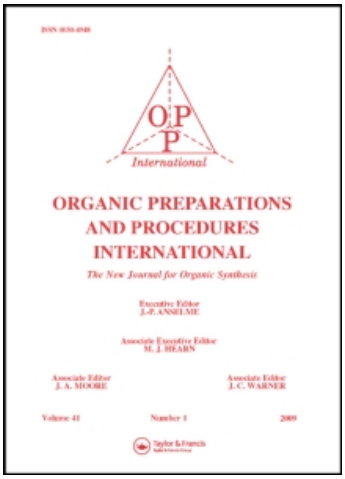

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A NEW SYNTHESIS OF AN AMINO ACID BASED SWEETENER

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A NEW SYNTHESIS OF AN AMINO ACID BASED SWEETENER

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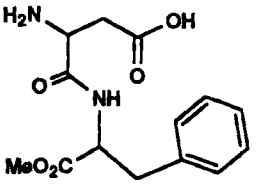
We wish to report a novel synthesis of a precursor to the sweetener aspartame (N-L-phenylalanyl-L-aspartic acid methyl ester). Our route to this dipeptide is based on the formation of the phenylalanine unit using a Mannich condensation between the protected isoasparagine **3**, phenylacetaldehyde and benzotriazole. Displacement of the benzotriazole with cyanide leads to the α-acylamino nitrile **5**, which on hydrolysis would yield the aspartyl- phenylalanine dipeptide.



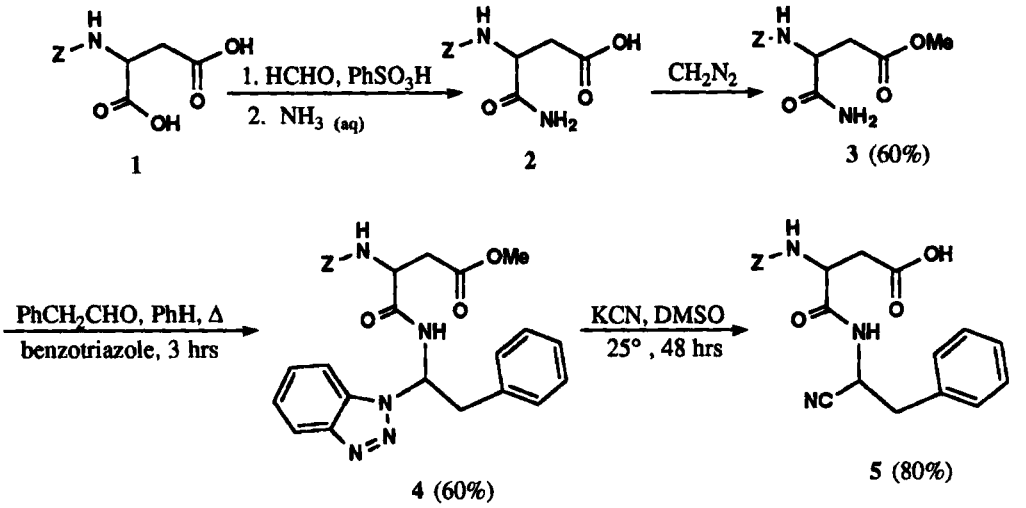
Aspartame

Benzotriazole has been developed in one of our laboratories as an inexpensive and highly efficient synthetic auxiliary group.[1] Two-step reaction sequences consisting of a Mannich condensation of benzotriazole, an aldehyde and a NH-compound, followed by displacement of the benzotriazole moiety by a nucleophile, have been shown to be convenient high yielding methods for the N-substitution of nitrogen compounds. Recently, we reported on the preparation of benzotriazole Mannich derivatives with protected amino acid amides, which underwent nucleophilic substitution of benzotriazole with ammonia to give monoacylaminals.[2] Similarly, such derivatives could undergo elimination of benzotriazole with cyanide giving α-acylamino nitriles which by subsequent hydrolysis to the α-amino amide and repetition of the sequence provides a method of peptide elongation.[3] We now show how this method can be applied to the preparation of the dipeptide unit 5 from protected isoasparagine **3**.

The overall synthesis is outlined in Scheme 1. Using the procedure of Straka and Zaoral,[4] benzyloxycarbonyl protected aspartic acid (**1**) was condensed with paraformaldehyde and the resulting oxazolidinone underwent *in situ* ammonolysis to afford Z-isoasparagine (**2**). Attempts to condense the amido group of **2** in Mannich reactions with benzotriazole failed. However, the methyl ester of Z-isoasparagine (**3**)[5] underwent the desired Mannich reaction with benzotriazole and phenyl-

acetaldehyde in refluxing benzene to give derivative **4**. Displacement of the benzotriazole from **4** was then accomplished by potassium cyanide in dimethyl sulfoxide to give the α-acylamino nitrile **5**. During work-up the ester function was hydrolyzed to the acid.

Scheme 1



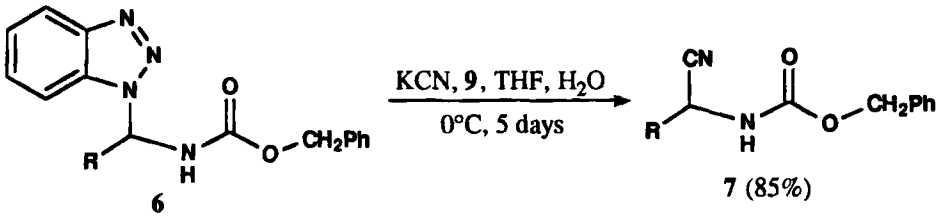
1 2 3 (60%) 4 (60%) 5 (80%)

Previous investigations demonstrated that the nucleophilic substitution with cyanide could be carried out in either dimethyl sulfoxide or in a tetrahydrofuran/water two-phase system with a phase-transfer catalyst (PTC).[3] In dimethyl sulfoxide, the reaction is generally faster and the α-acylamino nitrile **5** was obtained in 80% yield.

The PTC method has the potential of achieving asymmetric substitution of the benzotriazole by employing chiral phase-transfer catalysts. Chiral PTCs have been gaining attention in recent years.[6] Work with N-alkyl derivatives of the various cinchona alkaloids had established N-benzylcinchoninium chloride (BCNC) as the most effective catalyst of the group, although enantioselectivities were modest (20-30%).[7] Interestingly, although primarily used for alkylations of active methylene compounds,[7a] oxidations[7b] and Michael additions,[7c] BCNC has been reported to catalyze an asymmetric nucleophilic substitution reaction involving an α-bromoester, albeit with low selectivity (<4% ee).[7d] A significant improvement in chiral PTC methodology came with the highly efficient alkylation of indanone derivatives in 94% ee using [*p*-(trifluoromethyl)-N-benzyl]cinchoninium bromide (*p*-CF_3BCNB).[8] Recently, O'Donnell has employed *p*-CF_3BCNB and BCNC in asymmetric alkylations of benzophenone imine glycine esters to give α-amino acids with up to 66% selectivity.[9] In an extension of this work, Miller has shown that the aldol reaction between imine protected glycine esters and aldehydes under chiral PTC conditions proceeds with 3-12% ee.[10] These recent encouraging developments and the rewards in terms of synthetic simplicity, yield and cost prompted us to examine the chiral phase-transfer route as the key step in the preparation of the second amino acid unit.

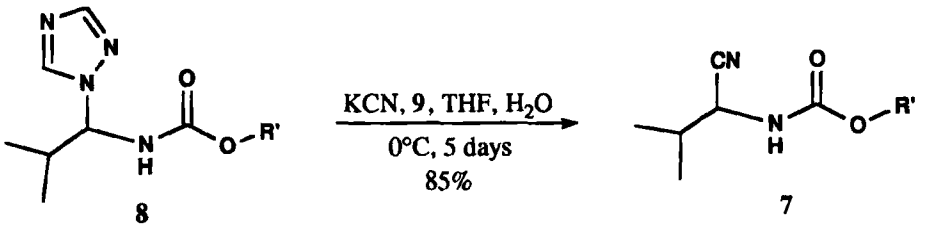
To determine the feasibility of this approach to our system, Mannich derivatives **6a, 6b**[2] and **8a, 8b** derived from benzotriazole or 1,2,4-triazole, an aldehyde and a carbamate were prepared and treated with potassium cyanide under chiral PTC conditions. The results are outlined in Scheme 2. Several variables were studied to determine which conditions gave the highest optical yield. Three cinchona derived chiral catalysts were examined, BCNC (**9a**), *p*-CF_3BCNB (**9b**), and *p*-(*t*-butyl)BCNB) (**9c**), with catalyst **9b** showing the highest selectivity. Replacement of the benzotriazole leaving group by 1,2,4-triazole resulted in enhanced selectivity. Lowering the reaction temperature to 0° increased the optical yield; however at -78°, or with change of solvent from tetrahydrofuran to toluene, only traces of the desired product were obtained. The α-cyano carbamate **7a**, displaying the highest optical rotation was determined by chiral HPLC to have an enantiomeric excess of 5.4%.

Scheme 2



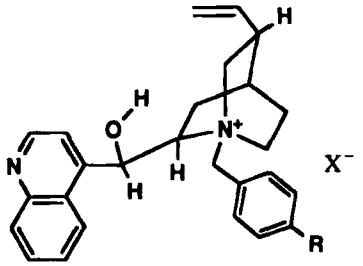
6

a) R = *i*-Pr **b)** R = Ph



8 **7**

a) R' = $PhCH_2$ **b)** R' = *t*-Bu



9a (R = H, X = Cl)
9b (R = CF_3, X = Br)
9c (R = *t*-Bu, X = Br)

Substrate	Catalyst	Product	$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) (max. obs.)
6a	**9a**	**7a**	1.9
6b	**9b**	**7b**	0.25
8a	**9c**	**7a**	3.3
8b	**9b**	**7c**	1.56

Hydrolytic enzymes are known to catalyze the stereoselective hydrolysis of various functional groups.[11] An alternative stereoselective route to the second amino acid unit is the enzyme-

catalyzed hydrolysis of the nitrile group of the D,L-α-aminonitrile **5** into the corresponding L-α-amino acid. This approach is currently under investigation.

In summary, a vital intermediate in a novel route to the dipeptide L-aspartyl-L-phenylalanine has been prepared. The key steps are the formation of a Mannich derivative from protected isoasparagine, benzotriazole and phenylacetaldehyde and subsequent displacement of benzotriazole with cyanide. Exploratory work has shown that modest chirality in nucleophilic displacement with cyanide can be induced by use of chiral PTC methodology.

EXPERIMENTAL SECTION

Column chromatography was carried out on MCB silica gel (230-400 mesh). Melting points were determined with a Kofler hot stage apparatus and are uncorrected. ^1H and, ^{13}C NMR spectra were recorded on a Varian VXR 300 MHz spectrometer in $CDCl_3$ using TMS as an internal reference for ^1H spectra and $CDCl_3$ for ^{13}C spectra (abbreviations used: s singlet, d doublet, t triplet, m multiplet, bs broad singlet, bd broad doublet and dd doublet of doublets). Elemental analyses were performed on a Carlo Erba-1106 instrument under the supervision of Dr. D. Powell. Determination of optical purity was obtained by chromatography using a chiral OD 25 cm 4.6 mm using 10% (*v/v*) IPA in hexane as the mobile phase. The chiracel OD column was silica coated with the tris (3,5-dimethylphenylcarbamate) derivative of cellulose. Z-Isoasparagine (**2**)[4] and methyl Z-isoasparagine (**3**)[5] were prepared by the previously reported methods. The synthesis of [N-(l-benzotriazol-1-yl-2-methyl)propyl]benzylcarbamate (**6a**) and [N-(l-benzotriazol-1-yl-1-phenyl)methyl]benzylcarbamate (**6b**) have been previously described by this group.[2] Catalysts **9a** and **9b** are commercially available (Fluka). Catalyst **9c** was prepared from cinchonine and *tert*-butyl bromide in refluxing THF.[7c]

Methyl [3-(benzyloxycarbonyl)amino-4-(l-benzotriazol-1-yl-2-phenylethyl)amino-4-oxo]-butanoate (4).- To a solution of benzotriazole (0.72 g, 6 mmol) and methyl Z-isoasparagine (**3**) (1.16 g, 4 mmol) in benzene (20 mL) was added phenylacetaldehyde (0.7 mL, 6 mmol) and *p*-toluenesulfonic acid (0. 1 g) and the resulting mixture refluxed for 3 hrs with azeotropic removal of water. On completion, the solution was allowed to cool, washed successively with aqueous K_2CO_3 (100 mL) and water (100 mL), and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude product which was chromatographed on silica gel with hexane: EtOAc (3:1) as the eluent to yield **4** (1.21 g, 60%, mp 133-135°) as a 1:1 mixture of diastereoisomers. The NMR data for the single diastereoisomer which crystallized from the eluent is detailed. ^1H NMR: δ 2.6 (m, 1H), 2.9 (m, 1H), 3.6 (s, 3H, $OC\underline{H}_3$), 3.5-3.8 (m, 2H), 4.5 (m, 1H), 5.1 (s, 2H, $PhC\underline{H}_2O$), 5.9 (bd, 1H, N<u>H</u>), 6.8 (m, 1H, C<u>H</u>-NH), 7.0-7.5 (m, 13H, ArH), 7.9 (bd, 1H, N<u>H</u>), 8.0 (d, J = 9Hz, 1H, ArH). ^{13}C NMR δ 35.7 ($\underline{C}H_2CO$), 40.1 ($PhCH_2$), 50.8 (<u>C</u>HCO), 51.8 (N-<u>C</u>H-N), 63.4 ($O\underline{C}H_3$), 67.2 ($Ph\underline{C}H_2O$), 109.4, 119.7, 124.0, 127.l, 127.5, 127.9, 128.1, 128.4, 128.5, 129.0, 132.8, 134.5, 135.8, 145.2 (ArH), 155.9 (<u>C</u>ONH), 170.4, 172.4 (<u>C</u>OO).

Anal. Calcd for $C_{27}H_{27}N_5O_5$: C, 64.66; H, 5.43; N, 13.96. Found: C, 64.41; H, 5.39; N, 14.00

3-(Benzyloxycarbonyl)amino-4-(1-cyano-2-phenylethylamino)-4-oxobutanoic Acid (5).- Finely powdered potassium cyanide (1.2 g, 19 mmol) was added to a solution of methyl [3-(benzyloxycar-

bonyl)amino-4-((benzotriazol-1-ylbenzyl)methyl)amino-4-oxo]butanoate (4) (5.01 g, 10 mmol) in DMSO (20 mL) at 25° and the resulting mixture stirred for 48 hrs. The reaction mixture was then quenched with ice-water (20 mL) and the resulting precipitate filtered off. The filtrate was dissolved in CH_2Cl_2 (20 mL), which on drying ($MgSO_4$) and evaporation under reduced pressure yielded **5** (1.16 g, 80%) as a thick foamy low melting solid. A 1:1 mixture of diastereoisomers is observed in the ^{13}C NMR spectra and some signals are duplicated. ^1H NMR: δ 2.80 (m, 1H), 3.00 (m, 1H), 3.25 (m, 1H), 3.45 (m, 1H), 4.10-4.30 (m, 1H), 5.15 (m, 3H), 5.65 (m, 1H), 7.30 (m, 10H). 13C NMR δ 35.3, 35.6 ($\underline{C}H_2CO$), 36.2, 36.0 ($\underline{C}HCN$), 41.7, 41.9 ($Ph\underline{C}H_2$), 49.9, ($\underline{C}HCO$), 67.6 ($Ph\underline{C}H_2O$), 115.0, ($\underline{C}N$), 128.0, 1281, 128.5, 128.6, 129.0, 129.2, 129.3, 133.6, 135.6 (ArH), 155.8 ($\underline{C}ONH$), 171.9, 173.6 ($\underline{C}OO$). MS (*m/z*, relative intensity, FAB) 395 (M^+, 18), 378 (M^+ -OH, 100); exact mass (MH^+ -OH, CI) $C_{21}H_{21}N_3O_4$ requires 379.1532, found 379.1533.

α-Cyanocarbamates 7. Typical Procedure.- The appropriate carbamate **6** or **8** (25 mmol) in THF (6.25 mL) was mixed with an aqueous solution of potassium cyanide (3 mL, 1M soln.) and the catalyst N-benzyl cinchonium chloride (BCNC) (0.1 g) was added. The reaction mixture was stirred at 0° for five days. On completion, Et_2O (20 mL) was added, the aqueous phase separated and the organic phase washed successively with aqueous K_2CO_3 (25 mL, 1M soln.), and water (50 mL). On drying ($MgSO_4$) and evaporation, the crude product was purified by chromatography (silica gel; hexane-CH_2Cl_2, 3: 1) to give the α-cyano carbamate **7.**

[N-(1-Cyano 2-methyl)propyl]benzyl carbamate (7a): obtained as an oil in 70% yield from [N-(1-benzotriazol-1-yl-2-methyl)propyl]benzyl carbamate **6a** and in 77% yield from [N-(l-2-4-triazol-1-yl-2-methyl)propyl]benzyl carbamate **8a**. All spectral data matched those of the known compound.[2]

[N-(1-Cyano 2-phenyl)methyl]benzyl carbamate (7b): obtained in 72% yield as a white crystalline solid, mp. 108-110°, lit.[2] mp. 103-105° from [N-(l-benzotriazol-1-yl-2-phenyl)methyl]benzyl carbamate **6b**.

[N-(1-Cyano 2-methyl)propyl]-*t*-butyl carbamate (7c): obtained in 75% yield as white crystalline solid mp. 75-77° from [N-(1,2,4-triazol-1-yl-2-methyl)propyl]-*t*-butyl carbamate **8b**. ^1H NMR: δ 1.08 (d, 3H, *J* = 5Hz, $CH(C\underline{H}_3)_2$), 1.12 (d, 3H, *J* = 5Hz, $CH(C\underline{H}_3)_2$), 1.48 (s, 9H, $C(C\underline{H}_3)_3$) 2.20 (m, 1H, $(\underline{C}H_3)_2CH$), 4.50 (m, 1H, $C\underline{H}$-NH), 4.80 (bs, 1H, $N\underline{H}$). ^{13}C NMR δ 17.9 ($(\underline{C}H_3)_2CH$), 18.4 ($(\underline{C}H_3)_2CH$), 28.1 ($(\underline{C}H_3)_3C$), 31.7 ($(CH_3)_2\underline{C}H$), 48.3 ($\underline{C}H$-CN), 80.9 ($Me_3\underline{C}$), 118.0 ($\underline{C}N$), 154.5 (CO).

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.48; H, 9.55; N, 13.82

[N-(1,2,4-Triazol-1-yl-2-methyl)propyl] carbamates 8. General Procedure.- 1,2,4-Triazole (2.06 g, 20 mmol), *i*-butyraldehyde (1.8 mL, 20 mmol) and the respective carbamate (20 mmol) were added to toluene (100 mL) containing, *p*-toluenesulfonic acid (150 mg) and the resulting solution refluxed for 5 hrs with azeotropic removal of water. The solution was allowed to cool and washed successively with aqueous K_2CO_3 (50 mL) and water (50 mL). Upon drying ($MgSO_4$) and evaporation of the toluene, the crude product was obtained as a solid which was recrystallized from Et_2O.

[N-(1,2,4-Triazol-1-yl-2-methyl)propyl]benzyl carbamate 8a: obtained in 87% yield as a white

crystalline solid, mp. 158-159°. ^{1}H NMR: δ 0.74 (d, J = 6.6Hz, 3H, CH(CH_3)$_2$), 1.08 (d, J = 6.6Hz, 3H, CH(CH_3)$_2$), 2.4 (m, 1H, (CH_3)$_2$CH), 5.1 (m, 2H, PhCH_2O), 5.6 (t, 1H, J = 9.5Hz, CH), 6.1 (bd, 1H, NH), 7.3 (m, 5H, Ph), 8.0 (s, 1H), 8.2 (s, 1H). ^{13}C NMR δ 18.5 ((CH_3)$_2$C), 18.6 ((CH_3)$_2$CH), 32.2 (Me$_2$CH), 67.4 (PhCH_2O), 71.4 (N-CH_2), 128.1, 128.4, 128.6, 143.5, 152.4 (CO).

Anal. Calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 60.89; H, 6.61; N, 20.73

[N-(1,2,4-Triazol-1-yl-2-methyl)propyl]-*t*-butyl carbamate (8b): obtained in 85% yield as a white crystalline solid, mp. 153-155°. ^{1}H NMR δ 0.75 (d, 3H, J = 6.7Hz, CH(CH_3)$_2$), 1.09 (d, 3H, J = 6.7Hz, CH(CH_3)$_2$), 1.40 (s, 9H, C(CH_3)$_3$) 2.45 (m, 1H, (CH_3)$_2$CH), 5.50 (m, 1H, CH-N), 6.20 (bs, 1H, NH), 8.00 (s, 1H), 8.25 (s, 1H). ^{13}C NMR δ 18.5 ((CH_3)$_2$CH), 28.1 ((CH_3)$_3$C), 32.1 ((CH_3)$_2$CH), 71.1 (N-CH-N), 80.5 ((CH_3)$_3$C) 143.4, 152.1, 154.8 (CO).

Anal. Calcd for $C_{11}H_{20}N_4O_2$: C, 54.98; H, 8.39; N, 23.31. Found: C, 54.59; H, 8.53; N, 23.15

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