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Formal Synthesis of Antihistaminic Drug Olopatadine Hydrochloride via DDQ-Oxidation

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ABSTRACT

A formal synthesis for the olopatadine hydrochloride is described. The present strategy involves DDQ mediated dehydrogenation for the construction of the key side chain (3-(dimethylamino)propylidene group).

Keywords: Antihistaminic Drugs, Dehydrogenation, DDQ, Olopatadine, Isoxepac.

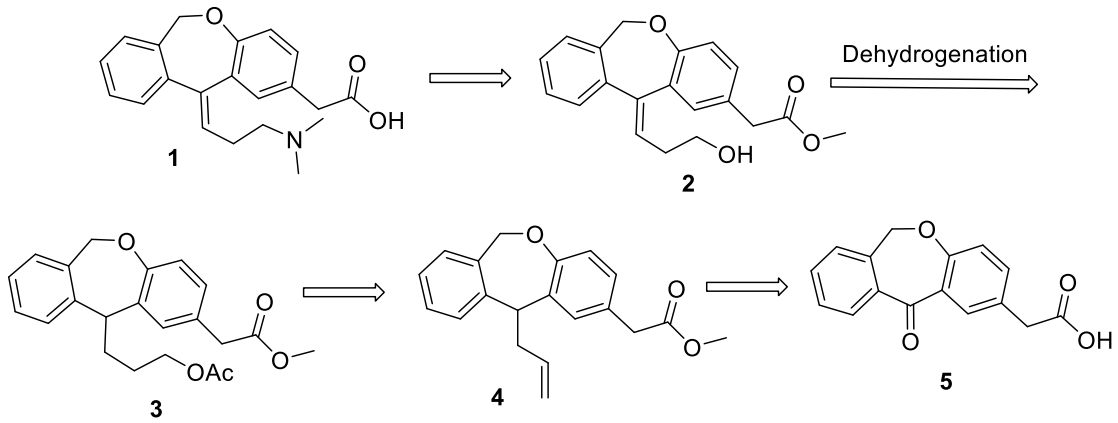
I. INTRODUCTION

Olopatadine hydrochloride is a selective histamine H_1 receptor antagonist *in vitro* and *in vivo* as demonstrated by its ability to inhibit binding and histamine-stimulated vascular permeability in the conjunctiva following topical ocular administration. Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscuarinic type 1 and 2, and serotonin receptors. Only cis isomer of olopatadine being useful in treating allergic eyes diseases in humans, which comprises of stabilizing conjuctival mast cells by topical administration to the human eye. Literature review reveals a number of synthetic strategies to access olopatadine, mostly in the form of patents.[1] In most of the synthesis, the key side chain has been introduced *via* 'Grignard reaction' or 'Wittig olefination'.[1d,2] In most of the previous approaches, the main drawback has been the low *E*/*Z* stereoselectivity. Recently, Bosch *et al.* have utilized a stereoselective Heck reaction for the selective generation of *Z*-isomer *via* the intramolecular cyclization of an *E*-alkene intermediate.[3] Nishimura *et al.* too reported a stereospecific route to **1** under palladium catalysis. In their synthetic route, the *Z*-stereoselectivity was controlled by an intramolecular stereospecific seven-membered ring cyclization from an alkyne intermediate using palladium catalyst.[4] Unfortunately most of the reported syntheses involves expensive reagents and harsh reaction conditions which are operationally difficult to perform on a large scale.

II. PRESENT WORK

The envisaged retrosynthetic strategy for olopatadine **1** is delineated in Scheme 1. A linear synthetic strategy was invoked wherein homoallyl alcohol **2** was conceived as the ideal precursor to **1**. Elaboration of the

intermediate **2** to **1** is well documented in the literature.[4] Homoallyl alcohol **2** upon mesylation, dimethylamination and hydrochlorination would lead to olopatadine hydrochloride salt. In turn the focus was the construction of the key side chain. The homoallyl alcohol **2** could be accessed from intemediate **3** by DDQ mediated dehydrogenation, which in turn can be synthesized from allyl compound **4** by hydroboration and protection. The allyl compound **4** could be accessed from known intermediate 2-(11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetic acid (**5**, also known as Isoxepac) through reduction followed by allylation.

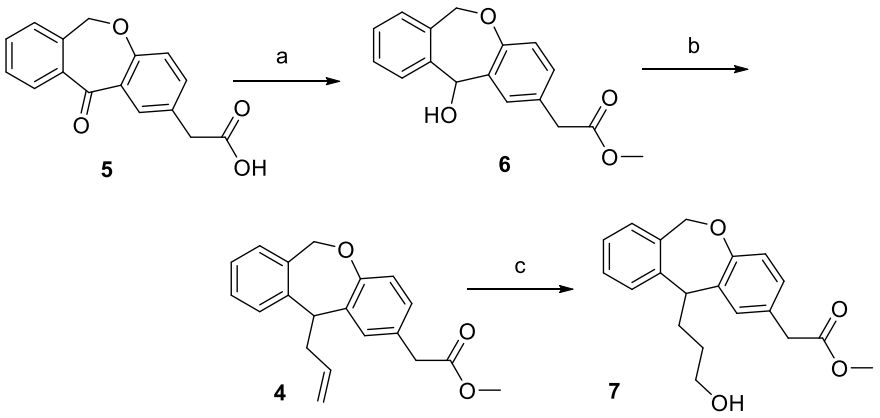


Scheme 1. *Retrosynthetic analysis for olopatadine **1***

III. RESULTS AND DISCUSSION

According to retrosynthetic plan (Scheme 1), synthesis of olopatadine (**1**) began from Isoxepac (**5**).[5] **5** on treatment with thionyl chloride in methanol gave the corresponding Isoxepac methyl ester in quantitative yield. This methyl ester was reduced using sodium borohydride in methanol furnished alcohol **6** in 93% yield. The IR spectrum of compound **6** showed strong bands at 3462 and 1739 cm^{-1} indicating the presence of hydroxyl and ester functionalities. The ^1H NMR spectrum of compound **6** showed peak at δ 3.64 as singlet corresponding to the three protons indicating the presence of a methyl ester compound. Peak at δ 5.55 appeared as a singlet accounting for one proton adjacent to hydroxyl group. The ^{13}C NMR spectrum showed peak at δ 172.2 corresponding to ester functional group. Its DEPT NMR spectrum showed presence of peak at δ 76.1 corresponding to characteristic benzylic methine carbon. MS spectrum of compound **6** showed signal appearing at *m/z*: 307 (M + Na), further confirmed its molecular formula (Scheme 2).

Alcohol **6** was converted into allyl compound **4** using allyltrimethylsilane and $BF_3{\cdot}OEt_2$ in DCM in 83% yield. The IR spectrum of compound **4** showed absence of band at 3462 cm^{-1} indicating the absence of hydroxyl group. ^1H NMR spectrum showed signals that appeared in olefinic region at δ 5.63-5.87 (m, 1 H), as multiplet integrating for one proton (-$\underline{CH}$=CH_2) and the multiplet which appeared at 2.78-3.13 (m, 2 H) integrating for two protons (-$\underline{CH_2}$-CH=CH_2) was attributed to the allylic methylene protons while rest of the proton peaks associated with the compound resonated at expected positions. ^{13}C NMR and DEPT NMR spectra of compound **4** showed the signals that appeared at δ 136.6 (CH_2-$\underline{CH}$=CH_2), 116.3 (CH_2-CH=$\underline{CH_2}$) and 43.6 ($\underline{CH_2}$-CH=CH_2) corresponding to allyl chain carbons while rest of the carbons associated with the compound resonated at their expected positions. Finally, HRMS analysis (calculated for $C_{20}H_{21}O_3$-309.1485, observed-309.1480) confirmed the formation of **4**.

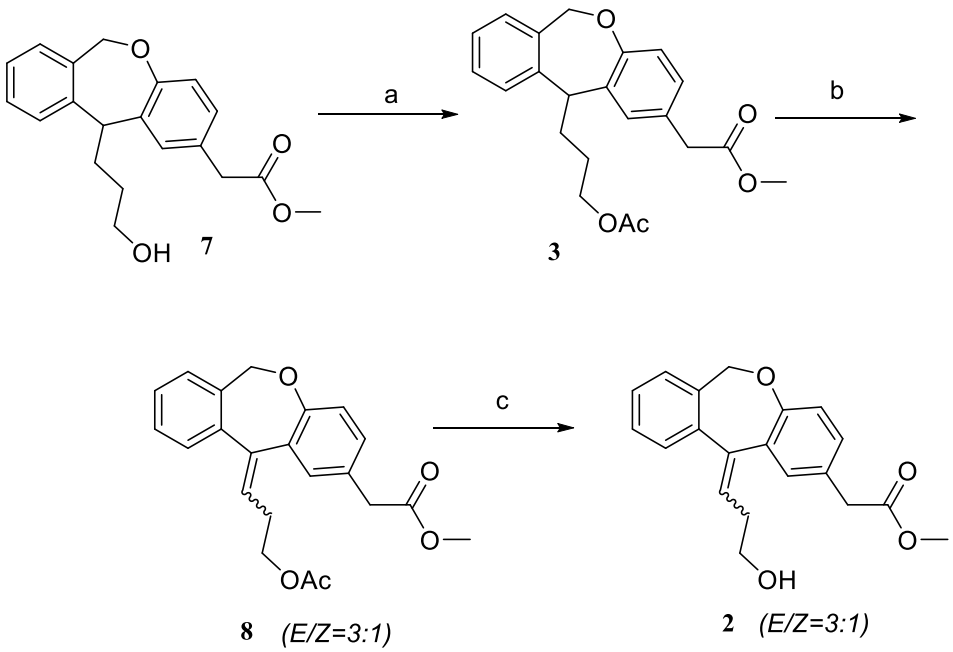


Scheme 2. *Reagents and conditions: a) i) $SOCl_2$, MeOH, 24 h, rt, quent; ii) $NaBH_4$, MeOH, 0 ºC, 2 h, 93%; b) Allyl-TMS, $BF_3{\cdot}Et_2O$, 0 ºC-rt, DCM, 4 h, 83%; c) $BH_3{\cdot}DMS$, NaOH, H_2O_2, THF, 0 ºC-rt, 12 h, 81%.*

Hydroboration was carried out on **4** using $BH_3{\cdot}DMS$ which was quenched by sodium hydroxide and hydrogen peroxide, afforded alcohol **7** in 81% yield.[6] IR spectrum of the product **7** indicated the presence of a hydroxyl group by revealing broad absorption at 3444 cm^{-1} confirming hydroboration-oxidation. ^1H NMR spectrum showed no peak in the olefinic region corresponding to allyl protons and ^{13}C NMR and DEPT NMR spectra of compound **7** showed signals that appeared at δ 31.6, 35.4, 40.3, 62.5 and 72.7 corresponding to methylene (-CH_2-) carbon confirming hydroboration-oxidation. Finally, the structure of compound **7** was confirmed by HRMS analysis (calculated for $C_{20}H_{23}O_4$-327.1591, observed-327.1584).

The primary hydroxyl group of **7** was protected as its acetate using pyridine and acetic anhydride, afforded acetate **3** in 96% yield. The IR spectrum of compound **3** showed absorption bands at 1742 and 1732 cm^{-1} for the corresponding ester and acetate functionalities respectively. ^1H NMR spectrum of compound **3** showed singlet at δ 2.02 which indicated the formation of acetate compound **3**. Its ^{13}C NMR and DEPT NMR spectra showed peaks at δ 170.6 and δ 20.8 corresponding carbonyl group ($CH_3\underline{CO}$-) and methyl group ($\underline{CH_3}CO$-) of acetate respectively. Finally, the structure of compound **3** was confirmed by HRMS analysis.

Next job was the introduction of key double bond. Accordingly, compound **3** was subjected to DDQ oxidation.[7] Here although desired compound **8** (*E/Z*=3/1) was obtained, but in low (40%) yield. ^1H NMR spectrum of compound **8** showed characteristic triplet at δ 5.69 (t, *J*=7.1 Hz) and 6.02 (t, *J*=7.1 Hz) integrated for 0.25 H and 0.75 H corresponding to *Z*-isomer and *E*-isomer respectively. Interestigly, ^1H NMR spectrum of compound **8** showed a broad peak at δ 5.16 (brs, 2 H) as a hump corrosponding to two protons (benzylic proton of oxepin ring) indicating presence of a double bond at C-11. Acetate deprotection smoothly worked in potassium carbonate and methanol in 30 min resulted in the formation of hydroxyl compound **2** (*E/Z*=3/1) in quantitative yield (Scheme 3).



7 3 8 *(E/Z=3:1)* 2 *(E/Z=3:1)*

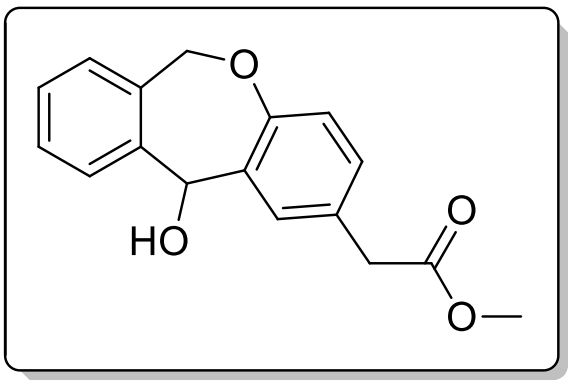
Scheme 3. *Reagents and conditions: a) Py, Ac_2O, 0 ºC-rt, DCM, 4 h, 96%; b) DDQ, Dioxane, Reflux, 12 h, 40%; c) K_2CO_3, MeOH, 30 min, 90 %.*

Elaboration of the intermediate **2** upon mesylation, dimethylamination and hydrochlorination would lead to olopatadine hydrochloride salt is well documented in the literature.[4]

IV. EXPERIMENTAL SECTION

General remarks: All reagents and solvents were used as received from the manufacturer. Melting points are recorded using Buchi B-540 melting point apparatus in capillary tubes and are uncorrected. The temperatures are reported in centigrade scale. The reaction progress was monitored by the TLC analysis on thin layer plates precoated with silica gel 60 F254 (Merck) and visualized by fluorescence quenching or iodine or by charring after treatment with p-anisaldehyde and also 2,4-DNP. Merck's flash silica gel (230-400 mesh) was used for column chromatography.

Methyl 2-(11-hydroxy-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (6):



2-(11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetic acid (5 g, 18.65 mmol) was dissolved in methanol (100 mL) and cooled at 0 ˚C. Thionyl chloride (2.06 mL, 27.98 mmol) was added dropwise during a half hour period and the solution was stirred at room temperature for 24 h. The solvent was evaporated almost to dryness and the residue was partitioned between dichloromethane (50 mL) and saturated sodium bicarbonate solution (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, giving ketoester, which was used without further purification.

Ketoester (5 g, 17.66 mmol) was dissolved in methanol (50 mL) and cooled to 0 ˚C. Sodium borohydride (0.65 g, 17.66 mmol) was added portionwise over a period of half hour. After complete addition, the reaction mixture was stirred for additional 2 h. After completion of the raction (TLC), the reaction mixture was quenched by

addition of 10% HCl solution and evaporated almost to dryness and then extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine solution were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by flash column chromatography (silica gel, pet. ether: EtOAc, 7:3) to furnish **6** as colorless liquid.

R_f = 0.3 (pet. ether-ethyl acetate, 7:3)

Yield: 4.8 g, 96% over two steps.

MF: $C_{17}H_{16}O_4$, **MW:** 284.30.

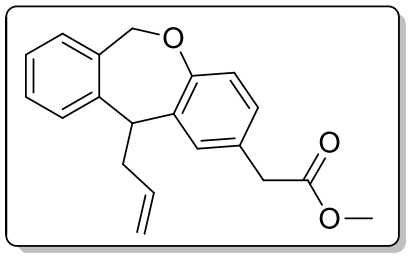
IR ($CHCl_3$, cm^{-1}): νmax 3462, 2951, 1739, 1496.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 3.01 (brs, 1 H), 3.51 (s, 2 H), 3.64 (s, 3 H), 4.93 (d, *J* = 12.8 Hz, 1 H), 5.55 (s, 1 H), 5.83 (d, *J* = 12.8 Hz, 1 H), 6.83 (d, *J* = 8.3 Hz, 1 H), 7.09 (dd, *J* = 8.3 Hz and 2.2 Hz, 1 H), 7.17-7.37 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 39.9, 51.9, 70.6, 76.1, 120.5, 126.5, 127.4, 127.9, 128.4 (2 C), 128.6, 130.6, 131.6, 134.7, 140.6, 155.8, 172.2.

MS (ESI): *m/z*: 307.00 $(M+Na)^+$.

Methyl 2-(11-allyl-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (4):



To a stirred solution of **6** (4 gm, 14.08 mmol) in dry CH_2Cl_2 (40 mL) was added Allyl-TMS (3.34 mL, 3.59 mmol) at 0 °C, after 10 min $BF_3{\cdot}Et_2O$ was added slowly over period of 15 min and stirred for another 15 min. TLC showed complete conversion of hydroxyl to allyl. Reaction mixture was quenched by careful addition of saturated solution of NH_4Cl, after which organic layer was separated and aqueous layer was washed with CH_2Cl_2 (3 × 40 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, to yield colorless oil of **4** which was purified using flash chomatography (silica gel, pet. ether: ethyl acetate, 2:8) furnished allyl compound **4** as colorless liquid.

R_f = 0.6 (pet. ether-ethyl acetate, 2:8)

Yield: 4.03 g, 93%.

MF: $C_{20}H_{20}O_3$, **MW:** 308.37.

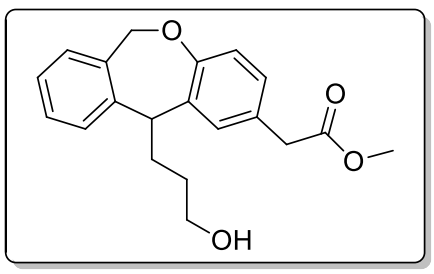
IR ($CHCl_3$, cm^{-1}): νmax 2950, 1732, 1500.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.78-3.13 (m, 2 H), 3.63 (s, 2 H), 3.76 (s, 3 H), 3.90 (t, *J* = 7.8 Hz, 1 H), 4.90-5.14 (m, 3 H), 5.57 (d, *J* = 14.6 Hz, 1 H), 5.63-5.87 (m, 1 H), 6.98-7.08 (m, 1 H), 7.08-7.21 (m, 3 H), 7.21-7.33 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 40.4, 43.6, 51.9, 52.6, 72.8, 116.3, 121.3, 126.7, 127.2, 127.4, 128.4, 128.9, 130.4, 131.5, 133.6, 135.8, 136.6, 140.1, 156.8, 171.8.

HRMS (ESI) $[M + H]^+$ Calculated for $C_{20}H_{21}O_3$-309.1485, observed-309.1480.

Methyl 2-(11-(3-hydroxypropyl)-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (7):



The allyl compound **4** (2 g, 6.49 mmol) was dissolved in dry THF (15 mL) in an oven-dried flask under a nitrogen atmosphere, then $BH_3{\cdot}DMS$ (1.31 mL, 12.98 mmol) was added dropwise *via* syringe at 0 °C, stir it for 4 h. Then the reaction mixture was quenched with 3 M NaOH (2.4 mL) at 0 °C, followed by the dropwise addition of 30% H_2O_2 (2.2 mL) and the resulting solution was stirred for additional 6 h at room temperature. The organic phase was separated and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under

reduced pressure. The crude product was subjected to flash column chromatography (silica gel, pet. ether: ethyl acetate, 7:3) to obtain primary alcohol **7** as liquid.

R_f = 0.5 (pet. ether-ethyl acetate, 1:1)

Yield: 1.9 g, 90 %.

MF: $C_{20}H_{22}O_4$, **MW:** 326.38.

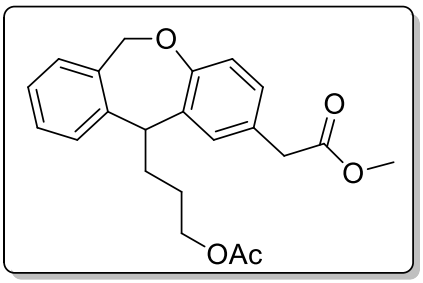
IR ($CHCl_3$, cm^{-1}): νmax 3444 (broad), 2952, 1738, 1500.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.35-1.58 (m, 2 H), 1.96-2.35 (m, 3 H), 3.46-3.61 (m, 4 H), 3.68 (s, 3 H), 3.74 (t, *J* = 7.8 Hz, 1 H), 4.95 (d, *J* = 14.5 Hz, 1 H), 5.48 (d, *J* = 14.5 Hz, 1 H), 6.98-6.87 (m, 1 H), 6.99-7.11 (m, 3 H), 7.11-7.23 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 31.6, 35.4, 40.3, 51.9, 52.2, 62.5, 72.7, 121.3, 126.7, 127.2, 127.5, 128.4, 128.9, 130.2, 131.5, 134.0, 135.7, 140.6, 156.7, 172.0.

HRMS (ESI) $[M + H]^+$ Calculated for $C_{20}H_{23}O_4$-327.1591, observed-327.1584.

Methyl 2-(11-(3-acetoxypropyl)-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (3):



1 g (3.08 mmol) of alcohol **7** was dissolved in dry DCM (10 mL) and the solution was stirred. To the stirred solution was added 0.49 mL (6.16 mmol) of pyridine at 0 °C and the mixture was stirred for five minutes. Acetic anhydride (0.72 mL, 7.71 mmol) was added dropwise, and stirred well while warming to room temperature for 4 h. Reaction mixture was quenched by saturated solution of $NaHCO_3$ (10 mL), The organic phase was separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was subjected to flash column chromatography (silica gel, pet. ether: ethyl acetate, 8:2) to obtain acetate **3** as sticky liquid.

R_f = 0.6 (pet. ether-ethyl acetate, 7:3)

Yield: 1.1 g, 98 %

MF: $C_{22}H_{24}O_5$, **MW:** 368.42.

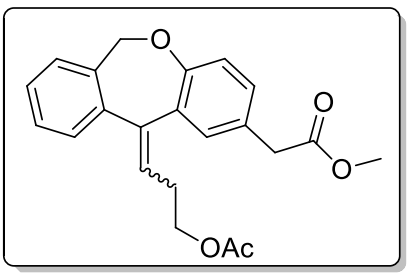
IR ($CHCl_3$, cm^{-1}): νmax 2950, 1742, 1732, 1503.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 1.49-1.62 (m, 2 H), 2.02 (s, 3 H), 2.05-2.17 (m, 1 H), 2.17-2.30 (m, 1 H), 3.55 (s, 2 H), 3.68 (s, 3 H), 3.74 (t, 1 H), 4.02 (t, 2 H), 4.95 (d, *J* = 14.5 Hz, 1 H), 5.47 (d, *J* = 14.5 Hz, 1 H), 6.96 (d, *J* = 8.7 Hz, 1 H), 7.01-7.11 (m, 3 H), 7.13-7.24 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 20.8, 27.4, 35.2, 40.2, 51.8, 51.9, 64.0, 72.6, 121.3, 126.7, 127.1, 127.3, 128.5, 128.9, 130.1, 131.3, 133.9, 135.6, 140.1, 156.6, 170.6, 171.7.

HRMS (ESI) $[M + H]^+$ Calculated for $C_{22}H_{25}O_5$-369.1697, observed-369.1692.

Methyl 2-(11-(3-acetoxypropylidene)-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (8): To a solution of acetate



7 (1 g, 2.71 mmol) in dry dioxane (10 mL), DDQ (2.98 mmol) was added. The reaction mixture was refluxed for 6 h. After completion of the reaction, the precipitated solid $DDQH_2$ was removed by filtration and the filtrate was evaporated. The residue was taken in ethyl acetate (20 mL) and was washed with water (2 × 10 mL), saturated solution of $NaHCO_3$ (2 × 5 mL), brine (2 × 10 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to afford a crude yellow liquid. The crude product was

subjected to purification by flash column chromatography (silica gel, pet. ether: ethyl acetate, 8:2) to furnish acetate **8** as an oil (*E/Z* = 3:1).

R_f = 0.6 (pet. ether-ethyl acetate, 7:3)

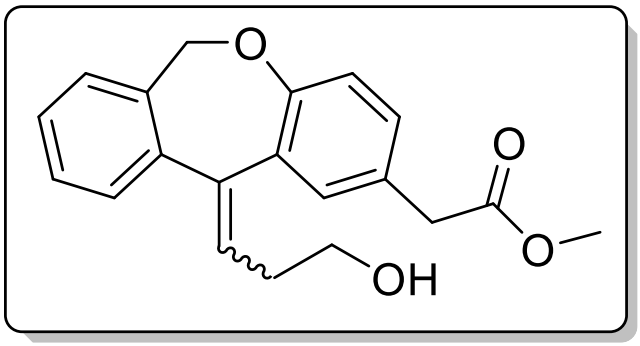
Yield: 0.39 g, 40 %

MF: $C_{22}H_{22}O_5$, **MW:** 366.14.

IR ($CHCl_3$, cm^{-1}): νmax 2950, 1742, 1732, 1503.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4) (*E/Z* = 3:1): δ 2.04 (s, 2.25 H, for *E*-isomer), 2.07 (s, 0.75 H, for *Z*-isomer), 2.51 (dt, *J* = 7.1 and 6.7 Hz, for *E*-isomer), 2.77 (dt, *J* = 7.1 and 6.7 Hz, for *Z*-isomer), 3.54 (s, 2 H), 3.69 (s, 3 H), 4.13-4.23 (m, 2 H), 5.16 (brs, 2 H), 5.69 (t, *J* = 7.1 Hz, 0.25 H, for *Z*-isomer), 6.02 (t, *J* = 7.1 Hz, 0.75 H, for *E*-isomer), 6.71 (d, *J* = 8.24 Hz, 0.75 H, for *E*-isomer), 6.81 (d, *J* = 8.24 Hz, 0.25 H, for *Z*-isomer), 7.03-7.40 (m, 6 H).

Methyl 2-(11-(3-hydroxypropylidene)-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetate (2): To a stirred solution of acetate **8** (0.3 g, 0.81 mmol) in MeOH was added K_2CO_3 (0.22 g, 1.63 mmol) at room temperature and stirred for 30 min. The MeOH was evaporated, diluted with EtOAc (10 mL) and solid K_2CO_3 was filtered. The filtrate was washed with water (20 mL), brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to afford a crude product. The crude product was subjected to flash column chromatography (silica gel, pet. ether: ethyl acetate, 7:3) to obtain homoallyl alcohol **2** as a white solid (*E/Z* = 3:1).



R_f = 0.4 (pet. ether-ethyl acetate, 6:4)

Yield: 0.25 g, 96 %

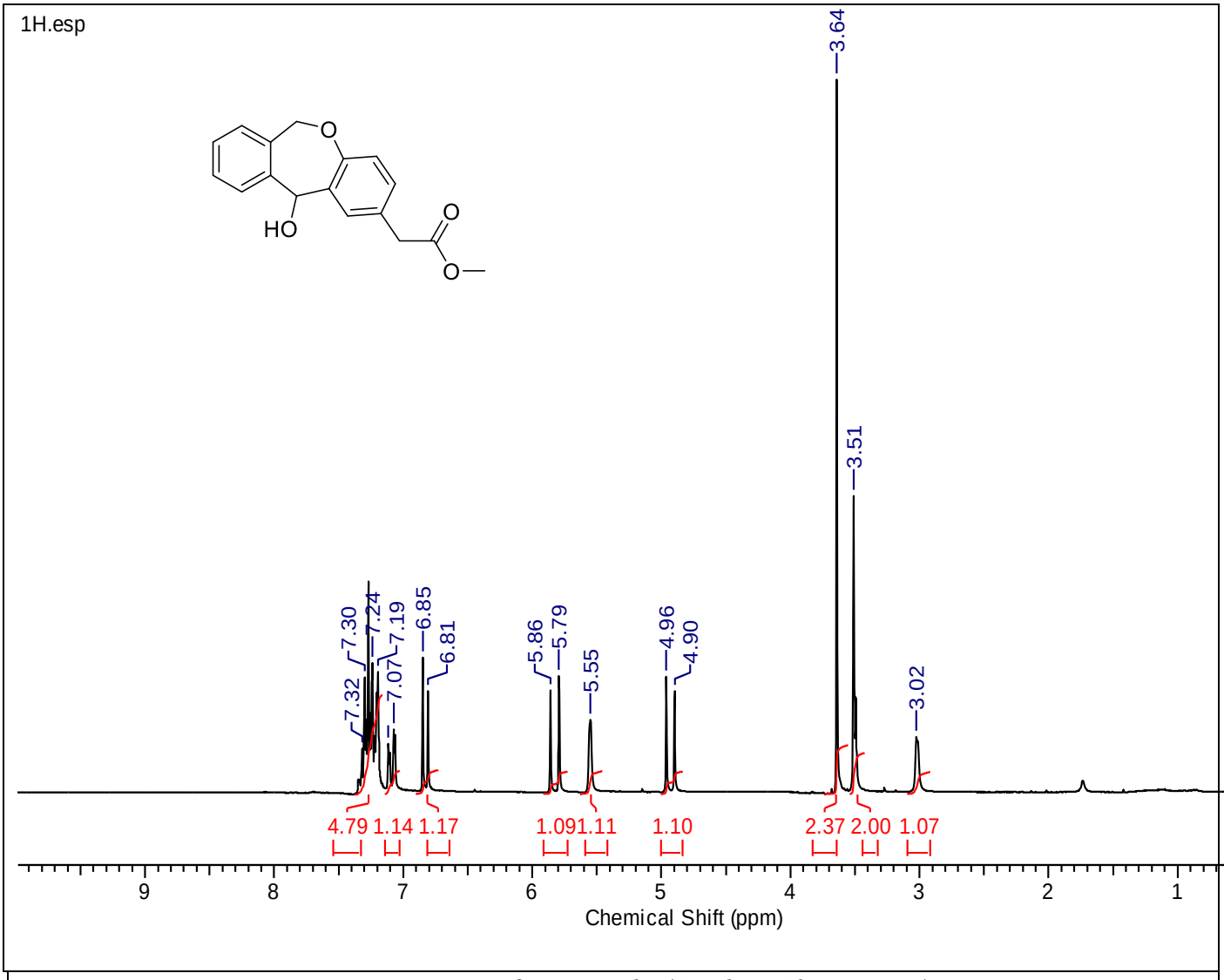
MF: $C_{20}H_{20}O_4$, **MW:** 324.13.

IR ($CHCl_3$, cm^{-1}): νmax 3446, 2921, 1736, 1463.

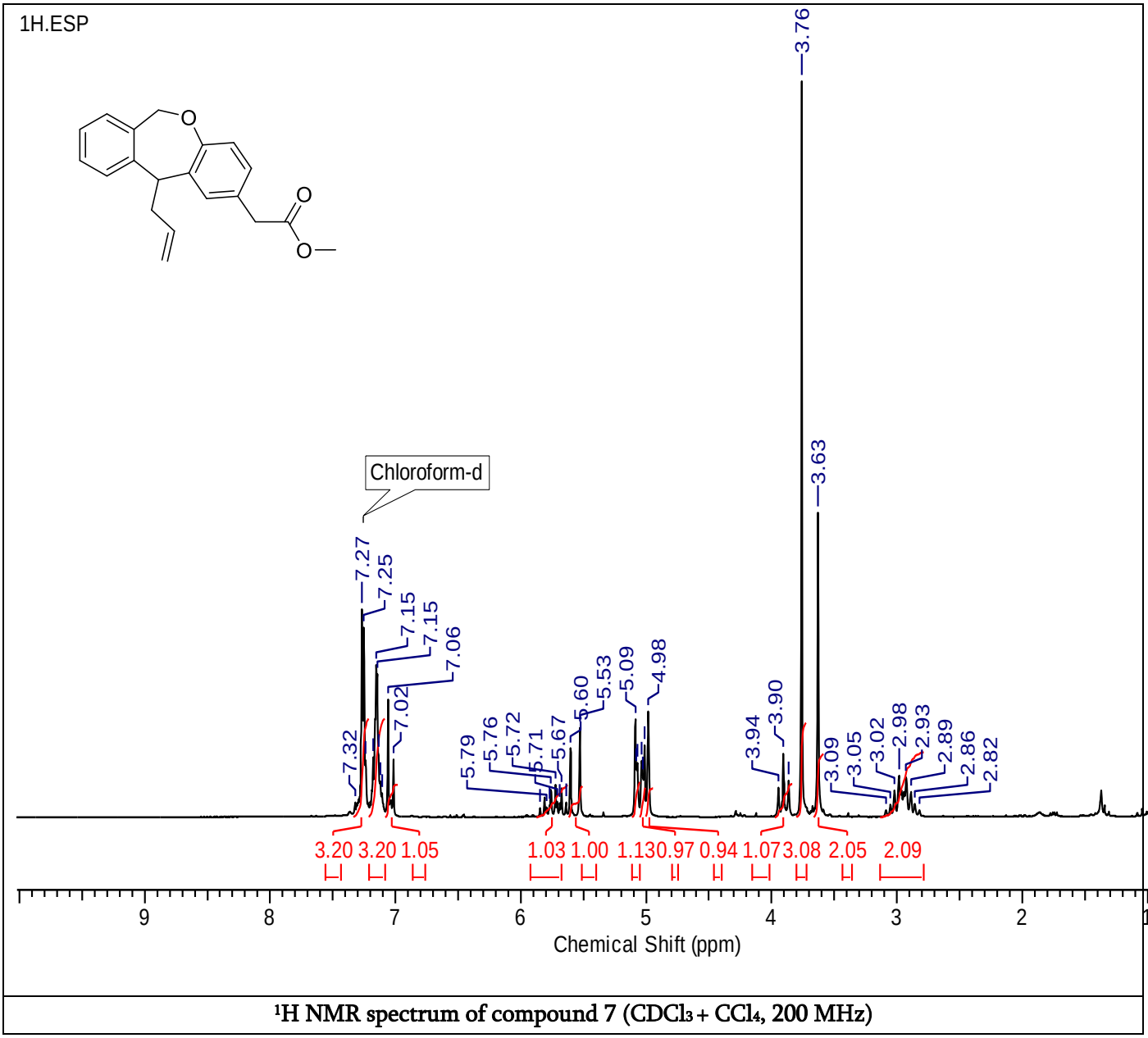
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.38-2.49 (m,0.8 H, *E*-Form), 2.63-2.73 (m,1.2 H, *Z*-Form), 3.53 (s, 2 H), 3.68 (s, 3 H), 3.75 (m, 0.8 H, *E*-Form), 3.81 (t, *J*=6.3 Hz, 1.2 H), 5.19 (brs, 2 H), 5.73 (t, *J*=7.8 Hz, 0.6 H, *Z*-Form), 6.06 (t, *J*=7.8 Hz, 0.4 H, *E*-Form), 6.70 (d, *J*=8.2 Hz, 0.4 H, *E*-Form), 6.79 (d, *J*=8.2 Hz, 0.6H, *Z*-Form), 7.00-7.34 (m, 6H).

V. SPECTRA

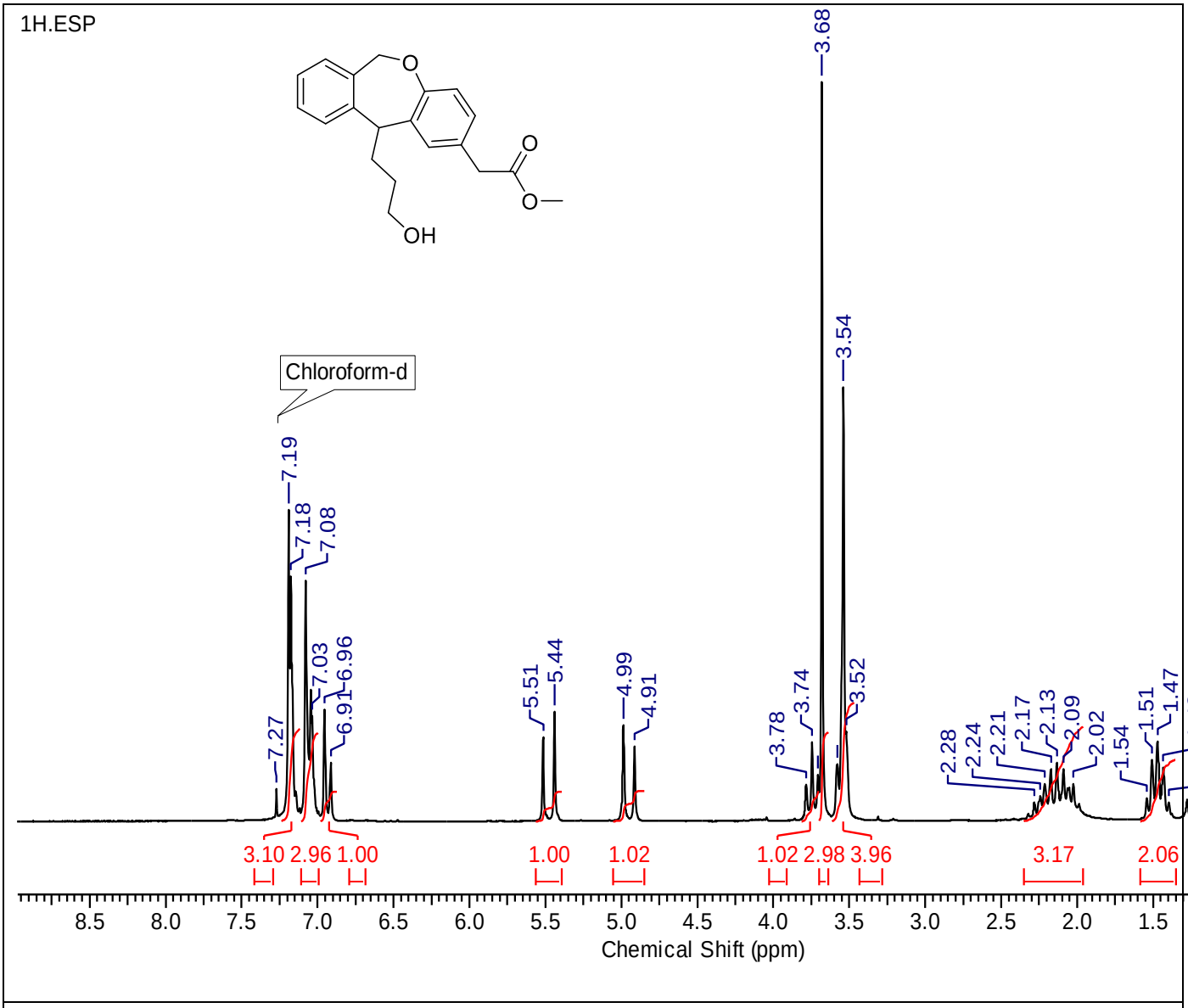
^{1}H NMR spectrum of compound 6 ($CDCl_3$ + CCl_4, 200 MHz)



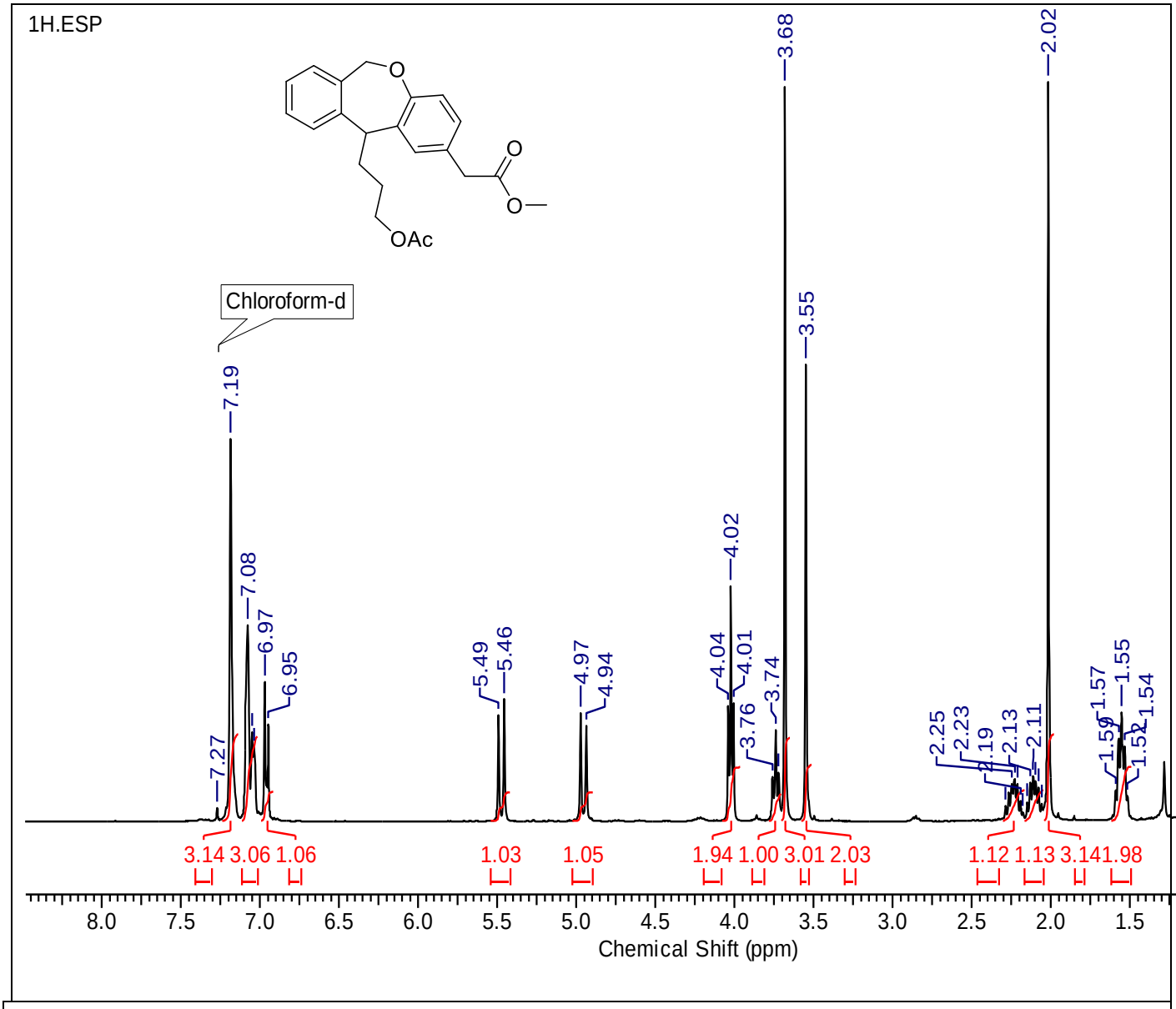
^{1}H NMR spectrum of compound 4 ($CDCl_3$ + CCl_4, 200 MHz)



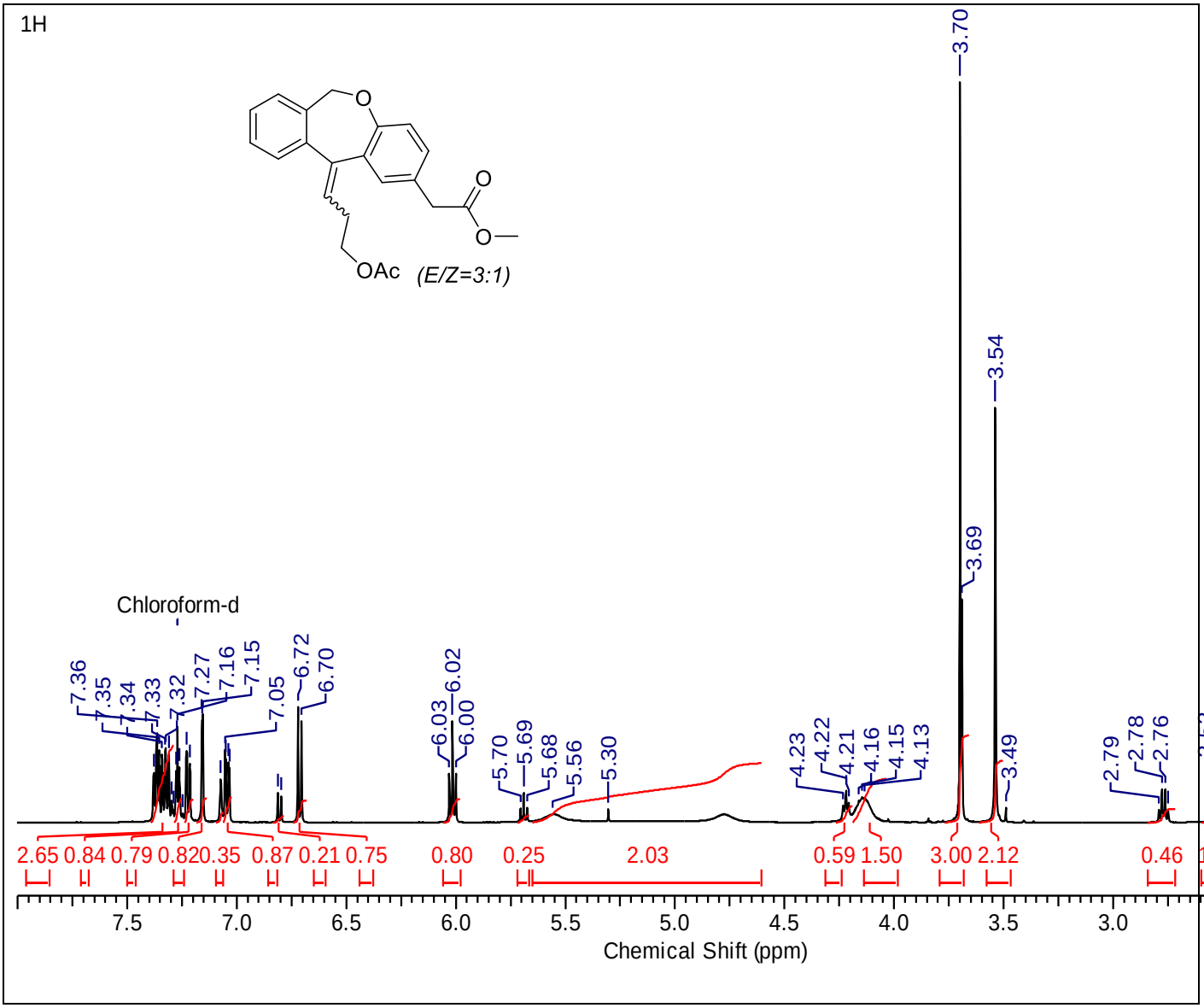
^{1}H NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 200 MHz)



^{1}H NMR spectrum of compound 3 ($CDCl_3$ + CCl_4, 200 MHz)



^{1}H NMR spectrum of compound 8 ($CDCl_3$ + CCl_4, 400 MHz)



VI. CONCLUSIONS:

In the present investigation we have developed a formal synthesis for antihistaminic drug, olopatadine hydrochloride using DDQ-oxidation. The research involves DDQ mediated dehydrogenation for the synthesis of the key side chain (3-(dimethylamino)propylidene group).

VII. REFERENCES

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