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Short Research Article

Synthesis of isotopically labeled 2-pyridinyloxyisobutanoic acid, a building block for CB-1 inhibitors as drug candidates for obesity treatment†

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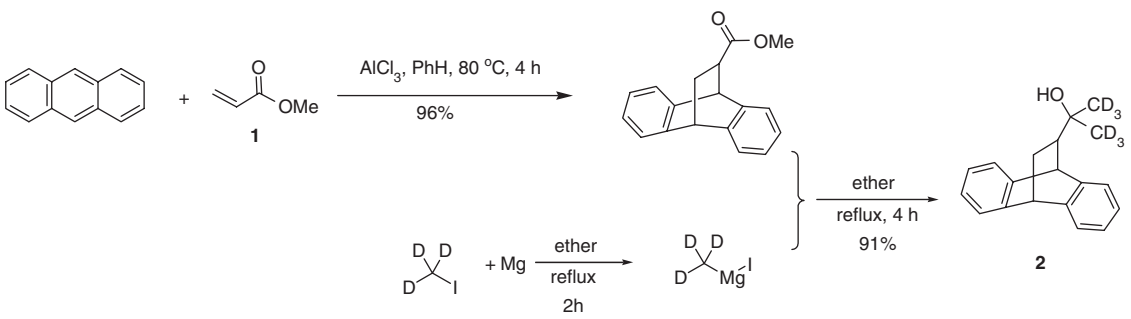
Introduction

Substituted isobutanoic acids are widely used as building blocks in the synthesis of pharmaceuticals and various drug-like small molecules. The synthesis of isotopically labeled variants of this motif is thus of general interest. In the present case, we were particularly interested in a stable isotope-labeled analog of a 2-pyridinyloxy-isobutanoic acid structure present in a potential CB-1 inhibitor for the treatment of obesity. This material was required for use as an internal standard for LC/MS assays. Herein, we report a synthetic protocol to make stable isotope-labeled 2-pyridinyloxyisobutanoic acid. The strategy may be extended to the synthesis of other labeled α-hydroxyacids and tertiary allylic alcohols.

Results and discussion

The Lewis acid catalyzed Diels–Alder reaction of anthracene with methyl acrylate gave the adduct, which was reacted with Methyl-D_3 Grignard reagent in ether at reflux for 4 h affording tertiary alcohol **2** (Scheme 1). Six deuterium labels were thus introduced in alcohol **2**, and it was isolated in good yield after recrystallization from methanol. Upon heating, a retro Diels–Alder reaction of **2** released the allylic alcohol which was collected in a cold (−78°C) flask. Subsequent ozonolysis with a reductive work-up resulted in the aldehyde. Oxidation with PCC followed by esterification with ethanol gave the ester **3** in good yield (Scheme 2). The one-step ozonolysis with oxidative workup was explored but the resulting yield was



Scheme 1

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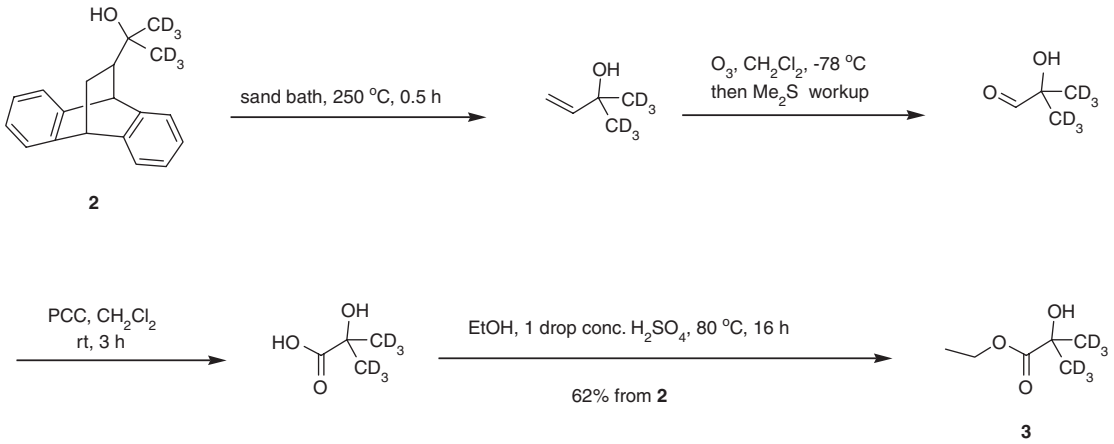
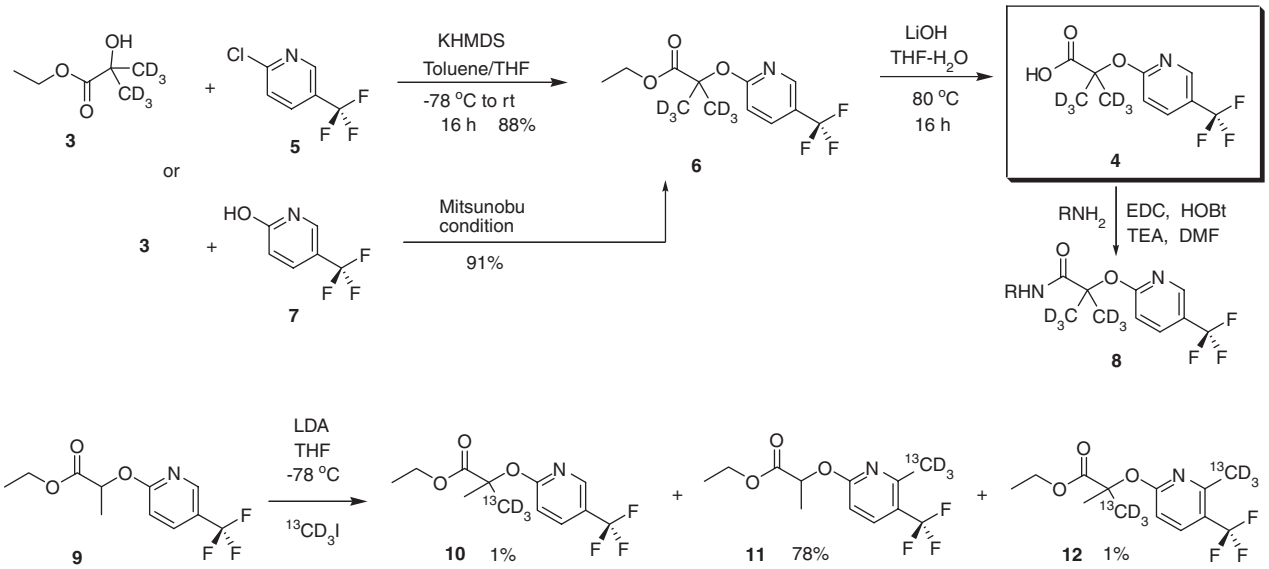


Scheme 2



Scheme 3

inferior. The 4-step sequence outlined above was carried out in one-pot fashion with an overall yield of 62%.

Compound **3** can be coupled with either 2-chloropyridine **5** via nucleophilic aromatic substitution or 2-hydroxylpyridine **7** under Mitsunobu conditions to form desired product **6** (Scheme 3). Hydrolysis with LiOH in THF/water gave rise to acid **4**. The final tracer **8** was obtained by a simple EDC coupling. During this tracer synthesis we also explored an alternate strategy to make the stable isotope standard using [$^{13}CD_3$]methyl iodide to alkylate **9** affording **10** (Scheme 3). Stable isotope-labeled **10** obtained by this route would have achieved an acceptable $M+4$ increase in mass, however, the poor 1% overall yield obtained by this approach made it unattractive. The major product obtained by this route was **11**, in which $^{13}CD_3$ was incorporated at the free acid position on the pyridine ring.

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