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A practical synthesis of deuterium-labeled cefuroxime

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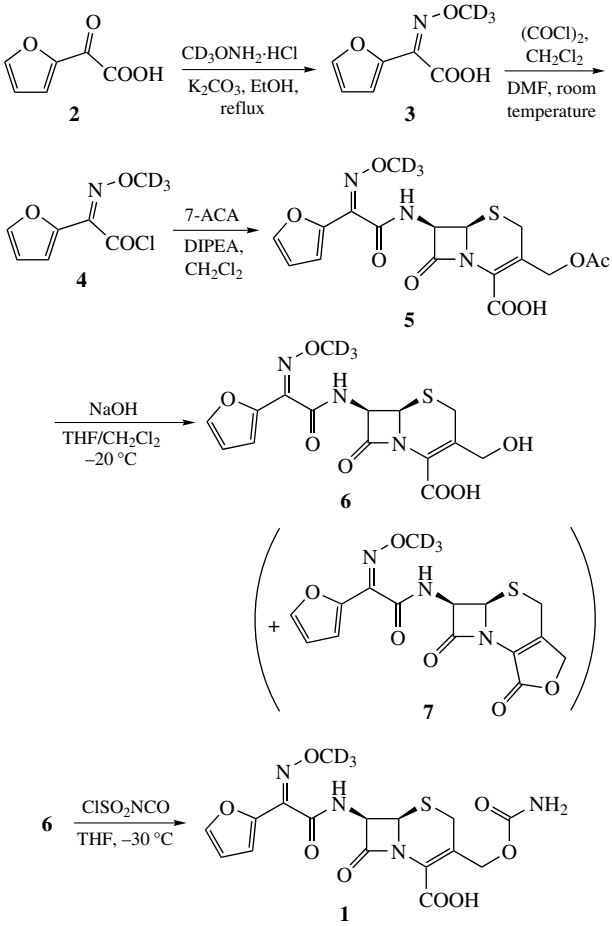
The deuterium-labeled cefuroxime, an internal standard drug, has been achieved in 5 steps from the commercially available methoxyl-d_3-amine hydrochloride with 14% overall yield and chemical purity >99%, the isotope purity was over 98%.

Cefuroxime is a second-generation cephalosporin antibiotic drug used in clinical treatment for patients with bacterial infections of respiratory tract, urinary tract, skin and soft tissues, meningeal and central nervous system. It was marketed by GlaxoSmithKline under the trade name Zinacef. Unlike most other second-generation cephalosporins, cefuroxime can cross the blood-brain barrier.[1,2] In addition, Pichichero's results have shown no increased risk for a crossallergic reaction for cefuroxime and several other second-generation or later cephalosporins.[3] The pediatric doses of cefuroxime (25–50 mg kg^{-1}) can be used in infants and children undergoing cardiopulmonary bypass (CPB) for surgical-site infection prophylaxis, however, a second intraoperative dose, administered through the CPB circuit, provides no additional prophylactic advantage.[4] Accordingly, pharmacokinetics, distribution and metabolism on cefuroxime should be extensively performed to support clinical studies. Thus, a stable isotope-labeled standard is required. Some researchers have described the synthetic procedures of unlabeled cefuroxime starting from 7-aminocephalsporanic acid (7-ACA) and (*Z*)-2-(2-furyl)-2-(methoxyimino)acetyl chloride (SMIF-Cl). However, only few literature entries focused on the detailed methods and reaction rates for cefuroxime labeled at different positions.[5–9] Here, a deuterium-labeled cefuroxime **1** was synthesized by a convenient five-step procedure from the commercially available methoxyl-d_3-amine hydrochloride, commercially available 2-(2-furyl)-2-oxoacetic acid **2** and 7-ACA. It can be used in pharmacological studies.

The synthesis procedure for cefuroxime-d_3 **1** is shown in Scheme 1. d_3-(2*Z*)-2-(2-Furyl)-2-(methoxyimino)acetic acid **3** was prepared in 66% yield by treating 2-(2-furyl)-2-oxoacetic acid **2** with methoxyl-d_3-amine hydrochloride in ethanol at reflux for 6 h.[10] Compound **3** was treated with oxalyl chloride in the presence of DMF to form acid chloride **4** which was used directly in the next step without further purification. Acylation of 7-ACA was carried out with acid chloride **4** in dichloromethane in the presence of DIPEA to give amide **5** in 67% yield.† Following treatment of product **5** with NaOH (< –20 °C, ~5 h) in CH_2Cl_2–THF (1 : 2) caused hydrolysis of ester group. However, it was observed that an intramolecular esterification of acid **6** into lactone **7** readily occured when neutralization was performed at room temperature (see Scheme 1). In order to improve the outcome of the procedure, the workup temperature was reduced below –20 °C, which provided 73% yield of hydroxy acid **6**.‡



Scheme 1

† For experimental details and characteristics of compounds obtained, see Online Supplementary Materials.

‡ d$_3$-*(6*R*,7*R*)-3-Hydroxymethyl-7-{[(2Z)-2-(2-furyl)-2-(methoxyimino)-acetyl]amino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic *acid* **6**. A 4 M aqueous solution of NaOH (4 equiv., 4.7 ml) was added dropwise to a solution of compound **5** (2.00 g, 4.7 mmol) in CH_2Cl_2–THF (1 : 2, 30 ml) at –30 °C for 1 h. The reaction mixture was stirred at –20 °C for 5 h and then adjusted to pH 7 with diluted hydrochloric acid (2 M) at –20 °C. The resulting solution was poured into ice-water (50 ml). The precipitated solid was filtered and purified by chromatography on a silica gel column (CH_2Cl_2–MeOH, 4 : 1) to afford 1.32 g (73%) of compound **6** as a yellow solid. ^{1}H NMR (DMSO-d_6) δ: 13.72 (br. s, 1H, COOH), 9.67 (d, 1H, =CHO, *J* 7.8 Hz), 7.90 (d, 1H, =CHO, *J* 1.5 Hz), 7.29 (m, 1H, =CH), 6.67 (br. s, 1H, NH), 6.63–6.75 (br. s, 1H, OH), 5.83 [dd, 1H, COC*H*(NH), *J* 4.4 and 7.8 Hz], 5.22 [d, 1H, (NH)C*H*S, *J* 3.4 Hz], 4.94–5.01 (m, 2H, CH_2O), 3.47–3.63 (m, 2H, SCH_2). ^{13}C NMR (DMSO-d_6) δ: 167.7, 166.4, 155.2, 146.3, 144.9, 143.8, 131.1, 118.3, 115.0, 112.8, 65.2, 62.1, 58.2, 55.7, 24.6. MS-EI, *m*/*z*: 385.1 $[M+H]^+$.

Reaction of compound **6** with chlorosulfonyl isocyanate (2 equiv.) in THF at –30 °C for 4 h afforded cefuroxime-d_3 **1** in 52% yield.[§]

In conclusion, a convenient five-step protocol for the laboratory-scale synthesis of cefuroxime-d_3 with chemical purity > 99% has been developed, the isotope purity was higher than 98% (MS data). The stable isotope-labeled cefuroxime-d_3 can be used as an internal standard for LC-MS analysis in pharmacokinetics studies.[11]

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.07.005.

[§] *Cefuroxime*-d_3 **1**. $ClSO_2NCO$ (0.88 g, 6.2 mmol) was added dropwise to a solution of compound **6** (1.20 g, 3.1 mmol) in THF (30 ml) at –30 °C for 1 h. The mixture was stirred at –30 °C for 4 h and quenched with H_2O (10 ml). The solvent was removed and the residue was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic phase was washed successively with saturated $NaHCO_3$ solution (20 ml) and brine (20 ml), dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The crude product was purified by chromatography on a silica gel column (CH_2Cl_2–MeOH, 3 : 1) to afford 0.69 g (52%) of cefuroxime-d_3 **1** as an off-white solid, mp 171–173 °C. ^{1}H NMR (DMSO-d_6) δ: 13.65 (br. s, 1H, COOH), 9.61 (d, 1H, =CHO, *J* 7.7 Hz), 7.85 (d, 1H, =CHO, *J* 1.4 Hz), 7.26 (m, 1H, =CH), 6.53–6.70 (m, 3 H, NH, NH_2), 5.79 [dd, 1H, COC*H*(NH), *J* 4.3 and 7.7 Hz], 5.18 [d, 1H, (NH)C*H*S, *J* 3.2 Hz], 4.89 (m, 2 H, CH_2O), 3.45–3.61 (m, 2 H, SCH_2). ^{13}C NMR (DMSO-d_6) δ: 168.3, 167.5, 162.9, 156.8, 147.1, 145.3, 144.5, 132.0, 119.1, 115.9, 113.7, 65.3, 62.9, 59.0, 56.1, 24.8. MS-EI, *m*/*z*: 450.1 $[M+Na]^+$. HPLC [XDB–C18 column, MeCN/TFA (0.01%)–H_2O/TFA (0.01%) from 5 to 95% in 15 min, 1.2 ml min^{-1}]: t_R 7.36 min (99.37%). Isotopic purity of cefuroxime-d_3 **1** determined by MS analysis was over 98%.

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