Research Article

Synthesis of New Tetralone Intermediates for Podophyllotoxin Analogues

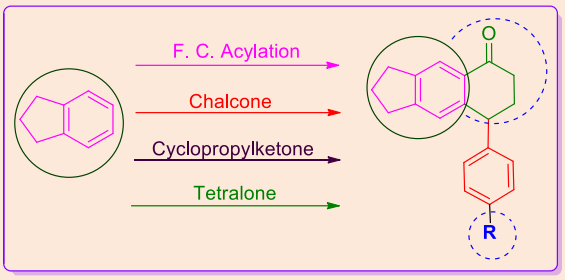
Dabbeghatta Chikkachar Umesha, Yeriyur Basavaiah Basavaraju*, Basavaiah Umesha

Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysuru–570 006, Karnataka, India

Abstract

Podophyllotoxin is a potent antimitotic agent. Podophyllin is a resinous extract of medicinal plant such as podophyllum peltatum, podophyllum emodi, podophyllum pleianthum, podophyllum hexandrum anthriscus sylvertris and juniperus Sabina. It belongs to the family Berbideraceae. Podophyllotoxin is one of the main constituent of podophyllin resin. The toxicity of podophyllotoxin liberates as diarrhea, nausea, vomiting and less soluble in water. Hence a modification in structure of podophyllotoxin is required to reduce its toxicity and to enhance its biological activity. The biologically active and less cytotoxic new tetralone analogues of podophyllotoxin have been synthesized and also to avoid the toxic side effects. It was planned to synthesize the analogues of podophyllotoxin with different functional groups and modification of structure might enhance the biological activity. Some synthesized analogues of podophyllotoxin showed better anticancer, cathartic, antimitotic, antimicrobial, antifungal, antirheumatic, antimalarial, antiasmatic, reverse transcriptase inhibition and anti-HIV activity, immunomodulating biological activity.

The structures of the synthesized new tetralone compounds were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data. They will be screened for biological activities.



Keywords: Indane, chalcones, cyclopropylketones, tetralone, podophyllotoxin.

***Correspondence**

Author: Y. B. Basavaraju

Email: basavaraju_yb@yahoo.co.in

Introduction

Podophyllotoxin (**Figure 1**) is a potent antimitotic agent [1, 2]. Podophyllin is a resinous extract of medicinal plants Podophyllum emodi and Podophyllum peltatum belonging to the family Berbideraceae in which the podophyllotoxin is one of the main constituent [3]. The toxicity of podophyllotoxin liberates as diarrhea, nausea, vomiting. Hence modifications in podophyllotoxin structure are required to reduce its toxicity and to enhance its biological activity [4]. The biologically active and less cytotoxic new tetralone intermediates of podophyllotoxin have been synthesized. The modification of podophyllotoxin structure might enhance the biological activity with favorable solubility and reduced toxicity [5, 6]. Some synthesized analogues of podophyllotoxin showed better antibacterial activity. The structures of the synthesized new tetralone compounds were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data. They will be screened for biological activities.

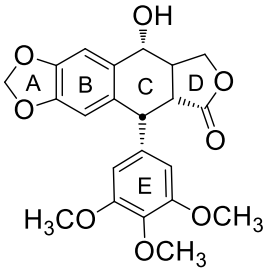


Figure 1 Podophyllotoxin

It was planned to synthesize analogues of podophyllotoxin by modifying ring-A with trimethylene moiety, The trimethoxy groups tetralone intermediates 4a, 4b, 4c and 4d in this scheme chalcone route with some linked to ring E is replaced by H, methyl, fluoro and nitro group and also lactone ring is modified [7].

The starting material 5-acetyl indane (1a) was prepared by Friedel-Craft acylation of indane with acetic anhydride in presence of fused $ZnCl_2$ gave the product in good yield [8]. Chalcones (4a-d) were prepared by claisen reaction of 5-acetyl indane (1a) with *p*-methyl, *p*-nitro, *p*-fluro benzaldehyde separately in the presence of sodium hydroxide in water-ethanol mixture. Cyclopropyl ketones (3a-d) were prepared in good yields by the reaction of chalcones 2a-d with Trimethylsulfoxoniumiodide in presence of powdered sodium hydride in dry benzene [9, 10]

The tetralones (4a-d) were prepared by Friedel-Crafts intramolecular cyclization of cyclopropyl ketones (3a-d) in presence of anhy. stannic chloride and acetic anhydride in dichloromethane. The structures of 4a, 4b, 4c and 4d were based on IR, ^{1}H- NMR, ^{13}C NMR, mass spectra and elemental analysis data. The tetralone intermediates of podophyllotoxin (4a-d) were synthesized and their structures are confirmed by spectral data.

Experimental

Materials and methods

All the reagents and chemicals were purchased from Merck chemicals used without further purification. Melting points were taken in open capillary tubes and are uncorrected. TLC is performed with E. Merck precoated silica gel plates (60F-254) with iodine as a spot developing agent. Acme, India silica gel, 60–120 mesh is used for column chromatography. IR spectra in KBr were recorded on Perkin-Elmer model 683 spectrometers. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded $CDCl_3$ solvent containing tetra methyl silane (TMS) as internal references were recorded on Bruker spectrometer; Elemental analyses were performed on a Perkin-Elmer 2400. Mass spectra were obtained by Water-Q-TOF ultima spectrometer. Micro analytical data were obtained by elemental-Vario EL-III.

Synthesis

Procedure for the synthesis of 1-(2, 3-Dihydro-1H-inden-5-yl)ethanone (1a): 5-Acetylindane was prepared in good yield by Friedel-Craft's acylation reaction of Indane (1) with acetic anhydride in presence of fused zinc chloride. The reaction mixture was stirred for 12 hours at room temperature.

1-(2, 3-Dihydro-1H-inden-5-yl)ethanone: Color: Thick red oily liquid. Yield**:** 87.66%. IR (KBr, ν, cm^{-1}): 2988 (Ar-CH), 1650 (C=O), 1590 (C=C); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.81 (d, 1H, Ar-H) 7.31 (s, 1H, Ar-H), 2.89-2.85 (t, 4H) 2.56 (s, 3H –CH_3), 2.00 (m, 2H), ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 198.2, 150, 144.4, 135.6, 126.1, 125.9, 32.8, 26.7,25.3 MS (ESI) m/z: 160.09 (M^+). *Anal*. Calcd. for $C_{11}H_{12}O$: C, 82.46, H, 7.55. Found: C, 82.45, H, 7.53%

General procedure for the synthesis of chalcones (2a-d)

1-(2, 3-Dihydro-1H-inden-5-yl)ethanone (0.05 mol) (1a**)** and substituted benzaldehyde (6.68 ml, 0.05 mol) were stirred in water (40 ml) and ethanol (25 ml) mixture in the presence of sodium hydroxide (2.00 g, 0.06 mol) at 15-30 ^{0}C for 4 hrs. The reaction mixture was kept overnight in an ice bath. The precipitated products were filtered and recrystallized from ethanol.

*1-(2,3-Dihydro-1H-inden-5-yl)-3-phenylprop-2-en-1-one (2a):*Color: yellow solid. Yield: 81.65 %. M.p.: 91-92 ^{0}C. IR (KBr, ν, cm^{-1}): 3368-2963 (Ar-CH), 1653 (C=O), 1591 (C=C); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.89 (d, 1H, *J* = 8.06 Hz, β-CH), 7.83-7.25 (m, 9H, Ar-H and α C-H), 2.99- 2.521(t, 4H), 2.16-2.09 (m, 2H), ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 198.2, 150.2, 144.7,135.6, 128.6, 127.5, 124.2, 32.8 25.3, MS (ESI) m/z: 248.15 (M^+). *Anal*. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 87.03; H, 6.45%.

1-(2,3-Dihydro-1H-inden-5-yl)-3-(p-tolyl)prop-2-en-1-one (2b): Color: Light brown solid. Yield: 86.12 %. M.p.: 108-109^{0}C. IR (KBr, ν, cm^{-1}): 2960-2940 (Ar-CH), 1653 (C=O), 1588 (C=C); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.87(d, 1H, *J* = 7.5 Hz, β-CH), 7.82-7.18 (m, 8H, Ar-H and α C-H), 2.97-2.41(t, 4H) 2.32-2.10 (s, 3H CH_3), 2.07 (m, 2H), ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 190.5, 149.9, 144.8, 136.7, 132.3, 129.8, 128.4, 127.0, 121.3, 33.0, 25.4, 21.5, MS (ESI) m/z: 262.15 (M^+). *Anal*. Calcd. for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.97; H, 6.91%.

1-(2,3-Dihydro-1H-inden-5-yl)-3-(4-flurophenyl)prop-2-en-1-one (2c): Color: Light yellow solid. Yield: 86.10 %. M.P.: 99-101 ^{0}C. IR (KBr, ν, cm^{-1}): 2981 (Ar-CH), 1656 (C=O), 1586 (C=C); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.87 (d, 1H, *J* = 7.5 Hz, β-CH), 7.82-7.10 (m, 8H, Ar-H and α C-H), 2.98 (t, 4H); 2.15-2.08 (m, 2H), ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 190.14, 162.6, 150.15, 144.9, 136.5, 130.3, 127.0, 124.4, 122.0, 115.9, 33.0, 25.38, MS (ESI) m/z: 266.11 (M^+). *Anal*. Calcd. for $C_{18}H_{15}FO$: C, 81.18; H, 5.68.Found: C, 81.15; H, 5.66%.

1-(2,3-Dihydro-1H-inden-5-yl)-3-(4-nitrophenyl)prop-2-en-1-one (2d): Color: Light yellow solid. Yield: 77.53 %. M.p.: 116-118 ^{0}C. IR (KBr, ν, cm^{-1}): 3130-2957 (Ar-CH), 1660 (C=O), 1601 (C=C); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 8.25 (d, 1H, *J* = 8.3 Hz, β-CH), 7.89-7.35 (m, 8H, Ar-H and α C-H), 2.99 (t, 4H), 2.16-2.05(m, 2H,); ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 189.4, 150.8, 148.3, 145.1, 141.3, 135.9, 128.8, 126.2, 124.1, 32.9, 25.3, MS (ESI) m/z: 293.11 (M^+). *Anal*. Calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15. Found: C, 73.72; H, 5.14%.

General procedure for the synthesis of cyclopropyl ketone (3a-d)

Sodium hydride (0.48 g of 0.02 mol) was added in portions to the stirred suspensions of trimethylsulfoxonium iodide (4.41 g of 0.02 mol) in dry benzene (20 ml) under nitrogen gas atmosphere. The reaction mixture was stirred for 10 minutes at 25-30 ^{0}C (until the evolution of the H_2 gas ceased). Chalcones (0.02 mol) (2a-d) in dry benzene (15 ml) were added drop wise during 30 mins. to the above solution. The reaction mixture was stirred at 26-28 ^{0}C for 2 hours and raised the temperature to 50-60 ^{0}C for 1 hour. The completion of the reaction was confirmed by TLC. The reaction mixture was poured into water (20 ml). The precipitated gummy residue was extracted into chloroform. The combined organic layer was washed with water, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. They were recrystallized from ethanol.

(2,3-dihydro-1H-inden-5-yl)(2-phenylcyclopropyl)methanone (3a): Color: Dark brown solid. Yield: 72.78 %. IR (KBr, ν, cm^{-1}): 3058-2926 (Ar-CH), 1683 (C=O); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.88-7.13 (m, 8H, Ar-H), 2.99-2.91 (t, 4H,), 2.89-2.10 (t, 2H) 1.29 (m, 2H) 0.85 (t, 2H, *J* = 7.3 Hz, cyclopropyl CH_2); ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 1922, 147.3, 144.3, 141.5, 134.0, 127.9, 126.5, 126.0, 125.1, 32.8, 27.0, 25.3, 25.1, 14.6; MS (ESI) m/z: 262.14 (M^+). *Anal*. Calcd. for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.97, H, 6.91%.

(2,3-Dihydro-1H-inden-5-yl)(2-(p-tolyl) cyclopropyl) methanone (3b): Color: Dark brown solid. Yield: 78.61 %. IR (KBr, ν, cm^{-1}): 2956-2853 (Ar-CH), 1683 (C=O); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.87-7.18 (m, 7H, Ar-H), 2.97 (t, 4H), 2.36 (s, 3H, CH_3), 2.10-2.09 (m, 2H, cyclopropyl CH), 1.254 (m, 2H) 0.85 (t, 2H, *J* = 7.1 Hz, cyclopropyl CH_2); ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 190.4, 149.8, 144.2, 136.7, 132.2, 129.6, 128.4, 126.9, 125.8, 124.4, 32.5, 29.7, 25.3, 21.4, 14.6 MS (ESI) m/z: 276.15 (M^+). *Anal*. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 86.90; H, 7.27%.

(2,3-Dihydro-1H-inden-5-yl)(2-(4-fluorophenyl) cyclopropyl) methanone (3c): Color: Dark brown solid. Yield: 78.02 %. IR (KBr, ν, cm^{-1}): 2923-2853 (Ar-CH), 1682 (C=O); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.92-7.20 (m, 7H, Ar-H), 2.91 (t, 4H) 2.10-2.03 (m, 2H, cyclopropyl CH), 1.66 (m, 2H) 0.83 (t, 2H, *J* = 7.5 Hz, cyclopropyl CH_2); ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 191.4, 159.1, 147.4, 144.1, 137.2, 134.0, 128.1, 126.0, 125.5, 114.9, 32.8, 27.0, 25.3, 14.6; MS (ESI) m/z: 280.13 (M^+). *Anal*. Calcd. for $C_{19}H_{17}FO$: C, 81.40; H, 11.0,. Found: C, 81.39; H, 10.99%.

(2,3-Dihydro-1H-inden-5-yl)(2-(4-nitrophenyl)cyclopropyl)methanone (3d): Color: Dark brown solid. Yield: 70.28 %. IR (KBr, ν, cm^{-1}): 2922-2853 (Ar-CH), 1683 (C=O); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 8.28-7.26 (m, 7H, Ar-H), 2.99-2.22 (t, 4H), 2.18-2.11 (m, 2H, cyclopropyl CH), 1.29-0.89 (m, 2H) 0.83 (t, 2H, *J* = 7.2 Hz, cyclopropyl CH_2); ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 189.4, 150.7, 148.4, 145.1, 141.2, 136.0, 126.1, 124.5, 124.1, 33.0, 29.6,

25.3, 25.1, 14.7 MS (ESI) m/z: 307.12 (M^+). *Anal*. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58. Found: C, 74.23; H, 5.57%.

General procedure for the synthesis of tetralones (4a-d)

Cyclopropyl ketones (0.01 mol) *(3a-d)* was dissolved in dry dichloromethane (50 ml). Acetic anhydride (0.94 ml, 0.01 mol) and anhydrous stannic chloride (1.17 ml, 0.01 mol) were added under nitrogen gas atmosphere. The resultant reaction mixture was stirred at 25-28 ^{0}C for 3 hrs. The completion of reaction was known by TLC. The reaction mixture was poured into 5% NaOH solution (20 ml), the product was extracted into dichloromethane. The organic layer was washed with 5% HCl followed by water, dried over anhyd. Na_2SO_4 and concentrated under vacuum using a rotary evaporator to give brown residue. The product was purified by column chromatography using silica gel (60-120 mesh) as adsorbent and benzene as eluent. The benzene solution was concentrated to a small volume (20 ml) and hexane (100 ml) was added drop wise to give products in good yields. They were recrystallized from ethanol.

8-Phenyl-2, 3, 7, 8-tetrahydro-1H-cyclopenta[b]naphthalene-5(6H)-one (4a): Color: Dark brown gummy solid. Yield: 67.34 %. IR (KBr, ν, cm^{-1}): 2923-2853 (Ar-CH), 1683 (C=O); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.86-7.03 (m, 7H, Ar-H), 4.71 (t, 1H, *J* = 6.3 Hz, CH), 2.86-2.77 (t, 4H), 2.70-2.00 (tt, 4H, *J* = 6.1 Hz, *J* = 6.8 Hz, CH_2), 1.69-1.16 (m, 2H), ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 197.8, 149.1, 145.5, 144.6, 136.9, 131.3, 129.0, 128.1, 127.3, 125.2, 45.2, 37.3, 32.7, 30.6, 25.1; MS (ESI) m/z: : 262.14 (M^+). *Anal*. Calcd. for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.97; H, 6.90%.

8-(p-Tolyl)-2, 3, 7, 8-tetrahydro-1H-cyclopenta[b]naphthalene-5(6H)-one (4b): Color: Dark brown gummy solid. Yield: 66.50 %. IR (KBr, ν, cm^{-1}): 2923-2853 (Ar-CH), 1679 (C=O); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.98-6.84 (m, 6H, Ar-H), 4.24 (t, 1H, *J* = 6.4 Hz, CH), 2.89-2.73 (t, 4H), 2.61-2.25 (tt, 4H, *J* = 6.0 Hz, *J* = 6.2 Hz, CH_2),2.20 (s, 3H, -CH_3) 1.99-1.27 (m, 2H), ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 197.8, 149.4, 145.5, 142.0, 137.6, 131.2, 129.1, 129.3, 128.0, 127.1, , 37.3, 32.7, 30.7, 25.1, 21.2 MS (ESI) m/z: : 276.15 (M^+). *Anal*. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 86.90; H, 7.28%.

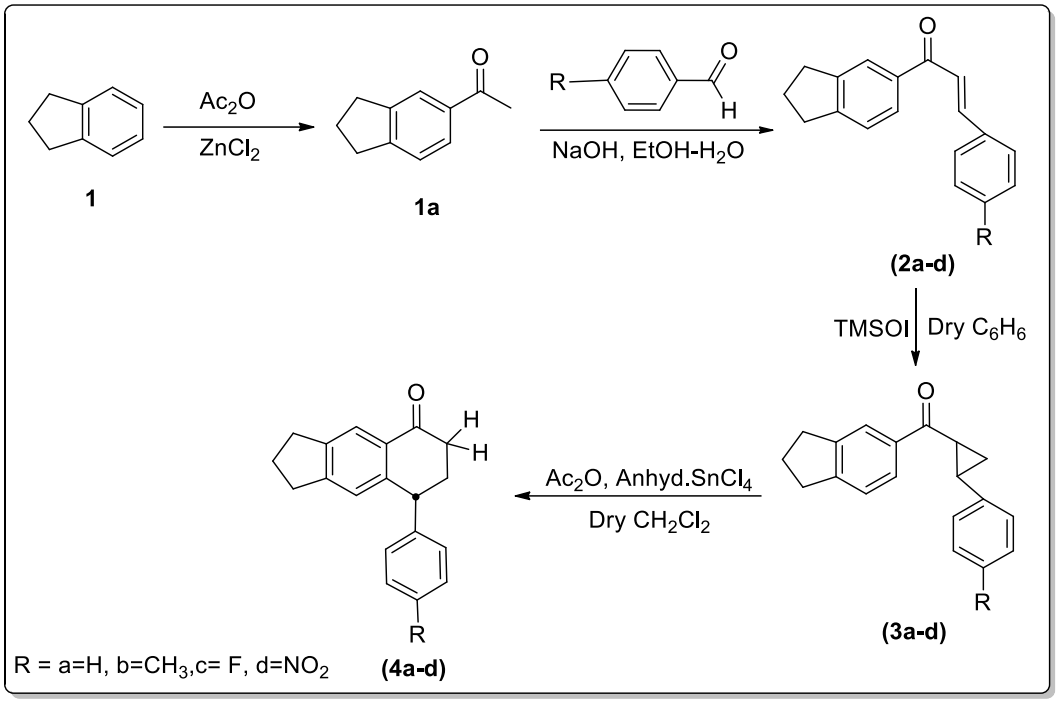
8-(4-Fluorophenyl)-2, 3, 7, 8-tetrahydro-1H-cyclopenta[b]naphthalene-5(6H)-one (4c): Color: Dark brown gummy solid. Yield: 70.12 %. IR (KBr, ν, cm^{-1}): 2923-2853 (Ar-CH), 1680 (C=O); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 7.24-6.90 (m, 6H, Ar-H), 3.71-3.68 (t, 1H, *J* = 6.5 Hz, CH), 2.88-2.81 (t, 4H), 2.33-2.10 (tt, 4H, *J* = 6.4 Hz, *J* = 6.3 Hz, CH_2), 2,01 (m, 2H), ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 197.8, 160.1, 149.5, 145.3, 140.1, 137.5, 131.1, 129.3, 129.0, 115.7, 45.2, 37.3, 32.7, 31.0, 25.1 MS (ESI) m/z: : 280.13 (M^+). *Anal*. Calcd. for $C_{19}H_{17}FO$: C, 81.40; H, 6.11. Found: C, 81.38; H, 6.09%.

8-(4-Nitrophenyl)-2, 3, 7, 8-tetrahydro-1H-cyclopenta[b]naphthalene-5(6H)-one (4d): Color: Dark brown gummy solid. Yield: 60.16 %. IR (KBr, ν, cm^{-1}): 2923-2853 (Ar-CH), 1681 (C=O); ^{1}H NMR ($CDCl_3$-400 MHz) δ ppm: 8.17-7.24 (m, 6H, Ar-H), 3.29 (t, 1H, *J* = 6.3 Hz, CH), 2.86 (t, 4H), 2.66-2.19 (tt, 4H, *J* = 5.9 Hz, *J* = 6.6 Hz, CH_2), 1.93 (m, 2H), ^{13}C NMR ($CDCl_3$-100 MHz) δ ppm: 197.8, 151.1, 149.5, 145.5, 145.3, 137.5, 131.2, 129.1, 124.2, 121.0, 37.3, 32.7, 30.0, 25.1 ; MS (ESI) m/z: : 307.12 (M^+). *Anal*. Calcd. for $C_{19}H_{17}NO3$: C, 74.25; H, 5.58. Found: C, 74.23; H, 5.57%.

Results and Discussion

Chemistry

The new tetralone analogues of podophyllotoxin were synthesized by chalcone route **Scheme 1**. The 5-acetyl indane (1a) was prepared in high yield by Fridel-Craft's acylation reaction of Indane (1). Benzylideneacetophenones (chalcones) (2a-d) were prepared in high yields by Claisen-Schmidt reaction of 5-acetyl indane (1a**)** with benzaldehyde, 4-methylbenzaldehyde, 4-fluorobenzaldehyde and 4-nitrobenzaldehyde in the presence of sodium hydroxide in water-ethanol mixture. The structures of the chalcones were confirmed by IR and ^{1}H NMR spectra. IR spectra of compounds (2a-d) showed the C=C stretching frequency in the range 1601-1591 cm^{-1} and ^{1}H NMR showed the absence of aldehyde proton at 9.83 ppm.



Scheme 1 Synthesis of new tetralone intermediates of podophyllotoxin analogues (4a-d)

The cyclopropyl ketones (3a-d) were prepared in good yields by the reaction of chalcones (2a-d) with trimethylsulfoxonium iodide (TMSOI) in the presence of sodium hydride in dry benzene. The sodium hydride acts as a base which abstracts a proton from the methyl group in trimethylsulfoxonium iodide to form a dimethylsulfoxonium methylide. It attacks nucleophilically the β-carbon atom of the chalcone which acts as Michael receptors to form an enolate ion, which undergoes nucleophilic attack on the methylene carbon atom bearing the dimethylsulfoxonium cation intramolecularly to form the desired cyclopropyl ketones. The structures of compounds (3a-d) were confirmed by IR spectra. The IR spectra showed the C=O stretching band in the range 1664-1653 cm^{-1} and ^1H NMR showed the cyclopropane CH and CH_2 peak at the range 2.21-2.00 and 0.83-0.78 ppm respectively.

Tetralones (4a-d) were prepared in good yields by the Friedel-Craft's intramolecular cyclization reaction of cyclopropyl ketones (3a-d) in the presence of anhyd. Stannic chloride and acetic anhydride in dry dichloromethane. The cyclopropyl ketones undergoes electrophilic ring opening in the presence of Lewis acid to give benzylcarbocationic intermediate which is intramolecularly attacked by aryl ring π-electrons resulting in the formation of a six membered ring with a pendant carbocation. This readily gives up proton to form tetralones. Acetic anhydride which facilitates the formation of desired tetralones. In its IR spectra appeared absorption bands in the range 2923-2853cm^{-1} and 1683-1675 cm^{-1} corresponds respectively to C-H and C=O stretching frequencies and ^1H NMR of the ring B protons appears in the range 2.65-2.18 ppm. They are key intermediates for the synthesis of the novel nitrogen containing analogues of podophyllotoxin.

Conclusion

The tetralone intermediates (4a-d) were prepared, which are very essential for the synthesis and study of antimitotic activity of analogues of podophyllotoxin.

Acknowledgement

The authors are thankful to University of Mysore for giving NON-NET Fellowship and providing NMR, MASS, IR spectra.

References

[1] Smissman E E, Murray R J, McChesney J D, Houston L L, Pazdernik T L, J Med Chem **1976**, 19, 148-153.
[2] Jungi W F, Senn H J, Cancer Chemother Rep **1975**, 59, 737-742.
[3] Podwyssotzki V, Arch Exp Pathol Pharmakol **1880**, 13, 29-52.
[4] Lokanatha Rai K M, Murthy C A, Radhakrishna P M, Synth Commun **1990**, 20, 1273-1277.
[5] Sadashivamurthy B. Basavaraju Y B, Bulg Chem Comm **2005**, 37, 135-139.
[6] Umesha B, Basavaraju Y B, Mahendra C, Med Chem Res **2015**, 24, 142-151.
[7] Ward R S, Chem Soc Rev **1982**, 11, 75-125.
[8] David Jackson E, Paul Dewick M, Phytochemistry **1985**, 24, 2407-2409.
[9] Damayanthi Y, Lown W, Curr Med Chem **1998**, 5, 205-252.
[10] Erdtmann E J, Haworth H D, J Chem Soc **1942**, 448-456.

Publication History
Received 09th May 2015
Revised 13th May 2015
Accepted 15th May 2015
Online 30th May 2015