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Synthesis and Characterization of New Tetralone Esters

M. H. Krishna, Y. B. Basavaraju*, B. Umesha and S. B. Shivakumar

Department of Studies in Chemistry, University of Mysore,
Manasagangotri, Mysore-570 006, India

**Corresponding address:*
Prof. Y. B. Basavaraju
DOS in Chemistry, University of Mysore
Manasagangotri, Mysore-570 006
Karnataka, India
Tel: +91–9480441804

Abstract. Podophyllotoxin belongs to the cyclolignan family of natural products. It exhibits cathartic, cytotoxic, antimitotic, anticancer and other biological activities. The new tetralone esters **4**, **5**, **6** and **7** of podophyllotoxin analogues were synthesized in very good yields by chalcone route. They were synthesized by modifying 1,3-methylene dioxy ring A, ring C, the lactone ring D and the ring E of podophyllotoxin **1** to study structure activity relationship. All the products were characterized by spectral and elemental analysis data.

Keywords: *o*-Fluoro toluene, Acetophenone, Chalcone, Ethyl chloroacetate, Powdered sodium, Cyclopropyl ketoester, Tetralone ester

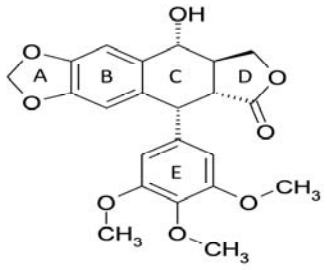
Introduction

Podophyllotoxin **1** acts as a strong antimitotic, inhibiting tubulin family [1, 2], which has been extracted from two important medicinal plants *Podophyllum emodi* (an Indian species) and *Podophyllum Peltatum* (a North American species) [3]. It has also been extracted from many other plants belonging to the Podophyllum group of species [4]. It belongs to a large family of natural products called lignans [5].

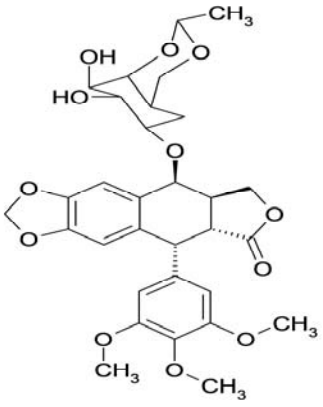
Podophyllotoxin showed a wide variety of biological activities such as cathartic, cytotoxic, antimitotic, anticancer, antiAIDS, antitropical skin disease, antimalarial, virucidal, fungicidal etc. Podophyllotoxin **1** is used as the therapeutic agent in the treatment of neoplastic disease is restricted due to toxic side effects. Its semi synthetic derivatives etoposide **2** and teniposide **3** exhibit antimitotic activity with less side effects and are important clinical chemotherapeutic agents [6]. A number of modifications have been done on podophyllotoxin structure and some of the congeners exhibit a potent antitumor activity [7]. In view of these reports, it was decided to synthesize the tetralone esters **4**, **5**, **6** and **7** by modifying 1,3-methylene dioxy ring A, ring C, the lactone ring D and the ring E of Podophyllotoxin **1**.

Chemistry

In this paper, the chalcone route has been followed with some changes in experimental procedure to synthesize new tetralone esters **4**, **5**, **6** and **7** (Scheme-1). The starting material *o*-Fluoro toluene **8** was purchased. 4^1-Fluoro-3^1-methyl-acetophenone **9** was prepared in high yield by Friedel-Crafts acylation reaction of *o*-Fluoro toluene **8** with acetic anhydride in the presence of fused zinc chloride [8]. Chalcones **11a-d** were prepared in excellent yields by Claisen-Schmidt reaction of 4^1-Fluoro-3^1-methyl-acetophenone **9** with benzaldehydes **10a-d** in the presence of sodium hydroxide in water-ethanol mixture [9]. Cyclopropyl ketoesters **12a-d** were prepared in good yields by the reaction of chalcones **11a-d** with ethyl chloroacetate in the presence of powdered sodium in dry benzene [10, 11].



1



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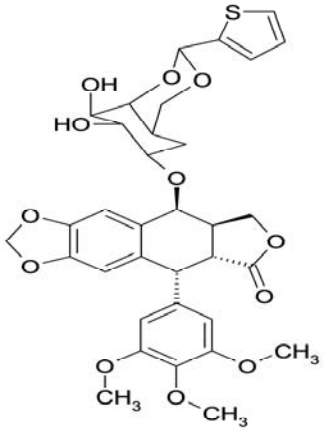

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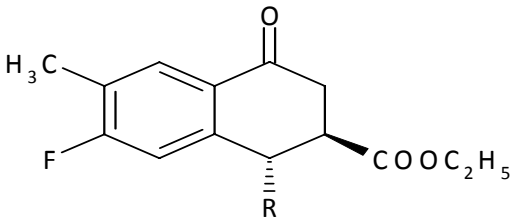
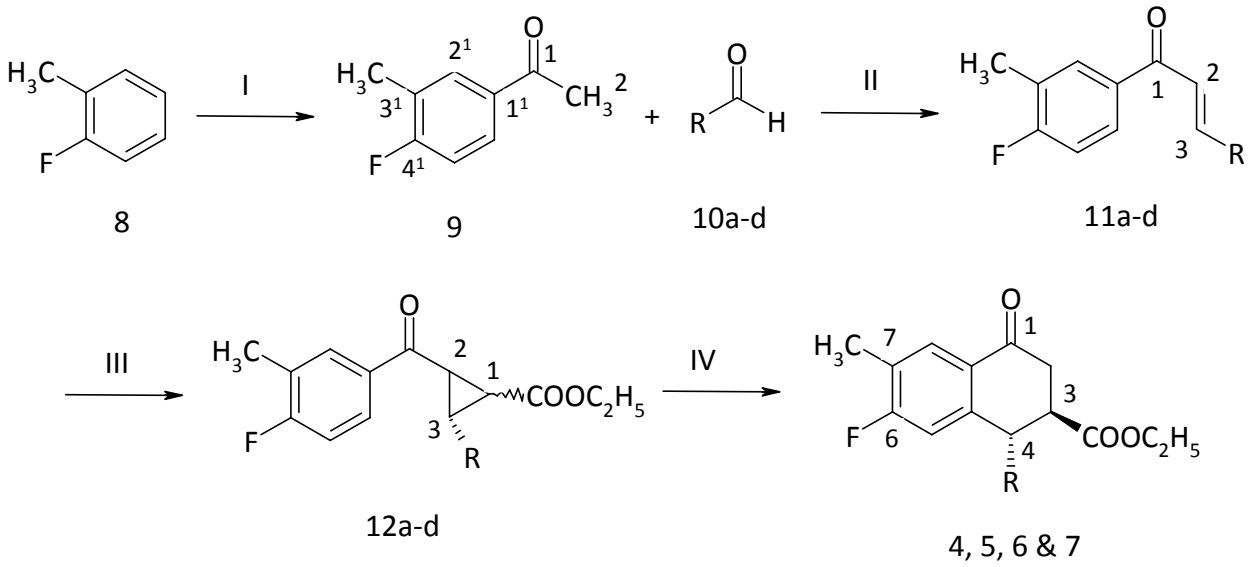


4, 5, 6 & 7

4, R=p-Tolyl
5, R=p-Anisyl
6, R=p-Thioanisyl &
7, R=3,4-Dimethylphenyl

Tetralone esters **4**, **5**, **6** and **7** were prepared in good yields by intramolecular cyclization of cyclopropyl ketoesters **12a-d** in the presence of anhyd.Stannic chloride and acetic anhydride in dry dichloromethane [4, 7]. The structure of the compounds were based on IR, ^{1}H NMR, Mass spectra and elemental analysis data.



I. Ac_2O, Anhyd.$ZnCl_2$
II. NaOH, C_2H_5OH-H_2O, r.t.
III. $ClCH_2COOC_2H_5$, Powdered Na, Dry C_6H_6, r.t.
IV. Anhyd.$SnCl_4$, Ac_2O, Dry CH_2Cl_2, 0-25 ^0C

Scheme-1

Experimental Section

Melting points were determined by open capillary method and are uncorrected. The IR spectra were recorded on a FT-IR in KBr disc or nujol mull. The ^1H NMR spectra were recorded on Jeol 300MHz and Jeol GSX-400 spectrometer using $CDCl_3$ or DMSO as solvent and TMS as an internal reference. The chemical shifts were expressed in δ values. The mass spectra (ESI-MS) were recorded by Bruker daltonics on ESQUIRE-3000 instrument. The purity of the compounds was checked by TLC on silica gel glass plates in benzene and ethyl acetate mixture (7:0.5). The compounds were purified by column chromatography using silica gel (60-120 mesh) as adsorbent and benzene as eluent.

The starting material *o*-Floro toluene **8** was purchased from the chemical suppliers.

4^1-Fluoro-3^1-methyl-acetophenone 9: *o*-Fluoro toluene **8** (10g, 0.0908 mole) in acetic anhydride (50ml) containing fused zinc chloride (12.37g, 0.0908 mole) were stirred at room temperature for 12hr. After usual workup, the product was obtained as a brown semi solid in 81% yield (11.2g), IR (KBr): 1671cm^{-1} (C=O), 1597 (C=C). ^{1}H NMR ($CDCl_3$): δ 2.57 (s, 3H, -$COCH_3$), 2.23 (s, 3H, $C_3{}^1$-CH_3), 7.06-7.82 (m, 3H, Ar-H). Anal. Cald. for C_9H_9FO: C, 71.04; H, 5.96%. Found: C, 71.01; H, 5.92%.

1-(4^1-Fluoro-3^1-methyl-phenyl)-3-(4^{11}-methylphenyl)-prop-2-ene-1-one (Chalcone) 11a: 4^1-Fluoro-3^1-methyl-acetophenone **9** (5g, 0.0328 mole) and p-methylbenzaldehyde **10a** (3.94g, 0.0328 mole) were stirred vigorously in water (40ml) and ethanol (20ml) mixture in the presence of sodium hydroxide (1.31g, 0.0328 mole) at 15-30^{o}C for 4hr. The reaction mixture was kept overnight in an ice bath. The precipitated product was filtered and recrystallized from ethanol. The yellow crystalline compound was obtained in 93.65% yield (7.82g), m.p.115-117^{o}C. IR (KBr): 1661cm^{-1} (C=O), 1593 (aromatic C=C), ^{1}H NMR ($CDCl_3$): δ 2.23-2.36 (s, 6H, $C_3{}^1$-CH_3 & $C_4{}^{11}$-CH_3), 8.04 (d, 1H, J=12Hz, C_3-H), 7.16-7.65 (m, 8H, Ar-H & C_2-H). Anal. Cald. for $C_{17}H_{15}FO$: C, 80.29; H, 5.95%. Found: C, 80.22; H, 5.92%. ESI-MS: Calc. for ($C_{17}H_{15}FO$+H), 255; Found, 255.14.

1-(4^1-Fluoro-3^1-methyl-phenyl)-3-(4^{11}-methoxyphenyl)-prop-2-ene-1-one (Chalcone) 11b: Was obtained as yellow crystalline compound in 87.64% yield (7.8g), m.p.70-72^{o}C. IR (KBr): 1663cm^{-1} (C=O), 1594 (aromatic C=C), ^{1}H NMR (DMSO): δ 2.34 (s, 3H, $C_3{}^1$-CH_3), 3.83 (s, 3H, -OCH_3), 8.03 (d, 1H, J=13Hz, C_3-H), 6.78-7.84 (m, 8H, Ar-H & C_2-H). Anal. Cald. for $C_{17}H_{15}FO_2$: C, 75.54; H, 5.59%. Found: C, 75.51; H, 5.55%. ESI-MS: Calc. for ($C_{17}H_{15}FO_2$+H), 271; Found, 271.10.

1-(4^1-Fluoro-3^1-methyl-phenyl)-3-(4^{11}-methylthiophenyl)-prop-2-ene-1-one (Chalcone) 11c: Was obtained as orange crystalline compound in 89.57% yield (8.42g), m.p.118-120^{o}C. IR (KBr): 1658cm^{-1} (C=O), 1597 (aromatic C=C), ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, $C_3{}^1$-CH_3), 2.52 (s, 3H, -SCH_3), 8.05 (d, 1H, J=12Hz, C_3-H), 7.24-7.65 (m, 8H, Ar-H & C_2-H). Anal. Cald. for $C_{17}H_{15}FOS$: C, 71.30; H, 5.28%. Found: C, 71.26; H, 5.23%. ESI-MS: Calc. for ($C_{17}H_{15}FOS$+H), 287; Found, 287.08.

1-(4^1-Fluoro-3^1-methyl-phenyl)-3-(3^{11},4^{11}-dimethylphenyl)-prop-2-ene-1-one (Chalcone) 11d: Was obtained as pale yellow crystalline compound in 89.9%

yield (8.82g), m.p.103-105°C. IR (KBr): 1662cm^{-1} (C=O), 1596 (aromatic C=C), ^{1}H NMR ($CDCl_3$): δ 2.27-2.43 (s, 9H, C_3^1-CH_3, C_3^{11}-CH_3 & C_4^{11}-CH_3), 8.03 (d, 1H, J=12Hz, C_3-H), 6.91-7.65 (m, 7H, Ar-H & C_2-H). Anal. Cald. for $C_{18}H_{17}FO$: C, 80.57; H, 6.39%. Found: C, 80.53; H, 6.34%. ESI-MS: Calc. for ($C_{18}H_{17}FO$+H), 269; Found, 269.4.

Ethyl-2-(4^1-fluoro-3^1-methyl-benzoyl)-3-(4^{11}-methylphenyl)-cyclopropane-1-carboxylate 12a: Chalcone **11a** (5g, 0.0196 mole), freshly distilled ethyl chloro acetate (2.4g, 0.0196 mole) and powdered sodium (0.9g, 0.0392 mole) were stirred in dry benzene (120ml) at room temperature for 30hr. The unreacted sodium and its salts were filtered off. The filtrate was washed with 5% aqueous sodium hydroxide solution (2X50ml) followed by 2% brine solution (2X50ml) and dried over anhyd.Sodium sulphate. The solvent was removed by distillation to give a crude product, which was purified by column chromatography using chloroform as eluent. The product was obtained as yellow semi solid in 83.4% yield (5.58g). IR (KBr): 1740cm^{-1} (C=O of ester), 1677 (C=O), 1595 (aromatic C=C); ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 6H, C_3^1-CH_3 & C_4^{11}-CH_3), 4.04-4.25 (q, 2H, J=4Hz, COO$\underline{CH_2}CH_3$), 0.96-1.30 (t, 3H, J=4Hz, $COOCH_2\underline{CH_3}$), 1.93-2.78 (m, 3H, C_1-H, C_2-H & C_3-H), 7.17-7.94 (m, 7H, Ar-H). Anal. cald. for $C_{21}H_{21}FO_3$: C, 74.10; H, 6.22%. Found: C, 74.05; H, 6.18%. ESI-MS: Calc. for ($C_{21}H_{21}FO_3$), 340.15; Found, 340.94.

Ethyl-2-(4^1-fluoro-3^1-methyl-benzoyl)-3-(4^{11}-methoxyphenyl)-cyclopropane-1-carboxylate 12b: Was obtained as yellow crystalline solid in 89.68% yield (5.91g). m.p.68-70°C, IR (KBr): 1734cm^{-1} (C=O of ester), 1679 (C=O), 1594 (aromatic C=C); ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, C_3^1-CH_3), 3.86 (s, 3H, -OCH_3), 4.06-4.22 (q, 2H, J=4Hz, COO$\underline{CH_2}CH_3$), 0.85-1.31 (t, 3H, J=4Hz, $COOCH_2\underline{CH_3}$), 1.98-2.99 (m, 3H, C_1-H, C_2-H & C_3-H), 7.59-7.88 (m, 3H, Ar-H), 6.93-7.40 (m, 4H, Ar-H). Anal. cald. for $C_{21}H_{21}FO_4$: C, 70.77; H, 5.94%. Found: C, 70.73; H, 5.89%. ESI-MS: Calc. for ($C_{21}H_{21}FO_4$+Na), 379.14; Found, 379.1.

Ethyl-2-(4^1-fluoro-3^1-methyl-benzoyl)-3-(4^{11}-methythiophenyl)-cyclopropane-1-carboxylate 12c: Was obtained as yellow semi solid in 89.54% yield (5.82g), IR (KBr): 1738cm^{-1} (C=O of ester), 1679 (C=O), 1598 (aromatic C=C); ^{1}H NMR (DMSO): δ 2.34 (s, 3H, C_3^1-CH_3), 2.53 (s, 3H, -SCH_3), 3.87-4.15 (q, 2H, J=4Hz, COO$\underline{CH_2}CH_3$), 0.98-1.28 (t, 3H, J=4Hz, $COOCH_2\underline{CH_3}$), 2.12-2.73 (m, 3H, C_1-H, C_2-H & C_3-H), 7.07-7.39 (m, 4H, Ar-H), 7.68-7.94 (m, 3H, Ar-H). Anal. cald. for

$C_{21}H_{21}FO_3S$: C, 67.72; H, 5.68%. Found: C, 67.68; H, 5.64%. ESI-MS: Calc. for ($C_{21}H_{21}FO_3S$+Na), 395.12; Found, 395.1.

Ethyl-2-(4^1-fluoro-3^1-methyl-benzoyl)-3-(3^{11},4^{11}-dimethylphenyl)-cyclopropane-1-carboxylate 12d: Was obtained as orange semi solid in 83.48% yield (5.51g), IR (KBr): 1739cm^{-1} (C=O of ester), 1681 (C=O), 1594 (aromatic C=C); ^{1}H NMR ($CDCl_3$): δ 2.23-2.54 (s, 9H, $C_3{}^1$-CH_3, $C_3{}^{11}$-CH_3, $C_4{}^{11}$-CH_3), 4.01-4.23 (q, 2H, J=4Hz, COO$\underline{CH_2}CH_3$), 0.97-1.31 (t, 3H, J=4Hz, $COOCH_2\underline{CH_3}$), 1.93-2.74 (m, 3H, C_1-H, C_2-H & C_3-H), 7.18-7.98 (m, 3H, Ar-H), 6.85-7.09 (m, 3H, Ar-H). Anal. cald. for $C_{22}H_{23}FO_3$: C, 74.56; H, 6.54%. Found: C, 74.52; H, 6.53%. ESI-MS: Calc. for ($C_{22}H_{23}FO_3$+Na), 377.16; Found, 377.1.

3-Ethylcarboxy-4-(4^1-methylphenyl)-6-fluoro-7-methyl-1-tetralone 4: A solution of cyclopropyl ketoester **12a** (5g, 0.0146 mole) in dry dichloromethane (75ml) was added dropwise to a magnetically stirred solution of anhyd.Stannic chloride (3.80g, 0.0146 mole) and acetic anhydride (2.98g, 0.0292 mole) in dichloromethane (75ml) for half an hr. at 0^{o}C and further stirred for 6hr. After treating the reaction mixture with 5N HCl solution (50ml), the organic layer was washed with 10% NaOH solution (2X50ml) and finally with water. The product was purified by column chromatography using benzene as eluent to give tetralone ester as dark brown semi solid in 82% yield (4.10g), IR (KBr): 1743cm^{-1} (C=O of ester), 1702 (C=O), 1593 (C=C of aromatic), ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 6H, C_7-CH_3, & $C_4{}^1$-CH_3), 3.91-4.23 (q, 2H, J=4Hz, -COO$\underline{CH_2}CH_3$), 0.94-1.32 (t, 3H, J=4Hz, -$COOCH_2\underline{CH_3}$), 4.32 (d, 1H, J=12Hz, C_4-H), 2.32-2.44 (dd, 2H, C_2-H), 3.44-3.65 (q, 1H, J=4Hz, C_3-H), 7.12-7.39 (m, 4H, Ar-H), 6.63-6.84 (m, 2H, C_5-H, C_8-H). Anal. Cald. for $C_{21}H_{21}FO_3$: C, 71.30; H, 5.28%. Found: C, 71.27; H, 5.24%. ESI-MS: Calc. for ($C_{21}H_{21}FO_3$+H), 341; Found, 341.68.

3-Ethylcarboxy-4-(4^1-methoxyphenyl)-6-fluoro-7-methyl-1-tetralone 5: Was obtained as orange semi solid in 86.4% yield (4.32g), IR (KBr): 1746cm^{-1} (C=O of ester), 1697 (C=O), 1598 (C=C of aromatic), ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H, C_7-CH_3), 3.89-4.28 (q, 2H, J=4Hz, -COO$\underline{CH_2}CH_3$), 0.11-1.34 (t, 3H, J=4Hz, -$COOCH_2\underline{CH_3}$), 3.72 (s, 3H, -OCH_3), 4.23 (d, 1H, J=12Hz, C_4-H), 2.34-2.52 (dd, 2H, C_2-H), 3.64-3.76 (q, 1H, J=3Hz, C_3-H), 6.78-6.93 (m, 4H, Ar-H), 7.26-7.82 (m, 2H, C_5-H & C_8-H). Anal. Cald. for $C_{21}H_{21}FO_4$: C, 70.77; H, 5.94%. Found: C, 70.75; H, 5.91%. ESI-MS: Calc. for ($C_{21}H_{21}FO_4$+H), 356; Found, 356.15.

3-Ethylcarboxy-4-(4^1-methylthiophenyl)-6-fluoro-7-methyl-1-tetralone 6: Was obtained as dark brown semi solid in 84.6% yield (4.23g), IR (KBr): 1747cm^{-1} (C=O of ester), 1692 (C=O), 1589 (C=C of aromatic), ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H, C_7-CH_3), 3.69-4.22 (q, 2H, J=4Hz, -COO$\underline{CH_2}CH_3$), 0.98-1.30 (t, 3H, J=4Hz, -$COOCH_2\underline{CH_3}$), 2.42 (s, 3H, -SCH_3), 4.57 (d, 1H, J=4Hz, C_4-H), 2.52-2.67 (dd, 2H, C_2-H), 3.21-3.58 (q, 1H, J=3Hz, C_3-H), 7.03-7.38 (m, 4H, Ar-H), 6.67-6.83 (m, 2H, C_5-H & C_8-H). Anal. Cald. for $C_{21}H_{21}FO_3S$: C, 67.72; H, 5.68%. Found: C, 67.68; H, 5.63%. ESI-MS: Calc. for ($C_{21}H_{21}FO_3S$+H), 372; Found, 372.61.

3-Ethylcarboxy-4-(3^1,4^1-dimethylphenyl)-6-fluoro-7-methyl-1-tetralone 7: Was obtained as dark brown semi solid in 83% yield (4.15g), IR (KBr): 1741cm^{-1} (C=O of ester), 1696 (C=O), 1592 (C=C of aromatic), ^{1}H NMR ($CDCl_3$): δ 2.25-2.35 (s, 9H, C_7-CH_3, $C_3{}^1$-CH_3, $C_4{}^1$-CH_3), 3.71-4.26 (q, 2H, J=4Hz, -COO$\underline{CH_2}CH_3$), 0.95-1.33 (t, 3H, J=4Hz, -$COOCH_2CH_3$), 4.42 (d, 1H, J=4Hz, C_4-H), 2.25-3.09 (dd, 2H, C_2-H), 3.23-3.53 (q, 1H, J=3Hz, C_3-H), 6.85-7.12 (m, 3H, Ar-H), 7.36-7.73 (m, 2H, Ar-H). Anal. Cald. for $C_{22}H_{23}FO_3$: C, 74.56; H, 6.54%. Found: C, 74.52; H, 6.52%. ESI-MS: Calc. for ($C_{22}H_{23}FO_3$+H), 355; Found, 355.21.

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Conclusion

The tetralone ester compounds **4**, **5**, **6** and **7** were prepared in excellent yields as analogues of podophyllotoxin.

References

[1]. J.D. McChesney, R.J. Murray, E.E. Smissman, Podophyllotoxin analogs. I. Synthesis and biological evaluation of certain trans-2-aryl-trans-6-hydroxymethyl-3-cyclohexene-carboxylic acid lactones as antimitotic agents*, J. Med. Chem*., **19** (1976), 148.

[2]. W.F. Jungi, H.J. Senn, Clinical study of the new podophyllotoxin derivative, 4'-demethylepipodophyllotoxin 9-(4,6-O-ethylidene-3-D-glucopyranoside) (NSC-141540;VP-16-213), in solid tumors in man, *Cancer Chem. Rep*., **59** (1975), 737-742.

[3]. V. Podwyssotzki, Pharmakologische Studien uber Podophyllum peltatum, *Arch. Exp. Pathol. Pharmakol*., **13** (1880), 29-52.

[4]. E. David Jackson and M. Paul Dewick, Tumour-inhibitory aryltetralin lignans from Podophyllum pleianthum, *Phytochemistry*, **24** (1985), 2407.

[5]. E.J. Erdtmann, H.D. Haworth, The chemistry of the lignan group of natural products, *J. Chem. Soc*.**,** 1942, 448-456.

[6]. T.W. Dyle, In Etoposide (VP-16). *Current Status and New Developments; Academic Press*: New York, 1984.

[7]. William Lown and Yalamati Damayanthi, Podophyllotoxin: Current status and recent developments, *Current medicinal chemistry*, **5** (1998), 205-252.

[8]. M. Nencki, N. Sieber, The ring acylation of phenols with acids in the presence of zinc chloride, or the modification of the Friedel-Crafts reaction, q.v., by substitution of ferric chloride for aluminum chloride, *J. Prakt. Chem*., **23** (1881), 147.

[9]. *Vogel's Text Book of practical organic chemistry, 5th Edn*., ELBS and Longman, UK**,** 1989, P.1034.

[10]. K.M. Lokanatha Rai, C.A. Murthy, P.M. Radhakrishna, An improved method for the synthesis of cyclopropyl ketoesters, *Synth. Commun*., **20** (1990), 1273.

[11]. C. Ananthamurthy and Y.B. Basavaraju, Synthesis of podophyllotoxin and related analogues: Part X - Tetralone esters as intermediates for the synthesis of analogues of β-apopicropodophyllotoxin, *Indian Journal of Chemistry*, **388** (1999), 137-140.

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