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Steroids

α,β-Dibenzyl-γ-butyrolactone lignan alcohols: total synthesis of (±)-7′-hydroxyenterolactone, (±)-7′-hydroxymatairesinol and (±)-8-hydroxyenterolactone

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Abstract

Two *trans*-α,β-dibenzyl-γ-butyrolactone lignans carrying a hydroxyl group at the β-benzylic carbon atom and a α-hydroxy α,β-dibenzyl-γ-butyrolactone lignan were synthesized in racemic form using the tandem conjugate addition reaction to construct the basic lignan skeleton. Subsequent reaction steps involved either a catalytic reduction of the regenerated keto group to the alcohol, or a hydrogenolysis to benzylic methylene followed by lactone enolate formation and oxidation to give the α-hydroxybutyrolactones. These procedures were applied for the synthesis of 7′-hydroxyenterolactones and 7′-hydroxymatairesinols, and 8-hydroxyenterolactones, respectively. The diastereomeric mixtures of these compounds were separated either by HPLC techniques or column chromatography and the structures were elucidated using NMR spectroscopy.

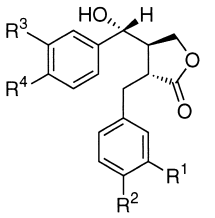
Keywords: Lignans; Lactones; Alcohols; Michael reactions; Synthesis

1. Introduction

Only a few *trans*-α,β-dibenzyl-γ-butyrolactone lignans, carrying a hydroxyl group at a benzylic position, are known in nature. These are hydroxymatairesinol **1a** and its isomer allohydroxymatairesinol **2a** [1,2], (−)-parabenzlactone **1b** [3,4], and hydroxyarctigenin **2c** [5]. The corresponding oxidation products, the oxo-compounds **3a** and **3b**, are also naturally occurring [1,6]. The derivatives of matairesinol occur frequently in various plants, especially trees, which makes them possible intermediates in lignin biosynthesis [7].

Kawamura et al. [8,9] established the main constituents causing photodiscoloration in sapwood of Western hemlock (*Tsuga heterophylla*) to be hydroxymatairesinol **1a**, allohydroxymatairesinol **2a** and oxomatairesinol **3a**. They also investigated the chemical reaction mechanisms responsible for the onset of photodiscoloration.

Hydroxymatairesinol **1a** and its isomer **2a** were isolated from the heartwood of Norway spruce (*Picea abies*) as a mixture, and their structures were elucidated by NMR spectroscopy and molecular modelling [10]. Hydroxymatairesinol has been identified from this tree as an inhibitor against the growth of the fungus *F. annosus* [11], whereas (−)-parabenzlactone is one of the insect feeding inhibitors found in *Parabenzoin trilobum* Nakai [3].



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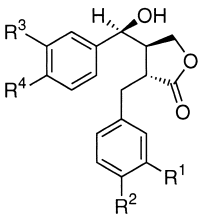

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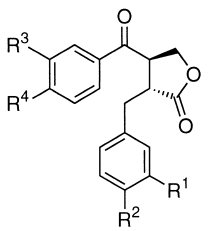

3

a) $R^1=R^3=OMe$, $R^2=R^4=OH$
b) $R^1R^2=R^3R^4=OCH_2O$
c) $R^1=R^3=R^4=OMe$, $R^2=OH$
d) $R^1=R^3=OH$, $R^2=R^4=H$

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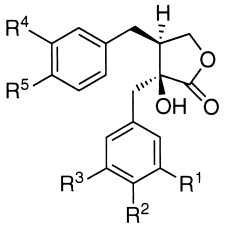
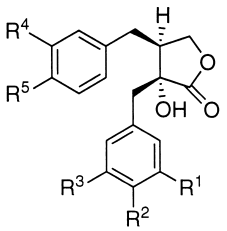
Natural lignans of the α,β-dibenzyl-γ-butyrolactone series, carrying a hydroxyl group α to the carbonyl group, are widely distributed in plants [12]. The antileukemic action of wikstromol/(+)-nortrachelogenin **4a** isolated from *Wikstroemia viridiflora* [13], and anti-HIV and cytostatic activity of trachelogenin **4d** isolated from *Ipomoea cairica* [14,15], make them the most interesting of the naturally occurring α-hydroxybutyrolactones **4a–g** and **5a–d**.



4

4 a) wikstromol (nortrachelogenin)
b) meridinol
c) benchequiol
d) trachelogenin
e) methyltrachelogenin
f) hydroxythujaplicatin trimethyl ether
g) hydroxythujaplicatin methyl ether

5 a) epiwikstromol (epinortrachelogenin)
b) epimeridinol
c) guayadequiol
d) epitrachelogenin

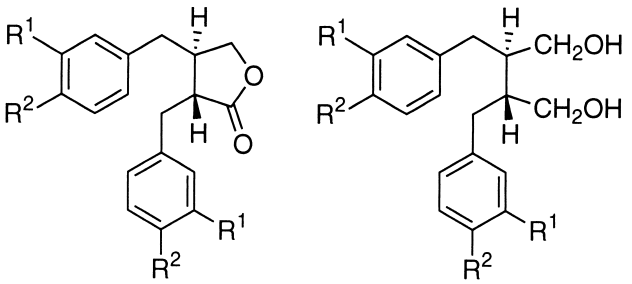


5

a) R^1=R^4=OMe, R^2=R^5=OH, R^3=H
b) R^1R^2=OCH_2O, R^3=H, R^4R^5=OCH_2O
c) R^1=R^2=OMe, R^3=H, R^4R^5=OCH_2O
d) R^1=OMe, R^2=OH, R^3=H, R^4=R^5=OMe
e) R^1=R^2=R^4=R^5=OMe, R^3=H
f) R^1=R^2=R^3=R^4=R^5=OMe
g) R^1=R^3=R^4=OMe, R^2=R^5=OH

The synthesis of a diastereomeric mixture of (±)-parabenzlactone and the partial synthesis of hydroxymatairesinol have been reported [16–20]. There are no experimental details, however, regarding the synthesis of hydroxymatairesinol or the characterization of the separated isomers. Such compounds hold considerable interest as intermediates for the synthesis of aryltetralin lignans such as (±)-cycloolivil and (±)-α-conidendrin by intramolecular cyclisation reactions [19,20]. Total syntheses of both racemic and optically active wikstromol **4a** and trachelogenin **4d** have been published [21–23].

Since the detection of the mammalian lignans enterolactone **6a** and enterodiol **7a** in human urine [24–26], there has been much discussion about their biological function. Especially interesting is their suggested role as antiestrogens and anticarcinogens among other possible biological activities [27]. Enterolactone **6a**, alone or together with enterodiol **7a**, has more recently been detected in human plasma and other biological fluids as well [28–31]. Human diet has been shown to contain plant lignans, which act as precursors for the mammalian lignans [32–34]. The enterolignans are produced by the action of intestinal microflora on the precursors (i.e. matairesinol **6b** and secoisolariciresinol **7b**) in dietary fibre. The precursor lignans have also been detected in human urine and plasma [28,35,36]. A third mammalian lignan, 7′-hydroxyenterolactone **1d** and/or **2d**, has been detected and tentatively identified in human urine, together with two isomeric hydroxymatairesinols **1a** and **2a** [37,38]. The latter are well known plant constituents and may thus be precursors of the new mammalian lignan.



6 **7**

a) R^1=OH, R^2=H
b) R^1=OMe, R^2=OH

To study the mechanism by which mammalian lignans are formed in human metabolism, various synthetic reference compounds are needed to identify the intermediates and precursors. We present here the synthesis of (±)-7′-hydroxyenterolactone, (±)-7′-hydroxymatairesinol and (±)-8-hydroxyenterolactone as a mixture of diastereomers, and the separation of these mixtures by HPLC techniques and column chromatography, and preliminary report of the NMR spectroscopic studies.

2. Experimental

All experiments were monitored by thin layer chromatography using aluminium 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 open capillary tube and are uncorrected. The HPLC experiments, both analytical and semi-preparative, were performed with a Waters (Milford, MA, USA) liquid chromatograph consisting of a Waters 600E multisolvent delivery system and a Waters 996 photodiode array detector. Components were monitored by measuring the absorption at 260 nm. The ^{1}H and ^{13}C NMR spectra were recorded on 200 MHz Varian GEMINI or 300 MHz Varian INOVA spectrometers in $CDCl_3$ or acetone-d_6 and chemical shifts are relative to internal tetramethylsilane (TMS); *J* values are given in Hz. EIMS and HRMS were obtained using JEOL JMS-SX102 spectrometer. The GC analysis was carried out using a Hewlett Packard 6890 instrument equipped with a HP-5 crosslinked 5% phenyl

methyl siloxane (15.0 m × 0.32 mm × 0.25 μm) capillary column directly connected to the ion source. THF was freshly distilled from sodium benzophenone ketyl and toluene and benzene were distilled. Other solvents were of analytical grade. The solvents used in HPLC experiments were of HPLC grade. Other commercially available chemicals were used as supplied by the manufacturers.

*2.1. (±)-trans-2-(3-Benzyloxybenzyl)-3-[3′-benzyloxy-α,α-bis(phenylthio)benzyl]butyrolactone **(12)***

Compound **12** was synthesized according to the reported method [39].

*2.2. (±)-trans-2-(3-Benzyloxybenzyl)-3-(3′-benzyloxy-α-benzoyl)butyrolactone **(14)***

A mixture of compound **12** (2.0 g, 2.88 mmol) in aqueous THF (15%, 160 ml) and yellow mercuric oxide (2.49 g, 11.5 mmol) was placed in the reaction flask equipped with an argon inlet and a magnetic stirrer bar. The mixture was stirred vigorously at room temperature while a solution of boron trifluoride etherate (2.45 g, 17.3 mmol) was added dropwise. Stirring was maintained for 4 h after which ether was added to the reaction mixture, and the precipitated salts were filtered off. The filtrate was washed with saturated Na_2CO_3 and with saturated NaCl, and dried over $MgSO_4$. Evaporation afforded a crude product, which was dissolved in chloroform, and the undissolved solids were filtered off. Evaporation of the chloroform and purification by flash column chromatography (CH_2Cl_2) gave **14** as a gum (1.07 g, 75%). Recrystallization from a mixture of chloroform and ether gave pure **14** as a white solid: mp 91°C: IR (KBr) ν_{max} 1779, 1671, 1580, 1440, 1375, 1256, 1154, 1021, 786, 739, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.98 (1 H, dd, *J* 7.5, 13.9, H-7), 3.14 (1 H, dd, *J* 5.4, 14.0, H-7), 3.53 (1 H, ddd, *J* 5.4, 7.4, 8.2, H-8), 4.05 (1 H, m, overlapping, H-8′), 4.12 (1 H, t, *J* 8.3, H-9′), 4.34 (1 H, t, *J* 8.3, H-9′), 4.89 (2 H, s, C*H*$_2$), 5.05 (2 H, s, C*H*$_2$), 6.68–6.80 (m, 3 ArH), 7.08–7.42 (m, 15 ArH); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 34.96, 44.35, 47.07, 67.94, 69.67, 70.14, 113.56, 113.61, 115.51, 120.86, 121.13, 121.79, 127.33, 127.45, 127.86, 128.18, 128.47, 128.62, 129.82, 136.15, 136.71, 138.48, 158.91, 159.04, 176.91, 196.24; HRMS *m/z* calcd for $C_{32}H_{28}O_5$ (M^+) 492.1937, found 492.1935; EIMS *m/z* 492 (M^+, 28%), 401 (8), 281 (4), 211 (3), 181 (7), 106 (6), 91 (100), 77 (5).

2.3. (8R,8′R*,7′R*)-(±)-7′-Hydroxyenterolactone **(1d)** and (8R*,8′R*,7′S*)-(±)-7′-Hydroxyenterolactone **(2d)***

Compound **14** (0.22 g, 0.45 mmol) was dissolved in small amounts of tetrahydrofuran (5 ml), and ethanol (50 ml) and W-2 Raney nickel (7.3 g) was added to the solution. The reaction mixture was stirred for 1 h under hydrogen atmosphere at room temperature. The catalyst was removed by filtration and rinsed with acetone. Evaporation of the solvents gave the crude product as an amorphic solid (0.10 g, 73%). Analysis of the ^1H NMR spectrum of the crude product revealed this material to contain a mixture of the two diastereoisomers **1d** and **2d** in an approximate ratio of 1.5:1. The mixture of the two isomers was separated by reversed-phase HPLC using a Merck LiChrospher 100 RP-18e column (250×10 mm i.d.), 5 μm. The mobile phase was CH_3CN/H_2O (10:90 to 50:50, gradient v/v); flow rate, 2.5–5.0 ml min^{-1}.

Isomer **1d**: ^1H NMR (acetone-d_6, 300 MHz) δ 2.68 (1 H, m, H-8′), 2.71 (1 H, dd, *J* 13.7, 5.0, H-7b), 2.99 (1 H, m, H-8), 3.02 (1 H, dd, *J* 13.7, 4.7, H-7a), 3.88 (1 H, t, *J* 8.1, H-9′b), 4.02 (1 H, dd, *J* 8.1, 7.8, H-9′a), 4.75 (1 H, d, *J* 5.7, H-7′), 6.57 (1 H, dt, *J* 7.3, 1.2, H-6), 6.67 (1 H, ddd, *J* 7.8, 1.9, 1.0, H-4), 6.69 (1 H, t, *J* 1.2, H-2), 6.76 (1 H, ddd, *J* 8.1, 2.4, 1.0, H-4′), 6.82 (1 H, dt, *J* 7.6, 1.2, H-6′), 6.91 (1 H, dd, *J* 2.0, 1.9, H-2′), 7.06 (1 H, t, *J* 8.6, H-5), 7.17 (1 H, t, *J* 7.8, H-5′); ^{13}C NMR (acetone-d_6, 300 MHz) δ 35.7 (C-7), 43.5 (C-8), 45.8 (C-8′), 68.9 (C-9′), 74.6 (C-7′), 113.9 (C-2′), 114.3 (C-4), 115.2 (C-4′), 117.5 (C-2), 118.1 (C-6′), 121.9 (C-6), 130.0 and 130.2 (C-5 or C-5′), 140.5 (C-1), 145.6 (C-1′), 158.2 and 158.4 (C-3′ or C-3), 179.3 (C-9); HRMS *m/z* calcd for $C_{18}H_{18}O_5$ (M^+) 314.1154, found 314.1149; EIMS *m/z* 314 (M^+, 71%), 296 (M-H_2O, 100), 268 (10), 207 (19), 189 (26), 147 (29), 123 (37), 107 (79), 95 (29), 85 (35), 77 (28).

Isomer **2d**: ^1H NMR (acetone-d_6, 300 MHz) δ 2.64 (1 H, qd, *J* 8.7, 4.8, H-8′), 2.76 (1 H, dd, *J* 13.7, 5.5, H-7b), 2.85 (1 H, dd, *J* 13.7, 6.5, H-7a), 2.95 (1 H, ddd, *J* 8.7, 6.5, 5.5, H-8), 3.90 (1 H, t, *J* 8.7, H-9′b), 4.21 (1 H, t, *J* 8.7, H-9′a), 4.51 (1 H, d, *J* 4.8, H-7′), 6.67 (1 H, dm, *J* 7.8, H-6), 6.70 (1 H, dm, *J* 7.8, H-4), 6.73 (1 H, dm, *J* 7.8, H-4′), 6.76 (1 H, dm, *J* 7.8, H-6′), 6.77 (1 H, m, H-2), 6.86 (1 H, t, *J* 2.0, H-2′), 7.11 (1 H, t, *J* 7.8, H-5), 7.15 (1 H, t, *J* 7.8, H-5′); ^{13}C NMR (acetone-d_6, 300 MHz) δ 35.4 (C-7), 43.4 (C-8), 47.2 (C-8′), 67.5 (C-9′), 72.8 (C-7′), 113.5 (C-2′), 114.4 (C-4), 115.1 (C-4′), 117.2 (C-6′), 117.5 (C-2), 121.4 (C-6), 130.2 (C-5 and C-5′), 140.6 (C-1), 145.9 (C-1′), 158.4 (C-3 and C-3′), 179.0 (C-9); HRMS *m/z* calcd for $C_{18}H_{18}O_5$ (M^+) 314.1154, found 314.1152; EIMS *m/z* 314 (M^+, 19%), 296 (M-H_2O, 100), 268 (7), 207 (14), 189 (18), 149 (25), 121 (26), 107 (39), 95 (17), 85 (15), 77 (16).

*2.4. (±)-trans-2-(3-Methoxy-4-benzyloxybenzyl)-3-[3′-methoxy-4′-benzyloxy-α,α-bis(phenylthio)benzyl]butyrolactone **(13)***

Compound **13** was prepared according to the reported method [39]. The crude product was used directly in the next step without purification.

*2.5. (±)-trans-2-(3-Methoxy-4-benzyloxybenzyl)-3-(3′-methoxy-4′-benzyloxy-α-benzoyl)butyrolactone **(15)***

Following the same procedure as for **14**, compound **13** was converted to **15** as a solid in 61% yield after flash

column chromatography (CH_2Cl_2). Recrystallization from a mixture of chloroform and ether gave **15** as a white solid: mp 163–164°C (lit. [19], 164–165°C; lit. [20], 157–160.5°C). The spectral data [IR (KBr), ^1H and ^{13}C NMR ($CDCl_3$), 200 MHz] were in agreement with those of the previously synthesized products [19,20]. HRMS *m/z* calcd for $C_{34}H_{32}O_7$ (M^+) 552.2148, found 552.2144; EIMS *m/z* 552 (M^+, 43%), 462 (7), 461 (7), 284 (5), 241 (17), 151 (8), 106 (32), 105 (29), 91 (100), 77 (25).

2.6. (8R,8′R*,7′R*)-(±)-7′-Hydroxymatairesinol (**1a**) and (8R*,8′R*,7′S*)-(±)-7′-allohydroxymatairesinol (**2a**)*

Following the same procedure as for **1d** and **2d**, compound **15** was converted to a mixture of compounds **1a** and **2a** as an oil in 64% yield. Analysis of the ^1H NMR spectrum of the crude product revealed this material to contain a mixture of the two diastereoisomers in an approximate ratio of 1.5:1. The mixture of the two isomers was separated by normal-phase HPLC using a Merck LiChrospher Si-60 column (250×10 mm i.d.), 5 μm. The mobile phase was *n*-hexane/$CHCl_3$/MeOH (70:15:15, v/v/v); flow rate, 3.0 ml min^{-1}.

The spectral data [^1H NMR and ^{13}C NMR ($CDCl_3$ and acetone-d_6), 300 MHz] were in agreement with those of the natural hydroxymatairesinol and allohydroxymatairesinol [8,10].

Isomer **1a**: HRMS *m/z* calcd for $C_{20}H_{22}O_7$ (M^+) 374.1365, found 3374.1369; EIMS *m/z* 374 (M^+, 10%), 356 (M-H_2O, 100), 241 (12), 153 (20), 137 (23).

Isomer **2a**: HRMS *m/z* calcd for $C_{20}H_{22}O_7$ (M^+) 374.1365, found 374.1350; EIMS *m/z* 374 (M^+, 7), 356 (M-H_2O, 100), 241 (13), 153 (17), 137 (25).

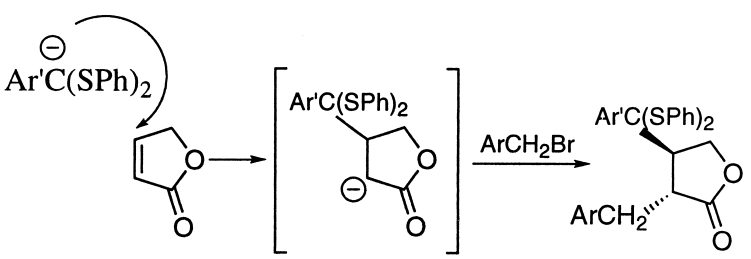
*2.7. (±)-trans-2,3-Bis(3-benzyloxybenzyl)butyrolactone (**16**)*

To a stirred solution of **12** (1.66 g, 2.4 mmol) in dry toluene (25 ml) maintained under argon at 90°C was added in small portions for 30 min, a mixture of tri-*n*-butyltin hydride [40] (2.78 g, 9.6 mmol) and AIBN (0.098 g, 0.60 mmol). The reaction mixture was stirred for 2 h. Evaporation of toluene and purification by flash column chromatography toluene/hexane (1:1) and EtOAc/hexane (1:4) gave **16** as a colorless amorphic solid (1.02 g, 89%): ^1H NMR ($CDCl_3$, 200 MHz) δ 2.36–2.66 (4 H, m, H-7′, H-8′, H-8), 2.88 (1 H, dd, *J* 6.9, 13.8, H-7), 3.05 (1 H, dd, *J* 4.8, 13.9, H-7), 3.80 (1 H, dd, *J* 6.8, 9.1, H-9′), 4.04 (1 H, dd, *J* 6.3, 9.1, H-9′), 5.00 (2 H, s, C*H*$_2$), 5.02 (2 H, s, C*H*$_2$), 6.57–6.60 (m, 2 ArH), 6.74–6.87 (m, 4 ArH), 7.13–7.40 (m, 12 ArH); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 5.07, 38.43, 41.17, 46.22, 69.86, 71.09, 112.89, 113.37, 115.39, 115.69, 121.19, 121.85, 127.45, 127.48, 127.94, 128.03, 128.56, 128.61, 129.71, 129.74, 136.80, 136.88, 139.31, 139.53, 158.96, 159.02, 178.45; HRMS *m/z* calcd for $C_{32}H_{30}O_4$ (M^+) 478.2144, found 478.2152; EIMS *m/z* 478 (M^+, 13%), 387 (10), 203 (5), 181 (8), 106 (15), 91 (100), 77 (10).

*2.8. Oxidation of the metal enolate of 2,3-bis(3-benzyloxybenzyl)butyrolactone (**16**)*

Lithium bis(trimethylsilyl)amide (5.7 mmol) was prepared in 5 ml of dry benzene by the reported method [41]. LiHMDS was placed in the reaction flask equipped with argon inlet and magnetic stirrer bar, and 30 ml of dry benzene was added to the solution. The solution was cooled to 0°C and **16** (1.59 g, 3.3 mmol) in dry benzene (35 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, followed by addition of 18-crown-6 (0.098 g, 0.37 mmol). The argon inlet was removed and dry oxygen was bubbled through the reaction mixture for 3 h. The mixture was quenched by addition of saturated aqueous Na_2SO_3 (20 ml) and stirred for 15 min. The mixture was acidified with 2 N HCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with aqueous 5% $NaHCO_3$-solution and brine and dried over $MgSO_4$. Evaporation of the solvents provided the crude product (1.59 g, 97%) as a white amorphic solid. The crude product was purified by flash column chromatography CH_2Cl_2/EtO_2 (97:3) to give three fractions including 0.32 g (19.5%) of starting material **16**. The two isomers **17a** and **17b** were recovered in 0.37 g (22.6%) and 0.27 g (16.5%), respectively.

Isomer **17a**: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.56–2.66 (2 H, m, H-7′), 2.90–3.23 (4 H, m, H-8′, H-7, O*H*), 3.94–4.11 (2 H, m, H-9′), 5.08 (4 H, s, C*H*$_2$), 6.75–6.97 (m, 6 ArH), 7.22–7.50 (m, 12 ArH); ^{13}C NMR ($CDCl_3$, 200 MHz) δ



Scheme 1.

1.88, 42.25, 43.52, 69.82, 69.86, 70.17, 76.25, 112.84, 113.88, 115.57, 116.67, 121.43, 122.80, 127.43, 127.50, 127.91, 127.95, 128.50, 128.55, 129.64, 129.69, 135.89, 136.77, 136.83, 140.13, 158.89, 159.00, 178.47; HRMS *m/z* calcd for $C_{32}H_{30}O_5$ (M^+) 494.2093, found 494.2090; EIMS *m/z* 494 (M^+, 13%), 403 (8), 287 (4), 197 (7), 181 (7), 106 (11), 91 (100), 77 (9).

Isomer **17b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.67 (1 H, dd, *J* 11.6, 12.8, H-7′), 2.84–3.00 (4 H, m, H-8′, H-7, O*H*), 3.16 (1 H, dd, *J* 3.7, 13.2, H-7′), 3.85 (1 H, m, H-9′), 4.14 (1 H, dd, *J* 7.6, 9.1, H-9′), 5.07 (4 H, s, CH_2), 6.77–6.97 (m, 6 ArH), 7.22–7.48 (m, 12 ArH); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 2.35, 38.56, 47.87, 69.25, 69.94, 75.86, 113.03, 114.05, 115.26, 116.94, 121.01, 122.94, 127.46, 127.54, 127.96, 128.04, 128.57, 128.61, 129.62, 129.92, 134.85, 136.79, 136.84, 139.44, 158.87, 159.09, 177.53; HRMS *m/z* calcd for $C_{32}H_{30}O_5$ (M^+) 494.2094, found 494.2098; EIMS *m/z* 494 (M^+, 17%), 403 (5), 287 (8), 197 (7), 181 (6), 106 (8), 91 (100), 77 (6).

2.9. (8S,8′S*)-(±)-8-Hydroxyenterolactone (**4h**) and (8R*,8′S*)-(±)-8-hydroxyenterolactone (**5h**)*

A suspension of **17a** (0.27g, 0.55 mmol) in ethanol (125 ml) and W-2 Raney nickel (12 g) was refluxed for 4 h. The catalyst was removed by filtration and rinsed with acetone. Evaporation of the solvents left the crude product, which was purified by flash column chromatography CH_2Cl_2/acetone (4:1) to give **4h** (0.16 g, 67%): ^{1}H NMR (acetone-d_6, 300 MHz) δ 2.51 (1 H, m, H-8′), 2.58 (1 H, dd, *J* 13.1, 10.5, H-7′b), 2.83 (1 H, dd, *J* 13.1, 3.9, H-7′a), 3.00 (1 H, d, *J* 13.4, H-7b), 3.17 (1 H, d, *J* 13.4, H-7a), 3.94 (1 H, dd, *J* 8.7, 7.3, H-9′b), 4.00 (1 H, t, *J* 8.7, H-9′a), 5.17 (1 H, s, 8-OH), 6.64–6.72 (4 H, m, H-6′, H-2′, H-4′, H-4), 6.74 (1 H, m, H-6), 6.82 (1 H, t, *J* 2.1, H-2), 7.10 (1 H, t, *J* 7.4, H-5′), 7.14 (1 H, t, *J* 8.2, H-5), 8.24 and 8.29 (1 H, s, 3-OH or 3′-OH); ^{13}C NMR (acetone-d_6, 300 MHz) δ 32.0 (C-7′), 41.7 (C-7), 43.8 (C-8′), 70.5 (C-9′), 76.4 (C-8), 113.9 (C-4′), 114.4 (C-4), 116.3 (C-2′), 117.7 (C-2), 120.5 (C-6′), 122.2 (C-6), 129.9 (C-5), 130.1 (C-5′), 137.8 (C-1), 141.4 (C-1′), 158.0 and 158.1 (C-3′ or C-3), 178.1 (C-9); HRMS *m/z* calcd for $C_{18}H_{18}O_5$ (M^+) 314.1154, found 314.1151; EIMS *m/z* 314 (M^+, 60%), 189 (28), 161 (8), 145 (16), 134 (17), 108 (93), 107 (100), 91 (4), 77 (12).

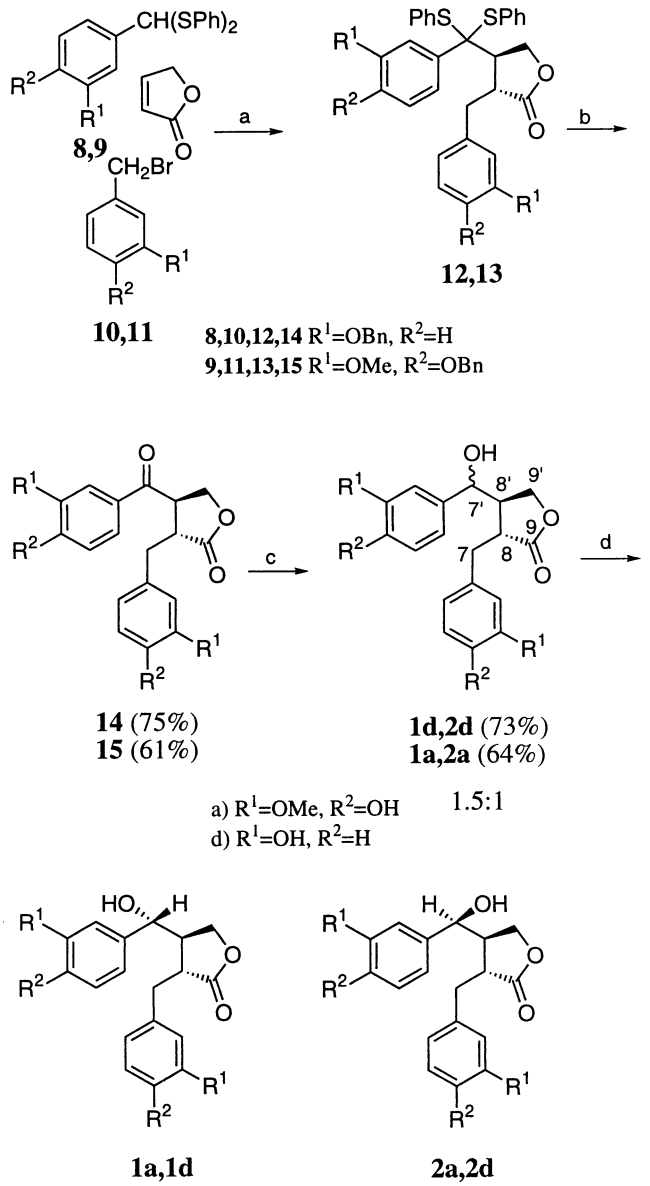
Similar treatment of **17b** gave **5h** (0.08 g, 12%): ^{1}H NMR (acetone-d_6, 300 MHz) δ 2.69 (1 H, m, H-7′b), 2.81 (1 H, m, H-8′), 2.99 (1 H, d, *J* 14.3, H-7b), 3.06 (1 H, m, H-7′a), 3.12 (1 H, d, *J* 14.3, H-7a), 3.83 (1 H, t, *J* 8.8, 8.7, H-9′b), 4.11 (1 H, dd, *J* 8.8, 7.1, H-9′a), 4.73 (1 H, s, 8-OH), 6.68 (1 H, dt, *J* 8.0, 1.2, H-6′), 6.69 (1 H, br s, H-2′), 6.71 (1 H, m, H-4′), 6.74 (1 H, ddd, *J* 8.0, 2.4, 1.0, H-4), 6.85 (1 H, dt, *J* 8.0, 1.3, H-6), 6.88 (1 H, dd, *J* 2.4, 1.3, H-2), 7.13 (2 H, t, *J* 8.0, H-5 and H-5′), 8.23 (1 H, s, 3-OH), 8.28 (1 H, s, 3′-OH); ^{13}C NMR (acetone-d_6, 300 MHz) δ 32.8 (C-7′), 39.3 (C-7), 49.5 (C-8′), 69.3 (C-9′), 77.4 (C-8), 114.2 (C-4), 114.6 (C-4′), 116.3 (C-2′), 118.2 (C-2), 120.5 (C-6′), 122.4 (C-6), 129.9 (C-5), 130.5 (C-5′), 137.7 (C-1), 141.5 (C-1′), 158.0 (C-3), 158.5 (C-3′), 177.9 (C-9); HRMS *m/z* calcd for $C_{18}H_{18}O_5$ (M^+) 314.1154, found 314.1155; EIMS *m/z* 314 (M^+, 47%), 279 (20), 189 (19), 167 (28), 149 (66), 133 (25), 108 (100), 107 (91).

3. Results and discussion

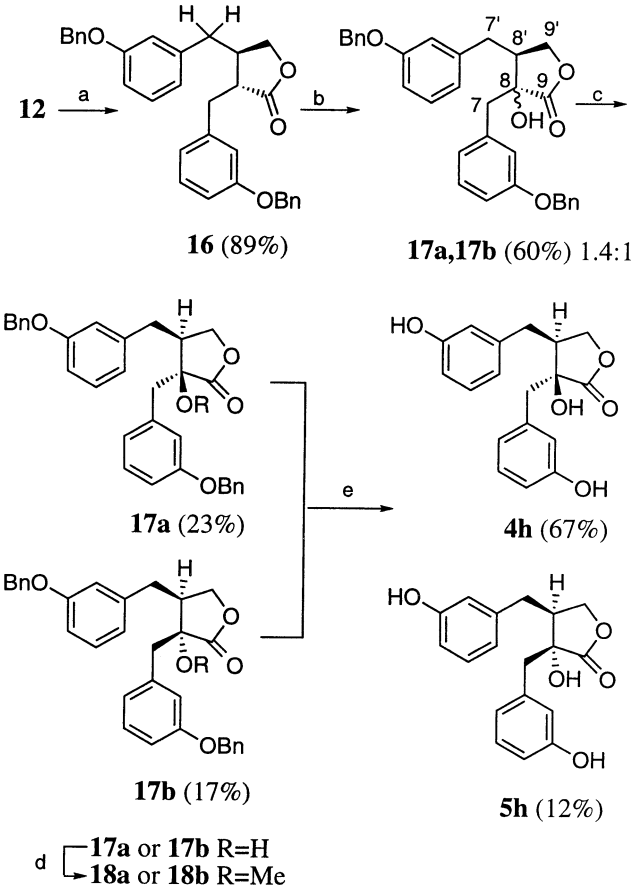
The *trans*-α,β-dibenzyl-γ-butyrolactone framework is generally obtained by the Michael addition of an anion derived from dithioacetal to butenolide followed by benzylation in situ (Scheme 1) [39,42,43].

The introduction of a secondary hydroxyl group in the benzylic position is presented in Scheme 2. The bis(phenylthio) moiety can be hydrolyzed to parent carbonyl group either by treatment with iodine in refluxing methanol [44] or hydrolysis with mercuric oxide and boron trifluoride etherate in aqueous tetrahydrofuran [45]. The former procedure with the *trans*-adduct **12** or **13** gave a mixture of reaction products in low yields, whereas hydrolysis with mercuric oxide produced a clean reaction to give the carbonyl compound **14** or **15**. In the next step the aim was to reduce the carbonyl group and remove the benzyl ether protective groups simultaneously. Catalytic hydrogenation under standard conditions using Raney nickel proceeded smoothly to afford a diastereomeric pair of alcohols **1a** and **2a** or **1d** and **2d** in a ratio of *ca*. 1.5:1. The ratio was determined by ^{1}H NMR and GLC. The isomeric products were separated by semi-preparative HPLC. Satisfactory separation of the isomers of hydroxymatairesinol **1a** and **2a** was achieved using normal-phase silica HPLC column, whereas no separation between the isomers of hydroxyenterolactone **1d** and **2d** was accomplished. The HPLC column was therefore changed to C_{18} reversed-phase column. The diastereomers were characterized by NMR analysis and molecular modelling [46], and the results were compared with those of Kawamura et al. [8] and Mattinen et al. [10]. Although definite conclusions on the absolute configurations made by NMR analyses are not possible [10] by NMR, as proposed by Kawamura et al. [8], it should be possible to assign the relative configuration at C-7′ using molecular modelling to obtain minimum energy conformations and NMR analyses to obtain average coupling constants between H-8′ and H-7′. Also the NOE interactions should be different for the two diastereomers. We will report shortly on these results [46].

The introduction of a tertiary hydroxyl α to the lactone carbonyl group is presented in Scheme 3. α-Hydroxylation of carbonyl compounds, such as lignan lactones involves generally oxidation of a metal enolate [21,22]. For optimal results, the enolate was generated by hexamethyldisilazane from the benzyl lactone **16**, obtained from the bis(thioether) **12** by reduction with tributyltin hydride in the presence of AIBN [47]. A variety of oxidants have been developed for α-hydroxylation, and molecular oxygen has been found to



Scheme 2. *Reagents and conditions*: (a) compound **8** or **9**, *n*-butyllithium, THF, −78°C, then 2-butenolide, THF, −78°C, then benzyl bromide **10** or **11**, HMPA, THF, −78°C; (b) HgO, $BF_3 \cdot OEt_2$/THF-H_2O; (c) H_2, Raney nickel, ethanol; (d) separation.



Scheme 3. *Reagents and conditions*: (a) *n*-Bu_3SnH, AIBN/toluene; (b) LiHMDS, 18-crown-6, [O]/benzene; (c) separation; (d) MeI, KOH, DMSO; (e) Raney nickel, ethanol, reflux.

produce the two diastereomers in about equal amounts [21–23,48]. Although certain other oxidants would presumably have given a more selective reaction, both diastereomers were in fact desirable at this stage to allow the confirmation of the stereostructures of the natural products. The enolate oxidation produced a mixture of diastereomeric alcohols **17a** and **17b** in a ratio of *ca*. 1.4:1, and the alcohols were isolated by column chromatography to give the two tertiary alcohols **17a** and **17b** in 39.1% yield (if recovered starting material is taken into account, the overall yield is 58.6%). Careful examination of the spectral data revealed that the major product was the isomer **17a**, which was also confirmed by conversion of the protected stereoisomeric alcohols to α methyl ethers **18a** and **18b** by methylation with MeI and KOH in DMSO [46,49]. A strong NOESY correlation was found in NMR analyses between the methoxy group at C-8 and proton at C-8′ in isomer **18b** but not in isomer **18a**. The benzyl ether protecting groups were removed from the separated isomers **17a** and **17b** with Raney nickel in refluxing ethanol instead of hydrogenation under standard conditions in order to avoid a mixture of products. A minor problem, not encountered with isomer **17a**, was the partial deoxygenation of the tertiary alcohol in isomer **17b** by Raney nickel [50]. The isomeric products **4h** and **5h** were fully characterized with NMR spectroscopy [46].

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