Racemic Origins of the Stereochemically Homogeneous Biosphere. Biased Stereoselectivities in the Formation of Oligomeric Peptides

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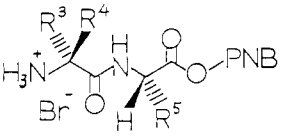
Abstract: Each of the competitive processes used to form the 34 di-, tri-, and tetrapeptides of alanine, aspartic acid, and glycine, 3 of the most abundant amino acid products of geosimulation experiments, was found to be stereoselective. The majority of them (70%) displayed biases in favor of isotactic growth with diastereomeric enrichments ranging between 4.2% and 56.6%. Isotactic growth of prevital polymers is likely to be an important part of any mechanism that satisfactorily accounts for the enantioselective passage of biomolecules from their racemic beginnings to the stereochemical homogeneity of contemporary life.

In recent years the association of optical activity and life, which stems from the time of Louis Pasteur, has focused on efforts to uncover potential mechanisms by which the putative enantioselective passage of biomolecules from their racemic beginnings to the configurational one-sidedness of contemporary life may be satisfactorily explained.[1] Experimental work in this area reveals that nonracemic samples may be generated abiotically from racemic material through the imposition of various, chiral, nonracemic physical agents.[2] Enantiomeric imbalances are, however, uniformly so low as to make it very difficult to imagine any of these processes as a direct source of the stereohomogeneous biosphere. Bonner et al.[3] in appreciation of this difficulty, have put forth a reasonable amplification mechanism to enhance such small, abiotically produced, enantiomeric enrichments. An entirely different approach, however, is contained in an earlier suggestion made by Wald.[4]

In Wald's scheme resolution takes place at the cellular or protocellular level, and it does not require a nonracemic chiral agent. Enantiomeric homogeneity comes about as a result of higher efficiency. Wald imagined primitive life to be racemic, consisting of separate all L and all D (isotactic) biopolymers. Subsequent changes, such as development of metabolic interdependence, provide a cardinal evolutionary advantage to those systems able to function with only one enantiomer, thus triggering the inexorable journey to the configurationally one-sided, contemporary biosphere. The principal ingredient of this scheme is the ability of prevital polymers to form isotactically. Wald suggested that the α-helix, formed during peptide growth, may function as the stereoselectivity agent, favoring the incorporation of one amino acid enantiomer over the other. Supporting the idea of isotactic polymers are a number of experiments which show or suggest the occurrence of stereoselectivity during polymerization of α-amino acid *N*-carboxylic acid anhydrides, including some that indicate the predominance of isotactic products.[3,5]

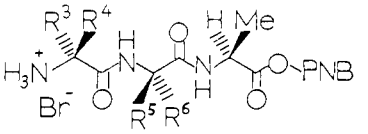
If a general tendency of amino acids to form racemic, isotactic peptides exists, then it must be viewed as the basis of a powerful stereochemical amplification mechanism, whatever resolution

Table I. Enantiomerically Pure Dipeptide Esters



compd	R^3	R^4 (config)	R^5 (config)
5	H	H	Me (L)
6	H	H	CH_2CO_2Me (L)
7	H	Me (L)	H
8	H	Me (L)	Me (L)
9	Me	H (D)	Me (L)
10	H	CH_2CO_2Me (L)	CH_2CO_2Me (L)
11	CH_2CO_2Me	H (D)	CH_2CO_2Me (L)

Table II. Enantiomerically Pure Tripeptide Esters



compd	R^3	R^4 (config)	R^5	R^6 (config)
12	H	Me (L)	H	Me (L)
13	Me	H (D)	Me	H (D)
14	Me	H (D)	H	Me (L)
15	H	Me (L)	Me	H (D)

(1) Accounts of the vast majority of this work may be found in the following reviews: Bonner, W. A. In *Exobiology*; Ponnomperuma, C., Ed.; North-Holland: Amsterdam, 1971; Chapter 6. Thiemann, W. *Naturwissenschaften* **1974**, *61*, 476-483. Norden, B. *J. Molec. Evol.* **1978**, *11*, 313-332. For two recent discussions of the problem, see: Cairns-Smith, A. G. *Chem. Br.* **1986**, 559-5561 and Brewster, J. H. *J. Chem. Ed.* **1986**, *63*, 667-670.

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(3) Bonner, W. A.; Blair, N. E.; Dirbas, F. M. *Origins of Life* **1981**, *11*, 119-134.

(4) Wald, G. *Ann. N. Y. Acad. Sci.* **1957**, *69*, 352-368.

(5) Blout, E. R.; Idelson, M. *J. Am. Chem. Soc.* **1956**, *78*, 3857-3858. Doty, P.; Lundberg, R. D.; Doty, P. *Ibid.* **1957**, *79*, 3961-3972. Idelson, M.; Blout, E. R. *Ibid.* **1958**, *80*, 2387-2393. Ballard, D. G. H.; Bamford, C. M.; Elliot, A. *Markomol. Chem.* **1960**, *35*, 222-238; Nylund, R. E.; Miller, W. G. *Biopolymers* **1964**, *2*, 131-134; Matsuura, K.; Inoue, S.; Tsuruta, T. *Makromol. Chem.* **1965**, *85*, 284-286. Tsuruta, T.; Inoue, S.; Matsuura, K. *Biopolymers* **1967**, *5*, 313-319; Inoue, S.; Matsuura, K.; Tsuruta, J. *J. Polym. Sci.* **1968**, *C23*, 721-732. Buhrer, H. G.; Elias, H.-G. *Makromol. Chem.* **1973**, *169*, 145-162. Akaike, T.; Aogaki, Y.; Inoue, S. *Biopolymers* **1975**, *14*, 2577-2583. Hashimoto, Y.; Aoyama, A.; Imamishi, Y.; Higashimura, T. *Ibid.* **1976**, *15*, 2407-2420. Imanishi, Y.; Aoyama, A.; Hashimoto, Y.; Higahimura, T. *Ibid.* **1977**, *16*, 187-197. Hashimoto, Y.; Imanishi, Y.; Higashimura, T. *Ibid.* **1978**, *17*, 2561-2572. Hashimoto, Y.; Imanishi, Y. *Ibid.* **1980**, *19*, 655-668. Blair, N. E.; Bonner, W. A. *Origin Life* **1980**, *10*, 255-263. Hashimoto, Y.; Imanishi, Y. *Biopolymers* **1981**, *20*, 489-505 and 507-524.

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Scheme I

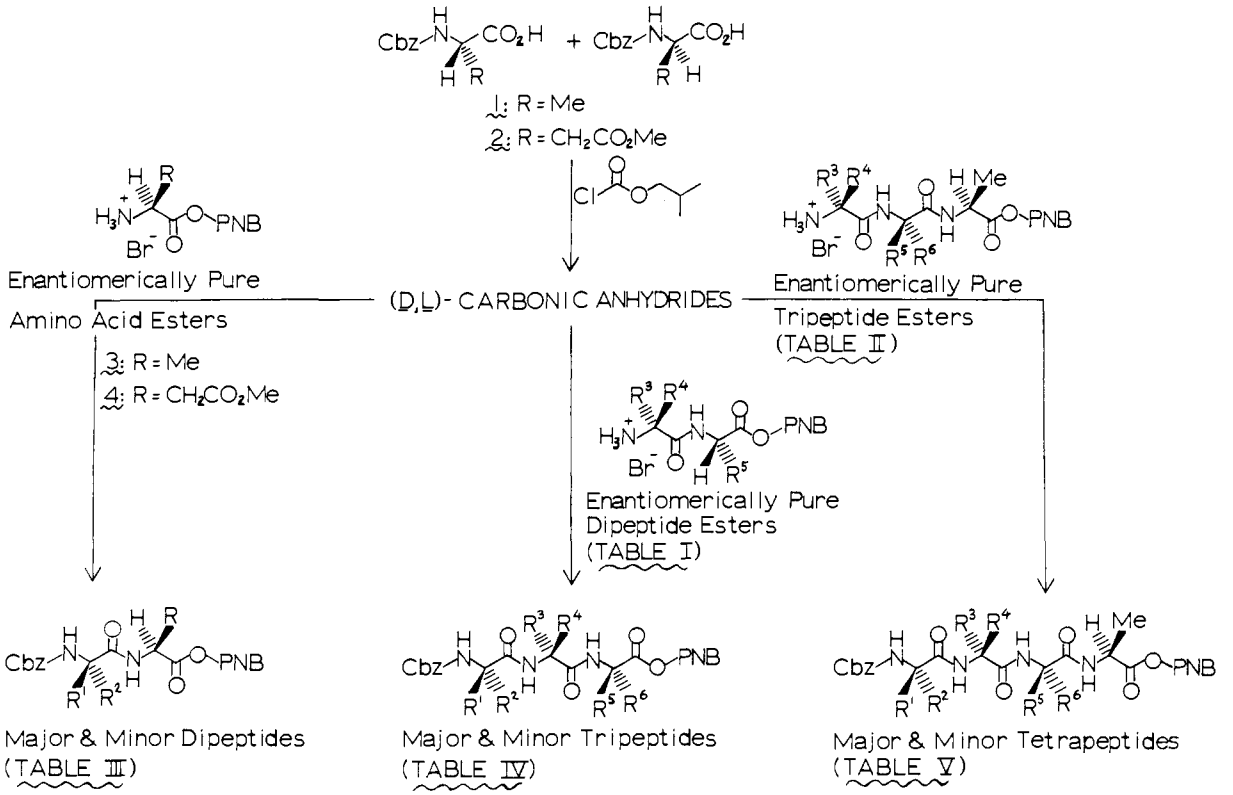
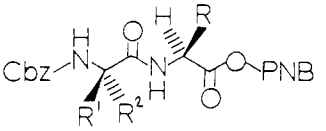


Table III. Major and Minor Dipeptides Competition Products



expt	product	R^1	R^2 (config)	R (config)	composition, %	diastereomeric enrichment[11]
1	**16a**	H	Me (L)	Me (L)	58.0 ± 1.7	16.0 ± 3.4
	16b	Me	H (D)	Me (L)	42.0 ± 1.7	
2	**17a**	H	CH_2CO_2Me (L)	CH_2CO_2Me (L)	55.8 ± 1.5	11.6 ± 3.0
	17b	CH_2CO_2Me	H (D)	CH_2CO_2Me (L)	44.2 ± 1.5	
3	**18a**	H	Me (L)	CH_2CO_2Me (L)	52.1 ± 1.0	4.2 ± 2.0
	18b	Me	H (D)	CH_2CO_2Me (L)	47.9 ± 1.0	
4	**19a**	H	CH_2CO_2Me (L)	Me (L)	55.3 ± 0.5	10.6 ± 1.0
	19b	CH_2CO_2Me	H (D)	Me (L)	44.7 ± 0.5	

process eventually prevails. In isotactic peptides the myriad stereochemical choices stand highly organized and poised for the ultimate selection: simply that of object or mirror image.

If a stable secondary structure, such as the α-helix, is to be the agent of isotaticity in a growing peptide, as proposed by Wald[4] and supported by others,[6] there is, however, an annoying conundrum to confront: peptides must be isotactic and contain between 8 and 12 amino acid residues as minimum requirements merely for the onset of helicity.[9] Even in the most conservative consideration, stereorandom formation of octapeptide means that only two isomers (the octa-L and the octa-D) out of the total of 2^8 or 256 have to carry the load of subsequent isotactic growth. But stereorandomness need not be the case.

The present investigation was undertaken in an effort to assess the tendency of an arbitrarily chosen system of peptide assembly to display biased stereoselectivity. By use of only alanine, aspartic acid, and glycine, three of the must abundant amino acid products of geosimulation experiments,[10] the results reported herein support the notion that reaction conditions may be found to allow or promote the stepwise assembly of chiral monomers into even small chains with significant levels of stereoregularity.

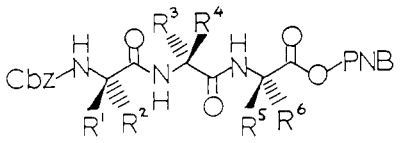
Every reaction leading to the 34 di-, tri-, and tetrapeptides of the present study was found to be stereoselective, and the majority of them (70%) displayed biases in favor of isotactic growth.

Results and Discussion

In each experiment (Scheme I), 2 equiv of racemic, amino-blocked amino acid (**1** and **2**) was converted to racemic carbonic anhydride, and the latter was allowed to compete for 1 equiv of enantiomerically pure amino acid ester (hydrobromides, **3–15**) in cold (dry ice) dimethylformamide solution containing triethylamine. The mixture of the two diastereomerically related

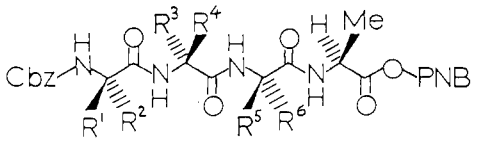
(6) Three review articles[3,7,8] contain brief accounts of this subject.
(7) Tsuruta, T. *J. Polym. Sci.* **1972**, *D6*, 179–250.
(8) Klabunovski, E. I. *Russ. Chem. Rev. (Engl. Transl.)* **1968**, *37*, 969–984.
(9) Blout, E. R.; Doty, P.; Yang, J. T. *J. Am. Chem. Soc.* 1957, *79*, 749–750. Goodman, M.; Schmitt, E. E.; Yphantis, D. A. *Ibid.* **1962**, *84*, 1288–1296. Goodman, M.; Listowsky, I.; Schmitt, E. E. *Ibid.* **1963**, *85*, 2491–2497. Goodman, M.; Listowsky, I.; Masuda, Y.; Boardman, F. *Biopolymers* **1963**, *1*, 33–42. Goodman, M.; Rosen, I. G. *Ibid.* **1964**, *2*, 537–559. Goodman, M.; Langsam, M.; Rosen, I. G. *Ibid.* **1966**, *4*, 305–319. Schechter, B.; Schecter, I.; Ramachandran, J.; Conway-Jacobs, A.; Sela, M. *Eur. J. Biochem.* **1971**, *20*, 301–308.
(10) Lemmar, R. M. *Chem. Rev.* **1970**, *70*, 95–109. Ponnamperuma, C. *Q. Rev. Biophys.* **1971**, *4*, 77–106.

Table IV. Major and Minor Tripeptides Competition Products



expt	product	R^1	R^2 (config)	R^3	R^4 (config)	R^5 (config)	composition, %	diastereomeric enrichment[11]
5	**20a**	H	Me (L)	H	H	Me (L)	42.0 ± 1.3	−16.0 ± 2.6
	20b	Me	H (D)	H	H	Me (L)	58.0 ± 1.3	
6	**21a**	H	CH_2CO_2Me (L)	H	H	CH_2CO_2Me (L)	75.0 ± 1.5	50.0 ± 2.5
	21b	CH_2CO_2Me	H (D)	H	H	CH_2CO_2Me (L)	25.0 ± 1.0	
7	**22a**	H	Me (L)	H	H	CH_2CO_2Me (L)	34.0 ± 1.0	−32.0 ± 2.0
	22b	Me	H (D)	H	H	CH_2CO_2Me (L)	66.0 ± 1.0	
8	**23a**	H	CH_2CO_2Me (L)	H	Me (L)	H	55.0 ± 1.0	10.0 ± 2.0
	23b	CH_2CO_2Me	H (D)	H	Me (L)	H	45.0 ± 1.0	
9	**24a**	H	CH_2CO_2Me (L)	H	H	Me (L)	9.0 ± 1.5	−82.0 ± 3.0
	24b	CH_2CO_2Me	H (D)	H	H	Me (L)	91.0 ± 1.5	
10	**25a**	H	Me (L)	H	Me (L)	Me (L)	76.5 ± 1.0	52.0 ± 2.0
	25b	Me	H (D)	H	Me (L)	Me (L)	24.5 ± 1.0	
11	**26a**	Me	H (D)	Me	H (D)	Me (L)	60.0 ± 1.0	20.0 ± 2.0
	26b	H	Me (L)	Me	H (D)	Me (L)	40.0 ± 1.0	
12	**27a**	H	CH_2CO_2 (L)	H	CH_2CO_2Me (L)	CH_2CO_2Me (L)	29.0 ± 1.3	−42.0 ± 2.6
	27b	CH_2CO_2Me	H (D)	H	CH_2CO_2Me (L)	CH_2CO_2Me (L)	71.0 ± 1.3	
13	**28a**	CH_2CO_2Me	H (D)	CH_2CO_2Me	H (D)	CH_2CO_2Me (L)	42.8 ± 1.0	−13.4 ± 2.0
	28b	H	CH_2CO_2Me (L)	CH_2CO_2Me	H (D)	CH_2CO_2Me (L)	57.2 ± 1.0	

Table V. Major and Minor Tetrapeptides Competition Products



expt	product	R^1	R^2 (config)	R^3	R^4 (config)	R^5	R^6 (config)	composition, %	diastereomeric enrichment[11]
14	**29a**	H	Me (L)	H	Me (L)	H	Me (L)	78.8 ± 1.5	56.6 ± 3.0
	29b	Me	H (D)	H	Me (L)	H	Me (L)	21.2 ± 1.5	
15	**30a**	Me	H (D)	Me	H (D)	Me	H (D)	75.0 ± 2.0	50.0 ± 4.0
	30b	H	Me (L)	Me	H (D)	Me	H (D)	25.0 ± 2.0	
16	**31a**	Me	H (D)	Me	H (D)	H	Me (L)	63.3 ± 1.8	26.6 ± 3.6
	31b	H	Me (L)	Me	H (D)	H	Me (L)	36.7 ± 1.8	
17	**32a**	H	Me (L)	H	Me (L)	Me	H (D)	58.3 ± 1.5	16.6 ± 3.0
	32b	Me	H (D)	H	Me (L)	Me	H (D)	41.7 ± 1.5	

peptides (Tables III–V) that formed in each case was isolated constitutionally pure (thin-layer chromatography) but without separation of its diastereomeric components. The diastereomeric composition of each binary mixture—the average of two runs shown in Tables III–V—was determined from previously constructed linear correlations of chiroptical magnitudes and binary compositions of enantiomerically pure, authentic peptides. In each case a made-up mixture of the two diastereomeric peptides, different in composition from that obtained in the corresponding competition experiment, was submitted to the reaction and isolation conditions of the competition experiment. In all cases these control compositions were found not to exceed 2% of the known starting compositions. Thus, it was established that the compositions of the peptide competition products were kinetically controlled and not due to equilibration processes. These compositions were taken as the measures of stereoselectivity and used to compute each of the convenient comparatives, diastereomeric enrichments (d.e.),[11] shown in Tables III–V.

It is reasonable to designate peptide growth as being isotactic when the growing peptide takes on a new amino acid unit possessing the configuration already present in the amino acid residue of the growing end of the peptide. In this sense, 12 of the 17 competition experiments (experiments 1–4, 6, 8, 10, 11, 14–17) show isotactic growth, ranging in d.e. from a low of 4.2 ± 2.0 (experiment 3) to a high of 56.6 ± 3.0 (experiment 14). Although detailed quantitative comparisons of stereoselectivities cannot be made because of the lack of data on the kinetics that attend these reactions, the following observations suggest some intriguing trends.

1. Both alanine and aspartic acid prefer to form isotactic dipeptides in all cases (experiments 1–4).

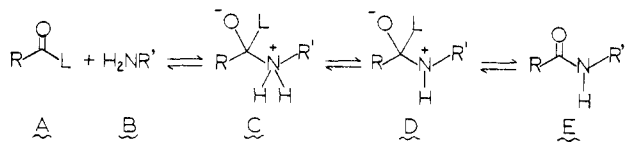
2. The homoalanines, without exception, prefer isotactic growth (experiments 1, 10, 11, 14–17), and they may be delegated to one of two categories. The first, the lower d.e., category is made up of those homoalanines where the configuration of the alanyl unit at the growing end is different from the configuration of the next alanyl unit: experiment (d.e.); 1 (16.0 ± 3.4); 11 (20.0 ± 2.0); 16 (26.6 ± 3.6); and 17 (16.6 ± 3.0). In the second, or higher d.e., category, the configuration of the alanyl unit at the growing end is identical with that of the other alanyl units present: 10 (52.0 ± 2.0); 14 (56.6 ± 3.0); and 15 (50.0 ± 4.0).

3. The homoaspartates, on the other hand, appear to display an increasing tendency toward nonisotactic growth with increasing aspartyl content: compare experiment 2 (11.6 ± 3.0) with experiments 12 and 13 (−42.0 ± 2.6 and −13.4 ± 2.0).

4. While the presence of a glycyl unit adjacent to the growing end does not have an observable effect [compare experiment 4 (10.6 ± 1.0) with experiment 8 (10.0 ± 2.0)], a glycyl unit at the growing end seems to cause reversals: compare experiment 1 (16.0 ± 3.4) with experiment 5 (−16.0 ± 2.6); experiment 3 (4.2 ± 2.0)

(11) Diastereomeric enrichment is defined as the difference of the percent compositions of the major and minor diastereomers. The negative sign means that the selectivity is nonisotactic.

Scheme II



with experiment 7 (−32.0 ± 2.0); experiment 4 (10.6 ± 1.0) with experiment 9 (−82.0 ± 3.0); and experiment 2 (11.6 ± 3.0) with experiment 6 (50.0 ± 2.5) where the trend noted above in item 3 is reversed.

Interpretation (and prediction) of the direction and degree of stereoselectivity in reaction systems such as the present one must be carried out within the context of the tetrahedral mechanism for nucleophilic substitution at the acyl carbon[12] as indicated in Scheme II. The acylating component is represented by A, and L stands for the various leaving groups used for carboxyl group activation. In order to judge whether (and to what extent), say L-A prefers to combine with D-B or L-B (the nucleophilic amino component), one must be able to evaluate the myriad pathways generated by each of the conformers of D-B and L-B adding to both the *re* and *si* faces of each of the conformers of L-A. Even in the event that a precise evaluation can be extracted from this matrix of diastereomerically related pathways, say, one favoring L-A, D-B addition over L-A, L-B addition, with each pathway leading to the corresponding complex set of protonated tetrahedral intermediates represented by C, the L-A, D-B net preference could be reversed by the rates governing removal of one or the other diastereotopic protons from C to give the deprotonated tetrahedral intermediates D. The relative amounts of all the contending D's and their rate constants would finally provide the actual ratio of the two diastereomerically related peptides, LD-E and LL-E. While application of the principles of stereoelectronic control[13] may be expected to provide considerable help, the remaining, and as yet unanswerable, conformational questions prevent a detailed interpretation of the stereochemical results of the present study as well as those from previous studies of α-amino acid *N*-carboxylic acid anhydrides[3,5] and of other α-amino acid derivatives.[14] Any interpretation based solely on consideration of the initial addition of A and B is incomplete and most likely inadequate.

In any case, isotactic formation of biopolymers remains a potentially powerful stereochemical amplifier, awaiting inclusion into a reasonable model that satisfactorily explains the origin of the configurational one-sidedness of life. A significant advance in the development of that model will be the demonstration of an experimental system that combines catalysis and stereoselectivity: a system that catalyzes isotactic combinations of chiral biomonomers.

Experimental Section

Syntheses of Stereochemically Authentic Peptides.[15,16] **(−)-*N*-Cbz-α-PNB-β-methyl-L-aspartate (33).** (−)-*N*-Cbz-β-methyl-L-aspartate (**34a**),[17] (8.2 g, 0.029 mol) was heated under reflux with a mixture of *p*-nitrobenzyl chloride (5.4 g, 0.031 mol), triethylamine (18 g, 0.18 mol), and ethyl acetate (140 mL) for 19 h. The mixture was filtered while it was hot, and the filtrate was allowed to cool to room temperature before it was extracted successively with 1 N HCl (300 mL), 1 N $NaHCO_3$ (300 mL), and water (2 × 200 mL). The organic residue was dried over anhydrous $MgSO_4$ before its volume was reduced to 100 mL and high-boiling petroleum ether added to the cloud point. After several hours white crystals formed. They were recrystallized from hot 95% ethanol, giving (−)-**33** as fine white needles: 5.4 g (45%); mp 78.5–79.5 °C; $[\alpha]^{25}_D$ −22.8° (*c* 2.00, DMF); IR (KBr) ν_{max} 3300 (amide), 1725 (ester carbonyl), 1675 (amide carbonyl), 1600 and 1400 (phenyl), 1530, 1350 (nitro), 1300, 1230, and 1170 cm^{-1} (ester C–O);[18] ^1H NMR ($CDCl_3$) δ 7.80 q and 7.31 s (9 H, phenyl), 5.80 d (1 H, amide), 5.26 s and 5.12 s (4 H, benzyl methylenes), 4.75 m (1 H, methine), 3.66 s (3 H, methyl ester), and 2.99 m (2 H, methylene). Anal. Calcd for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; M_r, 416. Found: C, 57.67; H, 5.06; M_r (mass spectrum), 416. A subsequent run twice the molar size gave a yield of 52%.

(−)-α-PNB-β-methyl-L-aspartate Hydrobromide (4a). (−)-*N*-Cbz-α-PNB-β-methyl-L-aspartate (**33**, 7.7 g, 0.019 mol) was dissolved in a 30% solution of hydrogen bromide in glacial acetic acid (15 mL), and the mixture was solidified after about 10 min. Anhydrous ether was added, and the tan solids were collected and recrystallized from hot methanol–ether, yielding the desired salt (**4a**) as white needle-shaped crystals: 6.6 g (98%); mp 170.5 °C; $[\alpha]^{26}_D$ −0.40° (*c* 1.99, DMF); IR (KBr) ν_{max} 3010–2900 (amine salt), 1755 and 1735 (ester carbonyl), 1610 and 1595 (phenyl), 1530 and 1360 (nitro), 1260, 1235, and 1200 cm^{-1} (ester C–O); ^1H NMR (Me_2SO-d^6) δ 8.04 q (4 H, *p*-disubstituted phenyl), 5.46 s (2 H, benzyl methylene), 4.62 t (1 H, methine), 3.68 s (3 H, methyl ester), and 3.14 d (2 H, methylene). Anal. Calcd for $C_{12}H_{15}BrN_2O_6$: C, 39.68; H, 4.16. Found: C, 39.76; H, 4.39.

(−)-*N*-Cbz-β-methyl-L-aspartyl-α-PBN-β-methyl-L-aspartate (17a). (−)-*N*-Cbz-β-methyl-L-aspartate (**34a**,[17] 0.84 g, 0.0030 mol) was dissolved in DMF (7 mL) and cooled to −10 °C in an external ice–salt bath. Isobutyl chloroformate (0.4 g, 0.003 mol) and triethylamine (0.3 g, 0.003 mol) were added and the reaction mixture stirred for 20 min. A solution of (−)-α-PBN-β-methyl-L-aspartate hydrobromide (**4a**, 1.1 g, 0.003 mol) in DMF (5 mL) was cooled to −10 °C and added to the reaction mixture. This was followed by the dropwise addition of triethylamine (0.3 g, 0.003 mol). Stirring was continued for 3.5 h as the mixture was allowed to warm to room temperature before it was poured into a volume of 0.05 N HCl 10 times the volume of the reaction mixture. After 1 h crystallization was complete, and the product was collected in a filter where it was washed copiously with water. The material was recrystallized from absolute ethanol to give (−)-**17a** as white crystals: 0.98 g (60%); mp 117.7–118.0 °C; $[\alpha]^{25}_D$ −27.6° (*c* 2.00, DMF); IR (KBr) ν_{max} 3300 (amide), 1750 and 1700 (ester carbonyls), 1670 (amide carbonyl), 1530 and 1360 (nitro), 1615 and 1450 (phenyl), and 1300–1170 cm^{-1} (ester C–O); ^1H NMR ($CDCl_3$) δ 7.83 and 7.31 m (9 H, phenyl), 5.15 and 5.03 s (4 H, benzyl methylene), 4.60 m (2 H, methine), 3.68 s (6 H, methyl ester), and 2.94 m (4 H, methylene); amide protons apparently lost in the base-line noise. Anal. Calcd $C_{25}H_{27}N_3O_{11}$: C, 55.04; H, 4.99; M_r, 545. Found: C, 54.87; H, 5.15; M_r (mass spectrum), 545.

(−)-*N*-Cbz-β-methyl-D-aspartyl-α-PNB-β-methyl-L-aspartate (17b). The procedure used was an exact duplication of that used to prepare the LL diastereomer except for the substitution of (+)-*N*-Cbz-β-methyl-D-aspartate (**34b**)[17] for its L enantiomer. The product was obtained as a white crystalline solid: 0.98 g (60%); mp 128–129 °C; $[\alpha]^{25}_D$ −7.6 (*c* 2.0, DMF); IR (KBr) ν_{max} 3300 (amide), 1740 and 1700 (ester carbonyls), 1660 and 1670 (amide carbonyls), 1530 and 1350 (nitro), 1605, 1440 (phenyl), and 1300–1170 cm^{-1} ester C–O); ^1H NMR ($CDCl_3$) δ 7.81 and 7.28 m (10 H, phenyl and amide), 5.93 d (1 H amide), 5.23 and 5.09 s (4 H, benzyl methylene), 4.70 m (2 H, methine), 3.63 s (6 H, methyl ester), 2.92 m (4 H, methylene). Anal. Calcd for $C_{25}H_{27}N_3O_{11}$: C, 55.04; H, 4.99; M_r, 545. Found: C, 55.12; H, 5.24; M_r (mass spectrum), 545.

(−)-*N*-Cbz-L-alanyl-α-PBN-β-methyl-L-aspartate (18a). A 10% solution of (−)-*N*-Cbz-L-alanine (**1a**,[19] 1.23 g, 0.00551 mol) in DMF was cooled to 100 °C in an external ice–salt bath before isobutyl chloroformate (0.72 mL, 0.0055 mol) and triethylamine (0.77 mL, 0.0055 mol) were added. After the reaction mixture was stirred for 20 min at −10 °C, a cold (−10 °C) 10% solution of (−)-α-PBN-β-methyl-L-aspartate hydrobromide (**4a**, 2.00 g, 0.00551 mol) in DMF was added, followed by dropwise addition of triethylamine (0.77 mL, 0.0055 mol). When the stirred reaction mixture reached room temperature (ca. 2.5 h), it was poured into 10 times its volume of 0.05 N HCl and left overnight. The deposited solids were collected and recrystallized from absolute ethanol to yield hygroscopic white crystals of the dipeptide **18a**: 1.22 g (45.4%); mp 147.5–148.0 °C; $[\alpha]^{25}_D$ −14.6 ± 0.2° (*c* 1.00, DCA); IR (KBr) ν_{max} 3300 (amide), 1730 and 1690 (ester carbonyls), 1650 (amide carbonyls), 1610 and 1450 (phenyl), 1530 and 1350 (nitro), and 1300–1170 cm^{-1} (ester C–O); ^1H NMR ($CDCl_3$) δ 8.27 d, 7.50 d, and 7.36 s (9 H, phenyl), 5.28 s and 5.12 s (4 H, benzyl methylene), 4.32 m (2 H, methine), 3.67 s (3 H, methyl ester), 2.96 m (2 H, methylene), 1.39 d (3 H, methyl ester), 2.96 m (2 H, methylene), and 1.39 d (3 H, methyl).

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(15) Each peptide is constant-melting material, i.e., each was recrystallized until its melting point did not change in three successive recrystallizations.
(16) The abbreviations Cbz and PNB stand for carbobenzyloxy ((benzyloxy)carbonyl) and *p*-nitrobenzyl, respectively. The solvents dichloroacetic acid and dimethylformamide are represented as DCA and DMF, respectively.
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Anal. Calcd for $C_{23}H_{25}N_3O_9$: C, 56.67; H, 5.17. Found: C, 56.64; H, 5.25.

(+)-*N*-Cbz-D-alanyl-α-PBN-β-methyl-L-aspartate (18b). The procedure, reagents, and quantities were the same as used in the preparation of the diastereomeric dipeptide **18a** except that (+)-Cbz-D-alanine (**1b**) was used instead of its L enantiomer. Purified **18b** was obtained a white crystals: 1.32 g (49.2%); mp 140.0–140.5 °C; $[\alpha]^{25}_D$ + 13.0 ± 0.2° (*c* 1.00, DCA); IR (KBr) ν_{max} 3300 (amide), 1740 and 1695 (ester carbonyls), 1665 and 1660 (amide carbonyls), 1610 and 1440 (phenyl), 1530 and 1350 (nitro), and 1300–1700 cm^{-1} (ester C–O). An ^1H NMR spectrum was not obtained owing to the compounds poor solubility in $CDCl_3$. Anal. Calcd for $C_{23}H_{25}N_3O_9$: C, 56.67; H, 5.17. Found: C, 56.68; H, 5.31.

(−)-*N*-Cbz-β-methyl-L-aspartyl-PBN-L-alanate (19a). A 10% solution of (−)-*N*-Cbz-β-methyl-L-aspartate (**34a**,[17] 1.38 g, 0.00492 mol) in DMF was cooled to −10 °C before equimolar amounts of isobutyl chloroformate and triethylamine were added. The reaction mixture was stirred at −10 °C for 10 min followed by addition of a cold 10% solution of (−)-PBN-L-alanate hydrobromide (**7**)[20,21] (1.50 g, 0.00492 mol) in DMF. After the dropwise addition of additional triethylamine (0.06 mL), the stirring was continued while the whole was allowed to come to room temperature (2.5 h). The reaction mixture was poured into a volume of 0.05 N HCl equal to 10 times its own volume. The deposited white solids were collected the next morning in a funnel, washed, and recrystallized from absolute ethanol to give pure (−)-(**19a**): 1.17 g (48.8%); mp 154.5–155.0 °C; $[\alpha]^{25}_D$ −15.4 ± 0.2° (*c* 1.00, DMF); IR (KBr) ν_{max} 3310 (amide), 1730 and 1690 (ester carbonyls), 1650 (amide carbonyl), 1600 and 1450 (phenyl), 1525 and 1345 (nitro), and 1300–1170 cm^{-1} (ester C–O); ^1H NMR ($CDCl_3$) δ 8.17 d, 7.44 d, and 7.28 s (9 H, phenyl), 5.22 s and 5.10 s (4 H, benzyl methylene), 4.57 m (2 H, methine), 3.65 s (3 H, methyl ester), 2.84 m (2 H, methylene), and 1.41 d (3 H, methyl). Anal. Calcd for $C_{23}H_{25}N_3O_9$: C, 56.67; H, 5.17. Found: C, 56.75; H, 5.20.

(−)-*N*-Cbz-β-methyl-D-aspartyl-L-alanate (19b). Preparation and purification was carried out following the procedure reported above for the diastereomeric material **19a** except for the use of (+)-*N*-Cbz-β-methyl-D-aspartate (**34b**)[17] instead of the L enantiomer **34a**: 1.13 g (47.0%); mp 166.5–167.0 °C; $[\alpha]^{25}_D$ +7.6 ± 0.2° (*c* 1.00, DMF); IR (KBr) ν_{max} 3310 (amide), 1740 and 1690 (ester carbonyls), 1650 (amide carbonyls), 1610 and 1440 (phenyl), 1530 and 1350 (nitro), and 1305–1180 cm^{-1} (ester C–O); ^1H NMR ($CDCl_3$) δ 8.16 d, 7.44 d, and 7.28 s (9 H, phenyl), 5.22 s and 5.17 s (4 H, benzyl methylene), 4.60 m (2 H, methine), 3.65 br s (3 H, methyl ester), 2.85 m (2 H, methylene), and 1.42 d (3 H, methyl). Anal. Calcd for $C_{23}H_{25}N_3O_9$: C, 56.67; H, 5.17. Found: C, 56.80; H, 5.46.

(−)-β-Methyl-L-aspartyl-α-PNB-β-methyl-L-aspartate (19b). (−)-*N*-Cbz-β-methyl-D-aspartyl-α-PNB-β-methyl-L-aspartate (**17b**, 6.39 g, 0.0117 mol) was dissolved in a 30% solution of HBr in glacial acetic acid (12 mL). After the solution remained at room temperature for 0.5 h, diethyl ether was added to the cloud point, and the product was precipitated as a white solid. Recrystallization from methanol–ether gave pure (−)-**19b** as white crystals: 4.99 g (86.5%); mp 169.5–170.5 °C; $[\alpha]^{25}_D$ −33.2° (*c* 1.90, DMF); IR (KBr) ν_{max} 3400 (amide), 2960–2860 (amine salt), 1745 and 1730 (ester carbonyls), 1685 (amide carbonyls), 1605, 1475, and 1445 (phenyl), 1525 and 1350 cm^{-1} (nitro); ^1H NMR (Me_2SO-d_6) δ 8.01 q (4 H, *p*-nitrophenyl), 5.37 s (2 H, benzyl methylene), 4.87 and 4.25 m (2 H, methines), 3.69 s (6 H, methyl esters), 2.96 d (4 H, methylenes). Anal. Calcd for $C_{17}H_{22}BrN_3O_9 \cdot H_2O$: C, 40.41; H, 4.74.

(+)-*N*-Cbz-β-methyl-L-aspartyl-β-methyl-L-aspartyl-α-PNB-β-methyl-L-aspartate (27a).[22] (−)-*N*-Cbz-β-methyl-L-aspartate (**34a**,[17,23] 0.56 g, 0.0020 mol) was dissolved in DMF (5 mL) and cooled to −10 °C in an external ice–water–salt bath before isobutyl chloroformate (0.28 g, 0.0021 mol) and triethylamine (0.2 g, 0.002 mol) were added and the whole was stirred at −20 °C for 20 min. (−)-β-Methyl-L-aspartyl-α-PNB-β-methyl-L-aspartate hydrobromide (**10**, 1.0 g, 0.0020 mol) was dissolved in DMF (3.5 mL) and cooled to −10 °C before it was added to the stirred reaction mixture. Triethylamine (0.2 g, 0.002 mol) was also added, and the whole was stirred for another 3 h before it was allowed to warm to room temperature. The mixture was poured into 0.05 N hydrochloric acid (100 mL), and it was allowed to remain overnight to assure complete precipitation. The solid material was collected and recrystallized from ethanol to give pure (+)-**27a** as white crystals: 0.70 g (50%); mp 139–140 °C; $[\alpha]^{26}_D$ +8.2° (*c* 2.00, $CHCl_3$); $[\alpha]_D$ −10.4° (*c* 1.00, DCA); $[\alpha]_D$ −16.9° (*c* 1.00, DMF); IR (KBr) ν_{max} 3330 (amide), 1735 and 1727 (ester carbonyls), 1640 (amide carbonyl), 1525 and 1345 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 7.85 q and 7.33 s (9 H, phenyls), 5.83 d (1 H amide), 5.25 and 5.14 s (4 H, benzyl methylenes), 4.84 m (3 H, methines), 3.67 (9 H, methyl esters), and 2.88 m (6 H, methylenes). Anal. Calcd for $C_{30}H_{34}N_4O_{14}$: C, 53.41; H, 5.08; M_r, 674. Found: C, 53.68; H, 5.29; M_r (mass spectrum), 674.

(−)-*N*-Cbz-β-methyl-D-aspartyl-β-methyl-L-aspartyl-α-PNB-β-methyl-L-aspartate (27b). (+)-*N*-Cbz-β-methyl-D-aspartate (**34b**)[17] was coupled with (−)-β-methyl-L-aspartyl-α-PNB-β-methyl-L-aspartate hydrobromide (**11**) in the manner described above to give (−)-**27b**, which was recrystallized from ethanol. It was necessary, however, to chromatograph the material on silica plates which were developed first with chloroform, air dried, and then redeveloped with a 5:4:1 (v/v/v) mixture of ether:chloroform:methanol. This gave −-**27b** as fluffy white crystals: 0.59 g (43%); mp 144–145 °C; $[\alpha]^{25}_D$ −30.5° (*c* 1.0, DMF); IR (KBr) ν_{max} 3275 (amide), 1725 (ester carbonyl), 1630 (amide carbonyl), and 1525 and 1345 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 7.84 and 7.33 m (9 H, phenyl), 5.94 d (1 H, amide), 5.24 and 5.11 s (4 H, benzyl methylenes), 4.83 m (3 H, methines), 3.63 (9 H, methyl esters), and 2.90 m (6 H, methylenes). Anal. Calcd for $C_{30}H_{34}N_4O_{14}$: C, 53.41; H, 5.08. Found: C, 53.24; H, 5.22.

(+)-*N*-Cbz-β-methyl-L-aspartyl-β-methyl-D-aspartyl-α-PNB-β-methyl-L-aspartate (28b). (−)-*N*-Cbz-β-methyl-L-aspartate (**34a**,[18] 0.73 g, 0.0026 mol) was used with (−)-β-methyl-D-aspartyl-α-PNB-β-methyl-L-aspartate hydbromide (**11**, 1.3 g, 0.0026 mol). The initial product was a yellow oil that could not be induced to crystallize, but the material was obtained as white crystals after silica chromatography [5:4:1 (v/v/v) ether:chloroform:methanol] and recrystallization from 95% ethanol: 0.2 g (11%); mp 131–132.5 °C; $[\alpha]^{26}_D$ +11.75° (*c* 2.00, $CHCl_3$); IR (KBr) ν_{max} 3300 (amide), 1735 (ester carbonyl), 1655 (amide carbonyl), and 1530 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.00 m and 7.41 s (9 H, phenyl), 5.30 s and 5.19 s (4 H, benzyl methylenes), 4.85 m (2 H, methines), 3.71 s (9 H, methyl esters), and 3.01 m (6 H, methylenes). Anal. Calcd $C_{30}H_{34}N_4O_{14}$: C, 53.41; H, 5.08. Found: C, 53.48; H, 5.18.

(−)-*N*-Cbz-β-methyl-D-aspartyl-β-methyl-D-aspartyl-α-PNB-β-methyl-L-aspartate (28a). (+)-*N*-Cbz-β-methyl-D-aspartate (**34b**,[17] 0.73 g, 0.0026 mol) was used with (−)-β-methyl-D-aspartyl-α-PNB-β-methyl-L-aspartate hydrobromide (**11**, 1.3 g, 0.0026 mol) to produce a white crystalline product which was further purified by chromatography on silica-coated plates (initial development with chloroform, follow by development with 5:14:1 (v/v/v) ether:chloroform:methanol: 0.40 g (22%); mp 144–145 °C; $[\alpha]^{26}_D$ −2.1° (*c* 1.8, $CHCl_3$); IR (KBr) ν_{max} 3300 (amide), 1760, 1750, 1745, and 1735 (ester carbonyls), 1665, 1655, and 1645 (amide carbonyls), 1570 and 1445 (phenyl), and 1530 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 7.94 q and 7.40 s (9 H, phenyl), 5.32 s and 5.18 s (4 H, benzyl methylenes), 4.88 m and 4.24 m (3 H, methylenes), 3.72 s (9 H, methyl esters), and 2.97 m (6 H, methylenes). Anal. Calcd for $C_{30}H_{34}N_4O_{14}$: C, 53.41; H, 5.08. Found: C, 53.26; H, 5.25.

(−)-*N*-Cbz-L-alanylglycyl-PNB-L-alanate (20a). Glycyl-PNB-L-alanate hydrobromide (**5**) was prepared by dissolving (−)-*N*-Cbz-glycyl-PNB-L-alanate (**36**,[19] 4.50 g, 0.0108 mol) in a 30% HBr solution in glacial acetic acid (23 mL). Ether was added to the could point, and the product was crystallized. After it was washed with several portions of anhydrous ether, the product was recrystallized from butanol–anhydrous ether to give **5** as pale-yellow crystals: 3.3 g (84%).

Isobutyl chloroformate (1.40 g, 0.0102 mol) was added to a cold (−8 °C) solution of triethylamine (1.01 g, 0.0100 mol) and (−)-*N*-Cbz-L-alanine (**1a**,[19] 2.20 g, 0.00987 mol) in DMF (11.0 mL). This was combined with a solution containing triethylamine (1.00 g, 0.0100 mol) and glycyl-PNB-L-alanate hydrobromide (**5**, 3.60 g, 0.00994 mol) in DMF (18.0 mL) and left over night at room temperature. The reaction mixture was poured into 0.05 N hydrochloric acid to produce a precipitate which was collected, washed with water, and dried before it was recrystallized from ethyl acetate to give (−)-**20a** as white crystals: 2.40 g (50%); mp 170.5–171.0 °C; $[\alpha]^{26}_D$ = −18.8° (*c* 1.00, DCA); IR (KBr) ν_{max} 3300 (amide), 1745 (ester carbonyl), 1695 (carbamate carbonyl), 1645 (amide carbonyl), 1550 and 1455 (phenyl), and 1530 and 1355 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 1.33 d and 1.45 d (6 H, methyls), 3.85–4.85 complex (4 H, methylene and methines), 5.09 s and 5.24 s (4 H, benzyl methylenes), 5.62 br and 7.15 br (2 H, amides), 7.32 s and 7.88 q (9 H, phenyl). Anal. Calcd for $C_{23}H_{26}N_4O_8$: C, 56.78; H, 5.39. Found: C, 56.86; H, 5.53.

(−)-*N*-Cbz-D-alanylglycyl-PNB-L-alanate (20b). The procedure described above for preparation of (−)-**20a** was followed except for the substitution of (+)-*N*-Cbz-D-alanine (**1b**)[19] for its L enantiomer **1a**, which

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(21) Shields, J. E.; McGregor, W. H.; Carpenter, F. *J. Org. Chem.* **1961**, *26*, 1491–1494.
(22) The same procedure was followed for preparation of each of the four aspartic acid tripeptides, (+)-**27a**, (−)-**27b**, (−)-**28a**, and (+)-**28b**. Full experimental details are given for (+)-**27a**, while only the essential facts surrounding preparation of the other three are presented.
(23) Prigot, M.; Pollard, C. B. *J. Am. Chem. Soc.* **1948**, *70*, 2758–2759.

gave (-)-**20b** as white needles: 2.9 g (60%); mp 157.8–158.0 °C; $[\alpha]^{27}_D$ -3.0° (*c* 1.0, DCA); IR (KBr) ν_{max} 3300 (amide), 1755 (ester carbonyl), 1690 (carbamate carbonyl), 1655 (amide carbonyl), 1450 (phenyl), and 1530 and 1355 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 1.39 d and 1.52 d (6 H, methyls), 3.97–4.95 complex (4 H, methylene and methines), 5.85 br and 7.39 br (2 H, amides), 7.51 s and 8.06 q (9 H, phenyl). Anal. Calcd for $C_{23}H_{26}N_4O_8$: C, 56.78; H, 5.39. Found: C, 57.02; H, 5.45.

(-)-Glycyl-α-PNB-β-methyl-L-aspartate Hydrobromide (6). A 10% solution of *N*-Cbz-glycine (**37**,[19] 3.3 g, 0.016 mol) in DMF was cooled to −10 °C before isobutyl chloroformate (2.2 g, 0.016 mol) and triethylamine (1.6 g, 0.016 mol) were added, and the whole was stirred for 20 min at −10 °C. A cold (−10 °C) solution of (-)-α-PNB-β-methyl-L-aspartate hydrobromide (**4a**, 5.7 g, 0.016 mol) was added, followed by dropwise addition of an equimolar amount of triethylamine. After the reaction mixture reached room temperature (~2.5 h), it was poured into 0.05 N hydrochloric acid 10 times its volume. The collected solid product was recrystallized from ethyl acetate–petroleum ether to give (+)-**38** as a white solid: 4.8 g (65%); mp 85.5–86.0 °C; $[\alpha]^{25}_D$ −23.4° (*c* 1.00, DMF); IR (KBr) ν_{max} 3300 (amide), 1730–1720 (ester carbonyls), 1665–1650 (amide carbonyls), 1610 (phenyl), and 1530 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.10 d, 7.40 d, and 7.24 s (9 H, phenyl), 5.20 s and 5.06 s (4 H, benzyl methylenes), 3.60 s (methyl ester), and 2.92 m (2 H, aspartyl methylene).

A sample of (+)-**38** (4.75 g, 0.0100 mol) was dissolved in a 30% solution of HBr in a glacial acetic acid (9.5 mL), and the solid that soon formed was collected and recrystallized from methanol–ether to give (-)-**6** as white crystals: 2.94 g (69.9%); mp 228–229 °C; $[\alpha]^{25}_D$ −13.0° (*c* 1.00, DMF). Anal. Calcd for $C_{14}H_{18}BrN_3O_7$: C, 40.02; H, 4.32. Found: C, 40.26; H, 4.24.

(-)-N-Cbz-L-alanylglycyl-α-PNB-β-methyl-L-aspartate (22a). Cold (−10 °C) solutions containing equimolar amounts of (-)-*N*-Cbz-L-alanine (**1a**,[19] 0.096 g, 0.43 mmol), isobutyl chloroformate (0.069 g, 0.43 mmol), and triethylamine (0.43 g, 0.43 mmol) in DMF (10 mL) and (-)-glycyl-α-PNB-β-methyl-L-aspartate hydrobromide (**6**, 0.18 g, 0.43 mmol) in DMF (10 mL) were prepared, combined, and allowed to warm to room temperature. The solid product, formed as a result of pouring the reaction mixture in 0.05 N hydrochloric acid (200 mL), was collected and recrystallized from absolute ethanol to give (-)-**22a** as white crystals: 0.15 g (64%); mp 164.0–164.5 °C; $[\alpha]^{28}_D$ 8.4° (*c* 1.00, DCA); IR (KBr) ν_{max} 3300 (amide), 1730 (ester carbonyls), 1645 (amide carbonyls), 1440 (phenyl), and 1520 and 1355 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.12 d, 7.59 d, and 7.23 s (9 H, phenyl), 5.20 s and 5.00 s (4 H, benzyl methylenes), 3.58 s (methyl ester), 2.83 m (2 H, aspartyl methylene), and 1.29 s (methyl). Anal. Calcd for $C_{25}H_{28}N_4O_{10}$: C, 55.15; H, 5.18. Found: C, 55.09; H, 5.28.

(+)-N-Cbz-D-alanylglycyl-α-PNB-β-methyl-L-aspartate (22b). (+)-*N*-Cbz-D-alanine (**1b**, 0.096 g, 0.43 mmol) was coupled with (-)-glycyl-α-PNB-β-methyl-L-aspartate hydrobromide (**6**, 0.18 g, 0.43 mmol) in the manner used for preparation of (-)-**22a** to give white crystals (ethanol) of (+)-**22a**: 0.10 g (42%); mp 148.5–149.0 °C; $[\alpha]^{28}_D$ +14.2° (*c* 1.00, DCA); IR (KBr) ν_{max} 3300 (amide), 1725 (ester carbonyls), 1680 and 1650 (amide carbonyls), 1610 and 1445 (phenyl), and 1530 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.14 d, 7.41 d, and 7.25 s (9 H, phenyl), 5.22 s and 5.05 s (4 H, benzyl methylenes), 3.60 s (3 H, methyl ester), 2.93 m (2 H, glycine methylene), and 1.38 d (3 H, methyl). Anal. Calcd for $C_{25}H_{28}N_4O_{10}$: C, 55.15; H, 5.18. Found: C, 55.15; H, 5.38.

(-)-N-Cbz-β-methyl-L-aspartylglycyl-α-PNB-β-methyl-L-aspartate (21a). A cold (−10 °C) 10% solution of (-)-*N*-Cbz-β-methyl-L-aspartate (**34a**,[4] 0.335 g, 1.19 mmol), containing isobutyl chloroformate (0.162 g, 1.19 mmol) and triethylamine (1.20 g, 1.19 mmol) in DMF was combined with a cold (−10 °C) solution of (-)-glycyl-α-PNB-β-methyl-L-aspartate hydrobromide (**6**, 0.500 g, 1.19 mmol) and triethylamine (1.20 g, 1.19 mmol) in DMF (10 mL). The whole was stirred while it was poured into 0.05 N hydrochloric acid (200 mL). The deposited solids were collected and recrystallized from ethanol to give white crystals of (-)-**21a**: 0.404 g (56.4%); mp 144.5–145.0 °C; $[\alpha]^{25}_D$ −27.0° (*c* 1.00, DMF); IR (KBr) ν_{max} 3300 (amide), 1740 (ester carbonyls), 1640 (amide carbonyls), 1445 (phenyl), and 1515 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.11 d, 7.39 d, and 7.25 s (9 H, phenyl), 5.18 s and 5.07 s (2 H, benzyl methylene), 3.93 m (2 H, glycyl methylene), 3.62 s and 3.60 s (6 H, methyl esters), and 2.92 m (4 H, aspartyl methylenes). Anal. Calcd for $C_{27}H_{30}N_4O_{12}$: C, 53.82; H, 5.02. Found: C, 54.03; H, 5.14.

(-)-N-Cbz-β-methyl-D-aspartylglycyl-α-PNB-β-methyl-L-aspartate (21b). (+)-*N*-Cbz-β-methyl-D-aspartate (**34b**,[17] 0.335 g, 1.19 mmol) was coupled with (-)-glycyl-α-PNB-β-methyl-L-aspartate hydrobromide (**6**, 0.500 g, 1.19 mmol) in the manner used for preparation of (-)-**21a** to give white crystals (ethanol) of (-)-**21b**: 0.373 g (52.0%); mp 154.0–154.5 °C; $[\alpha]^{25}_D$ −6.4° (*c* 1.00, DMF); IR (KBr) ν_{max} 3300 (amide), 1740 and 1725 (ester carbonyls), 1660 (amide carbonyls), 1440 (phenyl), and 1520 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.14 d, 7.42 d, and 7.27 s (9 H, phenyl), 5.22 s and 5.08 s (4 H, benzyl methylenes), 3.97 m (2 H, glycyl methylene), 3.63 s and 3.60 s (6 H, methyl esters), and 2.93 m (4 H, aspartyl methylenes). Anal. Calcd for $C_{27}H_{30}N_4O_{12}$: C, 53.82; H, 5.02. Found: C, 53.81; H, 5.18.

(+)-N-Cbz-β-methyl-L-aspartylglycyl-PNB-L-alanate (24a). (-)-*N*-Cbz-β-methyl-L-aspartate (**34a**,[17] 0.338 g, 1.38 mmol) was dissolved in DMF (5 mL) and cooled to −10 °C before equimolar amounts of isobutyl chloroformate and triethylamine were added. After the solution was stirred at −10 °C for 20 min, a cold (−10 °C) solution of glycyl-PNB-L-alanate hydrobromide (**5**, 0.500 g, 1.38 mmol) in DMF (5 mL) was added followed by dropwise addition of triethylamine (0.139 g, 1.38 mmol). Stirring was continued for 4 h after the reaction had come to room temperature but before it was poured in 0.05 N hydrochloric acid (100 mL). The oily material obtained was chromatographed on silica [ether:chloroform:methanol, 5:4:1 (v/v/v)] to give a colorless oil which finally formed white crystals of (+)-**24a** after prolonged drying: 0.090 g (13%); mp 75–76 °C; $[\alpha]^{25}_D$ +22.6° (*c* 1.00, CH_2Cl_2); IR (KBr) ν_{max} 3300 (amide), 1735 and 1695 (ester carbonyls), 1640 (amide carbonyls), 1440 (phenyl), and 1525 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.11 d, 7.42 d, and 7.27 s (9 H, phenyl), 5.19 s and 5.08 s (4 H, benzyl methylenes), 4.50 m (2 H, methines), 3.93 m (2 H, glycyl methylene), 3.63 s (3 H, methyl ester), 2.92 m (2 H, aspartyl methylene), and 1.43 d (3 H, methyl). Anal. Calcd for $C_{25}H_{28}N_4O_{10}$: C, 55.15; H, 5.18. Found: C, 55.26; H, 5.42.

(-)-N-Cbz-β-methyl-D-aspartylglycyl-PNB-β-methyl-L-alanate (24b). (+)-*N*-Cbz-β-methyl-D-aspartate (**34b**,[17] 0.388 g, 1.38 mmol) was used with glycyl-PNB-L-alanate hydrobromide (**5**, 0.500 g, 1.38 mmol) as described in the preparation of (+)-**24a** to give white crystals of (-)-**24b**: 0.406 g (56.8%); mp 106–107 °C; $[\alpha]^{23}_D$ −19.0° (*c* 1.00, CH_2Cl_2); IR (KBr) ν_{max} 3400 and 3300 (amide), 1745 and 1735 (ester carbonyls), 1660 (amide carbonyls), 1610 and 1460 (phenyl), and 1530 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.13 d, 7.42 d, and 7.26 s (9 H, phenyl), 5.18 s and 5.07 s (4 H, benzyl methylenes), 4.54 m (2 H, methine), 3.95 (2 H, glycyl methylene), 3.62 s (3 H, methyl ester), 2.97 m (2 H, aspartyl methylene), and 1.43 d (3 H, methyl). Anal. Calcd for $C_{25}H_{28}N_4O_{10}$: C, 55.15; H, 5.18. Found: C, 54.94; H, 5.28.

(+)-N-Cbz-L-alanyl-PNB-glycinate (39). A 10% solution of (-)-*N*-Cbz-L-alanine (**1a**,[19] 4.49 g, 0.0201 mol) in DMF was cooled (−10 °C) before equimolar amounts of isobutyl chloroformate and triethylamine were added. The whole was stirred for 20 min before a cold (−10 °C) solution of PNB-glycinate hydrobromide (**40**,[24] 5.85 g, 0.021 mol) in DMF (6 mL) was added followed by dropwise addition of triethylamine (2.03 g, 0.0201 mol). Stirring was continued for 16 h after the mixture had warmed to room temperature, and then it was poured into 0.05 N hydrochloric acid. The collected solids were recrystallized from ethanol to give white crystals of (+)-**39**: 2.6 g (31%); mp 110.5–111.0 °C [lit.[25] mp 104–106 °C; lit.[26] (D enantiomer) mp 116–117 °C]; $[\alpha]^{25}_D$ +12.8° (*c* 0.500, $CHCl_3$) (no literature value); IR (KBr) ν_{max} 3320 (amide), 1740 and 1690 (ester carbonyls), 1655 (amide carbonyls), 1610 and 1450 (phenyl), and 1520 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.13 d, 7.41 d, and 7.25 s (9 H, phenyl), 5.22 s and 5.06 s (4 H, benzyl methylenes), 4.32 m (1 H, methine), 4.10 s and 4.02 s (2 H, glycyl methylene), and 1.39 d (3 H, methyl). Anal. Calcd for $C_{20}H_{21}N_3O_7$: C, 57.82; H, 5.10. Found: C, 57.79; H, 5.11.

(+)-L-Alanyl-PNB-glycinate Hydrobromide (7). (+)-*N*-Cbz-L-alanyl-PNB-glycinate (**39**, 1.3 g, 0.0031 mol) was dissolved in a 30% solution of HBr in glacial acetic acid (2.6 mL). Addition of anhydrous ether (30 min later) caused the formation of a solid which was collected. Recrystallization of this material from methanol–ether gave (+)-**7** as white crystals: 0.96 g (84%); mp 186.0–186.5 °C; $[\alpha]^{25}_D$ +16.4° (*c* 0.500, DMF); IR (KBr) ν_{max} 3300 (amide), 3120–2960 (amine salt), 1760 (ester carbonyl), 1670 (amide carbonyl), 1475 (phenyl), and 1520 and 1350 cm^{-1} (nitro); ^1H NMR (D_2O) δ 8.18 d and 7.55 d (4 H, phenyl), 5.33 s and 5.23 s (2 H, benzyl methylenes), and 1.54 (3 H, methyl). Anal. Calcd for $C_{12}H_{16}BrN_3O_5$: C, 39.79; H, 4.45. Found: C, 39.91; H, 4.73.

(-)-N-Cbz-β-methyl-L-aspartyl-L-alanyl-PNB-glycinate (23a). Equimolar amounts (0.497 mmol) of isobutyl chloroformate and triethylamine were added to a cold (−10 °C) 10% solution of (-)-*N*-Cbz-β-methyl-L-aspartate (**34a**,[17] 0.140 g, 0.497 mmol) in DMF. After the mixture was stirred for 20 min at −10 °C, a cold (−10 °C) 10% solution of (+)-L-alanyl-PNB-glycinate hydrobromide (**7**, 0.180 g, 0.497 mmol) in DMF was added followed by dropwise addition of a second equivalent

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of triethylamine. The reaction was allowed to warm to room temperature, and the stirring was continued for 2.5 h before the whole was poured into 0.05 N hydrochloric acid (200 mL). The precipitated solids were collected and recrystallized from methanol to give white crystals of (−)-**23a**: 0.070 g (26%); mp 151.0–151.5 °C; $[\alpha]^{25}_D$ −3.6° (*c* 0.500, DMF); IR (KBr) ν 3300 (amide), 1740–1690 (ester carbonyls), 1654 (amide carbonyls), 1610 and 2450 (phenyl), and 1525 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.19 d, 7.47 d, and 7.32 s (9 H, phenyl), 5.23 s and 5.10 s (4 H, benzyl methylenes), 4.13 s and 4.03 s (2 H, glycyl methylene), 3.65 s (3 H, methyl ester), 2.85 m (2 H, aspartyl methylene), and 1.37 d (3 H, methyl). Anal. Calcd for $C_{25}H_{28}N_4O_{10}$: C, 55.15; H, 5.18. Found: C, 55.00; H, 5.18.

(+)-***N*-Cbz-β-methyl-D-aspartyl-L-alanyl-PNB-glycinate (23b).** (+)-*N*-Cbz-β-methyl-D-aspartate (**34b**,[17] 0.0272 g, 0.966 mmol) was coupled with (+)-L-alanyl-PNB-glycinate hydrobromide (**7**, 0.350 g, 0.966 mmol) in the manner used for preparation of (−)-**23a** to give white crystals of (+)-**23b**: 0.181 g (34.4%); mp 156.0–157.0 °C; $[\alpha]^{25}_D$ +14.0° (*c* 0.500, DMF); IR (KBr) ν 3300 (amide), 1740, 1730, and 1690 (ester carbonyls), 1645 (amide carbonyls), 1440 (phenyl), and 1530 and 1350 cm^{-1} (nitro); ^1H NMR ($CDCl_3$) δ 8.18 d, 7.46 d, and 7.32 s (9 H, phenyl), 5.22 s and 5.12 (4 H, benzyl methylenes), 4.04 m (2 H, glycyl methylene), 3.63 s (3 H, methyl ester), 2.92 m (2 H, glycyl methylene), and 1.39 (3 H, methyl). Anal. Calcd for $C_{25}H_{28}N_4O_{10}$: C, 55.15; H, 5.18. Found: C, 55.19; H, 5.30.

Previously Reported Peptides. The following listed peptides and peptide intermediates were synthesized during the present study by procedures based on those cited with each compound. ***N*-Cbz-D,L-alanine (1)**: mp 112–113 °C [lit.[19] mp 114–115 °C]. (−)-***N*-Cbz-L-alanine (1a)**: mp 83.5–84.0 °C [lit.[19] mp 84 °C]; $[\alpha]^{23}_D$ −14.6 ± 0.2° (*c* 4.20, glacial acetic acid) [lit.[19] $[\alpha]^{17}_D$ −14.3 (glacial acetic acid)]. (+)-***N*-Cbz-D-alanine (1b)**: mp 84.0–84.5 °C; $[\alpha]^{25}_D$ +14.4 ± 0.2° (*c* 4.20, glacial acetic acid). (−)-***N*-Cbz-PNB-L-alanate (41a)**: mp 100.0–100.5 °C [lit.[20] mp 100.5 °C]; $[\alpha]^{24}_D$ −17.5 ± 0.3° (*c* 3.00, DCA) [lit.[20] $[\alpha]^{27}_D$ 17.4° (3% DCA)]. (+)-***N*-Cbz-PNB-D-alanate (41b)**: mp 100.0–100.5 °C [lit.[20] mp 100.5 °C]; $[\alpha]^{26}_D$ +17.5 ± 0.3° (*c* 3.00, DCA) [lit.[20] $[\alpha]^{27}_D$ +17.7° (3% DCA)]. (−)-**PNB-L-alanate hydrobromide (3a)**: mp 178.0–179.0 °C [lit.[20,21] mp 184, 177–178.5 °C]. (−)-***N*-Cbz-L-alanyl-PNB-L-alanate (16a)**: white needle-shaped crystals; mp 139.0–140.0 °C [lit.[20] mp 142 °C]; $[\alpha]^{26}_D$ −36.1 ± 0.3° (*c* 2.97, DCA) [lit.[20] $[\alpha]^{27}_D$ −36.1° (*c* 2.1, DCA)]. (+)-***N*-Cbz-D-alanyl-PNB-L-alanate (16b)**: white needle-shaped crystals; mp 171.5–172.0 °C [lit.[20] mp 165 °C]; $[\alpha]^{25}_D$ +3.2 ± 0.2° (*c* 4.4, DCA) [lit.[20] $[\alpha]^{27}_D$ +3.2° (*c* 4.48 DCA)]. (+)-**β-Methyl-L-aspartate hydrochloride (4b)**: white crystals; mp 189–190 °C dec [lit.[17,27] mp 204 °C dec, 191–193 °C]; $[\alpha]^{25}_D$ 12.4 ± 0.2° (*c* 1.00°, 1:3 ethanol:water) [lit.[4] $[\alpha]^{25}_D$ +12.4° (*c* 1, 1:3 ethanol:water)]. (−)-**β-Methyl-D-aspartate hydrochloride (4a)**: mp 178–180 °C dec. **β-Methyl-D,L-aspartate hydrochloride (4)**: white crystals; mp 188–189 °C dec [lit.[17,27] mp 204 °C dec, 191–193 °C dec]. (−)-***N*-Cbz-β-methyl-L-aspartate (42)**: (+)-β-methyl-L-aspartate hydrochloride (**4b**, 19.0 g, 0.103 mol) was dissolved in water (100 mL) and cooled to 0 °C before Na_2CO_3 (12 g, 0.11 mol) was added slowly. After the gas evolution had stopped, benzyl chloroformate (20.9 g, 0.123 mol) and a Na_2CO_3 solution (7.0 g, 0.06 mol in 50 mL water) were added (dropwise separately but simultaneously) to the stirred, chilled solution. When the additions were complete and the reaction mixture had warmed to room temperature, stirring was continued for about 3 h. After the reaction mixture was washed with ether (3 × 100 mL), the aqueous residue was acidified with concentrated HCl (pH 1, external indicator) and extracted with ethyl acetate (4 × 100 mL). The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$ and evaporated (reduced pressure) to a viscous oily residue which failed to crystallize and had to be purified via its piperazinium salt,[23] which was prepared by dissolving the crude oily residue (25 g) in ether (50 mL) and stirring the whole while a solution of piperazine hexahydrate (8.7 g, 0.047 mol) in 2-propanol (47 mL) was added in several portions. The white solid, which formed after about 1 h, was collected and recrystallized from acetone: 28.3 g (85%); mp 123–124 °C [lit.[17] mp 128 °C]. The piperazinium salt was shaken in a mixture of ether (200 mL) and 2 N HCl (200 mL). The separated etheral layer was dried over anhydrous $MgSO_4$ and partially evaporated to a final volume of 100 mL. Petroleum ether was added to the cloud point, and crystallization gave **42** as white crystals: 11.4 g (41.4%); mp 95–96 °C [lit.[17] mp 98 °C]; $[\alpha]^{25}_D$ 19.6° (*c* 2.50, pyridine) [lit.[17] $[\alpha]_D$ −18.5° (*c* 2.50, pyridine)]. In some later runs, **42** was crystallized by using seed crystals, thus avoiding conversion to the salt. (+)-***N*-Cbz-β-methyl-D-aspartate (34b)**. (+)-β-Methyl-D-aspartate hydrochloride (**4a**, 23.7 g, 0.129 mol) was treated with cold Na_2CO_3 solution as described above. Benzyl chloroformate (22.0 g, 0.14 mol) and Na_2CO_3 solution (14.9 g, 0.120 mol in 60 mL of water) were added as described, and the whole was stirred overnight. Extraction with ether, acidification of the aqueous residue, extraction of the latter with ethyl acetate, and evaporation gave a viscous yellow oil (29.8 g), which did not form a crystalline salt when treated with piperazine. Column chromatography on silica gel using chloroform and ether gave **34b** as a white solid: 14.5 g (40.0%); mp 94.5–69 °C [lit.[17] mp 97–98 °C]; $[\alpha]^{25}_D$ +18.4° (*c* 2.50, pyridine). ***N*-Cbz-β-methyl-D,L-aspartate (34)**: white crystals; mp 103.5–106.0 °C (racemic compound). (−)-***N*-Cbz-L-alanyl-L-alanyl-PNB-L-alanate (25a)**: white needles; mp 201.0–203.0 °C [lit.[20] mp 194 °C]; $[\alpha]^{27}_D$ −56.8 ± 0.8° (*c* 1.30, DCA) [lit.[20] $[\alpha]^{27}_D$ 56.6° (*c* 1.3, DCA)]. (−)-***N*-Cbz-D-alanyl-L-alanyl-PNB-L-alanate (25b)**: white needles; mp 168.0–169.5 °C [lit.[20] mp 165 °C]; $[\alpha]^{25}_D$ −30.4 ± 0.6° (*c* 1.70, DCA) [lit.[20] $[\alpha]^{27}_D$ −31.3° (*c* 1.7, DCA)]. (+)-***N*-Cbz-D-alanyl-D-alanyl-PNB-L-alanate (26a)**: white needles; mp 184.0–185.0 °C [lit.[20] mp 183 °C]; $[\alpha]^{27}_D$ +34.7 ± 0.7° (*c* 1.40, DCA) [lit.[20] $[\alpha]^{27}_D$ 35.0° (*c* 1.4, DCA)]. (+)-***N*-Cbz-L-alanyl-D-alanyl-PNB-L-alanate (26b)**: white needles; mp 146.0–147.5 °C [lit.[20] mp 146 °C]; $[\alpha]_D$ +3.7 ± 0.2° (*c* 4.2, DCA) [lit.[20] $[\alpha]^{27}_D$ +3.6° (*c* 4.2, DCA)]. (−)-***N*-Cbz-L-alanyl-L-alanyl-L-alanyl-PNB-L-alanate (29a)**: white crystals; mp 275.5–258.5 °C [lit.[20] mp 257 °C]; $[\alpha]^{25}_D$ −73.2 ± 0.8° (*c* 1.20, DCA) [lit.[20] $[\alpha]^{27}_D$ −72.5° (*c* 1.1, DCA)]. (−)-***N*-Cbz-D-alanyl-L-alanyl-Lalanyl-PNB-L-alanate (29b)**: white crystals; mp 183.5–184.5 °C [lit.[20] mp 181 °C]; $[\alpha]^{22}_D$ −45.0 ± 0.6° (*c* 1.60, DCA) [lit.[20] $[\alpha]^{27}_D$ −45.1° (*c* 1.6, DCA)]. (+)-***N*-Cbz-D-alanyl-D-alanyl-L-alanyl-PNB-L-alanate (31a)**: white crystals: mp 209.5–211.0 °C [lit.[20] mp 207 °C]; $[\alpha]^{22}_D$ +0.71 ± 0.5° (*c* 1.4, DCA) [lit.[20] $[\alpha]^{27}_D$ + 1.0° (*c* 2.4, DCA)]. (−)-***N*-Cbz-L-alanyl-D-alanyl-L-alanyl-PNB-L-alanate (31b)**: white crystals; mp 169.0–170.0 °C [lit.[20] mp 168 °C]; $[\alpha]^{22}_D$ −31.2 ± 0.6° (*c* 1.79, DCA) [lit.[20] $[\alpha]^{27}_D$ −31.2° (*c* 1.5, DCA)]. (−)-***N*-Cbz-L-alanyl-L-alanyl-D-alanyl-PNB-L-alanate (32a)**: white crystals; mp 193.5–194.0 °C [lit.[20] mp 192 °C]; $[\alpha]^{22}_D$ −22.8 ± 0.6° (*c* 1.60, DCA) [lit.[20] $[\alpha]^{27}_D$ −22.9° (*c* 1.6, DCA)]. (+)-***N*-PNB-D-alanyl-L-alanyl-D-alanyl-PNB-L-alanate (32b)**: white crystals; mp 188.5–189.5 °C; $[\alpha]^{21}_D$ +0.90 tu 0.50° (*c* 2.00, DCA). (+)-***N*-Cbz-D-alanyl-D-alanyl-D-alanyl-PNB-L-alanate (30a)**: white crystals; mp 213.0–214.0 °C [lit.[20] mp (enantiomer) 212 °C]; $[\alpha]^{22}_D$ +49.9 ± 0.6° (*c* 1.50, DCA) [lit.[20] $[\alpha]^{27}_D$ (enantiomer) −49.8° (*c* 1.5, DCA)]. (+)-***N*-Cbz-L-alanyl-D-alanyl-D-alanyl-PNB-L-alanate (30b)**: white crystals; mp 198.0–198.5 °C [lit.[20] mp (enantiomer) 197 °C]; $[\alpha]^{22}_D$ +24.1 ± 0.6° (*c* 1.60, DCA) [lit.[20] $[\alpha]^{27}_D$ (enantiomer) −24.1° (*c* 1.7, DCA)].

Stereoselectivity Determinations. General Reaction Procedure. Each racemic anhydride component (Scheme I) was prepared by cooling (−8 °C) a solution containing equimolar amounts of triethylamine and the *N*-Cbz-D,L-amino acid in DMF (10%) before adding an equimolar quantity of isobutyl chloroformate. The whole was kept for 30 min at −8 °C before cooling it to −78 °C (dry ice–acetone bath). A separate DMF solution (10%), containing only one-half the molar equivalency of the anhydride component, was prepared with equimolar amounts of each enantiomerically pure *p*-nitrobenzyl ester hydrobromide component and triethylamine and cooled to −78 °C. The two solutions were combined and kept at −78 °C for 2–3 h before the whole was poured into a large excess of 0.05 N hydrochloric acid and allowed to remain overnight. The deposited solid was collected in a filter, washed with water until the washings were neutral, and dried. The material was dissolved in the minimum volume of acetone, dichloromethane, or ethyl acetate and chromatographed on several preparative thin-layer plates. A mixture of ether–chloroform–methanol, 5:4:1 (v/v/v), was used as the development solvent for peptide pairs, **20a–20b**, **21a–21b**, **22a–22b**, **23a–23b**, **24a–24b**, **27a–27b**, and **28a–28b**, while a mixture of ether–chloroform, 7:3 (v/v), was used for all of the other pairs. The band corresponding to the diastereomeric peptide pair in each case was clear of the reaction debris, but the peptides themselves were not separated from each other (UV lamp). The bands were removed and extracted with acetone, dichloromethane, or ethyl acetate, which upon evaporation left the pair of diastereomeric peptides as white solids. The diastereomer composition of each pair (Tables III–V) was determined as described below.

Analyses. The composition of each pair of peptide competition products was determined from its rotatory magnitude, measured under previously established conditions. Prior to each competition experiment, a linear rotatory magnitude–composition relationship was established using five different compositions of the authentic peptide components. The measurement conditions in each case (concentration, solvent, and temperature) were chosen so that the slope of each linear relationship was large enough to provide sufficient sensitivity. The composition of the peptide pair from each experiment (competition and control) was determined from its rotatory magnitude measured under the same conditions used to establish the corresponding composition curve. The results, which are the average of two runs in each case, are shown in Tables III–V.

Controls. In each case a mixture consisting of the two peptide products was prepared from authentic material in a ratio different from that

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found in the corresponding competition experiment. These mixtures were dissolved in DMF (10% solutions), combined with equimolar amounts of triethylamine, and kept at -78 °C for 3 h. Each binary mixture of authentic peptides was then precipitated in 0.05 N HCl overnight and recovered by the chromatography extraction procedure used in the competition experiments. Determination of the composition of each recovered mixture from its rotatory magnitude established two points: First, it showed that neither the experimental conditions used in the competition reactions nor those of the isolation procedure caused a significant change in any of the binary peptide compositions, thus eliminating any isomerization effects. Second, the small difference between the initial composition and the chiroptically determined composition of each recovered authentic pair was used as the error of the corresponding competition experiment.

Photochemical Transformations. 45. Orbital Overlap Preferences in Excited-State Intramolecular Electron Transfers[1]

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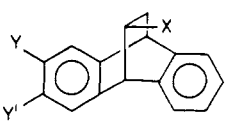
Abstract: Syntheses of a number of meta-methoxy-substituted 2,3;6,7-dibenzobicyclo[2.2.2]octadienes, substituted as well on the ethano bridge, have been carried out. These included the four acetates produced by Diels-Alder reactions between 2-methoxyanthracene and vinyl acetate. The acetates were converted to alcohols and to methanesulfonates. Ground-state acetolysis of each methanesulfonate led to a unique dibenzobicyclo[3.2.1]octadienol acetate (discounting exo-endo isomerism) via Wagner-Meerwein skeletal rearrangement, whose conversion to alcohol and oxidation to ketone showed clean anti aryl participation in the rearrangement. The isomer with the anti-homopara relationship between the methoxy group and the carbon bearing the methanesulfonate group was substantially more reactive than the other three isomers, which had approximately equivalent reactivities. Reaction of 2-methoxyanthracene with *cis*-1,2-dichloroethene gave a mixture of cis-anti and cis-syn 7,8-dichloro compounds, and the reaction with the *trans*-dichloroethene gave a mixture of the two trans dichlorides. In ground-state acetolyses promoted by silver acetate, those isomers with anti-homopara chlorine atoms reacted rapidly, while those without reacted more slowly. Conversion to 8-chlorodibenzobicyclo[3.2.1]octadien-4-ol acetates occurred, which in turn were converted to alcohols and ketones. ^{1}H NMR spectra were used to confirm structures of all compounds, and typical anti migrations were observed. Mixture compositions matched those anticipated from relative reactivities. Irradiations of the methanesulfonates were conducted in acetic acid-acetonitrile with 300-nm light. Of the four isomers, only the one with the anti-homometa relationship between the methanesulfonate group and the ring methoxy substituent was photoactive. The [3.2.1] product acetate resulted from syn (benzo) migration, rather than anti (anisolo) migration. All four isomeric dichlorides were photoactive (300-nm light in acetic acid), giving photo-Wagner-Meerwein rearranged [3.2.1] chlorides and acetates. The two isomers with anti-homometa chlorine atoms were considerably more photoactive than the other two. The syn-homometa and syn-homopara chlorines were less reactive than the anti-homometa chlorines, and the anti-homopara chlorines were almost photoinert. Differences between these results and those reported previously on analogous systems are noted. All products arose from Wagner-Meerwein skeletal rearrangements, with syn migration predominating over anti, regardless of whether the migration involved the benzo or anisolo ring.

Members of our research group have been interested for some time[2] in photoinduced solvolysis reactions and in the rearrangements which accompany them. As a result of these studies, it has been concluded that, for homobenzyl chlorides (or β-arylethyl compounds with other nucleofugal groups, such as bromides, methanesulfonates, or mercurials), the key requirement for reactivity, following excitation of the aromatic ring chromophore, is electron transfer of the π^* electron to the σ^* orbital of the carbon-nucleofuge bond.[3]

In the experiments reported earlier, electron transfer was observed to occur more readily (higher quantum yields) when the chromophoric ring had an anti disposition with respect to the carbon-nucleofuge bond, as, for example, in **1**, where Y and Y′ are auxochromic groups, rather than a syn disposition, as in **2**. A number of such examples were noted, and it was suggested that the favoring of electron transfer into anti C-X bonds could be



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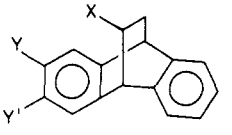

2

rationalized by the coulombic advantage in the resulting zwitterionic biradical over that in the syn system. Occupied σ^* orbitals of carbon-halogen bonds have a large fraction of their electron density in a lobe anterior to the carbon atom,[4] and one may estimate,[5] from a study of models, that electron transfer may be about 10 kcal/mol more favorable in the anti case.

All of the reactive systems reported thus far have been disubstituted (or nonsubstituted) in the light-absorbing ring, and reactivity correlations were made on the basis of Weller[6] electron-transfer free-energy calculations. Put another way, it was assumed that the electron transferability, as measured by relative

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