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Short Research Article

Solid-phase synthesis of isotope-labeled 2-propyloctanoic acid, a therapeutic agent for stroke and Alzheimer's disease†

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Introduction

Solid-phase organic synthesis plays an important role in modern drug discovery.[1] This technique is widely used as a tool for development of target structure–activity-relationship (SAR) toward lead compounds for drug development. However, utilization of solid-phase synthesis in obtaining small molecule isotopically

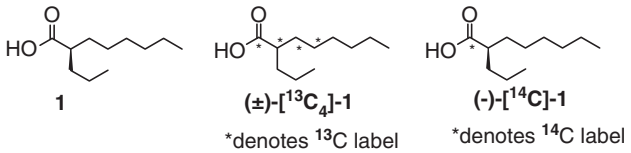
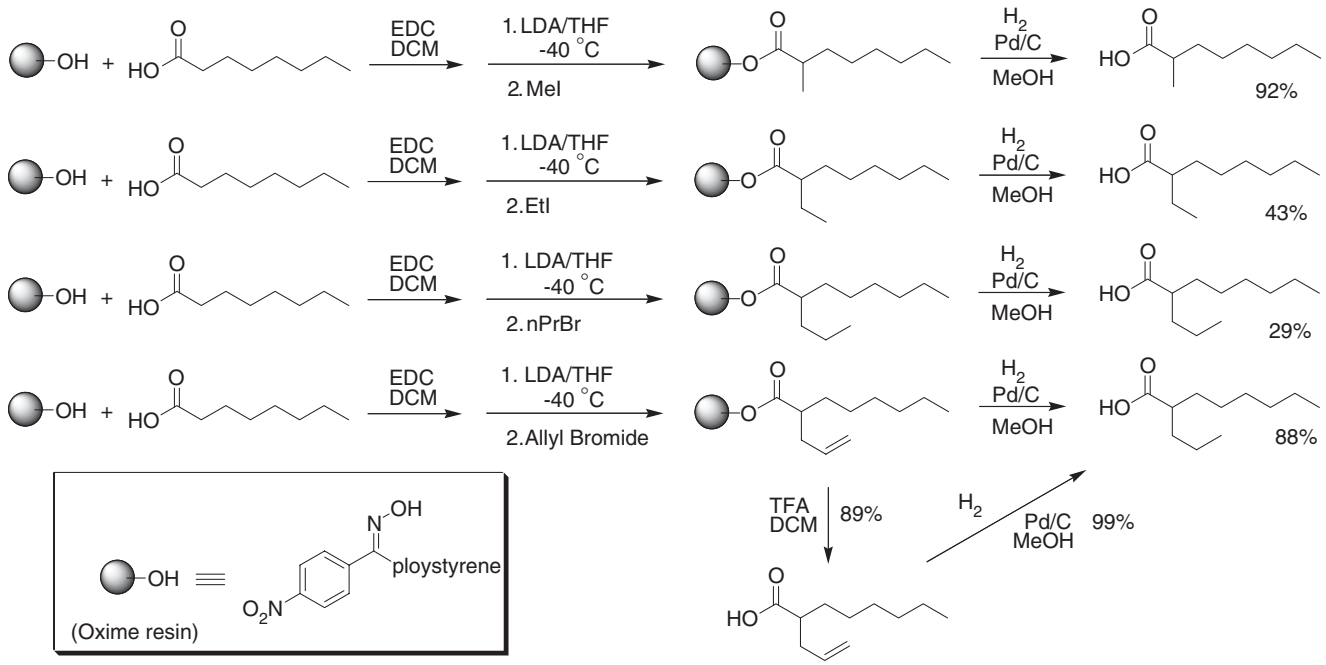


Figure 1 (2R)-2-proyloctanoic acid (1) and its isotopically labeled targets.



Scheme 1 Solid-phase synthesis using oxime resin.

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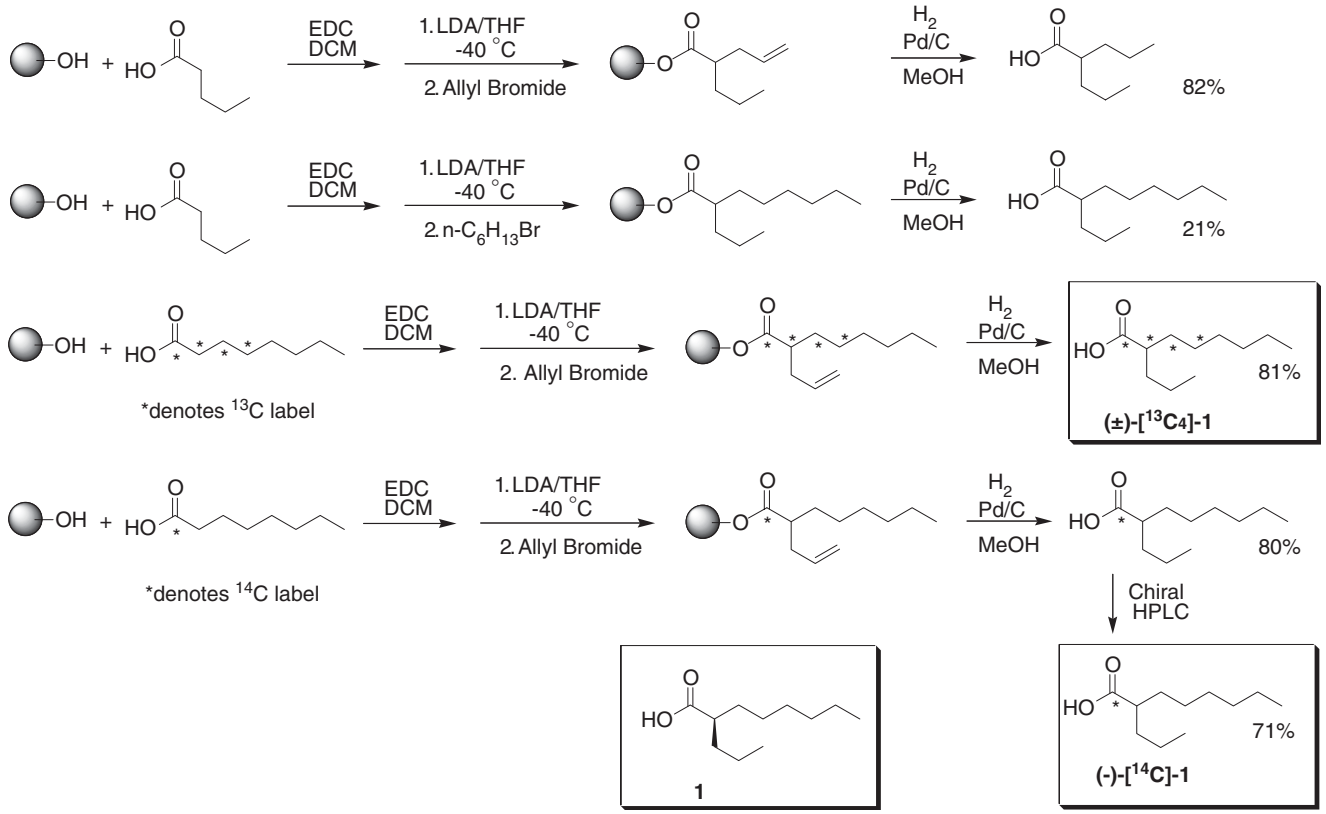

Scheme 2 Solid-phase synthesis of labeled targets.

labeled compounds has only been scarcely explored. (An example of the synthesis of C-14 labeled tracers by way of using solid-phase synthesis.[2]) Hence, we sought to develop an efficient solid-phase synthetic strategy that would allow the preparation of carboxylic acids, particularly, those for which standard purification and isolation would be difficult due to lack of a UV chromophore. We report herein a convenient method that takes advantage of the oxime resin as a solid support. Two C-isotope labeled compounds were made by application of this technology.

Results and discussion

(2*R*)-2-propyloctanoic acid (**1**)[3] was a compound licensed by Merck from Ono Pharmaceutical as a therapeutic agent for stroke and Alzheimer's disease. Isotopically labeled versions of **1** were required for ADME studies as well as stable-isotope labeled internal standard (Figure 1).

The oxime resin was chosen as solid support because the cleavage of compounds from this resin is readily achieved under catalytic hydrogenation conditions, strong acid conditions or mild nucleophilic conditions. Esterification of an acid and the resin is easily achieved by EDC mediated coupling or application of Mitsunobu reaction conditions. Although alkylation with methyl iodide proceeded easily, low yields were observed with either ethyl or *n*-propyl iodide (even when an excess amount of electrophile was used). Alkylation with allyl bromide resulted a good yield. Yields and identity were confirmed by cleavage of the olefin intermediate via TFA treatment. Catalytic hydrogenation of **2** not only reduces the carbon–carbon double bond but also releases the desired product **3** in a 'traceless' manner (Schemes 1 and 2).

REFERENCES

1. (a) Franzen RG. *J Comb Chem* 2000; **3**: 195; (b) Nafzi A, Ostresh JM, Houghten RA. *Chem Rev* 1997; **97**: 449.
2. Tan W, Iyer RP, Jiang Z, Yu D, Agrawal S. *Tetrahedron Lett* 1995; **36**: 5323.
3. Hasegawa T, Kawanaka Y, Kasamatsu E, Iguchi Y, Yonekawa Y, Okamoto M, Ohta C, Hashimoto S, Ohuchida S. *Org Proc Res Dev* 2003; **7**: 168.

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