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Structure-taste Relationship of Novel α-L-Aspartyl Dipeptide Sweetners*

Muneji Miyoshi, Ken-ichi Nunami, Hiroshi Sugano, and Toshiyuki Fujii
Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co. Ltd., Kashima-3-chome, Yodogawa-ku, Osaka 532

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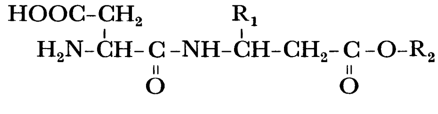
A sweetness potency was found in novel α-L-aspartyl dipeptide analogs which were quite stable on heating in an aqueous solution. The insertion of a methylene group into the peptide chain of α-L-aspartyl dipeptide esters mostly decreased the potency of the sweetness. However, the further exchange of the carbonyl and oxygen functions with each other on the ester group of a *C*-terminal β-alkyl-β-aminopropionic acid was found to increase the sweetness. Thus, *N*-(α-L-aspartyl)-*O*-pivaroyl-D-alaninol, *N*-(α-L-aspartyl)-*O*-cyclobutylcarbonyl-D-alaninol and *N*-(α-L-aspartyl)-*O*-cyclopropylcarbonyl-D-alaninol were all more than 200 times as sucrose.

Since the discovery[1)] of the potent sweet taste of the α-L-aspartyl-L-phenylalanine methyl ester (APM), the special interest in dipeptide sweetners has increased and a large number of analogs related to APM have been synthesized. In the light of the data on the structure-taste relationship so far accumulated,[2–6)] L-aspartic acid with unsubstituted α-amino and β-carboxyl groups is rather essential for sweetness. However, a considerable modification of a *C*-terminal amino acid may increase the sweetness when both the steric and hydrophobic properties fall into the requirements of a receptor site. In fact, Fujino[7)] replaced the phenylalanine moiety with aminomalonates and found that α-L-aspartylaminomalonic acid with methyl fenchyl diester groups has, surprisingly, a potency 22000—33000 times as sweet as sucrose.

Some of the α-L-aspartyl-D-alanyl and α-L-aspartyl-D-seryl dipeptides which have relatively larger ester groups on the *C*-terminal D-amino acid have also been found to show considerable sweetness. It has been elucidated that both of the substituents on the α-carbon of a *C*-terminal amino acid should be strictly restricted as to sterical requirements; one is "a smaller part", while the other is "a larger part" with a hydrophobic group. When both of the parts involve a carboxyl group such as the aminomalonates, the potency of the sweetness of the dipeptide is greater than any other analogs so far reported. We are interested in such a role of the carboxyl group as the third hydrophobic group.

On the other hand, the dipeptide ester has a serious disadvantage in its practical use as a low-calory sweetner. On heating the aqueous solution of a dipeptide ester, the presence of the ester group readily causes the formation of a piperazinedione, which in turn leads to a loss of sweetness. In order to exclude the cyclization of the dipeptide esters to piperazinedione, it would be of interest to synthesize a series of dipeptide analogs whose backbones are elongated by one more methylene group.

For inserting a methylene group, two potential positions are conceivable with respect to the α-L-aspartyl dipeptide ester, *i.e.*, two types of dipeptide esters with the following structures, (**Ia** and **Ib**), respectively:



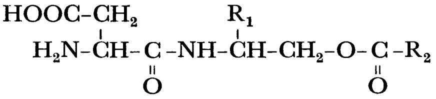
$$H_2N\text{-}\overset{HOOC\text{-}CH_2}{\overset{|}{CH}}\text{-}\underset{O}{\underset{\|}{C}}\text{-}NH\text{-}\overset{R_1}{\overset{|}{CH}}\text{-}CH_2\text{-}\underset{O}{\underset{\|}{C}}\text{-}O\text{-}R_2$$

(**Ia**)

$$H_2N\text{-}\overset{HOOC\text{-}CH_2}{\overset{|}{CH}}\text{-}\underset{O}{\underset{\|}{C}}\text{-}NH\text{-}CH_2\text{-}\overset{R_1}{\overset{|}{CH}}\text{-}\underset{O}{\underset{\|}{C}}\text{-}O\text{-}R_2$$

(**Ib**)

Another analog one in which both the carbonyl function and the oxygen function are replaced with each other on the *C*-terminal ester group of **Ia** may also be possible for this purpose; the structure of this type may be represented by the following general formula (**II**):



$$H_2N\text{-}\overset{HOOC\text{-}CH_2}{\overset{|}{CH}}\text{-}\underset{O}{\underset{\|}{C}}\text{-}NH\text{-}\overset{R_1}{\overset{|}{CH}}\text{-}CH_2\text{-}O\text{-}\underset{O}{\underset{\|}{C}}\text{-}R_2$$

(**II**)

In the present paper, we wish to report on the structure–taste relationship of α-L-aspartyl dipeptide analogs of the above three types; all of them have both an elongated peptide chain and a carboxyl group in the molecule.

Results and Discussion

Synthesis of α-L-Aspartyl Dipeptide Analogs. The types of **Ia** and **Ib** correspond to the dipeptide esters in which a *C*-terminal amino acid is replaced by either β-alkyl-β-amino-propionic acid or α-alkyl-β-aminopropionic acid respectively. Several β-alkyl-β-aminopropionic acids were synthesized from the corresponding diazoketones according to the method reported by Shiba.[8)] α-Alkyl-β-aminopropionic acids were obtained by the condensation of *N*-(chloromethyl)phthalimide with the diethyl alkylmalonates according to the method reported by Buco[9)] and Böhme.[10)] Some α-aminomethylmalonic acid esters were synthesized *via* a new method[11)] recently developed in our laboratory; the condensation of alkylmalonate with *N*-(benzyloxycarbonyl)-acetoxymethylamine, which had been prepared from benzyloxycarbonylglycine by an electrochemical oxidation. The synthesis of the desired dipeptide esters of **Ia** and **Ib** was carried out by the DCC coupling of O^4-benzyl *N*-benzyloxycarbonyl-α-L-aspartate with β-alkyl-β-aminopropionic acid or α-alkyl-β-aminopropionic acid respectively as an amino component, followed by catalytic hydrogenolysis. 2-Amino-D-alkanols were derived from the corresponding *N*-benzyloxycarbonyl

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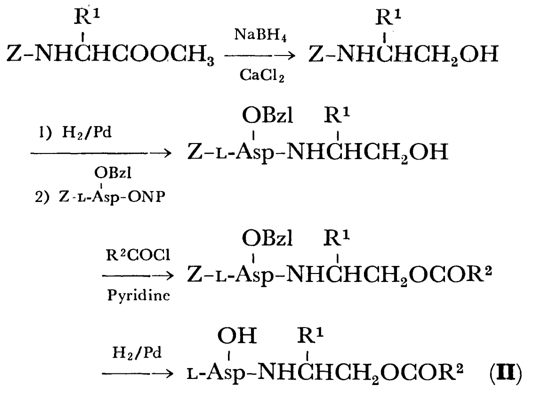
D-amino acid esters by $NaBH_4$ reduction,[12] followed by catalytic hydrogenolysis After coupling with O^1-*p*-nitrophenyl O^4-benzyl *N*-benzyloxycarbonyl-α-L-aspartate, *O*-acylation was carried out with various acyl halides in pyridine to give protected *O*-acyl-2-(α-L-aspartylamino)-alkanols. Subsequent hydrogenolysis afforded the desired dipeptide esters of the **II** type, as is shown in Scheme 1.



Scheme 1.

Stability in an Aqueous Solution. All of the α-L-aspartyl dipeptide analogs synthesized in the present study were found to be quite stable on heating in an aqueous solution. Table 1 presents the results of the stability test between APM and *N*-(α-L-aspartyl)-*O*-cyclobutylcarbonyl-D-alaninol (**46**), which is 220 times as sucrose. Aqueous solutions and the buffer solutions (pH 4 and pH 7), each containing 0.2% of one of the above compounds, were heated in a sealed tube at 100 °C for 1 h. The unchanged amounts of the compounds in each solution were determined by means of an amino-acid analyzer. All of the taste paneler felt that the solution of **46** was substantially unchanged in taste after heating as compared with the corresponding unheated solutions.

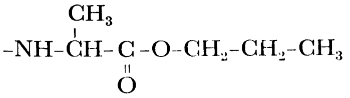
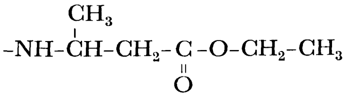
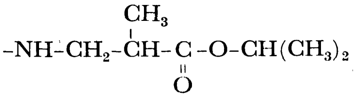
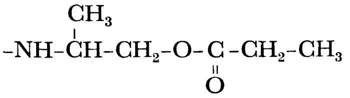
Table 1. Unchanged amounts after heating each solution at 100 °C for 1 h

Solution	APM (%)	**46** (%)
Water	94.5	96.6
pH 4 soln.	91.1	97.0
pH 7 soln.	9.2	85.8

Structure-taste Relationship. It has widely been accepted that in the structure of α-L-aspartyl dipeptide esters a side chain (R_1) of a *C*-terminal amino acid must be a larger hydrophobic group when the configuration is L-form, while the D-form is required when R_1 is a smaller one. In a series of APM, the ester group corresponds to the "smaller part" and the sweetness decreases as an alkyl chain (R_2) of the ester group becomes larger. In a series of α-L-aspartyl-D-alanine esters, the ester group comes to serve as the "larger part", thus, there would be room to elongate the ester group by the insertion of a methylene group within the allowable steric requirements mentioned above.

However, the elongation of a peptide chain would cause its bond angle to be more or less distorted and make it difficult to maintain the same conformation, even when both the configuration and the bulkiness of R_1 and R_2 are equal to those of the parent α-L-aspartyl dipeptide esters. As a typical example of how to estimate briefly such a steric effect of distortion, Table 2 shows a comparison of the sweetness among the analogs of L-Asp–D-Ala–OPr, all of which have, as a whole, the same chain length. Compound **Ib** scarcely showed any sweetness, probably because the insertion of a methylene into this position would effect a conformational change at both the side chain and the ester group of the *C*-terminal amino acid. On the contrary, in the cases of **Ia** and **II**, such a distortion can occur only at the position of the ester group; thus, a less conformational change would result in the exhibition of a considerable sweetness. It is of interest that **II** shows a greater sweetness than **Ia**. A CPK model of L-Asp–D-Ala–OPr is found to resemble the former rather than the latter because of the exchange of the carbonyl function and the oxygen atom.

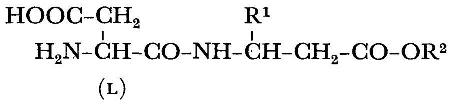
Table 2. Analogs of L-Asp-D-Ala-OPr

Type	L-Asp-X	Sweetness
D-Ala-OPr	 $-NH-\overset{CH_3}{CH}-\underset{O}{\overset{}{\underset{\|}{C}}}-O-CH_2-CH_2-CH_3$	170[3]
Ia(**1**)	 $-NH-\overset{CH_3}{CH}-CH_2-\underset{O}{\underset{\|}{C}}-O-CH_2-CH_3$	20
Ib(**18**)	 $-NH-CH_2-\overset{CH_3}{CH}-\underset{O}{\underset{\|}{C}}-O-CH(CH_3)_2$	2
II(**34**)	 $-NH-\overset{CH_3}{CH}-CH_2-O-\underset{O}{\underset{\|}{C}}-CH_2-CH_3$	100

None of the analogs in the types of **Ia** and **Ib** synthesized in the present study showed a potency than 20 times as sucrose. Further, α-L-aspartyl-amino-methylmalonates, which involve one more methylene group in the skeleton of α-L-aspartyl-amino-malonates reported by Fujino, had no sweetness at all. The results are summarized in Tables 3 and 4. Mazur[3] synthesized various L-aspartic acid amides and found that most of them showed less sweetness. The **Ib** type should, rather, be regarded as a kind of L-aspartic acid amide, one which has a branched primary amine with one or two carbonyl groups among its substituents. Taking the above observations into account, we mainly focused on the type of **II** and synthesized the analogs with various chain lengths at the ester group.

The potencies of the sweetness of *O*-acyl-2-(α-L-aspartylamino)alkanols (Type **II**) are listed in Table 5. The side chain (R_1) of 2-amino-D-alkanols corresponds to the "smaller part," and when R_1 is methyl, that is, D-alaninol, most of the analogs showed a considerable sweetness with a good aftertaste, like sucrose. In this case, the potency of the sweetness tends to in-

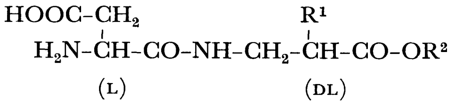
Table 3. Sweetness of L-aspartyl dipeptide(**Ia**)



$$H_2N\text{-}\underset{(L)}{\overset{HOOC\text{-}CH_2}{CH}}\text{-}CO\text{-}NH\text{-}\overset{R^1}{CH}\text{-}CH_2\text{-}CO\text{-}OR^2$$

Compd No.	R^1	R^2	Configuration	Mp (°C)	Sweetness
1	CH_3	CH_2CH_3	D	150—154	20
2	CH_3	$CH(CH_3)_2$	D	152.5—154.5	9
3	CH_3	$CH(CH_3)CH_2CH_3$	D	139.5—142	5
4	CH_3	$C(CH_3)_3$	D	109 (dec.)	6
5	CH_3	*cyclo*-C_5H_9	D	144.5—147	5
6	CH_2CH_3	CH_2CH_3	DL	136.5—138	5
7	CH_2CH_3	$CH(CH_3)_2$	DL	129—132	0
8	CH_2CH_3	*cyclo*-C_5H_9	DL	119—121	0
9	CH_2Ph	CH_2CH_3	L	124—127	0

Table 4. Sweetness of L-aspartyl dipeptide(**Ib**)



$$H_2N\text{-}\underset{(L)}{\overset{HOOC\text{-}CH_2}{CH}}\text{-}CO\text{-}NH\text{-}CH_2\text{-}\underset{(DL)}{\overset{R^1}{CH}}\text{-}CO\text{-}OR^2$$

Compd No.	R^1	R^2	Mp (°C)	Sweetneess
10	H	$CH_2CH_2CH_2CH_3$	163.5—165.5	0
11	H	$CH(CH_3)CH_2CH_3$	160.5—162.5	7
12	H	$C(CH_3)_3$	175.5—177.5	3
13	H	$CH(CH_2CH_3)_2$	150—152.5	5
14	H	$CH(CH_3)CH_2CH_2CH_3$	150—152.5	6
15	H	*cyclo*-C_5H_9	152.5—154	18
16	H	*cyclo*-C_6H_{11}	156.5—158	20
17	H	*cyclo*-$C_6H_{10}CH_3$[2-]	132—135	0
18	CH_3	$CH(CH_3)_2$	154—160	2
19	CH_3	$C(CH_3)_3$	136—138	4
20	CH_3	*cyclo*-C_5H_9	148—149	9
21	CH_3	*cyclo*-C_6H_{11}	150—152	10
22	CH_2Ph	CH_3	170—175	0
23	CO_2CH_3	CH_3	62— 66	0
24	CO_2CH_3	*cyclo*-C_5H_9	80— 84	0
25	CO_2CH_3	*cyclo*-C_6H_{11}	79— 84	0

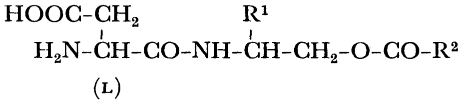
crease as an alkyl group (R_2) of the *O*-acyl residue—"a larger part"—becomes bulky with a branched short chain: *iso*-propyl and *t*-butyl isomers (**38**, **44**) are sweeter than those with less branched chains (**37**, **41**, **42**, **43**). Cycloalkyl isomers are also sweet. Thus, among the series of D-alaninol synthesized, *O*-pivaroyl (**44**) and *O*-cyclobutylcarbonyl (**46**) analogs become 240 and 220 times as sweet as sucrose respectively. When R_2 is a linear alkyl group, the potency of the sweetness decreases as the carbon number of an alkyl chain becomes greater, showing that the chain length of the dipeptide molecule must be strictly restricted; the order of sweetness is ethyl (**34**)> methyl (**33**)>butyl (**41**). A similar result was observed in the cycloalkyl groups: cyclobutyl (**46**)> cyclopropyl (**40**)>cyclopentyl (**49**), and the analogs with 3,3-dimethylcyclobutyl (**50**), cyclohexyl (**51**), or phenyl (**52**) were not sweet any more.

In a series of D-serinol, in which R_1 is the hydroxymethyl group, R_2 must be rather small to exhibit a considerable sweetness: the potency becomes 135 times as sucrose when R_2 is ethyl (**54**) or cyclopropyl (**55**), while it decreases as R_2 becomes bulky (**60** and **61**). Ariyoshi[5] reported on the dipeptide esters of β-hydroxy α-(α-L-aspartylamino)acids and found that L-Asp–D-Ser–OPr was the sweetest (320 times as sucrose). It is noted that this compound has the same chain length on the *C*-terminal amino acid as our *N*-(α-L-aspartyl)-*O*-propionyl-D-serinol (**54**).

In the cases of 2-amino-1-butanol (R_1; ethyl, **62**-**68**), *O*-methylserinol (R_1; methoxymethyl, **69**, **70**), and valinol (R_1; *iso*-propyl, **71**—**77**). the potency of the sweetness tends to decrease as compared with those of D-alaninol and D-serinol, though a tendency similar to that described above was observed concerning the requirement of the size of R_2. It was found that leucinol (**80**), isoleucinol (**81**), and phenylalaninol (**82**), which have such bulky groups on the side chain, showed no sweetness, not even when R_2 was the methyl group.

On the contrary, 2-aminoethanol (R_1; H), which has no side chain and which is the smallest analog

TABLE 5. SWEETNESS OF L-ASPARTYL DIPEPTIDE(**II**)



$$\underset{(\mathrm{L})}{H_2N\text{-}\overset{HOOC\text{-}CH_2}{CH}}\text{-}CO\text{-}NH\text{-}\overset{R^1}{CH}\text{-}CH_2\text{-}O\text{-}CO\text{-}R^2$$

Compd No.	R^1	R^2	Configuration	Mp (°C dec)	Sweetness
26	H	CH_3	—	163—165	3
27	H	CH_2CH_3	—	171—172	6
28	H	$CH_2CH_2CH_3$	—	172—174	5
29	H	$CH(CH_3)_2$	—	175—177	20
30	H	*cyclo*-C_3H_5	—	155—159	15
31	H	*cyclo*-C_4H_7	—	166.5—170	13
32	H	$C(CH_3)_3$	—	140—143	30
33	CH_3	CH_3	D	146—149	60
34	CH_3	CH_2CH_3	D	155—156	100
35	CH_3	$CH{=}CH_2$	D	226	100
36	CH_3	$CH_2CH_2CH_3$	DL	164—166	25
37	CH_3	$CH_2CH_2CH_3$	D	151—152	50
38	CH_3	$CH(CH_3)_2$	D	154—155	120
39	CH_3	$C(CH_3){=}CH_2$	D	230	130
40	CH_3	*cyclo*-C_3H_5	D	146.5—149	200
41	CH_3	$CH_2CH_2CH_2CH_3$	D	157—159	5
42	CH_3	$CH(CH_3)CH_2CH_3$	D	126	150
43	CH_3	$CH_2CH(CH_3)_2$	D	163—166.5	50
44	CH_3	$C(CH_3)_3$	D	145—147	240
45	CH_3	*cyclo*-$C_3H_4CH_3$[2-]	D	151—153	60
46	CH_3	*cyclo*-C_4H_7	D	168.5—170	220
47	CH_3	$CH(CH_2CH_3)_2$	D	126.5—127.5	40
48	CH_3	*cyclo*-$C_4H_6CH_3$[2-]	D	134—135	160
49	CH_3	*cyclo*-C_5H_9	D	162—165	60
50	CH_3	*cyclo*-$C_4H_6(CH_3)_2$[3,3-]	D	148—150.5	0
51	CH_3	*cyclo*-C_6H_{11}	D	186—188	0
52	CH_3	C_6H_5	D	179—182	0
53	CH_2OH	CH_3	D	206.5—207	25
54	CH_2OH	CH_2CH_3	D	203—204	135
55	CH_2OH	*cyclo*-C_3H_5	D	172.5—175	120
56	CH_2OH	$CH(CH_3)_2$	D	209—211	40
57	CH_2OH	$CH_2CH_2CH_3$	D	197—199	5
58	CH_2OH	*cyclo*-C_4H_7	D	185—190	65
59	CH_2OH	$C(CH_3)_3$	D	203—204	25
60	CH_2OH	$CH(CH_3)CH_2CH_3$	D	195—196	20
61	CH_2OH	*cyclo*-C_5H_9	D	191.5—192.5	10
62	CH_2CH_3	CH_3	DL	112—117	10
63	CH_2CH_3	CH_2CH_3	DL	128—130	20
64	CH_2CH_3	$CH(CH_3)_2$	DL	134—138	15
65	CH_2CH_3	*cyclo*-C_3H_5	DL	90—92	15
66	CH_2CH_3	*cyclo*-C_4H_7	DL	94.5—101	15
67	CH_2CH_3	$CH_2CH_2CH_2CH_3$	DL	131—135	0
68	CH_2CH_3	*cyclo*-C_6H_{11}	DL	135—138	0
69	CH_2OCH_3	CH_3	DL	50	2
70	CH_2OCH_3	CH_2CH_3	DL	77—79	10
71	$CH(CH_3)_2$	CH_3	DL	130—137	25
72	$CH(CH_3)_2$	CH_3	D	174—175	50
73	$CH(CH_3)_2$	CH_2CH_3	D	138—141	50
74	$CH(CH_3)_2$	$CH(CH_3)_2$	D	148—151	15
75	$CH(CH_3)_2$	*cyclo*-C_3H_5	D	129—133	20
76	$CH(CH_3)_2$	*cyclo*-C_4H_7	D	94.5—97	13
77	$CH(CH_3)_2$	$CH_2CH_2CH_3$	D	136—138	3
78	$CH_2CH_2CH_3$	CH_3	DL	175—177	3
79	$CH_2CH_2CH_3$	CH_2CH_3	DL	145—147	0
80	$CH_2CH(CH_3)_2$	CH_3	DL	112—117	0
81	$CH(CH_3)CH_2CH_3$	CH_3	DL	129—133	0
82	CH_2Ph	CH_3	L	89—92	0

of this series, was found to show some sweetness (**26**—**32**). It is noted that none of the *O*-acyl-2-(α-L-aspartylamino)-L-alkanol synthesized was sweet, showing that the configuration of the *C*-terminal amino acid must be D-form to exhibit the taste.

Summarizing the above observations, we may derive the following conclusions concerning the structure-taste relationship of our L-aspartyl dipeptide sweetners: (1) the insertion of a methylene group into the peptide chain generally causes a significant disadvantage; (2) the further exchange of the carbonyl and oxygen functions on the ester group of a *C*-terminal α-alkyl-β-aminopropionic acid has rather a good effect on exhibiting sweetness; (3) in the series of *O*-acyl-2-(α-L-aspartylamino)alkanols, the structural requirements for the mutual sizes between the side chain (R_1) and the alkyl group (R_2) of the *O*-acyl residue are nearly equal to those previously proposed for the structure-taste relationship of α-L-aspartyl dipeptide esters, and (4) the configuration of the 2-aminoalkanol esters should be D-form, the same as the corresponding α-L-aspartyl-D-alanine esters.

Experimental

The melting points were determined using a Yamato melting-point apparatus and were uncorrected. The IR spectra were measured with a Shimadzu IR-27G infrared spectrometer; the H^1 NMR spectra, with a Hitachi Perkin-Elmer R-20A high-resolution NMR spectrometer, using tetramethylsilane as the internal standard, and the optical rotations, with a Perkin-Elmer 141 polarimeter. The quantitative determination on peptides was performed by the use of a Hitachi KLA-3B automatic amino-acid analyzer.

*Typical Procedure for the Preparation of β-Alkyl-β-amino-propionic Acid and α-Alkyl-β-aminopropionic Acid Derivatives (**Ia** and **Ib**).* *D-3-(Benzyloxycarbonylamino)butyric Acid*: Methyl D-3-(benzyloxycarbonylamino)butyrate was obtained as a colorless oil from *N*-benzyloxycarbonyl-D-alanine (8.92 g) by means of the previously reported method.[8] This methyl ester was saponified with methanolic sodium hydroxide in the usual manner to give the title compound as colorless needles, which were then recrystallized from ethyl acetate-petroleum ether; yield, 4.0 g (42.2%); mp 104—104.5 °C; $[\alpha]_D^{22}$ −5.5° (*c* 1, acetone); IR (Nujol) 3300, 1685, 1550 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (d, 3H, *J*=6 Hz), 2.54 (d, 2H, *J*=6 Hz), 3.8—4.4 (m, 1H), 5.10 (s, 2H), 5.0—5.8 (broad, 1H), 7.32 (s, 5H), 7.2—7.5 (broad, 1H); Found: C, 60.81; H, 6.42; N, 5.81%. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90%.

DL-2-Methyl-3-(benzyloxycarbonylamino)propionic Acid: Diethyl phthalimidomethyl-methylmalonate was prepared from diethyl methylmalonate (21 g in THF 50 ml) with 65% sodium hydride (4.1 g) and *N*-(chloromethyl)phthalimide (19.5 g in THF 150 ml) by means of the previously reported method.[10] These crystals obtained were recrystallized from ethyl acetate-hexane; yield, 28.6 g (85.5%); mp 98—99 °C. The hydrolysis of the compound obtained above was followed by column chromatography (Dianion SK 1b, H^+ form). The eluate with 5% aqueous ammonia was concentrated to dryness *in vacuo* to afford DL-2-methyl-3-aminopropionic acid as colorless crystals, which were used without further purification. The benzyloxycarbonylation of this compound was carried out by Schotten-Baumann's method to afford the title compound as colorless needles, which were then recrystallized from ethyl acetate-hexane; yield, 7.0 g (73.8%); mp 65—66.5 °C; IR (Nujol) 3340, 1715, 1685 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (d, 3H, *J*=7 Hz), 2.4—3.1 (m, 1H), 3.40 (t, 2H, *J*=7 Hz), 5.10 (s, 2H), 5.1—5.6 (broad, 1H), 7.33 (s, 5H), 10.70 (s, 1H); Found: C, 60.68; H, 6.45; N, 5.79%. Calcd for $C_{12}H_{15}NO_4$: C, 60.72; H, 6.37; N, 5.90%.

Ethyl D-3-[(N-Benzyloxycarbonyl-O⁴-benzyl-α-L-aspartyl)-amino]butyrate: Ethyl D-3-(benzyloxycarbonylamino)butyrate was obtained as a colorless oil by treating D-3-(benzyloxycarbonylamino)butyric acid (2.73 g) with thionyl chloride (2 ml) in ethanol (10 ml). The oil was then dissolved in a mixture of *N,N*-dimethylformamide (5 ml) and tetrahydrofuran (20 ml), and the solution was cooled to 0 °C. To this were added O^4-benzyl *N*-benzyloxycarbonyl-α-L-aspartate (3.57 g), 1-hydroxybenzotriazole (1.35 g), and dicyclohexylcarbodiimide (2.1 g). The reaction mixture was stirred for 1 h at 0 °C and for 5 h at room temperature, and then the insoluble materials were filtered off. The filtrate was concentrated to dryness *in vacuo*, and the residue was dissolved in ethyl acetate (50 ml). The solution was washed with aqueous saturated sodium hydrogencarbonate (10 ml), 1% hydrochloric acid (10 ml), and water (10 ml), and then dried over magnesium sulfate. The solution was concentrated to dryness *in vacuo*, and the oily residue thus obtained was purified by chromatography on silica gel (80 g, Kiesel gel 60) with benzene-ethyl acetate (9:1) to afford the title compound as colorless needles, which were subsequently recrystallized from ethyl acetate-petroleum ether; yield, 2.7 g (57.4%); mp 91—92 °C; $[\alpha]_D^{22}$ −7.0° (*c* 0.5, MeOH), IR (Nujol) 3310, 1730, 1695, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (d, 3H, *J*=7 Hz), 1.22 (t, 3H, *J*=7 Hz), 2.45 (d, 2H, *J*=6 Hz), 2.5—3.27 (m, 2H), 4.11 (quartet, 2H, *J*=7 Hz), 4.1—4.8 (m, 2H), 5.12 (s, 4H), 5.92 (broad d, 1H, *J*=9 Hz), 6.89 (broad d, 1H, *J*=9 Hz), 7.33 (s, 10H); Found: C, 63.77; H, 6.53; N, 5.86%. Calcd for $C_{25}H_{30}N_2O_7$: C, 63.82; H, 6.43; N, 5.95%.

*Ethyl D-3-(α-L-Aspartylamino)butyrate (**1**)*: Ethyl D-3-[(*N*-benzyloxycarbonyl-*O*⁴-benzyl-α-L-aspartyl)amino]butyrate (1.2 g) was dissolved in methanol (20 ml). The hydrogenolysis of this compound was then carried out over palladium black (0.1 g) for 2 h at room temperature under an atmospheric pressure of hydrogen. After the catalyst had been filtered off, the filtrate was concentrated to dryness *in vacuo* to give **1** as crystals, which were then triturated with ether and filtered; yield 0.54 g (85.6%); mp 150—154 °C; $[\alpha]_D^{22}$ −9.7° (*c* 0.5, DMF); IR (Nujol) 3300, 1730, 1660 cm^{-1}; NMR (DMSO-d_6) δ 1.15 (d, 3H, *J*=7 Hz), 1.21 (t, 3H, *J*=7 Hz), 2.2—2.7 (m, 4H), 3.6—4.4 (m, 2H), 4.10 (quartet, 2H, *J*=7 Hz), 5.49 (s, 3H), 8.2—8.7 (broad, 1H); Found: C, 48.59; H, 7.51; N, 11.20%. Calcd for $C_{10}H_{18}N_2O_5$: C, 48.77; H, 7.36; N, 11.37%.

*Typical Procedure for the Preparation of (Aminomethyl)-Malonic Acid Derivatives (**Ib**).* *N-(Benzyloxycarbonyl)acetoxymethylamine*: Benzyloxycarbonylglycine (14.6 g) was dissolved in acetic acid (80 ml), to which we then added solium acetate (2.05 g). The solution was electrolyzed at 15—20 °C using 3×4 cm^2 of the carbon anode which was placed 0.5 cm apart from the carbon cathode. An electrolysis current was maintained at 1A during the electrolysis. After 6 h, the electrolyzed solution was evaporated to dryness *in vacuo*. The oily residue was dissolved in ethyl acetate, and the solution was washed with aqueous saturated sodium hydrogencarbonate and water, and then dried over magnesium sulfate. This solution was concentrated to dryness *in vacuo* to give the title compound as a colorless oil; yield, 12.7 g (79.4%); IR (film) 3340, 1730, 1520 cm^{-1}; NMR ($CDCl_3$), δ 2.0 (s, 3H), 5.13 (s, 2H), 5.16 (d, 2H), 5.9—6.5 (broad s, 1H), 7.35 (s, 5H).

Dicyclohexylammonium Cyclopentyl Malonate: The condensation of malonic acid (20.8 g) and cyclopentanol (41.28 g) was carried out under reflux in benzene (150 ml) containing *p*-toluenesulfonic acid monohydrate (3.8 g), using a Dean-Stark's apparatus, to give dicyclopentyl malonate as a colorless oil. This compound was subsequently saponified with 2.5 M methanolic potassium hydroxide (80 ml) at room temperature for 2 h. After acidification with 6 M hydrochloric acid, the solution was extracted with ether (300 ml). The organic layer was washed with water (30 ml) and then dried over magnesium sulfate. To the solution we added dicyclohexylamine (36.2 g) to afford the title compound as colorless needles; yield, 32.6 g (46.2%); mp 113—115 °C; IR (Nujol) 1735, 1635, 1570 cm^{-1}; NMR (DMSO-d_6), δ 0.7—2.3 (m, 28H), 2.65—3.20 (broad, 2H), 2.94 (s, 2H), 4.85—5.20 (broad, 1H), 6.8—7.4 (broad, 2H); Found: C, 67.59; H, 9.98; N, 3.96%, Calcd for $C_{20}H_{35}NO_4$: C, 67.30; H, 10.11; N, 4.03%.

Cyclopentyl Methyl Malonate: Dicyclohexylammonium cyclopentyl malonate (10.6 g) was suspended in ether (200 ml), and 1 M sulfuric acid (20 ml) was added to the mixture under stirring. The organic layer was washed with water (20 ml) and dried over magnesium sulfate. The solution was concentrated to dryness *in vacuo*, the oily residue was dissolved in ether (50 ml), and then diazomethane in ether was added to this solution. The reaction mixture was concentrated to dryness *in vacuo* to afford the title compound as a colorless oil, which was distilled at 93 °C at 3 mmHg; yield, 4.6 g (82.4%); IR (film) 1730 cm^{-1}; NMR (CDCl$_3$), δ 1.5—2.1 (m, 8H), 3.32 (s, 2H), 3.72 (s, 3H), 5.05—5.4 (broad, 1H).

Cyclopentyl Methyl (Benzyloxycarbonylaminomethyl)malonate: *N*-(Benzyloxycarbonyl)acetoxymethylamine (2.23 g) was dissolved in *N*,*N*-dimethylformamide (10 ml), after which the mixture was cooled to 0 °C. To this we added cyclopentyl methyl malonate (1.86 g) and 65% sodium hydride (0.4 g) in *N*,*N*-dimethylformamide under vigorous stirring. The reaction mixture was stirred at room temperature for 15 h and then concentrated to dryness *in vacuo*. The oily residue thus obtained was dissolved in ethyl acetate, and the solution was washed with water saturated with sodium hydrogencarbonate, 1% hydrochloric acid, and water, and then dried over magnesium sulfate. The dried solution was concentrated to dryness *in vacuo*, and the residue was purified on a silica gel column (80 g, Kiesel gel 60), using benzene–ethyl acetate (95:5) as the eluate, to give the title compound as a colorless oil; yield, 2.84 g (79.3%); IR (film) 3370, 1730, 1520 cm^{-1}; NMR (CDCl$_3$), δ 1.4—1.9 (m, 8H), 3.65 (2H), 3.72 (s, 3H), 5.1 (s, 2H), 5.1—5.7 (m, 3H), 7.36 (s, 5H).

*Cyclopentyl Methyl (*N*-Benzyloxycarbonyl-*O^4*-benzyl-α-*L*-aspartylamino)malonate*: Cyclopentyl methyl (benzyloxycarbonylaminomethyl)malonate (1.1 g) and oxalic acid dihydrate (0.2 g) were dissolved in methanol (20 ml). To this solution we added palladium black (0.1 g), and the hydrogenolysis was carried out under an atmospheric pressure of hydrogen. After the catalyst had been filtered off, the filtrate was concentrated to dryness *in vacuo* to give cyclopentyl methyl (aminomethyl)malonate as crystalline hemioxalic acid salt.

These crystals, O^1-*p*-nitrophenyl O^4-benzyl *N*-benzylocycarbonyl-α-L-aspartate (1.43 g), and 1-hydroxybenzotriazole (0.44 g), were dissolved in *N*,*N*-dimethylformamide (20 ml), after which the solution was cooled to 0 °C. Into this triethylamine (0.42 ml) was stirred. The reaction mixture was stirred at the same temperature for 30 min, and then diluted with ethyl acetate (100 ml). The solution was washed with aqueous saturated sodium hydrogencarbonate, 1% hydrochloric acid, and water, and then dried over magnesium sulfate. The dried solution was concentrated to dryness *in vacuo*, and the oily residue thus obtained was purified on a silica gel column (45 g, Kiesel gel 60), using benzene–ethyl acetate (83:17) as the eluate, to afford the title compound as a colorless oil; yield, 0.44 g (26.0%); IR (film) 3340, 1730, 1670, 1530 cm^{-1}; NMR (CDCl$_3$), δ 1.5—1.9 (m, 8H), 2.45—3.2 (m, 2H), 3.65 (2H), 3.72 (s, 3H), 3.7—3.85 (m, 1H), 4.45—4.7 (m, 1H), 5.12 (s, 4H), 5.1—5.3 (m, 1H), 5.82 (d, 1H, J=9 Hz), 6.7—7.1 (m, 1H), 7.32 (s, 10H).

*Cyclopentyl Methyl (α-*L*-Aspartylaminomethyl)malonate* (***24***): The hydrogenolysis of cyclopentyl methyl (*N*-benzyloxycarbonyl-O^4-benzyl-α-L-aspartylamino)malonate (0.4 g) was carried out in methanol using palladium black (0.1 g) under an atmospheric pressure of hydrogen. After the catalyst had been filtered off, the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in a small amount of water and then lyophylized; yield, 0.17 g (71.0%); mp 80—84 °C (dec); IR (Nujol) 1730, 1675 cm^{-1}; NMR (DMSO-d_6) δ 1.65 (broad s, 8H), 2.2—2.6 (2H), 3.65 (d, 2H, J=8 Hz), 3.68 (s, 3H), 3.7—3.9 (broad, 2H), 5.0—5.3 (broad s, 1H), 5.9—6.5 (broad s, 3H), 8.2—9.0 (broad s, 1H); Found: C, 48.16; H, 7.09; N, 7.89%. Calcd for $C_{14}H_{22}N_2O_7 \cdot H_2O$: C, 48.27; H, 6.74; N, 8.04%.

*Typical Procedure for the Preparation of 2-Amino-*D*-alkanol Derivatives (**II**).* *Methyl* N*-Acetyl-*O*-benzyl-*D*-serinate*: Thionyl chloride (16 g) was vigorously stirred, drop by drop, into methanol (80 ml) at −10 °C. To this solution we then added *N*-acetyl-*O*-benzyl-D-serine (19 g) at the same temperature. The reaction mixture was stirred at room temperature for 2 h and then concentrated to dryness *in vacuo* below 30 °C. The residue was disolved in ethyl acetate (100 ml), and the solution was washed with aqueous saturated sodium hydrogencarbonate (10 ml), 1% hydrochloric acid (10 ml), and water, and then dried over magnesium sulfate. The solution was concentrated to dryness *in vacuo* to give the title compound as colorless needles, which were subsequently recrystallized from ethyl acetate–petroleum ether; yield, 19.3 g (96.1%); mp 66—67 °C; $[\alpha]^{25}_{D}$ −11.8° (*c* 1.02, MeOH); IR (Nujol) 3290, 1750, 1635 cm^{-1}; NMR (CDCl$_3$) δ 2.01 (s, 3H), 3.55—4.00 (m, 2H), 3.72 (s, 3H), 4.50 (s, 2H), 4.65—4.88 (m, 1H), 6.50 (broad d, 1H, J=10 Hz), 7.30 (s, 5H); Found: C, 62.30; H, 6.86; N, 5.60%. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57%.

Methyl N*-Benzyloxycarbonyl-*D*-alaninate*: Thionyl chloride (6 ml) was vigorously stirred, drop by drop, into methanol (30 ml) at −10 °C. To this solution we then added *N*-benzyloxycarbonyl-D-alanine (6.7 g) at the same temperature. The reaction mixture was treated in the manner described above to give the title compound as colorless needles, which were subsequently recrystallized from ethyl acetate–hexane; yield, 6.40 g (90.0%); mp 48—49 °C; $[\alpha]^{25}_{D}$ +34.7° (*c* 1, MeOH); IR (Nujol) 3350, 1750, 1680 cm^{-1}; NMR (CDCl$_3$) δ 1.41 (d, 3H, J=7 Hz), 3.73 (s, 3H), 4.39 (quartet, 1H, J=7 Hz), 5.12 (s, 2H), 5.1—5.65 (broad, 1H), 7.35 (s, 5H); Found: C, 60.39; H, 6.44; N, 6.20%. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90%.

N*-Acetyl-*O*-benzyl-*D*-serinol*: To a suspension of sodium borohydride (3.42 g) and calcium chloride (10 g) in tetrahydrofuran (75 ml), we added methyl *N*-acetyl-*O*-benzyl-D-serinate (7.5 g) in tetrahydrofuran (75 ml) at room temperature. After the reaction mixture had then been stirred for 2 h at the same temperature, the insoluble materials were removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The oily residue was dissolved in ethyl acetate (100 ml). The solution was washed with water (20 ml) and dried over magnesium sulfate. The dried solution was concentrated to dryness *in vacuo* to give the title compound as a colorless oil; yield, 6.2 g (93.0%); $[\alpha]^{22}_{\mathrm{D}}$ −28.6° (*c* 0.71, MeOH); IR (film) 3300, 1650, 1550 cm^{-1}; NMR ($CDCl_3$) δ 2.00 (s, 3H), 3.19 (broad s, 1H), 3.55—4.34 (m, 5H), 4.52 (s, 2H), 6.36 (broad d, 1H, *J*=8 Hz), 7.33 (s, 5H).

N-*Benzyloxycarbonyl*-D-*alaninol*: To a suspension of sodium borohydride (3.4 g) and calcium chloride (10 g) in tetrahydrofuran (75 ml), we added methyl *N*-benzyloxycarbonyl-D-alaninate (7.11 g) in tetrahydrofuran (75 ml) at room temperature. The reaction mixture was then treated in the manner described above to give the title compound as colorless needles, which were subsequently recrystallized from ethyl acetate–hexane; yield, 4.7 g (75.0%); mp 81—82 °C; $[\alpha]^{25}_{\mathrm{D}}$ +4.9° (*c* 0.87, MeOH); IR (Nujol) 3460, 1695, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.12 (d, 3H, *J*=7 Hz), 2.93 (broad s, 1H), 3.41—4.15 (m, 3H), 5.09 (s, 2H), 5.10—5.40 (broad, 1H), 7.32 (s, 5H); Found: C, 62.78; H, 7.25; N, 6.74%. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69%.

O^3-*Benzyl*-D-*serinol Hydrochloride*: A solution of *N*-acetyl-O^3-benzyl-D-serinol (6.2 g) in 4 M hydrochloric acid (15 ml) was heated at 70 °C for 100 min under vigorous stirring. The reaction mixture was concentrated to dryness *in vacuo* to give the title compound as colorless needles, which were then recrystallized from methanol–ether; yield, 5.25 g (86.8%); mp 133.5—134.5 °C; $[\alpha]^{25}_{\mathrm{D}}$ +4.6° (*c* 1.01, MeOH); IR (Nujol) 3360, 1590, 1380 cm^{-1}; NMR (DMSO-d_6) δ 3.00—3.90 (m, 5H), 4.56 (s, 2H), 4.20—5.00 (broad, 1H), 7.39 (s, 5H), 8.36 (broad s, 3H); Found: C, 55.00; H, 7.41; N, 6.43; Cl, 16.41%. Calcd for $C_{10}H_{16}NO_2Cl$: C, 55.17; H, 7.41; N, 6.44; Cl, 16.29%.

N-*(*N-*Benzyloxycarbonyl*-O^4-*benzyl*-α-L-*aspartyl)*-O^3-*benzyl*-D-*serinol*: To a solution of O^3-benzyl-D-serinol hydrochloride (2.2 g), triethylamine (1.4 ml), and 1-hydroxybenzotriazole (1.4 g) in *N,N*-dimethylformamide (30 ml), we added O^1-*p*-nitrophenyl O^4-benzyl *N*-benzyloxycarbonyl-α-L-aspartate (4.8 g). The reaction mixture was stirred for 30 min at 0 °C and then diluted with ethyl acetate (100 ml). The solution was washed with 3% aqueous ammonia, 1% hydrochloric acid, and water, and then dried over magnesium sulfate. The dried solution was concentrated to dryness *in vacuo* to give the title compound as colorless needles, which were subsequently recrystallized from ethyl acetate–petroleum ether; yield, 3.25 g (62.5%); mp 102—104 °C; $[\alpha]^{22}_{\mathrm{D}}$ −22.3° (*c* 0.65, MeOH); IR (Nujol) 3450, 3300, 1730, 1680, 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.50—3.30 (m, 3H), 3.50—4.35 (m, 5H), 4.47 (s, 2H), 4.40—4.90 (m, 1H), 5.10 (s, 4H), 6.00 (d, 1H, *J*=10 Hz), 6.80—7.15 (m, 1H), 7.32 (s, 15H); Found: C, 66.87; H, 6.25; N, 5.20%. Calcd for $C_{29}H_{32}N_2O_7$: C, 66.91; H, 6.20; N, 5.38%.

N-*(*N-*Benzyloxycarbonyl*-O^4-*benzyl*-α-L-*aspartyl)*-D-*alaninol*: The hydrogenolysis of *N*-benzyloxycarbonyl-D-alaninol (1 g) in methanol over palladium black (0.1 g) was carried out for 1.5 h under an atmospheric pressure of hydrogen. After the catalyst had been filtered off, the filtrate was concentrated to dryness *in vacuo* to give D-alaninol as a colorless oil. The D-alaninol thus obtained and 1-hydroxybenzotriazole (0.7 g) were dissolved in *N,N*-dimethylformamide (15 ml) and the solution was cooled to 0 °C. To this solution we then added O^1-*p*-nitrophenyl O^4-benzyl *N*-benzyloxycarbonyl-α-L-aspartate (2.3 g). The reaction mixture was stirred for 30 min at 0 °C, and then diluted with ethyl acetate (10 ml). The solution was washed with 3% aqueous ammonia, 1% hydrochloric acid, and water, and then dried over magnesium sulfate. The dried solution was concentrated to dryness *in vacuo* to give the title compound as colorless needles, which were subsequently recrystallized from ethyl acetate-hexane; yield, 1.3 g (65.9%); mp 111—113 °C; $[\alpha]^{25}_{\mathrm{D}}$ −0.7° (*c* 0.76, MeOH); IR (Nujol) 3460, 3300, 1740, 1690, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (d, 3H, *J*=7 Hz), 2.60—3.20 (m, 3H), 3.30—4.25 (m, 3H), 4.30—4.85 (m, 1H), 5.09 (s, 4H), 6.08 (broad d, 1H, *J*=10 Hz), 6.47—6.85 (broad, 1H), 7.32 (s, 10H); Found: C, 63.72; H, 6.49; N, 6.93%. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.75; H, 6.32; N, 6.76%.

N-*(*N-*Benzyloxycarbonyl*-O^4-*benzyl*-α-L-*aspartyl*-O^1-*isobutyryl*-O^3-*benzyl*-D-*serinol*: *N*-(*N*-Benzyloxycarbonyl-O^4-benzyl-α-L-aspartyl)-O^3-benzyl-D-serinol (1.6 g) was dissolved in pyridine (20 ml), and the solution was cooled to 0 °C. To the solution we then added, drop by drop, isobutyryl chloride (0.96 g), after which the reaction mixture was stirred at room temperature for 1.5 h. The solution was concentrated to dryness *in vacuo*, and the resulting residue was dissolved in ethyl acetate (100 ml). The solution was washed with 1% hydrochloric acid, aqueous saturated sodium hydrogencarborate, and water, and then dried over magnesium sulfate. The dried solution was concentrated to dryness *in vacuo*, and the oily residue thus obtained was subjected to column chromatography on silica gel (50 g, Kiesel gel 60), using benzene–ethyl acetate (4:1). The eluate was concentrated to dryness *in vacuo* to give the title compound as colorless needles, which were subsequently recrystallized from ethyl acetate–petroleum ether; yield, 1.66 g (91.2%); mp 103—103.2 °C; $[\alpha]^{22}_{\mathrm{D}}$ −6.6° (*c* 1, MeOH); IR (Nujol) 3300, 3270, 1725, 1685, 1665 cm^{-1}; NMR ($CDCl_3$) δ 1.11 (d, 6H, *J*=7 Hz), 2.26—3.26 (m, 3H), 3.27—3.67 (m, 2H), 4.04—4.80 (m, 4H), 4.47 (s, 2H), 5.10 (s, 4H), 5.90 (broad d, 1H, *J*=10 Hz), 6.85 (broad d, 1H, *J*=8 Hz), 7.32 (s, 15H); Found: C, 67.11; H, 6.60; N, 4.90%. Calcd for $C_{33}H_{28}N_2O_8$: C, 67.10; H, 6.49; N, 4.74%.

N-*(*N-*Benzyloxycarbonyl*-O^4-*benzyl*-α-L-*aspartyl)*-O-*propionyl*-D-*alaninol*: *N*-(*N*-Benzyloxycarbonyl-O^4-benzyl-α-L-aspartyl)-D-alaninol (0.88 g) was dissolved in pyridine (15 ml), and the solution was cooled to 0 °C. To the solution propionyl chloride (0.6 g) was added, drop by drop, after which the reaction mixture was stirred at room temperature for 1.5 h. The solution was treated in the manner described above to give the title compound as colorless needles, which were subsequently recrystallized from ethyl acetate-hexane; yield, 0.88 g (88.0%); mp 90—91 °C; $[\alpha]^{25}_{\mathrm{D}}$ −4.0° (*c* 1, MeOH); IR (Nujol) 3310, 1740, 1700, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (d, 3H, *J*=6 Hz), 1.12 (t, 3H, *J*=7 Hz), 2.33 (quartet, 2H, *J*=7 Hz), 2.50—3.25 (m, 2H), 3.80—4.85 (m, 4H), 5.12 (s, 4H), 5.92 (broad d, 1H, *J*=9 Hz), 6.30—6.80 (broad, 1H), 7.33 (s, 10H); Found: C, 63.91; H, 6.55; N, 5.92%. Calcd for $C_{25}H_{30}N_2O_7$: C, 63.81; H, 6.43; N, 5.95%.

N-(α-L-*Aspartyl*)-O^1-*isobutyryl*-D-*serinol* ***(56)***: *N*-(*N*-Benzyloxycarbonyl-O^4-benzyl-α-L-aspartyl)-O^1-isobutyryl-O^3-benzyl-D-serinol (1.4 g) was dissolved in a mixture of methanol (100 ml) and water (5 ml). The hydrogenolysis of this compound was carried out over palladium black (0.2 g) for 20 h at room temperature at 3 kg/cm^2 of hydrogen. After the catalyst had then been filtered off, the filtrate was concentrated to dryness *in vacuo* to give **56** as crystals, which were subsequently triturated by methanol and filtered; yield, 0.63 g (96.3%); mp 209—211 °C (dec); $[\alpha]^{30}_{\mathrm{D}}$ +12.7° (*c* 0.5, AcOH); IR (Nujol) 3270, 1730, 1680 cm^{-1}; NMR (D_2O+TFA) δ 1.14 (d, 6H, *J*=7 Hz), 2.41—3.0 (m, 1H), 3.09 (d, 2H, *J*=7 Hz), 3.50—3.90 (m, 2H), 3.95—4.50 (m, 4H); Found: C, 47.91; H, 7.28; N, 10.14%. Calcd for $C_{11}H_{20}N_2O_6$ C, 47.82; H, 7.30; N, 10.14%.

N-(α-L-*Aspartyl*)-O-*propionyl*-D-*alaninol* ***(34)***: *N*-(*N*-Benzyloxycarbonyl-O^4-benzyl-α-L-aspartyl)-*O*-propionyl-D-alaninol (0.5 g) was dissolved in methanol (20 ml). The hydrogenolysis of this compound was carried out over palladium black (0.1 g) for 2 h at room temperature under an atmospheric pressure of hydrogen. After the catalyst had been filtered off, the filtrate was concentrated to dryness *in vacuo* to give **34** as crystals, which were subsequently triturated by ether and filtered; yield, 0.25 g (95.4%); mp 155—156 °C (dec.); [α]$^{22}_{D}$ +29.6° (*c*, 0.7, H_2O); IR (Nujol) 3310, 1740, 1660 cm^{-1}; NMR (DMSO-d_6) δ 1.03 (t, 3H, *J*=7 Hz), 1.10 (d, 3H, *J*=8 Hz), 2.34 (quartet, 2H, *J*=7 Hz), 2.30—2.65 (m, 2H), 3.40—4.45 (m, 4H), 5.28 (broad s, 3H), 8.1—8.65 (broad, 1H); Found: C, 45.59; H, 7.53; N, 10.74%. Calcd for $C_{10}H_{18}N_2O_5 \cdot H_2O$: C, 45.44; H, 7.63; N, 10.60%.

N-(α-L-*Aspartyl*)-O-*cyclopropylcarbonyl*-D-*alaninol* (**40**): *N*-(*N*-Benzyloxycarbonyl-*O*^{4}-benzyl-α-L-aspartyl)-*O*-cyclopropylcarbonyl-D-alaninol (0.96 g) was dissolved in methanol (20 ml). The hydrogenolysis of this compound was carried out in the manner described above. After the catalyst had been filtered off, the filtrate was concentrated to dryness *in vacuo* to give **40** as crystals, which were subsequently triturated by ether and filtered; yield, 0.5 g (96.9%); mp 146.5—149 °C (dec); [α]$^{25}_{D}$ +27.4° (*c* 0.52, H_2O); IR (Nujol) 3320, 1730, 1660 cm^{-1}; NMR (DMSO-d_6) δ 0.87 (d, 3H, *J*=7 Hz), 0.92—1.3 (m, 4H), 1.45—1.9 (m, 1H), 2.23—2.6 (m, 2H), 3.52—4.2 (m, 4H), 5.40 (broad s, 3H), 8.2—8.7 (broad, 1H); Found: C, 51.00; H, 7.12; N, 10.67%. Calcd for $C_{11}H_{18}N_2O_5$: C, 51.15; H, 7.02; N, 10.85%.

N-(α-L-*Aspartyl*)-O-*cyclobutylcarbonyl*-D-*alaninol* (**46**): *N*-(*N*-Benzyloxycarbonyl-*O*^{4}-benzyl-α-L-aspartyl)-*O*-cyclobutylcarbonyl-D-alaninol (0.99 g) was subjected to hydrogenolysis to afford **46** by the procedure described above; yield, 0.52 g (95.6%); mp 168—170 °C (dec); [α]$^{25}_{D}$ +29.8° (*c* 0.51, H_2O); IR (Nujol) 3330, 1730, 1660 cm^{-1}; NMR (DMSO-d_6) δ 1.06 (d, 3H, *J*=7 Hz), 1.8—2.6 (m, 8H), 2.9—3.3 (m, 1H), 3.6—4.2 (m, 4H), 5.40 (broad s, 3H), 8.1—8.7 (broad, 1H); Found: C, 52.69; H, 7.51; N, 10.15%. Calcd for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40; N, 10.29%.

Measurement of the Potency of Sweetness. The relative potencies of sweetness were determined based on a panel evaluation by six persons. A 100 mg portion of *O*-acyl-2-(α-L-aspartylamino)alkanol was dissolved in 5 ml of water. Various concentrations of aqueous solutions of sucrose (2, 4, 6, 8, 10, and 12%) were prepared as standard solutions. Every paneler kept 5 ml of the samples in his mouth for 5 s and compared the relative potencies of sweetness with that of the standard solution. When the potency of sweetness of a sample was higher than that of the standard solution, the solution of the sample was diluted more than twice in order to obtain the potency of sweetness more exactly.

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