O), 0.85 (s, 9 H, (CH<sub>3</sub>)<sub>3</sub>C); <sup>13</sup>C NMR δ 170.2, 169.1, 153.2, 137.9, 135.9, 135.5, 131.3, 129.0, 128.6, 128.5, 128.3, 127.3, 126.4, 80.1, 67.0, 61.8, 60.9, 60.3, 41.6, 36.1, 32.8 (br), 26.2, 14.1. Anal. (C33H38N2O5) C, H, N.

rac -1-(Benzyloxycarbonyl)-2-tert -butyl-3-[dimethyl(ethoxycarbonyl)methyl]imidazolidin-4-one (5) and *l*-1-(Benzyloxycarbonyl)-2tert-butyl-3-[dimethyl(ethoxycarbonyl)methyl]-5-methylimidazolidin-4-one (6). Imidazolidinone 1a (500 mg, 1.38 mmol) was dissolved in 2 mL of THF in a flame-dried flask under argon and added via a syringe down the side of the flask into a solution of LiHMDS (generated from 0.72 mL of HN(SiMe<sub>3</sub>)<sub>2</sub> and 1.6 mL of *n*-BuLi (1.6 M/hexane)) in 10 mL of THF at -78 °C. After 30 min MeI (0.50 mL, 8.0 mmol) was added and the reaction was stirred for 20 h at -78 °C. The reaction was quenched with 10% citric acid and washed with saturated NaHCO<sub>3</sub> and dried (MgSO<sub>4</sub>). Solvent removal and chromatography (flash) on a 105 × 30 mm SiO<sub>2</sub> column with 25% EtOAc/hexane gave 417 mg ( $R_f =$ 0.27) of 5 (77%) as a colorless oil and 64 mg ( $R_f =$  0.31) of 6 (12%) as a colorless oil. Use of 3 equiv of LiHMDS gave 6 as the major product.

5: IR (film) 3040–2860, 1745, 1710, 1393, 1360, 1330, 1293, 1267, 1214, 1191, 1145, 1098, 1027, 960, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.35 (s, 5 H, aromatic), 5.42 (br s, 1 H, CH acetal), 5.18 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 4.09 (A of AB system, J = 16.5 Hz, 1 H, HC(5)H), 4.03 (q, J = 7.1 Hz, 2 H, COOCH<sub>2</sub>CH<sub>3</sub>), 3.83 (B of AB system, J = 16.4 Hz, 1 H, HC(5)H), 1.72 (s, 3 H, CH<sub>3</sub>C(CH<sub>3</sub>)COOEt), 1.53 (br s, CH<sub>3</sub>C(CH<sub>3</sub>)COOEt), 1.11 (t, J = 7.2 Hz, 3 H, COOCH<sub>2</sub>CH<sub>3</sub>), 1.02 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR  $\delta$  173.9, 173.7, 155.3, 136.1, 128.6, 128.3, 128.1, 79.8, 67.8, 62.0, 61.5, 50.6, 39.5, 26.4, 24.9, 24.2, 14.0. Anal. Calcd for C<sub>21</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>: C, 64.60; H, 7.74; N, 7.17. Found: C, 64.14; H, 7.95; N, 7.04.

**6**: IR (film) 3040-2860, 1749, 1713, 1415, 1395, 1362, 1282, 1263, 1225, 1200, 1150, 1130, 1070, 1030, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.36 (s, 5 H, aromatic), 5.41 (br s, 1 H, CH acetal), 5.16 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 4.12 (ABX<sub>3</sub>,  $J_2 = 10.8$  Hz,  $J_3 = 7.1$  Hz, 2 H, COOCH<sub>2</sub>CH<sub>3</sub>), 4.14 (q, J = 7.1 Hz, 1 H, CH<sub>3</sub>C(5)H), 1.73 (s, 3 H, CH<sub>3</sub>C(CH<sub>3</sub>)COOEt), 1.53 (s, 3 H, CH<sub>3</sub>C(CH<sub>3</sub>)COOEt), 1.52 (br d,  $J \approx 7$  Hz, 3 H, C(CH<sub>3</sub>)COOEt), 1.21 (t, J = 7.1 Hz, 3 H, COOCH<sub>2</sub>CH<sub>3</sub>), 0.99 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>), <sup>13</sup>C NMR  $\delta$  175.5, 173.8, 135.9, 128.6, 128.5, 128.3, 77.7, 67.4, 61.6, 61.5, 56.4, 40.7, 26.8, 24.5, 23.7, 18.2 (br), 14.0. Anal. Calcd for C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>: C, 65.32; H, 7.97; N, 6.93. Found: C, 64.89; H, 8.12; N, 6.84.

(-)-1-(Benzyloxycarbonyl)-2(S)-tert-butyl-3-[(S)-methyl(methoxycarbonyl)methyl]-5(S)-methylimidazolidin-4-one ((-)-7a). LiHMDS Method. Imidazolidinone (-)-3a (320.6 mg, 0.88 mmol) was dissolved in 8 mL of THF and chilled to -78 °C. LiHMDS was generated by the addition of *n*-BuLi (0.5 mL, 1.6 M/hexane) to HN(SiMe<sub>3</sub>)<sub>3</sub> (0.30 mL, 1.4 mmol) and 2 mL of THF at -15 °C (ice/methanol). After 5 minutes the LiHMDS solution was added to the substrate. After 1 h at -78 °C, the reaction was colorless. MeI (0.20 mL, 3.0 mmol) was added and the reaction was stirred for 16 h at -78 °C. The reaction was quenched with 10% citric acid, extracted with EtOAc, washed with saturated NaHCO<sub>3</sub>, and dried over MgSO<sub>4</sub>. Filtration and solvent evaporation yielded 356 mg (> theoretical) of crystalline product. Recrystallization from EtOH gave 300 mg of colorless needles (90%): mp 112.0-112.5 °C,  $[\alpha]_D = -23.6^{\circ}$  (c = 1.82, EtOAc); IR (KBr) 3040-2860, 1741, 1702, 1690, 1460, 1400, 1359, 1290, 1278, 1231, 1121, 1042 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.36 (distorted s, 5 H, aromatic), 5.14 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 5.08 (s, 1 H, HC acetal), 4.048 (q, J = 6.9 Hz, 1 H, CH<sub>3</sub>CHCOOCH<sub>3</sub>), 1.05 (d, 6.7 Hz, 3 H, HC(5)CH<sub>3</sub>), 1.45 (d, J = 6.9 Hz, 3 H, COCCH<sub>3</sub>), 1.50 (d, 6.7 Hz, 3 H, HC(5)CH<sub>3</sub>), 1.45 (d, J = 6.9 Hz, 3 H, CH<sub>3</sub>CHCOOCH<sub>3</sub>), 1.01 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR  $\delta$  172.5, 170.4, 154 (br), 128.6, 128.4, 79.2, 67.6, 55.8, 54.4, 52.5, 41.3, 25.9, 17.5 (br), 14.7. Anal. (C<sub>20</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>) C, H, N.

LDA-3LiBr Method. Dry LiBr (300 mg, 3.4 mmol) was fused in a flame-dried flask under an argon stream. Imidazolidinone (-)-3a (325.7 mg, 0.899 mmol) was added and dissolved with 10 mL of THF. The reaction was chilled to -78 °C and LDA-2Et<sub>2</sub>O (0.80 mL, 1.0 M/hexane) was added dropwise down the side of the flask. After 15 min MeI (0.20 mL, 3.0 mmol) was added and the reaction was stirred for 16 h at -78 °C. Workup as before gave 358 mg of crude, crystalline product, which was chromatographed (flash) on a 100 × 30 mm SiO<sub>2</sub> column with 30% EtOAc/hexane to give 265 mg of pure (-)-7a.

(+)-1-(Benzyloxycarbonyl)-2(R)-tert-butyl-3-[(R)-methyl(methoxycarbonyl)methyl]-5(R)-methylimidazolidin-4-one ((+)-7a). LiBr (5.00 g, 57.6 mmol) was dried at 140 °C for 24 h under vacuum in a 100-mL flask. Imidazolidinone (+)-2a (5.00 g, 13.8 mmol) was added and dissolved in 60 mL of THF. The reaction was chilled to -78 °C and LDA-2Et<sub>2</sub>O (13.0 mL, 0.97 M/hexane) was added down the side of the flask over 10 min. After 30 min MeI (3.0 mL, 48 mmol) was added and the reaction was stirred for 18 h at -78 °C. The reaction was quenched with 10% citric acid and worked up with saturated NaHCO<sub>3</sub> as before to yield 5.4 g of yellow, crystalline material. Chromatography (flash) on a 120 × 50 mm SiO<sub>2</sub> with 30% EtOAc/hexane, followed by recrystallization from EtOAc/hexane, gave 3.93 g + 0.54 g (second crop) of pure (+)-7a (86%): mp 112.0-112.5 °C  $[\alpha]_D = +24.6^\circ$  (c = 2.05, EtOAc); IR and <sup>1</sup>H NMR spectra are identical with those of (-)-7a.

1-(Benzyloxycarbonyl)-2(S)-tert-butyl-3-[(R)-methyl(methoxycarbonyl)methyl]-5(R)-methylimidazolidin-4-one (7b). Nominally dry LiBr (160 mg, 1.8 mmol) and imidazolidinone 2b (123 mg, 0.339 mmol) were dissolved in 1.5 mL of THF and chilled to -78 °C and LDA·2Et<sub>2</sub>O (0.32 mL, 0.97 M/hexane) was added dropwise down the side of the flask. After 15 min, MeI (0.20 mL, 3.2 mmol) was added and the reaction stirred for 16 h at -78 °C. The reaction was quenched with 10% citric acid and worked up with saturated NaHCO3 as before. Chromatography on a 100  $\times$  30 mm SiO<sub>2</sub> column yielded 72.6 mg of pure 7b (57%): IR (film) 3040-2860, 1750, 1710, 1433, 1400, 1358, 1272, 1225, 1130, 1088, 1067, 1048, 1010 cm<sup>-1</sup>; <sup>1</sup>H NMR & 7.37 (s, 5 H, aromatic), 5.14 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 5.05 (br s, 1 H, CH acetal), 4.05  $(q, J = 6.6 \text{ Hz}, 1 \text{ H}, \text{ CH}_3\text{C}(5)H), 3.97 (q, J = 7.2 \text{ Hz}, 1 \text{ H},$  $CH_3CHCOOCH_3$ ), 3.70 (s, 3 H, COOCH<sub>3</sub>), 1.82 (d, J = 7.3 Hz, 3 H,  $CH_3CHCOOCH_3$ , 1.55 (br d, J = 6.6 Hz,  $CH_3C(5)$ H), 0.96 (s, 9 H,  $C(CH_3)_3$ 

(*R*)-Alanyl-(*R*)-alanine. Imidazolidinone (+)-7a (2.00 g, 5.31 mmol) was dissolved in 50 mL of THF and KOSi(CH<sub>3</sub>)<sub>3</sub> (1.60 g, 12.5 mmol) was added. The reaction was stirred at room temperature for 45 min, quenched with 15 mL of 1 N HCl, extracted with EtOAc, and dried (MgSO<sub>4</sub>). Filtration and solvent removal resulted in 1.89 g of glassy,

solid imidazolidinyl acid 8 (98%) [<sup>1</sup>H NMR δ (CDCl<sub>3</sub> + 1 drop DMSO  $d_6$ ) 7.35 (s, 5 H, aromatic), 5.6-4.4 (vbr s, 3 H, COOH + H<sub>2</sub>O), 5.14 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 5.12 (s, 1 H, CH, acetal), 4.08 (overlapping q,  $J \simeq 7$  Hz, 2 H, CH<sub>3</sub>CHCOOH + HC(5)CH<sub>3</sub>), 1.80 (d, J = 7.3 Hz, 3 H, CH<sub>3</sub>CHCOOH), 1.55 (dist q, J = 6.7 Hz, CH<sub>3</sub>C(5)H), 0.96 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>)]. The imidazolidinyl acid (0.90 g, 2.48 mmol) was dissolved in 25 mL of EtOAc under argon; 100 mg of Pd-C (10%) was added with vigorous stirring and H<sub>2</sub> (balloon) was introduced. After 2 h the reaction was purged with argon and filtered through Celite. Solvent removal resulted in 536 mg (99%) of crystalline imidazolidinyl amino acid 9 [mp 101-102 °C (sealed tube); <sup>1</sup>H NMR  $\delta$  6.0-4.5 (br s, 2 H,  $H_2N^+$ ), 4.04 (d, J = 1 Hz), 3.81 (q, J = 7.2 Hz, 1 H, CH<sub>3</sub>CHCOO<sup>-</sup>), 3.49 (d q,  $J_3(q) = 6.8$  Hz,  $J_4(d) = 1$  Hz, 1 H, HC(5)-CH<sub>3</sub>+NH<sub>2</sub>C(2)H), 1.67 (d, J = 7.2 Hz, 3 H, CH<sub>3</sub>CHCOO<sup>-</sup>), 1.21 (d,  $J = 6.8 \text{ Hz}, 3 \text{ H}, CH_3C(5)\text{H}, 0.91 \text{ (s, 9 H, } C(CH_3)_3)].$  The imidazolidinone amino acid was dissolved in 4 mL of deionized  $H_2O$  (pH ~5) and heated to 80 °C for 20 min. The reaction was cooled, diluted with EtOH, evaporated until almost dry, and then recrystallized from EtOH/EtOAc to yield 322 mg of crystalline D-alanyl-D-alanine (81%): mp 266-268 °C (sealed tube) (lit.<sup>43</sup> 298 °C cor);  $[\alpha]_D = +36.3^\circ$  (c = 1.05, 0.2 N HCl) (lit.<sup>44</sup>  $[\alpha]_{D} = +38.2^{\circ} (c = 0.8, 0.2 \text{ N HC})$ ). Analysis by HPLC<sup>11</sup> showed that the sample, coinjected with authentic L-alanyl-L-alanine, had an identical retention time and was clearly distinguishable from its diastereomer L-alanyl-D-alanine.

1-(Benzyloxycarbonyl)-2(R)-tert-butyl-3-(methoxy-(S)-alanyl-(R)alanyl)-5(R)-imidazolidin-4-one (10). The imidazolidinone acid (see the procedure for D-Ala-D-Ala, above) (900 mg, 2.48 mmol) was dissolved in 25 mL of EtOAc along with L-alanine methyl ester hydrochloride (350 mg, 2.50 mmol), DCC (520 mg, 2.52 mmol), and dried HOBT (335 mg, 2.50 mmol). Triethylamine (0.35 mL, 2.5 mmol) was added and the reaction was stirred overnight. The reaction was filtered, washed with 10% citric acid and saturated NaHCO<sub>3</sub>, and dried (MgSO<sub>4</sub>), and the solvent was removed. Chromatography (flash) on a  $110 \times 30 \text{ mm SiO}_2$ column with 50% EtOAc/hexane gave 762 mg of 10 as a colorless oil (68%): IR (film) 3440-3220, 3040-2860, 1745, 1735-1675, 1530, 1452, 1405, 1360, 1315, 1382, 1370, 1215, 1197, 1152, 1130, 1012, 747, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.65 (d, J = 6.9 Hz, 1 H, CONH), 7.36 (s, 5 H, aromatic), 5.23 (s, 1 H, CH acetal), 5.15 (AB system, 2 H, CH<sub>2</sub> benzyloxy), 4.52 (q, J = 7.1, 1 H, CONHCHCH<sub>3</sub>), 4.43 (q, J = 7.4 Hz, 1 H, CH<sub>3</sub>CHCONH), 4.15 (q, J = 6.6 Hz, 1 H, CH<sub>3</sub>C(5)H), 3.73 (s, 3 H, COOCH<sub>3</sub>), 1.61 (d, J = 7.3 Hz, 3 H, CH<sub>3</sub>CHCOOCH<sub>3</sub>), 1.58 (d, J = 6.5 Hz, 3 H,  $CH_3C(5)$ H, 1.37 (d, J = 7.2 Hz, 3 H,  $CH_3CCHCONH$ ), 0.92 (s, 9 H,  $(CH_3)_3C$ ); <sup>13</sup>C NMR  $\delta$  176.1, 172.8, 169.9, 155 (br), 135.6, 128.6, 128.4, 79.0, 67.6, 56.5, 55.0, 52.3, 48.2, 40.4, 26.0, 18.2, 17.6 (br), 13.8. Anal. Calcd for  $C_{23}H_{33}N_3O_6$ : C, 61.73; H, 7.43;, N, 9.39. Found: C, 61.34; H, 7.57; N, 9.26.

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