CONVENIENT RUTHENIUM-COMPLEX CATALYSED SYNTHESIS OF ENTEROLACTONE FROM THE CORRESPONDING DIBENZYLIDENE SUCCINIC ACID MOIETY

Massimo Bambagiotti-Alberti*, Silvia A. Coran, Franco P. Vincieri, and Pierandrea Lo Nostro[1]
Dipartimento di Scienze Farmaceutiche dell'Università
Via Gino Capponi 9, 50121 Firenze, Italy

Abstract - A convenient synthesis of enterolactone is outlined consisting mainly of a ruthenium carbonyl-hydride complex catalysed hydrogenation of bis(3-methoxybenzylidene)succinic acid.

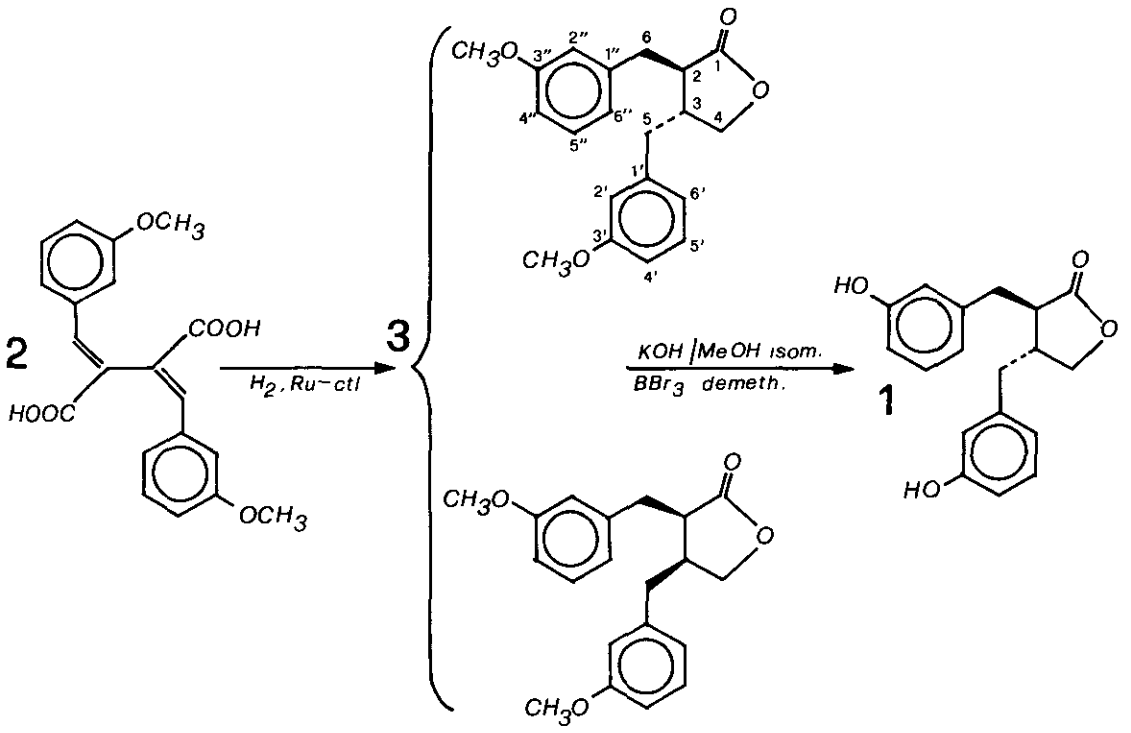
The recent discovery of enterolactone (2,3-bis(3-hydroxybenzyl)-4-butanolide) in human and various animal excretions[2-6] has prompted a renewed interest in the lignans, a well-known class of plant natural products[7-10] to which the above mentioned compound of animal origin can also be ascribed.

Many plant lignans exhibit a variety of biological activities[11-13] the most important being proven anticancer capabilities[14-23]. Consequently, a great wealth of research has been undertaken in the last five years on the role of enterolactone in human metabolism, which has also finally been regarded as a sort of endogenous protective agent connected to certain types of cancer[24]. Shortage of synthetic enterolactone for extensive biological tests has been, however, a common complaint in almost every paper concerned with this topic. To meet this requirement several syntheses based on multi-step procedures have been promptly proposed[25-27].

In order to obtain enterolactone (1) we exploited the ability of the soluble ruthenium carbonyl-hydride complex $H_4Ru_4(CO)_8(PBu_3)_4$ to catalyse the gamma-lactone ring formation[28,29] starting from the succinic acid moiety, obtained *via* the Stobbe condensation, in one step under usual high pressure catalytic hydrogenation conditions.

Bis(3-methoxybenzylidene)succinic acid (2) (mp 183-185°C from MeOH; ir (nujol): 3200-2200, 1683 cm^{-1}; ^1H nmr (60 MHz, DMSO-d6): 7.85(2H, =C<u>H</u>), 7.5-6.8 (8H, Ar-<u>H</u>), 3.70 (6H, $OC\underline{H}_3$); ms: $M^{+\cdot}$ 354(4), 336(56), 291(19), 264(12), 229(100), 108(65) m/z) was obtained by an *improved* Stobbe condensation in 50.5% yield (13.1g) by refluxing (2 h) in anhydrous toluene 3-methoxybenzaldehyde (21g,154mmol), dimethyl succinate (10.7g, 73mmol) and NaH (3.6g, 150mmol, dry powder). A catalytic amount of prepared Ru-catalyst (50mg)[30] and 2 (12.5g) were dissolved in toluene and the

solution placed in a high pressure autoclave. After 24 h at 170°C under hydrogen at 270-300 bars, a complete conversion to 2,3-bis(3-methoxybenzyl)-4-butanolide (**3**) (Found: $M^{+\cdot}$ 326.1518. $C_{20}H_{22}O_4$ requires $M^{+\cdot}$ 326.1518) was achieved by the simultaneous occurrence of double-bond saturation and butanolide formation. The reaction course was advantageously followed by mass spectrometry in the "direct electron impact" mode[31] allowing direct periodic monitoring of the crude reaction mixture ($M^{+\cdot}$ of **2** = m/z 354, $M^{+\cdot}$ of **3** = m/z 326). Gas chromatography (fused silica capillary column and PTV injector) and mass spectrometry (EI) revealed **3** as a 4:1 mixture of the trans- and cis-isomers the more abundant of which being the trans-form.



The toluene solution was dried and evaporated, the residue (11.5g) was treated with cold 1% methanolic potassium hydroxide solution (24 h) to obtain a complete conversion to the trans-form[32]. The exhausted ruthenium-complex catalyst was finally removed by solvent extraction (hexane, MeOH-aq 90%) giving trans-**1** dimethylether in 49% overall yield (colorless gum from dry column chromatography (silica gel and CH_2Cl_2); ir (neat): 2838, 1771 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): 2.40-2.70 (m, H-2, H-3, H-5a, H-5b), 2.50 (dd, H-6b), 3.06 (dd, H-6a), 3.75 (6H, $-OCH_3$), 3.86 (dd, H-4b), 4.10 (dd, H-4a), 6.5-7.3 (8H, arom.); ms: $M^{+\cdot}$ 326(38), 205(15), 191(3), 159(13), 147(27), 135(9), 122(100), 121(60), 117(7), 107(8), 91(31), 77(12)). Demethylation of this dimethylether with boron tribromide[25] gave

trans-**1** (8.2g) with spectroscopic data in agreement with those reported in the literature[25,33].

Further work is currently in progress for the full exploitation of this process to synthesize other lignans having a butanolide ring in their molecule.

ACKNOWLEDGMENTS

This research was supported by the Italian Consiglio Nazionale delle Ricerche within the program "Progetti Finalizzati Chimica Fine e Secondaria, Ca2".

Thanks are due to Profs. M.Bianchi and U.Matteoli, of this University, for helpful discussion and for making hydrogenation apparatus available.

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Received, 3rd March, 1987