

Short Research Article

Synthesis of two labeled forms of proteasome inhibitor MLN273[†]

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Introduction

MLN273, (R)-3-methyl-1-[(S)-2-(morpholine-4-carbox-amido)-3-(naphthalen-1-yl) propanamido]butylboronic acid, is a potent proteasome inhibitor that is under pre-clinical evaluation for the treatment of hematologic malignancies.¹ [¹⁴C]MLN273 **9** was synthesized in three radiochemical steps in order to support metabolite profiling and whole body autoradiography studies in experimental animals. [D₈]MLN273 **19** was required for biotransformation and pharmacokinetic studies.

Results and discussion

[¹⁴C]MLN273 was prepared via a modification of the previously described procedure (Scheme 1).² This new synthetic route was designed to incorporate the carbon-14 label at a later stage in the synthetic sequence. (1S,2S,3R,5S)-Pinanediol leucine boronate trifluoroacetate salt³ **1** (prepared according to literature procedures) was coupled with N-Boc protected L-naphthylalanine **2** in the presence of TBTU. To prepare the key intermediate **7**, commercially available [¹⁴C]phosgene **5** was used as the starting material. Treatment of **5** with morpholine **6** in tetrahydrofuran provided morpholine-4-[¹⁴C]carbonyl chloride **7**,⁴ which was reacted with the deprotected pinanediol ester of β-(1-naphthyl)-L-leucine boronic acid **4** in the

presence of diisopropylethylamine to generate the protected boronate **8**. Boronic acid deprotection was accomplished by two-phase transesterification with isobutyl boronic acid.² The desired product **9** was isolated by extraction and solvent washings.

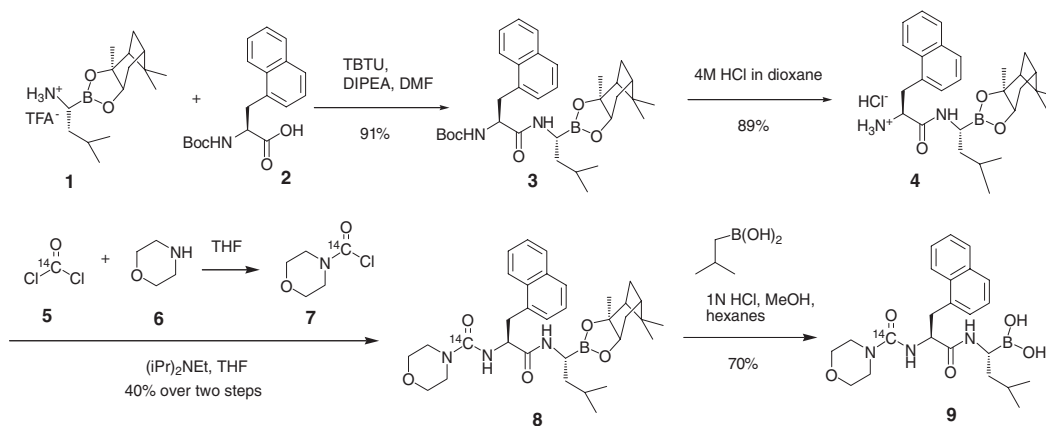
Although there are numerous biocatalytic processes to produce optically active phenylalanine analogs,⁵ there are no published reports for enantioselective chemical synthesis of L-naphthylalanine. We chose to utilize enantioselective hydrogenation of N-protected dehydro amino acid to prepare key labeled precursor L-naphthylalanine.

Commercially available [D₁₀]1-methylnaphthalene was used as the starting material for the synthesis of [D₈]1-methylnaphthalene. Treatment of [D₁₀]1-methylnaphthalene **10** with N-bromosuccinimide in carbon tetrachloride provided the bromide **11**. Refluxing **11** with hexamethylenetetramine in water and acetic acid yielded the aldehyde **12**. The Horner-Emmons olefination of aldehyde **12** with phosphonate **13** gave **14** with Z-configuration as the major product.⁶ The enantiomerically pure α-amino acid derivative **15** was synthesized by the use of Burk's DuPHOS-based Rh (I) catalyst.⁶ Successive steps of ester hydrolysis and amine deprotection produced the desired amino-acid L-[D₈]naphthylalanine **16** which was further utilized to prepare the required proteasome inhibitor.

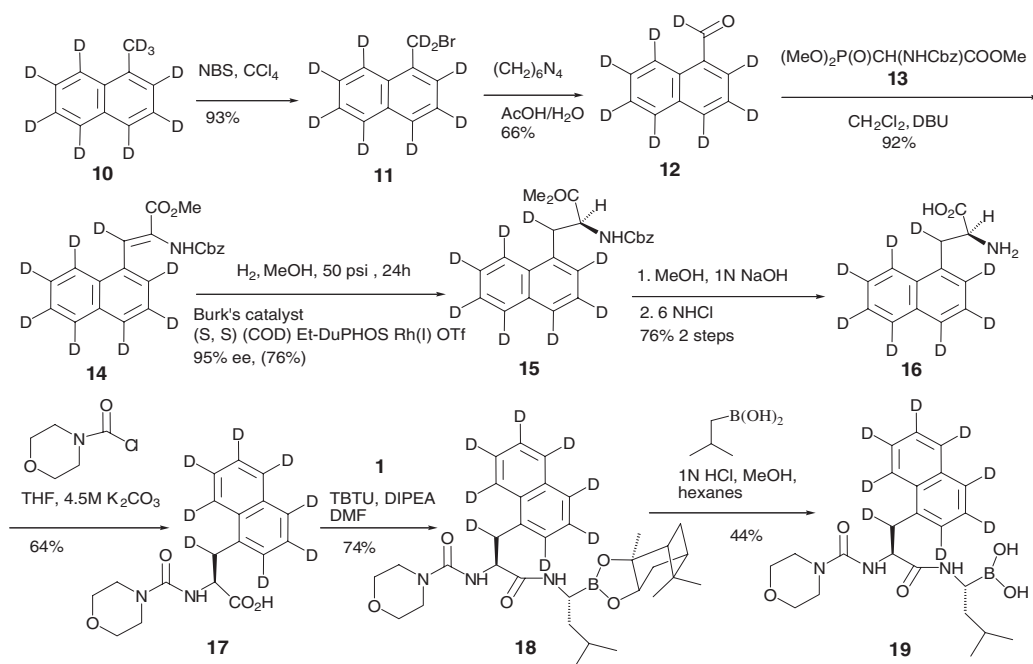
As illustrated in Scheme 2, synthesis of [D₈]MLN273 was completed by adaptation of the previously described procedure.² The stable isotope labeled L-[D₈]naphthylalanine **16** was N-acylated with 4-morpholinecarbonyl chloride, followed by coupling with the previously prepared R-aminoboronic ester **1** to provide the dipeptide boronate ester **18**. Boronic acid deprotection was accomplished by a procedure analogous to the one that was described in Scheme 1 to get the final product **19**.

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Scheme 1



Scheme 2

Conclusions

Utilization of [^{14}C]phosgene is a practical method for the efficient preparation of labeled heterocyclic acid chlorides. The labeled dipeptidyl boronic acid [^{14}C]MLN273, with label in the morpholine portion of the molecule, was prepared from [^{14}C]phosgene in a quick 3-step sequence affording product in a 28% overall radiochemical yield.

Application of the enantioselective rhodium-catalyzed hydrogenation of N-protected (Z)-dehydro-aminoacids, followed by deprotection, offers an efficient route for the synthesis of deuterium labeled chiral amino-acids. The (S,S) catalyst afforded the stable isotope labeled L-[D₈]naphthylalanine derivative with an absolute S configuration based on the selectivity of the (S,S)-Et-DuPHOS ligand, with a high yield and high ee.

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