Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 602–604.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1298

JLCR

Short Research Article

The preparation of carbon-14 and tritium radio-labeled PD-72953†

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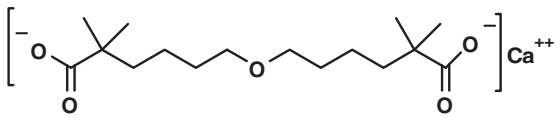
Received 24 July 2006; Revised 22 January 2007; Accepted 31 January 2007

Keywords: radioactive isotope; carbon-14; tritium; alkylation; palladium; reduction

Introduction

PD-72953 is a ligand for the peroxisomal proliferation activated receptor alpha (PPARα) and PPARγ.[1] In order to study its absorption, distribution, metabolism and excretion (ADME), and protein binding, the C-14 and tritium-labeled PD-72953 was required. This paper describes the synthesis of each labeled form.



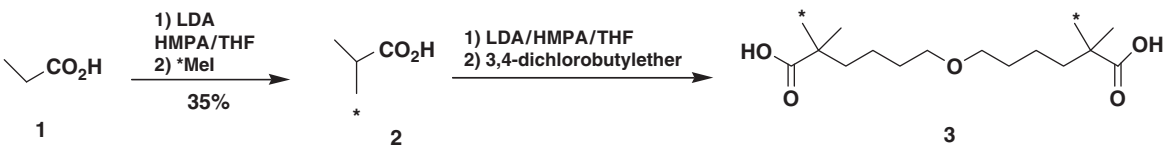
PD-72953

Results and discussion

Synthesis of (^{14}C) PD-72953

The initial synthesis of [^{14}C] PD-72953 was tried according to the original unlabeled synthetic approach (Scheme 1). In our trial experiment (2 mmol scale), it was found that a large excess methyl iodide was needed to draw the alkylation to completion, and the high solubility of isobutyric acid in water made it difficult to isolate the labeled compound with an acceptable yield.

With this result, we decided to introduce methyl group in the later step (Scheme 2). When propionic acid was treated with LDA in THF, a dianion was formed. This dianion reacted readily with 4-chlorobutyl ether to provide the non-labeled starting material, bis (α-methylhexanoic acid) ether **4**. The crude reaction mixture still contained the un-reacted starting material chlorobutyl ether, which can be removed by vacuum distillation. When compound **4** was treated with 4 equivalents of LDA, followed by methyl iodide, a mixture of un-reacted **4**, mono-methylated compound **5** and the desired [^{14}C] PD-72953 (**3**) was formed. By adjusting the molar ratio of [^{14}C]MeI and compound **4**, we were able to make a mixture with the desire [^{14}C] PD-72953 as the major product. After HPLC purification, we were able to obtain 89 mCi of [^{14}C]PD-72953 out of 175 mCi of methyl iodide (50.8%) with a radio-



Scheme 1

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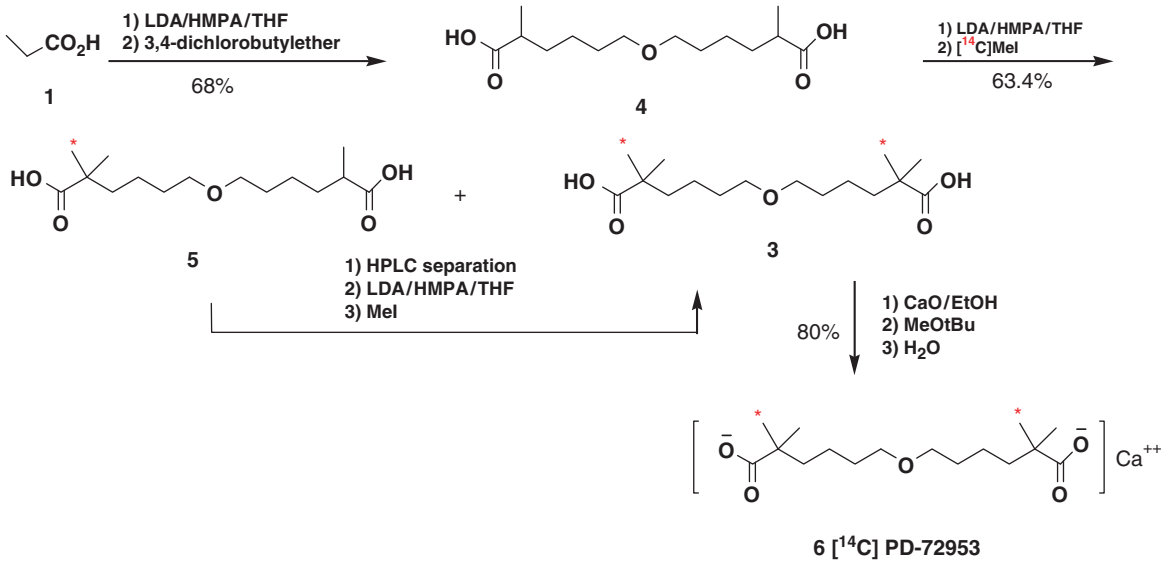
†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.



Scheme 2 This scheme is available in colour online at www.interscience.wiley.com

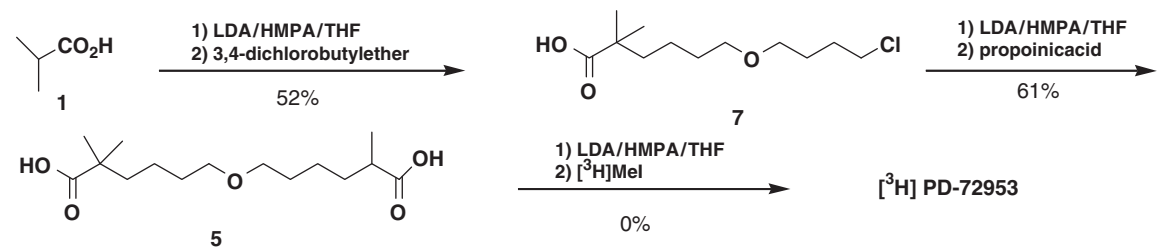
chemical purity >99%. The free acid **3** was then treated with 1 equiv. of CaO in ethanol to give [^{14}C]PD-72953 calcium salt. The final carbon-14-labeled material was found to be 98.74% radiochemical pure with a specific activity of 19.2 mCi/mmol.

Synthesis of (^{3}H)PD-72953

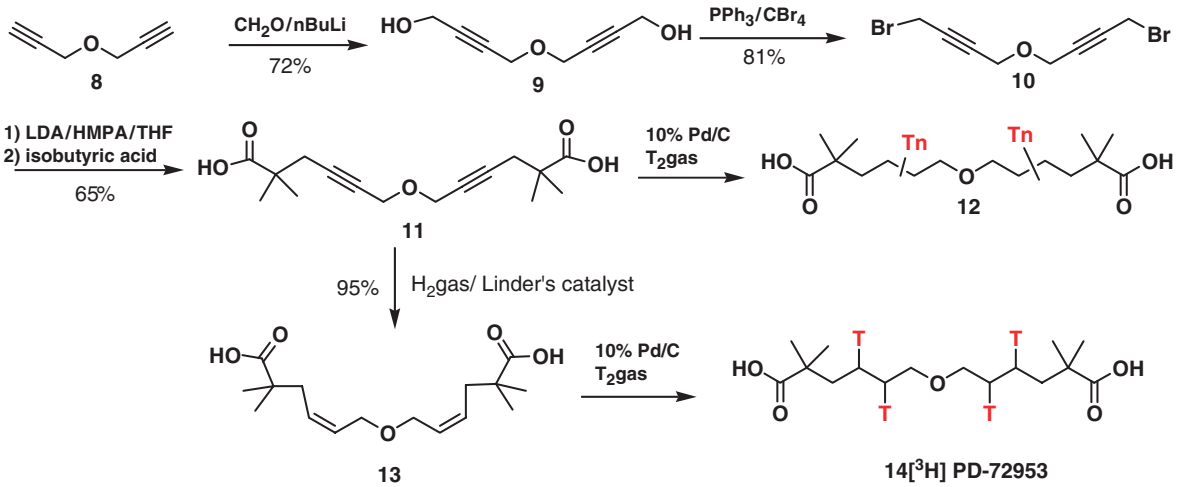
Our initial plan for preparing [^{3}H]PD-72953 was to methylate the intermediate **5** using [^{3}H]MeI (Scheme 3). The treatment of isobutyric acid with excess 4-chlorobutyl ether (2.5 equiv.) gave a mixture of mono-alkylated product **7** (20%) and di-alkylated by-product (30%). By increasing the mole ratio of 4-chlorobutyl ether and isobutyric acid from 2.5/1 to 5/1, and adding the pre-prepared isobutyric acid dianion solution to the 4-chlorobutyl ether, we were able to make a mono-alkylated product **7** as the major product. The alkylation of propionic acid with the chloride **7** afforded the desired precursor **5** of PD-72953. However, the methylation of the precursor **5** turned out to be very unreliable under micro-scale and was not pursued. An alternate approach to [^{3}H]PD-72953 was developed based on the catalytic reduction of the unsaturated precursor **11** or **13** (Scheme 4).

By adapting a published procedure,[2] the diol **9** was easily prepared in 72% by the treatment of commercially available alkyne **8** with excess formaldehyde in the presence of *n*-BuLi. The bromination of the diol **9** with PPh_3/CBr_4 in CH_2Cl_2 provided the desired di-bromide **10** in 81% yield. The alkylation of isobutyric acid with the di-bromide **10** furnished the unsaturated precursor **11** of PD-72953. Direct tritiation of the precursor **11** with two triple bonds gave the desired [^{3}H]PD-72953, which was

2. Synthesis of [3H] PD-72953



Scheme 3



Scheme 4 This scheme is available in colour online at www.interscience.wiley.com

not stable due to the high radiation effect. Therefore, the precursor with triple bond was partially reduced to the precursor **13** first in the presence of Linder's catalyst, and was then reduced to [^{3}H]PD-72953 with tritium gas (0.6 Ci) and 10% Pd/C. A total activity of 56 mCi was obtained with a specific activity of 103 Ci/mmol.

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