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Note

Synthesis of new ellagic acid derivatives

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Ellagic acid has been isolated from *Punica granatum*. A series of hexahydroxydiphenyl derivatives of ellagic acid have been synthesized and characterized by spectroscopic analysis.

Keywords: Ellagic acid, *Punica granatum*, ellagitannins, hexahydroxydiphenic acid

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Ellagic acid **1** is a naturally occurring phytonutrient. It is a phenolic lactone and widely distributed in woody dicotyledonous plants. It is present in plants in the form of hydrolyzable tannins called ellagitannins. Ellagitannins are esters of glucose with hexahydroxydiphenic acid; when hydrolyzed, they yield ellagic acid[1] **1**.

Ellagic acid **1** has been shown to possess numerous anticarcinogenic and antimutagenic properties towards a variety of different carcinogens, including nitrosamines, azoxymethane, mycotoxins and polycyclic aromatic hydrocarbons[2-7]. Different synthetic derivatives of ellagic acid **1** have been reported as potent anti HIV agents[8,9], as DNA gyrase inhibitor[10], as inhibitors of squalene epoxidase[11] and as inhibitors of protein kinase C[12]. Attempt has been made to synthesize new hexahydroxydiphenyl derivatives of ellagic acid **1**.

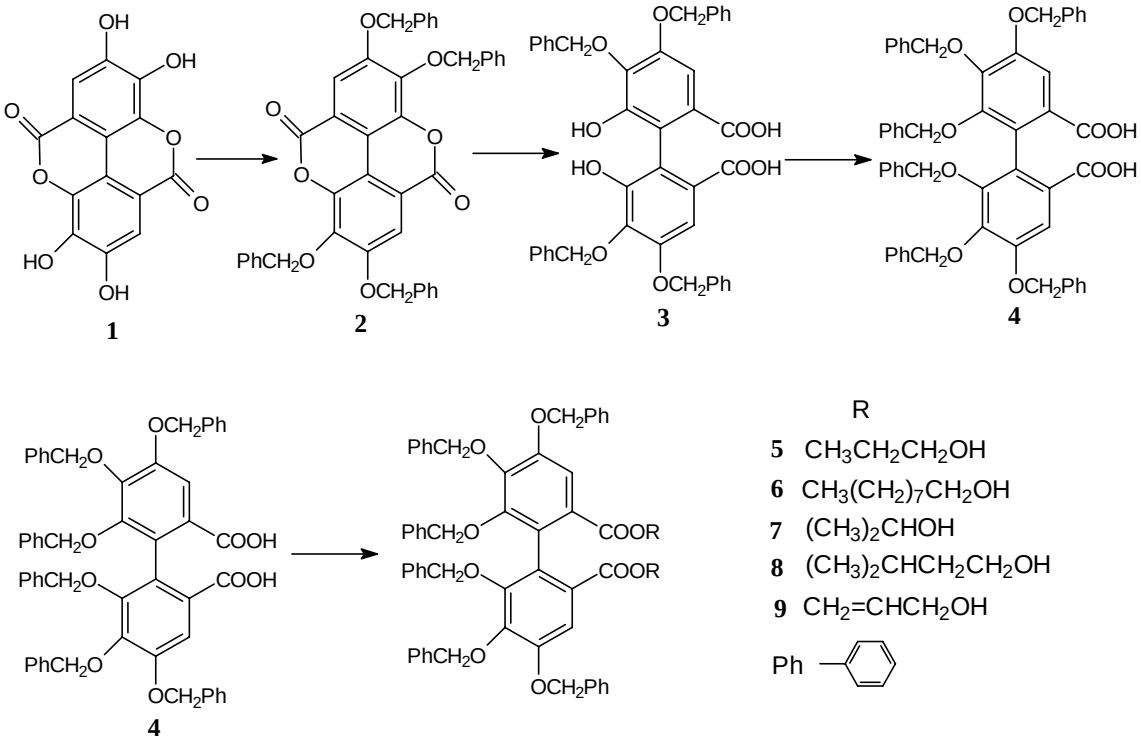
Ellagic acid **1** was isolated from *Punica granatum* Linn. (Pomegranate, Fam: Punicacea). The physical, chemical and spectral data of ellagic acid **1** were identical with those described in the literature[13-15]. The biphenyl derivatives **2-9** were synthesized from ellagic acid **1**. Ellagic acid **1** was benzylated with benzyl chloride and K_2CO_3, KI in acetophenone under reflux to give tetrabenzyl ellagic acid[9,12,16] **2**, yield 35%. Tetrabenzyl ellagic acid **2** was hydrolyzed with KOH-50% EtOH to give 2,2'-dihyroxy-3,3',4,4'-tetrakis(benzyloxy)-1, 1'-biphenyl-6, 6'-dicarboxylic acid **3** in 90% yield[12]. Benzylation of **3** with benzyl bromide and K_2CO_3 in dry acetone followed by hydrolysis with 2% NaOH gave 2,2',3,3',4,4'-hexakis(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylic acid **4** with 60% yield[12]. The physical and spectral data of compounds **2**, **3** and **4** were identical with those described in the literature[12].

Hexabenzyl diphenyl dicarboxylic acid **4** was converted to more reactive compound as acid chloride with thionyl chloride[11], which was further esterified with propanol, nonanol, isopropanol, isopentanol, allyl alcohol to yield the compounds *n*-dipropyl 2,2',3,3',4,4'-hexakis(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate **5**, *n*-dinonyl 2,2',3,3',4,4'-hexakis-(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate **6**, diisopropyl 2,2',3,3',4,4'-hexakis(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate **7**, diisopentyl 2,2',3,3',4,4'-hexakis(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate **8** and diallyl 2,2',3,3',4,4'-hexakis (benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate **9**, respectively (**Scheme I**). Benzene was found to be a suitable solvent for the esterification with respect to the yield. Mixture of mono- and diester was obtained, in which diester was predominant and purified by column chromatography. All the diesters were obtained in 50-75 % yield.

Experimental Section

Synthesis of esters of hexabenzyl diphenyl dicarboxylic acid. Hexabenzyl diphenyl dicarboxylic acid **4** (2 g) was refluxed in dry benzene (20 mL) with thionyl chloride (1 mL) for 2 hr using dimethyl formamide (0.2 mL) as a catalyst. After 2 hr, suspension of acid chloride was obtained in benzene. Benzene and unreacted thionyl chloride were distilled off under reduced pressure to get acid chloride. Acid chloride (1 mole) was resuspended in benzene and refluxed with respective alcohol (4 moles) in presence of pyridine (0.1 mL) for 2 hr. The reaction was monitored by TLC using *n*-hexane-acetone (6:4) as solvent system. After completion of reaction, the mixture was concentrated to syrup, which was chromatographed over silica gel. Elution with *n*-hexane-acetone (9:1) yielded the respective ester.

***n*-Dipropyl 2,2',3,3',4,4'-hexakis(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate 5**: Yield 75 %,



Scheme I

colourless syrup; IR ($CHCl_3$): 3019.1, 2969.3, 1717.3, 1592.5, 1454.5, 1326.9, 1215.9, 753.3 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 7.447-6.869 (32H, m, in total Ar-H, 5-H, 5'-H), 5.192-4.707 (12H, m, OCH_2Ph), 3.978-3.762 (4H, t, OCH_2), 1.555-1.152 (4H, m, CH_2), 0.839-0.607 (6H, t, CH_3); MS: m/z 964.42 (M^+).

***n*-Dinonyl 2,2',3,3',4,4'-hexakis(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate 6**: Yield 65%, colourless syrup; IR ($CHCl_3$): 3017.1, 2928.5, 1715.5, 1592.3, 1454.5, 1327.9, 1215.9, 756.5 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 7.378-6.877 (32H, m, in total Ar-H, 5-H, 5'-H), 5.188-4.711 (12H, m, OCH_2Ph), 3.913 (4H, m, OCH_2), 1.193-0.843 (34H, m, $(CH_2)_7CH_3$, a typical long chain *n*-alkyl pattern); MS: m/z 1132.22 (M^+).

Diisopropyl 2,2',3,3',4,4'-hexakis(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate 7: Yield 50%, light yellow waxy solid; IR ($CHCl_3$): 3019.8, 1697.6, 1592.6, 1412.6, 1320.9, 1215.8, 754.7 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 7.468-6.865 (32H, m, in total Ar-H, 5-H, 5'-H), 5.216-4.540 (14H, m, OCH_2Ph, OCH), 0.945 (12H, d, J = 6.12 Hz, CH_3); MS: m/z 964.20 (M^+).

Diisopentyl 2,2',3,3',4,4'-hexakis(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate 8: Yield 60%, colourless syrup; IR ($CHCl_3$): 3019.6, 2960.9, 1714.0, 1592.2, 1454.2, 1325.6, 1216.0, 749.0 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 7.456-6.869 (32H, m, in total Ar-H, 5-H, 5'-H), 5.485-4.512 (12H, m, OCH_2Ph), 4.060-3.766 (4H, m, OCH_2), 1.250-1.059 (6H, m, CH_2CH), 0.855 (12H, d, J = 5.1 Hz, CH_3); MS: m/z 1020.26 (M^+).

Diallyl 2,2',3,3',4,4'-hexakis(benzyloxy)-1,1'-biphenyl-6,6'-dicarboxylate 9: Yield 50%, colourless syrup; IR ($CHCl_3$): 3019.1, 1721.6, 1592.3, 1454.0, 1325.0, 1215.9, 759.0 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 7.407-6.877 (32H, m, in total Ar-H, 5-H, 5'-H), 5.587-5.355(2H, m, CH), 5.171-4.719 (16H, m, OCH_2Ph, CH_2), 4.451 (4H, d, J = 5.16 Hz, OCH_2); MS: m/z 960.17 (M^+).

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