and angles are within chemically reasonable limits.

Acknowledgment. We gratefully acknowledge the contributions of Dr. James P. Springer for the crystal-structure determination, Dr. Anthony King and his colleagues (MSDRL Rahway, NJ) for carrying out the high-pressure hydrogenation reactions, Dr. Steve Pitzenberger for expert NMR help, Drs. Paul Reider, Len Weinstock, and co-workers for valuable starting materials, John Moreau for elemental analyses, and Vera W. Finley for typing the manuscript.

Supplementary Material Available: Tables containing the fractional coordinates, temperature parameters, bond distances, and bond angles for the maleate salt of **2** (4 pages). Ordering information is given on any current masthead page.

High Potency Dipeptide Sweeteners. 1. L-Aspartyl-D-phenylglycine Esters

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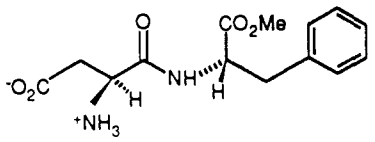
Twenty esters of L-aspartyl-D-phenylglycine, as well as two substituted analogues, an o-fluoro and a p-hydroxyphenylglycine ester, were prepared. The L-aspartyl-D-phenylglycine (−)-α- and (+)-β-fenchyl esters had the highest sweetness potency at 1200 and 3700 times that of sucrose, respectively. The high potency of these sweeteners is surprising as the phenyl group occupies a position previously believed to accommodate only much smaller groups.

Since the accidental discovery of aspartame (1) at the G. D. Searle laboratories in 1965,[1] there has been an enormous amount of work to examine the scope and potential of this promising class of sweeteners.[2] Systematic



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variations in the component parts of aspartame have shown that for sweetness the following hold true.

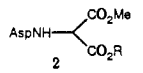
1. Few changes are allowed in the N-terminal aspartic acid. Hydrogen bonding to the sweet receptor with the NH_3^+ group as a donor and the CO_2^- as an acceptor is generally thought to be critical for sweetness.[1,3] The methylene group may be deleted (aminomalonic acid for aspartic acid), but an extra methylene group (glutamic acid for aspartic acid) eliminates sweetness. The curious early observation that the α-amino group can be trifluoroacetylated[5a] has recently been extended to include *N*-(*N'*-formyl)carbamoyl[5b], *N*-4-substituted-phenylcarbamoyl, -thiocarbamoyl, and *N*-cyanoguanidino derivatives,[5c] and amino acid amides.[5d]

2. The peptide bond cannot be inverted, methylated, or replaced by an ester.[6]

Table I. Known High Potency Dipeptide Sweeteners

R_1	R_2	sweetener	ref
CH_3	CO_2R	L-aspartyl-D-alanine esters	9a,b
CH_3	CONHR	L-aspartyl-D-alanine amides	10
CH_2OH	CONHR	L-aspartyl-D-serine amides	11
CO_2Me	CO_2R	L-aspartyl-D,L-aminomalonic acid diesters	12a–e
$CONMe_2$	CO_2R	L-aspartyl-D,L-aminomalonic acid ester amides	13

Table II. L-Aspartyl-D,L-aminomalonic acid diesters[12]



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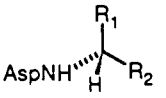
	R	sweetness potency
a)	 (−)-α	30000
b)	 (+)-α	1000
c)	 (−)-β	5000
d)	 (+)-β	50000

3. Proper stereochemistry at the existing chiral centers is critical. For example, of the four possible diastereomers for aspartylphenylalanine methyl ester only the L,L (aspartame) is sweet.[1]

4. Many changes are tolerated in the C-terminal part of the sweetener provided that the small and large R groups occupy the positions shown below.[1c,6a,7]



R_1 = small "upper" group

R_2 = large "lower" group

(1) (a) Mazur, R. H.; Schlatter, J. M.; Goldkamp, A. H. *J. Am. Chem. Soc.* **1969**, *91*, 2684. (b) Mazur, R. H.; Goldkamp, A. H.; James, P. A.; Schlatter, J. M. *J. Med. Chem.* **1970**, *13*, 1217. (c) Mazur, R. H.; Reuter, J. A.; Swiatek, K. A.; Schlatter, J. M. *J. Med. Chem.* **1973**, *16*, 1284.

(2) For reviews see: Pavlova, L. A.; Komarova, T. V.; Davidovich, Yu. A.; Rogozhin, S. V. *Russ. Chem. Rev.* **1981**, *50*, 316. Crosby, G. A.; DuBois, G. E.; Wingard, R. E., Jr. In *Drug Design*; Ariens, E. J., Ed.; Academic Press: New York, 1979; Vol. VIII, p 215. Ariyoshi, Y. *Kagaku Kyoiku* **1983**, *31*, 12.

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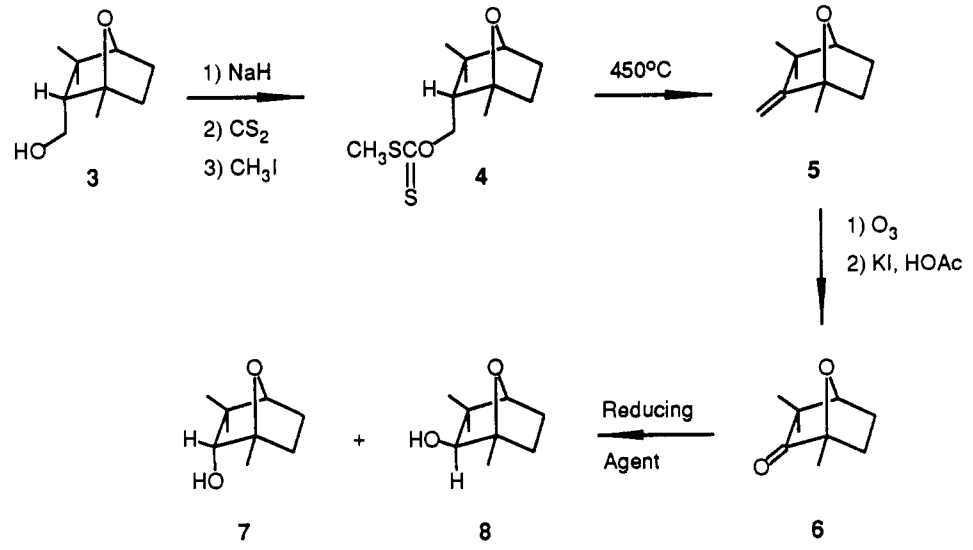
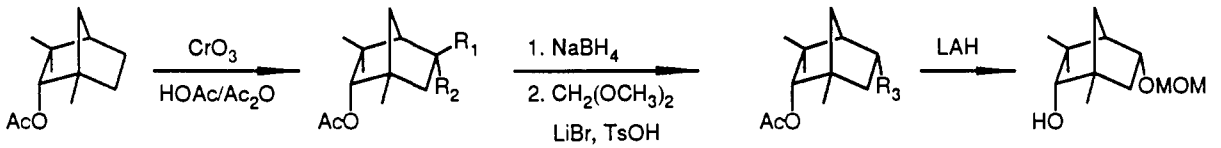
Scheme I



Scheme II



5. Many different functional groups can serve as R_1 and R_2 and it is the combination of the two groups that determines the sweetness potency.

Despite the fact that several hundred dipeptide-derived sweeteners have been prepared to date, fewer than 20 have potencies >1000 times that of sucrose.[8] These sweeteners have a bulky amide or ester group as R_2 with a variety of R_1 groups as shown in Table I.

The L-aspartyl-D,L-aminomalonic acid diesters **2** were the first compounds in this category to be reported and remain the most potently sweet dipeptides known (Table II).

These compounds are considerably less stable than aspartame,[9a] which limits their utility. To overcome this limitation, we chose to replace the labile methyl ester with stable groups. We reasoned that the sp^2 center and relatively flat shape of the ester might be important for sweetness. Our replacements are planar groups directly attached via an sp^2 center. This report summarizes our results with L-aspartyl-D-phenylglycine esters.[14]

Chemistry

Many of the requisite alcohols were available via literature procedures as described in the Experimental Section. 7-Oxafenchols **7** and **8** were prepared by dehomologation of (±)-*endo*-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane-2-methanol (**3**)[15] which was prepared according to the procedure of Yamada et al.[15c] (Scheme I). Although racemic **3** is only one of three products obtained from this oxidative rearrangement of geraniol, the reaction could be run efficiently on a large scale and the products could be separated chromatographically. Alcohol **3** was converted to *S*-methyl xanthate **4**, which was converted by vapor-phase pyrolysis[16] to olefin **5**. Ozonolysis of **5** followed by a standard workup procedure[17] afforded ketone **6**. Selective reduction with lithium aluminum hydride gave racemic α-alcohol **7** (95/5 α/β) while L-Selectride[33] gave β-alcohol **8** (95/5 β/α).

Hydroxylated fenchol derivative **14** was prepared in protected form by extending chemistry that was precedented in the borneol family of terpene alcohols (Scheme II). Remote oxidation[18] of (−)-α-fenchyl acetate **9** (CrO_3/HOAc/Ac_2O) afforded **10** and **11** (85:15 ratio), which were separated by flash chromatography. ^1H and ^{13}C NMR were used to distinguish **10** and **11**.[19] Reduction

(7) Ariyoshi, Y. *Agric. Biol. Chem.* **1976**, *40*, 983.
(8) This analysis excludes aspartyl-modified dipeptides which can have intensities >1000 times that of sucrose.[5c]
(9) (a) Nagakura, A.; Yuasa, Y.; Tsuruta, H.; Akutagawa, S. Japanese Patent 61-291,596, 61-291,597, 1986. (b) Zanno, P. R.; Roy, G. M.; Barnett, R. E. European Patent Application 256,475, 1988.
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(14) Janusz, J. M.; Gardlik, J. M. U.S. Patent 4,677,126, 1987. Janusz, J. M. U.S. Patent 4,692,512, 1987.
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(17) Meinwald, J.; Gassman, P. G. *J. Am. Chem. Soc.* **1960**, *82*, 5445.
(18) Darby, N.; Lamb, N.; Money, T. *Can. J. Chem.* **1979**, *57*, 742.

Table III. Physical Properties of Sweeteners 21–42

compound number[f]	method of final purification (% yield)	mp, °C	$[\alpha]_D$,[a] deg	diastereomer ratio (HPLC)[b]	HRMS[c]
21[d]	recryst CH_3CN (44%)	126–128	−20.0	12:88	$C_{18}H_{27}N_2O_5$
22[d]	recryst 5/1 EtOH/MeOH (75%)	178.5–179	−75.7	7:90:2	$C_{19}H_{27}N_2O_5$
22[e]	none[i] (quantitative)	198–200	−79.4	24:76	$C_{19}H_{27}N_2O_5$
23[d]	recryst MeOH (22%)	188–191	−74.3	19:78:3	$C_{20}H_{29}N_2O_5$
24[e]	RP MPLC[j] 3:1 MeOH/H_2O, then flash chromat[k] on silica gel using 17:81:1:2 MeOH/$CHCl_3$/HOAc/H_2O (55%)	133–135	−61.8	5:95	$C_{21}H_{31}N_2O_5$
25[e,g]	recryst EtOAc/hexane (21%)	169.5–170	−44.6	8:88:5	$C_{19}H_{27}N_2O_5S$
26[d]	flash chromat[k] on silica gel using 92:8 EtOH/H_2O, then flash chromat[k] on silica gel using 40:60:1 MeOH/$CHCl_3$/HOAc (24%)	77–79	−15.7	15:23:62	$C_{19}H_{25}N_2O_5$
27[d]	RP MPLC[j] 45:55 MeOH/H_2O, then 80:20 MeOH/H_2O (51%)	119–132	−5.8	52:48	
28[d]	none[i] (quantitative)	130–150	−51.6	14:40:45	$C_{19}H_{25}N_2O_5$
29[e]	recryst MeOH/H_2O (86%)	176–177	−103.2	100	$C_{22}H_{31}N_2O_5$
30[d,h]	ion-exchange chromat,[m] then RP MPLC[j] 3:1 MeOH/H_2O (47%)	146–155	−2.3	41:57	$C_{22}H_{31}N_2O_5$[h]
31[e]	flash chromat[k] on silica gel using 99:1 EtOH/HOAc, then RP MPLC[j] 70:30 MeOH/H_2O (57%)	125–128	−40.0	9:91	$C_{22}H_{31}N_2O_5$
32[e]	activated carbon in MeOH (74%)	156–165	−65.9	12:88	$C_{22}H_{31}N_2O_5$
33[d]	flash chromat[k] on silica gel using 95:5 EtOH/H_2O	132–135	−42.9	34:66	$C_{22}H_{31}N_2O_5$
34[e]	recryst MeOH/EtOAc (66%)	164–165	−33.8	100	$C_{21}H_{28}N_2O_6$
35[e]	recryst Et_2O/hexane (79%)	109–112.5	−27.7	6:94	$C_{21}H_{28}N_2O_6$
36[e]	recryst MeOH/Et_2O (58%)	178–181		100	$C_{21}H_{28}N_2O_6$
37[e]	recryst MeOH/EtOAc (42%)	185–186.5		100	$C_{21}H_{28}N_2O_6$
38[e]	none[i] (89%)			50:50	$C_{22}H_{30}N_2O_6$
39[e]	prep HPLC[l] using 50:50 MeOH/0.02 M NaOAc in H_2O (pH adjusted to 5.4 with HOAc)			2:98	$C_{22}H_{30}N_2O_6$
40[e]	none[i] (88%)			50:50	$C_{20}H_{24}N_2O_6$
41[e]	RP MPLC[j] 60:40 MeOH/H_2O, then flash chromat[k] on silica gel using 35:65:1:2 MeOH/$CHCl_3$/H_2O/HOAc, then RP MPLC[j] 60:40 MeOH/H_2O (7%)	140–142	−80.0	9:88	$C_{22}H_{31}N_2O_6$
42[d]	none[i] (97%)	123–124	−13.2	51:49	$C_{22}H_{30}N_2O_5F$

[a] Recorded at room temperature in methanol at concentrations ranging from 0.1 to 4.5 g/100 mL, in most cases 0.1–1.0 g/100 mL. [b] The values represent the percent composition of each component in the order eluted. The analytical HPLC was carried out using a C-18 reverse-phase column by monitoring the eluent by UV detection at 210 or 254 nm. Complete details are available in the supplementary material. [c] All of the indicated compounds gave experimental accurate mass values to within 11 ppm of their calculated values. [d] The benzyloxycarbonyl group was used to protect the amino group of phenylglycine during the esterification step. [e] The (*o*-nitrophenyl)sulfenyl group was used to protect the amino group of phenylglycine during the esterification step. [f] N-Cbz-β-Bzl-L-Asp-*p*-NO_2-phenyl ester was used in the final coupling reaction unless otherwise indicated. [g] *N*-(Thiocarboxy)-L-aspartic anhydride was used in the final coupling reaction. See ref 37. [h] N-Boc-β-Bzl-L-Asp-*p*-NO_2-phenyl ester was used in the final coupling reaction. [i] The deprotection step was sufficiently clean to eliminate the need for purification of the final sweetener. [j] An EM Reagents Lobar LiChroprep RP-8 Size B column was used for the RP MPLC. [k] See ref 29. [l] A Whatman Magnum 9 ODS-3 column was used. [m] Dowex 50W-X8 resin (H^+ form) was used.

of **10** with $NaBH_4$ produced *endo*-alcohol **12**, which was protected as its methoxymethyl ether **13** (dimethoxymethane/LiBr/*p*-TSA).[20] Cleavage of the acetate ester (LAH/ether) afforded the desired alcohol **14** with the remote hydroxyl group suitably protected.

The alcohols were coupled with D-phenylglycine by using two routes differing only in the N-protecting group (Scheme III). Our earlier method involved benzyloxycarbonyl (Z) protected[21] D-phenylglycine **15**. Low-temperature dicyclohexylcarbodiimide (DCC) coupling promoted by catalytic 4-(dimethylamino)pyridine (DMAP)[22] provided amines **19** after hydrogenolysis. However, we noted that, on conversion to (−)-α-fenchol-derived sweetener **29**, a 3/1 diastereomeric mixture of products was obtained, suggesting partial racemization at the phenylglycine center. Repetition of the DCC/DMAP coupling in the presence of a 10-fold excess of (−)-α-fenchol increased the diastereomeric ratio to 9/1. Likely mechanisms for the racemization at the phenylglycine center involve enolization[23a] or formation of an oxazolone which rapidly racemizes.[23b] Higher concentrations of fenchol intercept the activated D-phenylglycine before racemization.

Rather than use an excess of the alcohol component, we changed the N-protecting group to (*o*-nitrophenyl)sulfenyl (*o*-Nps),[24] which minimized racemization. DCC/DMAP coupling of *o*-Nps-D-phenylglycine (**17**) followed by deprotection with 5 N HCl in acetone gave amines **19**.

Coupling of the amines with *N*-(benzyloxycarbonyl)-β-benzyl-L-aspartic acid *p*-nitrophenyl ester[1,25] in THF occurred readily overnight to give diprotected sweeteners **20**. Hydrogenolysis of the protecting groups provided the free sweeteners **21–42** (Tables IV and V). Selected physical data for the sweeteners are given in Table III. The absolute stereochemistry of the oxafenchol sweeteners was tentatively assigned by indirect means. The diastereomeric diprotected L-aspartyl-D-phenylglycine (±)-α-7-oxafenchyl esters (**20n,o**) were separated by MPLC on silica. One of the diastereomers was treated with excess lithium aluminum hydride to cleave the ester linkages. Flash chromatography allowed the isolation of the resolved oxafen-

(19) The regiochemistry of the oxidation reaction was easily determined to have taken place at C-5 by comparing the ^{13}C chemical shifts of the adjacent bridgehead carbons in product **10** and in the starting material **9**. The chemical shift of C-4 in **9** is 48.3 ppm while the chemical shift of C-4 in **10** is 62.5 ppm, consistent with the presence of an oxo group at C-5. A similar effect was seen in ^{13}C NMR spectrum of **11**.

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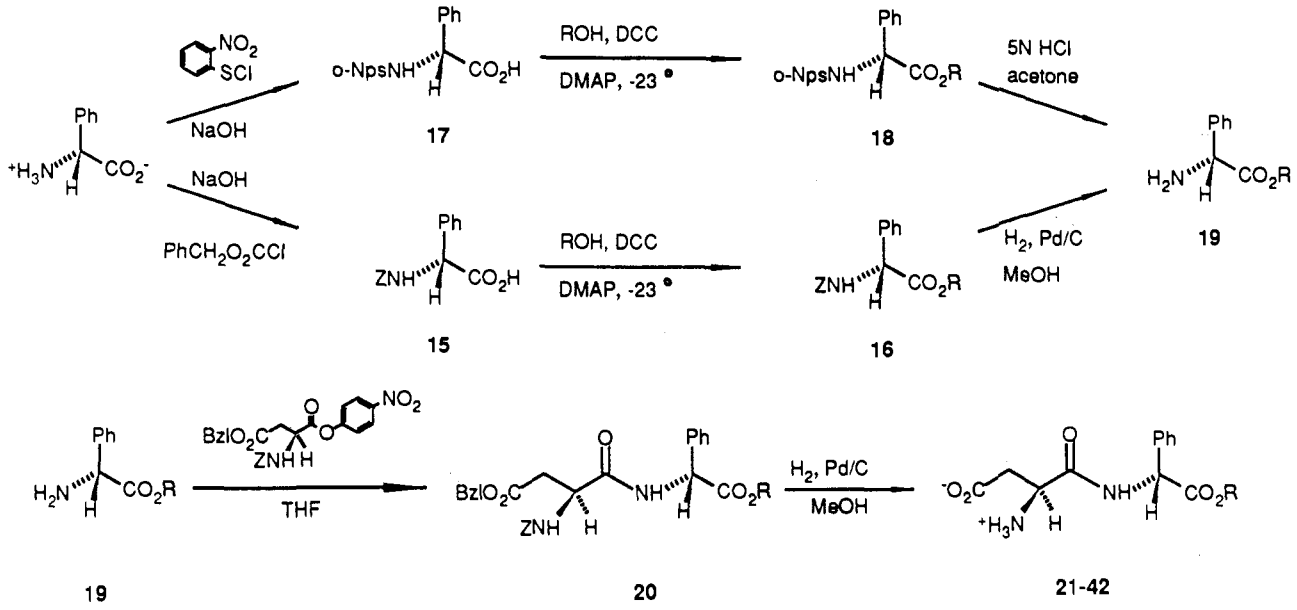
(25) (a) Bodanszky, M. *Nature* **1955**, *175*, 685. (b) Guttmann, S. *Helv. Chim. Acta* **1961**, *44*, 721.

Scheme III[a]

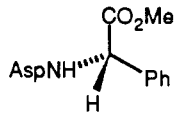


[a] The intermediates **16** and **18–20** are distinguished by their R groups and are assigned the letters a–v corresponding to the sweeteners **21–42**.

chyl alcohol, with an optical rotation of $[\alpha]_D$ +2.6°. This result proves that diprotected sweetener **35** contains the (+)-enantiomer of the starting oxafenchol, but it does not completely address the matter of its absolute configuration. However, ^{1}H NMR data and molecular mechanics calculations, which will be reported seaparately, show strong similarities between oxafenchyl sweeteners **34–37** and the corresponding fenchyl esters **29–32**, whose absolute configurations are known with certainty. These similarities suggest that the absolute configuration of the resolved alcohol above corresponds to the absolute configuration of (+)-α-fenchol.

Discussion

The structural requirements for sweet dipeptide derivatives enumerated at the outset require a small group in the R_1 position. The phenyl group in our phenylglycine esters is considerably larger than precedented R_1 groups. For example, among alkyl R_1 groups, methyl generally leads to higher potency than larger alkyl groups.[1b,c,10] Similarly, aspartame is more potent than analogous dipeptides with ethyl or propyl (vs methyl) esters.[1a] Phenylglycine is a lower homologue of phenylalanine and, not surprisingly, sweet L-aspartyl-L-phenylglycine esters are known.[26] For example, dipeptide **43**, a lower homologue



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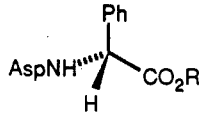


44

of aspartame, is claimed to be 175 times more potent than sucrose.[26b] In these compounds, the ester moiety is the small R_1 group and phenyl is the large R_2 group. In L-aspartyl-D-phenylglycine sweeteners (**44**), the roles of R_1 and R_2 groups are reversed.

The compounds prepared are shown in Tables IV and V. The first column of Table IV gives the potency of sweeteners derived from acyclic and monocyclic alcohols. Acyclic sweetener **21** has low potency, which is likely a reflection of the similarity in size of the R_1 and R_2 groups. The monocyclic compounds **22–25** all have methyl substitution α to the CO_2CH, which is known to increase potency.[12a] These cyclic branched esters all have similar potencies in the range of 200–400 times that of sucrose. While the tetramethylthietane group provided the highest potency for L-aspartyl-D-alanine amides,[10] here sweetener **25** had a potency similar to that of the other monocyclic sweeteners.

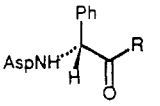
The remaining compounds in Table IV and V derive from bicyclic or, in one case, tricyclic alcohols. The increased rigidity of these alcohols may be another factor related to potency in addition to the methyl substitution mentioned above, and we systematically examined each factor. The (±)-*endo*-2-norborneol-derived sweetener **26** had very low potency, suggesting that the rigid bicyclic framework alone was insufficient to impart highly potent sweetness. *Exo*-methyl substitution at C-2 in **27** increased the potency somewhat. Inverting the stereochemistry at C-2 in **28** with (±)-*exo*-2-norborneol gave a significant increase in potency although branched monocyclic compounds **22–25** were still more potent. We then prepared all four diastereomeric fenchol-based sweeteners to examine the importance of branching and to extend the exo versus endo comparison made in the norbornyl system. The potency among the diastereomers varied over 17-fold. Exo isomer **32** was more potent than the corresponding endo isomer **30** although the reverse was true for **31** vs **29**. The sweeteners **29** and **32** from (−)-α and (+)-β-fenchols were the most potent, with potencies of 1200 and 3700 times that of sucrose, respectively. Diastereomeric sweeteners **29–32** should have similar physical properties and we attribute the differences in potency primarily to conformational differences.[27]

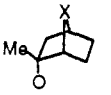
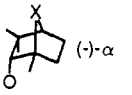
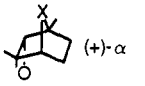
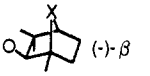
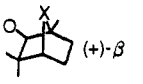
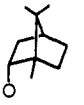
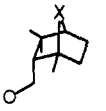
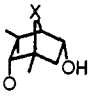
At the time we began our work, we were unaware of the Chinese work[12c] with the diastereomeric L-aspartyl-D,L-aminomalonic acid diesters **2a–d**. The relative sweetness

(26) (a) Jolles, G. German Patent 2,102,988, 1971. (b) Dahlmans, J. J.; Boesten, W. H. J. *Neth. Patent* 70-12,899, 1972. (c) Moriarty, C. L.; Tritsch, G. L. U.S. Patent 3,972,860, 1976.

(27) Detailed NMR and molecular mechanics studies on the conformational preferences of these sweeteners will be reported separately.

Table IV. L-Aspartyl-D-phenylglycine Esters



compd	R	potency[a]	compd	R	potency[a] X = CH_2	potency[a] X = O
21	OCH(Me)-*t*-Bu	30 ± 20	26		20 ± 10	
22		380 ± 30	27		40	
23		210 ± 40	28		180 ± 60	
24		190 ± 70	29, 34		1200 ± 300	700
25		300	30, 35		220 ± 40	70
			31, 36		480 ± 160	40
			32, 37		3700 ± 1100	400
			33		0	
			38			0
			39		100	
			40		80	

[a] Sweetness potency vs 5–10% sucrose. Data are mean ± the 95% confidence limits. See the Experimental Section for details.

potency among diastereomers **29–32** and **2a–d** are the same. The importance of the position of the methyl groups on the bicyclic framework can be seen by comparing fenchyl sweetener **29** with isomeric bornyl compound **33**. In this case, the shift of the geminal methyl groups to the one carbon bridge eliminates sweetness.

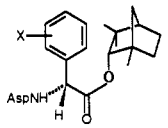
While the potency of fenchyl esters **29** and **32** is high, their time–intensity profile (TIP) differs from that of sucrose. The fenchyl esters show a slightly delayed onset of sweetness and a persistent sweet aftertaste. A qualitative relationship between persistence and hydrophobicity was noted. For this reason, we prepared a series of sweeteners from more hydrophilic bicyclic alcohols to examine the effect on the TIP and potency. While oxafenchyl esters **34–37** showed a TIP considerably more like that of sucrose, the potency decreased by factors of 2–10, with (−)-α-isomer **34** being the most potent at 700 times sucrose. This sweetener is still three times more potent than aspartame, but the lack of a ready source of oxafenchol precludes further development. Nonetheless, the increase in hydrophilicity did improve the TIP.

Synthetic precursor **3** (Scheme I) to the oxafenchols was also used to prepare dipepetide **38**. This compound was not sweet probably due to the increased size and conformational flexibility with the addition of an extra methylene group.

Introduction of oxygen at other positions on the bicyclic framework was briefly examined. Sweetener **39** derived from *endo*-5-hydroxy-(−)-α-fenchol (from **14**, Scheme II) was about 12 times less potent than the corresponding fenchyl sweetener **29**. Carbon substitution at C-5 in the form of a tricyclic ether (**40**) gave about half the potency of the closely related *exo*-norbornyl sweetener **28**. Sweeteners **39** and **40** demonstrate that substitution on the remote two-carbon bridge still provides sweet compounds although of lower potency.

Substituted D-phenylglycines provided another way to increase hydrophilicity (Table V). L-Aspartyl-D-*p*-hydroxyphenylglycine (−)-α-fenchyl ester **41** showed an improved TIP, but again potency was reduced to about

Table V. L-Aspartyl-Substituted Phenylglycine Esters



compd	potency[a]
41, X = *p*-OH	420 ± 60
42, X = *o*-F	720 ± 160

[a] Sweetness potency vs 5–10% sucrose. Data are mean ± the 95% confidence limits. See the Experimental Section for details.

$^1/_3$ that of the unhydroxylated parent **29**. The extra length provided by the hydroxy group is likely responsible for the reduction in potency. *o*-Fluoro-D,L-phenylglycine (−)-α-fenchyl ester **42** was similar in potency and TIP with unfluorinated **29**. This observation is interesting in view of the quantitative structure–activity relationship (QSAR) studies of Iwamura,[28] who found that electron-withdrawing substituents at R_1 and R_2 increase sweetness potency. However, for **42**, the additional electron-withdrawal by the ortho fluorine had no such effect.

In summary, L-aspartyl-D-phenylglycine esters are a new class of highly potent dipeptide sweeteners. They are both more potent and more stable than aspartame. The phenylglycine and *p*-hydroxyphenylglycine groups can serve the role of the "small" hydrophobic group well despite their unprecedented size. The lingering sweet aftertaste of certain of these compounds can be reduced by increasing their hydrophilicity although potency also diminishes. An extension of this work to sweeteners derived from a variety of heteroaromatic-substituted glycines will be reported separately.

Experimental Section

Melting points were obtained with a Thomas-Hoover melting point apparatus or hot-stage microscope and are uncorrected. Optical rotations were obtained at room temperature in a 1-dm cell with a Rudolph Autopol III polarimeter. Infrared spectra were obtained with a Perkin-Elmer Model 298 infrared spectrophotometer. ^{1}H NMR spectra were obtained with either a Varian T-60 spectrometer, a JEOL FX-270 spectrometer, or a General Electric GN-500 spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained with a JEOL FX-270 spectrometer. ^{13}C Assignments were made on the basis of off-resonance decoupled spectra or INEPT spectra. Mass spectra were obtained on a Hewlett-Packard 5985B GC/MS system. High-resolution mass determinations were done with a ZAB-2F mass spectrometer in the peak-matching mode with nominal resolution of 10 000. GC analyses were obtained with a Hewlett-Packard 5830A gas chromatograph equipped with a 30 m J&W DB-1 capillary column. All TLC analyses were obtained in the indicated solvent systems with Analtech Uniplates, Silica gel GF or GHLF; the plates were visualized by dipping them in either a 5% solution of phosphomolybdic acid in 2-propanol or a 10% solution of vanillin in 95:5 ethanol/sulfuric acid or by spraying with a 0.5% solution of ninhydrin in 99:1 butanol/acetic acid and heating them on a hot plate until no further spots appeared. Flash chromatography was carried out according to the method of Still.[29] HPLC analyses were obtained with a modular isocratic system. Normal-phase analyses were run on a 25 cm × 4.6 mm i.d. Altex Ultrasphere Si (5 μm) column. Reverse-phase analyses were run on 25 cm × 4.6 mm i.d. Altex Ultrasphere ODS (5 μm), Rainin Microsorb (5 μm), Whatman ODS-3 (10 μm), or Waters μ-Bondapak C-18 (10 μm) columns. Mobile phases for all reverse-phase analyses were prepared by diluting the appropriate amount of a concentrated aqueous buffer solution (0.5 M Na_2HPO_4, pH adjusted to 6 with phosphoric acid) with the proper amount of water and methanol or acetonitrile needed to produce a final buffer concentration of 0.01 M. For both normal and reverse-phase analyses, UV detection at 210 or 254 nm was used. Preparative HPLC was carried out with the same system on a Whatman Magnum 9 ODS-3 column while the eluent was monitored with a Knauer refractive index detector. The solvents were prepared as described for analytical HPLC above except that NH_4OAc was used as a volatile buffer. Compounds were isolated by freeze drying. Reversed-phase MPLC was done with a Lobar LiChroprep RP-8 column (size B, 310 × 25 mm, Merck).

Dry THF and dry ether were obtained by distillation from sodium/benzophenone under argon immediately before use. Dry dichloromethane was obtained by distillation from calcium hydride. Elemental analyses were obtained from Galbraith Laboratories, Inc., Knoxville, TN.

Taste Panels. All compounds were first tested for acute toxicity via a single oral dose in the rat. The potency of the aspartic acid amides was determined by taste comparisons with sucrose standards. Five to ten expert male panelists were asked to taste and spit 10 mL of a sweetener solution and to rate the sweetness potency and quality versus five standard sucrose solutions ranging from 0.04 M (1.4%) to 0.35 M (12.0%). The concentration of the test sweetener was generally equivalent to 5–10% sucrose. The ratio of the sucrose concentration perceived as equally sweet to the actual concentration of the test sweetener is the sweetness potency quoted in this report. The data are presented as the mean ± the 95% confidence limit. Informal tastings with two or three panelists were done in the same way when there was insufficient sample for a larger panel. In these cases, the potency is an estimate and is given as the mean.

Starting Materials. I. Alcohols. The following alcohols were commercially available: 2,6-dimethylcyclohexanol, 3,3-dimethyl-2-butanol, *endo*-norborneol, *exo*-norborneol, and (−)-borneol were from Aldrich; (+)-α-fenchol was from Aldrich or Pfaltz & Bauer as a 94/6 α/β mixture, $[\alpha]_D$ +10.7° (*c* 1.0, ethanol) [lit.[30a] $[\alpha]_D$ +10.5° (ethanol)]. The following alcohols were prepared by lithium aluminum hydride reduction (Et_2O, 0°C) of the corresponding ketones: 2,5-dimethylcyclopentanol (ketone from Aldrich); 2,2,5,5-tetramethylcyclopentanol (ketone prepared from cyclopentanone[10]); (−)-α-fenchol, $[\alpha]_D$ −12.4° (c 3.2, ethanol) [lit.[30b] $[\alpha]_D$ −12.7° (c 3.0, 95% ethanol)], from (+)-fenchone (Fluka), $[\alpha]_D$ +65.5° (c 5.0, ethanol); and 2,2,4,4-tetramethylthietan-3-ol (ketone prepared from diisopropyl ketone[10]). *Exo*-2-methyl-*endo*-2-norborneol was prepared by methyl Grignard addition to norcamphor.[31] The β-fenchols were prepared by reduction of (+)- or (−)-fenchone with aluminum isopropoxide[30a] or copper chromite/H_2.[30b] Details are given below.

(−)-β-Fenchol.[30a] (+)-Fenchone (50 g, 0.33 mol) was dissolved in 225 mL of dry toluene, and aluminum isopropoxide (67 g, 0.33 mol) was then added. The mixture was refluxed for 5 days. On days 3–5, toluene was allowed to distill off to remove any 2-propanol formed; the solvent volume was maintained by the addition of fresh dry toluene. More aluminum isopropoxide (50 g) was added and the reaction was continued as described above for two more days. Workup gave 48 g of crude product. Analysis by GC (program 60 °C to 90 °C at 5 °C/min) showed a 41/26/33 ratio of (+)-fenchone/(−)-α-fenchol/(−)-β-fenchol. The (−)-β-fenchol was isolated by preparative liquid chromatography with a Waters Prep LC/system 500 equipped with two PrepPak-500 silica gel cartridges using RI detection with methyl *tert*-butyl ether/hexane (14/86) as the eluting solvent. Two passes afforded 94% pure (−)-β-fenchol (β/α = 94/6): $[\alpha]_D$ −25.7° (*c* 4.9, methanol), [lit.[30a] $[\alpha]_D$ −21.8° (*c* 4, ethanol, 94.4% pure)]; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.00–1.84 (m, 7 H), 2.93 (br s, 1 H, C*H*OH).

(+)-β-Fenchol. By the procedure outlined above, 50 g of (−)-fenchone [Aldrich, $[\alpha]_D$ −51.1° (*c* 5.4, ethanol)] was converted to 45 g of crude product, which was a 52/16/32 mixture of (−)-fenchone/(+)-α-fenchol/(+)-β-fenchol.

An alternative catalytic procedure was also used.[30b] Copper chromite (0.5 g) in 25 mL of methanol was activated by heating

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(30) (a) Coulombeau, A.; Rassat, A. *Bull. Soc. Chim. Fr.* **1965**, 3338. (b) Doering, W. von E.; Aschner, T. C. *J. Am. Chem. Soc.* **1949**, *71*, 838.
(31) Sauers, R. R. *J. Am. Chem. Soc.* **1959**, *81*, 4873.

to 125 °C under 1600 psi of H_2 for 10 min. After cooling, (−)-fenchone (10 g, 0.066 mol) in 25 mL of methanol was added. The reaction mixture was heated at 175 °C under a hydrogen pressure of 2900 psi for 19 h. The reaction mixture was cooled, the catalyst was filtered off, and the methanol was evaporated to yield 8.7 g of product.

Analysis by GC showed a 3/61/37 ratio of (−)-fenchone/(+)-α-fenchol/(+)-β-fenchol. Chromatography of these two fenchone/fenchol mixtures as described for (−)-β-fenchol yielded 96.8% pure (+)-β-fenchol (β/α = 96.8/3.2): $[\alpha]_D$ +22.8° (c 4.2, methanol), [lit.[32] $[\alpha]_D$ +21.5° (c 5, ethanol)]; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 1.00–1.83 (m, 7 H), 2.92 (d, 1 H, J = 2 Hz, CHOH).

Route to (±)-*exo*/*endo*-2-Hydroxy-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane (7, 8; Scheme I). **(±)-*endo*-1,3,3-Trimethyl-7-oxabicyclo[2.2.1]heptane-2-methanol (3).** The procedure of Yamada et al.[15c] was used. Reaction of 4 g of geraniol gave 3.0 g of a dark liquid consisting of three components (10%, 50%, and 30%, respectively, using GC analysis). The three components were separated by medium-pressure liquid chromatography using 30% ethyl acetate in hexane. The first eluting component was the desired bicyclic alcohol **3**. This material was further purified by Kugelrohr distillation (90–105 °C, 1.0 mm) affording 0.54 g (12%) of **3** (95% purity, GC analysis) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.20–1.90 (m, 5 H, aliphatic), 2.00 (br s, 1 H, OH), 3.64 (m, 2 H, CH_2O), 3.82 (m, 1 H, bridgehead).

***S*-Methyl Xanthate Ester of (±)-*endo*-1,3,3-Trimethyl-7-oxabicyclo[2.2.1]heptane-2-methanol (4).** The procedure of Nace[16] was used to convert alcohol **3** (2.13 g, 12.6 mmol) to 2.78 g (85%) of xanthate ester **4** (purity 90%, GC analysis) as a yellow oil after Kugelrohr distillation. A sample for spectral and elemental analyses was purified by flash chromatography using 45% ether in pentane, followed by Kugelrohr distillation: IR (neat) 2960, 1220, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.20–2.00 (m, 5 H, aliphatic), 2.80 (s, 3 H, CH_3 on sulfur), 3.85 (br d, 1 H, bridgehead), 4.60 (br d, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$) δ 18.98 (CH_3), 19.32 (CH_3), 21.60 (CH_3), 26.43 (CH_2), 29.54 (CH_2), 31.76 (CH_3), 42.36 (quaternary), 54.74 (CH), 72.69 (CH_2), 85.89 (bridgehead CH), 86.64 (bridgehead quaternary), 215.70 (thiocarbonyl). Anal. ($C_{12}H_{20}S_2O_2$) C, H, S.

(±)-1,3,3-Trimethyl-2-methylene-7-oxabicyclo[2.2.1]heptane (5). Xanthate ester **4** (2.78 g, 10.7 mmol) was pyrolyzed[16] in the vapor phase at 450 °C (0.1 mm) by slow distillation into a glass tube packed with glass beads and heated in a cylindrical furnace. The pyrolysate was collected with two traps, in series, both cooled to −78 °C. The yellow pyrolysate, which contained a small amount of white solid, was dissolved in ether and filtered. The solvent was carefully evaporated, affording 1.27 g (78%) of olefin **5** as a yellow liquid (purity 90%, GC analysis): IR (neat) 2980, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 1.20–2.00 (m, 4 H, aliphatic), 3.90 (br d, 1 H, bridgehead), 4.65 (d, 2 H, J = 10 Hz, olefinic); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_3), 23.9 (CH_3), 26.0 (CH_2), 28.8 (CH_3), 35.8 (CH_2), 46.0 (quaternary), 84.7 (bridgehead), 86.7 (bridgehead quaternary), 98.1 (olefinic CH_2), 165.0 (olefinic).

(±)-1,3,3-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-one (6). Ozonolysis via the procedure of Meinwald and Gassman[17] was used to convert **5** (1.20 g, 7.9 mmol) into 1.12 g (92%) of ketone **6** as a yellow liquid (purity 80%, GC analysis) which was used for the next step without further purification. A sample for spectral and elemental analysis was purified by flash chromatography using 7% ether in pentane, followed by Kugelrohr distillation: IR (neat) 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.60–2.20 (m, 4 H, aliphatic), 4.15 (m, 1 H, bridgehead); ^{13}C NMR ($CDCl_3$) δ 14.9 (CH_3), 20.1 (CH_3), 23.0 (CH_3) 25.6 (CH_2), 31.2 (CH_2), 49.0 (quaternary), 83.8 (bridgehead CH), 86.1 (bridgehead quaternary), 217.9 (carbonyl). Anal. ($C_9H_{14}O_2$) C, H.

(±)-*endo*-2-Hydroxy-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane (7). Ketone **6** (1.1 g, 7.1 mmol) in 50 mL of dry THF at 0 °C was reduced with 15.0 mL of a 1 M solution of lithium aluminum hydride in ether at 0 °C for 0.5 h. After warming to room temperature, the reaction was carefully quenched with saturated sodium sulfate solution and filtered. The filtrate was evaporated and the residue was purified by Kugelrohr distillation (90–100 °C, 1.0 mm) affording 0.82 g (74%) of a colorless oil, which was a 95:5 mixture of *endo*-alcohol **7** and *exo*-alcohol **8** (GC analysis). A sample for spectral and elemental analyses was purified by flash chromatography using 45% ether in pentane, followed by Kugelrohr distillation: IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.60–2.20 (m, 4 H, aliphatic), 2.35 (br s, 1 H, OH), 3.28 (d, 1 H, J = 1.4 Hz, CHOH), 3.92 (m, 1 H, bridgehead); ^{13}C NMR ($CDCl_3$) δ 18.8 (CH_3), 19.9 (CH_3), 26.5 (CH_2), 26.7 (CH_2), 29.8 (CH_3), 41.8 (quaternary), 83.9 (CH), 86.4 (CH), 86.7 (quaternary). Anal. ($C_9H_{16}O_2$) C, H.

(±)-*exo*-2-Hydroxy-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane (8). Ketone **6** (0.50 g, 3.2 mmol) in 10 mL of dry THF cooled to −78 °C was reduced with 10.0 mL of a 1 M solution of L-Selectride in THF.[33] Workup gave 0.39 g (78%) of 95:5 mixture of *exo*-alcohol **8** and *endo*-alcohol **7** after Kugelrohr distillation (65 °C, 1.0 mm). A sample for spectral and elemental analyses was purified by flash chromatography using 45% ether in pentane, followed by Kugelrohr distillation: IR (neat) 3440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 6 H, CH_3's), 1.45 (s, 3 H, CH_3), 1.50–1.80 (m, 4 H, aliphatic), 1.88 (br d, 1 H, J = 10 Hz, OH), 3.27 (d, 1 H, J = 10 Hz, CHOH), 3.95 (m, 1 H, bridgehead); ^{13}C NMR ($CDCl_3$, INEPT) δ 16.7 (CH_3), 21.9 (CH_3), 24.7 (CH_3), 26.2 (CH_2), 32.8 (CH_2), 46.5 (quaternary), 84.7 (CH), 85.3 (CH), 87.5 (bridgehead quaternary). Anal. ($C_9H_{16}O_2$) C, H.

Route to *endo*-5-[(Methoxymethyl)oxy]-(−)-α-fenchol (14; Scheme II). **(−)-α-Fenchyl Acetate (9).** (−)-α-Fenchol (5.0 g, 32.4 mmol) was converted to the acetate by the method of Cousineau et al.[34] Kugelrohr distillation (75 °C, 1.0 mm) of the crude product gave 4.75 g (75%) of **9** as a colorless liquid: $[\alpha]_D$ −58.9° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.77 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.20–1.90 (m, 7 H, aliphatic), 2.08 (s, 3 H, acetate CH_3), 4.40 (m, 1 H, CHO); ^{13}C NMR ($CDCl_3$, INEPT) δ 19.3 (CH_3), 20.0 (CH_3), 20.9 (CH_3), 25.8 (CH_2), 26.5 (CH_2), 29.7 (CH_3), 39.4 (quaternary), 41.3 (CH_2), 48.1 (bridgehead quaternary), 48.3 (bridgehead CH), 86.1 (C α to ester O), 171.5 (carbonyl).

5-Oxo-(−)-α-fenchyl Acetate (10). Fenchyl acetate **9** (4.5 g, 23 mmol) was oxidized with CrO_3/HOAc/Ac_2O via the procedure of Darby et al.[18] Workup gave a yellow liquid which contained two products in ratio of 85:15 (GC analysis). The products were separated by flash chromatography using 20% ether in hexane. The first eluting material, the minor product, was purified by Kugelrohr distillation (100 °C, 1.0 mm) to afford 0.6 g (10%) of **11** as a colorless liquid: IR (neat) 1735, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.55 (br s, 2 H, aliphatic), 1.90 (br s, 2 H, aliphatic), 2.03 (s, 3 H, acetate CH_3), 2.10 (s, 3 H, acetate CH_3), 4.40 (m, 1 H, CHO), 5.05 (br d, 1 H, J = 8 Hz, CHO); ^{13}C NMR ($CDCl_3$, INEPT), δ 18.5 (CH_3), 19.2 (CH_3), 20.7 (CH_3), 21.3 (CH_3), 29.4 (CH_3), 37.0 (CH_2), 37.6 (CH_2), 39.1 (quaternary), 47.4 (bridgehead quaternary), 52.8 (bridgehead CH), 74.9 (C α to ester O), 84.5 (C α to ester O), 170.6 (carbonyl), 171.2 (carbonyl).

The second eluting material, the major product, was purified by Kugelrohr distillation (100 °C, 1.0 mm) affording 2.48 g (52%) of **10** as a colorless liquid which solidified on standing: IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.57 (d, 1 H, J = 11.2 Hz, H on C_7 syn to the carbonyl group), 1.76 (d, 1 H, J = 18.1 Hz, exo H on C_6), 1.92 (dd, 1 H, J = 11.2 Hz, J = 4.3 Hz, H on C_7 anti to the carbonyl group), 2.10 (s, 3 H, acetate CH_3), 2.17 (s, 1 H, bridgehead), 2.40 (dd, 1 H, J = 18.1 Hz, J = 4.3 Hz, endo H on C_6), 4.59 (s, 1 H, CHOAc); ^{13}C NMR ($CDCl_3$, INEPT) δ 18.9 (CH_3), 20.4 (CH_3), 20.8 (CH_3), 28.0 (CH_3), 38.7 (CH_2), 40.4 (quaternary), 43.2 (CH_2), 46.3 (bridgehead quaternary), 62.5 (bridgehead CH), 83.6 (C α

(32) Guenther, E.; Althausen, D. *The Essential Oils*; D. Van Nostrand: New York, 1949; Vol. 2, p 254. Rotations for all four fenchols are given.

(33) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(34) Cousineau, T. J.; Cook, S. L.; Secrist, J. A., III *Synth. Commun.* **1979**, *9*, 157.

to ester O), 170.7 (ester carbonyl), 214.8 (ketone carbonyl).

***endo*-5-Hydroxy-(−)-α-fenchyl Acetate (12).** Ketone **10** (2.82 g, 13.4 mmol) in 50 mL of EtOH was reduced with sodium borohydride (2.03 g, 53 mmol) at 0 °C. Flash chromatography using 35% ether in hexane gave 2.39 g (84%) of **12** as a viscous liquid: IR (neat) 3440, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.20–1.90 (m, 5 H, aliphatic), 2.10 (s, 4 H, acetate CH_3 and OH), 4.10–4.60 (m, 2 H, CHO's).

***endo*-5-[(Methoxymethyl)oxy]-(−)-α-fenchyl Acetate (13).** Hydroxyfenchyl acetate **12** (2.34 g, 11 mmol) was converted to the MOM ether via the procedure of Gras et al.[20] Flash chromatography using 10% ether in hexane gave 2.08 g (74%) of **13** which was greater than 95% pure (GC analysis): ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.20–1.90 (m, 5 H, aliphatic), 2.08 (s, 3 H, acetate CH_3), 3.35 (s, 3 H, OCH_3), 4.15 (dq, 1 H, X part of an ABCX spin system, J_{ax} = 11 Hz, J_{bx} = 3 Hz, J_{cx} = 3 Hz, H α to MOM), 4.45 (m, 1 H, CHO), 4.60 (s, 2 H, OCH_2O).

***endo*-5-[(Methoxymethyl)oxy]-(−)-α-fenchol (14).** Reduction of **13** (2.08 g, 8.13 mmol) with 1 M lithium aluminum hydride in ether (24.4 mL, 24.4 mmol) at room temperature for 30 min followed by a saturated aqueous Na_2SO_4 quench gave 1.63 g (94%) of 14 as a colorless liquid which was greater than 90% pure (GC analysis): ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.15–2.00 (m, 6 H, aliphatic and hydroxyl), 3.35 (s, 4 H, OCH_3 and C*H*OH), 4.10 (dq, 1 H, X part of an ABCX spin system, J_{ax} = 11 Hz, J_{bx} = 3 Hz, J_{cx} = 3 Hz, H α to MOM), 4.60 (s, 2 H, OCH_2O).

II. Amino Acids and Derivatives. The following amino acids were commercially available: D-phenylglycine, D-*p*-hydroxyphenylglycine, and D,L-*o*-fluorophenylglycine were from Aldrich. D-*p*-(benzyloxy)phenylglycine was prepared from D-*p*-hydroxyphenylglycine according to a literature procedure:[35] mp 217–220 °C; $[\alpha]_D$ −55.3° (*c* 0.3, 0.1 N NaOH) [lit.[35] mp 225–228 °C dec; $[\alpha]_D$ −55° (*c* 0.3, 0.1 N NaOH)]. *N*-(Benzyloxycarbonyl)-β-benzyl-L-aspartic acid was from BaChem and was recrystallized from benzene or acetic acid/water before use. *N*-(Benzyloxycarbonyl)-β-benzyl-L-aspartic acid *p*-nitrophenyl ester was prepared by DCC coupling with *p*-nitrophenol.[25] *N*-(*tert*-Butoxycarbonyl)-β-benzyl-L-aspartic acid *p*-nitrophenyl ester, and *N*-(*tert*-butoxycarbonyl)-β-*tert*-butyl-L-aspartic acid *p*-nitrophenyl ester were from BaChem. *N*-Formyl-L-aspartic anhydride was prepared from L-aspartic acid, formic acid, and acetic anhydride.[36] *N*-(Thiocarboxy)-L-aspartic anhydride was prepared from L-aspartic acid by PBr_3 treatment of a thionourethane derivative.[37]

***N*-(Benzyloxycarbonyl)-D-phenylglycine (15).** D-Phenylglycine [50 g, 0.33 mol, $[\alpha]_D$ −154.3° (c 1.0, 1 N HCl)] was added to 82 mL of 4 N NaOH. The mixture was cooled to 0 °C and benzyl chloroformate (51 mL, 0.36 mol) was added dropwise over 30 min. Additional NaOH was added as needed to keep the reaction mixture basic and 150 mL of H_2O was added to facilitate stirring. After 10 min, 100 mL of H_2O was added and the solution was filtered. The clear filtrate was extracted twice with ether and then adjusted to pH 3 with 5 N HCl. The resulting precipitate was filtered, washed twice with H_2O, and then vacuum dried. The crude product was dissolved in ethyl acetate and filtered. The filtrate was evaporated and the resulting solid was crystallized from ethyl acetate/hexane to yield 35 g (49%) of **15** (note that sodium bicarbonate can be used in place of sodium hydroxide): mp 125–128 °C; $[\alpha]_D$ −108.5° (*c* 1.0, methanol); IR ($CDCl_3$) 3500–2400, 3430, 3270, 3065, 3035, 1720, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.88 (s, 2 H, $C_6H_5CH_2O$), 5.24 (br d, 1 H, *J* = 7 Hz, C_6H_5CH), 6.05 (br d, 1 H, NH), 6.80–7.40 (m, 10 H, C_6H_5's), 10.65 (s, 1 H, CO_2H).

***N*-(Benzyloxycarbonyl)-D,L-*o*-fluorophenylglycine.** D,L-*o*-Fluorophenylglycine (5.0 g, 29.5 mmol) was converted to the benzyloxycarbonyl derivative (8.4 g, 94%) by using the procedure outlined above except that ethyl acetate was used instead of ether to extract the product: IR (KBr) 3500–2300, 3325, 3030, 2900, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.94 (s, 2 H, $C_6H_5CH_2O$), 5.51 (d, 1 H, *J* = 7 Hz, C_6H_4FCH), 6.70–7.44 (m, 9 H, C_6H_4F and C_6H_5), 7.80 (br s, 1 H, NH), 9.72 (s, 1 H, CO_2H); MS (NH_3/CI) *m*/*z* 321 $(MNH_4)^+$, 304 $(MH)^+$, 213 $(MH - C_6H_5CH_2)^+$.

***N*-[(*o*-Nitrophenyl)sulfenyl]-D-phenylglycine (17).** D-Phenylglycine (51 g, 0.34 mol) was dissolved in a mixture of 180 mL of 2 N NaOH and 200 mL of dioxane. (*o*-Nitrophenyl)sulfenyl chloride (64 g, 0.34 mol) was added in small portions over 1 h with simultaneous addition of 180 mL of 2 N NaOH. The reaction mixture was stirred for 2 h and then diluted with 500 mL of H_2O. The mixture was filtered, and the solids were washed with H_2O. The filtrate was acidified with H_2SO_4 and then extracted three times with ether. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, and then evaporated. The crude product was recrystallized from ethyl acetate/hexane to give 64.5 g (62%) of product: mp 159–161 °C; −179.5° (*c* 0.4, methanol); IR (KBr) 3400–2700, 3350, 1710, 1500 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6/CD_3OD) δ 4.47 (s, 1 H, C_6H_5CH), 7.32 (s, 5 H, C_6H_5), 7.00–8.34 (m, 4 H, *o*-Nps).

***N*-[(*o*-Nitrophenyl)sulfenyl]-D-*p*-(benzyloxy)phenylglycine.** D-*p*-(Benzyloxy)phenylglycine (10.0 g, 38.9 mmol) was converted to the *o*-Nps derivative (11 g, 69%) by using the above procedure: mp 49–50 °C; $[\alpha]_D$ −154.9° (*c* 0.7, methanol); IR ($CHCl_3$) 3500–2400, 1710, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.50 (s, 1 H, 4-ROC_6H_4CH), 5.00 (s, 2 H, $C_6H_5CH_2O$), 6.77–8.33 (m, 13 H, aromatic); MS (FAB) *m*/*z* 411 $(MH)^+$, 256 $(MH - C_6H_4(NO_2)SH)^+$.

General Synthetic Procedures. Esterification of Protected Phenylglycines. To a mixture of 1 equiv of alcohol and 1 equiv of *N*-*o*-Nps-D-phenylglycine or *N*-Z-D-phenylglycine in dry dichloromethane at −78 °C under argon was added 1.2 equiv of dicyclohexylcarbodiimide and 0.04 equiv of 4-(dimethylamino)pyridine in one portion. The reaction mixture was stirred at −78 °C for 0.5 h, allowed to warm to −23 °C, and stirred for 3–6 h. The precipitated dicyclohexylurea was removed by filtration and washed with cold dichloromethane. The filtrate was washed with water, 4% $NaHCO_3$, brine, dried, and evaporated to yield crude product **16**/**18**.

Deprotection of Phenylglycine Esters: Benzyloxycarbonyl Derivatives. Protected phenylglycine ester **16** was hydrogenated in MeOH in a Parr apparatus at 50 psi over 5 or 10% Pd/C (25–100 mg of catalyst/g of substrate) for 2–24 h. Filtration and evaporation gave crude product which was dissolved in 0.1 N HCl and extracted with ether to remove nonbasic impurities. The aqueous layer was adjusted to pH 9–10 with NaOH and was extracted three times with ether. The combined extracts were successively washed with H_2O and brine and then dried over $MgSO_4$, filtered, and evaporated to give product **19**.

Deprotection of Phenylglycine Esters: (*o*-Nitrophenyl)sulfenyl Derivatives. Protected phenylglycine ester **18** in acetone at 0 °C or room temperature was treated with 1.1 equiv of 5 N HCl for 15–45 min. Evaporation of the solvent and acid/base workup as described for the Z derivative gave product **19**.

Coupling with Protected Aspartic Acid. Amino ester **19** and 1 equiv of *N*-(benzyloxycarbonyl)-β-benzyl-L-aspartic acid *p*-nitrophenyl ester were stirred for 24 h in dry THF. The solvent was evaporated and the residue taken up in ether. The ether solution was washed with cold 4% $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated to give product **20**.

Aspartyl Deprotection. Parr hydrogenolysis as described above for the preparation of the amino ester **19** provided sweeteners **21**–**42**.

Sweeteners. Route to L-Aspartyl-D-phenylglycine (−)-α-Fenchyl Ester (29). *N*-[(*o*-Nitrophenyl)sulfenyl]-D-phenylglycine (−)-α-Fenchyl Ester (18i). Esterification of (−)-α-fenchol (2.0 g, 13.2 mmol) gave 7.0 g of crude **18i** which was contaminated with fenchol. A small sample was purified by silica gel flash chromatography with 20% acetone/hexane for characterization: $[\alpha]_D$ −83.2° (c 0.05, methanol); IR (neat) 3320, 2940, 2855, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (s, 3 H, CH_3), 0.80 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 0.80–1.80 (m, 7 H, fenchyl), 3.82 (d, 1 H, *J* = 8 Hz, NH), 4.28 (d, 1 H, *J* = 1 Hz, CO_2CH), 4.52 (d, 1 H, *J* = 8 Hz, C_6H_5CH), 7.23 (s, 5 H, C_6H_5), 6.93–8.29 (m, 4 H, *o*-Nps).

D-Phenylglycine (−)-α-Fenchyl Ester (19i). Deprotection of **18i** (7 g, 15.9 mmol) gave 1.0 g (44% when corrected for fenchol

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(36) Bachman, G. L.; Oftedahl, M. L.; Vineyard, B. D. U. S. Patent 3,933,781, 1976.
(37) Vinick, F. J.; Jung, S. *J. Org. Chem.* **1982**, *47*, 2199.

in 18i) of 19i: $[\alpha]_D$ -94.5° (c 2.0, methanol); IR (neat) 3375, 3300, 3050, 3020, 2945, 2860, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 0.80–1.80 (m, 7 H, fenchyl), 1.95 (s, 2 H, NH_2), 4.28 (d, 1 H, J = 2 Hz, CO_2CH), 4.54 (s, 1 H, C_6H_5CH), 7.22 (s, 5 H, C_6H_5).

N-(Benzyloxycarbonyl)-β-benzyl-L-aspartyl-D-phenylglycine (-)-α-Fenchyl Ester (20i). Coupling of **19i** (1.0 g, 3.5 mmol) gave a crude product which was purified by silica gel flash chromatography with 25% ethyl acetate/hexane to give 2.2 g (quant) of **20i**: $[\alpha]_D$ -63.3° (c 0.4, methanol); IR (neat) 3310, 3045, 3020, 2945, 2860, 1720, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 0.80–1.77 (m, 7 H, fenchyl), 2.63–3.00 (m, 2 H, Asp CH_2), 4.23 (d, 1 H, J = 2 Hz, CO_2CH), 4.37–4.70 (m, 1 H, Asp CH), 5.00 (s, 2 H, $C_6H_5CH_2O$), 5.03 (s, 2 H, $C_6H_5CH_2O$), 5.41 (d, 1 H, J = 7 Hz, C_6H_5CH), 5.82 (br d, 1 H, J = 7 Hz, NH), 7.07–7.30 (m, 15 H, C_6H_5's), 7.50 (br d, 1 H, NH); MS (FAB) m/z 627 $(MH)^+$.

L-Aspartyl-D-phenylglycine (-)-α-Fenchyl Ester (29). Deprotection of **20i** (2.2 g, 3.5 mmol) gave 1.2 g (86%) of sweetener **29** after recrystallization from methanol/water: mp 176–177 °C; $[\alpha]_D$ -103.2° (c 0.5, methanol); TLC R_f = 0.57 (4:1:1 butanol/acetic acid/water), 0.54 (23:75:1:2 methanol/chloroform/acetic acid/water); HPLC t_R before recrystallization 34.4 (6%) and 35.6 min (94%), after recrystallization 34.8 min (100%), spiked with **29** racemized at phenylglycine center 34.6 (14%) and 36.0 min (86%) (Altex Ultrasphere ODS, 65:35 methanol/aqueous phosphate buffer at 1 mL/min); IR ($CHCl_3$) 3400–2400, 2940, 1720, 1670, 1545 (br) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.66 (s, 3 H, bridgehead CH_3), 0.83 (s, 3 H, endo CH_3), 1.07 (s, 3 H, exo CH_3), 0.80–1.75 (m, 7 H, fenchyl), 2.48–2.68 (m, 2 H, AB part of Asp ABX, J_{AB} = 17.0 Hz, J_{AX} = 5.3 Hz, J_{BX} = 8.9 Hz, Asp CH_2), 4.17–4.23 (m, 1 H, X part of Asp ABX, J_{AX} = 5.2 Hz, J_{BX} = 8.9 Hz, Asp CH), 4.30 (d, 1 H, J = 2 Hz, CO_2CH), 5.55 (s, 1 H, C_6H_5CH), 7.30–7.44 (m, 5 H, C_6H_5); MS (FAB) m/z 403 $(MH)^+$, 267 $(MH - C_{10}H_{16})^+$, 137 $(C_{10}H_{17})^+$; HRMS (FAB, MH^+) calcd for $C_{22}H_{31}N_2O_5$ 403.2233, found 403.2220; sweetness potency 1240 ± 333 (equivalent to 9.3% sucrose).

Route to L-Aspartyl-D-phenylglycine (-)- and (+)-*endo*-1,3,3-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl Esters (34, 35). ***N*-[(*o*-Nitrophenyl)sulfenyl]-D-phenylglycine (±)-*endo*-1,3,3-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl Ester (18n,o).** Esterification of (±)-*endo*-1,3,3-trimethyl-7-oxabicyclo[2.2.1]-heptan-2-ol (**7**, 0.36 g, 2.3 mmol) gave a yellow semisolid residue. This residue was purified by flash chromatography using 35% ether in pentane. The desired ester (0.75 g, 74%) was obtained as a mixture of diastereomers (**18n,o**) and was used without further purification: ^1H NMR ($CDCl_3$) δ 0.33 (s, 1.5 H, CH_3), 0.80 (s, 1.5 H, CH_3), 1.15 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.20–1.80 (m, 4 H, aliphatic), 3.70–4.05 (m, 2 H, bridgehead and NH), 4.30–4.50 (m, 1 H, CO_2CH), 4.60 (s, 0.5 H, C_6H_5CH), 4.70 (s, 0.5 H, C_6H_5CH), 7.45 (s, 5 H, C_6H_5), 7.50–8.50 (m, 4 H, *o*-Nps).

D-Phenylglycine (±)-*endo*-1,3,3-Trimethyl-7-oxabicyclo-[2.2.1]heptan-2-yl Ester (19n,o). Deprotection of **18n,o** (0.75 g, 1.7 mmol) gave 0.31 g (63%) of **19n,o** as a nearly colorless oil, which was used without further purification: ^1H NMR ($CDCl_3$) δ 0.30 (s, 1.5 H, CH_3), 0.80 (s, 1.5 H, CH_3), 1.13 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.30–1.90 (m, 4 H, aliphatic), 2.05 (br s, 2 H, NH_2), 3.70–4.05 (m, 1 H, bridgehead), 4.33 (s, 1 H, CO_2CH), 4.70 (s, 1 H, C_6H_5CH), 7.43 (s, 5 H, C_6H_5).

***N*-(Benzyloxycarbonyl)-β-benzyl-L-aspartyl-D-phenylglycine (±)-*endo*-1,3,3-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl Esters (20n,o).** Coupling of **19n,o** (0.31 g, 1.1 mmol) gave 0.62 g (90%) of **20n,o** as a viscous oil after purification by flash chromatography with 30% ethyl acetate in hexane. Analysis by HPLC (25% ethyl acetate in isooctane) indicated that this material was a 50:50 mixture of diastereomers **20n** and **20o**.

Separation of Diastereomers 20n and 20o by MPLC. The above mixture (0.62 g) was applied to a 1 m × 25 mm i.d. Altex glass column packed with 258 g of silica gel 60 (230–400 mesh), which had been previously equilibrated in 25% ethyl acetate in hexane. Elution with the same solvent system at a flow rate of 20 mL/min while the separation was monitored by UV at 254 nm produced a series of fractions which were divided into three groups. The residue from the first group weighed 0.14 g and contained 100% of the first eluting (-)-endo isomer **20n**: HPLC t_R 11.1 min (Altex Ultraphere Si, 25% ethyl acetate in isooctane at 1.5 mL/min); ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.60–2.00 (m, 4 H, aliphatic), 2.70–3.00 (m, 2 H, Asp CH_2), 3.82 (m, 1 H, bridgehead), 4.25 (s, 1 H, CO_2CH), 4.55–4.75 (m, 1 H, Asp CH), 5.08 (s, 2 H, $C_6H_5CH_2$), 5.13 (s, 2 H, $C_6H_5CH_2$), 5.50 (d, 1 H, J = 8 Hz, C_6H_5CH), 5.92 (d, 1 H, J = 8 Hz, NH), 7.30 (m, 15 H, C_6H_5's), 8.10–8.20 (m, 1 H, NH). The residue from the second group weighed 0.06 g and was a 60:40 mixture of the two diastereomers **20n** and **20o**. The residue from the third group weighed 0.28 g and contained 97% of the second eluting (+)-endo isomer **20o**: HPLC t_R 12.4 min (conditions as described above); ^1H NMR ($CDCl_3$) δ 0.20 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.60–2.00 (m, 4 H, aliphatic), 2.70–3.00 (m, 2 H, Asp CH_2), 3.82 (m, 1 H, bridgehead), 4.25 (s, 1 H, CO_2CH), 4.55–4.75 (m, 1 H, Asp CH), 5.08 (s, 2 H, $C_6H_5CH_2$), 5.13 (s, 2 H, $C_6H_5CH_2$), 5.45 (d, 1 H, J = 8 Hz, C_6H_5CH), 5.92 (d, 1 H, J = 8 Hz, NH), 7.30 (m, 15 H, C_6H_5's), 8.10–8.20 (m, 1 H, NH).

Determination of the Absolute Configuration of Diastereomers 20n and 20o. A 50-mg sample of the second eluting isomer from the above separation was treated with a large excess of lithium aluminum hydride in ether. Standard workup followed by flash chromatography with 30% ether in pentane gave 3.2 mg of material which was identified as the resolved bicyclic alcohol and determined to be pure by GC analysis, $[\alpha]_D$ +2.6° (c 0.16, ethanol). This experiment proves that diastereomer **20o** (the second eluting isomer) is the ester of (+)-*endo*-2-hydroxy-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane. Diastereomer **20n** (the first eluting isomer) is, therefore, the ester of (-)-*endo*-2-hydroxy-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane.

L-Aspartyl-D-phenylglycine (-)-*endo*-1,3,3-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl Ester (34). Deprotection of **20n** (0.14 g, 0.2 mmol) gave 0.062 g (66%) of **34** as a white powder after recrystallization from methanol/ethyl acetate (1:10): mp 164–165 °C; $[\alpha]_D$ -33.8° (c 0.1, methanol); TLC R_f = 0.7 (4:1:1 butanol/acetic acid/water); HPLC t_R 25.4 min, (Altex Ultrasphere ODS, 50:50 methanol/aqueous phosphate buffer at 0.8 mL/min); ^1H NMR (CD_3OD) δ 0.84 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 1.06 (m, 1 H, aliphatic), 1.14 (s, 3 H, CH_3), 1.60 (m, 1 H, aliphatic), 1.73 (m, 1 H, aliphatic), 1.86 (m, 1 H, aliphatic), 2.52 and 2.62 (m, 2 H, AB part of Asp ABX, J_{AB} = 17.0 Hz, Asp CH_2), 3.88 (d, 1 H, J = 5.2 Hz, bridgehead), 4.18 (m, 1 H, X part of Asp ABX, J_{AX} = 5.2 Hz, J_{BX} = 8.9 Hz, Asp CH), 4.21 (d, 1 H, J = 1.4 Hz, CO_2CH), 5.56 (s, 1 H, C_6H_5CH), 7.40 (s, 5 H, C_6H_5); ^{13}C NMR (CD_3OD) δ 19.1 (CH_3), 20.0 (CH_3), 27.1 (CH_2), 29.0 (CH_3), 29.1 (CH_2), 38.5 (Asp CH_2), 43.2 (quaternary C), 52.3 (Asp CH), 58.4 (phenylglycine CH), 86.8 (bridgehead CH), 86.9 (quaternary bridgehead C), 88.0 (C α to ester O), 128.6 (aromatic CH), 129.9 (aromatic CH), 130.1 (aromatic CH), 137.3 (aromatic ipso C), 170.3 (carbonyl), 171.8 (carbonyl), 176.0 (carbonyl); sweetness potency 700 (informal tasting).

L-Aspartyl-D-phenylglycine (+)-*endo*-1,3,3-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl Ester (35). Deprotection of **20o** (0.14 g, 0.2 mmol) followed by recrystallization of the product from ether/hexane (1:1) afforded 0.071 g (79%) of a white powder, which contained 94% of **35** and 6% of **34** by HPLC: mp 109–112.5 °C; $[\alpha]_D$ -27.7° (c 0.1, methanol); TLC R_f = 0.7 (4:1:1 butanol/acetic acid/water); HPLC t_R 32.6 (94%) and 25.4 min (6%) (conditions as for **34**); ^1H NMR (CD_3OD) δ 0.25 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.24 (m, 1 H, aliphatic), 1.37 (s, 3 H, CH_3), 1.58 (m, 1 H, aliphatic), 1.67 (m, 1 H, aliphatic), 1.99 (m, 1 H, aliphatic), 2.52 and 2.64 (m, 2 H, AB part of Asp ABX, J_{AB} = 17.0 Hz, Asp CH_2), 3.80 (d, 1 H, J = 5.1 Hz, bridgehead), 4.20 (m, 1 H, X pa rt of Asp ABX, J_{AX} = 5.4 Hz, J_{BX} = 8.7 Hz, Asp CH), 4.26 (d, 1 H, J = 1.4 Hz, CO_2CH), 5.54 (s, 1 H, C_6H_5CH), 7.40 (m, 5 H, C_6H_5); ^{13}C NMR (CD_3OD) δ 18.5 (CH_3), 20.2 (CH_3), 27.0 (CH_2), 29.1 (CH_3), 29.2 (CH_2), 38.4 (Asp CH_2), 43.5 (quaternary C), 52.1 (Asp CH), 58.4 (C_6H_5CH), 86.7 (bridgehead CH), 87.0 (quaternary bridgehead C), 87.9 (C α to ester O), 129.5 (aromatic CH), 130.0 (aromatic CH), 137.2 (aromatic ipso C), 170.2 (carbonyl), 171.7 (carbonyl), 176.0 (carbonyl); sweetness potency 70 (informal tasting).

All the remaining sweeteners were prepared by the procedures outlined above except for sweeteners **25** and **30** which are described below.

L-Aspartyl-D-phenylglycine 2,2,4,4-Tetramethylthietanyl Ester (25). Crude D-phenylglycine tetramethylthietanyl ester

19e (2.45 g, 8.8 mmol) was dissolved in 40 mL of dry THF and cooled to 0 °C. *N*-(Thiocarboxy)-L-aspartic anhydride (1.53 g, 8.8 mmol) in dry THF was added dropwise and the reaction was stirred for 3 h and then stored in the freezer overnight. Another 0.15 g of the anhydride was added, but no change was noted by TLC. The solvent was evaporated to give 4 g of crude product, which was purified by silica gel flash chromatography with 23:75:1:2 methanol/chloroform/acetic acid/water to give 2.2 g of a white solid. Recrystallization in portions from ethyl acetate/hexane or THF/hexane gave 0.72 g (21%) of **25** as a white solid: mp 169.5–170 °C; $[\alpha]_D$ −44.6° (c 4.5, methanol); TLC R_f = 0.64 (4:1:1 butanol/acetic acid/water); HPLC t_R 12.55 (8%), 12.91 (88%), and 17.07 min (5%) (conditions as for **29**); IR (KBr) 3700–2200, 2960, 2920, 1735, 1675, 1550 (br) cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 1.08 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.50 (s, 3 H CH_3), 2.47–2.69 (m, 2 H, AB part of Asp ABX, J_{AB} = 16.8 Hz, J_{AX} = 5.1 Hz, J_{BX} = 8.8 Hz, Asp CH_2), 4.15–4.23 (m, 1 H, Asp CH), 5.14 (s, 1 H, CO_2CH), 5.56 (s, 1 H, C_6H_5CH), 7.36–7.45 (m, 5 H, C_6H_5); MS (FAB) *m/z* 395 $(MH)^+$, 267 $(MH - C_7H_{12}S)^+$, 129 $(C_7H_{13}S)^+$; HRMS (FAB, MH^+) calcd for $C_{19}H_{27}N_2O_5S$ 395.1641, found 395.1636; sweetness potency 300 (informal tasting, sulfur off-notes).

***N*-(*tert*-Butoxycarbonyl)-β-benzyl-L-aspartyl-D,L-phenylglycine (+)-α-Fenchyl Ester (20j).** Coupling of **19j** (120 mg, 0.42 mmol) and *N*-(*tert*-butoxycarbonyl)-β-benzyl-L-aspartyl-*p*-nitrophenyl ester (180 mg, 0.42 mmol) in the same manner as that described for the *N*-Z derivative in the general synthetic procedures, gave 125 mg (50%) of **20j**: $[\alpha]_D$ −9.7° (c 0.9, methanol); IR (neat) 3330, 2950, 2865, 1725, 1690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.22 (s, CH_3), 0.71 (s, CH_3), 0.82 (s, CH_3), 1.02 (s, CH_3), 1.09 (s, CH_3), 1.10 (s, CH_3), 1.47 (s, *t*-Bu), 1.50 (s, *t*-Bu), 1.05–1.78 (m, 7 H, fenchyl), 2.60–3.05 (m, 2 H, Asp CH_2), 4.30–4.40 (m, 1 H, CO_2CH), 4.62 (br s, 1 H, Asp CH), 5.05–5.22 (m, 2 H, $C_6H_5CH_2O$), 5.47–5.60 (m, 1 H, C_6H_5CH), 5.78 (br s, 1 H, NH), 7.34 (s, 10 H, C_6H_5's), 7.76 (br s, 1 H, NH).

L-Aspartyl-D,L-phenylglycine (+)-α-Fenchyl Ester (30). Diprotected aspartylphenylglycine fenchyl ester **20j** (120 mg, 0.21 mmol) in 2.5 mL of acetic acid was stirred with 0.5 mL of trifluoroacetic acid for several hours at 35 °C. The temperature was raised to 70 °C and another 0.5 mL of trifluoroacetic acid was added. After 5 h, the solvent was evaporated and the residue was dissolved in 24 mL of 60% methanol/water with 3 drops of acetic acid. The mixture was hydrogenated in a Parr apparatus for 3 h at 48 psi over 5% palladium on carbon. The catalyst was filtered and the solvent was evaporated. The crude product was purified by ion-exchange chromatography (H^+, 50W-X8) eluting with acetic acid, water, and then 5% pyridine/water to give 51 mg of sweetener. Reversed-phase MPLC on a Lobar LiChroprep RP-8 column with 25% water/methanol gave 40 mg (47%) of **30**: mp 146–155 °C; $[\alpha]_D$ −2.3° (c 0.2, methanol); TLC R_f = 0.56 (40:60:2:1 methanol/chloroform/acetic acid/water); HPLC t_R 30.5 (41%) and 33.1 min (57%), (Waters μ BONDAPAK C18, 58:42 methanol/phosphate buffer at 1 mL/min); ^1H NMR (CD_3OD) δ 0.20–1.90 (m, 16 H, fenchyl, s at 0.24, 0.70, 0.79, 1.00, 1.08, CH_3), 2.50–2.97 (m, 2 H, Asp CH_2), 4.06–4.45 (m, 2 H, CO_2CH, Asp CH), 5.53 (s, 1 H, C_6H_5CH), 7.38 (s, 5 H, C_6H_5); HRMS (FAB, MH^+) calcd for $C_{22}H_{31}N_2O_5$ 403.2233, found 403.2231. A major difference in the solubility of the diastereomers was noted. Dissolution of the sweetener was never complete even at concentrations less than 0.1% For example, 97.6 mg of the sweetener was stirred in 100 mL of water. The insolubles were filtered (73.4 mg) and the filtrate (0.02% solution) was tasted by 6 panelists resulting in a potency of 254 ± 56 times that of sucrose (equivalent to 5.1% sucrose). HPLC analysis of the solution showed it to be a 1/11.5 ratio of diastereomers. Note that the second eluting isomer is the sweet one. The corrected potency is, therefore, 276X. A second sweetener panel with a 0.036% solution gave a corrected potency of 221 ± 41 (equivalent to 7.5% sucrose).

Registry No. **3**, 85545-27-3; **4**, 103251-81-6; **5**, 103251-82-7; **6**, 103251-83-8; **7**, 103251-84-9; **8**, 87129-04-2; **9**, 69651-95-2; **10**, 124510-29-8; **11**, 124510-30-1; **12**, 124510-31-2; **13**, 124441-51-6; **14**, 124441-52-7; **15**, 17609-52-8; **16a** (diastereomer 1), 124441-55-0; **16a** (diastereomer 2), 124441-56-1; **16b**, 124441-57-2; **16c**, 124441-58-3; **16f** (diastereomer 1), 124441-59-4; **16f** (diastereomer 2), 124441-60-7; **16g** (diastereomer 1), 124441-61-8; **16g** (diastereomer 2), 124441-62-9; **16h** (diastereomer 1), 124441-63-0; **16h** (diastereomer 2), 124441-64-1; D-**16j**, 124510-33-4; L-**16j**, 124510-34-5; **16m** (diastereomer 1), 124441-65-2; **16m** (diastereomer 2), 124441-66-3; D-**16v**, 124441-73-2; L-**16v**, 124441-74-3; **17**, 16679-41-7; **18b**, 124460-96-4; **18d**, 124441-67-4; **18e**, 103300-61-4; **18i**, 103300-59-0; D-**18k**, 124510-35-6; L-**18k**, 124510-36-7; D-**18l**, 124578-39-8; L-**18l**, 124510-37-8; **18n**, 116050-31-8; **18a**, 124510-38-9; **18p**, 124510-39-0; **18q**, 124510-40-3; **18r** (diastereomer 1), 124441-68-5; **18r** (diastereomer 2), 124510-41-4; **18s** (MOM ether), 124441-69-6; **18t** (diastereomer 1), 124441-70-9; **18t** (diastereomer 2), 124510-42-5; D-**18u**, 124441-71-0; L-**18u**, 124441-72-1; **19a** (diastereomer 1), 124441-75-4; **19a** (diastereomer 2), 124441-76-5; **19b**, 124441-77-6; **19c**, 124441-78-7; **19d**, 124441-79-8; **19e**, 103300-62-5; **19f** (diastereomer 1), 124441-80-1; **19f** (diastereomer 2), 124441-81-2; **19g** (diastereomer 1), 124441-82-3; **19g** (diastereomer 2), 124441-83-4; **19h** (diastereomer 1), 124441-84-5; **19h** (diastereomer 2), 124441-85-6; **19i**, 103300-54-5; D-**19j**, 124510-43-6; L-**19j**, 124510-44-7; D-**19k**, 124510-45-8; L-**19k**, 124510-46-9; D-**19l**, 124510-47-0; L-**19l**, 124510-48-1; **19m** (diastereomer 1), 97792-62-6; **19m** (diastereomer 2), 97792-63-7; **19n**, 124510-49-2; **19o**, 124510-50-5; **19p**, 124510-51-6; **19q**, 124510-52-7; **19r** (diastereomer 1), 124441-86-7; **19r** (diastereomer 2), 124510-53-8; **19s**, 124441-87-8; **19t**, 124441-88-9; **19t**, 124510-54-9; D-**19u**, 103300-72-7; L-**19u**, 124510-55-0; D-**19v**, 124441-89-0; L-**19v**, 124441-90-3; **20a** (diastereomer 1), 124441-91-4; **20a** (diastereomer 2), 124510-56-1; **20b**, 124441-92-5; **20c**, 124441-93-6; **20d**, 124441-94-7; **20f** (diastereomer 1), 124441-95-8; **20f** (diastereomer 2), 124510-57-2; **20g** (diastereomer 1), 124441-96-9; **20g** (diastereomer 2), 124510-58-3; **20h** (diastereomer 1), 124510-59-4; **20h** (diastereomer 2), 124510-60-7; **20i**, 103300-55-6; (L,D)-**20j**, 124441-97-0; (L,L)-**20j**, 124510-61-8; (L,D)-**20k**, 124510-62-9; (L,L)-**20k**, 124510-63-0; (L,D)-**20l**, 124510-64-1; (L,L)-**20l**, 124510-65-2; **20m** (diastereomer 1), 124441-98-1; **20m** (diastereomer 2), 124510-66-3; **20n**, 116050-32-9; **20o**, 124510-67-4; **20p**, 124510-68-5; **20q**, 124510-69-6; **20r** (diastereomer 1), 124441-99-2; **20r** (diastereomer 2), 124510-70-9; **20s**, 124442-00-8; **20t** (diastereomer 1), 124442-01-9; **20t** (diastereomer 2), 124510-71-0; (L,D)-**20u**, 124442-02-0; (L,L)-**20u**, 124510-72-1; (L,D)-**20v**, 124442-03-1; (L,L)-**20v**, 124510-73-2; **21** (diastereomer 1), 124510-74-3; **21** (diastereomer 2), 124510-75-4; **22**, 103300-58-9; **23**, 103300-57-8; **24**, 124442-04-2; **25**, 103300-63-6; **26** (diastereomer 1), 124510-76-5; **26** (diastereomer 2), 124510-77-6; **27** (diastereomer 1), 124442-05-3; **27** (diastereomer 2), 124510-78-7; **28** (diastereomer 1), 124510-79-8; **28** (diastereomer 2), 124510-80-1; **29**, 103366-56-9; (L,D)-**30**, 124510-81-2; (L,L)-**30**, 124510-82-3; (L,D)-**31**, 103300-60-3; (L,L)-**31**, 124510-83-4; (L,D)-**32**, 103365-67-9; (L,L)-**32**, 124510-84-5; **33** (diastereomer 1), 124442-06-4; **33** (diastereomer 2), 124510-85-6; **34**, 103251-85-0; **35**, 103303-60-2; **36**, 124578-40-1; **37**, 124510-86-7; **38** (diastereomer 1), 124442-07-5; **38** (diastereomer 2), 124510-87-8; **39**, 124442-08-6; **40** (diastereomer 1), 124442-09-7; **40** (diastereomer 2), 124510-88-9; (L,D)-**41**, 103300-73-8; (L,L)-41, 124510-89-0; (L,D)-**42**, 124442-10-0; (LL)-**42**, 124510-90-3; H-D-Phg-OH, 875-74-1; Cbz-DL-Phg(*o*-F)-OH, 124441-53-8; *o*-Nps-D-Phg(*p*-OBzl)-OH, 103300-70-5; H-DL-Phg(*o*-F)OH, 84145-28-8; H-D-Phg(*p*-OBzl)-OH, 69489-40-3; Cbz-Asp(OBzl)-OH, 3479-47-8; Cbz-Asp(OBzl)-ONp, 2419-54-7; BOC-Asp(OBzl)-ONp, 26048-69-1; BOC-Asp(OBu-*t*)-ONp, 29365-05-7; Asp-NTA, 77217-04-0; H-Asp-OH, 56-84-8; (±)-$CH_3CH(OH)CMe_3$, 20281-91-8; geraniol, 106-24-1; *N*-formyl-L-aspartic anhydride, 33605-73-1; (−)-fenchone, 7787-20-4; 2,5-dimethylcyclopentanone, 4041-09-2; 2,2,5,5-tetramethylcyclopentanone, 4541-35-9; (+)-fenchone, 4695-62-9; 2,2,4,4-tetramethylthietan-3-one, 58721-01-0; (±)-norcamphore, 22270-13-9; 2,6-dimethylcyclohexanol, 5337-72-4; (±)-*endo*-norborneol, 24325-44-8; (±)-*exo*-norborneol, 60133-16-9; (−)-borneol, 464-45-9; (+)-α-fenchol, 2217-02-9; 2,5-dimethylcyclopentanol, 22417-55-6; 2,2,5,5-tetramethylcyclopentanol, 15231-50-2; (−)-α-fenchol, 512-13-0; 2,2,4,4-tetramethylthietan-3-ol, 89975-69-9; (−)-β-fenchol, 470-08-6; (+)-β-fenchol, 64439-31-2; (±)-*exo*-2-methyl-*endo*-2-norborneol, 124441-54-9; (±)-3a,3aβ,5a,6β,6aβ-hexahydro-3,5-methano-2*H*-cyclopenta[6]furan-6-ol, 124510-32-3.

Supplementary Material Available: Purification procedures and spectral data for remaining compounds **16a–v**, **18a–v**, **19a–v**, **20a–v**, and **21–42** (32 pages). Ordering information is given on any current masthead page.