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Synthesis of enterolactone and enterodiol precursors as potential inhibitors of human estrogen synthetase (aromatase)

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Abstract

A series of variably substituted derivatives of lignan lactones and diols were prepared using tandem conjugate addition reaction as a key step. These theoretical precursors of the mammalian lignans enterolactone **1** and enterodiol **3** are moderate or weak inhibitors of human aromatase activity.

Keywords: Lignan; Lactones; Michael reactions; Synthesis

1. Introduction

Lignans have attracted much interest over the years on account of their widespread occurrence in various plant species [1], and their broad range of biologic activity [2]. Since the detection of the mammalian lignans enterolactone **1** and enterodiol **3** in human urine [3–6], there has been much discussion about their biologic function. Especially interesting is their suggested role as antiestrogens and anticarcinogens among other possible biologic activities [7]. Enterolactone **1**, alone or together with enterodiol **3**, has more recently been detected in human plasma and other biologic fluids as well [8–10]. Human diet has been shown to contain plant lignans, which act as precursors for the mammalian lignans [8,11,12]. The enterolignans are produced by the action of intestinal microflora on the precursors (i.e. matairesinol **2** and secoisolariciresinol **4**) in dietary fiber. The precursor lignans have also been detected in human urine and plasma [13,14].

Earlier studies have shown that some isoflavonoid phytoestrogens inhibit human estrogen synthetase (aromatase) [15,16], but no research data have, to our knowledge, appeared concerning inhibition of human aromatase by mammalian lignans. Using human placental microsomes, Adlercreutz et al. [17] first reported that these lignans were competitive inhibitors of aromatase, and that enterolactone **1** has the same effect on a human choriocarcinoma cell line JEG-3. Later the activity was also observed in whole cells derived from primary cultures of human tissue [18]. In addition to the mammalian lignans, enterolactone **1** and enterodiol **3**, several of their theoretical precursors were studied. Similar intermediates have been identified in primate urine, suggesting that they are true physiological intermediates [6].

In this paper we report the synthesis of these theoretical precursors, four lignan lactones, 3,3′-didemethoxymatairesinol (DDMM) **5**, 3-demethoxymatairesinol **6**, 3-demethoxy-3′-*O*-demethylmatairesinol (DMDM) **7**, and 4,4′-dihydroxyenterolactone **8**, and three lignan diols, 3′-demethoxysecoisolariciresinol (DMSI) **9**, 3′-*O*-demethylsecoisolariciresinol (ODSI) **10**, and 3,3′-*O*,*O*′-didemethyl-secoisolariciresinol (DDSI) **11**. Lactones **5**-**7** and diols **9**-**11** are all novel compounds.

2. Experimental

All experiments were monitored by thin layer chromatography using aluminum based, precoated silica gel sheets (Merck 60 F_{254}, layer thickness 0.2 mm). Silica gel 60 (230–400 mesh, Merck) was used for flash column chromatography. Melting points were determined on an Electrothermal melting point apparatus in an open capillary tube and are uncorrected. UV spectra were recorded on Shi-

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madzu UV-200 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded 200 MHz Varian GEMINI spectrometer in acetone-d_6 and chemical shifts are relative to tetramethylsilane (TMS) as an internal standard. EIMS and HRMS were obtained using JEOL JMS-SX102 spectrometer. CH_2Cl_2 was distilled, and THF was freshly distilled from sodium benzophenone ketyl. All commercially available chemicals were used as supplied by the manufacturers.

2.1. General procedure for the preparation of lactones: 3,3′-Didemethoxymatairesinol **5**

To a stirred solution of **12a** (5.0 g, 12 mmol) in dry THF (30 ml) maintained under argon at −78°C was added a solution of *n*-butyllithium in hexanes (1.6 M, 12 mmol). The resulting solution was stirred for 2.5 h, and a solution of 2-butenolide (1.0 g, 12 mmol) dissolved in dry THF (4 ml) was added. The reaction mixture was stirred for a further 2.5 h at −78°C and then treated dropwise with a solution of **13a** (3.3 g, 12 mmol) and HMPA (2.1 ml, 12 mmol) in dry THF (10 ml). The reaction mixture was allowed to reach room temperature overnight, and then the reaction was quenched with water. The mixture was extracted with EtOAc, washed with water and dried over Na_2SO_4. Evaporation of the solvent left a gum, which was purified by flash column chromatography eluting with CH_2Cl_2/pentane (2:1, v/v) to give **14** as an amorphous solid.

A suspension of **14** (2.1 g, 3.0 mmol) in ethanol (150 ml) and W-2 Raney nickel (36 g) was refluxed for 3 h. The catalyst was removed by filtration and rinsed with acetone. Evaporation of the solvents left a grude product, which was purified by recrystallization from chloroform to give 0.12 g (13%) of **5**.

5: White solid from chloroform, m.p. 186–188°C; UV (EtOH) λ_{max} nm (log ϵ) 280 (3.32); ^{1}H NMR (200 MHz, d_6-acetone) δ 2.48–2.67 (4 H, m, H-7′, H-8, H-8′), 2.89 (2 H, dd, J = 3.9, 5.6 Hz, H-7), 3.86 (1 H, m, H-9′), 4.03 (1 H, dd, J = 6.9, 9.3 Hz, H-9′), 6.73–6.80 (m, 4 ArH), 6.97 (dd, J = 2.0, 6.5 Hz, 2 ArH), 7.07 (dd, J = 1.9, 6.7 Hz, 2 ArH), 8.27 (2 H, br s, O*H*); ^{13}C NMR (200 MHz, d_6-acetone) δ 34.48 (C-7), 37.87 (C-7′), 42.26 (C-8′), 47.06 (C-8), 71.50 (C-9′), 116.09 (C-3′, C-5′), 116.17 (C-3, C-5), 129.86 (C-1′), 130.40 (C-1), 130.57 (C-2′, C-6′), 131.36 (C-2, C-6), 156.87 (C-4′), 157.02 (C-4), 178.91 (C-9); HRMS *m/z* calcd for $C_{18}H_{18}O_4$ (M^+) 298.1205, found 298.1197; EIMS *m/z* 298 (M^+, 4), 164 (41), 134 (32), 133 (20), 120 (0), 108 (59), 107 (100), 95 (18), 91 (18), 85 (20), 77 (31).

6: Amorphous solid; UV (EtOH) λ_{max} nm (log ϵ) 281.5 (3.51); ^{1}H NMR (200 MHz, d_6-acetone) δ 2.51–2.64 (4 H, m, H-7′, H-8, H-8′), 2.89 (2 H, t, J = 5.5 Hz, H-7), 3.80 and 3.87 (4 H, s and m, MeO and H-9′), 4.07 (1 H, dd, J = 6.5, 7.9 Hz, H-9′), 6.57 (dd, J = 1.9, 7.9 Hz, ArH), 6.69 (d, J = 1.9 Hz, ArH), 6.73–6.82 (m, 3 ArH), 7.07 (dd, J = 1.9, 6.6 Hz, 2 ArH), 7.47 (1 H, s, O*H*), 8.29 (1 H, s, O*H*); ^{13}C NMR (200 MHz, d_6-acetone) δ 34.06 (C-7), 37.83 (C-7′), 41.78 (C-8′), 46.51 (C-8), 55.72 (CH_3O), 71.17 (C-9′), 112.50 (C-2′), 115.32 (C-5′), 115.62 (C-3, C-5), 121.49 (C-6′), 129.44 (C-1′), 130.58 (C-1), 130.91 (C-2, C-6), 145.49 (C-4′), 147.82 (C-3′), 156.49 (C-4), 178.67 (C-9); HRMS *m/z* calculated for $C_{19}H_{20}O_5$ (M^+) 328.1311, found 328.1302; EIMS *m/z* 328 (M^+, 70), 164 (43), 138 (62), 137 (92), 122 (14), 108 (20), 107 (100), 95 (15), 94 (12), 85 (15), 77 (19).

2.2. General demethylation procedure: 3-Demethoxy-3′-O-demethylmatairesinol ***7***

To a stirred solution of **6** (0.3 g, 0.9 mmol) in dry CH_2Cl_2 (9 ml) maintained under argon at −78°C was added dropwise a solution of BBr_3 in CH_2Cl_2 (1 M, 5.0 mmol). The reaction mixture was allowed to warm to room temperature during the same day, and then treated with water. The mixture was stirred for fifteen minutes, and then extracted with ether, dried over Na_2SO_4 and evaporated. The grude product was purified by flash column chromatography eluting with ethyl acetate/hexane (4:1, v/v) to afford 0.20 g (69%) of **7**.

7: Amorphous solid; UV (EtOH) λ_{max} nm (log ϵ) 283, 227 (3.48, 3.95); ^{1}H NMR (200 MHz, d_6-acetone) δ 2.41–2.69 (4 H, m, H-7′, H-8, H-8′), 2.89 (2 H, dd, J = 3.6, 5.8 Hz, H-7), 3.85 (1 H, m, H-9′), 4.03 (1 H, dd, J = 7.2, 8.8 Hz, H-9′), 6.46 (dd, J = 2.0, 8.0 Hz, ArH), 6.63 (d, J = 2.0 Hz, ArH), 6.71–6.82 (m, 3 ArH), 7.08 (dd, J = 1.7, 6.7 Hz, 2 ArH); ^{13}C NMR (200 MHz, d_6-acetone) δ 34.19 (C-7), 37.87 (C-7′), 41.95 (C-8′), 46.82 (C-8), 71.32 (C-9′), 115.84 (C-3, C-5, C-5′), 116.35 (C-2′), 120.56 (C-6′), 129.59 (C-1′), 131.12 (C-1, C-2, C-6), 144.21 (C-4′), 145.70 (C-3′), 156.74 (C-4), 178.78 (C-9); HRMS *m/z* calcd for $C_{18}H_{18}O_5$ (M^+) 314.1155, found 314.1150; EIMS *m/z* 314 (M^+, 58), 298 (25), 164 (14), 150 (20), 149 (24), 124 (15), 123 (28), 108 (17), 107 (100), 91 (9), 77 (13).

8: Amorphous solid; UV (EtOH) λ_{max} nm (log ϵ) 284 (3.56); ^{1}H NMR (200 MHz, d_6-acetone) δ 2.42–2.60 (4 H, m, H-7′, H-8, H-8′), 2.84 (2 H, dd, J = 3.4, 5.5 Hz, H-7), 3.83 (1 H, m, H-9′), 4.02 (1 H, m, H-9′), 6.45 (dd, J = 2.1, 8.0 Hz, ArH), 6.60 (dt, J = 2.0, 8.9 Hz, 2 ArH), 6.79–6.71 (m, 3 ArH), 7.65 (2 H, br s, O*H*); ^{13}C NMR (200 MHz, d_6-acetone) δ 33.90 (C-7), 37.32 (C-7′), 41.40 (C-8′), 46.25 (C-8), 70.90 (C-9′), 115.31 (C-5′), 115.39 (C-5), 115.83 (C-2′), 116.49 (C-2), 120.11 (C-6′), 121.06 (C-6), 129.98 (C-1′), 130.64 (C-1), 143.59 (C-4′), 143.81 (C-4), 145.07 (C-3, C-3′), 178.51 (C-9); HRMS *m/z* calcd for $C_{18}H_{18}O_6$ (M^+) 330.1103, found 330.1100; EIMS *m/z* 330 (M^+, 3), 207 (1), 150 (12), 149 (10), 124 (74), 123 (100), 110 (4), 105 (7), 91 (4), 85 (13), 77 (37).

2.3. General procedure for the preparation of diols: 3′-Demethoxysecoisolariciresinol ***9***

To a stirred solution of compound **19** (0.14 g, 0.4 mmol) in dry THF (10 ml) maintained under argon at room tem-

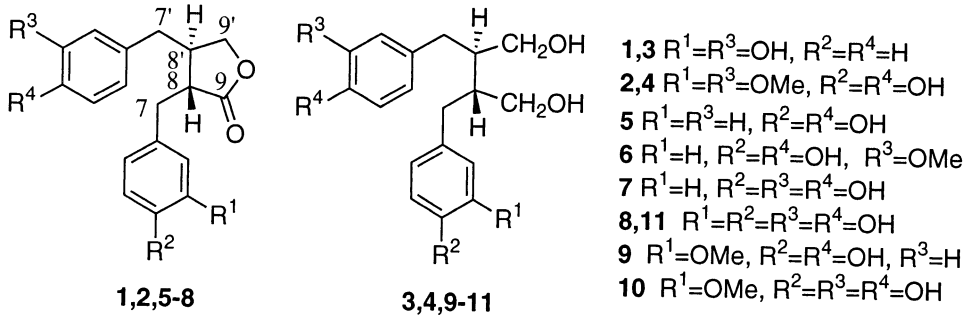


Fig. 1. The structures of compounds **1–11**.

perature was added $LiAlH_4$ (0.030 g, 0.8 mmol). The reaction mixture was stirred for 2 h, treated with 2 N H_2SO_4 and extracted with ether. Ether was washed with water and dried over $MgSO_4$. Evaporation of the solvent left a grude product, which was purified by recrystallization from $CHCl_3$ to give 0.07 g (50%) of **9**.

9: White solid from chloroform, m.p. 108–110°C; UV (EtOH) λ_{max} nm (log ϵ) 282, 227 (3.52, 4.05); ^{1}H NMR (200 MHz, d_6-acetone) δ 1.92 (2 H, m, H-8, H-8′), 2.64–2.73 (4 H, m, H-7, H-7′), 3.14 (2 H, br s, O*H*), 3.55 (2 H, m, H-9), 3.70 (2 H, dd, J = 2.0, 11.2 Hz, H-9′), 3.77 (3 H, s, OMe), 6.61 (dd, J = 1.8, 8.0 Hz, ArH), 6.72 (dt, J = 1.8, 8.1 Hz, 4 ArH), 6.99 (dd, J = 1.8, 8.4 Hz, 2 ArH); ^{13}C NMR (200 MHz, d_6-acetone) δ 35.50 (C-7′), 36.03 (C-7), 44.79 (C-8′), 44.93 (C-8), 56.16 (OCH_3), 61.06 (C-9′), 61.11 (C-9), 113.29 (C-2), 115.48 (C-5), 115.83 (C-5′, C-3′), 122.40 (C-6), 130.87 (C-6′, C-2′), 132.93 (C-1′), 133.58 (C-1), 145.44 (C-4), 148.12 (C-3), 156.29 (C-4′); HRMS *m/z* calcd for $C_{19}H_{24}O_5$ (M^+) 332.1624, found 332.1622; EIMS *m/z* 332 (M^+, 11), 314 (92), 138 (87), 137 (100), 123 (8), 108 (12), 107 (54), 77 (7).

10: Light yellow solid from chloroform, m.p. 145–147°C; UV (EtOH) λ_{max} nm (log ϵ) 284 (3.69); ^{1}H NMR (200 MHz, d_6-acetone) δ 1.93 (2 H, m, H-8, H-8′), 2.60–2.70 (4 H, m, H-7, H-7′), 3.51 (2 H, dd, J = 3.0, 11.2 Hz, H-9), 3.69 (2 H, dd, J = 3.3, 11.0 Hz, H-9′), 3.78 (3 H, s, OMe), 6.50 (dd, J = 2.1, 8.0 Hz, ArH), 6.62 (dd, J = 1.8, 7.9 Hz, ArH), 6.68–6.79 (m, 4 ArH); ^{13}C NMR (200 MHz, d_6-acetone) δ 35.71 (C-7′), 35.95 (C-7), 44.73 (C-8′), 44.88 (C-8), 56.10 (OCH_3), 61.04 (C-9′, C-9), 113.19 (C-2), 115.38 (C-2′), 115.76 (C-5′), 116.98 (C-5), 121.15 (C-6′), 122.32 (C-6), 133.54 (C-1′), 133.89 (C-1), 143.82 (C-4′), 145.37 (C-3′), 145.62 (C-4), 148.05 (C-3); HRMS *m/z* calculated for $C_{19}H_{24}O_6$ (M^+) 348.1573, found 348.1570; EIMS *m/z* 348 (M^+, 20), 330 (57), 175 (9), 138 (53), 137 (100), 124 (25), 123 (33), 77 (7).

11: Light brown solid from chloroform, m.p. 208°C; UV (EtOH) λ_{max} nm (log ϵ) 285.5 (3.76); ^{1}H NMR (200 MHz, d_6-acetone) δ 1.90 (2 H, m, H-8, H-8′), 2.59–2.63 (4 H, m, H-7, H-7′), 3.50 (2 H, m, H-9), 3.67 (2 H, dd, J = 3.2, 11.0 Hz, H-9′), 4.19 (2 H, br s, O*H*), 6.51 (dd, J = 2.0, 8.1 Hz, 2 ArH), 6.68–6.72 (m, 4 ArH), 7.72 (4 H, br s, O*H*); ^{13}C NMR (200 MHz, d_6-acetone) δ 35.67 (C-7, C-7′), 45.09 (C-8, C-8′), 60.97 (C-9, C-9′), 115.81 (C-2, C-2′), 117.01 (C-5, C-5′), 121.19 (C-6, C-6′), 133.98 (C-1, C-1′), 143.84 (C-4, C-4′), 145.63 (C-3, C-3′); HRMS *m/z* calculated for $C_{18}H_{22}O_6$ (M^+) 334.1416, found 334.1423; EIMS *m/z* 334 (M^+, 15), 316 (36), 175 (15), 161 (9), 149 (10), 124 (66), 123 (100), 91 (4), 77 (9).

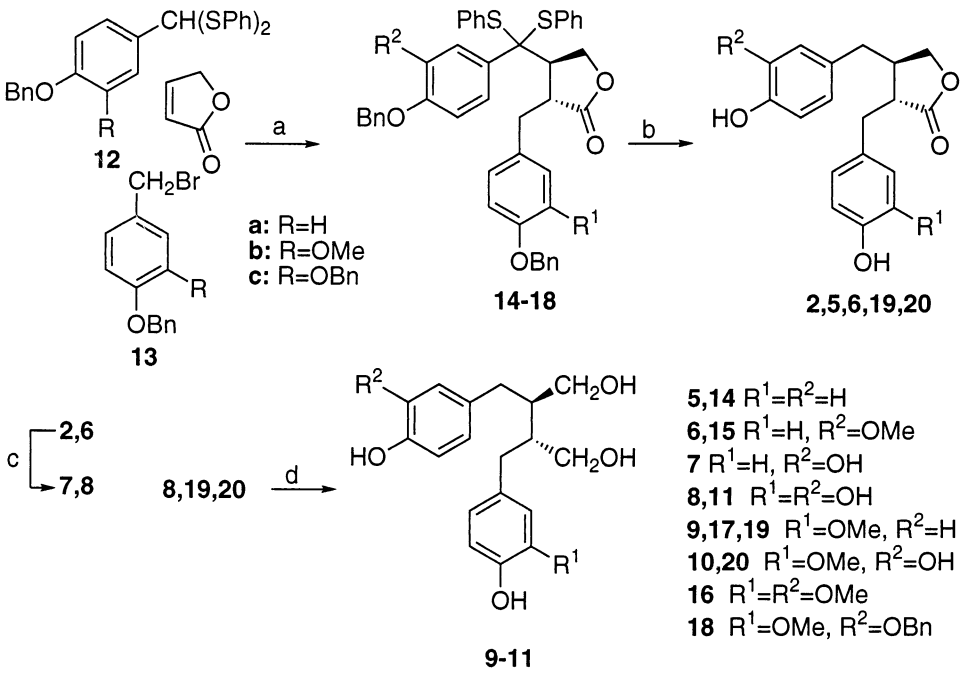
Enterolactone **1** and enterodiol **3** were prepared as a white powder from chloroform, m.p. 140–142°C (lit[27,28] 141–143°C, 142–143°C) and m.p. 175–179°C (lit.[27] 171–173°C), respectively. Spectroscopic data were in agreement with those reported in the literature [6,29].

3. Results

The *trans*-α,β-dibenzyl-γ-butyrolactone framework is generally obtained by the Michael addition of an anion derived from dithioacetal to butenolide followed by benzylation in situ [19–21]. In our synthetic study, the method was chosen for general use due to the flexibility in regard to the aromatic ring substituents. The resultant intermediate lactones can subsequently be transformed into target lactones and diols in 1 to 3 steps.

Thioacetal derivatives of dibenzylbutyrolactone **14** through **18** were prepared from the corresponding dithioacetals [22] **12a-c** by reaction with *n*-butyllithium and 2-butenolide in THF followed by in situ alkylation with the properly substituted benzyl bromides [23] **13a-b** in the presence of HMPA (Scheme 1) [21]. Simultaneous desulfurization and debenzylation were achieved by treatment with Raney nickel in refluxing ethanol to afford directly two of the desired lactones **5** and **6** [21]. To avoid polymerization caused by abundant phenolic hydroxy groups, lactones **7** and **8** were prepared by demethylation with BBr_3 in CH_2Cl_2 at −78°C from 3-demethoxymatairesinol **6** and matairesinol **2**, respectively [24]. The desired diols **9–11** were prepared by reduction with $LiAlH_4$ in dry THF from the corresponding lactones **19**, **20**, and **8**, respectively [21].

In the biologic studies enterolactone **1** and its theoretical precursors **5-8** were found moderate inhibitors whereas enterodiol **3** and its precursors **9** through **11** were weak inhibitors [17,18]. Lactones **7** and **8** were the most potent inhibitors in whole cell and placental microsome system,



Reagents: (a) *n*-butyllithium, THF, -78 °C, then 2-butenolide, THF, -78 °C, then benzyl bromide, **13a** or **13b**, HMPA, THF, -78 °C; (b) Raney nickel, ethanol, reflux; (c) BBr_3, CH_2Cl_2; (d) $LiAlH_4$, THF.

Scheme 1. The synthesis of lignan lactones **5–8** and diols **9–11**.

respectively. Compound **8** has also been found the most active inhibitor in the study of HIV-1 integrase [25]. The semisynthetic compound **8** was obtained from natural matairesinol by demethylation procedure with $AlCl_3$ and pyridine in CH_2Cl_2. The receptor binding activity of compound **5** among some other possible non-steroidal antiprogestins has been evaluated with no noticeable activity [26].

4. Discussion

In conclusion, a series of lignan lactones and diols with variably substituted aromatic rings were prepared using tandem conjugate addition reaction and subsequent modification procedures. A number of these compounds are moderate or weak inhibitors of human aromatase activity and thereby may contribute to the prevention of hormone dependent cancers [17,18]. Enterodiol **3** is a weaker aromatase inhibitor than enterolactone **1**. The observed difference in potency may result in the structural differences. Although both are diphenolic compounds, enterolactone **1** and its theoretical precursors have a lactone ring as distinct from the diols. The presence of the ring moiety may either directly increase the affinity of enterolactone **1** to aromatase enzyme, or increase lipid solubility, allowing enterolactone **1** and other lactones to enter the cell more easily and gain access to the binding site of aromatase. The ring effect on lipid solubility may also explain the difference in potency between enterolactone **1** and enterodiol **2** to be greater in whole cell than in placental microsome system, with enterodiol **3** being a far weaker inhibitor in whole cells. Another characteristic feature is the catecholic structure in aromatic rings that seems to increase the ability to inhibit aromatase activity. This would in part explain why lactones **7** and **8** are the most potent inhibitors.

Acknowledgments

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