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Short Research Article

Synthesis of (1-^{14}C)butyl, ($^{13}C_2$-dimethyl)butyl and ($^{2}H_6$-dimethyl)butyl-neotame†

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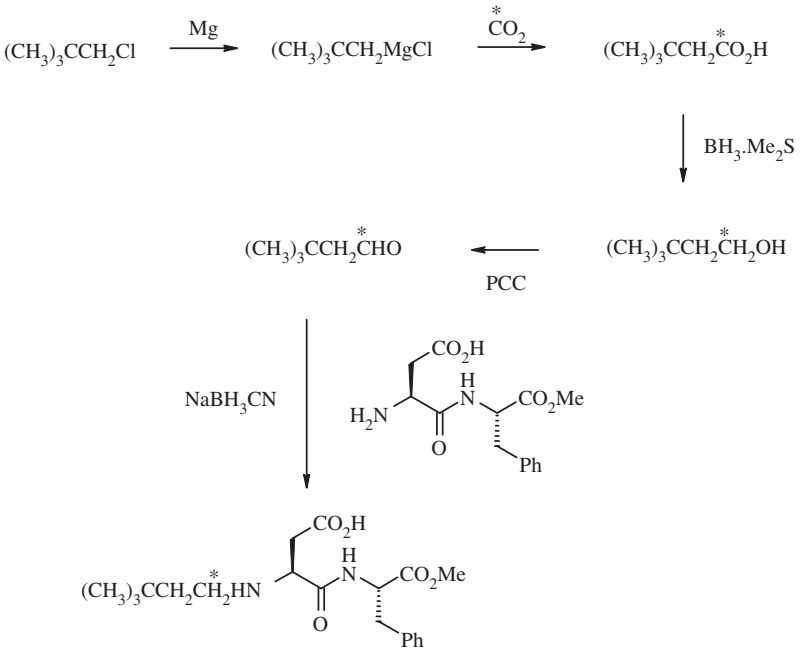
Introduction

Neotame, N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester is a high intensity sweetener. As part of the safety testing programme, neotame was synthesized labelled with ^{14}C at the 1-position in the dimethylbutyl side chain and with $^{13}C_2$ and separately $^{2}H_6$ in the terminal methyl groups of the same side chain.



Scheme 1

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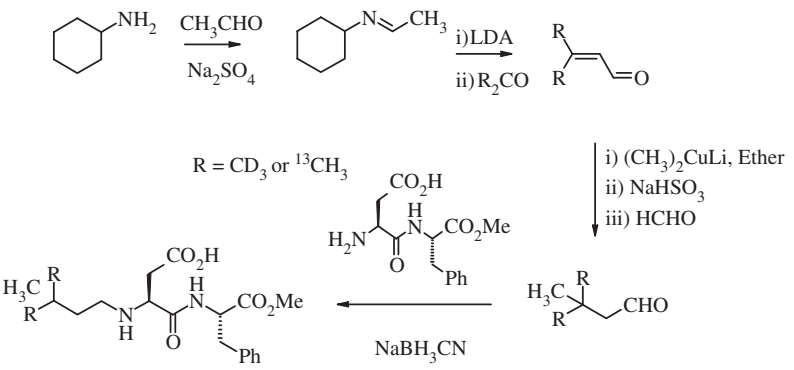

Scheme 2

Results and discussion

(1-^{14}C)butyl-neotame synthesis

The synthesis of [1-^{14}C]butyl-neotame was initiated by carbonation of 2,2-dimethylpropyl magnesium chloride with [^{14}C]carbon dioxide to form 3,3-dimethyl-[1-^{14}C]butyric acid. Reduction of this acid with borane-dimethyl sulphide complex produced the alcohol which was oxidized successfully with pyridinium chlorochromate to the aldehyde. Reductive coupling of the 3,3-dimethyl[1-^{14}C]butyraldeyde with aspartame gave the [1-^{14}C]butyl-neotame with a specific activity of 22 mCi/mmol. The radiochemical purity was >99%. The identity of [1-^{14}C]neotame was confirmed by co-chromatographic and spectrometric comparison with neotame reference standard (Scheme 1).

($^{13}C_2$-dimethyl)butyl-neotame

Synthesis of the [$^{13}C_2$-dimethyl]butyl-neotame was initiated by reaction of cyclohexylamine with acetaldeyde to form ethylidene cyclohexylamine which was reacted with 1,3-$^{13}C_2$acetone to form the labelled dimethylacrylaldehyde. Methylation of this aldehyde by Michael-type addition using dimethyl lithium cuprate gave the labelled dimethylbutyraldehyde which was reductively coupled with aspartame to form [$^{13}C_2$-dimethyl]butyl-neotame. Estimated isotopic purity was >98 atom % ^{13}C. The identity of the product was confirmed by spectrometric comparison with neotame reference standard (Scheme 2).

($^{2}H_6$-dimethyl)butyl-neotame synthesis

Synthesis of the [$^{2}H_6$dimethyl]butyl-neotame was conducted by the same synthetic route except that ethylidene cyclohexylamine was reacted with $^{2}H_6$-dimethyl-acetone (Scheme 2).

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