Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6891-6894, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01391-8

The Sweetness and Stereochemistry of L-Aspartyl-Fenchylaminoalcohol Derivatives

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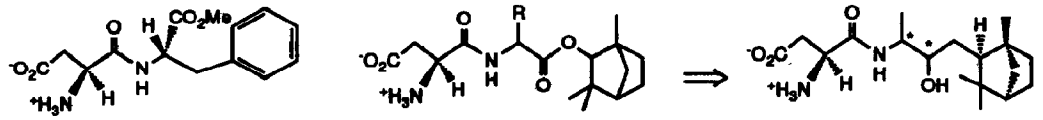
Key words: *Sweetener, Fenchone, Oxo reaction, L-Aspartyl-fenchylaminoalcohol*

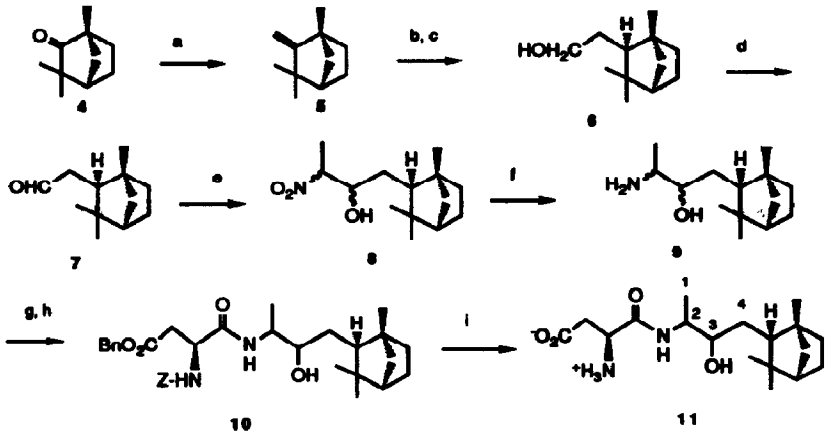
Abstract: *Four fenchylaminoalcohols were derived from (+)-fenchone in five steps. They were resolved with (+)- and (-)-tartaric acid, then condensed with N-carbobenzoxy-L-aspartic acid β-benzylester followed by hydrogenolysis to give four L-aspartyl-fenchylaminoalcohols. By the evalution of their taste, only (2R, 3R)-aminoalcohol showed potent sweetness.*

Since the original discovery of aspartame **1** in 1969,[1] a large number of analogues have been prepared by many groups[2] seeking more stable and more potent dipeptides. In particular, fenchyl esters of L-aspartyl-D,L-aminomalonic acid **2a** and L-aspartyl-2-furylglycine **2b** are known to have a high sweetness potency.[3] Their sweetness were >10000 times more potent than sucrose. However, these compounds are unstable for practical use because the ester part is labile to be hydrolyzed. To improve the chemical stability, we changed the ester unit to aminoalcohol **3**. We now report that one of the stereoisomer of **3** showed intensive sweet taste with enough stability for practical use.



1 **2a, 2b** (a: R=CO_2Me, b: R=) **3**

Treatment of (+)-fenchone **4** with methyltriphenylphosphonium bromide, followed by the oxo reaction[4] with a rhodium catalyst[5] gave an α/β isomeric mixture of the fenchylalcohol **6** (Scheme I). Fractional distillation[6] of **6** gave the α isomer with high purity, which was oxidized with pyridinium dichromate (PDC) to afford the fenchylacetaldehyde **7**. Subsequent reaction with nitroethane gave the nitroalcohol **8**, which was reduced with Raney nickel to form a diasteromeric mixture of **9**; the ratio of **9a** : **9b** : **9c** : **9d** was determined by using a capillary GC (PEG-HT column: 0.15μm, 0.25mmID x 25m). The isomer was successfully separated as shown in Fig.1 by resolution with (+) and (-)-tartaric acids followed by repeated recrystallization thus affording **9a** - **9d** but the yield was unsatisfactory.



Scheme I

a) PPh_3MeBr, n-BuLi, hexane, rfx. 24 h (62%), b) CO / H_2 = 50/50 Kg/cm², $[Rh(COD)Cl]_2$, benzene, Et_3N, 105°C, 39 h, α/β=83/17 (85%), c) Fract.dist. α/β=98/2 (55%), d) PDC, CH_2Cl_2, r.t. α/β=99/1 (89%), e) $EtNO_2$, KF, i-PrOH, r.t. 24 h (97%), f) H_2 =20 Kg/cm², RaneyNi, EtOH, r.t. 24 h (86%), g) Resolution: (+)- and (-)-tartaric acid, h) Z-L-Asp(OBn)OH, DCC, HONB, dioxane, r.t. 18 h (96%), i) H_2 / 5%Pd-C, MeOH, r.t. 5 h (95%).

Structure of **9a** and **9b**, and **9c** and **9d** were assigned *threo* and *erythro*, respectively, on the known basis that the NMR spectra of aminoalcohols have been shown to exhibit a larger (ca. 6Hz) vicinal coupling between the N-CH and O-CH for the *threo* isomer and a smaller (ca. 4Hz) in the *erythro* case[7] (Fig. 2). The absolute configuration of the aminoalcohols was determined by X-ray crystallographic analysis of the N-*p*-bromobenzoate of **9d**, to have the (2R,3S) configuration.[8] The N-*p*-bromobenzoylaminoketone derived from **9a** by oxidation with the PDC was proved to be identical with the aminoketone derived from **9d** by the same oxidation.

The absolute configurations of **9a**, **9b**, and **9c** were thus assigned (2R,3R), (2S,3S), and (2S,3R), respectively.

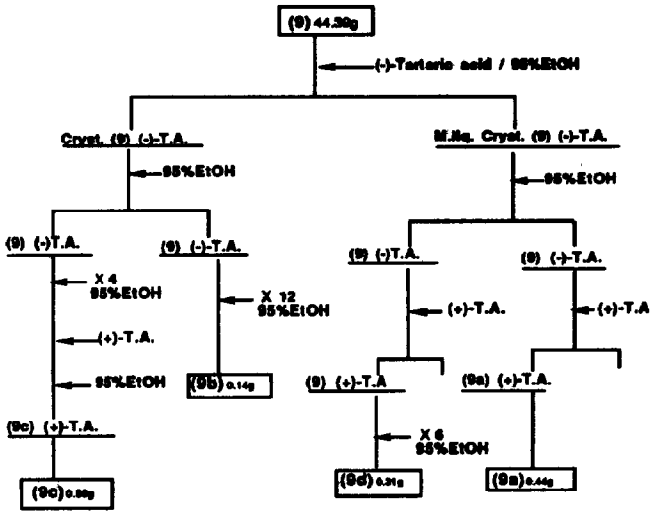


Fig.1 Resolution of Fenchyl Aminoalcohols

The aminoalcohols **9a** - **9d** were reacted with N-carbobenzoxy-L-aspartic acid β-benzylester and deprotected by hydrogenolysis to give the respective L-aspartyl-fenchylaminoalcohols **11a** - **11d**.

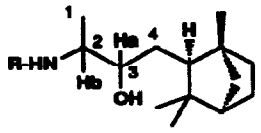
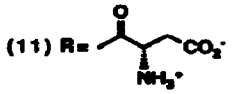


Fig. 2

(9) R=H	(9a) (2R,3R)	(9b) (2S,3S)	(9c) (2S,3R)	(9d) (2R,3S)
Product Ratio (GC)	18%	32%	22%	28%
R=H; $J_{a,b}$ Hz	6.5	6.7	3.0	3.1
(11) R= 	(11a)	(11b)	(11c)	(11d)
Sweetness (X sucrose)	12500	—	—	—

By the evaluation of their taste, only L-aspartyl-fenchylaminoalcohol **11a**, having the (2R,3R)-configuration, showed sweetness whose potency was 12500 times greater than that of sucrose.[9]

Highly intensively sweet molecules was suggested to have both hydrophilic and hydrophobic groups in their structures.[10] We assume that the hydroxy group in this aminoalcohol **11a** acts as an anchor which allows the hydrophobic fenchyl group to fit into hydrophobic binding sites in the taste receptors.[11] Compound **11a** is very stable in aqueous solution.

Acknowledgement. The authors thank Professor C. Kibayashi, Tokyo College of Pharmacy, for his advice in this work.

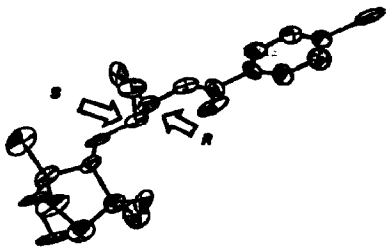
References and Notes

1. Mazur, R.H.; Schlatter, J. M.; Goldkamp, A. H. *J. Am. Chem. Soc.*, **1969**, *91*, 2684.
2. For reviews see: Pavlova, L. A.; Komarova, T. V; Davidovich, Yu. A.; Rogozhin, S. V. *Russ. Chem. Rev.* **1981**, *50*, 316. Ariyoshi, Y. *Kagaku Kyoiku* **1983**, *31*, 12.
3. Fujino, M.; Wakimatu, M.; Tanaka, K.; Nakajima, N.; Aoki, H. *Chem. Pharm. Bull.*, **1976**,*24*, 2112. Yinzeng, L.; Le, Z.; Shaoyu, W.; Wejun, X.; Tingseng, H. *Acta Biochem. Biophophys. Sin.* **1984**, *16*, 581. Janusz, J. M.; Young, P.A.; Blum, R. B.; Riley, C. M. *J. Med. Chem.*, **1990**, *33*, 1052. ibid., **1990**, *33*, 1676.
4. For an example of the oxo reaction with camphene, see: LocCicero, J. C.; Johnson, R.T. *J. Am. Chem. Soc.*, **1952**, *74*, 2094.
5. The results of other catalysts are shown below.

Entry	Catalyst	Amine	CO/H_2	Temp.	Time	Conv.	Product	α/β ratio
1	$CO_2(CO)_8$	pyridine	35/35Kg/cm²	120°C	8hr	92%	6	54/46
2	$Rh(CO)Cl(PPh_3)_2$	pyridine	35/35Kg/cm²	120°C	50hr	75%	7	55/45
3	$Rh(COD)Cl : 2PPh_3$	Et_3N	50/50Kg/cm²	105°C	16hr	45%	7	54/46

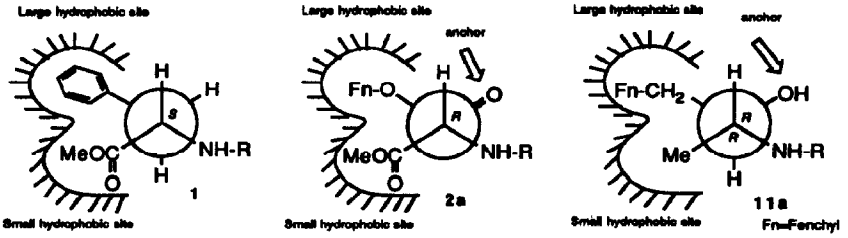
6. The Helipak No.2 filling was used.
7. Seebach, D.; Beck, A. K.; Muhopodhyay, T.; Thomas, E. *Helvetica. Chim. Acta.* **1982**, *65*, 1101

8. X-ray crystal data of N-*p*-bromobenzoate of **9d**: mp.139 -140°C (benzene-cyclohexane), crystal size; 0.6 x 0.4 x 0.3mm, $C_{27}H_{36}O_2NBr$, Orthorhombic, space group $P2_12_12_1$, Z=4, a=14.504 (11)Å, b=28.613 (17)Å, c=6.169 (9)Å, α=90.00 (8)°, β=90.00 (10)°, γ=89.99 (5)°, V=2559.7 (4.4)A^3, D_c= 1.2628g/cm^3. μ for CuKα=14.6cm^{-1}.



Diffraction data were measured on an Rigaku AFC-5S diffractometer. 1386 unique reflections were considered and used in the analysis. The structure was solved by the MULT 84 method. The R and Rw factors were 0.0955 and 0.0972. The supplementary materials is deposited at the Cambrige Crystallograhic Data Centre.

9. Sweetness potency of (2R,3R)-fenchylaminoalcohol sweetener derived from (-)-fenchone was 2100 times greater than that of sucrose .
10. Ariyoshi, Y. *Agr. Biol. Chem.*, **1976**,*40*, 983.
11. To elucidate the hydrophobic binding site in the taste receptor, the conformation of three sweeteners, Aspartame **1**, L-Aspartyl-D,L-aminomalonic acid diester **2a** and L-Aspartylaminoalcohol **11a**, is shown below using Newman projections. It is expected that the (2R,3R)- configuration of **11a** is perceived as sweet.



12. Data for representative compounds. **5**: bp$_{55}$ 82-83°C, $[\alpha]_D^{23}$ =+81.5° (c=1.2,$CHCl_3$), IR (neat) 1650 cm^{-1}.^{1}H-NMR (400MHz, $CDCl_3$) δ 1.02, 1.07 and 1.18 (each 3H, s,CH_3), 4.53 and 4.60 (each 1H, s, olefinic). **6**: bp$_2$ 94-96°C, $[\alpha]_D^{23}$ =-55.6° (c=1.76, EtOH), IR (neat) 3320 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.89, 0.96 and 1.04 (each 3H, s, CH_3), 3.52 - 3.57 and 3.63 - 3.67 (each 1H, m, CH_2OH). **7**: bp$_1$ 65°C, $[\alpha]_D^{23}$ =-47.3° (c=2.05, $CHCl_3$), IR (neat) 1725cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.80, 1.02 and 1.03 (each 3H, s, CH_3), 2.39 (2H, ddd, J =63.9, 17.1, 2.3Hz, CH_2CHO), 9.81 (1H, s,CHO). **8**: bp$_1$ 130 - 135°C, IR (neat) 3400, 1550cm^{-1}. **9a**: oil. [(+)-tartarate: mp. 198 - 199 °C $[\alpha]_D^{24}$ =+9.43° (c=0.5,H_2O)]. ^{1}H-NMR (400MHz,$CDCl_3$) δ 0.88, 0.99 and 1.05 (each 3H, s,CH_3), 1.12 (3H, d, J=6.4 Hz, CH_3CHN), 2.81 - 2.83 (1H, brd.t, J=6.5Hz, CH-N), 3.15 - 3.19 (1H,brd.t, J=6.7Hz, CH-O). **9b**: oil.^{1}H-NMR (400MHz, $CDCl_3$) δ 0.88, 1.03 and 1.04 (each 3H,s,CH_3), 1.12 (3H, d, J=6.5Hz, CH_3CHN), 2.67 - 2.73 (1H, brd.t, J= 6.7Hz, CH-N), 3.12 - 3.17 (1H, ddd, J=10.7, 6.7, 1.4Hz, CH-O). **9c**: oil.^{1}H-NMR (400MHz, $CDCl_3$) δ 0.91, 0.99 and 1.05 (each3H, s, CH_3), 1.00 (3H, d, J=6.3Hz, CH_3CH-N), 3.05 - 3.06 (1H, brd.d, J=3.0Hz, CH-N), 3.45 - 3.50 (1H, dt, J=6.9, 3.0Hz, CH-O). **9d**: oil. [(+)-tartarate: mp. 195 - 196°C , $[\alpha]_D^{23}$ = -7.78° (c=0.2, H_2O)]. ^{1}H-NMR (400MHz, $CDCl_3$) δ 0.86, 1.03 and 1.05 (each 3H, s, CH_3), 1.03 (3H, d, J=6.3Hz, CH_3CHN), 2.91 - 2.98 (1H, dd, J=6.9, 3.1Hz, CH-N), 3.41 - 3.45 (1H, dq, J=10.2, 3.1, 1.5Hz, CH-O). **10a**: viscous liquid. ^{1}H-NMR (400MHz, CD_3OD) δ 0.84, 1.01 and 1.04 (each 3H, s, CH_3), 1.15 (3H, d, J=6.7Hz, CH_3CH-N), 2.7 (1H, dd, J=17.2, 4.5Hz, Aspβ–CH_2), 3.10 (1H, dd, J=17.2, 4.5Hz, Aspβ–CH_2), 3.47 (1H, dq, J=6.9, 3.0Hz, CH-N), 3.91 - 3.95 (1H, m, CH-O), 4.55- 4.60 (1H, m, Aspα–CH), 5.05 - 5.16 (4H, m, 2xCH_2Ph), 7.36 (10H, brs, AromH). **11a**: mp.134 -136°C, $[\alpha]_D^{24}$ =+11.63° (c=1.0, MeOH). ^{1}H-NMR (400MHz, CD_3OD) δ 0.91, 0.99 and 1.04 (each 3H, s, CH_3), 1.19(3H, d, J=7.1Hz, CH_3CH-N), 2.56 (1H, dd, J=17.0, 8.9Hz, Aspβ–CH_2), 2.68 (1H, dd, J=17.0, 5.2Hz, Aspβ–CH_2), 3.46 - 3.52 (1H, m, CH-N), 3.93 - 4.02 (1H, m, CH-O), 4.05 (1H, dd, J=8.9, 5.2Hz, Aspα–CH).

(*Received in Japan* 14 *January* 1994; *accepted* 24 *May* 1994)