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Rac- and *R*-(+)-[4,4′,5,5′-$^2H_4$]-2-(1′-[2″,6″-dichlorophenoxy]-ethyl)-Δ^2-imidazoline (lofexidine)

Ashish P. Vartak, Vijayakumar Sonar, and Peter A. Crooks*

The synthesis of the d_4-forms of *rac*- and *R*-lofexidine was accomplished. Two methods are described; one method is a two-step synthesis of *rac*-d_4-lofexidine from 2-chloropropionitrile, the second method is a three-step preparation of *R*-d_4-lofexidine in absolute enantiomeric purity from *S*-methyl lactate. The commercial availability of *R*-methyl lactate makes this latter enantioselective synthesis applicable also to the synthesis of *S*-d_4- lofexidine. These procedures also conserve the utilization of the relatively expensive [1,1′,2,2′-$^2H_4$]ethylene diamine precursor. The availability of *S*- and *R*-d_4-lofexidines will enable pharmacokinetic studies to be carried out to determine if differential in vivo metabolism of the two enantiomers of lofexidine occurs.

Keywords: lofexidine; deuterated; enantioselective

Introduction

Lofexidine, or 2-(2,6-dichlorophenoxy)ethyl-Δ^2-imidazoline (**1**) (Figure 1), is an α_2-adernergic agonist that is currently utilized in Europe as Britlofex® for the treatment of the symptoms of opiate addiction. A phase-III clinical trial has recently been conducted in the United States.[1] In addition, US WorldMeds is currently developing the enantiomeric forms of lofexidine as second-generation therapeutics with potentially superior side-effect profiles.

During our ongoing investigations into the metabolism of *rac*-, *R*- and *S*-lofexidine,[2,3] we were faced with the need for an isotopically labeled internal standard for HPLC-MS-MS quantification of lofexidine enantiomers in biological fluids. *Rac*-d_4-lofexidine (**2**) has been previously synthesized by Closter and Odenthal,[3] however, this synthetic methodology is not easily adaptable for the preparation of enantiomers of d_4-lofexidine (i.e. it is an eight-step procedure). Thus, we were in need of an efficient and versatile synthetic route that could afford the enantiopure *S*- and *R*-products in reasonable overall yields. We also were interested in improving the utilization of the relatively expensive deuterated starting material, [1,1′,2,2′-$^2H_4$]ethylene diamine (d_4-ED) in these processes.

Results and discussion

We utilized two distinct approaches to the synthesis of (±)-**2** (Figure 1). In our first approach (Scheme 2), 2,6-dichlorophenol (**3**) was alkylated with (±)-α-chloropropionitrile in 2-butanone with K_2CO_3 as the base, yielding the nitrile (**4**), which was then subjected to imidazoline formation by the methodology of Biedermann *et al.*, by first converting the nitrile into the corresponding ethylimino ether hydrochloride **5**, followed by condensation with d_4-ED in place of the unlabeled precursor. The resulting free base (±)-**2** was converted to the hydrochloride salt. A yield of 68%, relative to the amount of labeled precursor, was obtained.

We have recently developed a scalable enantioselective synthetic approach toward the enantiomers of lofexidine that relies on the electrophilic alkylation of the primary amide **7** (Scheme 3) by trialkyloxonium salts to transform this carboxamide into imidazoline **2** in a one-pot sequence.[4] Reported herein is the applicability of this sequence to the synthesis of **2**, with particular attention being paid to maximizing the utilization of the relatively expensive d_4-ED precursor.

The synthetic sequence we have developed begins with a Mitsunobu reaction of 2,6-dichlorophenol on the α-carbon of *rac*-methyl lactate (**6**), followed by amidation of the methyl ester, to yield **7**. Carboxamide **7** is then reacted with an equivalent of trimethyloxonium tetrafluoroborate in CH_2Cl_2 to yield the imino ether tetrafluoroborate **8**, which is used directly in the subsequent cyclization step to afford **2**. Addition of an ethanolic solution of d_4-ED (0.95 equiv.) to a solution of **8** in CH_2Cl_2 led to complete scavenging of the deuteron-label. After aqueous workup and crystallization, **2** was isolated in 94% yield based on the amount of d_4-ED employed (for comparison, the method previously described in Reference[5] yields rac-d_4-lofexidine in 39% yield, based on the amount of d_4-ED employed). Free base **2** was then converted to its hydrochloride salt in quantitative yields and isolated in an analytically pure form after crystallization. An identical reaction sequence carried

Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 725 Rose Street, 501A, Lexington, KY 40536, USA

**Correspondence to: Peter A. Crooks, Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 725 Rose Street, 501A, Lexington, KY 40536, USA.*
E-mail: pcrooks@email.uky.edu

out on (–)-methyl lactate (**6**) proceeded essentially with a net inversion of configuration about the α-carbon, yielding *R*-(+)-**2** and *R*-(+)-**2.**HCl. Enantiomeric purities of *R*-(+)-**2** and *R*-(+)-**2**.HCl were determined by coupling of the free base to 2*S*-*tert*-butyldimethylsiloxy propanoic acid followed by gas chromatographic analysis of the product(s). In each case, the enantiomeric excess was determined to be 100%.

Experimental

[1,1′,2,2′-$^2H_4$]ethylene diamine (98 g at%) was purchased from C.D.N. Isotopes, Montreal, Canada. Solvents were of ACS-grade unless otherwise specified. THF was distilled over Na-benzophenone ketyl under an atmosphere of argon. All other reagents were used as received. Gram atom percentages were calculated utilizing PIDC (Positional Isotopometer Distribution Calculator), Department of Computer Sciences, University of Helsinki.

2-(2,6-Dichlorophenoxy)propionitrile

This compound was prepared in accordance with the method of Biedermann *et al.*[5]; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm, 7.57 (d, *J* = 8.1, 2H), 7.29 (t, *J* = 8.25, 1H), 5.34 (q, *J* = 6.9, 1H), 1.73–1.75 (d, *J* = 6.6, 3H).

(±)-[4,4′,5,5′-$^2H_4$]-2-(1′-[2″,6″-Dichlorophenoxy]-ethyl)-Δ^2-imidazoline ((±)-2. HCl) (Method 1)

A solution of 2-(2,6-dichlorophenoxy)propionitrile (365 mg, 1.7 mmol) in absolute ethanol (5 mL) was cooled to 0°C, saturated with dry HCl gas and the mixture was stored at 4°C in a refrigerator overnight. After evaporation of solvent, the resulting imino ester hydrochloride (not isolated) was treated with an ethanolic solution of d_4-ED (108.8 mg in 5 mL EtOH, 1.7 mmol) and the mixture was refluxed for 5 h. The crude product was converted to the hydrochloride salt (a small amount of ester formed by the hydrolysis of the imino ether hydrochloride was removed during this process, by washing the hydrochloride salt with diethyl ether). The yield obtained was 68% (250 mg). mp = 235–240°C; Anal. calc. C; 44.10%, H+D; 4.37%, N; 9.35%, found: C; 44.05%; H; 4.29%; N; 9.19%. EI-LRMS *m/z* 263.0 $(M+H)^+$ and 265 $(M+2+H)^+$. Gram at % deuterium = 99.8%;

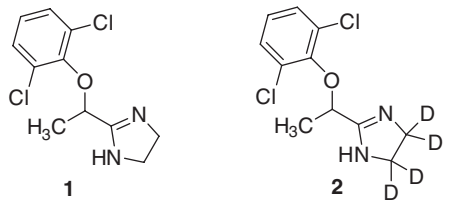


Figure 1. *Rac*-Lofexidine (**1**) and *rac*-d_4-lofexidine (**2**).

(±)-2-(2,6-Dichlorophenoxy)propionamide (7)

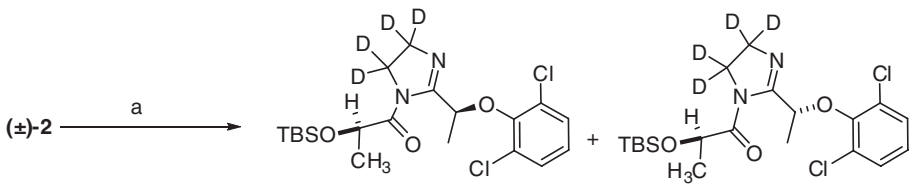
To a solution of (±)-methyl lactate (**6**) (5.00 g, 48 mmol), Ph_3P (12.6 g, 481 mmol) and 2,6-dichlorophenol (7.83 g, 48 mmol) in THF (40 mL) at 0°C was added drop-wise DIAD (9.8 g, 48 mmol) over a period of 15 min. The solution was warmed to ambient temperature over 4 h. Evaporation under reduced pressure afforded an amber gum that was stirred in 1:2 diethyl ether-hexanes (100 mL) for 30 min, during which time a 1:1 molar complex of $Ph_3P=O$ and diisopropoxycarbonyl hydrazine crystallized. The mixture was filtered, the filter cake washed with hexanes (50 mL), and the filtrate was evaporated to afford an amber oil. A solution of this oil in EtOH (30 mL) at 0°C was treated with gaseous NH_3 for 30 min and then stirred at ambient temperature. The white crystals that formed during this time were redissolved by heating the mixture to reflux for 45 min. The mixture was then filtered to remove a small amount of a yellow insoluble powder. Cooling of the filtrate at 4°C in the refrigerator for two hours led to the deposition of white needles, which were isolated by filtration and dried in air to afford **7** (9.0 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.35−7.25 (m, 2H, Ar). 7.03 (t, *J* = 8.4 Hz, 1H, Ar), 6.93 (br, s, NH), 6.08 (br, s, NH), 4.93 (q, 1H, *J* = 6.9 Hz), 1.50 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 174.2, 148.9, 129.7, 129.4, 125.7, 79.3, 18.1; mp = 196−198°C (EtOH) EI-LRMS *m/z* 233.0 $(M)^+$.

S-(–)-2-(2,6-Dichlorophenoxy)propionamide ((–)-7)

This compound was synthesized from (–)-methyl lactate, according to the procedure for (±)-**7** described above; 80% yield, $[\alpha]_D^{23} = -21.4°$ (c 1.0, acetone)[4,5] $[\alpha]_D^{20} = -19.9°$ (c 1.0, acetone) and for (+) −**7** = +20.1° (c 1.0, acetone).

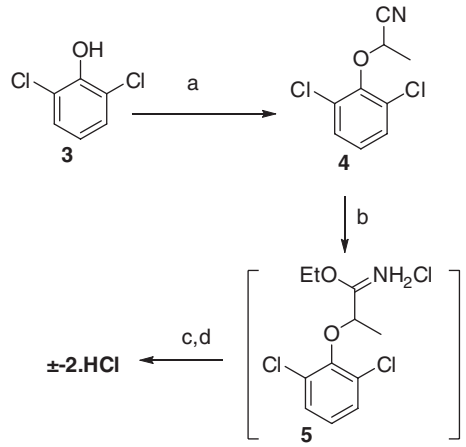
(±)-[4,4′,5,5′-$^2H_4$]-2-(1′-[2″,6″-Dichlorophenoxy]-ethyl)-Δ^2-imidazoline ((±)-2)

A mixture of **7** (1.00 g, 4.29 mmol) and trimethyloxonium tetrafluoroborate (664 mg, 1.1 equiv.) in CH_2Cl_2 (30 mL) was stirred at ambient temperature for 48 h, during which time the coarse suspension changed to a clear solution. Thereupon, the solution was cooled to–30°C (dry ice, glycol-EtOH bath) and treated drop-wise with a solution of [1,1′,2,2′-$^2H_4$]ethylene diamine (260 mg, 0.95 equiv.) in EtOH (5 mL). The resulting hazy solution was allowed to stir at ambient temperature for 10 min and then evaporated to dryness. The pasty white residue obtained was partitioned between



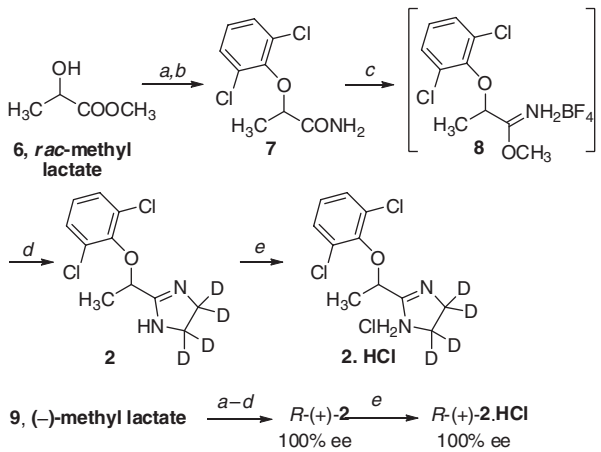
Reagents and Conditions: a. 2*S*-tert-butyldimethylsilyl propanoic acid (10 equiv.), DIC (10 equiv.), CH_2Cl_2, rt, 2h

Scheme 1. Conversion of *rac*- and (+)-d_4-lofexidine to their diastereomeric 2*S*-*tert*-butyldimethylsiloxy propanamide derivatives.



Reagents and Conditions: a. K_2CO_3, 2-butanone, 2-chloro propionitrile, reflux, 5h. b. HCl, ethanol, 0 °C, c. 1,1',2,2'-$^2d_4$-ethylene diamine, EtOH, d. HCl, i-PrOH (68% over 2 steps)

Scheme 2. Synthesis of (±)-**2**; Method 1.



a. 2,6-dichlorophenol, Ph_3P, DIAD, THF, rt, 4h; *b.* NH_3, EtOH (80% over two steps); *c.* Me_3OBF_4,CH_2Cl_2; *d.* [1,1,2,2'-$^2H_4$]ethylenediamine, EtOH 94% (over two steps, based on [1,1,2,2'-$^2H_4$]ethylenediamine); *e.* aq. HCl, Et_2O/EtOH, quant.

Scheme 3. Synthesis of (±)-**2**, *R*-(+)-**2** and their HCl salts; Method 2.

5% aq. K_2CO_3 (20 mL) and CH_2Cl_2 (50 mL). The aqueous layer was washed with another portion of CH_2Cl_2 (50 mL), and the combined organic layers were dried (anhydrous $MgSO_4$) and evaporated to afford a white solid residue that was recrystallized from boiling hexanes (100 mL) to give (±)-**2** (1.00 g, 94%); mp = 131–133°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ ppm 7.46–7.44 (m, 2H, Ar), 7.14 (t, *J* = 7.8 Hz, 1H, Ar), 6.45 (s, 1H, NH), 4.79 (q, *J* = 6.6 Hz, 1H), 1.47 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, d_6-DMSO) δ ppm 168.2, 149.0, 131.2, 129.4, 128.2, 73.1, 19.3. EI-LRMS *m/z* 262.0 $(M)^+$.

R-(+)-[4,4′,5,5′-$^2H_4$]-2-(1′-[2″,6″-Dichlorophenoxy]-ethyl)-Δ^2-imidazoline ((+)-2)

This compound was synthesized from (–)-**7** (100 mg, 0.42 mmol) as described above for (±)-**2**, yield = 70 mg (66%) mp = 129–131°C $[\alpha]_D^{23} = +73.4°$ (*c* 1.0, EtOH) (for (+)-**2**:[5] $[\alpha]_D^{20} = +73.7°$ (*c* 1.0, EtOH).[6] $[\alpha]_D^{20}$ for (–)-**2** = –80.7° (*c* 1.0, EtOH)); LR-EIMS *m/z* 262 $(M)^+$ and 264 $(M+2)^+$.

For determination of enantiomeric purity, (+)-**2** (1.08 mg, 0.00387 mmol) was treated with 2*S*-*tert*-butyldimethylsiloxy propanoic acid (8 mg, 0.0387 mmol, 10 equiv.) and diisopropyl carbodiimide (5 mg, 0.0387 mmol, 10 equiv.) in CH_2Cl_2 (100 μL) at room temperature. After 2 h, the entire mixture was diluted with CH_2Cl_2 (1 mL) and injected into a gas chromatograph (Agilent 6890 GC system with Agilent 5973 MSD equipped with EI-mass spectrometer). A sample of (±)-**2** was similarly treated and the resulting reaction mixture also injected into the GC. The following were noted: (1) all of the lofexidine in both reactions had been consumed under the reaction conditions; (2) the reaction mixture resulting from (±)-**2** gave rise to two distinct base-line resolved peaks (ratio 1:1) appearing at R_t = 15.19 min (*m/z* = 448) and R_t = 15.37 min (*m/z* = 448); (3) the reaction mixture resulting from (+)-**2** gave rise to only one peak at R_t = 15.19 min (Scheme 1). Consequently, the enantiomeric excess of (+)-**2** was judged to be 100%.

(±)-[4,4′,5,5′-$^2H_4$]-2-(1′-[2″,6″-Dichlorophenoxy]-ethyl)-Δ^2-imidazoline ((±)-2. HCl)

To a solution of (+)-**2** (1.00 g, 3.33 mmol) in 9:1 Et_2O/EtOH (10 mL) was added in a drop-wise fashion conc. aqueous HCl (0.3 mL, 1.3 equiv.). Upon stirring for 10 min the suspension was diluted with diethyl ether (10 mL), filtered and the filter-cake was washed with diethyl ether (3 × 10 mL) and air-dried, affording (±)-**2**.HCl (1.13 g, 100%). ^{1}H NMR (300 MHz, d_6-DMSO) δ ppm 10.59 (s, 2H, NH), 7.53 (d, *J* = 8.1 Hz, 2H, Ar), 7.23 (t, *J* = 8.1 Hz, 1H, Ar), 5.16 (q, *J* = 6.6 Hz, 1H) 3.87 (s, br, 4H), 1.63 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) δ ppm 169.5, 149.2, 130.3, 129.1, 127.5, 73.9, 44.6, 19.4; mp = 222–223°C; gram at % deuterium: 99.2%, Anal. calc. C: 44.10%, H+D: 4.37%, N: 9.35%, found: C: 44.24%: H; 4.12%; N: 9.30%.

R-(+)-[4,4′,5,5′-$^2H_4$]-2-(1′-[2″,6″-Dichlorophenoxy]-ethyl)-Δ^2-imidazoline hydrochloride ((+)-2. HCl)

This compound was synthesized from 70 mg of (+)-**2** as described above for (±)-**2. HCl**, 40 mg (46 %); mp = 202–204°C, $[\alpha]_D^{23} = +31.8°$ (*c* 1.0, EtOH) (for (+)-**2.HCl**:[5] $[\alpha]_D^{20} + 37.9°$ (*c* 1.0, EtOH)[6] $[\alpha]_D^{20}$ for (–)-**2** = –33.4° (*c* 1.0, EtOH). The enantiomeric excess of (+)-**2.HCl** was calculated to be 100% by conversion to (+)-**2** and diastereomer formation followed by gas chromatographic analysis, in a manner similar to that described in the preparation of (+)-**2**.

Conclusions

A new route to both *rac*- and *R*-d_4-lofexidine has been successfully developed. This route effectively maximizes the utilization of the expensive labeled precurssor, d_4-ED, thereby providing access to gram quantities of each of the final deutero-products.

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