NEW SYNTHETIC ROUTE TO BUTANOLIDE LIGNANS BY A RUTHENIUM COMPLEX CATALYZED HYDROGENATION OF THE CORRESPONDING STOBBE'S FULGENIC ACIDS

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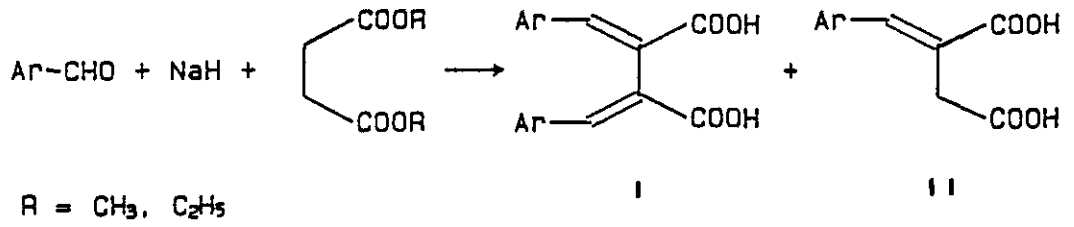
Abstract - A new two-step total synthesis of butanolide lignans (or dibenzylbutyrolactone lignans) is described, which affords the title compounds in good yield and with a very short work-up time. It involves a ruthenium carbonyl hydride complex-catalyzed hydrogenation of the corresponding dibenzylidene succinic acids (fulgenic acids).
Since the catalytic hydrogenation (second step) is a total yielding process, the overall yield determining step is the preparation of the fulgenic acid intermediates by the Stobbe condensation (first step), which has consequently been revised to improve many details.
This simple process moreover allows hexadeuterated butanolide lignans to be readily obtained for isotopic dilution mass spectral measurements.
The syntheses of a selection of lignans, namely enterolactone, matairesinol, hinokinin, dimethylmatairesinol and cordigerine, are described to illustrate the whole procedure.

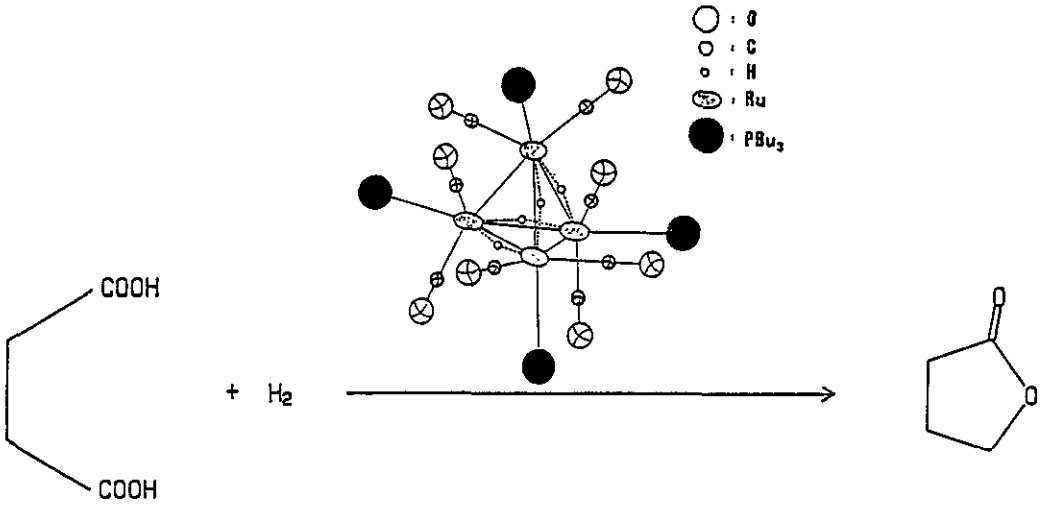
Lignans are a class of naturally-occurring compounds possessing a variety of structures which have attracted much interest over the years on account of their wide-spread occurrence in nature[2]. The lignans characterized by a gamma-lactone ring as the main structural feature are referred to as butanolide lignans (or dibenzylbutyrolactone lignans) and constitute a sub-class of numerous individual molecules[3].
The first serious attempts at total synthesis of these lignans date back to the

mid-thirties[4-8] and were multistep procedures starting from Stobbe's "fulgenic" acids (I) i.e. dibenzylidensuccinic acids generally prepared by the well-known Stobbe condensation[9] together with various amounts of the related monobenzylidensuccinic acids, or "itaconic" acids (II).



In the following years a variety of biological activities were ascribed to butanolide lignans[10-13] with an ever-increasing demand for these substances to undertake extensive pharmacological tests. Consequently, their synthetic preparation, flanking isolation from natural sources, has been further encouraged, giving rise to new elegant procedures[14,15] as alternatives to the classical routes.

Combining our long-standing interest in the pharmacological evaluation of naturally occurring compounds with that in lignan chemistry, we planned to set up a general synthetic procedure for dibenzylbutyrolactones with the primary emphasis on simplicity and rapidity of execution. We then directed our attention towards a high-pressure hydrogenation process based on the ability of the soluble ruthenium carbonyl hydride complex $H_4Ru_4(CO)_8(PBu_3)_4$ to catalyze the gamma-lactone ring formation, in 100% yield, starting from a succinic acid moiety[16].



This catalytic hydrogenation process, being a rapid, unattended operation, seemed actually to meet all the above requirements, as recently seen by us when preparing enterolactone from a corresponding dibenzylidensuccinic acid intermediate obtained by Stobbe condensation[17]. A considerable advantage in using this particular Ru-catalyst on the fulgenic acids was that butanolide formation occurred simultaneously with double-bond saturation (see Scheme below), leading to a complete, one-step conversion to the desired lignan molecule in a maximum of 48 h at 180° C and H_2 pressure over 200 bar. This behaviour showed that fulgenic acids were well-suited to be butanolide lignan precursors.

Moreover, this process offered a very efficient way to deuterium-labelled lignans for mass spectral quantitation by isotopic dilution experiments[18], simply by using D_2 instead of H_2 in identical experimental conditions. In fact, six deuterium atoms were constantly introduced into the molecule giving rise to a 100% hexadeuterated product and consequently to a single 100% $(M+6)^{+\cdot}$ molecular ion instead of a cluster of differently deuterated molecular ions.

As regards stereoselectivity, in all cases reported here hydrogenation afforded the lignans as an approx. 7-9:1 mixture of trans- and cis-isomers, respectively (see Scheme below). This procedure can therefore also provide access to the cis-isomers which are otherwise difficult to obtain[19]. As a matter of fact, we are currently forcing the hydrogenation conditions towards the cis-isomers by changing the phosphine substituents of the catalyst and the reaction temperature.

The preparation of the succinic intermediates by one-pot reaction leaves no alternative to the above-mentioned Stobbe condensation. It is well-known, however, that this apparently simple reaction is very sensitive to procedural details, giving indeed a multitude of side-products and low fulgenic acid yields, as is often pointed out in the literature from 1904 onwards. The Stobbe condensation, as the overall yield determining step, was thus to be improved in order to make our rapid two-step process fully competitive in all respects.

The literature directions were run through from the beginning[9,20] and the reaction conditions improved in order to maximize the fulgenic acid formation with a minimum of itaconic acid. As reported elsewhere[20,21], dry NaH worked far better than sodium or potassium alkoxides as the base and mixing of the total amounts of reagents (aldehyde, succinic acid ester and NaH) at the start of the reaction, carried out in refluxing toluene, gave the best results.

The perfect dryness of the reaction medium, which was not given adequate emphasis in previous reports, was crucial. It was also found that adding traces of alchool to prime the reaction as recommended elsewhere[20] was ineffective, and that applying too long reaction times (over 12 h) was damaging. The reaction rate, however, was greatly influenced by aldehyde ring substitution, the benzyl-protected moieties reacting faster (2-3 h) than the others (4-12 h).

Under these conditions, the itaconic acid in the crude fulgenic acid was usually absent; moreover the Cannizzaro dismutation, which removed part of the aldehyde from the condensation, was contained as demonstrated by the corresponding benzoic acid not exceeding 1-3% in the crude product.

For the post-reaction work-up we chose to separate first the acids precipitated as sodium salts from the solvent which retained the most of the unwanted side products, of which Cannizzaro benzyl alcohol was one.

In this way most of the isolation problems reported elsewhere were circumvented and the purification was usually completed simply by washing repeatedly with solvents of increasing polarity. If required, a deeper purification might be performed by washing with even more polar solvents (acetone or alcohols) provided that the sodium salts are transformed into completely insoluble barium salts, as suggested early on by Stobbe[9].

For the subsequent hydrogenation step, the salts had to be converted into the acids. The fact that the co-present Cannizzaro benzoic acids were left with the fulgenic acids was unimportant since aromatic monocarboxylic acids remained unaffected in our hydrogenation conditions and were easily removed during the final dry column chromatography (DCC) purification.

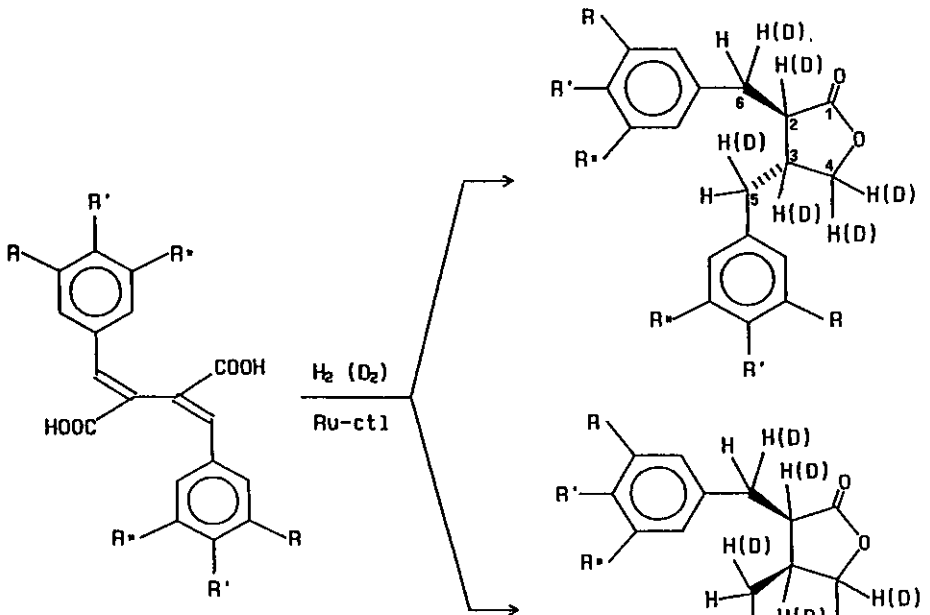
Bis(3-benzyloxybenzylidene)succinic acid (**1**), bis(3-methoxy-4-benzyloxybenzylidene)succinic acid (**2**), bis(3,4-methylendioxybenzylidene)succinic acid (**3**), bis(3,4-dimethoxybenzylidene)succinic acid (**4**), and bis(3,4,5-trimethoxybenzylidene)succinic acid (**5**) were then prepared in order to obtain 2,3-bis(3-benzyloxybenzyl)-4-butanolide (**6**), 2,3-bis(3-methoxy-4-benzyloxybenzyl)-4-butanolide (**7**), 2,3-bis(3,4-methylendioxybenzyl)-4-butanolide (**8**), 2,3-bis(3,4-dimethoxybenzyl)-4-butanolide (**9**) and 2,3-bis(3,4,5-trimethoxybenzyl)-4-butanolide (**10**), as summarized in the Scheme. Total conversion of **6-10** to the corresponding trans forms (**11-15**) was performed as usual by treatment with methanolic potassium hydroxide solution[7].

It is worth noting that the benzyl protection of **6** and **7** remained unaffected by our catalyst, permitting their safer storage for longer periods than the corresponding less stable enterolactone (**11**) and matairesinol (**12**) phenolic lignans. When required, restoration of the phenolic function in the lignans carrying the benzyl protection was easily performed by means of a conventional (Pd/charcoal) hydrogenolysis in quantitative yield, just before biological tests.

It may be observed that enterolactone can be obtained as described here, or alternatively by demethylation of dimethylenterolactone, as communicated elsewhere[15,17]. When dimethylenterolactone was not required, however, the present way from **6** was more convenient in terms of simplicity of execution and final yield.

In conclusion, the described procedure would seem to be very convenient for

synthesizing "symmetrical" butanolide lignans i.e. lignans having equally-substituted aromatic rings, to give access to the cis-isomers and for the easy preparation of deuterated molecules. Finally, the use of the Ru-catalyst prepared with chiral phosphines seems promising for the enantioselective synthesis of the same class of lignans[22,23]. This study is currently in progress.



1 - 5

6 - 10

1 : R = O-CH_2-Ph ; R'= R* = H	⟶	**6** (trans : cis = 7.5: 1)
2 : R = O-CH_3 ; R'= O-CH_2-Ph ; R* = H	⟶	**7** (trans : cis = 7.5: 1)
3 : R,R'= O-CH_2-O ; R* = H	⟶	**8** (trans : cis = 9 : 1)
4 : R = R'= O-CH_3 ; R* = H	⟶	**9** (trans : cis = 9 : 1)
5 : R = R'= R* = O-CH_3	⟶	**10** (trans : cis = 9 : 1)

EXPERIMENTAL

Melting points were determined on a Gallenkamp hot-air apparatus and are uncorrected. Ir spectra were measured in nujol mull with a Perkin-Elmer 983 spectrophotometer linked to a Perkin-Elmer 7500 computer (CDS software) allowing the subtraction of the nujol bands. ^{1}H and ^{13}C nmr spectra were recorded in DMSO-d_6 or $CDCl_3$ on Varian EM 360L, FT 80 and Bruker MSL 200, quoting chemical shifts in δ values with tetramethylsilane as internal standard. Mass spectrometry utilized a VG Analytical 7070 EQ instrument operating in electron impact mode, with 70eV ionizing potential and 200-230° C source temperature; in order to avoid thermal decomposition, solid sampling in the ion source was performed by the "direct electron impact" (DEI) technique[24]. Fast atom bombardment (FAB) ionization, in the negative ion mode, was also employed (8 KeV xenon atoms and glycerol as liquid matrix). High resolution mass measurements were performed with a VG Analytical ZAB 2F.

Preparative separations were carried out by dry column chromatography (DCC)[25,26] using Woelm silica TSC and 25 mm $\varnothing$ nylon film tubing (columns lenghts and eluents as indicated).

All the lignans reported were found to be amenable to gas chromatography without derivatization, provided that highly inert fused silica capillary columns and a programmed temperature vaporizer (PTV) were employed; here a Perkin-Elmer 8320 instrument equipped with PTV and a built-in data-handling facility was adopted using a SGE 12QC2/BP1 0.25 column.

Freshly twice-distilled (sodium wire) toluene was strictly required for the Stobbe condensation. Dimethyl succinate (Fluka, 98%) and NaH dry powder (Aldrich, 99%) were used as obtained.

Commercial 3,4-methylenedioxybenzaldehyde (piperonal), 3,4-dimethoxybenzaldehyde (veratraldehyde) and 3,4,5-trimethoxybenzaldehyde were recrystallized prior to use.

Benzyl protection of phenolic aldehydes was performed as usual by reacting benzyl chloride with the aldehyde in alkaline acqueous medium. 4-benzyloxy-3-methoxybenzaldehyde and 3-benzyloxybenzaldehyde were obtained, after vacuum distillation, as colorless viscous oils which readily solidified into white crystalline masses, mp 60-61° C and 56-57° C, respectively. Their identities were confirmed by spectroscopy.

Preparation of the fulgenic acids by the Stobbe condensation - General procedure

About 25 mmol of dimethyl succinate and 51 mmol of the appropriate aldehyde were dissolved in 150 ml of anhydrous toluene. To this solution a toluene (50 ml) suspension of 52 mmol of NaH dry powder was added. No gas bubble evolution must be

observed at this point for the right dryness of the reaction medium. The mixture was brought to gentle reflux under stirring.

Heating was maintained until (2-12 h) the reaction mixture appeared as a creamy orange-brown suspension. The cold suspension was settled by centrifugation and the supernatant toluene layer discarded. Again the solid was shaken with fresh toluene and centrifuged; the toluene was then eliminated until colourless toluene resulted. The procedure was repeated with ether and ethyl acetate. The purified solid, consisting almost exclusively of the fulgenic acid disodium salt, was assayed for the absence of the corresponding itaconic acid disodium salt by FAB-ms and finally dissolved in water from which the fulgenic acid was precipitated by acidification with dilute HCl.

This acid was filtered, washed with water to neutrality and dried, then submitted to the subsequent hydrogenation step without further purification. A small aliquot was recrystallized for spectral measurements.

Bis(3-benzyloxybenzylidene)succinic acid (1)

10.0 g of 3-benzyloxybenzaldehyde, 3.50 g of dimethyl succinate and 1.13 g of NaH were allowed to react for 2 h and worked up as described above, yielding 6.10 g of 1 (49 %).

White crystalline powder, mp 178-179°C (from benzene); ir (nujol): 3200-2200, 1677, 740, 690 cm^{-1}; ^1H nmr (60 MHz, DMSO-d_6): 12.70 (2 H, -COO<u>H</u>), 7.77 (2 H, s, =C<u>H</u>-), 7.60-6.85 (18 H, m, Ar-<u>H</u>), 5.04 (4 H, s, -OC<u>H</u>$_2$-)[27]; DEI-ms (230°C): $M^{+\cdot}$ 506.1730 (1%) $C_{32}H_{26}O_6$ requires 506.17294, 488 (13), 397 (15), 181 (13), 91 (100), 65 (6) m/z.

FAB-ms of the disodium salt (S1): 527 (S1-Na$|^-$), 505 (S1-2Na+H$|^-$) m/z.

Bis(3-methoxy-4-benzyloxybenzylidene)succinic acid (2)

22.1 g of 3-methoxy-4-benzyloxybenzaldehyde, 6.72 g of dimethyl succinate and 2.18 g of NaH were allowed to react for 3 h and worked up as above yielding 13.3 g of 2 (51%).

Crystallized as dihydrate from methanol containing traces of water in bright, yellow prisms, mp 167-168°C; ir (nujol): 3494, 3200-2200, 1711, 1665, 740, 690 cm^{-1}; ^1H nmr (60 MHz, DMSO-d_6): 12.50 (2 H, -COO<u>H</u>), 7.81 (2 H, s, =C<u>H</u>-), 7.60-6.85 (16 H, m, Ar-<u>H</u>), 5.10 (4 H, s, -OC<u>H</u>$_2$-), 3.70 (6 H, s, -OC<u>H</u>$_3$), 3.22 (4 H, <u>H</u>$_2$O); DEI-ms (230°C): $M^{+\cdot}$ 566.1940 (1%) $C_{34}H_{30}O_8$ requires 566.19407, 548 (51), 457 (11), 425 (42), 91 (100), 65 (1) m/z.

FAB-ms of the disodium salt (S2): 587 (S2-Na$|^-$), 565 (S2-Na+H$|^-$) m/z.

Bis(3,4-methylendioxybenzylidene)succinic acid (3)

11.0 g of 3,4-methylendioxybenzaldehyde, 5.36 g of dimethyl succinate and 1.77 g of NaH were allowed to react for 4 h and worked up as above to yield 7.50 g of **3** (53%).

Yellow prism from methanol (with traces of water), mp 199-202°C (decomp.); ir (nujol): 3200-2200, 1666 cm^{-1}; ^1H nmr (60 MHz, DMSO-d_6): 12.40 (2 H, -COOH), 7.72 (2 H, s, =CH-), 7.25-6.80 (6 H, m, Ar-H), 6.02 (4 H, s, -O-CH_2-O-); DEI-ms (200°C): $M^{+\cdot}$ 382.0689 (12%), $C_{20}H_{14}O_8$ requires 382.06887, 364 (100), 336 (8), 319 (6), 292 (48), 243 (50), 176 (40), 135 (24), 122 (63), 91 (77) m/z.

FAB-ms of the disodium salt (S3): 403 (S3-Na$|^-$), 381 (S3-2Na+H$|^-$) m/z.

Bis(3,4-dimethoxybenzylidene)succinic acid (**4**)

8.70 g of 3,4-dimethoxybenzaldehyde, 3.80 g of dimethyl succinate and 1.56 g of NaH gave in 12 h 6.0 g of **4** (56%) using the same procedure.

Orange-yellow prisms from methanol, mp 210.5-211.5°C (decomp.); ir (nujol): 3289, 1709 cm^{-1}; ^1H nmr (60 MHz, DMSO-d_6): 12.40 (2 H, -COOH), 7.80 (2 H, s, =CH-), 7.35-6.80 (6 H, m, Ar-H), 3.78 (6 H, s, $-OCH_3$ meta), 3.70 (6 H, s, $-OCH_3$ para); DEI-ms (230°C): $M^{+\cdot}$ 414.1315 (26%), $C_{22}H_{22}O_8$ requires 414.13147, 396 (96), 351 (9), 321 (18), 309 (16), 259 (41), 151 (30), 138 (100) m/z.

FAB-ms of the disodium salt (S4): 435 (S4-Na$|^-$), 413 (S4-2Na+H$|^-$) m/z.

Bis(3,4,5-trimetoxybenzylidene)succinic acid (**5**)

28.84 g of 3,4,5-trimetoxybenzaldehyde, 10.67 g of dimethyl succinate and 3.53 g of NaH reacted for 4 h to give 14.30 g of **5** (41%).

It slowly crystallized from methanol in large bright yellow triclinic prisms, mp 210.5-212.5°C; ir (nujol): 3200-2200, 1678 cm^{-1}; ^1H nmr (60 MHz, DMSO-d_6): 12.60 (2 H, -COOH), 7.80 (2 H, s, =CH-), 6.95 (4 H, s, Ar-H), 3.70 (12 H, s, $-OCH_3$ meta), 3.68 (6 H, s, $-OCH_3$ para); DEI-ms (200°C): $M^{+\cdot}$ 474.1526 (9%), $C_{24}H_{26}O_{10}$ requires 474.15260, 456 (57), 381 (9), 289 (28), 181 (18), 168 (100), 153 (25) m/z.

FAB-ms of the disodium salt (S5): 495 (S5-Na$|^-$), 473 (S5-2Na+H$|^-$) m/z.

Synthesis of the butanolide lignans by catalytic hydrogenation of the related fulgenic acids - General procedure

Homogeneous catalytic hydrogenation of the fulgenic acids was carried out in toluene using a 200 ml stainless "Hastelloy C" steel rocking autoclave heated in a thermostated (±2° C) oil bath.

Usually up to 9.0-10.0 g of fulgenic acid substrate and $H_4Ru_4(CO)_8(PBu_3)_4$ catalyst[28], in a proportion of 15 mg of catalyst/mmol of substrate, were placed in

the autoclave; the vessel was closed and evacuated of air. Toluene, not exceeding 100 ml, was introduced as the solvent by suction. The vessel was then pressurized with hydrogen (99.98%) at 150-180 bar (room temperature) and rocked in the oil bath at 180° C, the pressure rising to 230-280 bar. Hydrogen was resupplied during the course of the reaction if pressure fell below 200 bar. Deuteration was performed under identical conditions, using D_2 (99.5%).

The reaction was completed within a maximum of 48 h. The toluene reaction solution was dried and evaporated giving a crude product from which the lignan was isolated as a trans- and cis-form mixture by DCC, under gc control. The total conversion to the trans-form was performed in cold 1% methanolic potassium hydroxide solution (MeOD and KOD in the case of deuterated compounds). After 24-48 h the solution was neutralized with the calculated amount of HCl (DCl) and the trans-lignan recovered by ether extraction. When required, hydrogenolysis of the benzyl protection was carried out in ethylacetate with 1% Pd/charcoal in a Parr apparatus at room temperature and H_2 at 2-4 bar (4 h).

An aliquot was submitted to spectral measurements after further purification (crystallization or chromatography).

2,3-Bis(3-benzyloxybenzyl)-4-butanolide (**6**)

5.0 g of **1** were hydrogenated with 150 mg of Ru-catalyst under the conditions described in the general procedure. The crude product obtained on evaporation was purified by DCC (50 cm, two runs 2.5 g each) eluted with cyclohexane-ethyl acetate 3:1, to give 4.30 g (93%) of **6** as a colorless gum consisting of a 7,5:1 trans- and cis-isomer mixture (gc); ir (neat): 1767, 741, 697 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$): 7.30-6.35 (18 H, m, Ar-H), 4.93 (2 H, s, $-OCH_2-$), 4.90 (2 H, s, $-OCH_2-$), 4.05-3.50 (2 H-4, m), 2.95-2.70 (2 H-6, m) and 2.60-2.10 (H-2, H-3, 2 H-5, m); DEI-ms (200°C) $M^{+\cdot}$ 478.2146, $C_{32}H_{30}O_4$ requires 478.21441.

2,3-Bis(3-methoxy-4-benzyloxybenzyl)-4-butanolide (**7**)

8.0 g of **2** were hydrogenated in the same manner as above with 200 mg of Ru-catalyst to give a crude product from which 7.2 g (95%) of **7** were obtained after DCC purification (60 cm, cycloexane-ethyl acetate 2.5:1, two runs 4.0 g each), as a colorless gum consisting of a 7.5:1 trans- and cis-isomer mixture (gc); ir (nujol): 1766, 740, 698 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$): 7.50-6.30 (16 H, m, Ar-H), 5.10 (4 H, s, $-OCH_2-$), 4.25-3.40 (2 H-4, m), 3.82 (3 H, s, $-OCH_3$), 3.79 (3 H, s, $-OCH_3$), 3.00-2.82 (2 H-6, m) and 2.60-2.42 (H-2, H-3, 2 H-5, m); DEI-ms (200°C): $M^{+\cdot}$ 538.2356, $C_{34}H_{34}O_6$ requires 538.23554.

2,3-Bis(3,4-methylendioxybenzyl)-4-butanolide (**8**)

6.0 g of **3** were hydrogenated as above with 230 mg of Ru-catalyst. DCC purification (60 cm, CH_2Cl_2, two runs 3.0 g each) afforded 5.2 g (94%) of **8** as a 9:1 mixture of trans- and cis-isomers (gc): mp 100-105°C; ir (nujol): 1767 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$): 7.30-6.40 (6 H, m, Ar-H), 5.95 (4 H, s, -O-CH_2-O-), 4.15-3.90 (2 H-4, m), 3.00-2.81 (2 H-6, m) and 2.65-2.40 (H-2, H-3, 2 H-5, m); DEI-ms (220°C): $M^{+\cdot}$ 354.1104, $C_{20}H_{18}O_6$ requires 354.11034.

2,3-Bis(3,4-dimethoxybenzyl)-4-butanolide (**9**)

Hydrogenation of 6.0 g of **4** with 220 mg of Ru-catalyst gave, after DCC purification (55 cm, CH_2Cl_2, two runs 3.0 g each), 5.2 g (94%) of **9** as a 9:1 mixture of trans- and cis-isomers (gc): mp 101-110°C; ir (nujol): 2838, 1755 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$): 6.95-6.45 (6 H, m, Ar-H), 4.35-3.60 (2 H-4, m), 3.83 (6 H, s, -OCH_3), 3.81 (3 H, s, -OCH_3), 3.79 (3 H, s, -OCH_3), 3.05-2.80 (2 H-6, m) and 2.70-2.35 (H-2, H-3, 2 H-5, m); DEI-ms (220°C): $M^{+\cdot}$ 386.1730, $C_{22}H_{26}O_6$ requires 386.17294.

2,3-Bis(3,4,5-trimethoxybenzyl)-4-butanolide (**10**)

10.0 g of **5** were hydrogenated in presence of 315 mg of Ru-catalyst and gave, after DCC purification (60 cm, CH_2Cl_2, three runs 3.3 g each), 8.75 g (93%) of a 9:1 mixture of **10** trans- and cis-isomers (gc) as an amorphous solid; ir (nujol): 2835, 1767 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$): 6.40 (2 H, s) and 6.20 (2 H, s) (Ar-H), 4.20-3.70 (2 H-4, m), 3.81 (12 H, broad s, -OCH_3), 3.79 (6 H, s, -OCH_3), 2.99-2.88 (2 H-6, m) and 2.70-2.45 (H-2, H-3, 2 H-5, m); DEI-ms (220°C): $M^{+\cdot}$ 446.1942, $C_{24}H_{30}O_8$ requires 446.19407.

trans-2,3-Bis(3-hydroxybenzyl)-4-butanolide (enterolactone) (**11**)

4.0 g of **6** were dissolved in about 200 ml of cold 1% methanolic potassium hydroxide solution and allowed to stand for 48 h. After neutralization with the calculated amount of HCl and ether extraction, trans-**6** was obtained quantitatively (99%, gc; DEI-ms (200°C): $M^{+\cdot}$ 478 (14%), 387 (7), 281 (2), 198 (4), 181 (8), 91 (100), 65 (9) m/z).

This product was dissolved in ethyl acetate without further purification and hydrogenolysed with 1% Pd/charcoal (H_2 at 2-4 bars, room temp., 4 h) to give **11** in quantitative yield with spectroscopic data identical to those reported in the literature[15,29,30].

trans-2,3-Bis(3-methoxy-4-hydroxybenzyl)-4-butanolide (matairesinol) (**12**)

5.0 g of **7** were converted into the corresponding trans form by treatment with methanolic KOH under the same conditions as above. The resulting trans-**7** (99%, gc;

DEI-ms (200°C): $M^{+\cdot}$ 538 (36%), 448 (30), 358 (7), 227 (13), 137 (65), 91 (100), 65 (25) m/z) was hydrogenolysed to remove benzyl protection as described for **11**. Matairesinol was thus obtained in quantitative yield; ir (nujol): 3429, 1761; ($CDCl_3$) 3545, 1767 cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$): 6.90-6.55 (6 H, m, Ar-H), 4.25-3.70 (2 H-4, m), 3.85 (3 H, s, $-OCH_3$), 3.82 (3 H, s, $-OCH_3$), 3.05-2.80 (2 H-6, m), 2.70-2.40 (H-2, H-3, 2 H-5, m); ms[31].

trans-2,3-Bis(3,4-methylendioxybenzyl)-4-butanolide (hinokinin) (**13**)

Total conversion of 4.0 g of **8** into **13** (98.5%, gc) was performed as described above. The structure was confirmed by comparison with published data[31,32].

trans-2,3-Bis(3,4-dimethoxybenzyl)-4-butanolide (dimethylmatairesinol) (**14**)

3.9 g of **14** (98%, gc) were obtained by treating 4.0 g of **9** as above; ir (nujol): 2838, 1760 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): 6.90-6.45 (6 H, m, Ar-H), 4.20 (H-4a, dd), 3.98 (H-4b, dd), 3.83 (6 H, s, $-OCH_3$), 3.81 (3 H, s, $-OCH_3$), 3.79 (3 H, s, $-OCH_3$), 3.01 (H-6a, dd), 2.94 (H-6b, dd), 2.70-2.40 (H-2, H-3, 2 H-5, m); DEI-ms (200°C): $M^{+\cdot}$ 386 (60%), 235 (6), 208 (8), 177 (14), 152 (38), 151 (100), 137 (7), 121 (4), 107 (12), 91 (8), 77 (9) m/z.

trans-2,3-Bis(3,4,5-trimethoxybenzyl)-4-butanolide (cordigerine) (**15**)

6.0 g of **10** were treated as above giving 5.9 g of **15** (99%, gc) with spectral data in agreement with published values[33].

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