Amino Acid Derivatives That Stabilize Secondary Structures of Polypeptides. 4. Practical Synthesis of 4-(Alkylamino)-3-cyano-6-azabicyclo[3.2.1]oct-3-enes (Ben Derivatives) as γ-Turn Templates

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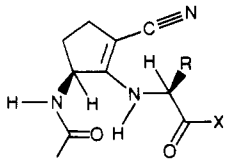
Received July 28, 1987

A practical synthesis of the conformationally restricted amino acid analogue methyl *N*-[4-[6-(benzyloxycarbonyl)-3-cyano-6-azabicyclo[3.2.1]oct-2-enyl]]-L-alaninate (**12ab**) from 4-hydroxyproline is described. Blocking and Barton cyanoethylation generates *N*-(benzyloxycarbonyl)-4-(2-cyanoethyl)proline methyl ester (**10ab**), which is converted by potassium *tert*-butoxide into racemic 6-(benzyloxycarbonyl)-3-cyano-4-keto-6-azabicyclo[3.2.1]octane (**4ab**) and thence to 6-(benzyloxycarbonyl)-3-cyano-4-chloro-6-azabicyclo[3.2.1]oct-3-ene (**15ab**). Resolution was achieved by reaction with L-alanine as its Triton B salt, chromatographic separation of diastereomers, and hydrolysis to the pure enantiomers **4a** and **4b**. Less than 0.2% epimerization accompanies reaction of **15** with alanine or isoleucine salts. The reactions of isoleucine and *allo*-isoleucine salts with **15ab** are shown to be highly enantioselective.

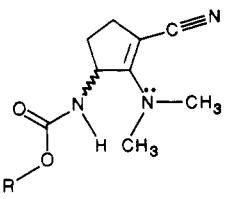
In preliminary reports[1,2] we have described synthesis and study of two analogues, **1** and **2**, of dipeptides in which the secondary amide function of normal polypeptides has been replaced by β-enamino nitriles. The aim of this work is the development of a series of conformationally restricted analogues of α-amino acids, each with its particular steric requirements. Addition of ring-forming atoms to the acyclic backbone of a normal polypeptide has been a popular strategy[3-6] for achieving conformational restriction, and replacement of the hydrogen of the secondary amide by carbon to form a lactam has been the commonest tactic. Necessarily, this change abolishes the hydrogen bond donor capacity of the amide and introduces steric bulk below the amide nitrogen, in the $x(0)y(+)z(-)$ region of the octant diagram of the β-turn of Figure 1. The β-enamino nitriles are attractive complementary amide analogues because bond fixation can be achieved leaving the space near the NH free and populating the $x(+)y(-)z(0)$ region evident from the figure.

In our earlier discussions we have presented X-ray crystallographic evidence in support of the indicated conformation of **1** and ^{1}H NMR evidence that establishes the rotational barrier at the enamine bond of **1b** as 12 kcal/mol. We have also briefly outlined syntheses of **1** and **2**. In this paper we give a detailed account of the synthesis and properties of **2**.

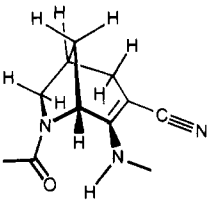
Synthetic Routes to Bicyclic α-Cyano Ketones 4ab. Since α-cyano ketones and β-enamino nitriles are interconvertible, likely routes to **2** involve cyclization of the cyano ester **3** to the cyano ketone **4**, followed by reaction with an α-aminoacyl derivative to form **2**. The readily



1a



1b



2

available L-hydroxyproline **5** is a natural starting material for the preparation of **3**, and two routes to this species are shown in parts A and B of Scheme I.

Any practical synthesis of **2** should ideally be short, convenient, and stereospecific. Unfortunately it has not been possible to achieve all three of these features in a single route. Although Wittig-type condensations involving **6** followed by hydrogenation are an attractive strategy for generating **3**, unfortunately the unsatisfactory behavior of cyclopentanones under Wittig conditions has limited our choice of nucleophiles to the anion of *tert*-butyl (trimethylsilyl)acetate, which gives **7** in only moderate yield.[7] Hydrogenation generates a single isomer, which has the cis configuration (see below). The *N*-Boc derivatives **8** was carefully recrystallized and converted to its crystalline dicyclohexylamine salt, which was reconverted to **8**; no change in melting point or $[\alpha]$ were noted as the result of this purification. Although **8** could be converted to **3** by selective reduction and substitution, the overall yield by this route was only 5%. By contrast, Barton cyanoethylation[8] of Z-L-Hypro-OMe proceeds smoothly, gener-

(1) Kemp, D. S.; Carter, J. S. *Tetrahedron Lett.* **1987**, *28*, 4641.
(2) Kemp, D. S.; Carter, J. S. *Tetrahedron Lett.* **1987**, *28*, 4645.
(3) Kemp, D. S.; McNamara, P. *Tetrahedron Lett.* **1982**, *23*, 3759 and 3761. Kemp, D. S.; McNamara, P. *J. Org. Chem.* **1984**, *49*, 2286; **1985**, *50*, 5934.
(4) Freidinger, R. M.; Tischler, M. H.; Ikeler, T. J.; Springer, J. P.; Tristam, E. W.; Patchett, A. A. In *Peptides: Structure and Function*; Proceedings of the 8th American Peptide Symposium; Hruby, V. J., Rich, D. H., Eds.; Pierce Chemical Co.: Illinois, 1983, p 551. Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooks, J. R.; Saperstein, R. *Science (Washington, D.C.)* **1980**, *210*, 7. Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104.
(5) Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647. Piela, L.; Nemethy, G.; Scheraga, H. *J. Am. Chem. Soc.* **1987**, *109*, 4477.
(6) Freidinger, R. M.; Schwenk, D. A.; Veber, D. F. In *Peptides, Structure and Biological Function*; Proceedings of the 6th American Symnposium; Gross, E., Meienhofer, J., Eds.; Pierce Chemical Co.: Illinois, 1979, p 703.
(7) Shimoji, K.; Taguchi, H.; Oshima, K.; Tamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620. Hartzell, S. L.; Sullivan, D. F.; Rathke, M. W. *Tetrahedron Lett.* **1974**, 1403.
(8) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. Rasmussen, J. R.; Slinger, C. R.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843. Kozikowski, A. P.; Nieduzak, T. R.; Scripke, J. *J. Organomet.* **1982**, *1*, 675.

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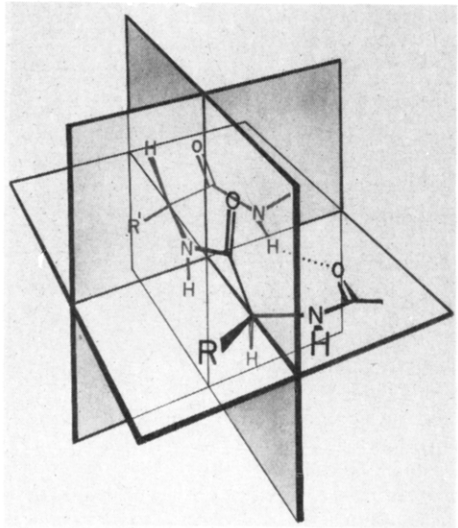
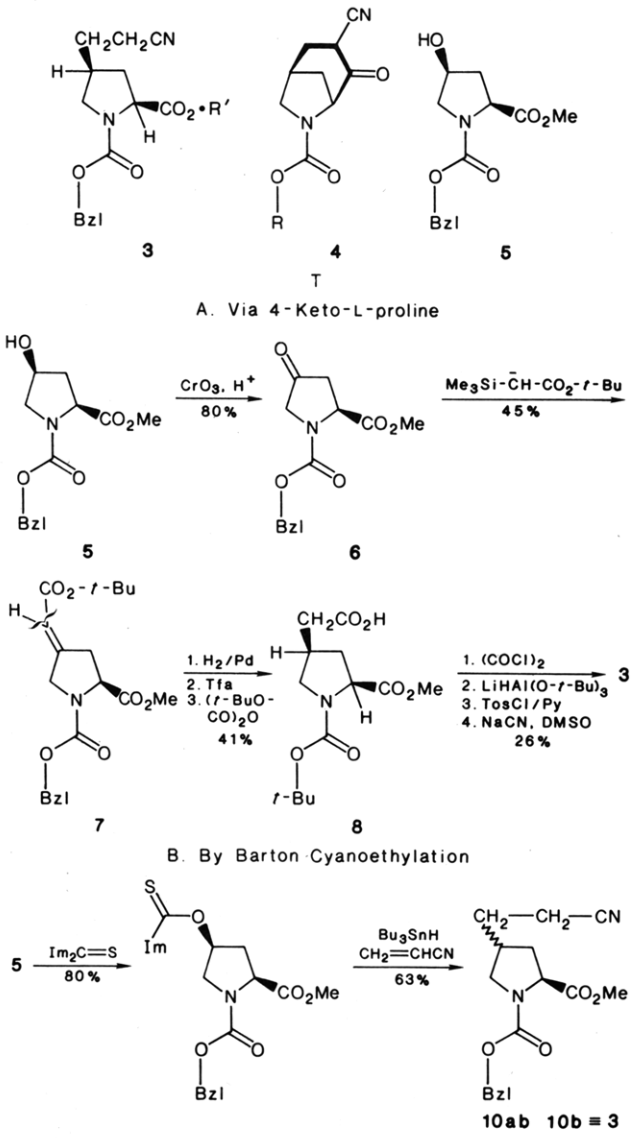


Figure 1. A type II β-turn oriented in *xyz* coordinate space to show the octant relationships of the structure.

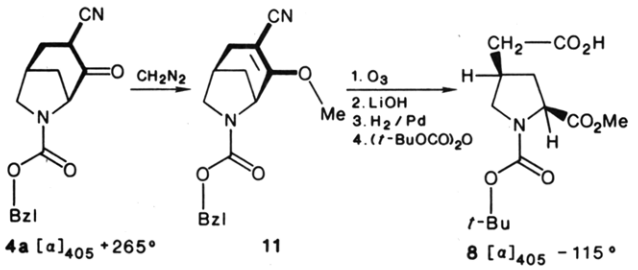
Scheme I. Routes to 3



ating **10** in 50% yield in two steps but as a 1:1 mixture of diastereomers, **10a** and **10b** (3).

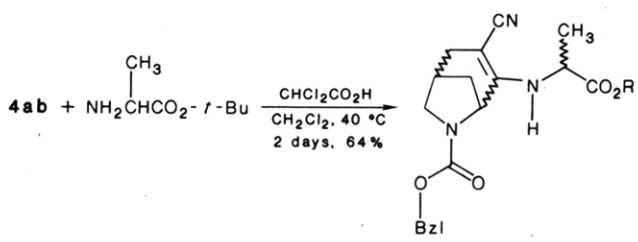
Since **10** must retain chiral integrity at the 2-position, and since the two substituents must be cis oriented to undergo Dieckmann-like cyclization to form **4**, a stereospecific synthesis of **4** from **10ab** could be achieved in 50% yield if cyclization conditions could be found that generate the α-cyano carbanion without epimerization of the 2-center. In fact, **10ab** reacts with LDA at −78 °C in THF to give **4** in 10% yield with an $[\alpha]_{405}$ +265°, which corresponds to an enantiomeric ratio of 10:1. Unfortunately, yield-increasing modifications of this reaction invariably reduced the optical purity of the product. An optimum yield of 65% is seen when potassium *tert*-butoxide in THF is used as base at 25 °C, and under these conditions completely racemic **4** is formed.

Although the reactions of Scheme IA,B did not constitute a stereospecific, practical synthesis of **4**, they did permit an unambiguous correlation of sign of rotation with absolute configuration for **4** and **8**. When **4** prepared by LDA-cyclization of **10ab** was treated sequentially with diazomethane, ozone, and hydroxide, an acid was obtained that could be converted to **8**, identical in properties and sign of rotation with **8** that was generated by Scheme IA. The bicyclic character of **4** establishes the cis orientation of the substituents of **8**, and the L configuration of the 2-position of the latter (which follows from its synthesis by Scheme IA) establishes the configuration of the dextrorotatory form of **4** as also L at position 2 of the pyrrolidine ring.



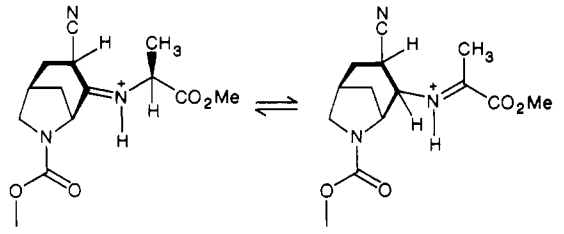
Since both **4a** and its enantiomer are attractive target molecules for synthesis of turn-forming amino acid analogues, we considered the possibility of physically separating the diastereomers **10ab** or salts of the acids resulting from ester saponification. Although more than a dozen highly crystalline salts of these acids were prepared, none permitted efficient separation of the diastereomers, nor were the esters themselves separable. Separation of chiral enamines derived from the racemic bicyclic ketones **4ab** was therefore examined.

Synthesis of β-Enamino Nitriles 2–12. As noted earlier,[1] monocyclic β-enamino nitriles **1** could be formed efficiently by reaction of the corresponding α-cyano ketone with amino acid esters in dichloromethane in the presence of a carboxylic acid catalyst, of which dichloroacetic acid was found to be the most efficient. The more hindered bicyclic α-cyano ketone **4** was found to react more sluggishly, and only *tert*-butyl esters of amino acids reacted cleanly in 2 days without competing formation of diketopiperazines.



Although **12**, R = tBu, obtained by use of H-L-Ala-OtBu, could be efficiently separated chromatographically into two diastereomeric fractions, each was found to be substantially

racemic. Evidently under the conditions of the acid-catalyzed synthesis, epimerization of the alanine α-center had occurred, and the diastereomeric separation had generated samples of (*RRR* + *SSS*) and (*RRS* + *SSR*) isomers. An investigation (see the Experimental Section) of the epimerizing tendency of **12** under a wide range of acidic and basic conditions showed that under nearly all conditions but those used in the above synthesis **12** is in fact chirally stable. A simple rationalization for the ease of epimerization of **12** under optimal conditions for its acid-catalyzed formation involves the intermediate **13**, which is obligatory for enamine formation and which is likely to be interconvertible with a tautomer **14**.



13 **14**

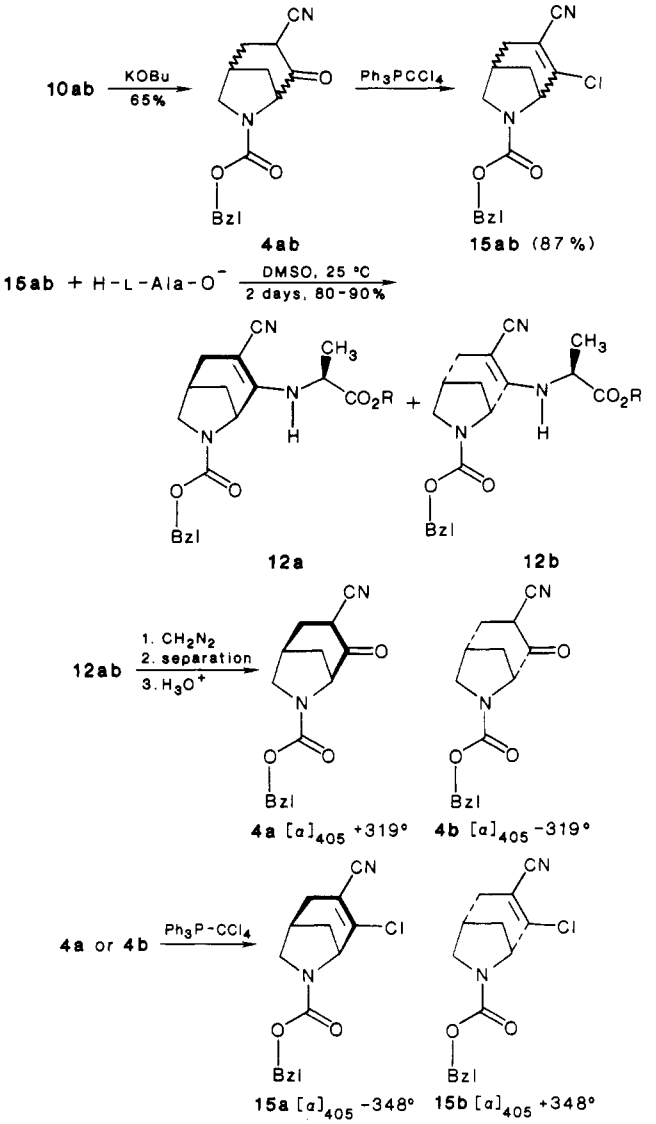
An alternative synthetic route to **12** involves the reaction sequence of Scheme II. Conversion to the β-cyano-α-chloroalkene **15ab** is followed by reaction with salts of amino acids in DMSO solution. (No reaction was seen when amino acid esters, which are much less nucleophilic than salts, are used.) Diazomethane esterification to form **12ab** followed by chromatographic separation of diastereomers and hydrolysis generates the pure enantiomeric β-cyano ketones **4a** and **4b** in preparatively useful scale. Each of these can be converted to chloroalkenes, **15a** and **15b**, suitable for reactions with other amino acid salts. The synthesis of this scheme therefore solves the problem of providing convenient access to amino acid derivatives containing the Ben structural unit. A remarkable feature of the optical rotation values of the series **4** → **15** → **12** is evident from data quoted in the scheme. In a given chiral series, the chloro ketone and the enamine have the same sign of rotation, but upon conversion to the cyano ketone the sign reverses. That this effect results from the conversion of a trigonal to the tetrahedral center at the α-carbon is evident when the rotation of **4a** is taken in methanol. In the pure solvent, a value of $[\alpha]_{405}$ +78° is seen, but addition of sodium methoxide to convert the ketone to its enolate changes the value to ca. −100° (a slow reverse Claisen reaction begins during the measurement). We have not explored the question of the stereochemistry at the α-cyano carbon or the magnitude or solvent dependence of the equilibrium constant for epimerization at this site. Given the high acidity of α-cyano ketones, one would expect an equilibrium mixture of epimers to be present under most conditions.

Since epimerization reactions attended acid treatment of the Mcc group 1 and the formation of **12** from **4** by acid-catalyzed imine formation, it was particularly important to assess the chiral integrity of the alanine-derived portion of **12ab**. Alanine recovered from the hydrolysis that converts **12a** or **12b** to **4a** or **4b** was acylated with the *N*-carboxy anhydride of L-leucine, and the resulting dipeptide was analyzed by ion-exchange chromatography for diastereomeric content.[9] Less than 0.25% of H-L-Leu-D-Ala-OH was detected.

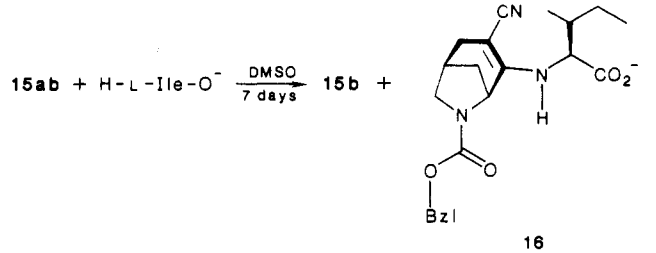
The β-branched amino acid isoleucine reacts very slowly with **15ab**, and monitoring of the diastereomeric purity of

(9) Manning, J. M.; Moore, S. *J. Biol. Chem.* **1968**, *243*, 5591.

Scheme II. Synthesis of 12a and 12b



isoleucine recovered from hydrolysis of the enamine therefore provides an unusually stringent test of the vulnerability of **16** to epimerization. After 1 week of exposure of **15ab** to 1.3 equiv of H-L-Ile-O⁻Me_3N-Bzl⁺ in DMSO at 25 °C, **16** was isolated and hydrolyzed; the resulting H-Ile-OH contained less than 0.2% H-*allo*-Ile-OH, by amino acid analysis.

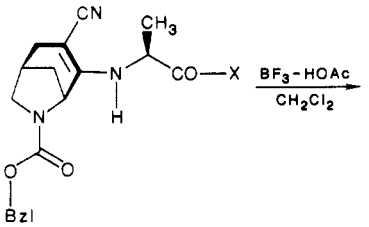


16

Although the following quantitative data from experiments that had a preparative focus are preliminary, it is striking that a reaction of the racemate **15ab** with H-Ile-O⁻ results in an efficient kinetic resolution. Much hydrolysis accompanied this slow reaction, but only the enamine **16** was isolated, and the recovered chloro derivative was found to be an 11:1 mixture of **15b** and **15a**. Reaction of **15ab** with the salt of the diastereomer D-*allo*-Ile also results in a single enamine and recovery of a 9:1 mixture of **15a** and

15b. Owing to the extensive hydrolysis, the recovery yield for **15** was only ca 5%; the uncertainties in the analysis and the detection by HPLC of only one diastereomeric enamine suggests that the enantioselectivity in this reaction may in fact be considerably higher.

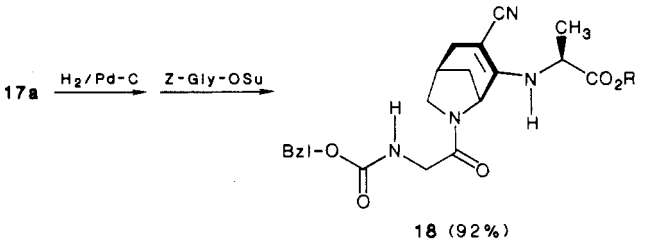
Acid Lability of the Enamine Group of 2. The enamine function of **2** is more difficult to form than that of **1**, and models suggest that the function itself may be somewhat strained. It is therefore not surprising to find an unusual lability to acidic hydrolysis for the enamine of **2**, and this property complicates the removal of acid-labile protective groups in molecules containing **2**. For example, when **17a** is treated with trifluoroacetic acid, even in the presence of 10% trifluoroacetic anhydride, a substantial yield of the cyano ketone **4** was formed, along with the desired acid. Successful cleavage to the acid was achieved with boron trifluoride–acetic acid[10] in dichloromethane, and the resulting acid could be coupled successfully with H-Phe-OMe.



17a: X = OBu

17b (X = OH) $\xrightarrow[\text{DCC-HOBt}]{\text{H-L-Phe-OMe}}$ **17c**: X = Phe-OMe, 41% overall

Hydrogenolysis of **17a** proceeded smoothly, and the resulting free amine could be acylated under conventional peptide coupling conditions to form **18**.



18 (92%)

Summary

In this preparatively oriented paper we have described the convenient synthesis of the enantiomeric **15a** and **15b**, which are natural precursors for preparation of Ben-containing peptide analogues. In addition, synthetic conditions for chain elongation from either the N or C-terminus of a Ben fragment are outlined. Future papers in this series will describe syntheses and conformational properties of Ben containing peptides.

Experimental Section

All reactions were performed under nitrogen atmosphere unless otherwise noted. Melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus. All 60-MHz ^{1}H NMR spectra were recorded on either a Varian T-60 or a Perkin-Elmer R-24B spectrometer. All 250-MHz ^{1}H NMR spectra were obtained on a Bruker WM-250 (FT) spectrometer. In all cases chemical shifts are reported on the δ scale relative to tetramethylsilane. Infrared spectra were obtained on a Perkin-Elmer 567, a Perkin-Elmer 283B, or an IBM IR/32 spectrometer with System 9000 computer, and UV spectra, on a Perkin-Elmer 554, a Perkin-Elmer Lambda 5, or a Perkin-Elmer 330 spectrometer. Optical rotation data was obtained on an Autopol III automatic polarimeter (Rudolph Research). Hydrogenations were performed in a Parr apparatus.

Flash chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Medium-pressure chromatography was carried out with an LKB Model 2138 UVICORD S detector and an LKB 2210 single-channel recorder. High-performance high-pressure liquid chromatography was carried out on a Waters system, which included two M-6000A pumps, a Model 660 solvent programmer, a U6K injector, a Model 440 absorbance detector, and a Model 730 data module recorder–integrator. Analytical reverse-phase HPLC was performed on a Vydac C_{18}218TP54 column and preparative reverse-phase HPLC on a Vydac C_{18}218TP54 column. Regular (silica) phase analytical HPLC was performed on a Waters Resolve column (5 μm spherical silica, 12 cm long column). Amino acid analyses were performed on a Glenco MM-60 instrument with Dionex Hi Phi eluents (Na A, Na B, and Na C) and ninhydrin solution prepared freshly, using Pierce 4.0 lithium acetate solution. Integration data for amino acid analysis was obtained on a Supergrator-2 (Columbia Scientific Industries) or as noted otherwise.

DMF was distilled under reduced pressure, and a center cut was taken; the center cut was redistilled from ninhydrin (ca. 1 g/L) under reduced pressure and was then stored over freshly activated 4-Å sieves. Triethylamine was distilled from CaH_2 and stored under nitrogen. Methylene chloride, toluene, and benzene were stored over freshly activated 4-Å sieves. DMSO was distilled under reduced pressure, and a center cut was taken, which was stored over freshly activated 4-Å sieves. All other reagents were used as obtained from the manufacturers. All natural amino acids used were of the L configuration unless otherwise noted.

Elemental analyses were obtained from either Galbraith Labs or MultiChem Laboratories.

2-Methyl 1-(Phenylmethyl) 4-[2-(1,1-Dimethylethoxy)-2-oxoethylidene]-1,2-pyrrolidinedicarboxylate (7). To a stirred solution of diisopropylamine (1.01 g, 10.0 mmol) in THF (40 mL) in a flame-dried round-bottom flask cooled to −78 °C was added *n*-BuLi (10.01 mmol, 2.9 M solution in hexane) via syringe over 5 min. The resulting pale yellow solution was stirred for 15 min followed by addition of *tert*-butyl α-trimethylsilylacetate[7] (1.88 g, 10.0 mmol) over 5 min via syringe, during which time the solution became turbid. After the solution was stirred for 10 min, Cbz-4-keto-L-Pro-OMe[11] (2.31 g, 8.34 mmol) in THF (20 mL) was added via syringe over 10 min, during which time the solution became clear and yellow. The solution was stirred 2.5 h and was quenched with citric acid buffer (25 mL) and HOAc (0.5 mL, added to adjust the pH to 4) after which the temperature was allowed to rise to 25 °C. During the addition of the citric acid and HOAc the solution became water white. The two-phase mixture was concentrated, removing the THF, and the remaining aqueous phase was extracted with EtOAc (3 × 50 mL). The combined EtOAc layers were washed with H_2O (1 × 25 mL) and brine (1 × 25 mL), dried over Na_2SO_4, filtered, concentrated, and further dried in vacuo, yielding the crude olefin product mixture (3.44 g) as a pale yellow clear oil. The crude product mixture was flash chromatographed (1:5 EtOAc/petroleum ether) in a rather difficult separation, yielding the desired olefin–diester **7** (1.49 g, 48%) as a clear pale yellow oil. Purity as a cis–trans mixture was ca. 97% by HPLC. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.45–7.31 (m, 5 H), 5.73 (br s, 1 H), 5.28–5.07 (m, 2 H), 4.68–4.54 (m, 3 H), 3.74 and 3.61 (s, 3 H), 3.22–3.05 (m, 1 H), 2.85 and 2.78 (br s, 1 H), 1.51–1.46 (m, 9 H). IR (neat): 2985, 1755, 1725, 1710, 1415, 1370, 1350, 1030, 770, 695 cm^{-1}. MS (*m/e*): 375 (M^+, 1), 214 (5), 172 (15), 158 (46), 114 (100).

2-Methyl 1-(*tert*-Butyl) (2*S*-*cis*)-4-(2-Hydroxy-2-oxoethyl)-1,2-pyrrolidinedicarboxylate (8). To a stirred solution of **7** (0.32 g, 0.86 mmol) and HOAc (5 mL) in a Parr pressure bottle was added PtO_2 (0.05 g) in one portion under an atmosphere of nitrogen. The bottle was charged with hydrogen (50 psi) and shaken for 5 h. By TLC no starting materials remained, and a new ninhydrin-active spot appeared at the origin. The reaction mixture was vacuum filtered through a bed of Celite, which was washed with CH_3OH until the filtrate was no longer ninhydrin active. The combined CH_3OH/HOAc rinses were concentrated in vacuo, yielding an oil. This oil was repetitively diluted with CH_3OH and concentrated in vacuo until the excess HOAc had

(10) Hiskey, R. G.; Beacham, L. M.; Matl, V. G.; Smith, J. N.; Williams, E. B.; Thomas, A. M.; Wolters, E. T. *J. Org. Chem.* **1971**, *36*, 488.

been removed. The resulting oil was dissolved in CH_2Cl_2 (4 mL) followed by the addition of TFA (4 mL) with stirring. The stirred solution was concentrated in vacuo after 1 h. Addition of Et_2O followed by concentration in vacuo yielded a semisolid, which upon addition of Et_2O and scratching yielded the free amino acid corresponding to **7** (0.18 g, 71%) as an off-white solid.

The saturated amino acid (0.44 g, 1.45 mmol) so obtained was dissolved in dioxane (2 mL) and NaOH solution (1N, 1.8 mL, 1.8 mmol). The resulting solution was stirred with the addition of di-*tert*-butyl dicarbonate (0.35 g, 1.60 mmol) for 5 h. The reaction was maintained at pH 9 by dropwise addition of Na_2CO_3 solution (pH 12). After disappearance of starting materials (determined by TLC), the solvent was evaporated, the resulting aqueous mixture was layered with EtOAc (10 mL), and 1 N HCl solution was added with vigorous stirring until the pH of the aqueous phase was 2. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The EtOAc phases were combined, washed with brine (1 × 5 mL), dried over $MgSO_4$, filtered, and concentrated, yielding **8** (0.30 g, 73%) as a clear oil. The oil could be solidified by scratching it in chilled hexane. The resulting solid was very difficult to recrystallize as the free acid, mp 62–64 °C. ^1H NMR ($CDCl_3$, 250 MHz): δ 4.36–4.19 (m, 1 H), 3.95–3.79 (m, 1 H), 3.72 (s, 3 H), 3.13 (br t, J = 9, 1 H), 2.70–2.39 (m, 4 H), 1.76–1.54 (m, 1 H), 1.46 and 1.39 (s, 9 H). IR (solution, $CHCl_3$): 2980, 1735, 1690, 1400, 1365, 1155 cm^{-1}. MS (m/e): 287 (M^+, 3), 228 (74), 186 (92), 172 (94), 128 (95), 41 (100). $[\alpha]_D$: −58.0°, $[\alpha]_{405}$ −141° (*c* 0.025, EtOAc). Anal. Calcd for $C_{13}H_{21}N_1$: C, 54.35; H, 7.37; N, 4.89. Found: C, 54.49; H, 7.33; N, 4.99.

2-Methyl 1-(Phenylmethyl) 4-(2-Cyanoethyl)-1,2-pyrrolidinedicarboxylate (10ab). Thiocarbonyldiimidazole[8] (40.0 g, 224 mmol) is added in one portion to a stirred solution of Cbz-*trans*-L-4-Hyp-OMe[11] (38.8 g, 139 mmol) in THF (1000 mL) at room temperature. The resulting yellow solution is refluxed under nitrogen for 3.5 h and allowed to stand overnight at 25 °C (the reaction probably does not need to stand overnight). Concentration of this solution yields an orange oil, which is dissolved in EtOAc (350 mL), washed with 1 N HCl (4 × 70 mL), saturated $NaHCO_3$ (3 × 50 mL), and brine (1 × 50 mL), dried over $MgSO_4$, filtered, and concentrated, yielding the crude thiocarbonylimidazole derivative (49.6 g, 90%) as an orange oil having an unpleasant sulfurous odor. This oil is 90% pure by NMR and can be used in the next reaction without further purification. Alternatively, purification can be accomplished by flash chromatography, deleting the extractive workup. For example, the crude product from a reaction of Cbz-*trans*-4-Hyp-OMe (0.90 g, 3.2 mmol) was flash chromatographed (1:1 gradient to 2:1, EtOAc/petroleum ether, 16 × 4 cm) without prior extractive workup yielding the thiocarbonyl derivative **9** (0.94 g, 75%) as a pale yellow oil, pure by NMR. The product decomposed on heating during an attempted vacuum distillation. The purified product was stable when stored in the dark and when stored in a freezer. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.27 (s, 1 H), 7.55 (d, J = 6, 1 H), 7.35 (s, 5 H), 7.06 (s, 1 H), 5.95 (s, 1 H), 5.30–5.05 (m, 2 H), 4.58 (quint, J = 8, 1 H), 4.14–3.89 (m, 2 H), 3.80 and 3.59 (s, 3 H), 2.71 (quint, J = 7, 1 H), 2.52–2.38 (m, 1 H). IR (neat): 3125, 2950, 1740, 1700, 1390, 1285, 1205, 1110, 970, 740, 700, 650 cm^{-1}. MS (m/e): 373 (2), 279 (7), 220 (16), 176 (34), 91 (100).

Toluene (600 mL) is heated to reflux in a 2000-mL round-bottom flask fitted with reflux condensor, magnetic stir bar, and 250-mL addition funnel. Acrylonitrile (32.7 g, 617 mmol) and tri-*n*-butyltin hydride (8.98 g, 30.8 mmol) are each added in one portion. The toluene solution is brought to reflux rapidly, and the above-prepared thiocarbonyl derivative (8.00 g, 20.6 mmol) in toluene (200 mL) is added dropwise over 20 min via the addition funnel.[8] Reflux is maintained for 10 h. The clear orange reaction mixture is concentrated on a high vacuum rotary evaporator with dry ice-acetone in the cold finger. Toluene (100 mL) is added and removed by concentration as above to aid in removal of excess acrylonitrile. The resulting dark orange oil is partitioned between CH_3CN (80 mL) and hexanes (3 × 20 mL). The CH_3CN phase is concentrated, yielding an orange oil (10.0 g), which is purified by flash chromatography (1:1, hexanes/EtOAc, 10 × 10 cm), yielding **10ab** (4.1 g, 63%) as a yellow oil. Attempted distillation of unchromatographed product resulted in extensive decomposition. It is possible to distill only a forefraction, which allows the removal of some relatively volatile tributyltin byproducts. The sulfurous odor could also be reduced by washing a solution of the crude cyano ester (in CH_2Cl_2) with saturated $CuSO_4$ solution. A sample of **10ab** was hydrolyzed to form the free acid, which could be recrystallized after formation of its dicyclohexylamine salt (mp: 160–175 °C as the mixture of diastereomers). Upon reconversion to the free acid after this recrystallization, the acid was treated with ethereal diazomethane. This sample of **10ab**, also an oil, was used for elemental analysis. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.42–7.24 (m, 5 H), 5.26–4.98 (m, 2 H), 4.57–4.24 (m, 1 H), 3.98–3.40 (m, 4 H), 3.21–3.03 (m, 1 H), 2.73–2.15 (m, 4 H), 2.04–1.60 (m, 3 H). IR (solution, $CHCl_3$): 3135, 3010, 2960, 2880, 2260, 1745, 1700, 1420, 1355, 1180, 1125, 910 cm^{-1}. MS (m/e): 316 (M^+, 1), 257 (10), 213 (22), 91 (100). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.39; H, 6.29; N, 8.84.

Racemic 6-(Benzyloxycarbonyl)-3-cyano-4-keto-6-azabicyclo[3.2.1]octane (4ab). A solution of Cbz-4-(2-cyanoethyl)-Pro-OMe (**10ab**) (5.23 g, 16.5 mmol) in THF (25 mL) was added dropwise to a stirred solution of t-BuOK (1.95 g, 17.3 mmol) in THF (200 mL) at room temperature over 5 min. During the addition the clear, colorless solution becomes cloudy and yellow (clear and orange at 80% addition). The solution is stirred for 45 min and is quenched by addition of HOAc (1 mL, 17 mmol), bringing the pH to 6.0. Upon quenching the clear orange solution becomes cloudy and yellow. The solution is evaporated, yielding a tan foam, which was dissolved in EtOAc (125 mL), washed with citric acid buffer (3 × 30 mL) and brine (1 × 30 mL), dried over $MgSO_4$, filtered, and concentrated, yielding the crude product (4.46 g) as a yellow viscous oil. The crude oil is distilled at 190 °C at 0.05 mm in a Kugelrohr distillation apparatus, yielding **4ab** (3.53 g, 75%) as a clear, tan, very stiff glass. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.46–7.28 (m, 5 H), 5.14 (br s, 2 H), 3.52 and 3.45 (br d, J = 7, 1 H), 3.91–3.66 (m, 2 H), 3.66–3.47 (m, 1 H), 2.70 (br s, 1 H), 2.61–2.28 (m, 2 H), 2.16 (t, J = 12, 1 H), 1.94 (d, J = 12, 1 H). IR (solution, $CHCl_3$): 3020, 3005, 2260, 1745, 1705, 1420, 1355, 1280, 1225, 910 cm^{-1}. MS (m/e): 284 (M^+, 2), 256 (36), 158 (54), 91 (100).

6-(Benzyloxycarbonyl)-3-cyano-4-chloro-6-azabicyclo-[3.2.1]oct-3-ene (15ab). To a stirred solution of cyano ketone **4ab** (37 mg, 0.13 mmol) in CCl_4 (2 mL) and CH_2Cl_2 (2 mL) is added triphenylphosphine (68 mg, 0.260 mmol) in one portion. The solution is heated to 65 °C for 30 h, becoming pale brown with the concomitant precipitation of triphenylphosphine oxide. On occasion, use of more triphenylphosphine is required to cause the reaction to proceed to completion. When the reaction is complete, as determined by thin-layer chromatography, the product mixture is allowed to warm to room temperature and concentrated. The resulting semisolid is purified by flash chromatography (4:1, CH_2Cl_2/EtOAc, 2 × 1 cm), yielding **15ab** (34 mg, 87%) as a clear oil. The crude product mixture generally consists of two major products, the desired chloroolefin and triphenylphosphine oxide. Since the chloro compound is very soluble relative to triphenylphosphine oxide, the oxide can be removed by chilling the crude mixture in a CH_2Cl_2–Et_2O solution. Most of the crystalline oxide can be removed, simplifying the ensuing chromatography. Upon prolonged standing or treatment with chilled hexane, this oil forms a white solid (mp 86–92 °C), which shows no signs of decomposition after storage for months at room temperature. Alternative syntheses of this compound with acidic reagents (e.g. oxalyl chloride or phosphorus trichloride) gave inferior yields. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.38 (s, 5 H), 5.23–5.06 (m, 2 H), 4.66 and 4.55 (d, J = 5, 1 H), 3.67–3.60 (m, 1 H), 3.35–3.25 (m, 1 H), 2.82–2.65 (m, 2 H), 2.40 (br d, J = 17, 1 H), 2.14–1.95 (m, 1 H), 1.94 (d, J = 13, 1 H). IR (solution, $CHCl_3$): 2985, 2900, 2220, 1690, 1410, 1350, 1330, 1280, 1165, 1205, 1040, 980, 935, 915 cm^{-1}. MS (m/e): 302 (M^+, 11), 267 (6), 186 (14), 150 (55), 91 (100). Anal. Calcd for $C_{16}H_{15}N_2O_2Cl$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.49; H, 5.21; N, 9.22.

Methyl *N*-[4-[6-(Benzyloxycarbonyl)-3-cyano-6-azabicyclo[3.2.1]oct-3-enyl]]-L-alaninate (Z-Ben-L-Ala-OMe, 12a and 12b). Finely powdered H-L-Ala-OH (2.06 g, 23.1 mmol) is dissolved in Triton B solution (8.65 mL of a CH_3OH solution, 40% solution, 23.1 mmol) and concentrated in vacuo. The resulting crude semisolid is placed in a round-bottomed flask and layered

(11) Patchett, A. A.; Witkop, B. *J. Am. Chem. Soc.* **1957**, *70*, 185.

with toluene (60 mL), and the flask is fitted with a Dean–Stark distilling head. The solution is heated to reflux for 12 h to remove the H_2O azeotropically. The salt could be obtained as a crisp off-white foam, which was stored under toluene until use (no more than 2 days in advance).

Finely powdered chloro olefin **15ab** (0.58 g, 1.94 mmol) is dissolved in dimethyl sulfoxide (7 mL) over 10 min. To this solution is added a portion of the tetramethylammonium salt of alanine (1.26 g, 7.76 mmol) in one portion with stirring. The solution becomes yellow within minutes, and the reaction is complete with 7 h as determined by TLC. The crude reaction mixture is concentrated on high vacuum, yielding a pale yellow semisolid. This material is mixed with EtOAc (50 mL) and washed with 1 N HCl (saturated with brine, 10 mL). The acidic aqueous phase is washed with EtOAc (15 mL), and the organic layers are combined and washed with brine (10 mL). Ethereal diazomethane is added to the wet EtOAc phase until the yellow color of diazomethane persists, and the solution is allowed to stand for 10 min and then dried over $MgSO_4$. (It should be noted that the $MgSO_4$ dries the solution and also catalyzes the decomposition of excess diazomethane.) At times addition of acetic acid to destroy excess diazomethane was required. The resulting dry solution is filtered and concentrated on aspirator vacuum and then high vacuum, yielding the crude dipeptide methyl ester (0.75 g) as an orange oil.

The crude product is flash chromatographed (7% EtOAc/93% CH_2Cl_2), yielding purified dipeptide mixture (0.67 g, 94%). This sample was combined with another sample (0.05 g), and the total (0.72 g) is separated into the diastereomers by medium-pressure liquid chromatography, yielding as first component a mixture of diastereomers (0.36 g, ca. 95:5) and the second component (0.36 g, pure), a single diastereomer. The first component is rechromatographed on MPLC under the same conditions as before, yielding both first and second fractions (0.34 g and 0.02 g) in pure form. The reaction and separation yields the first diastereomer (0.34 g) and the second diastereomer (0.38 g), giving an overall yield of 44% and 50%, respectively. MPLC is carried out at ca. 140 psi using Michel–Miller columns packed with either ICN silica gel (0.032–0.063 mm) or E. Merck silica gel 60 (0.040–0.063 mm); the eluant is 15% EtOAc–85% hexane. ^1H NMR ($CDCl_3$, 250 MHz) first eluted dipeptide (**12*b***): δ 7.40–7.29 (m, 5 H), 5.25–5.05 (m, 2.0 H), 4.95–4.89 (m) and 4.61–4.47 (m) (1 H), 4.95–4.89 (m) and 4.72 (d, J = 7) (1 H), 4.37 and 4.20 (d, J = 5, 1 H), 3.77 and 3.74 (s, 3 H), 3.65–3.51 (m, 1 H), 3.32–3.20 (m, 1 H), 2.73–2.56 (m, 2 H), 2.31–2.17 (m, 1 H), 2.05–1.80 (m, 2 H), 1.53–1.47 and 1.29–1.17 (m, 3 H). IR (cm^{-1}): 3391, 3023, 2187, 1741, 1695, 1620, 1520. MS (m/e, **12b**): 369 (12), 310 (11), 278 (9), 91 (100). HRMS: 369.1694 ± 0.0004 amu. UV (in CH_3OH, **12b**) (1.7 mg/50 mL): λ_{max} 210 (ϵ 10 000) and λ_{max} 272 nm (ϵ 9300). ^1H NMR ($CDCl_3$, 250 MHz) second eluted dipeptide (**12*a***): δ 7.36 (s, 5 H), 5.24–5.00 (m, 3 H, 1 exch), 4.94–4.79 and 4.73–4.63 (m, 1 H), 4.29 and 4.13 (d, J = 5, 1 H), 3.77 and 3.75 (s, 3 H), 3.64–3.47 (m, 1 H), 3.30–3.21 (m, 1 H), 2.70–2.55 (m, 2 H), 2.31–2.16 (m, 1 H), 2.00–1.81 (m, 2 H), 1.45 (d, J = 7) and 1.16 (d, J = 6), (combined 3 h). IR (cm^{-1}): 3390, 3011, 2187, 1742, 1695, 1622. MS (m/e, **12a**): 369 (10), 310 (9), 278 (9), 91 (100). HRMS found: 369.1692 ± 0.0006. UV (in CH_3OH, **12a**) (4.4 mg/100 mL): λ_{max} 210 (ϵ 6500) and λ_{max} 270 nm (ϵ 6300).

Hydrolysis of 12b: (1*R*,5*R*)-6-(Benzyloxycarbonyl)-3-cyano-4-keto-6-azabicyclo[3.2.1]octane (4b). To a stirred solution of **12b** (0.11 g, 0.30 mmol) in wet CH_2Cl_2 (4 mL) is added trifluoroacetic acid (0.17 g, 1.5 mmol) in one portion, and the resulting solution is stirred for 45 min at room temperature. The crude reaction mixture is concentrated on high vacuum and dissolved in EtOAc (25 mL). This solution is washed with $KHSO_4$ solution (pH 3, saturated with salt, 1 × 5 mL) and brine (1 × 5 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product could be purified by flash chromatography (1:1 hexane/EtOAc) if needed. In order to remove traces of solvent the purified cyano ketone is distilled (oven temperature ca. 190 °C, 0.10 mm) in a Kugelrohr apparatus, yielding distilled **4b** (0.07 g, 79%) with achiral properties identical with the racemate. At c 0.01, EtOAc: $[\alpha]_{633}$ −76.8°, $[\alpha]_{589}$ −92.6°, $[\alpha]_{546}$ −114.5°, $[\alpha]_{435}$ −236°, $[\alpha]_{405}$ −319°.

A sample of **4b** with the above properties was converted to **15b** as described above. The following optical rotation data were observed. c 0.009, EtOAc: $[\alpha]_{633}$ +99°, $[\alpha]_{589}$ +119°, $[\alpha]_{546}$ +145°, $[\alpha]_{435}$ +272°, $[\alpha]_{405}$ +348°.

Determination of the extent of racemization of alanine during the formation of **12b** was accomplished by collecting the aqueous phase obtained for the hydrolysis of **12*b*** as described in the preceding paragraphs. To half of the solution was added an equal volume of 12 N HCl to produce a 6 N HCl solution. This solution was heated to 90 °C for 9 h and became pale yellow. This solution was concentrated on high vacuum, dissolved in 1 mL of H_2O, and reconcentrated to yield a pale yellow glass. This material was dissolved in pH 12.4 borate buffer (2 mL); the solution was chilled to 0 °C followed by addition of L-Leu-*N*-carboxanhydride[9] (ca. 10 mg) with rapid stirring on a vortex mixer (high speed) for 3.5 min followed by quenching with 1 N HCl (3 mL) with rapid vortex mixing again. The solution was diluted with "Buffer A" and injected into the amino acid analyzer. The program for the amino acid analyzer was changed to allow separation of the diastereomeric dipeptides. As the peaks on the chromatogram exhibited base-line separation, the integration obtained from the attached integrator was used to determine the results. Samples of the diastereomeric dipeptides were prepared, and their retention times during amino acid analysis were determined. Upon comparison of the peaks obtained from the hydrolysate acylation, it was determined that less than 0.25% racemization had occurred. This procedure was repeated on the aqueous hydrolysis phase for **12a**, which gave the same results.

Reaction of 15ab with the Triton B Salt of H-L-Ile-OH. To a solution of **15ab** (0.30 g, 0.99 mmol) in DMSO (6 mL) was added a solution formed by dissolving H-L-Ile-OH (0.14 g, 1.09 mmol) in Triton B solution (40% in CH_3OH, 0.5 mL, ca. 1.2 mmol) and DMSO (4 mL). The reaction was allowed to proceed for 7 days (after 3 days on extra 0.5 equiv of freshly prepared Triton B–Ile salt was added to maintain pH 12) and was found to still contain unreacted **15ab** by TLC. After 7 days the reaction mixture was diluted with H_2O (20 mL) and extracted with Et_2O (3 × 5 mL). The ether layer contained unreacted **15ab** (qv). The aqueous phase (which contained the carboxylate salt of the title compound) was adjusted to pH 2 with 0.5 N HCl and extracted with EtOAc (3 × 10 mL). The combined EtOAc layers were washed with brine (1 × 5 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product (0.19 g) was flash chromatographed, yielding purified Z-Ben-L-Ile-OH, as determined by ^1H NMR. The samples obtained from this chromatography were found to decompose upon standing in solution (both acidic EtOAc–hexane and $CHCl_3$ solutions) to regenerate **4a** and H-L-Ile-OH.

For determination of possible epimerization of the Ile residue, a sample of the crude product was dissolved in amino acid analyzer Buffer A and extracted with Et_2O to remove 4. The resulting solution was then subjected to amino acid analysis. The method of quantitation of racemization was to use the most sensitive setting (0.1 Abs unit) on the analyzer, and to use the height of the D-*allo*-isoleucine peak and the value for the height of the L-isoleucine peak, which was off scale on the printer but not on the detector, obtained from the integrator printout to calculate the percent racemization. Data obtained for standards containing known percentages of L-isoleucine and D-*allo*-isoleucine were used to define a calibration curve, from which the percent epimerization was found to be 0.14% for the isoleucine obtained from the hydrolysis of Z-Ben-Ile-OH, formed by the reaction of **15ab** with the Triton B salt of H-L-Ile-OH.

Evaporation of the ether extract from the initial reaction gave unreacted **15** (23 mg, 8%), after flash chromatography. $[\alpha]_{405}$: +288.5° (c 0.01, EtOAc).

The same procedure was applied to obtain the unreacted chloro derivative **15** obtained from an analogous reaction of **15ab** with H-D-*allo*-Ile-OH. The yield of chromatographed recovered **15** was 0.024 g (8%). $[\alpha]_{405}$: −278°.

Cbz-Ben-Ala-OtBu (17, R = tBu). A stirred solution of H-Ala-OtBu (4.06 g, 28.0 mmol), cyano ketone **4ab** (3.53 g, 12.4 mmol) and dichloroacetic acid (0.32 g, 2.49 mmol) in CH_2Cl_2 (50 mL) was heated to reflux under nitrogen for 45 h. The reaction mixture was cooled to 25 °C and diluted with EtOAc (150 mL). This solution was washed with citric acid buffer (3 × 30 mL), saturated bicarbonate solution (3 × 30 mL), and brine (1 × 30 mL), dried over $MgSO_4$, filtered, and concentrated, yielding crude

12 (R = tBu) (5.13 g) as a yellow oil. The product was flash chromatographed (2:1, hexane/EtOAc, 15 × 5 cm), yielding 3.6 g of 17 (R = tBu) (70%) as a pale yellow oil, a mixture of diastereomers that could be separated by MPLC (silica gel) 15% EtOAc, 85% hexane, first compound eluted 4.5–5.6 h, second compound 5.6–6.5 h (some overlap still occurred). ^{1}H NMR ($CDCl_3$, 250 MHz) first diastereomer (as a racemate) eluted by silica gel, material obtained as a solid (purity: 95% by NMR, HPLC): δ 7.44–7.31 (m, 5 H), 5.24–5.04 (m, 2 H), 4.97 and 4.89 (d, J = 7, 1 H, exch), 4.83–4.69 (m) and 4.47–4.34 (m, including a doublet at 4.39, J = 5) and 4.18 (d, J = 5, 3 H), 3.61–3.50 (m, 1 H), 3.31–3.19 (m, 1 H), 2.63–2.55 (m, 2 H), 2.31–2.18 (m, 1 H), 2.05–1.80 (m, 2 H), 1.52–1.46 (m, includes a large singlet at 1.48) and 1.21 (d, J = 7, 12 H). ^{1}H NMR ($CDCl_3$, 250 MHz) second diastereomer (as a racemate) eluted on silica gel, material obtained as an oil, contaminated with ca. 10% of 1st diastereomer: δ 7.42–7.24 (m, 5 H), 5.18–5.04 (m, 2.5 H, 0.5 H exch), 4.84 (d, J = 8, 0.5 H, exch), 4.78–4.67 and 4.67–4.50 (m, 1 H), 4.26 and 4.12 (d, J = 5, 1 H), 3.63–3.51 (m, 1 H), 3.31–3.20 (m, 1 H), 2.71–2.57 (m, 2 H), 2.29 and 2.23 (s, 1 H), 2.00–1.78 (m, 2 H), 1.61–1.38 (m) and 1.15 (d, J = 7, 12 H). MS (m/e): 411 (M^+, 8), 355 (9), 311 (24), 202 (16), 91 (100).

Determination of the Ease of Epimerization of the Alanine α-CH in Z-Ben-Ala-OtBu. Either of the diastereomers separated in the above procedure could be used in the epimerization experiments. HPLC was used to detect formation of the other diastereomer under the reaction conditions. The following conditions gave no detectable epimerization (detection limit is ca. 0.5%; all conditions are 18 h and 50 °C unless otherwise specified): CH_3OH alone or containing HOAc or Et_3N or both; DMSO containing HOAc and Et_3N; Et_3N. The following experiments gave no detectible epimerization over 24 h at 25 °C: CH_2Cl_2 containing HOAc; CH_2Cl_2 containing H-Ala-OMe; CH_2Cl_2 containing 1:1 HOAc and H-Ala-OMe. In CH_2Cl_2 containing dichloroacetic acid at 25 °C for 24 h, 14% epimerization was observed, and addition of 1 equiv of H-Val-OMe raised the level of epimerization to 22%.

Cbz-Ben-Ala-Phe-OMe (17c). In a glovebag filled with N_2 was mixed BF_3·OEt_2 (0.1 mL), glacial HOAc (ca. 0.8 mL), and CH_2Cl_2 (8 mL). Solid Cbz-Ben-Ala-OtBu, **17**, X = tBu (49 mg, 0.12 mmol), was added in one portion with stirring at room temperature, and the mixture allowed to stand for 45 min. The crude reaction mixture was poured into a solution of EtOAc (30 mL) and washed with phosphate buffer saturated with NaCl (pH 7, 3 × 5 mL), $NaHCO_3$ solution (3 × 5 mL), and brine (1 × 5 mL). The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product mixture was dissolved in THF (2 mL), and 1-hydroxybenzotriazole (18 mg, 0.12 mmol) was added with stirring. After all HOBt had dissolved, the solution was chilled to 0 °C, and DCC (25 mg, 0.12 mmol) was added with stirring. After the mixture was stirred for 1 h, the free base of H-L-Phe-OMe (26 mg, 0.12 mmol) in THF (0.5 mL) was added. The solution was maintained at 0 °C for 1 h more and at room temperature for 12 h. Solid dicyclohexylurea was removed by filtration, and the DCU was washed with THF. The combined THF solutions were concentrated, and the crude mixture was flash chromatographed on silica gel (1:1 gradient to 1:2, hexane/EtOAc). The impure product was dissolved in EtOAc (25 mL) and washed with $NaHCO_3$ solution (3 × 5 mL) and brine (1 × 5 mL) providing **17C**, X = Phe-OMe (25 mg, 42%), as a white solid (mp 80 °C with decomposition), purity 97% by HPLC. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.46–7.06 (m, 10 H), 6.82 and 6.12 (d, J = 9, combined 1 H), 5.22–4.64 (m, 4 H), 4.40–4.03 (m, 2 H), 3.74 and 3.69 (s, 3 H), 3.72–3.35 (m, 2 H), 3.33–3.03 (m, 3 H), 2.70–2.48 (m, 2 H), 2.28–2.13 (m, 1 H), 2.05–1.05 (m, 14 H). MS (m/e): 516 (M^+, 13), 311 (33), 310 (71), 91 (100).

Cbz-Gly-Ben-Ala-OtBu (18). To a solution of Cbz-Ben-Ala-OtBu **17A** (100 mg, 0.243 mmol) in CH_3OH (2 mL) and glacial HOAc (28 μL) under an atmosphere of N_2 was added Pd/C (15 mg). The N_2 was displaced with H_2, and a positive pressure of H_2 was maintained with a H_2-filled balloon while the reaction mixture was stirred vigorously. Within 30 min the reaction was complete and purged with N_2. The crude reaction mixture was filtered through a pad of Celite, and the celite pad was washed with CH_3OH until the washes gave a negative ninhydrin test. The combined filtered reaction mixture and washes were concentrated, and HOAc was removed by azeotropic distillation with toluene, yielding a yellow oil. This oil was dissolved in CH_2Cl_2 (2 mL) to which was added Cbz-Gly-OSu (74 mg, 0.24 mmol) and diisopropylethylamine (31 mg, 0.24 mmol) with stirring. This solution was stirred at room temperature for 18 h. The crude reaction mixture was diluted with EtOAc (10 mL), washed with $KHSO_4$ solution (3 × 2 mL), $NaHCO_3$ solution (2 × 2 mL), and brine (1 × 2 mL), dried over $MgSO_4$, filtered, and concentrated, yielding **18** (105 mg, 92%) as an oil, purity 90% by HPLC. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.34 (s, 5 H), 5.79–5.62 (m, 1 H), 5.31–5.05 (m, 3 H), 4.80–4.48 (m, 2 H), 4.03–3.79 (m, 3 H), 3.65–3.48 (m, 1 H), 3.33–3.18 (m, 1 H), 2.86–2.60 (m, 2 H), 2.38–2.19 (m, 1 H), 1.95–1.78 (m, 2 H with a s at δ 1.90), and 1.49–1.34 (m, 12 H). MS (m/e): 468 (M^+, 3), 267 (20), 159 (24), 91 (100).

Acknowledgment. Financial support from the National Science Foundation (Grant 8116986) is gratefully acknowledged. We thank Dr. C. Costello of Prof. K. Biemann's group for high-resolution mass spectra and Tod Zenkel and Jim Boyd for technical assistance.

Stereochemical Effects in the Ozonolysis of (*E*)- and (*Z*)-1-Ethoxypropene

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Received August 3, 1988

The ozonolysis of (*E*)-1-ethoxypropene (or (*Z*)-1-ethoxypropene) gave cis and trans pairs of 1,2-dioxolanes, 1,2,4-trioxolanes (ozonides), and 1,2,4,5-tetroxanes. Ozonolysis of mixtures of the *E* and *Z* alkenes led to variation in the dioxolane stereoisomer ratios but not in the trioxolane ratios. Ozonolysis in the presence of added alcohol or aldehydes produced hydroperoxides or ozonides, respectively, from the methyl-substituted carbonyl oxide. The results are consistent with a Criegee ozonolysis mechanism if the two alkenes produce different relative amounts of the syn and anti carbonyl oxide (CH_3HCOO), which recombine at different rates with dipolarophiles.

Introduction

It was recently reported[1] that the ozonolysis of methyl vinyl ether gave 3-methoxy-1,2-dioxolane in 68% yield, along with small amounts of the normal ozonide or 1,2,4-trioxolane. The unexpected dioxolane could be explained by a Criegee mechanism involving reaction of a carbonyl

0022-3263/89/1954-0115$01.50/0