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Novel and Efficient Synthesis of Deuterium-Labeled Olopatadine-d_6

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Abstract—A novel and highly efficient synthetic approach has been developed for the synthesis of deuterium-labeled olopatadine-d_6 using inexpensive and commercially available dimethyl sulfate-d_6 at the stage of alkylation of primary amine intermediate. The proposed synthetic path makes it possible to avoid the use of expensive labeled reagents such as dimethyl amine-d_6 used as labeled precursor in the traditional synthetic route. The structure of the obtained olapatadine-d_6 has been confirmed by ^{1}H NMR and mass spectral data.

Keywords: olapatadine, olopatadine-d_6, antihistamine, deuterium-labeled compounds.

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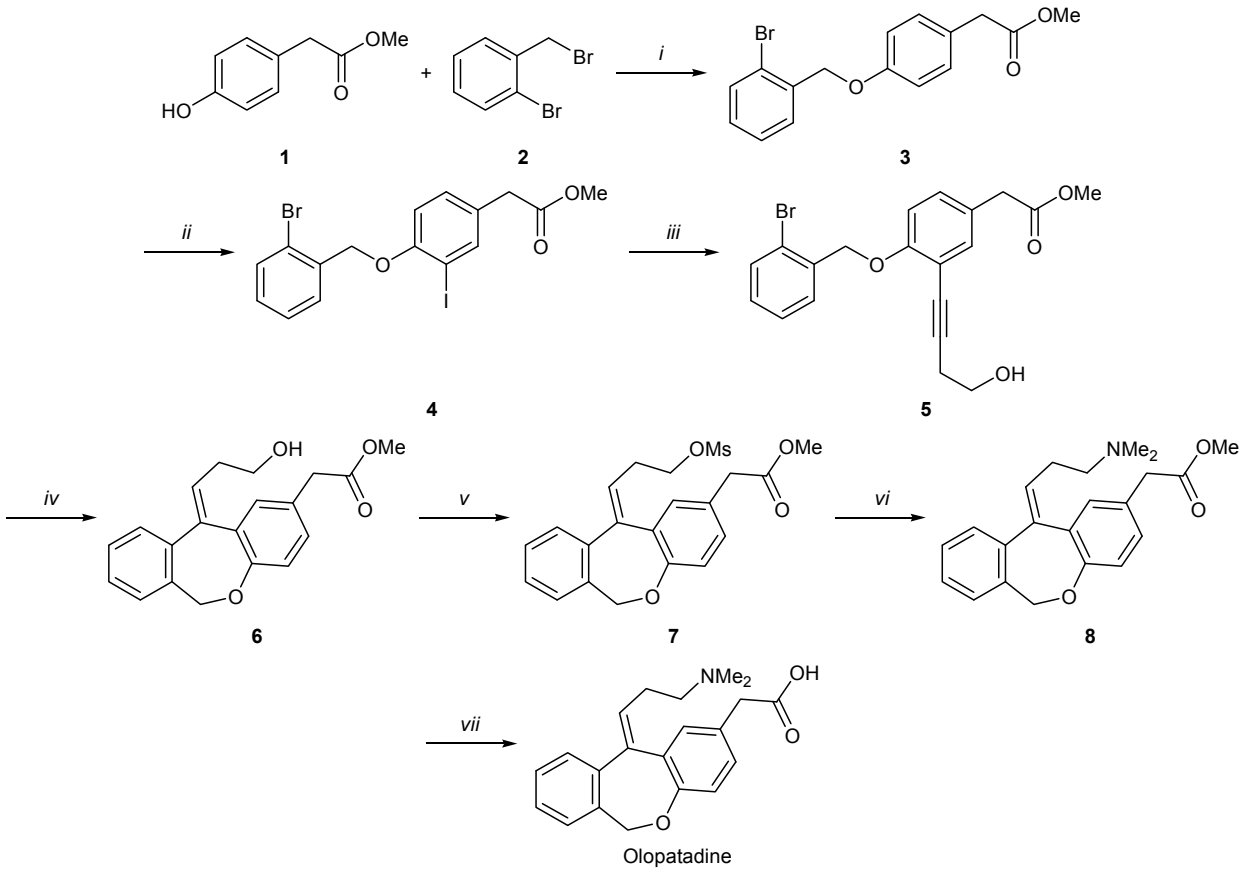
Since the discovery of highly active deuterium-labeled therapeutic organic molecules, the chemistry of deuterium substituted compounds has been grabbing attention from every nook and corner of chemical world [1]. Due to isotope effect, the stability and efficiency of existing drugs has been enhanced by substitution of deuterium for hydrogen. It is generally observed that carbon–deuterium (C–D) bonds are more resistant to chemical or enzymatic cleavage than carbon–hydrogen (C–H) bonds [2–3]. Moreover, the recent literature survey revealed that therapeutic activities of some clinical medicines have been notably improved by H–D displacements which could be noticed from the following remarkable examples. Deuterium-labeled amphetamines were more rapidly transported into the brain and were more persistent, and their activity was maintained for a longer time [4]; halogenated anesthetics such as selvoflane cease oxidation to form toxic metabolites within the body [5] through deuterium labeling; deuterium-labeled fluoro-D-phenylalanine and long-chain fatty acids were resistant to breakdown by their target microorganisms [6]. More recently, deuterium-labeled clinical medicines such as paroxetine (antidepressant), [7] atazanavir (HIV drug) [8], and venlafaxine (antidepressant) [9] were synthesized as long-lasting drug candidates by the pharmaceutical industry. Furthermore, olopatadine is an antihistamine as well as anticholinergic and mast cell stabilizer which has been developed by Kyowa Hakko Kirin Co. Ltd. [10] and is widely used as an eye solution for allergic conjunctivitis [11–13] and as an oral treatment for allergic rhinitis and skin diseases [14–16]. In general, both *Z* and *E* isomers of olopatadine show similar H1R affinities [17], but in fact the *Z* isomer of olopatadine is only being considered as a therapeutic drug because of the potent anti-allergic activity. Nevertheless, these deuterium-labeled drugs are being used as human drug metabolism investigation tracers and as internal standards for quantitative analysis using GC/MS or LC/MS [18, 19].

In view of the above mentioned facts, it was contemplated to design an inexpensive and facile synthetic path for the synthesis of deuterium-labeled olopatadine to enhance the efficiency and stability by incorporating deuterium in place of hydrogen atoms so that it could be used as an internal standard for quantitative analysis.

Literature review revealed a number of strategies for the synthesis of olopatadine [20–26]. In most of the reported syntheses, the key side chain has been introduced via Grignard reaction or Wittig olefination, and stereoselective synthesis of the *Z* isomer is a challenging issue. Nishimura et al. [27] reported a stereoselective route shown in Scheme 1. In this route, the *Z* stereoselectivity was controlled by palladium-catalyzed intramolecular closure of seven-membered ring in alkyne intermediate **5** to form dihydrodibenzo[*b*,*e*]-oxepine **6**. The same synthetic strategy was successfully applied to the synthesis of olopatadine-d_6 (Scheme 2). However, this synthetic strategy suffers

Scheme 1.

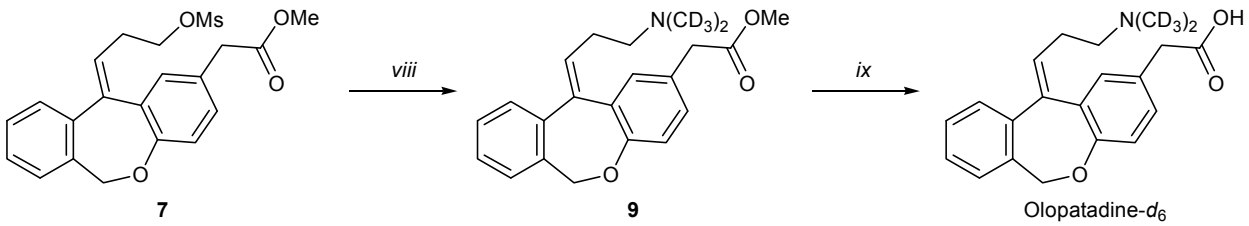


Reagents and conditions: *i*: K_2CO_3 (2.5 equiv), DMF, room temperature, 3 h, yield 97%; *ii*: I_2 (1.0 equiv), Ag_2SO_4 (1.0 equiv), MeOH, room temperature, 2 h, 87%; *iii*: but-3-yn-1-ol (2.0 equiv), $PdCl_2(PPh_3)_2$ (0.05 equiv), CuI (0.1 equiv), Et_3N (4.0 equiv), DMF, room temperature, 4 h, 93.6%; *iv*: $Pd(OAc)_2$ (0.1 equiv), tri-*o*-tolylphosphine (0.25 equiv), piperidine (7.0 equiv), formic acid (1.1 equiv), DMF, 95°C, 4 h, 74.8%; *v*: MsCl (1.2 equiv), pyridine, 90°C, 2 h, 89%; *vi*: 50% aqueous dimethylamine (18.0 equiv), MeOH, reflux, 3 h, 76%; *vii*: NaOH (1.5 equiv), MeOH–water (2 : 1), room temperature, 3 h, 88%.

from several limitations such as: (1) labeled dimethylamine-d_6 in D_2O is less commercially accessible and highly expensive; therefore, it was replaced by dimethylamine-d_6 hydrochloride; (2) replacement of the mesyl group by dimethylamine-d_6 hydrochloride was low yielding (~25%), because only 2.0 equiv of the reagent was used owing to its high cost, whereas in the synthesis of non-deuterated olopatadine we used 18.0 equiv of 50% aqueous dimethylamine. These limitations led us to try an alternative approach for the synthesis of olopatadine-d_6.

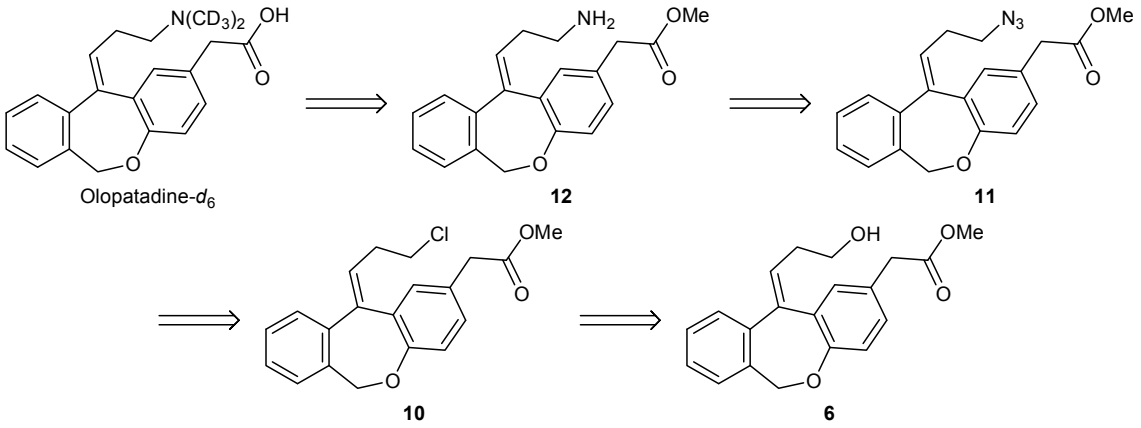
The retro-synthetic analysis for olopatadine-d_6 is outlined in Scheme 3. According to this approach, primary amine **12** could be the late stage intermediate which would give rise to olopatadine-d_6 via treatment with commercially available dimethyl sulfate-d_6, fol-

Scheme 2.



Reagents and conditions: *viii*: dimethylamine-d_6 hydrochloride (2.0 equiv), Et_3N (3.0 equiv), MeOH, reflux, 5 h, 25%; *ix*: NaOH (1.5 equiv), MeOH–water (2 : 1), room temperature, 3 h, 87%.

Scheme 3.



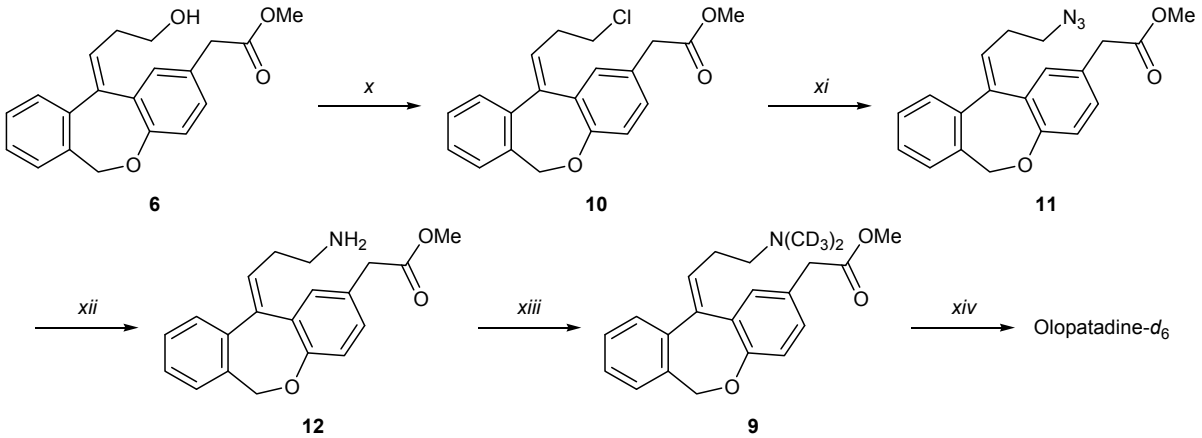
lowed by ester hydrolysis. Primary amine **12**, in turn, could be obtained by reduction of azide **11**, which could be prepared from alcohol **6** through chloro derivative **10**.

According to Scheme 1, methyl 2-(4-hydroxyphenyl)acetate (**1**) was alkylated with 1-bromo-2-(bromomethyl)benzene (**2**) in DMF in the presence of K_2CO_3 to give methyl 2-{4-[(2-bromobenzyl)oxy]phenyl}acetate (**3**) which was selectively iodinated with Ag_2SO_4/I_2 in MeOH to afford methyl 2-{4-[(2-bromobenzyl)oxy]-3-iodophenyl}acetate (**4**). Sonogashira coupling of **4** with but-3-yn-1-ol produced methyl 2-{4-[(2-bromobenzyl)oxy]-3-(4-hydroxybut-1-yn-1-yl)phenyl}acetate (**5**) in a good yield. Compound **5** was used in the key step (stereoselective palladium-catalyzed cyclization) to obtain methyl 2-{11-[(*Z*)-3-hydroxypropylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl}acetate (**6**) which was treated with mesyl chloride in pyridine. Mesyl derivative **7** thus formed was reacted with 50% aqueous dimethylamine (Scheme 1) and dimethylamine hydrochloride-d_6 (Scheme 2) in MeOH at 70°C to give tertiary amines **8** and **9**, respectively; and final alkaline hydrolysis in aqueous methanol afforded olopatadine and olopatadine-d_6 in separate experiments.

According to Scheme 4, methyl 2-{11-[(*Z*)-3-hydroxypropylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetate (**6**) was treated with $SOCl_2$ in toluene at 90°C to give chloro derivative **10** which was converted to azide **11** by reaction with sodium azide in DMF at 70°C. Azide **11** was reduced with triphenylphosphine in aqueous THF to access primary amine derivative **12**. The subsequent N-alkylation of **12** with dimethyl sulfate-d_6 in THF at 70°C furnished tertiary amine **13** in 62% yield, and basic hydrolysis of the latter in aqueous methanol afforded the desired olopatadine-d_6.

The structure and purity of olopatadine-d_6 synthesized by both routes was confirmed by ^{1}H NMR and

Scheme 4.



Reagents and conditions: *x*: $SOCl_2$ (1.2 equiv), toluene, 90°C, 2 h, 90.5%; *xi*: NaN_3 (1.2 equiv), DMF, 70°C, 3 h, 89%; *xii*: PPh_3 (2.0 equiv), THF–water, room temperature, 6 h, 75%; *xiii*: dimethyl sulfate-d_6 (2.2 equiv), NaOH (3.0 equiv), THF, reflux, 4 h, 62%; *xiv*: NaOH (1.5 equiv), MeOH–water (2 : 1), room temperature, 3 h, 87%.

mass spectra and HPLC analyses. The deuterium incorporation in [$^2H_6$]olopatadine was >98%. This corresponds well to the reported deuterium abundance for the labeled starting material (dimethyl sulfate-d_6, >98% D) and indicates that there was no loss of deuterium by exchange during the syntheses. These compounds were considered to be of acceptable quality for use as internal standards in bioanalytical studies.

EXPERIMENTAL

[$^2H_6$]Dimethyl sulfate (98% D) was obtained from CDN Isotopes, and all other chemicals and solvents were purchased from Sigma–Aldrich, Merck, and Combi-Blocks and were used without further purification. The ^{1}H NMR spectra were recorded on a Bruker AMX 300 spectrometer operating at 300 MHz or on a Bruker Avance 400 spectrometer at 400 MHz; the chemical shifts are referenced to tetramethylsilane as internal standard. The mass spectra were recorded on an Agilent Technologies instrument (multimode ion source, positive ion detection). Thin-layer chromatography (TLC) was performed using Whatman no. 4500-101 (Diamond No. MK6F silica gel 60 Å) plates; visualization under UV light (λ 254 nm).

Methyl 2-{4-[(2-bromobenzyl)oxy]phenyl}-acetate (3). Methyl 2-(4-hydroxyphenyl)acetate (**1**, 10.0 g, 60.2 mmol), was dispersed in DMF (100 mL), and 2-bromobenzyl bromide (**2**) (15.75 g, 63.2 mmol) and K_2CO_3 (20.77 g, 150.5 mmol) were added with stirring at room temperature. The mixture was stirred at room temperature for 3 h (TLC), diluted with water (300 mL), and extracted with *tert*-butyl methyl ether (MTBE, 3 × 300 mL). The combined extracts were washed with water (200 mL) and brine (200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Yield 19.8 g (97%), pale yellow oil. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 7.59–7.52 m (2H), 7.32 t (1H, J = 7.7 Hz), 7.25–7.15 m (3H), 6.93 d (2H, J = 8.7 Hz), 5.11 s (2H), 3.68 s (3H), 3.57 s (2H). Mass spectrum: m/z 337/335 $[M + H]^+$.

Methyl 2-{4-[(2-bromobenzyl)oxy]-3-iodophenyl}acetate (4). Iodine (7.56 g, 29.8 mmol) was added with stirring to a suspension of Ag_2SO_4 (9.29 g, 29.8 mmol) in methanol (30 mL), and the mixture was stirred until iodine dissolved completely. A solution of **3** (10.0 g, 29.8 mmol) in methanol (30 mL) was then added over a period of 15 min at room temperature, and the mixture was stirred for 2 h at room temperature. When the reaction was complete (TLC), the mixture was filtered through celite, and the sorbent was washed with ethyl acetate (300 mL). The filtrate was concentrated under reduced pressure to give yellow solid which was triturated with methanol, and the precipitate was filtered off and dried under reduced pressure. Yield 11.9 g (87%), colorless crystals. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 7.74 t (2H, J = 6.9 Hz), 7.57 d (1H, J = 8.1 Hz), 7.37 t (1H, J = 7.5 Hz), 7.23–7.17 m (2H), 6.82 d (1H, J = 8.4 Hz), 5.17 s (2H), 3.69 s (3H), 3.54 s (2H). Mass spectrum: m/z 463/461 $[M + H]^+$.

Methyl 2-{4-[(2-bromobenzyl)oxy]-3-(4-hydroxybut-1-yn-1-yl)phenyl}acetate (5). A solution of **4** (5.0 g, 10.9 mmol), but-3-yn-1-ol (1.85 mL, 21.8 mmol), and triethylamine (6.1 mL, 43.6 mmol) in DMF (50 mL) was degassed with argon for 10 min, and $PdCl_2(PPh_3)_2$ (382 mg, 0.545 mmol) and CuI (103 mg, 1.09 mmol) were added under argon atmosphere at room temperature. The mixture was stirred for 4 h (TLC), quenched with water (150 mL), and extracted with ethyl acetate (2 × 200 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (CombiFlash), using ethyl acetate–hexane (1 : 1). Yield 4.10 g, 93.6%), amber oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 7.64 d (1H, J = 6.9), 7.58 d (1H, J = 7.2 Hz), 7.37–7.32 m (2H), 7.21–7.13 m (2H), 6.85 d (1H, J = 8.7 Hz), 5.18 s (2H), 3.80 q (2H, J = 6.0 Hz), 3.69 s (3H), 3.53 s (2H), 2.73 t (2H, J = 6.3 Hz), 2.01 t (1H, J = 5.7 Hz). Mass spectrum: m/z 405/403 $[M + H]^+$.

Methyl 11-{[(*Z*)-3-hydroxypropylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl}acetate (6). A solution of **5** (4.0 g, 9.95 mmol), piperidine (6.88 mL, 69.6 mmol), and formic acid (0.42 mL, 10.94 mmol) in DMF (40.0 mL) was degassed with argon for 10 min, and $Pd(OAc)_2$ (223.0 mg, 0.995 mmol) and tri-*o*-tolylphosphine (754 mg, 2.48 mmol) were added at room temperature. The mixture was stirred for 4 h at 95°C (TLC), cooled to room temperature, diluted with water (150 mL), and extracted with ethyl acetate (2 × 300 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography (CombiFlash, ethyl acetate–hexane, 2:1). Yield 2.41 g (74.8%), white solid. ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 7.21–7.16 m (4H), 6.95 d (1H, J = 8.1 Hz), 6.72 d (1H, J = 8.1 Hz), 5.65 t (1H, J = 7.5 Hz), 5.05–5.60 br.s (2H), 3.71 t (2H, J = 6.3 Hz),

3.60 s (3H), 3.45 s (2H), 2.59 q (2H, J = 6.9 Hz), 1.92 br.s (1H). Mass spectrum: m/z 325.1 $[M + H]^+$.

Methyl 2-{11-[(*Z*)-3-(methanesulfonyloxy)-propylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl}-acetate (7). A solution of **6** (500 mg, 1.54 mmol) in pyridine (5.0 mL) was cooled to 0–5°C, methanesulfonyl chloride (0.24 mL, 3.08 mmol) was added dropwise over a period of 15 min, and the mixture was stirred for 3 h at 90°C. The mixture was cooled to room temperature, quenched with water (20 mL), and extracted with ethyl acetate (2×50 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Yield 550 mg (89%), light brown oil. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 7.35–7.27 m (4H), 7.08 d (2H, J = 7.5 Hz), 6.82 d (1H, J = 8.4 Hz), 5.74 t (1H, J = 7.2 Hz), 5.05–5.50 br.s (2H), 3.70 s (3H), 3.65 t (2H, J = 6.6 Hz), 3.55 s (2H), 3.04 s (3H), 2.92 q (2H, J = 6.6 Hz).

Methyl 2-{11-[(*Z*)-3-(dimethylamino)propylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl}acetate (8). Compound **7** (300 mg, 0.746 mmol) was dissolved in methanol (5.0 mL), 50% aqueous dimethylamine (2.2 mL, 13.43 mmol) was added, and the mixture was stirred under reflux for 3 h. When the reaction was complete (TLC), the mixture was cooled to room temperature and concentrated under reduced pressure, and the residue was diluted with water (20 mL) and extracted with ethyl acetate (3×50 mL). The combined extracts were washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by column chromatography (CombiFlash, CH_2Cl_2–MeOH, 95:5). Yield 200 mg (76%), light brown solid. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 7.32–7.24 m (4H), 7.04 d (2H, J = 10.2 Hz), 6.80 d (1H, J = 8.1 Hz), 5.70 t (1H, J = 6.9 Hz), 4.75–5.60 br.s (2H), 3.67 s (3H), 3.52 s (2H), 2.59 q (2H, J = 7.2 Hz), 2.44 t (2H, J = 7.2 Hz), 2.23 s (6H). Mass spectrum: m/z 352.1 $[M + H]^+$.

Methyl 2-{11-[(*Z*)-3-(($^2H_6$)dimethylamino)-propylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl}-acetate (9). Dimethylamine-d_6 hydrochloride (43.0 mg, 0.496 mmol) and triethylamine (0.10 mL, 0.744 mmol) were added to a solution of **7** (100 mg, 0.248 mmol) in methanol (3.0 mL). The mixture was stirred under reflux for 5 h, cooled to room temperature, and concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL), the combined extracts were washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure, and the crude material was purified by column chromatography (CombiFlash, CH_2Cl_2–MeOH, 95:5). Yield 22.0 mg (25%), light brown solid. ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm: 7.32–7.24 m (4H), 7.04 d (2H, J = 10.2 Hz), 6.80 d (1H, J = 8.1 Hz), 5.70 t (1H, J = 6.9 Hz), 4.80–5.60 br.s (2H), 3.67 s (3H), 3.52 s (2H), 2.59 q (2H, J = 7.2 Hz), 2.44 t (2H, J = 7.2 Hz). Mass spectrum: m/z 358.3 $[M + H]^+$.

Methyl 2-{11-[(*Z*)-3-chloropropylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl}acetate (10). A solution of **6** (2.20 g, 6.79 mmol) in toluene was cooled to 0°C, and thionyl chloride (0.59 mL, 8.15 mmol) was added dropwise over a period of 5 min. The mixture was heated at 90°C for 2 h (TLC), cooled to 0°C, slowly diluted with ice-cold water (100 mL), and extracted with ethyl acetate (2×200 mL). The combined extracts were washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Yield 2.10 g (90.5%), light yellow oil. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 7.31–7.26 m (4H), 7.06 d (2H, J = 7.5 Hz), 6.81 d (1H, J = 8.4 Hz), 5.72 t (1H, J = 7.2 Hz), 5.05–5.60 br.s (2H), 3.68 s (3H), 3.65 t (2H, J = 6.6 Hz), 3.53 s (2H), 2.90 q (2H, J = 6.6 Hz). Mass spectrum: m/z 343.1 $[M + H]^+$.

Methyl 2-{11-[(*Z*)-3-azidopropylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl}acetate (11). Sodium azide (597 mg, 9.18 mmol) was added to a solution of **10** (2.10 g, 6.12 mmol) in DMF (20 mL), and the mixture was heated at 70°C for 3 h. When the reaction was complete (TLC), the mixture was cooled to room temperature, diluted with water (60 mL), and extracted with ethyl acetate (3×100 mL). The combined extracts were washed with water (2× 100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Yield 1.91 g, 89%), off-white solid. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 7.33–7.26 m (4H), 7.06 d (2H, J = 3.3 Hz), 6.82 d (1H, J = 9.0 Hz), 5.68 t (1H, J = 7.2 Hz), 5.00–5.50 br.s (2H), 3.68 s (3H), 3.54 s (2H), 3.44 t (2H, J = 6.90 Hz), 2.73 q (2H, J = 6.90 Hz). Mass spectrum: m/z 350.1 $[M + H]^+$.

Methyl 2-{11-[(*Z*)-3-aminopropylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl}acetate (12). Triphenylphospine (2.86 g, 10.9 mmol) was added to a solution of **11** (1.91 g, 5.47 mmol) in THF–water (2:1, 30 mL), and the mixture was stirred at room temperature for 6 h. When the reaction was complete (TLC), the mixture was diluted with water (50 mL)

and extracted with ethyl acetate (2×50 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure, and the crude product was purified by column chromatography (CombiFlash, CH_2Cl_2–MeOH, 90:10). Yield 1.41 g, 75%), light brown gel. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 7.22–7.15 m (6H), 6.92 d (2H, J = 10.5 Hz), 6.72 d (1H, J = 8.4 Hz), 5.58 t (1H, J = 7.2 Hz), 4.45–5.50 br.s (2H), 3.57 s (3H), 3.47 s (2H), 3.10 t (2H, J = 7.2 Hz), 2.78 q (2H, J = 6.9 Hz). Mass spectrum: m/z 324.1 $[M + H]^+$.

Alternative synthesis of 2-{11-[(*Z*)-3-(($^2H_6$)dimethylamino)propylidene]-6,11-dihydrodibenzo-[*b*,*e*]oxepin-2-yl}acetate (9). Dimethyl sulfate-d_6 (233 mg, 1.70 mmol) and a solution of NaOH (186 mg, 4.65 mmol) in water (1.0 mL) were added with stirring to a solution of **12** (500 mg, 1.55 mmol) in THF (10 mL). The mixture was heated at 70°C for 2 h and cooled to 0°C, and an additional portion of dimethyl sulfate-d_6 (233 mg, 1.70 mmol) was added. The reaction mixture was refluxed for 2 h until the reaction was complete (MeOH–CH_2Cl_2, 5:95), cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (2×50 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the crude product was purified by column chromatography (CombiFlash; CH_2Cl_2–MeOH, 0 to 5% of the latter). Yield 340 mg (62%), light brown solid. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 7.32–7.24 m (4H), 7.04 d (2H, J = 10.2 Hz), 6.80 d (1H, J = 8.1 Hz), 5.70 t (1H, J = 6.9 Hz), 4.80–5.60 br.s (2H), 3.67 s (3H), 3.52 s (2H), 2.59 q (2H, J = 7.2 Hz), 2.44 t (2H, J = 7.2 Hz). Mass spectrum: m/z 358.3 $[M + H]^+$.

2-{11-[(*Z*)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetic acid (olopatadine). Sodium hydroxide (51.2 mg, 1.28 mmol) was added with stirring to a solution of **8** (300 mg, 0.854 mmol) in a 2:1 mixture of methanol and water (10 mL), and the mixture was stirred at room temperature for 3 h. When the reaction was complete (TLC, MeOH–CH_2Cl_2, 5:95), the mixture was concentrated under reduced pressure, diluted with water (10 mL), and acidified to pH ~2 with 2 N HCl, and the resulting solid was filtered off, washed with water (10 mL), and dried under reduced pressure. Yield 245 mg (88%), off-white solid. ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm: 7.38–7.26 m (6H), 7.06 d (2H, J = 1.8 Hz), 6.76 d (1H, J = 4.2 Hz), 5.65 t (1H, J = 7.2 Hz), 4.95–5.50 br.s (2H), 3.49 s (3H), 2.83 t (2H, J = 7.2 Hz), 2.63 q (2H, J = 7.2 Hz), 2.34 s (6H). Mass spectrum: m/z 338.1 $[M + H]^+$.

2-{11-[(*Z*)-3-(($^2H_6$)Dimethylamino)propylidene]-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetic acid (olopatadine-d_6) was synthesized in a similar way from 300 mg (0.854 mmol) of **9** using 50.4 mg (1.26 mmol) of sodium hydroxide. Yield 250 mg (87%), off-white solid. ^{1}H NMR spectrum (DMSO-d_6, 400 MHz), δ, ppm: 7.38–7.26 m (4H), 7.06 d (2H, J = 2.4 Hz), 6.77 d (1H, J = 5.6 Hz), 5.65 t (1H, J = 9.6 Hz), 4.95–5.50 br.s (2H), 3.50 s (3H), 2.82 t (2H, J = 9.6 Hz), 2.64 q (2H, J = 9.6 Hz). Mass spectrum: m/z 343.9 $[M + H]^+$.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

REFERENCES

1. Elison, E., Rapoport, H., Laursen, R., and Elliott, H.W., *Science*, 1961, vol. 134, p. 1078. doi 10.3390/molecules22101592
2. *Isotope Effects on Enzyme-Catalyzed Reactions* (Proc. Sixth Annual Harry Steenbock Symposium, Madison, Wisconsin, June 4 and 5, 1976), Cleland, W.W., O'Leary, M.H., and Northrop, D.B., Eds., Baltimore: University Park Press, 1977.
3. Gillette, J.R., Darbyshire, J.F., and Sugiyama, Y., *Biochemistry*, 1994, vol. 33, p. 2927. doi 10.1021/bi00176a024
4. Wenzel, M., *J. Labelled Compd. Radiopharm*., 1989, vol.27, p.1143. doi 10.1002/jlcr.2580271006
5. Baker, M.T., Ronnenberg, W.C., Ruzicka, J.A., Chiang, C.K., and Tinker, J.H., *Drug Metab. Dispos*., 1993, vol. 21, p.1170. PMID 7905401.
6. Kushner, D.J., Baker, A., and Dunstall, T.G., *Can. J. Physiol. Pharmacol*., 1999, vol. 77, p. 79. doi 10.1139/y99-005
7. Jones, A.D., Zelle, R.E., and Silverman, I.R., US Patent Appl. Pub. no. 2014336387, 2014.
8. Harbeson, S.L., and Tung, R.D., Int. Patent Appl. Pub. no. WO2008156632, 2008
9. Gant, T.G., Sarshar, S., and Woo, S.H., US Patent Appl. Pub. no. 20080234257.

10. Ohshima, E., Otaki, S., Sato, H., Kumazawa, T., Obase, H., Ishii, A., Ishii, H., Ohmori, K., and Hirayama, N., *J. Med. Chem*., 1992, vol. 35, no. 11, p. 2074. doi 10.1021/jm00089a020
11. Abelson, M.B. and Spitalny, L., *Am. J. Ophthalmol*., 1998, vol. 98, p. 797. doi 10.1016/S0002-9394(98)00044-0
12. Kateluris, C.H., Ciprandi, G., Missotten, L., Turner, E.D., Bertin, D., and Berdeaux, G., *Clin. Ther*., 2002, vol. 24, p. 1561. doi 10.1016/S0149-2918(02)80060-1
13. Spangler, D.L., Bensch, G., Berdy, G.J., and Clinic, A., *Clin. Ther*., 2001 vol. 8, p. 1072. doi 10.1016/S0149-2918(01)80106-5
14. Ohmori, K., Hayashi, K., Kaise, T., Ohshima, E., and Kobayashi, S., *Jpn. J. Pharmacol*., 2002, vol. 88, p. 379. doi 10.1254/jjp.88.379
15. Ashiro, M., Mochizuki, H., Sakurada, Y., Ishii, K., Oda, K., Kimura, Y., Sasaki, T., Ishiwata, K., and Yanai, K., *Clin. Pharmacol. Ther*., 2006, vol. 61, p. 16. doi 10.1111/j.1365-2125.2005.02514.x0
16. Hamilton, S.A., Duddle, J., Herdman, M.J., Trigg, C.J., and Davies, R.J., *Clin. Exp. Allergy*, 1994, vol. 24, p. 955. doi 10.1111/j.1365-2222.1994.tb02728.x
17. Shimamura, T., Shiroishi, M., Weyand, S., Tsujimoto, H., Winter, G., and Katritch, V., *Nature*, 2011, vol. 475, p. 65. doi 10.1038/nature10236
18. Ueno, E., Oshima, H., Saito, I., Matsumoto, H., Yoshimura, Y., and Nakazawa, H., *J. AOAC Int*., 2004, vol. 87, p.1003
19. Barreda, M., Lopez, F.J., Villarroya, M., Beltran, J., Garcia-Baudin, J.M., and Hernandez, F., *J. AOAC Int*., 2006, vol. 89, p.1080
20. Oshima, E., Kumazawa, T., Otaki, S., Obase, H., Ohmori, K., Ishii, H., Manabe, H., Tamura, T., and Shuto, K., US Patent no. 5116863, 1992.
21. Lever, W.O., Jr. and Leighton, H.J., EP Patent no. 0214779, 1990.
22. Bosch Cartés, J., Bachs Roca, J., Gomez Gomez, A.M., Alonso Marin, Y., and Bessa Sanchez, M., Int. Patent Appl. Pub. no. WO2006010459, 2006.
23. Tarur, V., Bhise, N., Sathe, D., Naidu, A., Aher, U., Patil, S., Verma, S., Sawant, K., Naik, T., and Amre, R., Int. Patent Appl. Pub. no. WO2007105234 A2, 2007.
24. Castellin, A., Ferrari, C., and Galvagni, M., US Patent Appl. Pub. no. 20110065936 A1, 2011.
25. Bosch, J., Bachs, J., Gomez, A.M., Griera, R., Marta, E., and Amat, M., *J. Org. Chem*., 2012, vol. 77, p. 6340. doi 10.1021/jo300925c
26. Sano, T., Sugaya, T., and Kasai, M., *Org. Process Res. Dev*., 1998, vol. 2, p.169. doi 10.1021/op970055u
27. Nishimura, K. and Kinugawa, M., *Org. Process Res. Dev*., 2012, vol. 16, p. 225. doi 10.1021/op200312m