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STEREOSPECIFIC SYNTHESES OF THE LIGNANS: 2-S-(3,4-DIMETHOXYBENZYL)-3-R-(3,4,5-TRIMETHOXYBENZYL) BUTYROLACTONE, AND ITS POSITIONAL ISOMERIC LACTONE

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Abstract:

A short, versatile and stereospecific synthesis of two lignans **1** and **2**, was achieved in 40% overall yield. Our strategy was based in the use of amino acids as chiral and readily available starting materials. Stereocontroled transformation of amino acids to chiral organic phosphonates gave the key intermediate of the synthetic sequence. A Horner-Wadsworth-Emmons (HWE) reaction followed by selective reduction and stereospecific hydrogenation in the last step resulted in the title compounds with the desired absolute stereochemistry.

Natural lignans belonging to the gamma butyrolactones series, such as guayadiquiene[1], hinokinin[2] and its analogs, have been interesting targets to synthetic chemists, due to their biological properties, including antitumoral activity[3]. Because of significant activity exhibited for these compounds, several synthetic routes towards optically active lignans have been reported[4], some approaches include optical resolution[5a], enantioselective synthesis of the lactone from L-glutamic acid[5b], and use of chiral auxiliary for the biphenyl coupling[5c].

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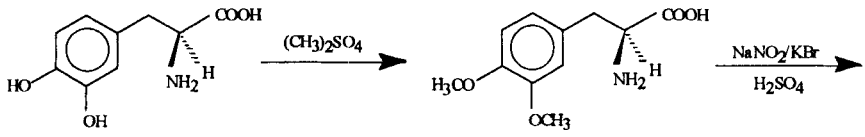
We have previously reported a highly convergent, short and stereoselective synthesis of a series of methoxy substituted 2,3 dibenzylbutyrolactones using a HWE reaction as the key step [6]. In the present communication, we report a short, and stereospecific synthesis of the lignans **1** and **2.**

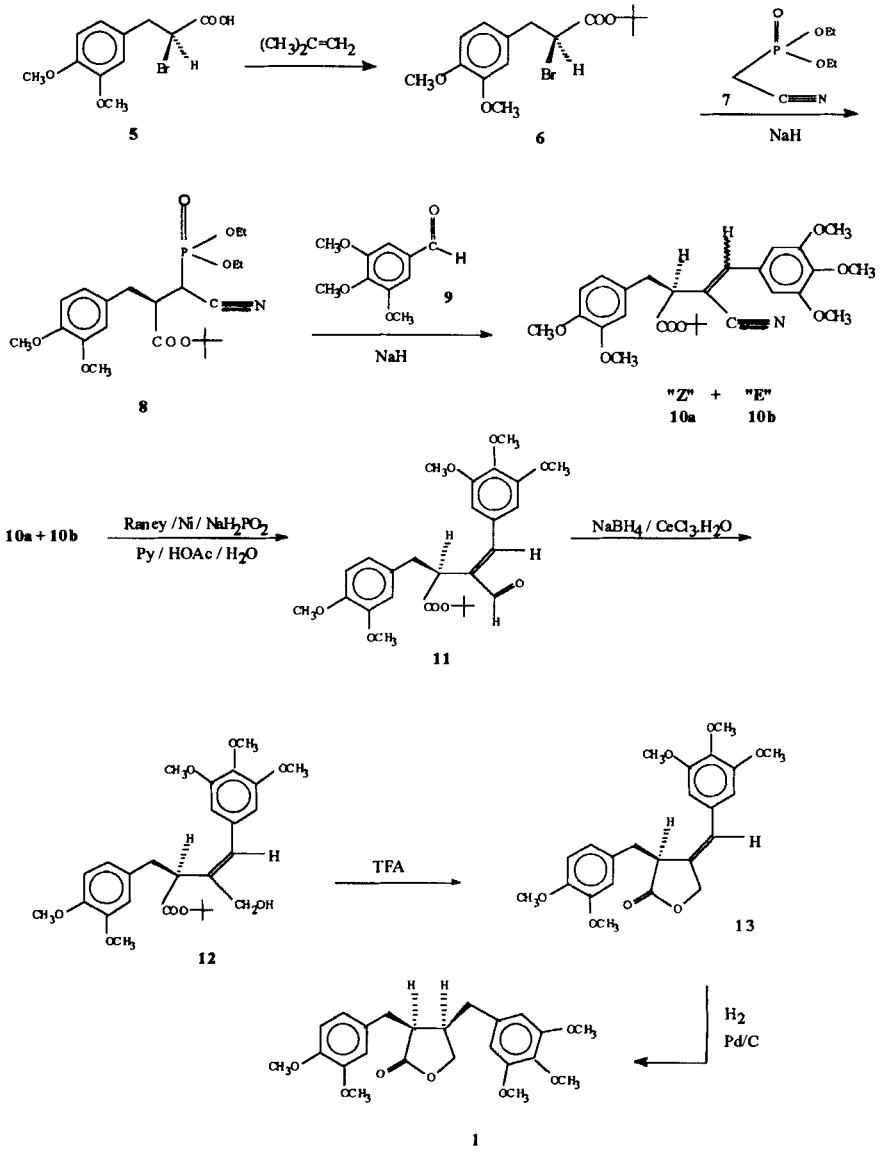
Our synthetic sequence for obtention of the lignan **1** is outlined in Scheme 1 and was based in the use of amino acids as chiral and readily available starting material. Treatment of the α bromo ester 6 with sodium cyanomethyl diethyl phosphonate resulted in the chiral organic phosphonate **8**. HWE reaction of **8** with substituted benzaldehyde afforded the common key intermediate for the two desired compounds **10**. Selective reduction of the tert-butyl ester or the nitrile group in **10** followed by lactonization, gave the two positional isomeric lactones **13** and **15**. Catalytic hydrogenation of **13** and **15** in the last step resulted in the title compounds with the desired stereochemistry.

This synthetic methodology represents a short, versatile and stereospecific route for the synthesis of substituted derivatives of dibenzyl gamma lactones from a key common intermediate.

SCHEME 1



3 **4**



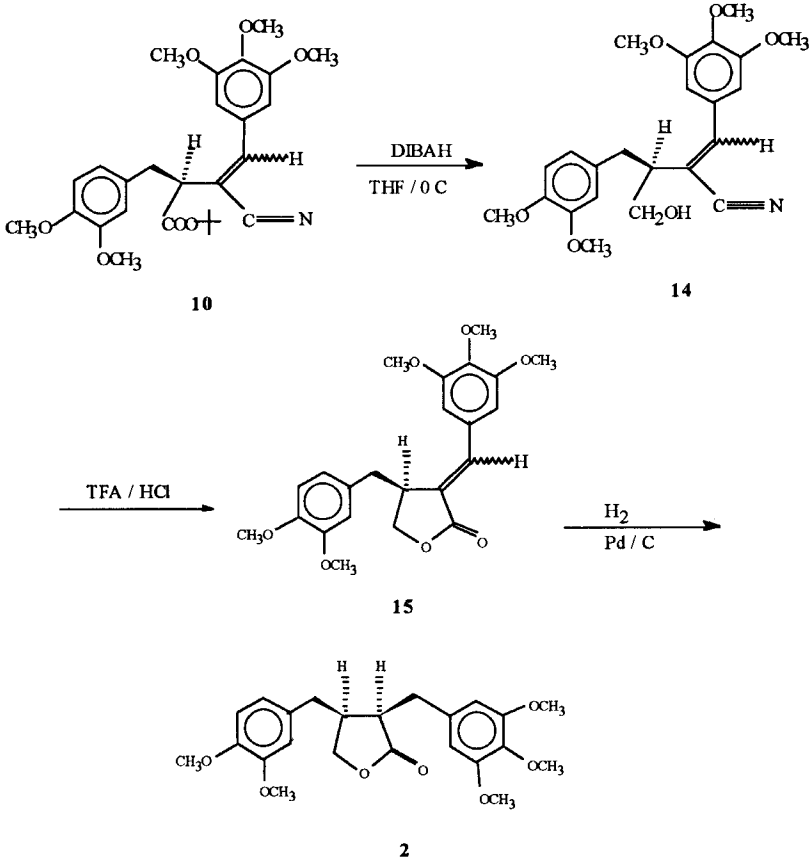
5 6 7 8 9 "Z" + "E" 10a 10b 10a + 10b 11 12 13 1

L-Dopa (3) was protected and treated with dimethyl sulphate in highly basic media[7], to provide the O-methyl derivative **4**. Bromination of the methylated amino acid **4** was carried out with $NaNO_2$ /H_2SO_4/KBr. This type of reaction has been previously reported to take place with retention of configuration[8,9]. Treatment of **5** with isobutene and catalytic quantities of sulfuric acid gave the bromo ester **6**. The use of a tert-butyl ester at this stage of the synthesis was dictated by its resistance to base hydrolysis. The bromo ester **6** was converted by alkylation with diethyl cyanomethylphosphonate **7** into the phosphonate ester **8**, in excellent yields. Based on a previous similar work[8] ,we assumed that during the alkylation, the invertion of the configuration at C 2 on **8** have occurred. The formation of the required phosphonate **8** was regarded as the key step in this synthesis. The ylide of **8** reacted easily with 3,4,5 trimethoxybenzaldehyde **9** to give a 3:7 Z/E olefin mixture **10a** and **10b,** respectively, in highl yields. Both isomeric olefins were separated by column chromatography and showed different mp.

At this point, our synthetic strategy was divided in two suitables routes for obtention of lactones **1** and **2**. First, the E cyano olefin **10b** (see scheme 1) was subjected to reduction of the nitrile group using Raney Ni/Sodium hypophosphite and pyridine[10]. This reaction afforded the ester-aldehyde **11** in 70% yield based on the E-Z mixture. The fact that the Z olefin (**10a**) was recovered during this reduction may be due to sterical hindrance caused by the trimethoxyphenyl group[10]. Subsequent treatment of the aldehyde **11** with $NaBH_4/CeCl_3.H_2O$ gave the intermediate **12**, which was hydrolized with trifluoroacetic acid and converted to the beta gamma unsaturated lactone **13** close to quantitative yield. Final catalytic reduction of **13** with 5% Pd on C gave the title compound **1** with the desired sterochemistry in good yield [11a].

In order to test the feasibility and the versatilily of our strategy for obtention of positional isomeric lactones, the title compound **2** was synthesized as shown in Scheme 2. In this case the regioisomeric lactone group was obtained..

SCHEME 2



10 **14** **15** **2**

The tert-butyl ester group of the olefin **10** was selectively reduced with DIBAH in THF at -5°C in 1/2 h, to give the cyano alcohol **14** as an yellow oil in 85% yield. The intermediate **14** was converted to the unsaturated lactone **15** under conditions of hydrolysis and cyclization by using 1:1 HCl/TFA for 10h. Upon hydrogenation with 5% Pd on C, the intermediate **15** afforded the lignan **2** with the desired stereochemistry[11a] in 40% overall yield.

Substituted dibenzylbutyrolactones may be readily converted to the corresponding dibenzyloctacyclodiene lactones[11], which are the basic moiety of natural products suchs as stegans, steganacins and steganols.

Experimental:

Melting points were determined in a Hans Bock Francfurt Apparatus and are uncorrected .NMR spectra were recorded on a Brucker WP-80 using TMS as internal standard, IR spectra were recorded on a Perkin Elmer 1310 spectrometer. Reaction products were purified by column chromatography using silica gel 60-230 Mesh. MS spectra were recorded on a HP-800 spectrometer. Glyme and THF were distilled from sodium and benzophenone under N_2. Unless otherwise noted all reactions were carried out under N_2.

(S)-3-(3,4-Dimethoxyphenyl)-2-bromopropanoic acid **5**.

In a 500 mL flask equipped with a magnetic stirrer, was placed 5.0 g (0.023 mol) of L-3,4-dimethoxyphenylalanine and 25 g (0.21 mol) of KBr dissolved in 250 mL of 2.5 N H_2SO_4 .This solution was cooled at -5°C using an ice/NaCl bath, 7.5 g (0.1 mol) of $NaNO_2$ dissolved in 5 mL of H_2O was added dropwise during 1h. The resultant solution was stirred at 0°C during 16h. The mixture was extracted with $CHCl_3$, the extracts dried over $MgSO_4$ and evaporated under reduced pressure resulting in a brownish oil wich was subjeted to Kugelhror distillation (87%)
^1H NMR ($CDCl_3$) δ : 3.3(m, H), 3.5-3.7(m, 2H), 3.8(s, 6H), 6.8-7.2(m, 3H) ; IR : 3300, 3100, 1725, 830 ; m/z 289.

(S) tert-Butyl-2-(3,4-dimethoxyphenyl)-2-bromopropanote **6**.

3.0 g (0.01 mol) of bromoacid **5** was dissolved in 5 mL of CH_2Cl_2 and cooled to -40°C under acetonitrile/CO_2 bath. To this cold solution, 5 mL of isobutylene and 0.1 mL of concentrated sulfuric acid were added and the mixture was stored at room temperature in a closed round bottomed flask for 3 days. The cooled solution

was poured into 10 mL saturated sodium bicarbonate and stirred for 1 h. The alkaline mixture was extracted with CH_2Cl_2. The organic extract dried and evaporated . The residue was distilled in a Kugelhror (85%).

^1H NMR ($CDCl_3$) δ : 1.25(s, 9H), 3.2-3.25(m, 2H), 3.8(s, 6H), 4.2-4.3(m, H), 6.7-7.1(m, 3H); IR: 3030, 2980, 1730; m/z 345.

(S)-tert-Butyl-2-(3,4-Dimethoxybenzyl)-3-(diethylphosphono)-3-cyanopropanoate **8**

0.069 g (0.0017mol) of sodium hydride (60% in mineral oil) was washed with dry hexane and suspended in 5 mL of dry glyme. To this mixture at 0°C, 0.3g (0.0017mol) of cyanomethyl diethyl phosphonate in glyme was added by syringe in 1 h. After 1 h of stirring at room temperature, this solution was cooled at 0°C and 0.75 (0.0017mol) of **6** 10 mL of solvent was added by syringe in 1/2 h. The above solution was quenched after 36 h of stirring at 55°C with 10 mL of H_2O and extracted with EtOAc (3 x 10 mL). The organic extract was evaporated and the residue was purified by flash chromatography over silica gel with $CHCl_3$/EtOAc/MeOH 7/2/1 to give 700 mg of **8** (80%).

^1H NMR ($CDCl_3$) δ :1.18-1.42(m, 15H), 1.67(s, H), 3.76-3.84(m, 6H), 4.0-4.26(m, 4H), 6.55-6.98(m, 3H); IR: 3010, 2850, 1730, 1360; m/z 441.

(E,Z)(S)-tert-Butyl-2-(3,4-Dimethoxybenzyl)-3-cyano-4-(3,4,5-trimethoxyphenyl)-3-butenoate **10**

100 mg (0.0249 mmol) of sodium hydride (60% in mineral oil) was washed with dry hexane and suspended in 5 mL of glyme . To this mixture at 0°C was added by syringe in 1h 130 mg (0.249 mmol) of the phosphonate 7 dissolved in 5 mL of glyme. The mixture was stirred at room temp. for 45 min . To the resulting solution at 0°C 40mg (0.249 mmol) of 3,4,5 trimethoxybenzaldehyde in 2 mL of glyme was added . The mixture was stirred for 1h at room temperature, and quenched with EtOAc (3 x 5 mL) and the extracts were dried with $MgSO_4$. Evaporation of the solvent in vacuo and chromatography over silica gel eluting with $CHCl_3$ /EtOAc/

Hexane 5/3/2 gave the olefins **10** (91%); E isomer mp=102 °C; Z isomer = oil. ^{1}H NMR ($CDCl_3$)δ: 1.1-1.3(s, 9H), 2.2-2.25(m, H), 3.0-3.2(m, 2H), 3.75-3.8 (m, 15H), 4.2-4.4(m, 2H), 6.7-7.0(m, 6H); IR: 3010, 2850, 2250, 1750, 1620;m/z 483

(E)(S)-tert-Butyl-2-(3,4-Dimethoxybenzyl)-3-formyl-4-(3,4,5-trimethoxyphenyl)-3-butenoate **11.**

To 100 mg (0.2 mmol) of the olefins **10** dissolved in a 2:2:1 mixture of Py/HOAc/H_2O (15 mL) was added 200 mg of Raney Ni and the mixture was refluxed for 20h .During the refluxing time, 150 mg portions of Raney Ni were added at intervals of 4h .The hot mixture was filtered with celite and washed with 5 ml of Py/HOAc/Water, 5 mL hot ethanol and 5mL $CHCl_3$, in that order. The product was extracted with $CHCl_3$ (3 x 10 mL) and the extracts were washed with brine and dried with $MgSO_4$ .The solvent was evaporated and the residue purified by chromatography over silica gel, eluting with $CHCl_3$/Hexane 7/3 to give the aldehyde **11** (61%); $[\alpha]_D^{25}$ = - 21° (c = 0.361,$CHCl_3$) ^{1}H NMR ($CDCl_3$) δ: 1.1-1.3(m, 9H), 2.2-2.25(m, H), 3.0-3.2(m, 2H), 3.8(3, 15H), 4.2-4.4(m, 2H), 6.7-7.0(m, 6H); IR : 3000, 2850, 1750, 1720,1620; m/z 486.

(E)(S)-ter-Butyl-2-(3,4-Dimethoxybenzyl)-3-hydroxymethyl-4-(3,4,5-trimethoxy-phenyl)-3-butenoate **12.**

To a solution of the aldehyde **11** 50 mg (0.1 mmol) in dry MeOH (5 ml) was added 75 mg of $NaBH_4$. After 15 min., the mixture was extracted with $CHCl_3$ (3 x 5 mL), dried with MgSO4 and evaporated to give the crude product wich was "filtered" over silica gel using $CHCl_3$ (98%); $[\alpha]_D^{25}$ = - 37° (c = 0.282,$CHCl_3$) ^{1}H NMR δ : 1.4-1.6(m, 9H), 3.0-3.2(m, 3H), 3.8(s, 15H), 6.7-7.2(m, 6H); IR: 3500, 3050, 2850, 1750, 1620; m/z 488.

(S)-2-(3,4-Dimethoxybenzyl)-3-(3,4,5-trimethoxybenzylidene)butyrolactone **13.**

45 mg (0.09 mmol) of **12** was dissolved in 5mL mixture of TFA/H_2O 1/1. This solution was stirred for 3h at room temp. The solvent was evaporated in vacuo and

quenched with saturated aqueous $NaHCO_3$ solution. The product was extracted with $CHCl_3$ (3 x 10mL) dried with Na_2SO_4. Evaporation of the solvent in vacuo afforded the unsaturated lactone **13** (92%); $[\alpha]_D^{25} = -36°$ (c = 0.194,$CHCl_3$)

^1H NMR δ : 2.7-3.2(m, 2H), 3.3-3.6(m, 3H), 3.8-3.9(s, 15H), 6.4-6.8(m, 6H); IR: 3050, 2850, 1770, 1630; m/z 414.

(2S,3R)-2-(3,4-Dimethoxybenzyl)-3-(3,4,5-trimethoxybenzyl)butyrolactone **1**.

A mixture of 45 mg (0.1 mmol) of **11** in 5 mL of ethanol anhydrous and 5 mg of 5% Pd on C was hydrogenated in a Parr reactor at 50 psi H_2 for 3h . The mixture was filtered and the solvent evaporated to give 98% of the saturated lactone **1** as an oil. $[\alpha]_D^{25} = +32°$ (c = 0.550,$CHCl_3$)

^1H NMR δ: 2.2-2.4.(m, 2H , J 6.5 Hz, cis), 2.5-2.7(br, 2H, J 6.5 Hz, cis), 3.7-3.8(m, 17H), 4.2(m, 2H), 6.5-6.8(m, 5H) ; IR : 3050, 2850, 1755 ,1600 ; m/z 416.

(E,Z)(2S)-2-(3,4-Dimethoxybenzyl)-3-cyano-3-(3,4,5-trymethoxybenzylidene)-1-butanol **14**

A solution of **10a 10b** mixture 100 mg (0.3 mmol) in dry THF (5mL) was cooled at 0°C . At this temperature 10 mL of a hexane solution of DIBAH was added and the mixture was stirred for 30 min at room temp. and quenched with 5 mL of 1:1 THF/H_2O. The mixture was extracted with $CHCl_3$ (3 x 10 mL). The extracts were dried (Na_2SO_4). Concentration and silica gel column chromatography ($CHCl_3$/MeOH) 9/1 afforded **14** (91%) as orange syrup.

^1H NMR ($CDCl_3$) δ : 2.0-2.2(br, H), 2.8-3.1(m, 3H), 3.5-3.7(br, 2H), 3.8(s, 15H), 6.6(m, H), 6.8-7.2(m, 5H); IR: 3050, 2850, 1650; m/z 413.

(E,Z)(2S)-2-(3,4,Dimethoxybenzylidene)-3-(3,4,5-trimethoxybenzylbutyrolactone **15**.

100 mg (0.38 mmol) of cyano alcohol **14** was dissolved in 10 mL of 1:1 TFA/HCl, and the mixture heated at reflux for 10h. Water (10 mL) was added and the mixture was extracted with ether . The extracts were dried (Na_2SO_4).

Purification by silica gel column chromatography ($CHCl_3$) afforded **15** in 88% yield. ^1H NMR ($CDCl_3$) δ: 2.3-3.2(m, 2H), 3.6-3.8(br, 1H), 3.9(s, 15H), 4.2-4.3 (br, 2H), 6.4-6.7(m, 5H), 7.3-7.4(br, 1H); IR: 3030, 2850, 1740; m/z 414.

2-(3,4,5-Trimethoxybenzyl)-3-(3,4-dimethoxybenzyl)butyrolactone **2.**

A mixture of 50 mg (0.12 mmol) of **15** in 5mL of anhydrous ethanol and 5 mg of 5% Pd on C were hydrogenated in a Parr reactor at 50 psi of H_2 for 3h. The mixture was filtered and the solvent evaporated to give 98% of the saturated lactone **2** as an oil. $[\alpha]_D^{25} = -37°$ (c = 0.436,$CHCl_3$)

^1H NMR δ : 2.3-2.5(br, 2H, J 6.7 Hz, cis), 2.7-3.2(m, 2H, J 6.7 Hz,cis), 3.6-3.8(br, 2H), 3.9(s, 15H), 4.2(m, 2H), 6.5-6.8(m, 5H);IR: 3050, 2850, 1755, 1600; m/z 416.

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