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(4+3) cycloaddition reactions in organic synthesis: Synthesis of Bishomomaprotiline [9,10-dihydro-9-(4-methylaminobutyl)-9,10-propanoanthracene]

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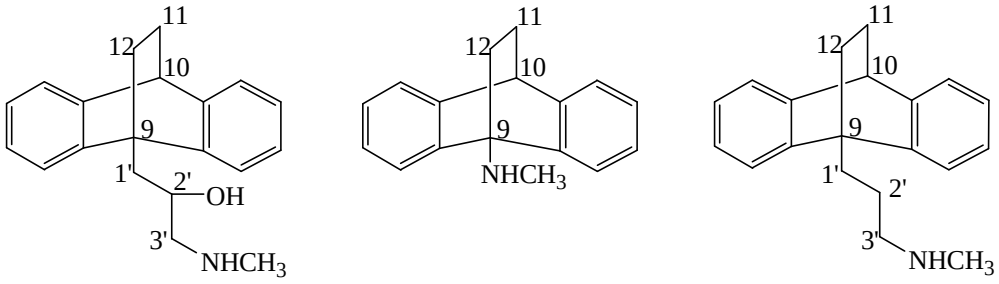
ABSTRACT

The reactions between oxyallyl cations and 9-substituted anthracene to obtain 9,10-dihydro-9,10-propanoanthracene substituted have not yet been studied extensively. For this reason, we used (4+3) cycloaddition reactions of 9-(4-pentenyl)-anthracene with 1,1,3,3-tetrabromoacetone as key step for preparation of a homologue of maprotiline which has been synthesized and developed into a clinically useful drug for the treatment of depressant by Ciba-Geigy research group in Switzerland.

Keywords: Oxyallyl Cations; (4+3) Cycloaddition Reactions; Homologue; Ludiomil; 1,1,3,3-Tetrabromoacetone.

INTRODUCTION

(4+3) cycloaddition reactions are one of the most powerful and straightforward methods for the synthesis of seven-membered rings from simple starting materials.[1] These reactions can be used as intermediate in organic synthesis. One of the most applications of (4+3) cycloaddition reactions are to use as intermediate in medicinal moiety. Although the importance of these reactions is that little research work has been done by using anthracene or anthracene derivatives as dienes to obtain 9,10-dihydro-9,10-propanoanthracene. For example, (4+3) cycloaddition reactions of α,α'-dibromoketones or α,α,α',α'-tetrabromoketones such as 1.3-dibromoacetone or 1.1.3.3-tetrabromoacetone as oxyallyl cations with anthracene, 9-methoxyanthracene, 9,10-dimethoxy anthracene, 9-alkenylanthracene and 9-phenylanthracene in the presence of reducing agents under different sets of conditions which afforded the cis and/ or trans cycloadducts in good yields.[2-5] In another example, Hardinger., [6,7] reported that the reactions of α,α'-bis(sulfonyl) ketones with anthracene in the presence of iron pentacarbonyl and $TiCl_4$ gave the expected (4+3) cycloadducts in good yields. The discovery of the antipsychotic activity of chlorpromazine opened the modern era of psychopharmacology. An intense effort ensued in many laboratories to investigate the structure-activity relationships of related compounds. There are many compounds are based on dihydroanthracene in its preparation such as oxaprotiline **1**, benzoctamine **2** and maprotiline **3** as shown in **(Figure. 1)**. The key step for synthesis of maprotiline (ludiomil) was Diels–Alder reactions of ethylene under high pressure, across the 9,10 positions to give the central 2,2,2-bicyclooctyl moiety.[8,9]



(1) **(2)** **(3)**

Figure.1 antidepressants drugs based on dihydroanthracene

Hoffmann and et al.,[10] synthesized homobenzoctamine and homomaprotiline by changing the head of bridge in benzoctamine and maprotiline. Bishomobenzoctamine, also synthesized by [4+2] and (4+3) cycloaddition of some 9-alkenylanthracenes with 2-bromoacrylaldehyde.[11-13]

EXPERIMENTAL SECTION

All Glassware was dried in the oven before use and all reactions were carried out under nitrogen unless otherwise stated. The synthesis of compounds was ascertained by thin layer chromatography (TLC, silica gel 60 F_{254}). Visualization of the TLC plates was carried by using a U. V. lamp and dipping in iodine or dipping in Acidic solution of Vanillin in ethanol then exposed heating by dryer. Column chromatography was performed using silica gel 60-120 mesh or by using thin layer chromatography (TLC) on Merck silica gel 60 covered Glass plates 20x20 cm plates F_{254}. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 covered alumina plates F_{254}. (TLC) plates were developed under UV light and dipping the (TLC) in iodine or in Acidic solution of Vanillin in ethanol followed by exposure to heating by dryer. Melting points were determined on a Mel-Temp (Melting temperature) II apparatus and are uncorrected. IR (KBr) spectra were recorded on a Perkin- Elmer 883 spectrophotometer and expressed as ν cm^{-1}. ^1H NMR and ^{13}C NMR spectra were measured by using JEOL ECP (400 MHz) in $CDCl_3$. ^1H chemical shifts are expressed as δ ppm and coupling constants J were given in Hz. MS spectra and HRMS were performed by using *EI* at 70 eV. The ultrasonic reaction was carried out using Sonerex 200, 50 W power and frequency 35 kHz.

Synthesis of 9-(4-pentenyl)-anthracene: (5)

A 500 mL clean and dry three-neck round-bottom flask was equipped with a magnetic stirrer, and a reflux condenser with balloon containing of nitrogen was attached, then magnesium (3.25 g, 135.42 mmol), THF dry (6 mL) and a small piece of I_2 was added followed by sealing of the rest of the side slots for flask by a rubber septum. To reaction mixture 5-Bromo-1-pentene (2 g, 13.44 mmol) was injected dropwise with stirring the mixture and rubbing the reaction vessel by hands for heating until the disappearance of violet colour for iodine. The remaining quantity from 5-Bromo-1-pentene (8 g, 53.68 mmol) was treated with 10 mL THF and it's added dropwise to the reaction mixture with continued stirring for 2h additional after completion and some the additive to obtain 4-pentenylmagnesium bromide (Grignard reagent).

Anthrone solution **4** (10 g, 45.67 mmol) in anhydrous THF (120 mL) was slowly added to reaction vessel which contains 4-pentenylmagnesium bromide with continued stirring to 2 h, we note the colour mixture is changed from yellow to white yellowish. The mixture is heated under reflux with stirred for 3-4 h at 50-55^oC, the colour of mixture is changed to dark yellow then it was allowed to cool to room temperature. The reaction mixture was stirred for 8 h at room temperature till reaction completes (checked by TLC) then hydrolyzed with 10 % HCl; if effervescence take place small pieces of ice was added. The organic layer was extracted with ether and the aqueous layer was extracted with ether (2×50 mL). The organic layer was washed with NH_4Cl, water, and brine then dried over $MgSO_4$ anhydrous. The solvent was evaporation and concentrate under vacuum. To crude product was added (80 mL) of anhydrous benzene and (10 g) P_4O_{10} with stirred for 6 h at room temperature, the P_4O_{10} was filtered off and the benzene was removed under vacuum. The crude product was purified by flash column chromatography (DCM: Hex) (1:1), give 9-pent-4-enyl-anthracene **5** as yellow solid; mp 71-72°C; IR (KBr) ν / cm^{-1} 3050, 2914, 2853, 1636, 1622, 1455, 916, 885, 733; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (qu, 2H, *J* 8.08, H2'), 2.33 (q, 2H, *J* 7.32, H3'), 3.60-3.64 (m, 2H, H1'), 5.06-5.16 (m, 1H, H5'), 5.93-6.00 (m, 1H, H4'), 7.25-8.44 (m, 9H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 27.50, 30.42, 34.35, 115.29, 138.51, 124.53, 124.89, 125.44, 125.50, 125.72, 126.31, 128.26, 129.30, 129.64, 131.71, 131.80, 135.11; HRMS (EI) *m/z*, Calcd. for $C_{19}H_{18}$ $[M]^+$: 246.1409, Found: 246.1410.

Synthesis of 9,10-Dihydro-9-(4-pentenyl)-9,10-propanoanthracene-12-one: (6)

Zinc powdered (4,38g, 66.98 mmol), CuCl (1.87 g, 19.10 mmol), and small amount of dry dioxane was placed into a flam-dried flask filled. The flask was suspended in an ultrasonic bath (15-20^{o}C). A solution of Me_3SiCl (3.67 g, 33.78 mmol) and 1.1.3.3-tetrabromoacetone (7.10 g, 19 mmol) was slowly added, followed by a solution of compound **5** (5 g, 20.30 mmol), in dry dioxane 5 mL. The bath temperature was maintained below 20°C for the first hour, and then allowed to slowly reach room temperature. After the mixture had been sonicated for 8 h, the dioxane was evaporated and MeOH (28 mL), zinc powdered (4.36 g, 66.98 mmol), CuCl (1.87 g, 19.10 mmol) and NH_4Cl (5.6 g) was added. After stirring for 6 h at room temperature, the reaction mixture was filtered through silica gel. The residue was washed with CH_2Cl_2, water, saturated aqueous NH_4Cl, H_2O and brine, dried with $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (EE: PP: 1:10) to give compound **6** as white solid; mp 171^{o}C; IR (KBr) ν / cm^{-1} 3072, 2945, 2884, 1694, 1640, 1476, 1454, 1402, 1286, 1132, 912, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87-0.93 (m, 2H, H2'), 2.28-2.30 (m, 2H, H1'), 2.37-2.41 (m, 2H, H3'), 2.61 (s, 2H, H13), 2.86 (d, 2H, *J* 3.68, H11), 4.29 (t, 1H, *J* 4.40, H10), 5.09 (dd, 2H, *J* 10.28, 15.40, H5'), 5.87-5.94 (m, 1H, H4'), 7.24-7.40 (m, 8H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.99, 23.94, 28.51, 33.76, 34.43, 40.94, 43.55, 43.58, 44.32, 50,61, 51,20, 60,32, 115.40, 124.46, 126.10, 126.29, 127.05, 127.09, 127.17, 138.30, 141.37, 141.92, 209.19 (s,-C=O); HRMS (EI) *m/z*, Calcd. for $C_{22}H_{22}O$ $[M]^+$: 302.1671, Found: 302.1673.

Synthesis of 9,10-Dihydro-9-(4-pentenyl)-9,10-propanoanthracene: (7)

A mixture of ketone **(6)** (1.76 g, 5.82 mmol), KOH (1.31 g, 23.35 mmol), hydrazine hydrate (4.71 g, 94.03 mmol) and triethyleneglycol (7 mL) was stirred with refluxed at 150^{o}C for 7 h. Then the water was removed by a Dean-Stark separator, and the reaction mixture was heated for a further 8 h to 200-210^{o}C. After cooling to room temperature, the reaction mixture was treated with dil. HCl (pH=2 was reached). The aqueous layer was extracted with toluene, and the combined organic phases were washed with brine, dried with ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel petroleum ether: ethyl acetate (5:1), give compound **7** as yellow oil; IR (KBr) ν / cm^{-1} 3067, 3019, 2930, 2859, 1474, 1452, 910, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92-0.95 (m, 2H, H12), 1.19-1.27 (m, 2H, H2'), 1.34-1.39 (m, 2H, H1'), 1.48-1.63 (m, 2H, H13), 2.28-2.30 (m, 2H, H11), 3.98 (t, 1H, *J* 3.64, H10), 5.05 (dd, 2H, *J* 9.56, 16.84, H5'), 5.91-5.95 (m, 1H, H4'), 7.18-7.35 (m, 8H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.50, 29.40, 31.72, 35.50, 39.97, 46.25, 46.49, 49.81, 118.60, 136.51, 123.11-142.85; HRMS (EI) *m/z*, Calcd. for $C_{22}H_{24}$ $[M]^+$: 288.1878, Found: 288.1881.

Synthesis of 4-(9, 10-Dihydro-9, 10-propanoanthracene-9-yl) butanal: (8)

The tetracyclic alkene **(7)** (0.75 g, 2.60 mmol) was dissolved in CH_2Cl_2 (ca.12 mL) and ozonolysed at -78^{o}C. After complete the reaction (blue colour), Me_2S (6 equiv) was added, and the reaction mixture was stirred for further 4 h at room temperature, the volatile components were removed under vacuum. The crude product was purified by flash column chromatography on silica gel petroleum ether: ethyl acetate (15:1), give compound **8** as white solid; mp136^{o}C; IR (KBr) ν / cm^{-1} 3069, 3019, 2926, 2870, 1726, 1474, 1452, 908, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.42 (m, 2H, H12), 1.49-1.52 (m, 2H, H2'), 1.62-2.17 (m, 6H, H11, H13, H1'), 2.31-2.35 (m, 2H, H3'), 3.98 (t, 1H, *J* 3.68, H10), 10.88 (s, CHO), 7.20-7.30 (m, 8H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.31, 18.82, 22.70, 29.79, 35.30, 46.27, 46.43, 46.53, 120.60, 123.86, 124.16, 125.27, 125.93, 126.12, 142.51, 143.49, 202.08; HRMS (EI) *m/z*, Calcd. for $C_{21}H_{22}O$ $[M]^+$: 290.1671, Found: 290.1673.

Synthesis of 9, 10-Dihydro-9-(4-methylaminobutyl)-9, 10-propanoanthracene: (9)

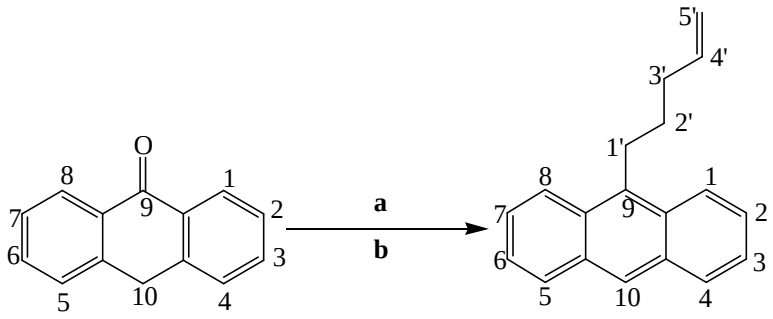
Titanium (IV) isopropoxide (0.20 mL, 0.50 mmol) was added to a commercially available solution of methylamine in methanol (2 mol L^{-1}, 15 mL) followed by the addition of the starting aldehyde **8** (0.44 mL, 0.44 mmol). The reaction mixture was stirred at ambient temperature for 5h, after which sodium borohydride (15.5 mg, 0.38 mmol) was added and the resulting mixture was further stirred for another period of 2h. The reaction was then quenched by the addition of water (0.2 mL), the resulting inorganic precipitate was filtered and washed with diethyl ether (4 mL). The organic layer was separated and the aqueous part was further extracted with diethyl ether (2x6 mL). The combined ether extracts were dried (K_2CO_3) and concentrated in vacuum, give bishomomaprotiline **9** as white viscous liquid; IR (KBr) c ν / m^{-1} 3410, 3073, 2963, 2926, 2870, 2853, 1599, 1476, 1450, 1261, 1093, 1020, 864, 800, 754, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.42 (m, 6H, H2', H3', H12), 1.75-2.05 (m, 6H, H1', H11, H13), 2.35 (s, 1H, N-H), 2.46 (s, 3H, CH_3), 2.57 (t, 2H, *J* 6, H4'), 3.97 (t, 1H, *J* 4.00, H10), 7.20-7.27 (m, 8H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.15, 24.48, 29.69, 32.35, 36.45, 39.53, 43.20, 46.48, 52.35, 123.49-144.14; HRMS (EI) *m/z*, Calcd. for $C_{22}H_{27}N$ $[M]^+$: 305.2144, Found: 305.2144.

RESULTS AND DISCUSSION

In this paper we describe the preparation of 9,10-dihydro-9,10-propanoanthracene-12-one **6**, which are used a key intermediate for the synthesis of target compound bishomomaprotiline **9** by using (4+3) cycloaddition reactions of

9-(4-pentenyl)-anthracene **5** with 1.1.3.3-tetrabromoacetone in ultrasonication at 15-20 ^{o}C. The structures of all compounds were established on the basis of literature precedence, analytical results and spectral data.

The first step was the Grignard reaction between anthrone **4** and 4-pentenylmagnesium bromide which was prepared from magnesium and 5-Bromo-1-butene in dry tetrahydrofuran by refluxing 3-4 h at 50-55^{o}C, followed by acid hydrolysis and dehydration with P_40_{10}, yielded 9-pent-4-enyl-anthracene **5** in good yield as shown in **(Scheme. 1).**

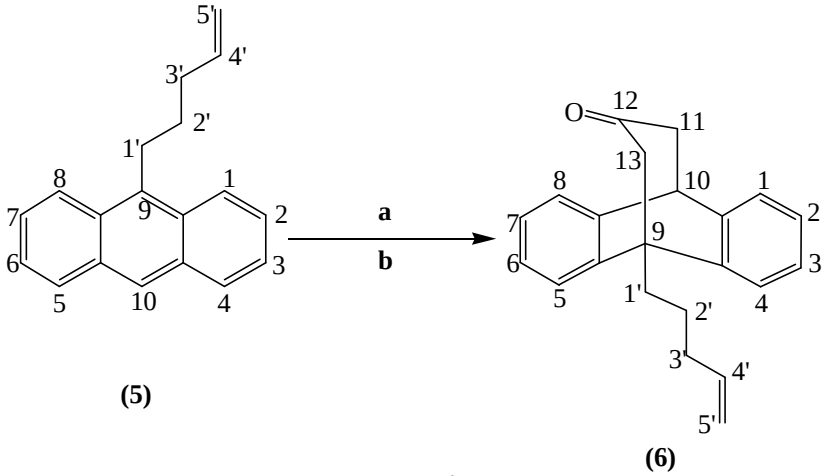


(4) **(5)**

Scheme1. (a) 5-bromo-1-pentene, Mg, THF, r. t (room temperature), 8h; (b) C_6H_6, P_2O_5, r. t, 6h, (yield 82%)

The IR spectrum for compound **5**, absorptions were observed in the range of 3050-2853 cm^{-1} indicating the presence of (C-H stretching aroma) and showed a peak in the range of 1636-1445 cm^{-1} for (C=C stretching), and the absorption band observed at 733 cm^{-1} for (C-H bonding). the ^{1}H NMR spectrum exhibit a characteristic quintet at δ 1.92 ppm for (two protons, H-2'), and showed quartet at δ 2.33 ppm for (two protons, H-3'), and showed multiple in the range of δ 3.60-3.64 ppm for (two protons, H-1'), and showed multiple in the range of δ 5.06-5.16 ppm for (two protons, H-5'), and showed multiple in the range of δ 5.93-6.00 ppm for (two protons, H-4'), and showed multiple in the range of δ 7.25-8.44 ppm for (9 proton aromatic). The ^{13}C NMR showed one peak at δ 27.50 ppm for (carbon C-1'), showed one peak at δ 30.42 ppm for (carbon C-2'), and showed one peak at δ 34.35 ppm for (carbon C-3'), and showed one peak at δ 115.29 ppm for (carbon C-5'), and showed one peak at δ 138.51 ppm for (carbon C-4'), and showed peaks in the range of δ 124.53-135.11 ppm for (aromatic carbons). The mass spectrum showed the molecular ion peak at *m/z* 246. The HRMS *EI* Calcd for $C_{19}H_{18}$ [M^{+}] 246.1409, Found 246.1410.

The second step was (4+3) cycloaddition reaction of 9-pent-4-enyl-anthracene **5** to 1.1.3.3-tetrabromoacetone using Zn, CuCl/ 1,4-dioxane and ultrasound at 15-20 ^{o}C followed by reduction of the dibromo cycloadduct with Zn/ CuCl/ NH_4Cl/ MeOH in same pot without isolation, the cycloadducts **6** was obtained in good yield as shown in **(Scheme. 2).**



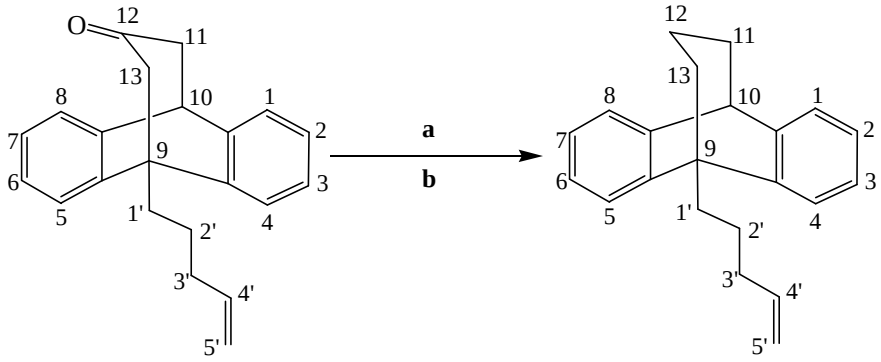
(5) **(6)**

Scheme2. (a) Tetrabromoacetone, Zn/CuCl, $(CH_3)_3SiCl$, dioxane, 15-20 ^{o}C, ultrasonication, 8h; (b) Zn/CuCl, NH_4Cl, methanol, r. t, 6h, (yield 72%)

The IR spectrum for compound **6** exhibited a strong peak at 1694 cm^{-1} for (C=O stretching). The ^{1}H NMR spectrum showed a multiple in the range of δ 0.87-0.93 ppm for (two proton, H-2'), and a multiple in the range of δ 2.28-2.30 ppm for (two proton, H-1'), and a multiple in the range of δ 2.37-2.41 ppm for (two proton, H-3'), and Singlet at δ 2.61 ppm for (two proton, H-13), and doublet at δ 2.86 ppm for (two proton, H-11), and triplet at δ 4.29 ppm for (one proton, H-10), and a multiple in the range of δ 5.87-5.94 ppm for (one proton, H-4'), and doublet of doublet at

δ 5.09 ppm for (two proton, H-5'). The ^{13}C NMR exhibit one peak at δ 209.19 ppm for carbon ketone (C=O). The mass spectrum showed the molecular ion peak at *m/z* 302. The HRMS *EI* Calcd for $C_{22}H_{22}O$ [M^+] 302.1671, Found 302.1673.

To convert the carbonyl group in to a methylene group, we used mild method at room temperature by conversion of ketone to tosylhydrazones, then reduction of hydrazone using $NaBH_3CN$, but this method did not prove successful on the ketone tetracyclic. Therefore, we used the Wolff-Kishner reduction modified (Huang-Minlon) by treatment of ketone tetracyclic **(6)** with hydrazine hydrate in the presence of potassium hydroxide at a high boiling solvent triethylene glycol to obtain tetracyclic hydrocarbon **7** as shown in **(Scheme. 3).**

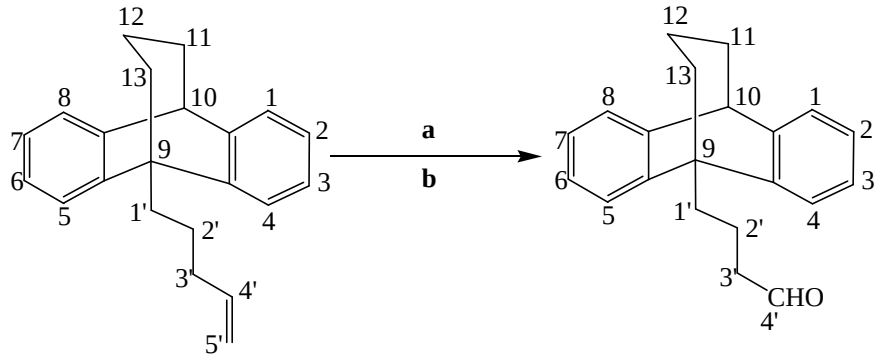


(6) **(7)**

Scheme3. (a) 85% H_2N-NH_2, KOH, triethylene glycol, 150 ^oC, 5h; (b) 200-220 ^oC, 5h, (yield 66%)

The IR spectrum for compound **7** disappearance a strong peak at 1694 cm^{-1} for (C=O). The ^{1}H NMR spectrum showed multiple in the range of δ 0.92-0.95 for (two proton, H-12). The ^{13}C NMR disappearance of singlet peak at δ 209.19 ppm for (C=O) indicative of transference carbonyl to methylene. The mass spectrum showed the molecular ion peak at *m/z* 288. The HRMS *EI* Calcd for $C_{22}H_{24}$ [M^+] 288.1878 Found 288.1881.

The reaction of tetracyclic hydrocarbon **7** with ozone by use dimethyl sulfide in methylene chloride is a general and selective method of cleaving carbon-carbon double bonds. This method gave the crystalline aldehyde **8** as shown in **(Scheme. 4).**

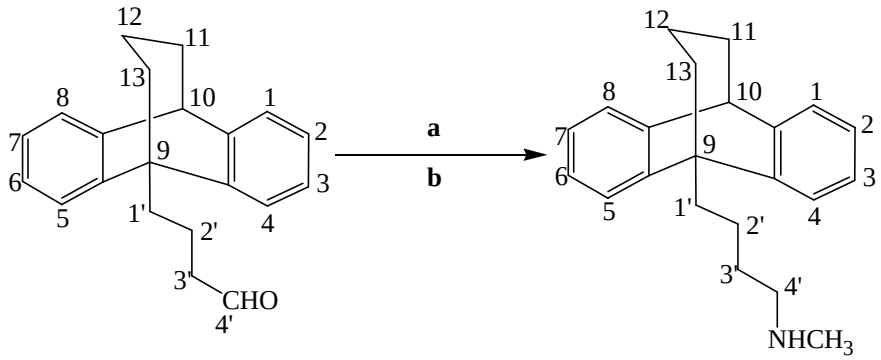


(7) **(8)**

Scheme4. (a) O_3, CH_2Cl_2, -78 ^oC, 0.5 h; (b) $(CH_3)_2S$, 4h, r. t, (yield 61%)

The IR spectrum for compound **8** showed strong peak at 1726 cm^{-1} for (C=O) aldehyde. The ^{1}H NMR showed a characteristic singlet at δ 10.88 ppm for (CHO). The ^{13}C NMR showed a peak at δ 202.08 ppm for carbon (CHO). The mass spectrum showed the molecular ion peak at *m/z* 290. The HRMS *EI* Calcd for $C_{20}H_{22}O$ [M^+] 290.1671 Found 290.1673.

As a part of our interest for reductive amination of aldehyde **8** to corresponding amine **9**, we chose a simple and efficient method in one-pot with inexpensive reagent systems and high yields of pure products. In this method we used a combination of titanium (IV) isopropoxide and sodium borohydride with methyl amine in methanol for obtain the target compound bishomomaprotiline **9** as shown in **(Scheme. 5).**



(8) **(9)**

Scheme5. (a) CH_3NH_2, CH_3OH, r. t, 4h; (b) $NaBH_4$, r. t, 6h, (yield 52%)

The IR spectrum for compound **9** showed one peak at 3410 cm^{-1} for (N-H secondary amine) with disappearance a strong peak at 1726 cm^{-1} for (CHO). In the ^1H NMR showed two peak singlet at δ 2.35 ppm and δ 2.46 ppm due to the active (N-H protons, 3H, CH_3). The ^{13}C NMR showed disappearance peak at δ 202.08 for carbon (CHO). The mass spectrum is revealed the molecular ion peak at *m/z* 305 which resembles the formula weight. The HRMS *EI* Calcd for $C_{22}H_{27}N$ [M^+] 305.2144 Found 305.2144.

CONCLUSION

In conclusion, we have described simple and flexible steps to synthesize of bishomomaprotiline **9**, from simple starting materials by changing the length of the hydrocarbon chain and bridgehead. The key step was accomplished through the ultrasonic (4+3) cycloaddition reactions of 1.1.3.3-tetrabromoacetone on 9-pent-4-enyl-anthracene **5**. The name and structures of all compounds were established on the basis of literature precedence, analytical results and spectral data. Our future plan is to study the relationship between the structure of the final compound and biological activity.

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