

Short Research Article

Synthesis of (1-¹⁴C)butyl, (¹³C₂-dimethyl)butyl and (²H₆-dimethyl)butyl-neotame[†]

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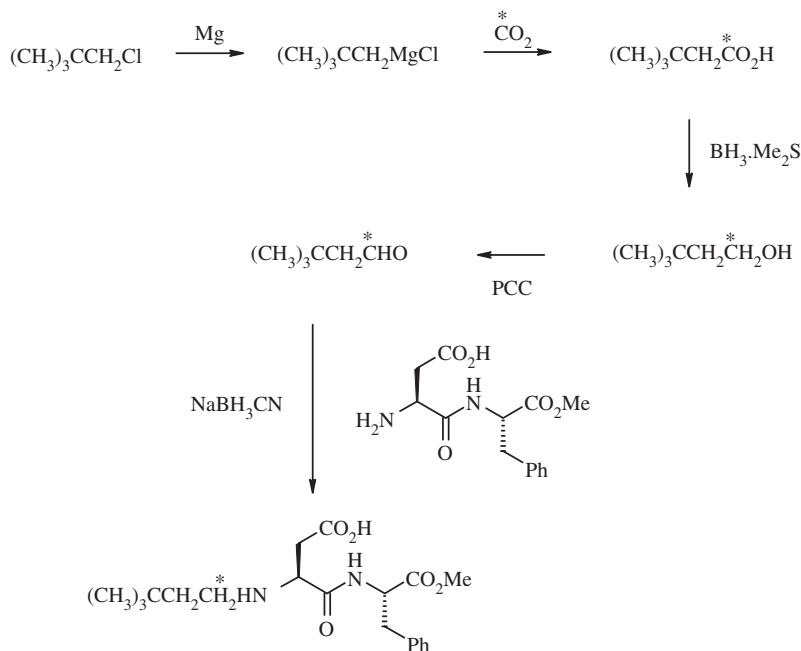
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Introduction

Neotame, N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine 1-methyl ester is a high intensity sweetener.

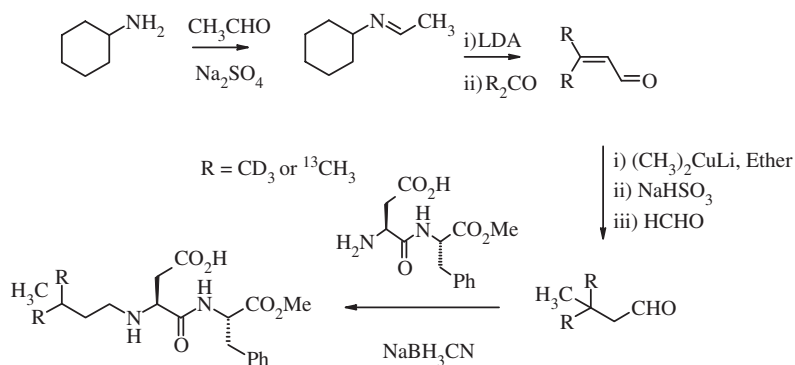
As part of the safety testing programme, neotame was synthesized labelled with ¹⁴C at the 1-position in the dimethylbutyl side chain and with ¹³C₂ and separately ²H₆ in the terminal methyl groups of the same side chain.



Scheme 1

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**Scheme 2**

Results and discussion

(1-¹⁴C)butyl-neotame synthesis

The synthesis of [1-¹⁴C]butyl-neotame was initiated by carbonation of 2,2-dimethylpropyl magnesium chloride with [¹⁴C]carbon dioxide to form 3,3-dimethyl-[1-¹⁴C]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[1-¹⁴C]butyraldehyde with aspartame gave the [1-¹⁴C]butyl-neotame with a specific activity of 22 mCi/mmol. The radiochemical purity was >99%. The identity of [1-¹⁴C]neotame was confirmed by co-chromatographic and spectrometric comparison with neotame reference standard (Scheme 1).

(¹³C₂-dimethyl)butyl-neotame

Synthesis of the [¹³C₂-dimethyl]butyl-neotame was initiated by reaction of cyclohexylamine with

acetaldehyde to form ethylidene cyclohexylamine which was reacted with 1,3-¹³C₂acetone 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 [¹³C₂-dimethyl]butyl-neotame. Estimated isotopic purity was >98 atom % ¹³C. The identity of the product was confirmed by spectrometric comparison with neotame reference standard (Scheme 2).

(²H₆-dimethyl)butyl-neotame synthesis

Synthesis of the [²H₆-dimethyl]butyl-neotame was conducted by the same synthetic route except that ethylidene cyclohexylamine was reacted with ²H₆-dimethyl-acetone (Scheme 2).