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An Improved Synthesis of (S)-Aspartyl-(7,7-Dimethyl-norborn-2R-yl)-(S)-Alanine Methyl Ester, A New High Intensity Artificial Sweetener‡

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Abstract: (S)-Aspartyl-(7,7-dimethylnorborn-2R-yl)-(S)-alanine methyl ester (**1**) was synthesized in nine steps from (+)-α-fenchyl alcohol (**3**) as a chiral synthon. Crucial steps for controlling the side-chain stereochemistry of **1**, required for the manifestation of sweetness, were the catalytic hydroformylation of the olefin **4** and the enzymatic resolution of the racemic amino acid **9** using acylase I.

Previous work[1] has demonstrated that replacement of the phenyl ring of the (S)-phenylalanine moiety in aspartame by a bicyclo alkyl moiety leads to a new series of sweet compounds, several of which possess significantly enhanced sweetness potencies (SP). These sweeteners were prepared as mixtures of stereoisomers using two synthetic approaches by which either bicycloalkyl methanols or exomethylene bicycloalkyls could be used as starting material to create the required bicycloalkyl alanine intermediates. A bicycloalkyl methanol could be converted to the corresponding tosylate which is in turn reacted with diethyl malonate, followed by hydrolysis, decarboxylation, α-bromination and finally displacement of the bromine with ammonia to give the bicycloalkyl-(R,S)-alanine. The exomethylene bicycloalkanes (generally obtained from the ketone *via* a Wittig reaction) were first treated with 9-borabicyclononane followed by alkylation of the 9-BBN adducts using methyl-N-(diphenylmethylene)-2-acetoxyglycinate.[2] Mild acid hydrolysis of this alkylation product then gives the desired bicycloalkyl-(R,S)-alanine methyl ester directly. With these bicycloalkyl-(R,S)-alanine esters in hand the sweeteners were readily prepared by coupling to N-carbobenzyloxy-(S)-aspartic acid-ß-benzyl ester followed by hydrogenolysis to remove the protecting groups.

While these two procedures allowed for the preparation of a number of new sweet compounds, they both suffered from a lack of stereochemical control. Also, scale-up of several of these reactions was both cumbersome and expensive, providing serious impediments to the potential commercialization of any of these sweet compounds.

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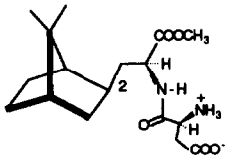
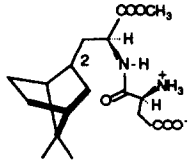
‡ This paper is dedicated to the memory of Dr. Akira Komatsu (1927-1990), President, The Takasago Research Institute, Tokyo, Japan, whose enthusiastic support greatly facilitated the successful completion of this effort.

During this initial work several points became clear with respect to the structural requirements for high sweetness potency (the levels being compared relative to a 10% sucrose solution) in this series of compounds. Firstly the alanine moiety must possess the (S)-configuration. Also, altering the number and position of methyl groups on the bicycloalkyl ring profoundly affects the sweetness potencies. In general, the lowest SP values were seen for the unsubstituted norbornyl ring, and a consistent increase of SP was noted for the sequence: norbornyl (SP = 800)→3-methylnorbornyl (SP = 1000)→7,7-dimethylnorbornyl (SP = 2000)→bornyl (SP = 4000), corresponding to the introduction of one, two and three methyl groups, respectively. The only exception found was the case of the fenchyl group (3 methyls, SP=20), apparently the result of steric crowding around the positions vicinal to the side chain junction. These results pointed to the existence of a unique structural shape at the hydrophobic binding region of the sweet receptor, an inference also suggested by numerous other studies.[3] Further insight into the requirements of the binding region came from the detailed study of the stereoisomerism of the 7,7-dimethylnorbornyl derivatives. Out of the four possible isomers, only the compounds **1** and **2** in which the attachment to the bicycloalkyl ring possessed the (R)-configuration exhibited SP > 2000, while the other two (2S-*endo*, SP = 300; 2S-*exo*, SP = 90) were found to be significantly less sweet. Thus, compounds **1** and **2** became the choice for further development, as they represented the best balance between high taste quality (matching the taste characteristics of aspartame) and high sweetness potency. Final selection of **1** as the target compound resulted from the realization that it could be produced from the abundant (+)-α-fenchyl alcohol as the chiral synthon (Scheme I), while **2** would require the rare (-)-α-fenchyl alcohol. Also, the stereoselectivity at C-2 resulting from the catalytic hydroformylation of **4**, provided for the *exo*-orientation of the side chain in the synthesis of **1**. Thus, this procedure could not be used for the preparation of the *endo*-isomer **2**.



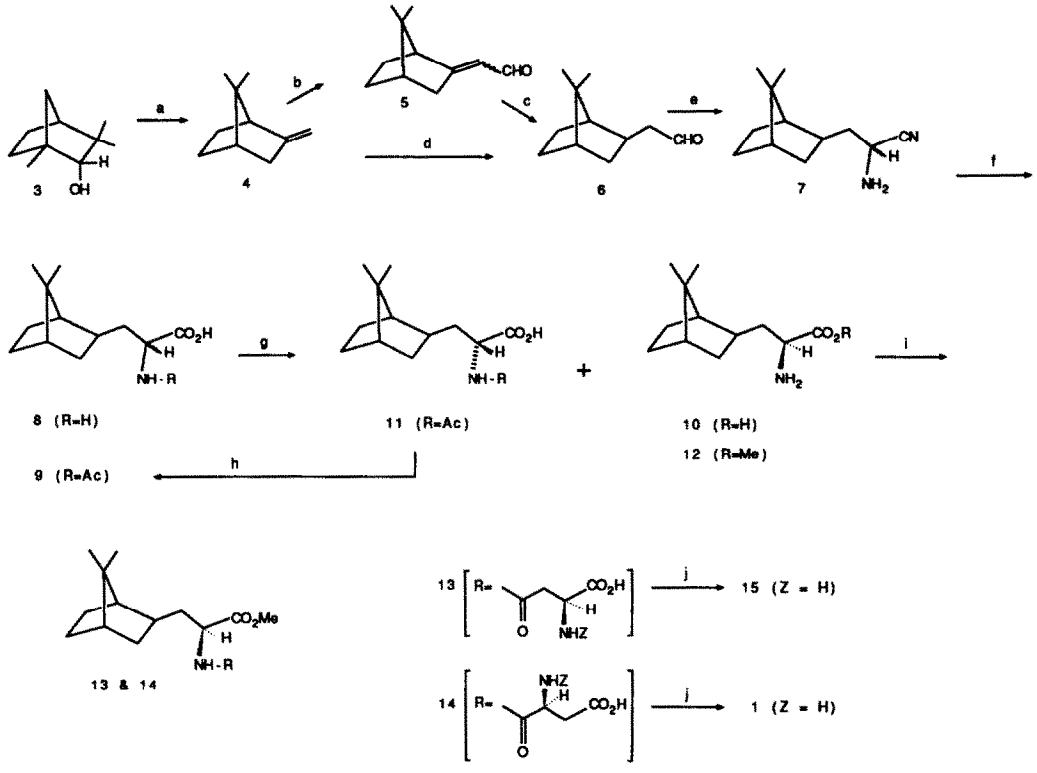
1 (SP = 2200)



2 (SP = 2500)

As the previously described procedures were inappropriate for the preparation of **1** on a large scale, a new and improved synthetic route has been developed. The final process, summarized in Scheme I, has resulted in the preparation of 20 kg of **1** in a 6% overall yield from (+)-α-fenchyl alcohol. Cumbersome, nonstereoselective reactions have been replaced by catalytic processes with a high degree of stereochemical control, resulting in a final, single pure isomer. Major improvements include: a) starting with (+)-α-fenchyl alcohol of high optical purity, pure (+)-α-fenchene was prepared by catalytic dehydration/ rearrangement in a neat process eliminating the need for solvents and setting the absolute stereochemistry of the bicycloalkyl ring; b) the alanine side chain was elaborated *via* catalytic hydroformylation, which gives good control of the *exo*/*endo* ratio at the bicycloalkyl ring attachment, followed by the Strecker reaction and hydrolysis; c) the N-acetyl-bicycloalkyl-(R,S)-alanine could be resolved *via* enzymatic hydrolysis to give the desired bicycloalkyl-(S)-alanine while allowing for racemization and recycling of the unreacted N-acetyl-(R)-isomer.

Scheme I.



a) Al_2O_3, 200°C; b) DMF, $POCl_3$, 60°C; c) H_2 (2 kg/cm^2), Pd/C, *n*-heptane, 22°C; d) CO/H_2 (80 kg/cm^2), $Rh/P(C_6H_5)_3$ catalyst, benzene, 90°C; e) NH_3, NaCN, MeOH, 22°C; f) 10N HCl, reflux/NaOH, Ac_2O; g) acylase I, H_2O, pH 8.0; h) $AcOH/Ac_2O$, 100°C; i) Z-asp anhydride, toluene, 22°C; j) H_2 (3 kg/cm^2), Pd/C, MeOH, 22°C.

The starting material for the production of **1** was (+)-α-fenchyl alcohol **3** which is commercially available as an enantiomeric mixture of 80% ee. This was further purified by repeated crystallizations from *n*-heptane at -35°C and gave rise to material having an optical purity in the range of 95-99% ee, varying somewhat from batch to batch.

Conversion of fenchyl alcohol to α-fenchene has been described in a few earlier reports. Hückel and Volkmann[4] have achieved this by first converting fenchyl alcohol into its tosylate using *p*-toluenesulfonyl chloride and pyridine, followed by heating of the isolated product with sodium acetate and acetic acid at reflux. While the conversion of the tosylate to α-fenchene proceeded in 90% yield this procedure is not generally applicable to large scale use due to problems of manipulation of large volumes of solvents, the need for purification of the tosylate and the need to either reclaim or dispose of large amounts of pyridine, acetic acid and *p*-toluenesulfonic acid. Alternatively, direct thermal dehydration and rearrangement of fenchyl alcohol

has been reported using potassium sulfate,[5] aluminum phosphate,[6] and zinc chloride [7] as catalysts. However, the yields in these cases were only in the range of 20-30%.

We found that the overall yield of this rearrangement could be significantly improved by the use of an aluminum oxide catalyst formed by calcination of freshly prepared aluminum hydroxide at 500°C. Heating (+)-α-fenchyl alcohol neat with 5% by weight of the above catalyst at 200°C followed by distillation of the reaction mixture gave a 54% yield of (+)-α-fenchene (**4**). This yield rose to 80% when (+)-β-fenchyl alcohol was used. However, because of the limited availability of (+)-ß-fenchyl alcohol, a similar rearrangement was tried with a 6/4 mixture of α/ß-fenchyl alcohols, prepared by reduction of (-)-fenchone with $NaBH_4$, which was found to give **4** in 65% yield (Table I). In evaluating the various catalysts for this reaction, while widely varying product mixtures were observed, it was found that the preferred ones were those with a Hammett acidity function of $-5.6 \leq H_o \leq -3.0$. In these cases the reaction gave moderate to high overall selectivity for α-fenchene.

Two different approaches were next explored for the conversion of (+)-α-fenchene (**4**) to (7,7-dimethylnorborn-2R-yl)-acetaldehyde (**6**). In the first, **4** was subjected to standard Vilsmeier reaction conditions[8] to give 7,7-dimethyl-2-formylmethylene norbornane (**5**) in 71% yield. Hydrogenation of **5** over Pd/C at 2 kg/cm^2 then afforded **6** with an *exo/endo* ratio of 98/2. The second procedure directly converted **4** to **6** *via* an oxo reaction using a rhodium catalyst. Although several catalysts for the carbonylation of olefins are known,[9, 10] we found $[1,5\text{-cyclooctadienyl}\cdot RhCl]_2\cdot 2P(Ph)_3$ in benzene, under a synthesis gas pressure of 80 kg/cm^2 at 90°C, afforded **6** in 93% yield with an *exo/endo* ratio of 85/15. As described in the experimental part, the *exo/endo* ratio could be increased to 90/10 with a somewhat lower overall yield. This latter method was determined to be the preferred one for the preparation of **6** for several reasons; a) it is a one step, catalytic process employing inexpensive reagents and easily recoverable solvents; b) the Vilsmeier reaction generates large quantities of salts and DMF which create disposal or reclamation problems; c) although the overall *exo/endo* ratio is higher in the Vilsmeier procedure, the absolute amount of the *exo* isomer is higher in the catalytic hydroformylation process due to the moderate yield of the Vilsmeier reaction. Also, as it turned out, the undesired *endo* isomer could be easily removed by recrystallization at a later stage. The rhodium/phosphine complexes are preferred as catalysts over other transition metals like cobalt because of their higher *exo/endo* stereoselectivity and the lower operating pressure required.

Conversion of **6** to the amino nitrile (**7**) by the Strecker reaction[11, 12] proceeded in 95% yield, and **7** was converted into the racemic amino acid (**8**) by refluxing in 10N HCl. The product was then isolated by crystallization from water at pH 4.0 as a diastereomeric mixture at the alanine center.

The resolution of **8** was achieved using acylase I [EC 3.5.1.14], a N-acyl-amino acid hydrolase of wide specificity.[13, 14] For this purpose, **8** was first acetylated with Ac_2O/10% NaOH to yield **9**, which was in turn selectively hydrolyzed with acylase I to give the desired (7,7-dimethylnorborn-2R-yl)-(S)-alanine (**10**). The unreacted N-acetyl-(7,7-dimethylnorborn-2R-yl)-(R)-alanine (**11**) was recovered and recycled following racemization of the amino acid center, done by heating it at 100°C with 2% Ac_2O in AcOH. This allowed for a high overall conversion of the (R,S)-amino acid **8** into the desired (S)-enantiomer **10**. This was esterified with HCl/MeOH to **12**, which was then ready to be coupled to a suitably functionalized (S)-aspartic acid derivative.

The classical procedures for small scale preparations of N-aspartyl dipeptides involve coupling of the free amino ester **12** with an activated form of N-Z-(S)-aspartic acid-ß-benzyl ester. The free carboxyl group of the aspartic acid moiety is converted to an activated leaving group using *p*-nitrophenol/DCC,

N-hydroxysuccinimide/DCC or isobutyl chloroformate/N-methyl morpholine and the free amino ester added.[15] While these procedures all worked well and resulted in the formation of the pure final product[1] they were not pursued further due to the expense of the reagents.

A simpler way to activate the aspartic acid moiety is conversion to an N-protected cyclic anhydride. This procedure has been investigated extensively for the synthesis of aspartame, with emphasis on the use of either N-formyl[14-18] or N-carbobenzyloxy[19-21] aspartic acid anhydride.

N-formyl-(S)-aspartic acid anhydride can be prepared in one step from (S)-aspartic acid and a formic acid-acetic anhydride mixture. It is then coupled with the appropriate amino ester in an organic solvent to give the α-N-formyl aspartyl amino ester along with a small amount (10-20%) of the ß-N-formyl aspartyl amino ester. In the case of aspartame the N-formyl group is then removed by warming with dilute hydrochloric acid, and the α-(S)-aspartyl-(S)-phenylalanine methyl ester separated from the ß-isomer by crystallization.

We have found that the (7,7-dimethylnorborn-2R-yl)-(S)-alanine methyl ester (**12**) couples in toluene with N-formyl aspartic acid anhydride to give an 80/20 mixture of the α- and ß-N-formyl-(S)-aspartyl-(S)-alanine esters. Unfortunately, attempts at selective acidic hydrolysis of the N-formyl group failed. In all cases we observed competing hydrolysis of the methyl ester function.

The use of N-Z-(S)-aspartic acid anhydride ultimately proved to be the method of choice. This material is readily prepared[19] and couples smoothly with the free amino ester. As Yang and Su have reported in the case of aspartame[21] the ratio of α-N-Z-aspartyl amino ester to the ß-isomer formed in the coupling is very solvent dependent. As shown in Table III, solvents with dielectric constants in the range 2-5 are optimal. In our process using toluene as the solvent at 5°C for 18 hours, α/ß ratios of 8-9/1 could be obtained.

The undesired ß-isomer (**13**) could be separated from the major product **14** by solvent/buffer partition, as described previously in the case of aspartame[22] and other N-Z-aspartyl dipeptides.[23, 24] However, this is essentially a countercurrent extraction procedure which is difficult to scale up and uses solvents that tend to form intractable emulsions. Thus, the procedure preferred for its operational simplicity was the fractional crystallization of the final N-deprotected mixture. This works quite well provided that the **1/15** ratio was greater than 8. After five crystallizations from 33% MeOH/H_2O, the sweetener **1** was obtained with a purity greater than 99%. A similar purification has been described for aspartame.[25]

EXPERIMENTAL SECTION

All chemicals were reagent grade and used as received from the supplier. All boiling and melting points are uncorrected. IR spectra were determined on a Perkin Elmer 281 spectrophotometer, optical rotations on a Perkin Elmer 241 polarimeter and ^1H and ^{13}C NMR spectra on a Varian Gemini 200 MHz or a Brucker 400 MHz spectrometer. Microanalyses were performed by Atlantic Microlab, Norcross, Georgia.

***Purification of (+)-α-fenchyl alcohol* (3).** Commercial α-fenchyl alcohol ($[\alpha]_D^{23}$ = +10.0° (c=5, EtOH); mp 43.2°C; 709.2 g) was dissolved in 355 g of *n*-heptane, and the solution was cooled to about -33°C. The crystals that precipitated were separated by filtration to give 493.6 g of a first crop of crystals ($[\alpha]_D^{24}$ = +11.6°; mp 45.2°C), Crop 1. The residue (228.9 g) left after evaporation of the filtrate was dissolved in 160 g of *n*-heptane and the solution was cooled to -50°C. The precipitate was filtered giving 128.6 g of a second crop of crystals ($[\alpha]_D^{24}$ = +10.2°; mp 43.2°C). These crystals were of the same quality as the starting material. They were again dissolved in 64 g of *n*-heptane, and the solution was cooled to about -33°C. The crystals that precipitated were separated by filtration to obtain 94.0 g of crystals ($[\alpha]_D^{23}$ = +11.5°; mp 45.1°C). These

crystals were combined with Crop 1 (total 587.6 g) and dissolved in 411 g of *n*-heptane. The solution was cooled to about -35°C. The crystals that precipitated were separated by filtration to obtain 416.2 g, Crop 2 ($[\alpha]_D^{24}$ = +11.9°; mp 45.7°C). Crop 2 was then dissolved in 310 g of *n*-heptane, and the solution was cooled to -31°C. The crystals that precipitated were separated by filtration to obtain 278.9 g, Crop 3 ($[\alpha]_D^{24}$ = +12.2°; mp 46.4°C). The mother liquors of Crop 2 and Crop 3 were combined, and the solution concentrated to yield 298.7 g of crystals ($[\alpha]_D^{23}$ = +9.84°). The resulting crystals were subjected to three cycles of crystallization in the same way as above to give 84.2 g, Crop 4 ($[\alpha]_D^{23}$ = +12.2°; mp 46.1°C). Crops 3 and 4 were combined to obtain 363.2 g of the desired (+)-α-fenchyl alcohol in a yield of 51.2 %.

The % ee of the resulting crops were measured by the method described below, with the following results:

	$[\alpha]_D^{23}$ (c=5, EtOH)	(% ee)
Starting material	+10.0°	81.0
Crop 1	+11.6°	89.9
Crop 2	+11.9°	92.1
Crop 3	+12.2°	94.8
Crop 4	+12.2°	94.8

Determination of % ee by GLC. N-Z-(S)-alanine (0.31 g, 1.4 mmol), N-N-dimethylaminopyridine (0.01 g, 0.1 mmol) and α-fenchyl alcohol (0.2 g, 1.28 mmol) were dissolved in 2 ml CH_2Cl_2, and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.27 g, 1.4 mmol) was added under N_2. After 30 min reaction, the solution was cooled to 25°C, and left for 1 hr at that temperature. After diluting with CH_2Cl_2 (10 ml), the solution was washed 10% citric acid, 4% Na_2CO_3, saturated NaCl solution, and was dried over anh. $MgSO_4$. After evaporation of the solvent, the residue was taken up in 5 ml MeOH and reduced with H_2 at normal pressure in the presence of 20 mg Pd black. The solution was analyzed by gas chromatography in a PEG-HT column, 0.25 mm i.d., 25 m long; inlet temperature 200°C; column temperature: 100-200°C range; gradient: 3°C/min; retention time: a range of about 11-12 min; separation coefficient: 1.02.

Preparation of aluminum oxide catalysts.

(a) Catalyst A. Two hundred grams of aluminum nitrate nonahydrate [$Al(NO_3)_3 \cdot 9H_2O$; reagent first class made by Junsei Chemical Co., Ltd.] was dissolved in 2 liters of water. The solution was slowly added dropwise with stirring to 500 g of 28% aqueous NH_3 (pH 8.0 final). After standing, the resulting aluminum hydroxide was aged overnight, filtered, washed with water, dried at 60°C for 24 hr, powdered in a mortar and calcined in an electric furnace at 500°C for 3 hr to give 28.4 g of aluminum oxide as a white powder. The Hammett acidity function[26] of this product was $-5.6 \leq H_o \leq -3.0$.

(b) Catalysts B, C and D were prepared in a similar fashion, starting respectively from hydrated aluminum sulfate [$Al_2(SO_4)_3 \cdot 14\text{-}18H_2O$; Junsei Chemical Co., Japan], hydrated aluminum chloride [$AlCl_3 \cdot 6H_2O$; Junsei Chemical Co., Japan], and sodium aluminate [$NaAlO_2 \cdot xH_2O$; Nakarai Tesque Co., Japan]. In all cases, the Al_2O_3 obtained reproduced the H_o value found for A.

(+)-α-Fenchene (4).

(a) A three-necked flask equipped with a Dean-Stark device, a stirrer, a thermometer and a reflux condenser was charged with 100 g (0.65 mole, purity 98.7% ee) of (+)-α-fenchyl alcohol and 5 g of catalyst A (5% by weight), and with stirring, the mixture was heated at a temperature range from about 195 to 200°C

for 10 hr. The reaction mixture was then coarsely distilled to give 95.8 g of an oily product. Gas chromatographic analysis showed the product to consist of 72% of fenchene isomers (in which α-fenchene accounted for 59%) and 28% of unreacted fenchyl alcohol. Rectification of the oily product gave 34.4 g of 4 (54.1%; 98.7% ee; Run No.1); bp 157-158°C (730 mm Hg); ($[\alpha]_D^{24}$ = +36.27°(neat); ^{1}H NMR ($CDCl_3$) δ: 0.97 and 0.98 (each 3H, s), 1.20 - 1.34 (2H, m), 1.65 (1H, t), 1.79 - 1.96 (3H, m), 2.03 (1H, d), 2.41 (1H, d), 4.60 and 4.81 (each 1H, s); MS (m/z): 136 (M+), 121, 107, 93, 79, 53, 41, 39.

Table I. Effect of catalyst composition on the yield and purity of fenchenes produced by dehydration of fenchyl alcohols.

Run No.	Catalyst*	Starting fenchyl alcohol	Amount of the catalyst based on the fenchyl alcohol (wt%)	Reaction conditions: Temp. (°C)	Reaction conditions: Time (hr)	Total fenchene selectivity (%)	α-Fenchene selectivity (%)
1	Catalyst A	α-	5	195-200	10	72	59
2	Catalyst A	α/ß=6/4	5	195-200	10	95	65
3	Catalyst A	ß-	5	195-200	3	98	80
4	Catalyst B	α-	5	195-200	10	82	44
5	Catalyst C	α-	5	195-200	10	70	47
6	Catalyst D	α-	5	195-200	10	70	53
7	Active alumina	α-	10	195-200	16	20	36
8	Active alumina	α-	10	195-200	16	4	32
9	$NiSO_4 \cdot 6H_2O$	α-	50	195-200	4	100	2
10	$NiSO_4 \cdot 6H_2O$	α-	50	195-200	4	98	10
11	$Al_2(SO_4)_3$	α-	50	195-200	4	88	6
12	$AlPO_4$	α-	50	195-200	16	8	23
13	Aluminum silicate	α-	50	195-200	6	97.5	0
14	Alum	α-	50	195-200	16	77.4	1

* For composition and mode of preparation of catalysts see Experimental Section.

(b) Catalyst A (5% by weight) was added to a mixture of (+)-α and (+)-ß-fenchyl alcohol (α/β = 6/4). The mixture was treated as in section (a) above to obtain an oily product. Gas chromatographic analysis showed the product to consist of 95% of fenchene isomers (in which (+)-α-fenchene accounted for 65%) (Run No. 2).

(c) Catalyst A (5% by weight) was added to (+)-ß-fenchyl alcohol (purity 95%). The mixture was heated at a temperature range of from about 195 to 200°C for 3 hours with stirring and then coarsely distilled. Gas chromatographic analysis of the distillate showed it to consist of 98% of fenchene isomers (in which (+)-α-fenchene accounted for 80%) (Run No. 3).

(d) Using catalysts B, C or D, (+)-α-fenchene was produced from (+)-α-fenchyl alcohol as above. The results are shown in Table I (Runs Nos. 4 to 6).

(e) The procedure as in (a) above was repeated except that catalyst A was replaced by commercial aluminum oxide catalysts having a Hammett acidity function of $+1.5 \leq H_0 \leq +3.3$ and $+3.3 \leq H_0 \leq +4.8$. (Runs Nos. 7 and 8), a catalyst obtained by calcining nickel sulfate hexahydrate at about 250°C for 3 hr (Run No. 9), a catalyst obtained by calcining nickel sulfate hexahydrate at about 400°C for about 3 hr (Run No. 10), aluminum sulfate (Run No. 11), a catalyst obtained by calcining aluminum phosphate at 500°C for about 3 hr (Run No. 12), aluminum silicate (Run No. 13) or alum (Run No. 14). The results are also shown in Table I.

The fenchenes were analyzed by gas chromatography using an OV-1 silica capillary column (diameter 0.25 mm, length 25 m) at a temperature of about 70°C.

***7,7-Dimethyl-2-formylmethylene norbornane* (5).** Fifty grams (0.368 mole) of (+)-α-fenchene (**4**) was added dropwise under a nitrogen stream at 50 to 60°C over 1 hr to a solution which had been prepared by adding 38 ml (0.415 mole) of $POCl_3$ to 92.5 ml (1.19 mole) of DMF. The mixture was reacted for 2 hr. The reaction solution was poured into 800 ml of a 10% aqueous solution of Na_2CO_3, and extracted twice with 300 ml of toluene. The combined toluene extracts were washed with water, and the solvent was evaporated. Fractional distillation under reduced pressure gave 50.5 g of **5** (71%): bp 76-80°C (1 mm Hg); ^{1}H NMR ($CDCl_3$) δ: *E-form* 0.98 and 1.08 (each 3H, s, CH_3), 5.94 (1H, d, J=7.9 Hz, olefinic H), 9.79 (1H, d, J=7.9 Hz, C<u>H</u>O); *Z-form* 0.97 and 1.08 (each 3H, s, CH_3), 5.86 (1H, d, J=8.4 Hz, olefinic H), 9.84 (1H, d, J=8.3 Hz, C<u>H</u>O); MS (m/z): *E-form* 150, 125, 109, 107, 82, 81 (base), 79, 67, 41; *Z-form* 165 (M^++1), 164 (M^+), 149, 121 (base), 93, 91, 79, 77, 41, 39.

***(7,7-Dimethylnorborn-2R-yl)-acetaldehyde* (6).**

(a) A 1 liter autoclave was charged with 20 g (0.12 mole) of **5**, 200 ml of *n*-heptane and 0.5 g of 5% Pd/C, and the reaction was carried out at room temperature under a hydrogen pressure of 2 kg/cm^2. After the reaction, the catalyst was filtered and the solvent was evaporated. The residue was distilled under reduced pressure to give 19.7 g of **6** (97.3%). The *exo/endo* ratio of this compound was found to be 98:2 by measurement of ^{1}H NMR; bp 54-55°C (0.2 mm Hg); ^{1}H NMR ($CDCl_3$) δ: *Exo-form* 0.97 and 1.08 (each 3H, s, CH_3), 2.60 (2H, d, d, d, J=2.1, 9.6, 5.9 Hz; C<u>H</u>$_2$CHO), 9.71 (1H, t, J=7.9Hz; C<u>H</u>O); *Endo-form* 1.02 and 1.08 (each 3H, s, CH_3), 9.76 (1H, t, J=7.9 Hz, C<u>H</u>O); MS (m/z): 166 (M^+), 151, 133, 123, 122 (base), 107, 95, 81, 79, 69, 67, 55, 41. <u>Anal</u>. Found: C, 79.40; H, 10.86. Calcd. for $C_{11}H_{18}O$: C, 79.52; H, 10.84.

Table II. Effect of catalyst on the yield and stereochemistry of **6** in the hydroformylation of **4**.

Run No.	Oxo reaction catalyst	Reaction conditions		Yield (%)	*Exo/endo* ratio
		temp. (°C)	time (hr)		
1	$[CODRhCl]_2 \cdot 2PPh_3$*	90	16	93	85/15
2	$[CODRhCl]_2 \cdot 2PPh_3$	50	64	35	89/11
3	$Rh_6(CO)_{16}$	70	18	80	66/34
4	$Rh_6(CO)_{16} \cdot 2PPh_3$	70	17	81	87/13

* COD = 1,5-Cyclooctadiene

(b) A 200 ml autoclave was charged with 5.0 g (0.037 mole) of **4**, 45.3 mg (0.18 mmole) of the dimer of rhodium (I) chloride-1,5-cyclooctadiene, 95 mg (0.36 mmole) of triphenylphospine, 0.5 ml of triethylamine and 25 ml of benzene, and the reaction was carried out at 90°C for 16 hr under a synthesis gas pressure of 80 kg/cm^2 (CO pressure 40 kg/cm^2; H_2 pressure 40 kg/cm^2). The solvent was evaporated, and the residue was fractionally distilled under reduced pressure to give 5.7 g (93.4%) of **6**. The *exo*/*endo* ratio of the product was determined to be 85:15 by ^{1}H NMR.

The effect of catalyst composition on the *exo*/*endo* ratio of **6** was examined, with the results shown in Table II.

***(7,7-Dimethylnorborn-2R-yl)-(R,S)-2-amino propionitrile* (7)**. Ammonia gas was passed through 400 ml of MeOH at 5°C for 15 minutes. To the resulting solution were added 17.5 g (0.357 mole) of NaCN, 17.8 g (0.333 mole) of NH_4Cl and 52.0 g (0.313 mole) of **6**. The reaction mixture was stirred overnight at room temperature and the MeOH was evaporated under reduced pressure. To the residue was added 750 ml of 2% aqueous Na_2CO_3, and the mixture was extracted twice with 350 ml of ether. The combined ether extracts were washed with water, and then extracted twice with 300 ml of 1 N HCl. The acidic extract was made alkaline with Na_2CO_3 and further extracted with 300 ml of ether three times. The ether extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated to give 57.4 g of **7** as a pale yellow oil (95.5%). A sample was converted to the hydrochloride; ^{1}H NMR (CD_3OD) δ: 1.07 and 1.11 (each 3H, s, CH_3), 1.25 (2H, m, CH_2), 1.54 (1H, m, CH), 1.6-2.1 (7H, m, CH_2), 2.2 (1H, m, CH), 4.38-4.49 (1H, m, CH(-NH_3^+)CN), 4.8 (b.s., NH_3^+).

***(7,7-Dimethylnorborn-2R-yl)-(R,S)-alanine* (8)**. 52.0 g (0.271 mole) of **7** was added to 200 ml of water and 900 ml of concentrated HCl, and the mixture was heated under reflux for 18 hr. The reaction solution was concentrated under reduced pressure and then cooled, when the amino acid hydrochloride precipitated. It was left to stand overnight at 5°C, filtered, and washed with 600 ml of ether to give 63.2 g (94.1%). ^{1}H NMR (CD_3OD) δ: 1.02 and 1.11 (each 3H, s, CH_3), 4.37-4.42 (1H, m, C<u>H</u>(NH_3^+)CO_2H).

The free amino acid (**8**) was prepared by neutralization of the hydrochloride and precipitation at pH 4.0: mp 216-218°C. IR ν_{max} (KBr) cm^{-1}: 3400, 2930, 1610, 1495, 1395, 1330 and 1100. ^{1}H NMR (CD_3OD) δ: 0.99 and 1.11 (each 3H, s, CH_3), 1.23 (2H, q, CH_2), 1.44 (1H, t, CH), 1.5-1.9 (7H, m, CH_2), 2.02 (1H, m, CH), 3.45-3.49 (1H, m, C<u>H</u>(NH_2)CO_2H), 4.8 (b.s., OH). ^{13}C NMR (CD_3OD) δ: 174.7, 56.2, 50.3, 47.5, 45.8, 42.1, 40.0, 39.7, 32.1, 28.7, 23.3, 23.2; diastereoisomer peaks: 174.6, 55.6, 49.9, 47.4, 45.7, 41.8, 39.1, 38.3, 32.0, 23.1.

(7,7-Dimethylnorborn-2R-yl)-(R,S)-alanine methyl ester. Hydrogen chloride gas (12.5 g) was bubbled into one liter of cold MeOH and 52.0 g (0.210 mole) of **8** added. The mixture was heated under reflux for 18 hr, cooled, and the solvent evaporated under reduced pressure. The residue was dissolved in 750 ml water and the pH of the solution adjusted to 8.5 with 50% aqueous NaOH (cooling). This mixture was then extracted twice with 250 ml ethyl acetate and the combined extracts dried over Na_2SO_4 and evaporated to give (7,7-dimethylnorborn-2R-yl)-(R,S)-alanine methyl ester (44.9 g) as a yellow oil. A sample was converted to the hydrochloride; mp 184-6°C; $[\alpha]_D^{23}$ = +29.5°(c=1.2, MeOH); <u>Anal</u>. Found: C, 59.37; H, 9.13; N, 5.38; Cl, 13.71. Calcd. for $C_{13}H_{24}NClO_2$: C, 59.66; H, 9.18; N, 5.35; Cl, 13.58.

***N*-Acetyl-(7,7-dimethylnorborn-2R-yl)-(R,S)-alanine (9)**. 60 g of **8** (0.242 mole) was dissolved in 300 ml of 10% aqueous NaOH, and then 32 g (0.314 mole) of acetic anhydride was added dropwise at 40°C. After standing for 30 minutes, the reaction solution was cooled to 10°C and adjusted to pH 3 with 6 N HCl. The precipitated crude crystals were filtered, washed with water and dried. The crude crystals were recrystallized from ethyl acetate and n-hexane to give 60 g of **9** (97.6%); mp 170-171°C; $[\alpha]_D^{24}$ = +36.6° (c=1, MeOH).

^{1}H NMR (CD_3OD) δ: 0.98 and 1.09 (each 3H, s, CH_3), 1.13-1.21 (2H, m, CH_2), 1.39 (1H, q, CH), 1.45-1.85 (7H, m, CH_2), 1.92 (1H, m, CH), 1.98 (3H, s, CH_3CO), 4.32-4.39 (1H, m, C<u>H</u>(NH)CO). ^{13}C NMR (CD_3OD) δ: 175.9, 173.3, 53.8, 50.3, 47.3, 45.7, 42.8, 39.8, 38.3, 32.3, 28.8, 23.3, 23.2, 22.3; diastereoisomer peaks: 175.8, 173.2, 53.0, 45.6, 42.5, 39.0, 32.2, 28.7. IR ν_{max} (KBr) cm^{-1}: 3340, 2955, 2940, 1710, 1615, 1555, 1445, 1420, 1375, 1350, 1230, 1195, 980.

***(7-7-Dimethylnorborn-2R-yl)-(S)-alanine* (10).** To a slurry composed of 450 ml of water, 28.8 g of Na_2HPO_4, 30 mg of $CoCl_2.6H_2O$ and 60 g (0.236 mole) of **9** a 4 <u>N</u> aqueous NaOH solution was added to adjust the pH to 8.0. A solution of 1.12 g of acylase I (Amano Pharmaceutical Co., Ltd., Japan) in 12 ml of 0.1<u>M</u> phosphate buffer (pH 8.0) was added, and the mixture stirred at 37°C for 20 hours. The reaction solution was adjusted to pH 1.4 with concentrated HCl and extracted three times with 200 ml of ethyl acetate. The aqueous layer was adjusted to pH 3.0 with aqueous NH_3. The crude crystals that precipitated were separated by filtration. The resulting crude crystals (18.3 g) were dissolved in 800 ml of hot water, and treated with 1.8 g of activated carbon to give 17.7 g (71.1%) of **10**; mp 224-226°C; $[\alpha]_D^{23}$ = +49.5° (c=1, MeOH). ^{1}H NMR (CD_3OD) δ: 0.99 and 1.11 (each 3H, s, CH_3), 3.44-3.47 (1H, m, C<u>H</u>(NH_2)CO_2H). <u>Anal</u>. Found: C, 61.62; H, 9.80; N, 5.95. Calcd. for $C_{12}H_{21}NO_2 \cdot 1.3\ H_2O$: C, 61.43; H, 10.07; N, 5.97.

Separately, the ethyl acetate extract was concentrated to give crude crystals (34.9 g). The crude crystals were recrystallized from ethyl acetate and n-hexane to give 26.6 g (88.7%) of **11**; $[\alpha]_D^{23}$ = +4.1° (c=1, MeOH).

***Racemization of N-acetyl-(7,7-dimethylnorborn-2R-yl)-(R)-alanine* (11).** Ten grams (0.039 mole) of **11** was dissolved in 50 ml of AcOH and 1.0 g of Ac_2O added. This solution was then heated at 100°C for 16 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The resulting crude crystals were dissolved in 35 ml of ethyl acetate and washed with water. The ethyl acetate phase was crystallized by adding n-hexane to give 6.8 g of **9**; $[\alpha]_D^{23}$ = +35.5° (c=1, MeOH).

***(7,7-Dimethylnorborn-2R-yl)-(S)-alanine methyl ester acetate* (12).** To a solution of 12.5 g of hydrogen chloride gas in 1 liter of MeOH was added 52.0 g of (7,7-dimethylnorborn-2R-yl)-(S)-alanine hydrochloride. The solution was heated at reflux for 18 hr, then the product isolated as described for the (R,S) compound to give 47.2 g of the amino ester as a pale yellow oil.

The product (45.0 g; 0.2 mole) was dissolved in 80 ml of ethyl acetate and 13.2 g (0.22 mole) of acetic acid was added under cooling and stirring. The crystals which precipitated were collected by filtration to give 48.8 g of **12**; mp 101-104°C; $[\alpha]_D^{25}$ = +66.6° (c=1.1, MeOH). ^{1}H NMR (CD_3OD) δ: 0.99 and 1.09 (each 3H, s, CH_3), 1.19 (2H, m, CH_2), 1.35 (1H, d, CH), 1.55-1.67 (4H, m, CH_2), 1.75-1.87 (3H, m, CH), 1.93 (3H, s, CH_3CO_2), 2.08 (1H, m, CH), 3.70 (1H, t, J = 6.7 Hz, C<u>H</u>(NH_3^+)CO_2), 3.77 (3H, s, CO_2CH_3). ^{13}C NMR (CD_3OD) δ: 177.9, 174.3, 54.4, 52.9, 50.1, 47.4, 45.8, 41.9, 41.2, 38.9, 31.9, 28.7, 23.2, 23.1, 22.6 (no diastereoisomer peaks). IR ν_{max} (KBr) cm^{-1}: 2940, 2905, 1735, 1620, 1495, 1415, 1385, 1360, 1265, 1200, 1175. <u>Anal</u>. Found: C, 62.98; H, 9.33; N, 5.10. Calcd. for $C_{15}H_{27}NO_4$: C, 63.16; H, 9.47; N, 4.91.

***(S)-Aspartyl-(7,7-dimethylnorborn-2R-yl)-(S)-alanine methyl ester* (1).** 24.9 g (0.1 mole) of N-carbobenzyloxy-(S)-aspartic acid anhydride was suspended in 500 ml of toluene and the suspension was cooled to 5°C. With stirring a suspension of 28.5 g (0.1 mole) of **12** in 50 ml of toluene was added. The mixture was then stirred overnight at 5°C, extracted three times with 500 ml of 0.1<u>M</u> phosphate buffer (pH 6.5) and the toluene layer dried over Na_2SO_4 and evaporated to afford 33.5 g (70.6%) of the **14/13** mixture (α/β = 80/20) (Table III).

In a 1-liter autoclave, 25.8 g (54.4 mmoles) of the mixture was dissolved in 400 ml of MeOH, and reduced with H_2 at 3 kg/cm^2 in the presence of 1.0 g of 5% Pd/C. After removing the catalyst by filtration

Table III. Effect of the solvent upon the product ratio in the coupling of N-Z-(S)-aspartic acid anhydride with **12**. Reaction of 1 part anhydride and 1 part amino ester in 100 parts solvent, at 5°C for 18 hr.

Solvent	**14/13** ratio†	Solvent Dielectric Constant (ε, 20°C)
Tetrahydrofuran	1.4	1.7
Hexane	* 1.5	1.9
Dioxane	2.2	2.2
Carbon Tetrachloride	* 5.0	2.2
Xylene	* 7.6	2.3
Toluene	* 8.6	2.4
Butyl Ether	* 6.8	3.0
Trichloroethylene	5.6	3.4
Ethyl Ether	* 7.7 (3.5)	4.3
Chloroform	5.1	4.8
Butyl Acetate	4.2	5.0
Ethyl Acetate	3.6	6.0
Acetic Acid	4.5	6.1
Cyclopentanone	1.7	18.0
Acetone	0.9	20.7
Acetonitrile	1.3	37.5
Dimethylformamide	0.08	37.6

* N-Z-(S)-aspartic acid anhydride was insoluble (suspension) at 5°C.

† Determined by peak heights on HPLC using an Altex C_{18} column with 60% acetonitrile/0.05M KH_2PO_4, pH 4.0 as solvent and UV detection at 210 nm.

through celite, the filtrate was concentrated under reduced pressure to give crude crystals, that after one recrystallization from chloroform/*n*-hexane afforded 14.4 g (77.8% yield) of **1** (α/ß = 90/10). Further purification resulted by recrystallizing four times from 33% MeOH in water (200 ml), to afford 10.0 g (38% from **12**) of pure **1** (α/ß = 99.2/0.8); mp 148-148.2°C; $[\alpha]_D^{23}$ = +30.5° (c=1, MeOH). Overall yield from purified (+)-α-fenchyl alcohol was 6%. The α/ß ratios were determined by peak heights on HPLC, using a Unisil Q C18 (Gasukuro Kogyo Co. Ltd.) column, with 40% MeCN/1% MeOH/59% 0.1M KH_2PO_4 pH = 4.0 as solvent, and UV detection at 220 nm. ^{1}H NMR (CD_3OD) δ: 0.98 and 1.10 (each 3H, S, CH_3), 1.17 (2H, m, CH_2), 1.38 (1H, m, CH), 1.55-1.85 (7H, m, CH_2), 2.11 (1H, m, CH), 2.53 (1H, dd, J=9.7 and 16.0 Hz, CH_2CO_2H), 2.78 (1H, dd, J=4.7 and 17.1 Hz, CH_2CO_2H), 3.70 (3H, S, OCH_3), 4.09 (1H, q, J=4.6 Hz, CH-(-NH_2)-CO_2H), 4.41 (1H, q, J=5.4 Hz, CH (NHCO)CO_2CH_3), 4.81 (bs, OH). ^{13}C NMR (CD_3OD) δ: 176.3, 173.6, 170.7, 54.0, 52.8, 52.2, 49.4, 47.3, 45.7, 42.5, 39.7, 38.9, 38.4, 32.1, 28.8, 23.2, 23.1 (no diastereoisomer

peaks). IR ν_{max} (KBr) cm^{-1}: 3420, 3200, 2950, 1740, 1685, 1560, 1395, 1215. Anal. Found: C, 54.44; H, 8.56; N, 7.48. Calcd. for $C_{17}H_{28}N_2O_5 \cdot 2H_2O$: C, 54.25; H, 8.51; N, 7.45.

Determination of the sweet potency (SP) of 1. A 45 ppm solution of **1** in distilled water at 22°C matched the sweetness of a 10% sucrose solution, as perceived by a four-member panel of tasters. Thus, the relative sweetness potency of **1** (weight basis) was determined to be SP = 2200 X sucrose.

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