SYNTHESIS OF (Z)-3-[4-(ACETYLOXY)-5-ETHYL-3-METHOXY-1-NAPHTHALENYL]-2-METHYL-2-PROPENOIC-2-^{14}C ACID (^{14}C-E5090)

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SUMMARY

(Z)-3-[4-(Acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic-2-^{14}C acid **7** (^{14}C-E5090) was synthesized in order to study the pharmacokinetic profile of E5090, an orally active inhibitor of IL-1 generation. ^{14}C-E5090 with a specific activity of 43.34mCi/mmol was prepared in 5 steps in 12.9% overall yield from 5-ethyl-3-methoxy-4-methoxymethoxy-1-naphthalenecarbaldehyde **1**.

Key words: inhibitor of IL-1 generation, E-5090, (Z)-3-[4-(acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic-2-^{14}C acid, 2-(diethoxyphosphinyl)propanoic-2-^{14}C acid ethyl ester

INTRODUCTION

Interleukin-1 (IL-1) which is one of the cytokines released mainly by macrophages, plays an important role in inflammatory and immunological processes.[1)]

In the course of developing an orally active inhibitor of IL-1 generation, we have discovered a series of 3-(1-naphthalenyl)-2-propenoic acid derivatives.[2)] Within this series, (Z)-3-[4-(acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic acid (E5090) [i.e. unlabelled compound **7**] was one of the most potent orally active inhibitors of IL-1 generation in the rat air-pouch inflammatory model.[3)]

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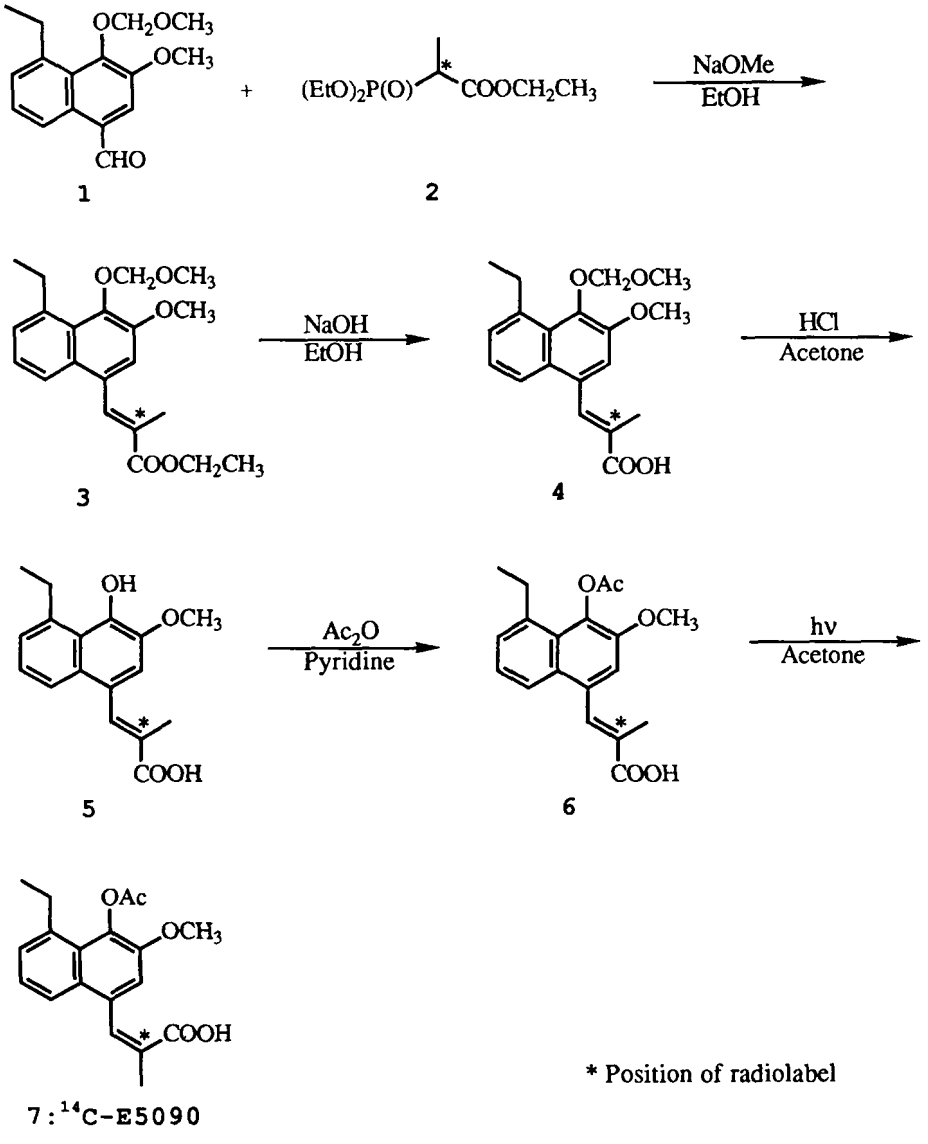
This paper describes the synthesis of ^{14}C-E5090 7 in order to study the pharmacokinetic profile of E5090.

The synthetic method of ^{14}C-E5090 7 is shown in Scheme.

Scheme Synthesis of ^{14}C-E5090



* Position of radiolabel

The Wadsworth-Emmons reaction between aldehyde 1[2] and ^{14}C-labelled phosphonate 2 gave ethyl (E)-propenoate 3, which was then hydrolyzed under

alkaline conditions (NaOH/aq.EtOH) followed by deprotection of the phenolic hydroxy group with HCl to yield the (E)-propenoic acid **5**. Compound **5** was acetylated in the presence of pyridine to give the E isomer of ^{14}C-E5090 **6**, which was then photoisomerized with a high pressure Hg lamp in acetone yielding a mixture of **6** and **7**. This mixture was purified by flash column chromatography to afford the target compound **7** with a radiochemical purity of 95.3% in 15.2% overall yield based on aldehyde **1**. After further purification using preparative HPLC, pure compound **7** was obtained in 12.9% overall yield based on aldehyde **1**. The structure of compound **7** was confirmed by comparison with an unlabelled authentic specimen of **7**. ^{14}C-E5090 **7** had a radiochemical purity of 99.2% and a specific activity of 43.34mCi/mmol.

EXPERIMENTAL

Thin layer chromatography (TLC) was developed using E. Merck silica gel 60F-254 precoated glass plates. Compounds were detected on TLC by UV light (254nm). E. Merck silica gel, 230-400 mesh, was used for flash column chromatography. Photochemical E-Z isomerization was performed with a high pressure Hg lamp (100W, Pyrex vessel). Preparative HPLC was carried out on a Shimadzu LC-8A pump with a Shimadzu SPD-6A detector using a MERCK LiChrospher RP-18(e) column (10mm × 250mm). Measurement of radioactivity was carried out using an Aloka LSC-9000 liquid scintillation spectrometer. Radiochemical purity was measured using a HPLC system, equipped with a Waters 510 pump, TOSOH RS-8000 radiodetector and MERCK LiChrospher RP-18(e) column (4mm × 250mm).

2-(Diethoxyphosphinyl)propanoic-2-^{14}C acid ethyl ester **2**

The labelled compound **2**, which was prepared from 2-bromopropionic-2-^{14}C acid ethyl ester and triethyl phosphite, was purchased from Amersham International Ltd. : Specific activity ; 45mCi/mmol : Radiochemical purity by radio gas-liquid chromatography ; 99.1±0.1%.

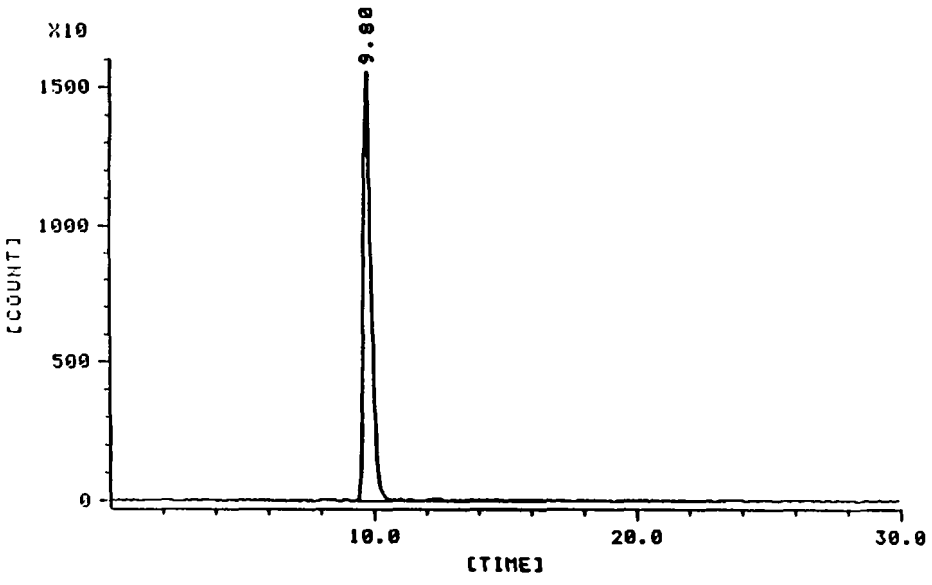
(E)-3-(5-Ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-2-propenoic-2-^{14}C acid **5**

To a mixture of 5-ethyl-3-methoxy-4-methoxymethoxy-1-naphthalene-

carbaldehyde 1 (1.22g, 4.44mmol) and MeONa (1.20g, 22.2mmol) in EtOH (3mL) at room temperature was added a solution of ^{14}C-labelled phosphonate 2 (200mCi, 4.44mmol) in EtOH (10mL) and the mixture was then stirred for 30min. After checking the formation of ethyl (E)-propenoate 3 on TLC (Rf=0.17; hexane / AcOEt = 95 / 5), aq.NaOH (0.24g / 4.2mL H_2O) was added and stirring continued at 40°C for 30min. After cooling the reaction to room temprature, dilute HCl was added and the resulting precipitate was collect by filtration to give the (E)-propenoic acid 4, which was used in the next step without further purification. To a solution of 4 in acetone (15mL) was added concentrated HCl (1mL) and this mixture was then stirred for 2.5h. The mixture was poured into water (100mL), and the resulting precipitate was collected by filtration to afford the crude product 5 as a yellowish brown solid. The identity of 5 was confirmed by comparison of its Rf value with an unlabelled authentic sample on TLC (Rf=0.36; hexane / AcOEt = 1 / 1).

(Z)-3-[4-(Acetyloxy)-5-ethyl-3-methoxy-1-naphthalenyl]-2-methyl-2-propenoic-2-^{14}C acid 7

To a solution of crude 5 in pyridine (6mL) at room temprature was added acetic anhydride (3mL). After stirring at 40°C for 30min, water (2mL) was added. The mixture was stirred for an additional 10min and poured into 0.5N-HCl (100mL). The resulting precipitate was collected by filtration to afford the E isomer of ^{14}C-E5090 6 as a reddish brown solid, which was used in the next step without further purification. A solution of 6 in acetone (200mL) was irradiated for 2h with a high pressure Hg lamp. The solvent was then evaporated and the resulting residue was purified by column chromatography on silica gel eluting with MeOH / $CHCl_3$ (3 / 97) to afford 7 (220mg, total 15.2%) having a radiochemical purity of 95.3%. Further purification by preparative HPLC (MeOH / H_2O / AcOH=70 / 30 / 0.1, 4mL/min, 240nm) gave pure 7 (189mg, total 12.9%) as a colorless solid having a radiochemical purity of 99.2% (MeOH / H_2O / AcOH=70 / 30 / 0.1, 1mL/min) and a specific activity of 43.34mCi/mmol. The identity of 7 was confirmed by comparison of its Rf value with an unlabelled authentic sample on TLC (Rf=0.12; hexane / AcOEt= 3 /7 , Rf=0.58; hexane / AcOEt / AcOH = 7 / 3 / 2).



HPLC radiochromatogram of ^{14}C-E5090

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