Technical Note

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Synthesis of ^{14}C-acanthoic acid

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^{14}C-Acanthoic acid was prepared in four steps by a degradation/reconstitution strategy.

Keywords: diterpene; pimaradiene; olefination; regioselective

Introduction

Acanthoic acid (**1**) is a pimaradiene diterpene that has been implicated in several biological activities, notably suppression of proinflammatory cytokines.[1] Theodorakis *et al*. described the enantioselective synthesis of acanthoic acid.[2] Here, we describe a four-step synthesis of the ^{14}C-labeled acanthoic acid for use in pharmacological studies. Our strategy involves degradation of the vinyl group of unlabeled acanthoic acid followed by reformation of the olefin to introduce the radiolabel. To this end, the acanthoic acid was dihydroxylated with osmium tetroxide to give vicinal diol **2** (Scheme 1A). Oxidative cleavage with sodium periodate gave aldehyde **3**, the substrate for radiolabeling. The ^{14}C-methylene Wittig reagent (**4**) was prepared under standard conditions and treated with aldehyde **3** to give ^{14}C-acanthoic acid (^{14}C-**1**; Scheme 1B). This straightforward synthesis afforded ^{14}C-**1** in a regioselective manner and high specific activity (52.7 mCi/mmol).

Experimental

Reactions were run under argon atmosphere. Thin layer chromatography (TLC) analyses were carried out on commercial pre-coated silica gel 60F254 plates (E. Merck, Darmstadt, Germany; 5 × 10 and 5 × 20 cm). The plates were scanned using a Bioscan System 200 Imaging Scanner (Bioscan, Washington, DC).

15,16-Dihydroxypimara-9(11)-en-19-oic acid (2)

To a solution of acanthoic acid (**1**; 479 mg, 1.5 mmol) and *N*-methylmorpholine *N*-oxide (215 mg, 1.83 mmol) in *t*-BuOH/THF/H_2O (16 mL, 10:3:1 ratio) at room temperature (RT) was added OsO_4 (500 μL, 2.5 wt.% in *t*-BuOH, 0.033 mmol). After 140 h, the reaction mixture was cooled to 0 °C, and an aqueous slurry of Na_2SO_3 and talc was added. The mixture was allowed to warm at RT. After 16 h, the mixture was filtered through Celite (Johns Manville, Lompoc, CA), which was washed with CH_2Cl_2 (5 × 20 mL). The filtrates were allowed to separate, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give **2** (468 mg, 87%) as a pale yellow solid, which was used in the next step without further purification.

15-Oxo-16-norpimara-9(11)-en-19-oic acid (3)

To a solution of diol **2** (468 mg, 1.38 mmol) and KH_2PO_4 (6.17 g, 45.3 mmol) in MeOH/H_2O (170 mL, 4:1 ratio) at RT was added $NaIO_4$ (921 mg, 4.30 mmol). After 4 h, the reaction mixture was diluted with ice (100 g) and extracted with CH_2Cl_2 (4 × 80 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give aldehyde **3** (339 mg, 80%).

^{14}C-Methylenetriphenylphosphorane (4)

Triphenylphosphine (322 mg, 1.2 mmol) was dried under vacuum (1 torr) for 24 h and then dissolved in dry THF (5 mL), and the solution was degassed (3 freeze/pump/thaw cycles). To this solution was added $^{14}CH_3I$ (1.8 mmol, 100 mCi, 53 mCi/mmol; Amersham CFQ9135, Piscataway, NJ). After 24 h at RT, the reaction mixture was cooled to −78 °C. KHMDS (5.0 mL, 0.5 M in PhMe, 2.5 mmol) was added dropwise, and the cold bath was removed. After 3 h at RT, the resulting solution of Wittig reagent **4** was used in the next step.

^{14}C-Acanthoic acid

The solution of Wittig reagent **4** prepared previously was cooled to −78 °C. A solution of aldehyde **3** (121 mg, 0.4 mmol) in dry THF (1.5 mL) was added dropwise. The mixture was allowed to warm slowly to RT. After 18 h, the reaction mixture was cooled to −78 °C and diluted with HCl (20 mL, 1 M in H_2O). The mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Two rounds of purification by column chromatography (SiO_2, 1 cm d × 10 cm column, 1:4 EtOAc : hexanes) gave ^{14}C-**1** (51 mg, 8.9 mCi, 52.7 mCi/mmol, 97.8% radiochemical purity by radio-TLC: 1:4 EtOAc : hexanes, R_f 0.45).

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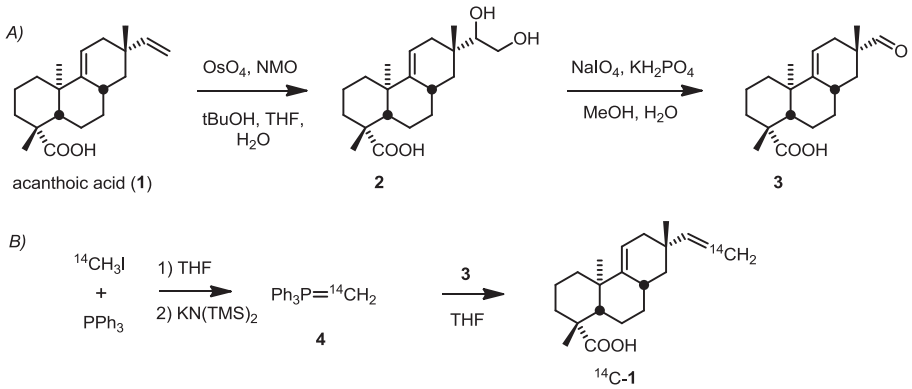

Scheme 1. Synthesis of ^{14}C-acanthoic acid. NMO = *N*-methylmorpholine *N*-oxide.

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Conflict of Interest

The authors did not report any conflict of interest.

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