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Synthesis of 4-Aryl-3-ethoxycarbonyl-1-oxo-1,2,3,4-tetrahydronaphthalene: An Important Frame Work in Lignan Family

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Abstract

4,4-diaryl-3-ethoxycarbonyl-3-butenoic acid (2a-d, Scheme 1) has been synthesized by Stobbe condensation of substituted benzophenones 1a-d with t-potassium butoxide and diethyl succinate. Compounds 2a-d on reduction with sodium amalgum furnished 4,4-diaryl-3-ethoxycarbonyl-3-butanoic acid 3a-d, which on intramolecular cyclization with polyphosphoric acid gave target compounds 4-aryl-3-ethoxycarbonyl-1-oxo--1,2,3,4-tetrahydronaphthalene 4a-d.

Keywords: *Lignans,* tetralins, tetralones *Benzophenone, 4-Aryl-3-ethoxycarbonyl-1-oxo-1,2,3,4-tetrahydronaphthalene*

Introduction

Lignans are derived biosynthetically from the phenylpropanoid pathway, which are ubiquitously distributed among plant species and play an important role in plant defence[1,2]. Aryltetralin lignans, which are considered as more restricted taxonomic distributor, are found in high amount in the plant of the genus Podophyllum. Among them Podophyllotoxin is the most important due to its biological activity like blocking mitosis[3,4] and it is used as starting compound in the semi-synthetic chemotherapeutic drugs such as etoposide, teniposide and etopophos[5].

The 1,2-dihydronaphthalene carbon skeleton is found in many lignans, which are distributed in plants. Although many methods have been devised to prepare such lignans[6-15]a recently reported method for the preparation of 1-aryl-1,2-dihydronaphthalene is exploited to prepare mangnoshinin, a naturally occurring lignan and cyclogalgravin (3,4-dehydrogalbulin), a derivative of natural lignan[15]. Tokoure et al.[16] described a method for photochemical conversion of 2,3-dibenzylidene succinate precursor to an optically active dihydronaphthalene and subsequent transformation of the dihydronaphthalene into the optically pure lignan (+)-lyoniresinol dimethyl ether. Considerable work has been devoted to the synthesis of lignans

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and their derivatives due to their wide-ranging pharmacological properties[6,17,18-20], their greater number of structural possibilities[21] and the chemical approaches to their synthesis[18,22].

The most important applications of lignans are as antitumor[23-27], antineoplastic, and antiviral[28] agents. In addition, a vast amount of research effort has been done to increase the efficacy of the drug against resistant organisms, such as Chaerophyllum aureum[29] and Pseudomonas aeruginosa[30]. Based on these, lignans have been investigated as antifungal[31] and antibacterial agents[30]. They also function as hormone controlling cell growth and other types of compounds of biological interest [32-35].

Formation of 1-oxo-2-methylene-4-phenyl-1,2,3,4-tetrahydronaphthalenes and 1-oxo-4-phenyl-1,2,3,4-tetrahydronaphthalenes skeleton commonly known as tetralins and tetralones respectively, a framework in the lignan family have been extensively studied by Garzino et al.[36]. For instance, 4-aryl-2-methylene tetralone analogues were synthesized based on new $SnCl_4$-induced rearrangement of 2,5-diaryl-2,3-dihydrofuran. In view of these significances, in this article we report the synthesis of some 4-aryl-3-ethoxycarbonyl-1-oxo-1,2,3,4-tetrahydronaphthalene derivatives.

Experimental

Scheme 1 shows the route of synthesis. Melting points were determined in open glass capillaries on the Buchi oil-bath melting point apparatus and are uncorrected. Infrared absorption spectra were recorded on a FT-IR Shimadzu 8300 spectrometer, ^{1}H NMR spectra on a Hitachi R-600 (60MHz) NMR spectrophotometer using $CDCl_3$ as solvent with TMS as an internal standard.

A typical procedure for 4-(4-methoxyphenyl)-4-(4-methoxyphenyl)-3-ethoxycarbonyl-3-butenoic acid (2a): To freshly prepared potassium t-butoxide, 1.56 g of K and 60 ml of t-butanol, was added quickly under nitrogen and refluxed for 1h. To this mixture freshly distilled diethylsuccinate (6.6 ml, 0.04 mol) 4, 4'-dimethoxy benzophenone (10.89 g, 0.045 mol) was added at once and refluxed for 30 h. The excess of t-butanol was removed by distillation under reduced pressure and the residue was acidified with 5 N HCl . The precipitate 2a was extracted into 10% $NaHCO_3$ solution and washed with diethyl ether (3 × 20 ml). Finally on acidification gave dl isomers of 2a as pasty yellow semisolid.

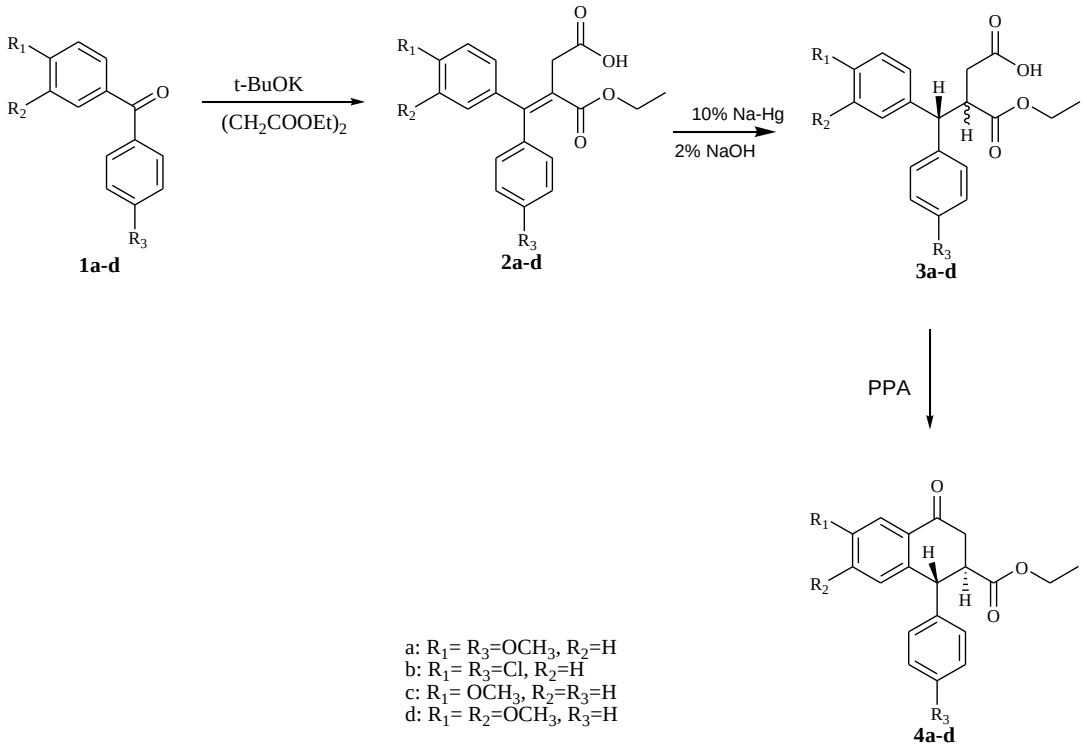
2a: IR (Neat): 1615 (C=C conjugated), 1700 cm^{-1} (C=O of acid), 1725 cm^{-1} (C=O of ester), 3100-3200 cm^{-1} (OH of carboxylic acid).

^{1}H NMR ($CDCl_3$): δ 1.02 (t, J=6Hz, 3H, CH_3), 3.3 (s, 2H, CH_2-C=O), 3.75 (s, 6H, 2OCH_3), 3.9 (q, J=7Hz, 2H, OCH_2), 6.8-7.5 (m, 8H, Ar-H), 10.5 (bs, 1H, COOH).

MASS (m/z, % abundance): 370 (M+, 15.7), 326 (M±44, 33.5), 325 (29.6); 324 (M±46, 82.2), 252 (100), 352 (17.1).

Anal. Calcd. For. $C_{21}H_{22}O_6$: C, 68.10; H, 5.94; Found: C, 68.12; H, 5.96%.

4-(4-Chlorophenyl)-4-(4-chlorophenyl)-3-ethoxycarbonyl-3-butenoic acid (2b): Obtained from 4,4-1dichloro benzophenone (11.2g, 0.04mol), diethylsuccinate (6.96ml, 0.04mol) potassium in 60ml t-butanol as a pale yellow solid in 75% yield.



scheme 1

M.P. 120-122°C.

IR (Nujol): 1620 (C=C conjugated), 1700 cm^{-1} (C=O of acid), 1730 cm^{-1} (C=O of ester), 3250-3360 cm^{-1} (OH of carboxylic acid).

^{1}H NMR (CDCl3): δ 1.04 (t, J=6Hz, 3H, CH_3), 3.25 (s, 2H, CH_2-C=O), 3.9 (q, J=7Hz 2H, OCH_2), 6.9-7.6 (m, 8H, Ar-H), 10.5 (bs, 1H, COOH)

MASS (m/z, % abundance): 379 (M+, 14.5), 335 (M±44, 35.2), 334 (30.4), 333 (M±46, 84.2), 261 (100), 361 (15.1).

Anal. Calcd. for. $C_{19}H_{16}Cl_2O_4$: C, 60.17; H, 4.22; Cl, 18.71 Found: C, 60.2; H, 4.20; Cl, 18.68%.

4-(4-Methoxyphenyl)-4-phenyl-3-ethoxycarbonyl-3-butenoic acid (2c): Obtained from 4-methoxy benzophenone and diethyl succinate as yellow pasty mass in 68% yield.

IR (Neat): 1615 (C=C conjugate), 1705 cm^{-1} (C=O of acid), 1710 cm^{-1} (C=O of ester), 3180-3290 cm^{-1} (OH of carboxylic acid).

^{1}H NMR ($CDCl_3$): δ 1.05 (t, J=6Hz, 3H, CH_3), 3.3 (s, 2H, CH_2-C=O), 3.85 (s, 3H, OCH_3), 3.9 (q, J=7Hz, 2H, OCH_2), 6.9-7.6 (m, 9H, Ar-H), 10.8 5 (bs, 1H, COOH).

MASS (m/z, % abundance): 340 (M+, 16.2), 296 (M±44, 38.2), 295 (35.6) 294 (M±46, 86.2), 222 (100), 322 (15.5)

Anal. Calcd. for. $C_{20}H_{20}O_5$: C, 68.10; H, 5.94; Found: C, 68.12; H, 5.93%.

4-(3,4-dimethoxyphenyl)-4-phenyl-3-ethoxycarbonyl-3-butenoic acid (2d): Obtained from 4,4-dimethoxy benzophenone (6 gm ,0.028 mol) , diethyl succinate (4.5 ml ,0.028 mol) ,K (0.936 gm , 0.028 mol) in 115 ml of t-butanol as yellow pasty mass in 77% yield.

IR (Neat): 1625 cm^{-1} (C=C conjugated), 1705 cm^{-1} (C=O of acid), 1710 cm^{-1} (C=O of ester), 3222-3330 cm^{-1} (OH of carboxylic acid).

^{1}H NMR ($CDCl_3$): δ 1.02 (t, J=6Hz, 3H, CH_3), 3.3 (s, 2H, CH_2-C=O), 3.85 (s, 6H, $2OCH_3$) 3.9 (q, J=7Hz, 2H, OCH_2), 6.8-7.5 (m, 8H, Ar- H), 10.9 (bs, 1H, COOH)

MASS (m/z, % abundance): 370 (M+, 14.2), 326 (M±44, 33.2), 325 (29.6); 324 (M±46, 86.1), 252 (100), 352 (16.9).

Anal. Calcd. for. $C_{21}H_{22}O_6$: C, 68.10; H, 5.94; Found: C, 68.9; H, 5.95%.

A typical procedure for 4-(4-methoxy phenyl)-4-(4-methoxyphenyl)-3-ethoxycarbonyl butanoic acid (3a): Powdered 10% sodium amalgam was added to cooled solution of 2a in 2% aqueous solution of sodium hydroxide. The reaction mixture was stirred and kept overnight at room temperature then filtered acidified with dilute HCl. The solid separated was filtered and recrystallized from benzene afforded pale yellow pasty mass in 70% yield.

IR (Neat): 1700 cm^{-1} (acid C=O), 1759 cm^{-1} (ester C=O), 3200-3400 cm^{-1} (OH of acid)

^{1}H NMR ($CDCl_3$): δ 1.2 (t, J=6Hz, 3H, ester), 2.7 (d, 2H, C2-H), 3.9 (s, 6H, $2OCH_3$), 3.2-3.6 (m, 2H, C3-H, C4-H), 4.2 (q, J=7Hz, 2H, OCH_2), 6.8-7.2 (m, 8H, Ar-H), 9.1 (bs, 1H, COOH).

MASS (m/z, % abundance): 372 (M+, 2.2), 354 (M±H2O, 10.5), 353 (22.3), 328 (M±CO2, 17.5), 326 (M-C_2H_5OH, 30.5), 228 (8.3), 227(100).

Anal. Calcd. for. $C_{21}H_{24}O_6$: C, 67.73; H, 6.30; Found: C, 67.78; H, 6.20%.

4-(4-Chlorophenyl)-4-(4-chlorophenyl)-3-ethoxycarbonyl butanoic acid (3b): Obtained from 2b and 10% sodium and in 89% yield.

IR (Nujol): 1705 cm^{-1} (acid C=O) 1755 cm^{-1} (ester C=O), 3500-3300 cm^{-1} (OH of acid).

1H NMR (CDCl3): δ 1.4 (t, J=6Hz, 3H, ester), 2.8 (d, 2H, C2-H), 3.1-3.5 (m, 1H, C3-H, C4-H), 4.2 (q, J=7Hz, 2H, OCH2), 6.8-7.5 (m, 8H, Ar-H), 9.2 (bs, 1H, COOH).

MASS (m/z, % abundance): 381 (M+, 3), 363 (M±H2O, 9.8), 362 (28.7), 347 (M±CO2, 16.9), 335 (M-C2H5OH, 38.4), 237 (20.5), 236 (100)

Anal. Calcd. For C19H18Cl2O4: C, 59.86; H, 4.76; Cl, 18.60 Found: C, 60.97; H, 4.27, 18.68%.

4-(4-Methoxyphenyl)-4-phenyl-3-ethoxycarbonyl butanoic acid (3c):

IR (Nujol): 1705 cm^{-1} (acid C=O), 1755 cm^{-1} (ester C=O), 3500-3300 cm^{-1} (OH of acid).

1H NMR (CDCl3): δ 1.3 (t, J=6Hz, 3H, ester), 2.9 (d, 2H, C2-H), 3.1-3.4 (m, 2H, C3-H, C4-H), 4.25 (q, J=7Hz, 2H, OCH2), 6.8-7.2 (m, 9H, Ar-H), 9.25 (bs, 1H, COOH)

MASS (m/z, % abundance): 342 (M+, 2.9), 324 (M±H2O, 8.9), 323 (30.7), 298 (M±CO2, 16.8), 296 (M-C2H5OH, 40), 210 (8.6%); 209 (100).

Anal. Calcd. for. C20H22O5: C, 70.16; H, 6.48; Found: C, 70.20; H, 6.55%.

4-(3,4-Dimethoxyphenyl)-4-phenyl-3-ethoxycarbonyl butanoic acid (3d):

IR (Nujol): 1705 cm^{-1} (acid C=O), 1755 cm^{-1} (ester C=O), 3400-3200 cm^{-1} (OH of acid)

^{1}H NMR (CDCl3): δ 1.3 (t, J=6Hz, 3H, ester), 2.9 (d, 2H, C2-H), 3.2-3.6 (m, 2H, C3-H, C4-H), 3.7(s, 6H, 2OCH3,), 4.35 (q, J=7Hz, 2H, OCH2), 6.6-7.1(m, 8H, Ar-H), 9.25 (bs, 1H, COOH) MASS (m/z, % abundance): 372 (M+, 1.9), 354 (M+-H2O, 8.9), 353 (25), 328 (M+-CO2, 14.5), 326(M-C2H5OH, 37.8), 228(18.9), 227(100).

Anal. Calcd. for. C21H24O6: C, 67.73; H, 6.30; Found: C, 67.80; H, 6.40%.

A typical procedure for 4-(4-methoxyphenyl)-3-ethoxycarbonyl-7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene(4a): Compound 3a (0.004 mol) was added to freshly prepared PPA at 90-100 and stirred vigorously for 2hrs, the pale yellow coloured reaction mixture was poured into crushed ice, the precipitate solid filtered and washed with water . the dried solid was dissolved in ether and washed with sodium bicarbonate ,water and dried over sodium sulphate .the pasty residue obtained after evaporation of solvent was recrystallized from ethanol give 4a as pale yellow solid in 64% yield.

M.P. 148-150˚C

IR (Nujol): 1675 (ring C=O), 1715 cm-1 (ester C=O)

1H NMR (CDCl3): 1.07 (t, J=6Hz, 3H, ester CH3), 2.7 (d, J=6Hz, 2H, C2-H), 3.2-3.7 (m, 1H, C3-H), 3.8 (s, 6H, 2OCH3), 4.2 (q, J=7Hz, 2H, OCH2) 4.4 (d, J=6Hz, 1H, C4-H), 7.2-7.4 (m, 7H, Ar-H)

MASS (m/z, % abundance): 354 (M+, 8.9), 326 (M-C2H4, 65.4), 284 (M±CO2, 22.5), 283 (100), 282 (17.8), 252 (31.5), 174 (9.8).

Anal. Calcd. for C21H22O5: C, 71.18; H, 6.21; Found: C, 71.20; H, 6.19%.

4-(4-Chlorophenyl)-3-ethoxycarbonyl-7-chloro-1-oxo-1,2,3,4-tetrahydronaphthalene (4b): Obtained from using PPA as white solid in 74% yield.

M.P. 168-170˚C

IR (Nujol): 1680 (ring C=O), 1710 cm-1 (ester C=O).

1H NMR (CDCl3): 1.05 (t, J=6Hz, 3H, ester CH3), 2.6 (d, J=6Hz, 2H, C2-H), 3.4-3.6 (m, 1H, C3-H), 4.15 (q, J=6Hz, 2H, OCH2), 4.5 (d, J=6Hz, 1H, C4-H), 7.2-7.4 (m, 7H, Ar-H)

MASS (m/z, % abundance): 363 (M+, 9.9), 334 (M-C2H4, 60.4), 290 (M±CO2, 21.8), 289 (100), 288 (15.8), 260 (29.5), 175 (8.6)

Anal. Calcd. for C19H16Cl2O3: C, 62.82; H, 4.40; Found: C, 62.80; H, 4.38%.

4-Phenyl-3-ethoxycarbonyl-7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene(4c): Obtained from 3c using PPA as yellow solid in 67% yield.

M.P. 135-137˚C

IR (Nujol): 1678 (ring C=O) 1713 cm-1 (ester C=O).

1H NMR(CDCl3): 1.03 (t, J=6Hz, 3H, ester CH3), 2.5 (d, J=6Hz, 2H, C2-H), 3.79 (s, 3H, OCH3) 3.2-3.6 (m, 1H, C3-H), 4.2 (q, J=7Hz, 2H, OCH2) 4.5 (d, J=6Hz, 1H, C4-H), 6.89-7.8 (m, 8H, Ar-H)

MASS (m/z, % abundance): 324 (M+, 10.4), 296 (M-C2H4, 65.4), 252 (M±CO2, 25.7), 228 (100), 227 (17.2), 229 (34.2), 150 (10.4)

Anal. Calcd. for C20H20O4: C, 74.07; H, 6.17; Found: C, 74.10; H, 6.15%.

4-Phenyl-3-ethoxycarbonyl-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (4d): Obtained from3d using PPA as white solid in 62% yield.

M.P. 112-114˚C

IR (Nujol): 1675 (ring C=O), 1720 cm-1 (ester C=O)

1H NMR (CDCl3): 1.1 (t, J=6Hz, 3H, ester CH3), 2.8 (d, J=6Hz, 2H, C2-H), 3.7(s, 6H, 2OCH3) 3.2-3.6 (m, 1H, C3-H), 4.25 (q, J=7Hz, 2H, OCH2), 4.6 (d, J=6Hz, 1H, C4-H), 7.2-7.4 (m, 7H, Ar-H)

MASS (m/z, % abundance): 354 (M+, 8.9), 326 (M-C2H4, 65.9), 284 (M±CO2, 24.5), 283 (100), 282 (18.2), 252 (31.9), 204 (19.9)

Anal. Calcd. for C21H22O5: C, 71.18; H, 6.21; Found: C, 71.22; H, 6.20%

Results and Discussion

The strategy in the synthesis of desired compounds is as follows. Stobbe condensation of benzophenones 1c-d with diethyl succinate in potassium t-butaoxide as base, furnished a mixture of E- and Z-isomeric corresponding 4,4-diaryl-3-ethoxycarbonyl-3- butenoic acid 2c-d due to their asymmetry structure but the benzophenone 1a-b gave dl isomers 4,4-diaryl-3-ethoxycarbonyl-3- butenoic acid 2a-b due to their symmetry structure. The (E-) and (Z-) isomeric hemiesters were separated by fractional crystallization. Compounds 2a-d on reduction with sodium amalgam furnished 4,4-diaryl-3-ethoxycarbonyl-3-butanoic acid 3a-d as major product and 4,4-diaryl-3-carboxy butanoic acid as minor due to alkaline hydrolysis of 4,4-diaryl-3-ethoxycarbonyl-3-butanoic acid during the reaction. The two products were separated by column chromatography over silica gel using choloroform: acetone (7:2) as eluent. Intra molecular cyclization of 3a-d with poly phosphoric acid (PPA) furnished the target compounds 4-Aryl-3-ethoxycarbonyl-1-oxo-1,2,3,4-tetrahydronaphthalene 4a-d as depicted in scheme 1.

The structures of all compounds were supported by IR, ^{1}HNMR data and microanalysis. The IR absorption of compound 2a showed bands at 3100-3200, 1725, 1700 and 1615 cm^{-1} assigned to carboxylic OH group, α,β-unsaturated carbonyl group, acid carboxyl group and conjugated C=C respectively. ^{1}HNMR spectrum of 2a showed a triplet centered at δ 1.02 with coupling constant J=6 Hz assigned to methylene protons of ester, two singlets at δ 3.3 and 3.75 assigned to two protons of methylene group adjacent to carbonyl group and two methoxy protons respectively, a quartet centered at δ 3.9 with coupling constant J=6 Hz assigned to methylene proton of ester group and a multiplet in the range δ 6.8 to 7.5 assigned to aromatic protons. In addition it showed a broad singlet centered at δ 10.5 due to the carboxylic proton. In the mass spectra of compounds 2a-d the molecular ion peaks were found at their respectively mass numbers m/z carboxylic acid respectively 370, 379, 340 and 370. Nevertheless compound 2a-d on reduction with sodium amalgam in presence of sodium hydroxide furnished 4,4-diaryl-3-ethoxycarbonyl-3-butanoic acid 3a-d. Compounds 3a-d on intramolecular cyclization with poly phosphoric acid in gave 2-ethoxy carbonyl-4-oxo-1-aryl-1,2,3,4-tetrahydro-naphthalene-2-ethanoic acid 4a-d as depicted in Scheme 1.

The IR absorption of compound 3a showed bands at 1700, 1759, 3200-3400 cm^{-1} assigned to acid carbonyl, ester carbonyl and hydroxyl group of carboxylic acid respectively. ^{1}H NMR spectrum of 3a indicates the presence of a triplet centered at δ 1.2 with coupling constant J=6 Hz assigned to methyl protons of ester, a doublet at δ 2.7 due to C2-H protons, a singlet at δ 3.9 due to two methoxy protons, a quartet centred at δ 4.2 due to methylene protons of ester group, two multiplet in the range δ 3.2-3.6 and 6.8-7.2 assigned to C3-H, C4-H and aromatic protons respectively. In addition it showed a broad singlet centered at δ 9.1 due to the carboxylic proton. In mass spectra of the compounds 3a-d the molecular ion peaks were found at their respective mass numbers m/z 372, 381, 342, and 372 respectively. The IR spectrum of compound 4a showed absorptions at 1675 and 1715 cm^{-1} assigned to six membered cyclic keto group and ester carbonyl group. The 1H NMR spectrum of the compound 4a showed triplet centered at δ 1.07 with coupling constant J=6Hz assigned to ester methyl protons, a doublet centered at δ 2.7 with J=6 Hz assigned to C2-H, a multiplet in the range δ 3.2-3.7 assigned to C3-H, a singlet at δ 3.8 due to six methoxy protons, one quartet centered at δ 4.2 with coupling constant J=7Hz due to methylene protons of ester group. In addition it showed doublet at δ 4.4 with J=6 Hz assigned to the C4-H and a multiplet in the range δ 7.2-7.4 due to aromatic protons. The large coupling constant indicated that C3 proton and C4 proton in 4a were diaxial to each other. Hence C3 ethoxycarboxyl and C4 methoxy phenyl group should be in trans position to each other, a configuration being thermodynamically more stable. The mass spectrum of 4a-d showed the molecular ion peak with respective mass numbers m/z 354, 363, 324, and 354 respectively.

Conclusion

The arylnaphthalene and arylnaphthol derivatives 3a-f and 4a-f which were prepared and these are very essential compounds for the study of antimitotic and viral reverse transcriptase inhibitory activity.

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