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RESEARCH ARTICLE

Efficient synthesis of D_6-clenproperol and D_6-cimaterol using deuterium isopropylamine as labelled precursor

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This report presents an efficient synthesis of D_6-clenproperol and D_6-cimaterol with 99.5% and 99.7% isotopic abundance in acceptable yields and excellent chemical purities with deuterium isopropylamine as labelled precursor. Their structures and the isotope-abundance were confirmed by proton nuclear magnetic resonance and liquid chromatography–mass spectrometry.

KEYWORDS

D_6-cimaterol, D_6-clenproperol, deuterium isopropylamine, labelled internal standards, synthesis

1 | INTRODUCTION

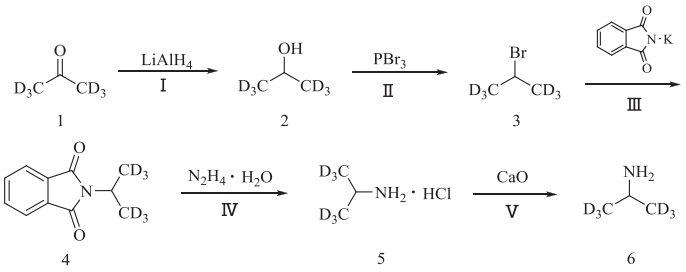
β-Agonistic drugs like clenproperol, clenbuterol, salbutamol, and cimaterol were widely used in the treatment of bronchial disease, which were also used in the feed of animals such as pigs, cattle, and sheep because they could increase the protein to fat ratio, resulting in a higher production efficiency. [1–3] However, *β*-agonistic drugs can be remained in the animals, the meat products obtained from treated animals may pose a potential risk for human health, and the abundant misuse raised serious concerns about a toxicological risk for the consumer. Thus, these drugs have been prohibited as a growth promoter of farm animals in several countries, such as the European Union, Japan, and China, and the detection of *β*-agonistic residue has been strengthened in all countries of the world. [4–6]

In recent years, numerous methods have been developed for the detection of clenproperol and other *β*-agonists in animal tissues, such as gas chromatography–mass spectrometry (GC-MS), high-performance liquid chromatography, and liquid chromatography–mass spectrometry (LC-MS). [7–9] But all of these methods have the uniform drawback for determining the residue of *β*-agonists because of matrix effects, which may interfere with analysis and affect the accuracy of the results significantly. Researchers have wanted to develop more prominent and reliable analytical methods desperately. Liquid chromatography isotope diluted tandem mass spectrometry has been widely used in food safety analysis because of the high precision, high accuracy, and simple pretreatment for samples, which could effectively avoid the interference caused by external factors. [10,11] But the most important for the detection is the labelled compounds of internal standards.

To the best of our knowledge, there were very few procedures described in the literature for the synthesis of labelled clenproperol and cimaterol. In this study, we would like to describe an efficient synthesis of D_6-clenproperol and D_6-cimaterol using deuterium isopropylamine as labelled precursor. The target compounds, with excellent isotopic and chemical purities, were synthesized in acceptable yield and could be used as an internal standard in the determination of *β*-agonists in animal tissues.

2 | RESULTS AND DISCUSSION

Based on the previous work about the synthesis of (1,3-D_6)-2-bromopropane before, the strategy of labelling deuterium on isopropyl group was designed. [12] The 5-step synthesis of the labelled isopropylamine **6** started with commercially available D_6-acetone as depicted in Scheme 1. First of all, D_6-acetone **1** was reduced with the minimum amount of $LiAlH_4$ to (1,3-D_6)-propan-2-ol **2** with 99.8% atom D at 0°C (93.6% yield). The (1,3-D_6)-propan-2-ol **2** was then

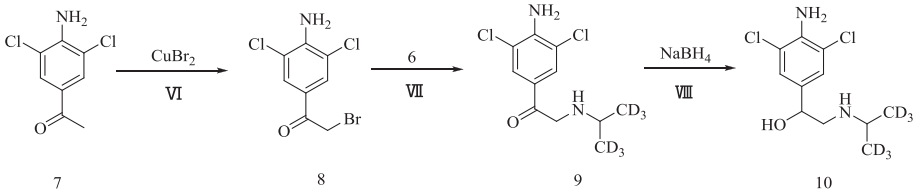


SCHEME 1 Synthesis of deuterium labelled isopropylamine. Reagents and conditions: (I) $LiAlH_4$, diglyme, diethylene glycol, 0°C, 1 h, 93.6% [a], 99.8% atom D[b]; (II) PBr_3, rt, overnight, 73.9%, 99.8% atom D; (III) potassium phthalimidate, DMF, 120°C, 4 h, 94.5%, 99.7% atom D; (IV) hydrazine hydrate, methanol, 80°C, 2 h, 79.1%, 99.7% atom D; (V) CaO, rt, 4 h, 75.2%, 99.7% atom D. [a]Isolated yield based on labelled materials. [b]Calculated by gas chromatography–mass spectrometry or mass spectra

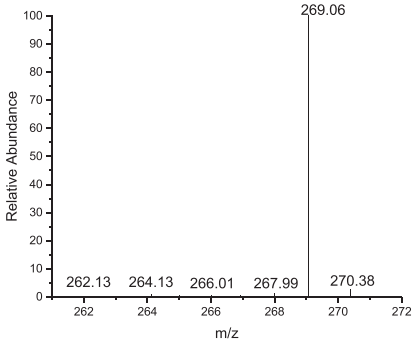
converted to (1,3-D_6)-2-bromopropane **3** with 99.8% atom D (73.9% yield) at room temperature in the presence of phosphorus tribromide. According to the Gabriel synthesis, [13] **3** was reacted with potassium phthalimide at 120°C, received D_6-N-isopropylphthalimide **4** with 99.7% atom D (94.5% yield). (1,3-D_6)-Isopropylamine **6** (99.7% atom D, 75.2% yield) was obtained via hydrazinolysis reaction of **4** with the excess amount of hydrazine hydrate in the presence of hydrochloric acid to get (1,3-D_6)-isopropylamine hydrochloride **5** (99.7% atom D, 79.1% yield); then, the hydrochloric acid was removed by excess amount of calcium oxide.

For synthesis of D_6-clenproperol **10** as depicted in Scheme 2, 1-(4-amino-3,5-dichlorophenyl)ethan-1-one **7** was reacted with cupric bromide at 70°C to get 4-amino-3,5-dichlorophenacylbromide **8** with 76.2% yield via further crystallization in chloroform. Through the subsequent amination of the (1,3-D_6)-isopropylamine, corresponding labelled intermediate **9** was obtained with 99.6% atom D (37.4% yield). Then reduction of **9** using sodium borohydride gave **10** with 99.5% atom D (76.3% yield) according to its mass spectrum (MS) of Figure 1 and the unlabelled clenproperol its MS was shown in Figure 2**.** The sodium borohydride was added twice to be able to ensure adequate reduction.

For synthesis of D_6-cimaterol **15** that was obtained by the modification of a known procedure[14] as depicted in Scheme 3, 1-(4-aminophenyl) ethan-1-one **11** was brominated with the equal amount of N-bromobutanimide in toluene with the temperature kept below 30°C, giving 1-(4-amino-3-bromophenyl) ethan-1-one **12** (95.2% yield). Then **12** was reacted with copper cyanide at 160°C, and corresponding intermediate 5-acetyl-2-aminobenzonitrile **13** was obtained with 66.6% yield. Subsequently, crude **13** was brominated with cupric bromide at 70°C, giving 2-amino-5-(2-bromoacetyl)benzonitrile **14** in 71.5% yield. Through the subsequent amination of the (1,3-D_6)-isopropylamine and reduction with sodium borohydride gave **15** in 36.7% yield, with 99.7% atom D according to its MS of Figure 3 and the unlabelled cimaterol its MS was showed in Figure 4**.**



SCHEME 2 Synthesis of D_6-clenproperol. Reagents and conditions: (VI) $CuBr_2$, $CHCl_3$, ethyl acetate, ethanol, 70°C, 2 h, 76.2%; (VII) $CHCl_3$, 63°C, 5 h, 37.4%, 99.6% atom D; (VII) $NaBH_4$, methanol, rt, overnight, 76.3%, 99.5% atom D



m/z	Intensity	Relative
262.13	52699.4	0.28
262.99	34964.7	0.18
264.13	190548.3	1.00
265.01	108082.7	0.57
266.01	97757.8	0.51
266.93	73432.2	0.38
267.99	232797.6	1.22
269.06	19115402.7	100.00
270.38	488614.1	2.56

FIGURE 1 Mass spectrum of **10**

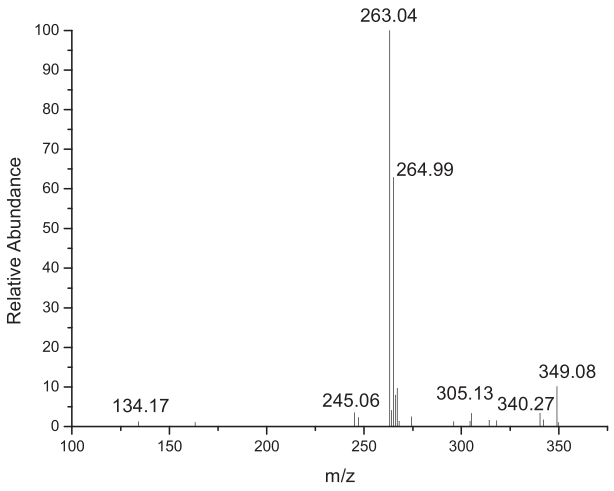


FIGURE 2 Mass spectrum of clenproperol

3 | EXPERIMENT

3.1 | Materials and instruments

D_6-Acetone (99.96% atom D) was purchased from J&K Chemical and used as received. All other reagents and solvents were commercially available and used without further purification. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AC-500 (500 MHz) spectrometer (Bruker Daltonics Inc, Billerica, Massachusetts, USA) in $CDCl_3$ (Tetramethylsilane (TMS) as internal standard). Mass spectra were recorded on a Finnigan TSQ Quantum Access spectrometer (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Gas chromatography–mass spectra were recorded using an Agilent Technologies 7890-7000C instrument (Agilent Technologies Inc, Palo Alto, California, USA) with a HP-5MS 30 m × 0.25 mm capillary apolar column (stationary phase: 5% diphenyldimethylpolysiloxane film, 0.25 μm).

3.2 | (1,3-D_6)-Propan-2-ol (2)

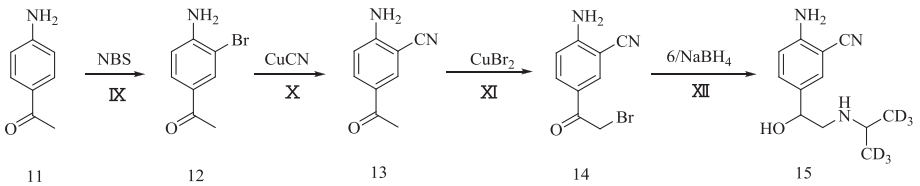
To a stirred suspension of $LiAlH_4$ (5 g, 132 mmol) in diglyme (80 mL, dried over CaH_2) under nitrogen at 0°C was slowly added D_6-acetone **1** (99.96% atom D, 20.0 g, 312 mmol). The solution was stirred at 0°C for 1 hour, and then diethylene glycol (70 mL) slowly added. The (1,3-D_6)-propan-2-ol was distilled from the reaction mixture, and the fraction boiling between 80°C and 107°C was collected to give **2** (19.27 g, 292 mmol, 93.6% yield, 99.8% atom D). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.91 (brs, 1H). GC-MS: m/z 48.

3.3 | (1,3-D_6)-2-Bromopropane (3)

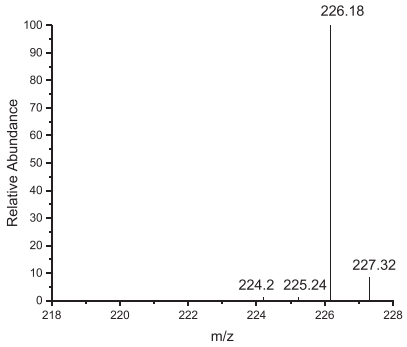
To a suspension of **2** (18.8 g, 284 mmol) stirred 10 minutes, at −10°C, was added dropwise phosphorus tribromide (49.8 g, 184 mmol). After that the resulting solution was stirred at room temperature overnight and the product **3** is isolated by distillation, the fraction boiling 50°C to 62°C was collected (27.07 g, 210 mmol, 73.9% yield, 99.8% atom D). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 4.23 (s, 1H). GC-MS: m/z 128, 130.

3.4 | (D_6)-N-Isopropylphthalimide (4)

A dry and nitrogen-flushed 250 mL 3-necked flask, was charged with potassium phthalimidate (8.892 g, 48 mmol), **3** (5.16 g, 40 mmol), and N,N-dimethylformamide (12.5 mL) were mixed and refluxed with stirring at 120°C for 4 hours. Then the mixture was cooling to 0°C, added with



SCHEME 3 Synthesis of D_6-cimaterol. Reagents and conditions: (IX) NBS, toluene, 30°C, 15 min, 95.2%; (X) CuCN, DMF, 160°C, 6 h, 66.6%; (XI) $CuBr_2$, $CHCl_3$, ethyl acetate, ethanol, 70°C, 2 h, 71.5%; (XII) $NaBH_4$, ethanol, 0°C, 6 h, 36.7%, 99.7% atom D



m/z	Intensity	Relative
219.54	244.8	0.06
220.53	122.5	0.03
221.51	307.2	0.07
222.18	6.2	0.00
223.09	623.1	0.15
224.20	4215.4	1.02
225.24	4253.1	1.03
226.18	411409.6	100.00
227.32	35168.8	8.55

FIGURE 3 Mass spectrum of **15**

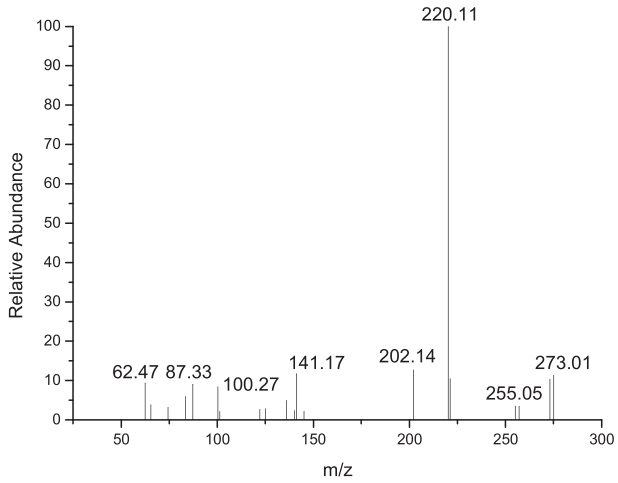


FIGURE 4 Mass spectrum of cimaterol

water (100 mL) and dichloromethane (100 mL). The organic layer was washed with saturated sodium bicarbonate solution (3 × 80 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuum to yield **4** (7.38 g, 37.8 mmol, 94.5% yield, 99.7% atom D). The crude **4** was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.82 to 7.80 (m, 2H), 7.70 to 7.68 (m, 2H), 4.50 (s, 1H). GC-MS: m/z 195, 177, 130.

3.5 | (1,3-D_6)-Isopropylamine hydrochloride (5)

To the **4** (5.08 g, 26 mmol) was added hydrazine hydrate (3.03 g, 60.5 mmol) in methanol (5.5 mL). The mixture was heated at 80°C for 1 hour and white solid separated during this time. Then addition of water (18 mL) and 12 mol/L hydrochloric acid (16 mL) and the mixture were reacted for 1 hour again at 80°C. After that the mixture was cooled to room temperature, phthalhydrazide was removed by filtration, and the filtrate were concentrated under reduced pressure to give **5** (2.09 g, 20.6 mmol, 79.1% yield, 99.7% atom D). ^{1}H NMR (500 MHz, D_2O) δ ppm: 3.24 (s, 1H). LC-MS: $[M+H]^+$ m/z 67.

3.6 | (1,3-D_6)-Isopropylamine (6)

Calcium oxide (2.668 g, 47.57 mmol) and (1,3-D_6)-isopropylamine hydrochloride **5** (2.0 g, 19.69 mmol) were mixed and stirred for 4 hours at the room temperature, then distilled under atmospheric pressure. The product **6** is isolated by distillation; the fraction boiling 30°C to 34°C was collected (0.964 g, 14.8 mmol, 75.2% yield, 99.7% atom D) in a flask cooled with liquid nitrogen. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.31 (s, 1H). LC-MS: $[M+H]^+$ m/z 67.

3.7 | 4-Amino-3,5-dichlorophenacylbromide (8)

A dry and nitrogen-flushed 500 mL 3-necked flask, equipped with a nitrogen inlet and a dropping funnel, was charged with 1-(4-amino-3,5-dichlorophenyl) ethan-1-one **7** (16.325 g, 80 mmol), $CuBr_2$ (35.741 g, 160 mmol), $CHCl_3$ (150 mL), and ethyl acetate (150 mL). The reaction mixture was stirred for 30 minutes at 70°C, then ethanol (90 mL) was added portionwise in 30 minutes. After completion of the addition, the mixture was stirred for 2 hours, then filtered while hot and the cake washed with 40 mL ethyl acetate. The filtrate was washed with water (200 mL) and saturated sodium chloride solution(3 × 150 mL); the organic layers dried over anhydrous magnesium sulfate and removed in vacuum, and crystallized in chloroform to give **8** (17.248 g, 60.96 mmol, 76.2% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.86 (s, 2H), 5.06 (brs, 2H), 4.31 (s, 2H). LC-MS: $[M-H]^-$ m/z 282.

3.8 | (D_6)-1-(4-Amino-3,5-dichlorophenyl)-2-(isopropylamino) ethan-1-one (9)

To a stirred solution of **8** (7.173 g, 25.35 mmol) in chloroform (40 mL) at 63°C in a 250 mL round bottom flask sealed with a rubber, (1,3-D_6)-isopropylamine **6** (1.1 g, 16.91 mmol) was injected by syringe slowly. The mixture was stirred for 5 hours, during this time a white solid generated, and the mixture was filtered, the solid washed with chloroform, and the combined filtrate and washings evaporated to dryness to yield **9** (1.69 g, 6.32 mmol, 37.4% yield, 99.6% atom D). ^{1}H NMR (500 MHz, D_2O) δ ppm: 7.81 (s, 2H), 4.53 (s, 2H), 3.45 (s, 1H). LC-MS: $[M+H]^+$ m/z 267.

3.9 | (D_6)-Clenproperol (10)

Sodium borohydride (0.256 g, 6.77 mmol) was added gradually to a solution of **9** (1.432 g, 5.36 mmol) and methanol (15 mL) in water (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 hours then neutralized with 6 mol/L hydrochloric acid to form a colorless liquid (pH = 3-5). The reaction mixture was further stirred at room temperature for 12 hours; then, the sodium borohydride (0.256 g, 6.77 mmol) was added gradually again. The reaction mixture was neutralized with 6 mol/L hydrochloric acid to weak acidic (pH = 3-5) after stirring at room temperature for 2 hours. The mixture was filtered, and the filtrate was added aqueous ammonia until weak alkaline (pH = 8-10). The mixture was filtered, and the filter cake was dried to yield **10** (1.1 g, 4.1 mmol, yield 76.3%, 99.5% atom D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 to 7.75 (m, 2H), 4.64 (d, J = 8.5 Hz, 1H), 4.49 (s, 1H), 2.88 (s, 2H). LC-MS: $[M+H]^+$ m/z 269.

3.10 | 1-(4-Amino-3-bromophenyl)ethan-1-one (12)

To a stirred solution of 1-(4-aminophenyl) ethan-1-one **11** (4.055 g, 30 mmol) in toluene (50 mL) was added N-bromosuccinimide (5.34 g, 30 mmol) in portions over 15 minutes; then, the mixture was stirred for 15 minutes at 30°C. After that the reaction mixture was washed with water (3 × 100 mL), dried with anhydrous magnesium sulfate, and evaporated in vacuum, giving a dark brown oil. The crude dark brown oil dissolved in ethanol (30 mL) and then water

(700 mL) added to precipitate the solid product, the filter cake was collected by filtration to get **12** (6.11 g, 28.56 mmol, yield 95.2%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 2.5 Hz, 1H), 7.74 (dd, J = 2.5, 2.5 Hz, 1H), 6.74 (d, J = 10.5 Hz, 1H), 4.57 (brs, 2H), 2.51 (s, 3H). LC-MS: $[M-H]^-$ m/z 212.

3.11 | 5-Acetyl-2-aminobenzonitrile (13)

A mixture of **12** (3.56 g, 16.63 mmol), cuprous cyanide (1.79 g, 20 mmol), and N,N-dimethylformamide (20 mL) was stirred at 160°C under nitrogen for 6 hours. After cooling to room temperature, the mixture was treated with a solution of ferric chloride (prepared from 6.6 g of ferric chloride, 6.6 mL of hydrochloric acid (12 mol/L), and 20 mL of water) and stirred for 30 minutes at 65°C. A 40 mL portion of water and 40 mL of dichloromethane were added. To facilitate phase separation, the mixture was filtered, and then the filtrate was extracted with 40 mL dichloromethane twice. The organic extracts were combined, washed with water (2 × 100 mL) and saturated sodium bicarbonate (3 × 100 mL); and the solvent was removed in vacuum to give **13** (1.77 g, 11.07 mmol, yield 66.6%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 1.5 Hz, 1H), 7.96 (dd, J = 2, 1.5 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 4.89 (brs, 2H), 2.51 (s, 3H). LC-MS: $[M-H]^-$ m/z 159.

3.12 | 2-Amino-5-(2-bromoacetyl)benzonitrile (14)

A dry and nitrogen-flushed 250 mL 3-necked flask, equipped with a nitrogen inlet and a dropping funnel, was charged with **13** (3 g, 18.7 mmol), $CuBr_2$ (8.4 g, 37.6 mmol), $CHCl_3$ (50 mL), and ethyl acetate (50 mL). The reaction mixture was stirred for 30 minutes at 70°C; then, ethanol (10 mL) was added portionwise in 30 minutes. After completion of the addition, the mixture was stirred for 2 hours, then filtered while hot and the cake washed with 20 mL ethyl acetate. The filtrate was washed with saturated sodium chloride solution (3 × 150 mL), the organic layers dried over anhydrous magnesium sulfate, and solvent removed in vacuum to give **14** (3.2 g, 13.37 mmol, yield 71.5 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 1.5 Hz, 1H), 7.98 (dd, J = 1.5, 2.0 Hz, 1H), 6.79 (d, J = 7 Hz, 1H), 4.97 (brs, 2H), 4.31 (s, 2H). LC-MS: $[M-H]^-$ m/z 237.

3.13 | (D_6)-Cimaterol (15)

14 (2.026 g, 8.5 mmol) was dissolved in ethanol (25 mL). The solution was stirred for 0.5 hour at 0°C, and **6** (1.1 g, 16.91 mmol) was injected by syringe slowly. The reaction mixture was stirred for 2 hours at room temperature, then cooled to 0°C, and the sodium borohydride (0.512 g, 13.53 mmol) was added slowly. After the completion of addition, the reaction mixture was stirred for 4 hours at room temperature and then added 30 mL of water and 40 mL of ethyl acetate. The combined organic layers were separated, washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuum to yield **15** (1.4 g, 6.2 mmol, yield 36.7%, 99.7% atom D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 1.5 Hz, 1H), 7.33 (dd, J = 1.5, 1.5 Hz, 1H), 6.72 (d, J = 7 Hz, 1H), 4.49 to 4.51 (m, 1H), 4.37 (s, 2H), 2.81 to 2.89 (m, 2H), 2.53 to 2.57 (m, 1H). LC-MS: $[M+H]^+$ m/z 226.

4 | CONCLUSIONS

In summary, D_6-clenproperol and D_6-cimaterol were prepared with 99.5% and 99.7% isotopic abundance, respectively. The structure was confirmed by ^{1}H-NMR and LC-MS.

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