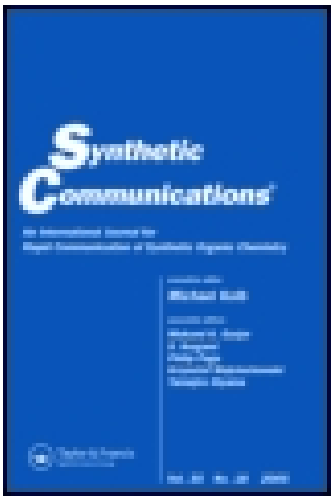

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 01 Apr 2009.

To cite this article: Reinaldo S. CompagnoneAlírica Suárez (1992) Stereoselective Synthesis of Methoxy Substituted 2, 3-Dibenzylbutyrolactones Via Organic Phosphonates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:21, 3041-3051, DOI: 10.1080/00397919209409252

To link to this article: http://dx.doi.org/10.1080/00397919209409252

SYNTHETIC COMMUNICATIONS, 22(21), 3041-3051 (1992)

STEREOSELECTIVE SYNTHESIS OF METHOXY SUBSTITUTED 2,3-DIBENZYLBUTYROLACTONES VIA ORGANIC PHOSPHONATES

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Abstract:

A highly convergent, short and stereoselective synthesis of a series of methoxy substituted 2,3-dibenzylbutyrolactones was achieved using a Horner-Wadsworth-Emmons (HWE) reaction as the key step in overall yields above 32%.

The chemistry of butanolide lignans has been the focus of special attention for many years due to their biological properties, especially their activity as antitumorals[1]. The natural occurrence of lignans characterized by the presence of a dibenzylbutyrolactone has been widely reported[2]. Extensive efforts has been directed towards the total synthesis of these lignans[3]. Recents approaches include: conjugated-addition methods[4] and phenylpropionic acids dianion coupling[5]. Because of long

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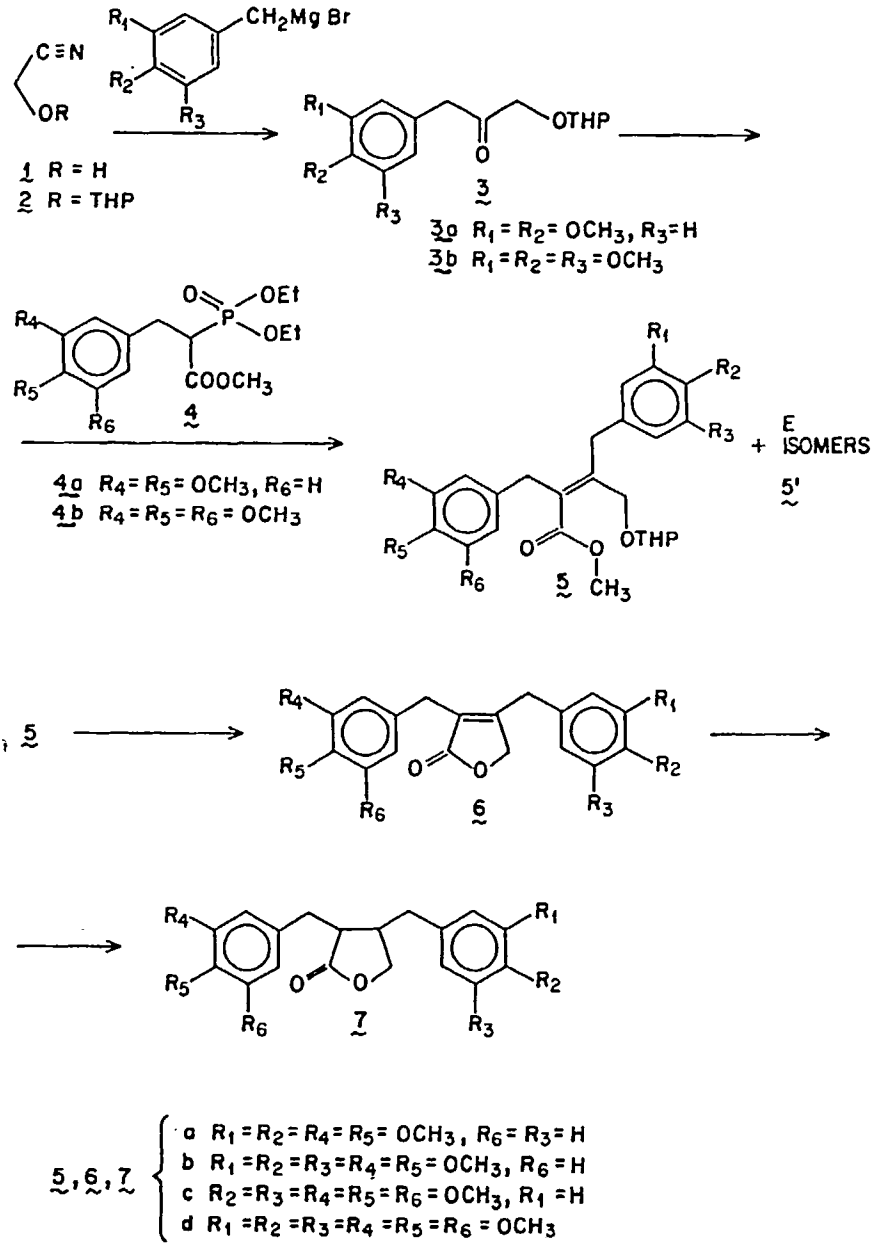
synthetic sequences and low overall yields, further improvements in synthetic approaches of these lignas would be welcome.

In this communication we describe an efficient, highly convergent route for the stereoselective formation of methoxysubstituted dibenzylbutyrolactones using organic phosphonates as key intermediates. Our strategy was based in the early formation of the carbon skeleton of the target molecules using a HWE reaction[6] as the key step for various methoxyarylphosphonate ester 4 and methoxybenzylhydroxymethyl ketone combinations 3. Once the carbon skeleton of the molecule was formed, deprotection of the hydroxymethyl group and lactonization was carried out. The stereochemistry of the two chiral centers C-2 and C-3 of the target molecules was developed in the last step, by a catalytic hydrogenation of the butenelactone 6, to give the cis lignans 7. The development of the relative stereochemistry in the late stage of the synthetic sequence, represents a practical improvement in methodology applied to the synthesis of lignans natural products. From the cis isomers, trans lactones may be obtained by epimerization of the C-2, according to reported methods[7].

Glyconitrile 1 was protected in excellent yield as the tetrahydropyranyl ether 2. Subsequent treatment of 2

with a series of methoxy substituted arylmagnesium bromides gave the ketones 3 in good yields. For this reaction, use of stoichiometric excess of the nitrile was necessary to avoid the formation of the corresponding tertiary alcohol. Phosphonates 4 were prepared in high yields from dimethoxy and trimethoxy benzyl alcohols by first converting them to the corresponding bromides with PBr_3[8], followed by alkylation with triethyl phosphonoacetate in potasium hydride. HWE reaction between phosphonates 4 and the protected ketones 3 afforded a 75:25 mixture of Z/E isomers of the olefins 5 in approximately 70% yield. The Z olefins 5 were deprotected with pyridine-p-toluensulphonate and inmediately converted, by treatment with base, to the unsaturated lactones 6 in approximately 90% yield. Catalytic hydrogenation of the unsaturated lactones 6, with 5% Pd on C, gave the title compounds in near quantitative yields as a racemic mixture of the cis lactones 7. The remaining E olefins 5 were readily isomerized photochemically to the Z olefins 5, and then converted near quantitatively to the desired compounds 6 and 7.

Methoxy substituted dibenzylbutyrolactones may be converted, by non-phenolic oxidative coupling[9], to the corresponding dibenzyloctacyclodiene lactones, which are the basic moiety of natural products such as stegans, steganacins and steganols[10].



EXPERIMENTAL:

Melting points were determined in a Hans Bock Frankfurt apparatus and are uncorrected. NMR spectra were recorded on a Brucker WP-80 spectrometer using TMS as internal standard. IR spectra were recorded on a Perkin Elmer 1310 spectrometer. Reaction products were purified by columm cromatography using silica gel 70-230 mesh. MS spectra were recorded on a HP 800 spectrometer. Glyme and THF were dried under N_2 with sodium and benzophenone. Unless otherwise noted, all the reactions were carried out under N_2.

Protected Glyconitrile 2

Gliconitrile (5 g, 0.09 mol) and 3,4-dihydro-2-pyran (15.12 g, 0.18 mol), were dissolved in 100 ml of dry CH_2Cl_2. The solution was cooled to 0 °C, and p-toluen-sulphonic acid (0.22 g, 0.0012 mol) was added. The solution was stirred at 0 °C for 10 min and for 1.5 h at room temp. A solution of 100 mL of 40:40:80 of brine, sat. sodium bicarbonate and water was added and the resulting mixture extracted with 100 mL of ether. The organic phase was dried and evaporated to give 11.84 g (92%) of the desired product as a colorless liquid. ^1H NMR ($CDCl_3$) δ 1.8 (bs,6H), 3.7 (bs,2H), 4.3 (s,2H), 4.9 (s,1H).

Ketone 3a-b (General procedure)

Magnesium (2.57 g, 0.106 mol), and 2,4-dimethoxybenzyl-bromide (24 g, 0.106 mol), were suspended in 300 mL of

dry ether at room temp. After the consumption of the magnesium, the grignard reagent was added by syringe to a solution of the protected nitrile 2 (15.26 g, 0.106 mol) in dry ether (150 mL). The mixture was refluxed for 2 h, followed by the addition of a water ice mixture (100 mL) and 2N sulphuric acid solution (50 mL). The reaction mixture was extracted with ether (250 mL). The organic phase was evaporated and chromatographed using 95:5 $CHCl_3$/MeOH, to give 3a (24.99 g, 80%)

3a: ^{1}H NMR ($CDCl_3$) δ 1.3-1.6 (m,6H), 2.0 (s,2H), 2.8 (s,2H), 3.8 (s,6H), 4.2-4.3 (m,3H), 6.6 (m,3H). m/z = 324.

3b: ^{1}H NMR ($CDCl_3$) δ 1.3-1.6 (m,6H), 2.1 (m,2H), 2.9 (s,2H), 3.8 (s,9H), 4.2-4.4 (m,3H), 6.4-6.6 (m,2H). m/z=324 (yield=82%)

Olefin 5a-d (General procedure)

Sodium hydride 60% in mineral oil (0.39g, 0.009 mol) was washed with dry hexane and suspended in glyme (20 mL). To this mixture at 0°C, was added by syringe over 1 h, the phosphonate 4a (3.24g, 0.009 mol). The mixture was stirred at room temp for 12 h, followed by treatment with water (200 mL). The solution was extracted three times with ethyl acetate (20 mL). Chromatography using 9:1 $CHCl_3$/MeOH, gave the product 5a as a yellowish oil (3.37 g, 75%).

5a: ^{1}H NMR ($CDCl_3$) δ 1.7 (m,6H), 2.3 (m,1H), 2.4-2.5 (m,2H), 3.3-3.5 (m,2H), 3.6 (s,2H), 3.8 (s,3H), 3.9 (m,12H),

4.1 (m,2H), 6.3-6.5 (m,6H); IR ($CHCl_3$) 3000, 2850, 1745, 1610, 1050 cm^{-1}; m/z=500.

5b: ^1H NMR ($CDCl_3$) δ 1.4-1.6 (m,6H), 1.7 (m,1H), 2.5 (s,2H), 3.1-3.2 (m,4H), 3.5 (s,3H), 3.8 (s,15H), 3.9-4.2 (m,2H), 6.3-6.5 (m,5H); IR ($CHCl_3$) 3000, 2850, 1740, 1600, 1250, 1150 cm^{-1}; m/z=530; (yield=72%).

5c: ^1H NMR ($CDCl_3$) δ 1.6 (m,6H), 1.8 (m,1H), 3.0 (s,2H), 2.3-3.4 (m,4H), 3.6 (s,3H), 3.8 (s, 15H), 4.3 (m,2H), 6.4-6.6 (m,5H); IR ($CHCl_3$) 3000, 2850, 1740, 1600, 1250, 1150 cm^{-1}; m/z=530; (yield=69%).

5d: ^1H NMR ($CDCl_3$) δ 1.5 (m,6H), 2.6 (m,1H), 3.2-3.4 (m, 2H), 3.5 (s,2H), 3.7 (m,2H), 3.8 (s,3H), 3.9 (s, 18H), 4.1 (m,2H), 6.4-6.5 (m,4H); IR ($CHCl_3$) 3000, 2850, 1745, 1600, 1250, 1150 cm^{-1}; m/z= 560; (yield=68%).

Dibenzyl-2-butenelactone 6a-d (General procedure)

The Z-E isomer mixture of 3a (3.55 g, 0.0071 mol) was treated with pyridine-p-toluensulfonate (0.2 g) in ethanol (30 mL) and refluxed for 3 h. The solvent was evaporated and the residue chromatographed to give a 75:25 mixture of the Z-E alchols (2.87 g, 97%). The Z-E alcohol mixture (0.7 g, 0.0017 mol),was dissolved in ethanol (15 mL), and treated with $NaHCO_3$ solid (300 mg). The mixture was heated at 50°C for 4 h, filtered and diluted with water (10 mL). The resulting aqueous solution was extracted with ether (15 mL). The organic phase was evaporated and chromatographed to give 6a as a yellowwish oil (0.46 g, 72%).

6a: ^{1}H NMR ($CDCl_3$) δ 3.0 (s,2H), 3.6 (s,4H), 3.8 (s,12H) 6.3-6.5 (m,6H); IR ($CHCl_3$) 3100, 2850, 1750, 1650, 1300, 1000 cm^{-1}; m/z=384.

6b: ^{1}H NMR ($CDCl_3$)δ2.8-3.0 (m,4H), 3.8 (m,2H), 3.9 (s,15H), 6.3 (m,5H); IR ($CHCl_3$) 3050, 2850, 1750, 1025, 1000 cm^{-1} m/z=414; (yield=69%).

6c: ^{1}H NMR ($CDCl_3$)δ2.3 (m,2H), 3.4 (m,2H), 3.8 (m,2H), 3.9 (s, 15H), 6.7 (m,5H); IR ($CHCl_3$) 3050, 2850, 1735, 1025, 1000 cm^{-1}; m/z=414; (yield=70%).

6d: ^{1}H NMR ($CDCl_3$) δ 2.4-2.6 (m,2H), 3.5 (m,2H), 3.8 (m, 18H), 4.1 (m,2H), 6.8 (m,4H); IR ($CHCl_3$) 3030, 2850, 1750, 1025, 1000 cm^{-1}; m/Z=444; (yield=73%).

Methoxy substituted-2,3-dibenzylbutyrolactone 7a-d

General Procedure

A mixture of 6a (0.42 g,0.0011mol) and Pd 5% on C (15mg) in ethanol anhydrous (20 mL), were hydrogenated in a Parr reactor at 50 psi H_2 for 3h. The solvent was evaporated to give the saturated lactone 7a (0.41 g, 98%) as an oil.

7a: ^{1}H NMR ($CDCl_3$) 2.0-3.1 (m,5H), 3.5-3.7 (m,3H), 3.8 (m,12H), 6.4-6.8 (m,6H); IR ($CHCl_3$) 3000, 1750, 1010 cm^{-1}; m/z=386.

7b: ^{1}H NMR ($CDCl_3$) 2.5-2.6 (m,4H), 2.9-3.0 (m,2H), 3.8 (m,15H), 4.0-4.2 (m,2H), 6.4-6.6 (m,5H); IR ($CHCl_3$) 3000, 1750, 16600, 1250, 1100 cm^{-1}; m/z=416; (yield=96%).

7c: ^{1}H NMRδ2.5-2.6 (m,4H), 2.8-2.9 (m,2H), 3.8 (m,15H),

4.1-4.2 (m,2H), 6.5-6.7 (m,5H); IR ($CHCl_3$) 3000,1755, 1600, 1250, 1100 cm^{-1}; m/z=416; (yield=98%).

7d: ^1H NMR ($CDCl_3$) δ 2.4-2.6 (m,4H), 2.7-2.9 (m,2H), 3.8 (m,18H), 4.2 (m,2H), 6.6-6.8 (m,4H); IR ($CHCl_3$) 3000, 1750, 1600, 1280, 1100; m/z=446; (yield=96%).

Phosphonate 4a-b (General procedure)

Sodium hydride,60% in mineral oil (0.65 g, 0.015 mol) was washed with dry hexane and suspended in dry glyme (50 mL). To this mixture at 0°C, diethyl methylphosphono acetate (3.15g, 0.015 mol) in glyme (10 mL) was added by syringe over 1 h. After 1 h of stirring at room temp, 3,4-dimethoxybenzylbromide[8] (3.40 g, 0.015 mol), in glyme (10 mL) was added by syringe over 1 h. The mixture was stirred at room temp for 12 h, and treated with water (40 mL), and extracted with EtOAc (50 mL). Evaporation of the solvent and column chromatography $CHCl_3$: EtOAc: Hexane 5:2:3, gave the product 4a, (4,86g, 90%), as a yellow oil.

4a: ^1H NMR ($CDCl_3$) δ 1.4 (t,6H), 3.0 (m,1H), 3.2 (m,2H), 3.6 (S,3H), 3.8 (2s,6H), 4.3 (c,4H), 6.7 (bs,3H); IR ($CHCl_3$) 3000, 2850, 1750, 1590, 1260 cm^{-1}; m/z=360.

4b: ^1H NMR ($CDCl_3$)δ1.4 (t,6H), 2.9 (m,1H), 2.9-3.1 (m, 2H), 3.7 (s,3H), 3.8-3.9 (3s,9H), 4.1 (c,4H), 6.4 (s,1H) 6.6(s,1H); IR ($CHCl_3$) 3000, 2850, 1740, 1600, 1260 cm^{-1}; m/z=390 (yield=92%).

E-Z olefin isomerization 5'→5

Using a 100 watt hanovia lamp, the remaining E olefin 5' (higher rf), was photochemically isomerized to the Z olefin 5 (lower rf). Both isomers were readily separated by silica gel column chromatography $CHCl_3$:hexane:EtOAc 5:4:1.

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from: INTERNATIONAL FOUNDATION FOR SCIENCE IFS, SWEDEN grant # F/1306-2; CDCH UNIVERSIDAD CENTRAL DE VENEZUELA, grant # 03-12-1843-91; CONICIT, grant # S1-1895.

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(Received in USA 12 June, 1992)