Synthesis of Optically Active 2-(4-(2-Thienylcarbonyl)phenyl)propionic Acid Labeled with Deuterium

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2-(4-(2-Thienylcarbonyl)phenyl)propionic acid (suprofen), an anti-inflammatory agent, was labeled with multiple-deuterium for the purpose of investigating the metabolism in man and animals by the ion cluster technique. Racemic suprofen-d4 was prepared by ten-step synthesis from bromobenzene-d5 in a 32% yield, and its deuterium content was 99 atom%. This racemic suprofen-d4 was resolved by use of an optically active α-methylbenzylamine, resulting that optically active suprofen-d4 was obtained in a 11% yield and was 96.5 atom% D. On the other hand, suprofen-d7 (99 atom% D) was obtained by five-step synthesis from toluene-d8 and methyl-d3 iodide in a 24% yield.

Key Words: 2-(4-(2-thienylcarbonyl)phenyl)propionic acid, ion cluster technique, deuterium labeling, optical antipode, mass spectrometry, bromobenzene-d5, α-methylbenzylamine, toluene-d8, methyl-d3 iodide, labeled compound

1. Introduction

2-(4-(2-Thienylcarbonyl)phenyl)propionic acid (suprofen) proved to be a potent inhibitor of acutely-induced inflammation and of prostaglandin biosynthesis\(^{31-33}\). Suprofen has one asymmetric carbon atom at the methin group and, therefore, occurs as either \(d(+)\) or \(l(-)\) isomer. It is well-known that the anti-inflammatory activity of phenylpropionic acids\(^{31-33}\) resides in the \(d(+)\) isomer. Recently, Fujimura, et al\(^{37}\) reported that \(d(+)\)-suprofen showed more potent activity than \(l(-)\)-suprofen whereas the toxicity of \(d(+)\) or \(l(-)\)-suprofen was completely contrary to the pharmacological effects. In order to obtain the basic information for pharmacological and toxicological properties, we have attempted to clarify the metabolism of suprofen and the metabolic differences between the optical antipodes in man and animals by the ion cluster technique. Therefore, it has become desirable for the metabolic studies to prepare \(d(+)\) and \(l(-)\)-suprofen labeled with stable isotope. Bromobenzene-d5, toluene-d8, toluene-d8, \(p\)-toluic acid-\(^{13}C\)_5, and acetic anhydride-\(^{13}C\)_2 are the commercially available starting materials for the purpose. Multiple deuterated compounds are generally useful in the study of drug metabolism by this technique, partly because highly enriched materials are commonly available. Thus, this paper deals with the syntheses of \(d(+)\) and \(l(-)\)-suprofen-d4 starting from bromobenzene-d5 and of suprofen-d7 as an internal standard compound for this technique from toluene-d8.

2. Results and Discussion

The synthetic scheme of racemic suprofen-\(d_4\) from bromobenzene-d5 was shown in Fig. 1. The Friedel-Crafts reaction\(^{44}\) of bromobenzene-d5 with acetic anhydride gave 4-bromoacetophenone-d4 (II), which was then treated with ethyl chloroacetate in the presence of potassium tert-butoxide to yield the corresponding adduct-d4 (II). Hydrolysis of II with aqueous ethanol containing sodium hydroxide gave the desired sodium carboxylate (III). The decarboxylation of III with hydrochloric acid gave the aldehyde (IV) in a good yield. For protection of the aldehyde group, V was acetalized with ethylene
The acetal (II) was reacted with magnesium in absolute tetrahydrofuran to yield the Grignard’s reagent (III), which was then treated with 2-thiophenealdehyde to obtain the desired adduct (IV). Finally, racemic suprofen-d₄ was obtained by oxidation of IV with Jones’ reagent, followed by deacetalization and then oxidation. The overall yield for this ten-step synthesis of racemic suprofen-d₄ from bromobenzene-d₅ amounted to 32%. This racemate thus obtained was resolved by use of optically active α-methylbenzylamine. Treatment of racemic suprofen-d₄ with d(+) or l(-) α-methylbenzylamine gave the crude salt, which was then recrystallized from aqueous ethanol to yield the salt with constant optical rotation $[\alpha]_{20}^D = +13.31^\circ$ or $[\alpha]_{20}^D = -13.52^\circ$. These optically active salts were hydrolyzed with hydrochloric acid, resulting that d(+)–suprofen-d₄ ($[\alpha]_{20}^D = +45.05^\circ$) and l(-)–suprofen-d₄ ($[\alpha]_{20}^D = -45.53^\circ$) were obtained in a 11% yield.

The infrared (IR) spectrum (KBr) of racemic suprofen-d₄ were greatly changed in the regions of 690–855 and 2255–2275 cm⁻¹ when compared with the nonlabeled compound. Figure 2 shows the partial mass (MS) and nuclear magnetic resonance (NMR) spectra of suprofen and suprofen-d₄. As the signals due to the benzene ring protons disappeared completely in the NMR spectrum of suprofen-d₄ and integration of the signals between δ 7.06 to 7.63 gave 3 protons for the thiophene ring, it was clarified that deuterium atom was not eliminated during synthetic steps of racemic suprofen-d₄ from bromobenzene-d₅ which involved the oxidation reaction with Jones’ reagent and decarboxylation with hydrochloric acid. Thus, the deuterium content of suprofen-d₄ calculated from the MS spectrum was 99 atom%, which was equal to that of the starting material. On the other hand, relative intensities of the ions $m/z$ 263 (M⁺-1) to $m/z$ 264 (M⁺) in the MS spectra of d(+)–suprofen-d₄ and l(-)–suprofen-d₄ were respectively 15.9 and 16.2%, indicating 96.6 and 96.5 atom% D. Accordingly, it showed that about 2.5% of deuterium atom was eliminated during the resolution reaction.

Synthesis of suprofen-d₇ was carried out using toluene-d₈ as illustrated in Fig. 3. The Friedel-Crafts reaction of toluene-d₈ with 2-thienyl chloride gave the corresponding adduct-d₇ (V). Treatment of V with N-bromosuccinimide converted it into the benzyl bromide-d₇ (VI), which was then heated with potassium cyanide to yield the benzyl cyanide-d₇ (VII). Finally, suprofen-d₇ was obtained by methylation of VII with methyl-d₇ iodide, followed by hydrolysis. The overall yield for this five-step synthesis of suprofen-d₇ from toluene-d₈ amounted to 24%. Figure 4
Fig. 3 Synthesis of 2-(4-(2-thienylcarbonyl)phenyl-d₄)propionic[methyl-da] acid.

shows the partial MS and NMR spectra of suprofen-d₇. It is noted that the molecular ion peak is not present at m/z 268 but at m/z 267, indicating that suprofen-d₇ was obtained. As the molecular ion of XII was present at m/z 231, two deuterium atoms at the methylene group of the benzyl cyanide was not eliminated at all. Integration of the signals in the NMR spectrum of suprofen-d₇ gave one proton as singlet at δ 4.03 for the benzylic proton and 3 protons as multiplet at δ 7.04-7.73 for the thiophene ring. These results indicate that the deuterium of the methin group is completely exchanged by hydrogen during the hydrolysis of gIII. Thus, the deuterium content of suprofen-d₇ calculated from the MS spectrum was 99 atom%.

Consequently, highly enriched d(+)- or l(-)-suprofen-d₄ and suprofen-d₇ were synthesized from bromotoluene-d₅ and toluene-d₈ in a good yield, respectively.

3. Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrophotometer, MS spectra with a Shimadzu LKB-9000B at 70 eV, and NMR spectra in CDC₁₅O with a JEO-L-MH-100 or JEO-L-PS-100 spectrometer using tetramethylsilane as an internal standard. Optical rotation (c=1, ethanol) was measured with a Yanaco OR-50D automatic polarimeter. Thin-layer chromatography was performed on Silicagel 60 F₂₅₄ precoated plates (0.25 mm, E. Merk, Darmstadt).

3.1 Chemicals

Bromobenzene-d₅, toluene-d₈, and methyl-d₅ iodide were purchased from Merk Sharp and Dohme Canada Ltd., Montreal. 2-Thiophenealdehyde and 2-thenoyl chloride were obtained from Tokyo Kasei Co., Tokyo, ethyl chloroacetate and ethylene glycol from Wako Pure Chemicals Ltd., Tokyo, and d(+)- or l(-)-α-methylbenzylamine from Aldrich Chemical Co., WI. All other reagents used were of reagent grade.

3.2 Ethyl-3-((4-bromophenyl-d₄) 2,3-epoxy-3-methyl)propionate (III)

p-Bromoacetophenone-d₄ (II, bp 116°C/7 mmHg) was prepared by the treatment of bromobenzene-d₄ with acetic anhydride according to the method of literature (117°C/7 mmHg). To a mixture of 10 g of II and 12 g of C₁₄H₂₀O₂C₆H₄ dissolved in 25 ml of absolute benzene and cooled to 0-5°C with an ice bath was added 7.8 g of potassium tert-butoxide in portions. After the complete addition, stirring was continued at room temperature for 12 hr. The mixture was poured into an ice cold water and extracted with benzene. The extract was washed with water, dried over Na₂SO₄, and evaporated to yield 10.9 g of colorless oil (III). IR νmax cm⁻¹: 1745 (CO), 2280 (CD). NMR (CDCl₃) δ: 0.92, 1.28 (cis: trans=1:1, 3 H, each t, J=8 Hz), 1.68, 1.72 (cis: trans=1:1, 3 H, each s), 3.43, 3.69 (cis: trans=1:1, 1 H, each s), 3.96, 4.32 (cis: trans=1:1, 2 H, each q, J=8 Hz). MS m/z: 291: 289=1:1 (M⁺).

3.3 2-(4-Bromophenyl-d₄)propionaldehyde (V)

A mixture of 10.9 g of II and 3.5 g of NaOH in ethanol-H₂O (3:1, v/v) was refluxed for 2 hr, which was then poured into water and
extracted with benzene to remove neutral compounds. The aqueous layer was made acidic (pH 1~2) and refluxed for 2 hr, which was then extracted with benzene. The extract was washed successively with water, NaHCO$_3$ solution, and water, dried over Na$_2$SO$_4$, and evaporated to yield 7.2 g of colorless oil (V). IR $\nu_{\text{max}}$ cm$^{-1}$: 1720 (CO), 2260 (CD). NMR (CDCl$_3$) $\delta$: 1.31 (3 H, d, $J=8$ Hz), 3.52 (1 H, q, $J=8$ Hz), 9.52 (1 H, s). MS m/z: 216 : 218=1 : 1 ($M^+$).

3.4 2-((4-Bromophenyl-$d_4$) 1,1-ethylene-glycol)propane (VI)

To 7.2 g of V dissolved in 80 ml of benzene was added 20 g of (CH$_2$OH)$_2$ and 0.2 g of p-toluenesulfonic acid. After the mixture was refluxed for 1 hr, the solution was washed with water, dried over Na$_2$SO$_4$, and evaporated to yield an oily compound, which was then distilled at 110°C/0.6mmHg pressure to give 6.2 g of colorless oil (VI). IR $\nu_{\text{max}}$ cm$^{-1}$: 2260 (CD). NMR (CDCl$_3$) $\delta$: 1.26 (3 H, d, $J=7$ Hz), 2.92 (1 H, m), 3.80 (4 H, s), 4.88 (1 H, d, $J=3$ Hz). MS m/z: 264 : 266=1 : 1 ($M^+$).

3.5 2-((4-(2-Thienylhydroxymethyl)phenyl-$d_4$) 1,1-ethyleneglycol)propane (VII)

To a mixture of VI (6.6 g) in 30 ml of absolute tetrahydrofuran (THF) and magnesium (1.5 g) in 10 ml of THE was slowly added 1 ml of C$_2$H$_5$Br while maintaining the temperature at 50°C, and the mixture was refluxed for 30 min. The mixture was then cooled to 5°C with an ice bath, and a solution of 2-thiophenealdehyde (3.0 g) in 10 ml of THE was slowly added. The solution was stirred for 12 hr, which was then poured into 100 ml of 5% hydrochloric acid and extracted with ether. The extract was washed successively with water, NaHCO$_3$ solution, and water, dried over Na$_2$SO$_4$, and evaporated to yield 7.4 g of clear yellow oil (VIII). IR $\nu_{\text{max}}$ cm$^{-1}$: 2290 (CD), 3450 (OH). NMR (CDCl$_3$) $\delta$: 1.24 (3 H, d, $J=7$ Hz), 2.87 (1 H, m), 3.73 (4 H, s), 4.92 (1 H, d, $J=3$ Hz), 5.82 (1 H, s), 6.85~7.44 (3 H, m). MS m/z: 294 ($M^+$).

3.6 2-((4-(2-Thienylcarbonyl)phenyl-$d_4$) 1,1-ethyleneglycol)propane (IX)

To 7.4 g of VIII dissolved in 30 ml of acetone and cooled to 10°C with an ice bath was slowly added 10 ml of a 25% H$_2$SO$_4$ solution of CrO$_3$ (2.1 g). After the addition was completed, stirring was continued for 1 hr, and the mixture was then poured into water and extracted with CHCl$_3$. The extract was washed with water, dried over Na$_2$SO$_4$, and evaporated to yield an oily compound, which was chromatographed on silica gel column with the elution medium of benzene–CH$_2$COOC$_2$H$_5$=5:1 (v/v). Evaporation of the eluate gave 6.5 g of colorless oil (IX). IR $\nu_{\text{max}}$ cm$^{-1}$: 1635(CO), 2290(CD). NMR (CDCl$_3$) $\delta$: 1.32 (3 H, d, $J=8$ Hz), 3.06 (1 H, m), 3.80 (4 H, s), 4.92 (1 H, d, $J=8$ Hz), 7.08~7.68 (3 H, m). MS m/z: 292 ($M^+$).

3.7 2-((4-(2-Thienylcarbonyl)phenyl-$d_4$)-propionic acid (I-$d_4$)

A mixture of IX (6.5 g), 10% hydrochloric acid (5 ml), and acetone (60 ml) was refluxed for 3 hr, which was then poured into water and extracted with CHCl$_3$. The extract was washed with water, dried over Na$_2$SO$_4$, and evaporated to yield 5.5 g of an oil. This crude oil was dissolved in 40 ml of acetone and added to 8 ml of a 25% H$_2$SO$_4$ solution of CrO$_3$ (1.68 g). The mixture was stirred for 1 hr, then poured into water and extracted with CHCl$_3$. The extract was washed with water, dried over Na$_2$SO$_4$, and evaporated to yield a crude solid, which was then chromatographed on silica gel column with the elution medium of CHCl$_3$-acetone=3:1 (v/v). Evaporation of the eluate and recrystallization from aqueous ethanol gave suprofen-$d_4$ (1-$d_4$) as colorless needles (mp 124°C) in a 4.71 g yield. IR $\nu_{\text{max}}$ cm$^{-1}$: 1735 (CO), 2255~2275 (CD). NMR (CDCl$_3$) $\delta$: 1.14 (3 H, d, $J=8$ Hz), 4.00 (1 H, q, $J=8$ Hz), 7.06~7.63 (3 H, m), 8.90 (1 H, q, $J=8$ Hz), 7.06~7.63 (3 H, m). MS m/z: 294 ($M^+$).

3.8 Optical resolution of suprofen-$d_4$ (1-$d_4$)

To 5.0 g of racemic suprofen-$d_4$ dissolved in 50 ml of ethanol was added 4.7 g of $d(+)$ or $l$ (−)–α-methylbenzylamine with stirring. The resultant precipitates were filtered and recrystallized from ethanol–H$_2$O=5:1 (v/v) 6 times. The salt thus obtained as colorless needles was added to 20 ml of 25% hydrochloric acid. The reaction mixture was stirred for 1 hr, which was...
then poured into water and extracted with ether. The extract was washed with water, dried over Na₂SO₄, and evaporated to yield optically active suprofen-d₄ as needles.

3.9 4-(2-Thienylcarbonyl)toluene-d₇ (X)
To a mixture of 2-thenoyl chloride (1.6 g) in 20 ml of CS₂ and 2.2 g of AlCl₃ was slowly added 1.0 g of toluene-d₈ in 10 ml of CS₂ with stirring. The reaction mixture was warmed at 40°C with an water bath for 2 hr, which was then poured into water and extracted with CHCl₃. The extract was washed with water, dried over Na₂SO₄, and evaporated to yield a crystalline solid. Recrystallization from n-hexane gave 1.6 g of colorless needles (mp 84°C). IR νmax cm⁻¹: 1635 (CO), 2260 (CD). NMR (CDCl₃) δ: 7.15~7.72 (3 H, m). MS m/z: 209 (M⁺).

3.10 4-(2-Thienylcarbonyl)benzyl-d₆ cyanide (XII)
A mixture of XII (1.5 g), N-bromosuccinimide (0.95 g), and benzyol peroxide (30 mg) in 40 ml of CCl₄ was refluxed for 3 hr. After the resultant precipitates were filtered off, the filtrate was evaporated to yield a crystalline solid. Recrystallization from ethanol gave 1.62 g of colorless needles (mp 90°C). To 1.50 g of XII dissolved in 20 ml of ethanol was added a solution of KCN (230 mg) in 10 ml of water dropwise and the mixture was then heated at 70°C for 3 hr. The solvent was evaporated, and the residue was extracted with CHCl₃. The extract was washed with water, dried over Na₂SO₄, and evaporated to yield a solid, which was then chromatographed on silica gel column. Elution with benzene and recrystallization from ethanol gave 1.22 g of colorless needles (mp 81°C). IR νmax cm⁻¹: 2245 (CN). NMR (CDCl₃) δ: 7.13~7.79 (3 H, m). MS m/z: 267 (M⁺).

3.11 Suprofen-d₇
Potassium tert-butoxide (0.4 g) was added to a solution of XII (1.20 g) in 40 ml of absolute benzene with stirring. After 0.6 g of methyl-d₃ iodide was added dropwise, the mixture was stirred for 2 hr, which was then poured into water and extracted with benzene. The extract was washed with water, dried over Na₂SO₄, and evaporated to yield 1.01 g of an oily residue. A mixture of this oil and 0.1 g of NaOH in 20 ml of ethanol-H₂O=1:1 (v/v) was refluxed for 6 hr, which was then poured into water and extracted with ether in order to remove neutral compounds. The aqueous layer was made acidic and extracted with CHCl₃. The extract was washed with water, dried over Na₂SO₄, and evaporated to yield a crystalline solid. Recrystallization from ethanol-H₂O=1:1 (v/v) gave suprofen-d₇ as colorless needles (mp 123°C) in a 0.63 g yield. IR νmax cm⁻¹: 1690 (CO), 2260 (CD). NMR (CDCl₃) δ: 4.03 (1 H, s), 7.04~7.73 (3 H, m). MS m/z: 231 (M⁺).

References

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光学活性 2-((4-(2-チロールカルボニル)フェニル)プロピオン酸の重水素標識化合物の合成

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抗炎症剤2-(4-(2-チロールカルボニル)フェニル)プロピオン酸（スプロフェン）のヒトおよび動物における代謝をイオンクラスタ法で検討するために、スプロフェンの重水素多重標識体を合成した。スプロフェン-d4はプロフェンベンゼン-d5から5ステップの反応を経て収率32%で得られ、その重水素含量は99 atom%であった。スプロフェン-d4はd(+)またはl(-)-α-メチルベンジルアミンを用いて光学分割したところ、d(+)またはl(-)-スプロフェン-d4(96.5 atom% D)が収率11%で得られた。一方、スプロフェン-d7(99 atom% D)はトルエン-d5とヨウ化メチル-d3から5ステップの反応を経て収率24%で得られた。