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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-carboxamido)-3-(naphthalen-1-yl) propanamido]butylboronic acid, is a potent proteasome inhibitor that is under preclinical evaluation for the treatment of hematologic malignacies.[1] [^{14}C]MLN273 **9** was synthesized in three radiochemical steps in order to support metabolite profiling and whole body autoradiography studies in experimental animals. [D_8]MLN273 **19** was required for biotransformation and pharmacokinetic studies.

Results and discussion

[^{14}C]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. (1*S*,2*S*,3*R*,5*S*)-Pinanediol leucine boronate trifluoroacetate salt[3] **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 [^{14}C]phosgene **5** was used as the starting material. Treatment of **5** with morpholine **6** in tetrahydrofuran provided morpholine-4-[^{14}C]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 [D_{10}]1-methylnaphthalene was used as the starting material for the synthesis of [D_8]1-methylnaphtalene. Treatment of [D_{10}]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-[D_8]naphthylalanine **16** which was further utilized to prepare the required proteasome inhibitor.

As illustrated in Scheme 2, synthesis of [D_8]MLN273 was completed by adaptation of the previously described procedure.[2] The stable isotope labeled L-[D_8]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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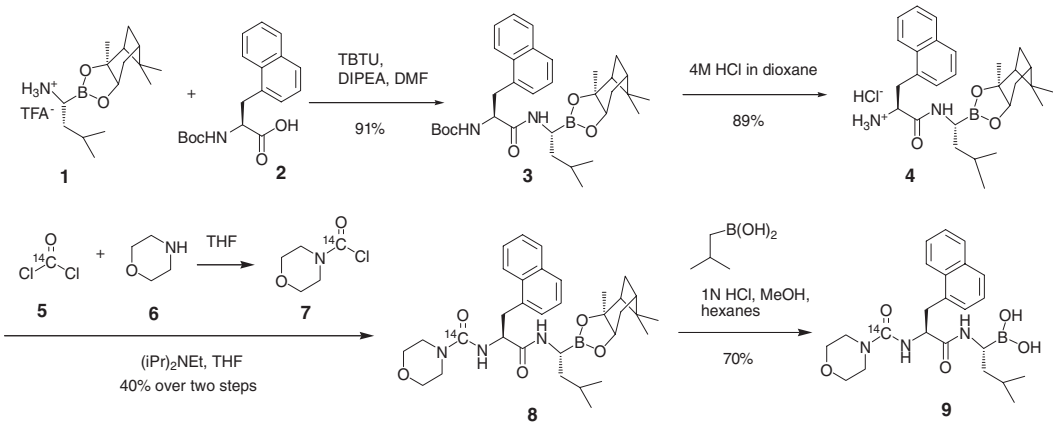
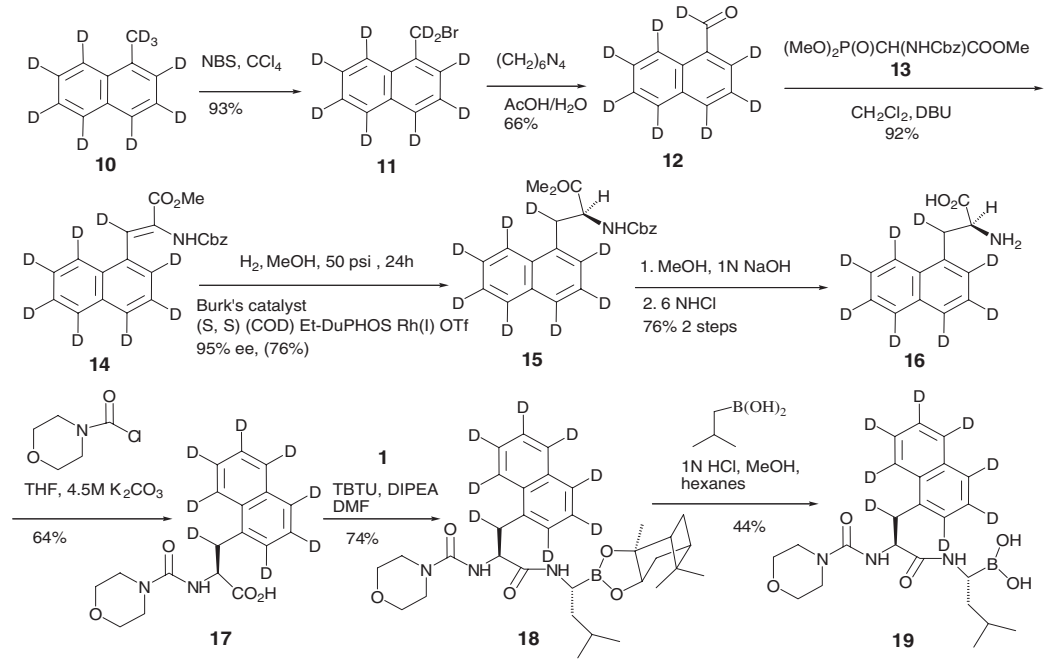


Scheme 1



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-[D_8]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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REFERENCES

1. Grisham MB, Palombella VJ, Elliott PJ, Conner EM, Brand S, Wong HL, Pien C, Mazzola LM, Destree A, Parent L, Adams J. *Methods Enzymol* 1999; **300**: 345–363.
2. Adams J, Ma Y-T, Stein R, Baevsky M, Grenier L, Plamondon L. *PCT Int Appl* 1996; WO 96/13266.
3. Kettner CA, Shenvi AB. *J Biol Chem* 1984; **259**: 15106–15114.
4. Plattner JJ, Marcotte PA, Kleinert HD, Stein HH, Greer J, Bolis G, Fung AKL, Bopp BA, Luly JR, Sham L, Kempf DJ, Rosenberg SH, Dellaria JF, De B, Merits I, Perun TJ. *J Med Chem* 1988; **31**: 2277–2288.
5. Liu W. US 5981239, US 1999.
6. Wang W, Cai M, Xiong C, Zhang J, Trivedi D, Hruby VJ. *Tetrahedron* 2002; **58**: 7365–7374.

DOI: 10.1002.jlcr