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# A Convenient Route to the Synthesis of Isotopomeric Dihydro-2(3H)furanones

PIERO FREDIANI,*,† LUCA ROSI,† MARCO FREDIANI,†
GIANLUCA BARTOLUCCI,‡ AND MASSIMO BAMBAGIOTTI-ALBERTI‡

Department of Organic Chemistry, University of Florence, Via della Lastruccia, 13-50019 Sesto F.no, Italy, and Department of Pharmaceutical Science, University of Florence, Via Ugo Schiff, 6-50019 Sesto F.no, Italy

A general synthetic procedure leading to isotopomeric dihydro-2(3H)furanones ($\gamma$-butyrolactones) containing two, four, or six deuterium atoms has been developed. The labeled dihydro-2(3H)furanones were synthesized in quantitative yield from the saturated diacid $C_4$ (succinic) or unsaturated diacids $C_4$ (fumaric, maleic, or acetylendicarboxylic) in the presence of $Ru_4H_4(CO)_8(PBu_3)_4$ using a deuterium pressure of 180 bar at 180 °C. This methodology was applied to the total synthesis of a hexadeuterated matairesinol lignan: The 3,4-bis{[3-methoxy-4-(phenylmethoxy)phenyl]methyl}dihydro-2(3H)furanone-[7,7′,8,8′,9′,9′-$D_6$] (benzyl-protected matairesinol-$D_6$) was fully characterized.

**KEYWORDS: Dihydro-2(3H)furanone; deuteration; ruthenium; catalyst; synthesis; isotope labeling; lignan**

## INTRODUCTION

The interest in dihydro-2(3H)furanones ($\gamma$-butyrolactones) as structural elements in organic compounds has grown in the last years. In fact, dihydro-2(3H)furanone is a typical moiety of a large variety of natural and synthetic compounds involved in agrochemicals, the food industry, and pharmaceuticals. Furthermore, compounds containing a dihydro-2(3H)furanone ring as the main structural feature exhibit broad biological properties, making them an attractive scaffold for new drugs (*1*). These compounds are also present as natural components of a wide range of foods such as fruits, wine, milk, and dairy products, providing intense and different fragrances (*2*). Some smelly dihydro-2(3H)furanones are added to many foodstuffs to increase the flavor (*3*): To do this, their amount is often required to be comparable to that naturally present. Consequently, the amount of these compounds when naturally present, artificially added, or eventually formed in metabolic processes is required.

The well-established isotope dilution assay carried out by mass spectrometry (MS-ID) is a powerful technique for quantification of analytes when stable isotopomers are readily available and affordable. So far, the possibility of developing a relatively simple method to obtain the complete sequence of differently deuterated dihydro-2(3H)furanones to be employed as an internal standard in the MS-ID assay appears desirable.

Despite the fact that a plethora of methods concerning the synthesis of dihydro-2(3H)furanones have been reported (*4*−*6*), only few procedures have been devoted to the regioselective multiple deuterium introduction into the dihydro-2(3H)furanone ring. Recently, Yoneda et al. (*7*) have prepared some saturated and unsaturated isotopomeric dihydro-2(3H)furanones by $Ru_3(CO)_{12}$-catalyzed cyclocarbonylation of deuterated allenyl alcohols. These dihydro-2(3H)furanones contain different deuterium percentages. Hislop et al. (*2*) have prepared dihydro-2(3H)furanones-$D_4$ with an alkyl moiety by deuterium reduction of protected hydroxypropionic acid and alkyl-substituted dihydro-2(3H)furanones-$D_3$ by free radical addition of 2-iodoacetamide to deuterated olefins.

Here, we report a simple one-step procedure to synthesize dihydro-2(3H)furanones containing, respectively, two, four, or six deuterium atoms by a ruthenium-catalyzed ring-closing deuteration carried out on $C_4$ dicarboxylic acids such as succinic, fumaric, maleic, or acetylendicarboxylic acid.

As an application of the described methodology, we have synthesized and fully characterized the 3,4-bis{[3-methoxy-4-(phenylmethoxy)phenyl]methyl}dihydro-2(3H)furanone-[7,7′,8,8′,9′,9′-$D_6$] (**1**) shown in **Figure 1**. This compound is a derivative of the 2(3H)furanoside lignan called matairesinol.

Lignans are a class of widespread natural compounds occurring in plants with a variety of structures (*8*, *9*). Some of these lignans, characterized by a dihydro-2(3H)furanone ring as the main structural feature, are referred to as furanoside lignans. Among these, matairesinol may be of dietary origin and it has been recognized as a precursor of the mammalian phytoestrogens such as enterolactone and enterodiol that are known for their beneficial effects on human health (*10*, *11*). Consequently, a great deal of analytical procedures aiming to determine these precursors in many plant foods have been proposed in the last years (*12*−*20*). In a previous paper, we reported a new synthetic route to furanoside lignans based on a one-step hydrogenation of the corresponding fulgenic acid catalyzed by the cluster ruthenium complex $Ru_4H_4(CO)_8(PBu_3)_4$

* To whom correspondence should be addressed. Tel: +0039 055 4573522. Fax: +0039 055 4573531. E-mail: piero.frediani@unifi.it.
† Department of Organic Chemistry.
‡ Department of Pharmaceutical Science.

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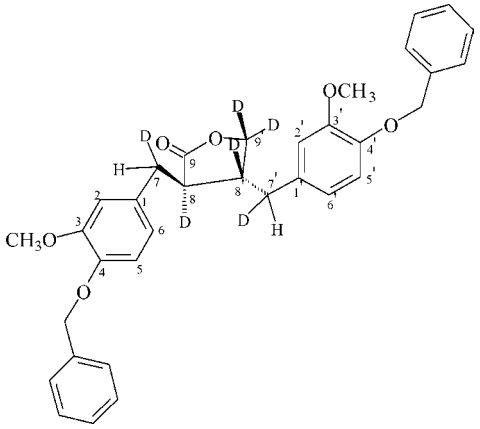


**Figure 1.** Trans form of 3,4-bis{[3-methoxy-4-(phenylmethoxy)phenyl]-methyl}dihydro-2(3H)furanone-[7,7′,8,8′,9′,9′-$D_6$] (**1**).

(**2**) (*21*). In the same paper, the use of the same process was established, by simply switching from $H_2$ to $D_2$, as a very efficient way to obtain isotopomeric lignans to be employed for mass spectral evaluation of nondeuterated compounds by isotopic dilution experiments, but no characterization of the isotopomeric products was reported.

## MATERIALS AND METHODS

**Chemicals.** All manipulations were carried out using standard Schlenk techniques in a dried nitrogen atmosphere. Toluene (Aldrich) was dried by refluxing it over Na under nitrogen atmosphere, distilled (bp 110 °C), and stored under nitrogen. Tetrahydrofurane (THF, Aldrich) was dried by refluxing it over $LiAlH_4$ under a nitrogen atmosphere, distilled (bp 65 °C), and stored under nitrogen. Diethyl ether (Aldrich) was dried by refluxing it over $LiAlH_4$ under a nitrogen atmosphere, distilled (bp 35 °C), and stored under nitrogen.

Commercial maleic and fumaric acids (Carlo Erba), succinic acid (Fluka AG), acetylenedicarboxylic acid (Aldrich), dimethyl succinate (Aldrich), and Silica gel 60 (0.040−0.063 mm) (Merck) were used as received. 3-Methyoxy-4-(phenylmethoxy)benzaldehyde was prepared as reported by Bambagiotti-Alberti et al. (*20*). $Ru_4H_4(CO)_8(PBu_3)_4$ (**3**) was prepared according to Piacenti et al. (*22*). Deuterium was supplied by Rivoira (99.8% pure).

**Instruments.** Gas chromatographic analyses were carried out using a Shimadzu GC-2010 instrument equipped with a SPB-5 capillary column (length, 60 m; internal diameter, 0.25 mm; film thickness, 0.25 $\mu$m) and a flame ionization detector (FID). The injection temperature was 250 °C, and the detection temperature was 260 °C. The initial temperature of the oven was kept at 130 °C for 5 min, after which the oven was heated at a rate of 5 °C/min to the final temperature of 250 °C, at which it was kept for 12 min. Gas chromatography−mass spectrometry (GC-MS) analyses were performed using a gas chromatograph with a Shimadzu QP 5050 mass spectrometer detector equipped with a SPB-1 column (length, 30 m; internal diameter, 0.25 mm; film thickness, 0.10 $\mu$m). The injection and detector temperatures were 250 °C. The oven temperature was held at 30 °C for 5 min, then heated at a rate of 5 °C/min up to 250, and kept at this temperature for 1 min. Multinuclear NMR spectra were registered using a Varian Mercury 400 spectrometer operating at 399.919 MHz for $^1$H and 100.570 MHz for $^{13}$C.

**Table 1.** Synthesis of Dihydro-2(3H)furanones[a]

| entry | acid | isotopomeric dihydrofuran-2-one | code | yield (%) | isotopic purity % (by NMR) |
|---|---|---|---|---|---|
| 1 | succinic | [5,5-$D_2$] | 4 | 100 | 96.3 |
| 2 | maleic | [3,4,5,5-$D_4$] | 5 | 100 | 94.9 |
| 3 | fumaric | [3,4,5,5-$D_4$] | 5 | 100 | 98.7 |
| 4 | acetylenedicarboxylic | [3,3,4,4,5,5-$D_6$] | 6 | 100 | ND |

[a] p($D_2$), 120 bar at room temperature; substrate:catalyst, 350:1; solvent, THF; temperature, 180 °C; and reaction time, 48 h.

The mass spectra of **1** were acquired in positive mode over 150:800 *m*/*z* range using a Varian 1200L triple quadrupole mass spectrometer equipped with atmospheric pressure chemical ionization (APCI) ion source. The APCI source was operated with the following settings: nitrogen nebulizing, drying and auxiliary gas at pressures of 3.0, 1.2, and 1.5 bar, respectively; nebulizing and auxiliary temperature at 350 °C; drying gas temperature at 200 °C; and corona current at 5 $\mu$A. Acquisition and processing data were performed using the software Varian MS on a workstation 6.6.

**Synthesis of Fulgenic Acid.** The fulgenic acid, bis[3-methoxy-4-(phenylmethoxy)phenyl]methylene-butanedioic acid (*23*) (**3**), was synthesized by the Stobbe condensation of 3-methoxy-4-(phenylmethoxy)benzaldehyde and dimethyl succinate as described in **Scheme 1**.

**Catalytic Deuteration of Dicarboxylic Acids: General Procedure.** Typically, homogeneous catalytic deuterations of dicarboxylic acids were carried out in a 150 mL stainless steel Parr autoclave electrically thermostated (±1 °C). A solution of $Ru_4H_4(CO)_8(PBu_3)_4$ catalyst (**2**) and substrate in dry THF was prepared in a Schlenk tube under nitrogen atmosphere and transferred into the air-evacuated autoclave by suction. The autoclave was pressurized with deuterium at 120 bar at room temperature. The reaction mixture was stirred and heated at 180 °C for 48 h. At the end of the reaction, the autoclave was cooled, the gas was vented out, the solution was collected, and the solvent was removed under vacuum. The catalyst was removed from the crude by flash chromatography using a glass column (length, 28 cm; internal diameter, 1.8 cm) filled with Silica gel 60 and diethyl ether as the eluent. A sample of the colorless eluted solution was taken, and after evaporation of the solvent, the residue was used for NMR, MS, and GC-FID analyses. Usually, the total yield was 100%, evaluated by GC-FID using 1,3,5-trimethylbenzene as an internal standard.

**Preparation of Isotopomeric Dihydro-2(3H)furanones.** The following compounds were prepared using the general procedure above-described.

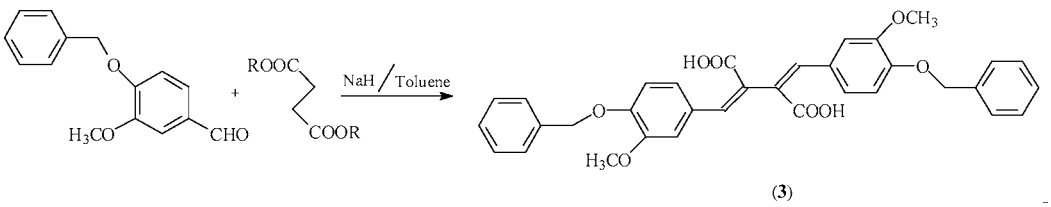
*Dihydro-2(3H)furanone-[5,5-$D_2$] (**4**).* A 151.81 mg (1.29 mmol) amount of succinic acid and 5.36 mg ($3.7 \times 10^{-3}$ mmol) of the catalyst in 30 mL of dry THF (entry 1, **Table 1**) were used.

*Dihydro-2(3H)furanone-[3,4,5,5-$D_4$] (**5**).* A 142.92 mg (1.23 mmol) amount of maleic acid and 5.02 mg ($3.5 \times 10^{-3}$ mmol) of the catalyst in 30 mL of dry THF (entry 2, **Table 1**) were used.

*Dihydro-2(3H)furanone-[3,4,5,5-$D_4$] (**5**).* A 145.94 mg (1.26 mmol) amount of fumaric acid and 5.02 mg ($3.5 \times 10^{-3}$ mmol) of the catalyst in 30 mL of THF (entry 3, **Table 1**) were used.

*Dihydro-2(3H)furanone-[3,3,4,4,5,5-$D_6$] (**6**).* A 142.81 mg (1.25 mmol) amount of acetylenedicarboxylic acid and 5.12 mg ($3.6 \times 10^{-3}$ mmol) of the catalyst in 30 mL of dry THF (entry 3, **Table 1**) were used.

**Scheme 1.** Synthesis of Fulgenic Acid




(**3**)

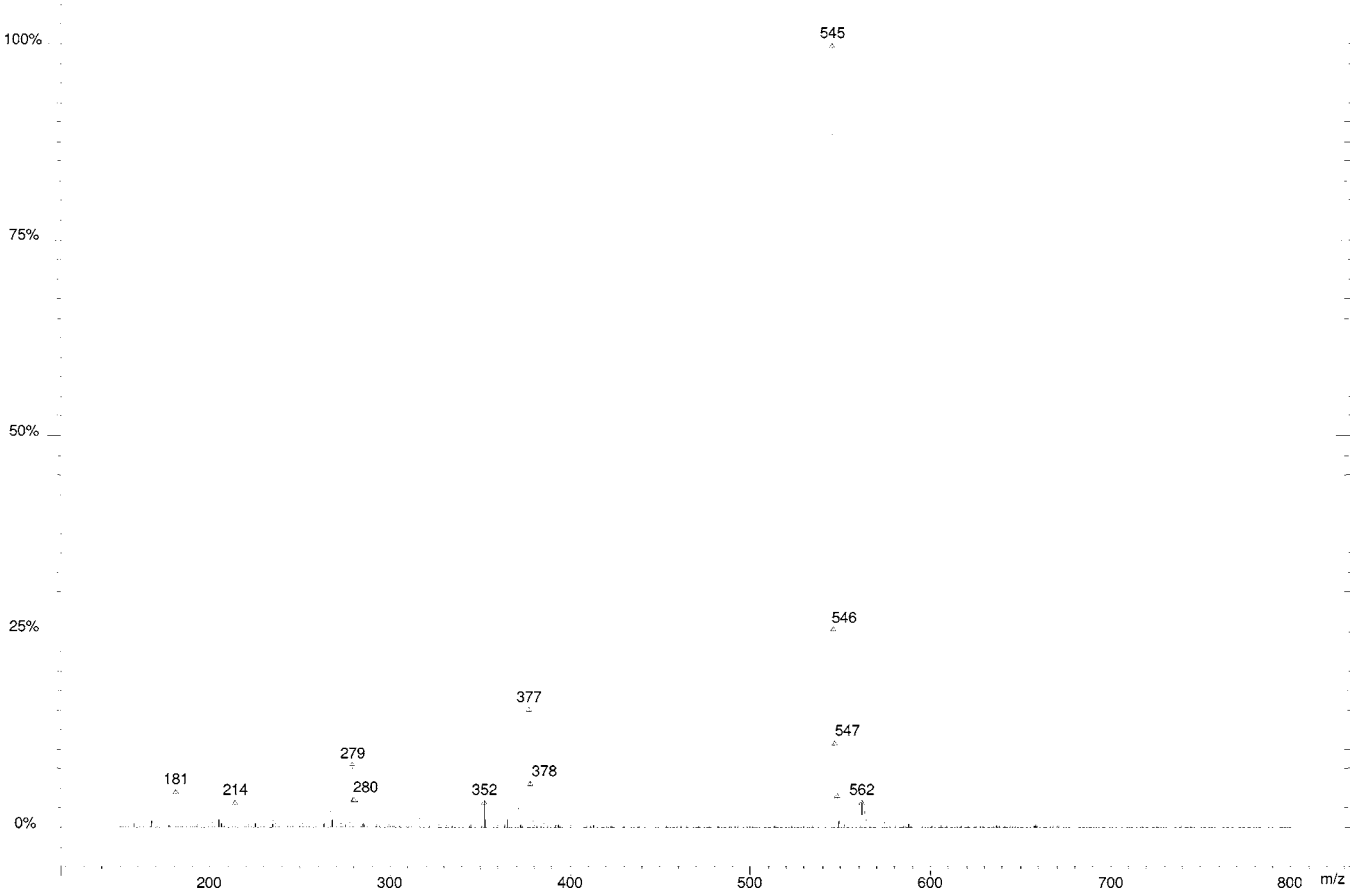



**Figure 2.** FIA-APCI-MS (flow injection analysis using an APCI-MS instrument) spectrum of 3,4-bis{[3-methoxy-4-(phenylmethoxy)phenyl]methyl}dihydro-2(3H)furanone-[7,7′,8,8′,9′,9′-$D_6$].

Because deuterations were obtained with a quantitative conversion, at the end of the deuteration, it was required only to remove the catalyst and the solvent from the reaction product. Preparative separations of the differently deuterated dihydro-2(3H)furanones were carried out as above-described.

**Catalytic Deuteration of Fulgenic Acid (3).** A 285.0 mg amount of **3** (5.03 mmol), 7.3 mg of **2** ($5.06 \times 10^{-3}$ mmol), and 25 mL of dried toluene were introduced in the autoclave under a nitrogen atmosphere; the vessel was closed, and the deuteration was performed as reported in the general procedure. At the end of the reaction, the reactor was cooled, the gas was vented out, and the solution was collected. The toluene solution was evaporated under vacuum to 2 mL, then dry methanol was added (10 mL), and the solution was left overnight. The weak gray gum precipitate was filtered and washed with methanol, obtaining the product with a 90% yield that was characterized through APCI-MS (**Figure 2**) and NMR analyses.

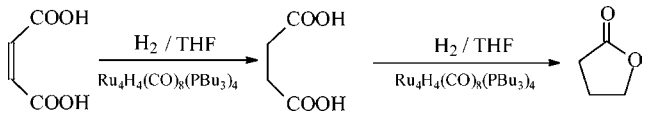
## RESULTS AND DISCUSSION

**Synthesis of Isotopomeric Dihydro-2(3H)furanones.** Metal ring-closing strategies have been widely developed for the synthesis of dihydro-2(3H)furanones (*5*). For instance, Trost et al. have prepared some dihydro-2(3H)furanones by ruthenium-catalyzed cycloisomerization-oxidation of propargyl alcohols (*24*).

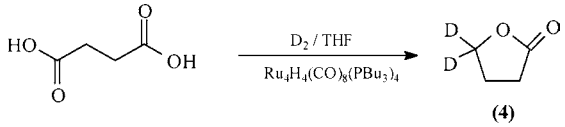
Our strategy has been developed in consideration of the well-known capability of the soluble ruthenium carbonyl hydride cluster (**2**) to catalyze the reduction of a C═C double bond of fumaric or maleic acid to succinic acid and its subsequent reduction to $\gamma$-hydroxy acid followed by ring closure to dihydro-2(3H)furanone, in 100% yield (*25*), according to **Scheme 2**.

With this background and with the aim of preparing isotopomeric dihydro-2(3H)furanones, we undertook the preparation

**Scheme 2.** Ring Closing Hydrogenation Catalyzed by $Ru_4H_4(CO)_8(PBu_3)_4$ (**3**)

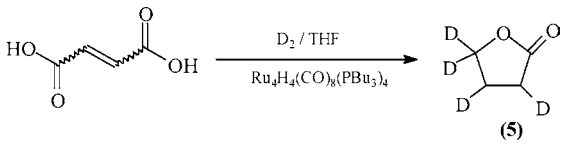



**Scheme 3.** Synthesis of Dideuterated Dihydro-2(3H)furanone-[5,5-$D_2$] (**4**) from Succinic Acid




(**4**)

**Scheme 4.** Synthesis of Tetradeuterated Dihydro-2(3H)furanone-[3,4,5,5-$D_4$] (**5**) from Maleic or Fumaric Acids

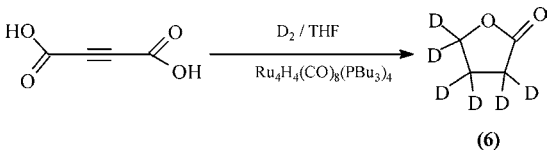



(**5**)

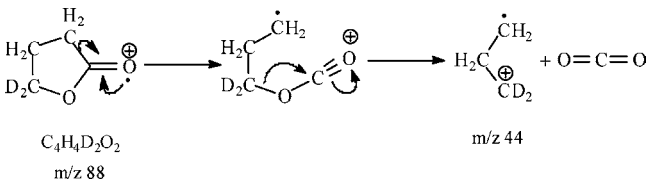
of dihydro-2(3H)furanone-[5,5-$D_2$] (**4**) starting from succinic acid (**Scheme 3**), then dihydro-2(3H)furanone-[3,4,5,5-$D_4$] (**5**) from maleic or fumaric acid (**Scheme 4**), and finally dihydro-2(3H)furanone-[3,3,4,4,5,5-$D_6$] (**6**) using acetylenedicarboxylic acid as the starting material (**Scheme 5**).

After initial attempts to find suitable reaction conditions, we converted succinic, maleic, fumaric, or acetylendicarboxylic acid into deuterated dihydro-2(3H)furanones with quantitative yield (**Table 1**).

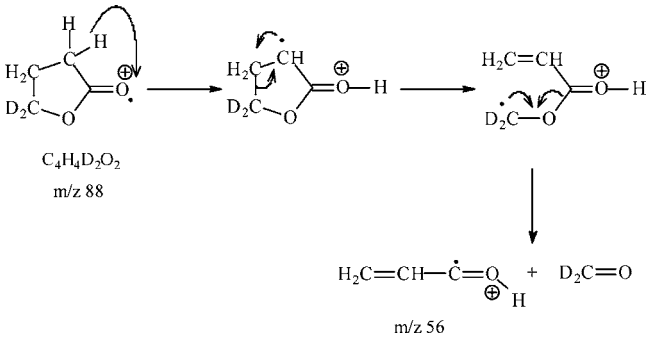
**Scheme 5.** Synthesis of Hexadeuterated Dihydro-2(3H)furanone-[3,3,4,4,5,5-$D_6$] (**6**) from Acetylenedicarboxylic Acid




**Scheme 6.** 3,5-Bond Splitting of Dihydro-2(3H)furanone-[5,5-$D_2$] (**4**)




**Scheme 7.** H-Rearrangement Followed by a 1,4-Bond Splitting of Dihydro-2(3H)furanone-[5,5-$D_2$] (**4**)



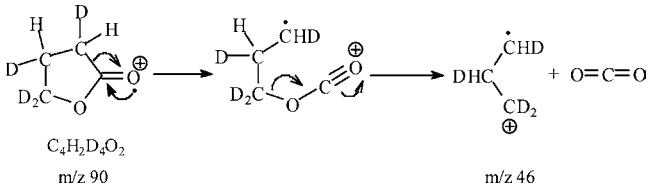

Dihydro-2(3H)furanone-[5,5-$D_2$] (**4**) (entry 1, **Table 1**) was prepared using THF as the solvent and succinic acid as the starting material. An uncolored fraction of **4** was collected, identified by GC, and characterized by MS and $^1$H NMR analysis.

Dihydro-2(3H)furanone -[3,4,5,5-$D_4$] (**5**) (entry 2, **Table 1**) was prepared using THF as the solvent and maleic acid as the starting material. An uncolored fraction of **5** was collected, identified by GC, and characterized by MS and $^1$H NMR analyses. The same experimental conditions were carried out employing fumaric acid (entry 3, **Table 1**) as the starting material providing the same product of entry 2 (**Table 1**) with almost the same yield.

Dihydro-2(3H)furanone -[3,3,4,4,5,5-$D_6$] (**6**) (entry 4, **Table 1**) was prepared using THF as the solvent and acetylenedicarboxylic acid as the starting material. An uncolored fraction of **6** was collected, identified by GC, and characterized by MS and $^1$H NMR analyses.

**MS and NMR Characterization of Isotopomeric Dihydro-2(3H)furanones.** *Dihydro-2(3H)furanone-[5,5-$D_2$] (4).* The mass spectrum of **4** shows peaks at *m*/*z* 88 $[M]^{+\cdot}$, 56 $[CH_2{=}CH{-}C{=}OH]^{+\cdot}$, and 44 $[CH_2{-}CH_2{-}CD_2]^{+\cdot}$ (100%). The interpretation of the mass spectrum of dihydro-2(3H)furanone-[5,5-$D_2$] has been provided on the basis of that of the dihydro-2(3H)furanone (*26*). The molecular ion peak is present at *m*/*z* 88, two mass units higher than the unlabeled compound, confirming the incorporation of two deuterium atoms into the dihydro-2(3H)furanone ring. **Schemes 6** and **7** illustrate two suggested fragmentations for **4**. The mass spectrum shows a base peak at *m*/*z* 44 formed through a 3,5-bond splitting from **4**. Another fragmentation involves the initial migration of a hydrogen of the alkyl chain followed by a loss of 32 ($D_2C{=}O$)

**Scheme 8.** 3,5-Bond Splitting of Dihydro-2(3H)furanone-[3,4,5,5-$D_4$] (**5**)




leading to the peak at *m*/*z* 56, indicating the incorporation of deuterium in the $CD_2O$ moiety.

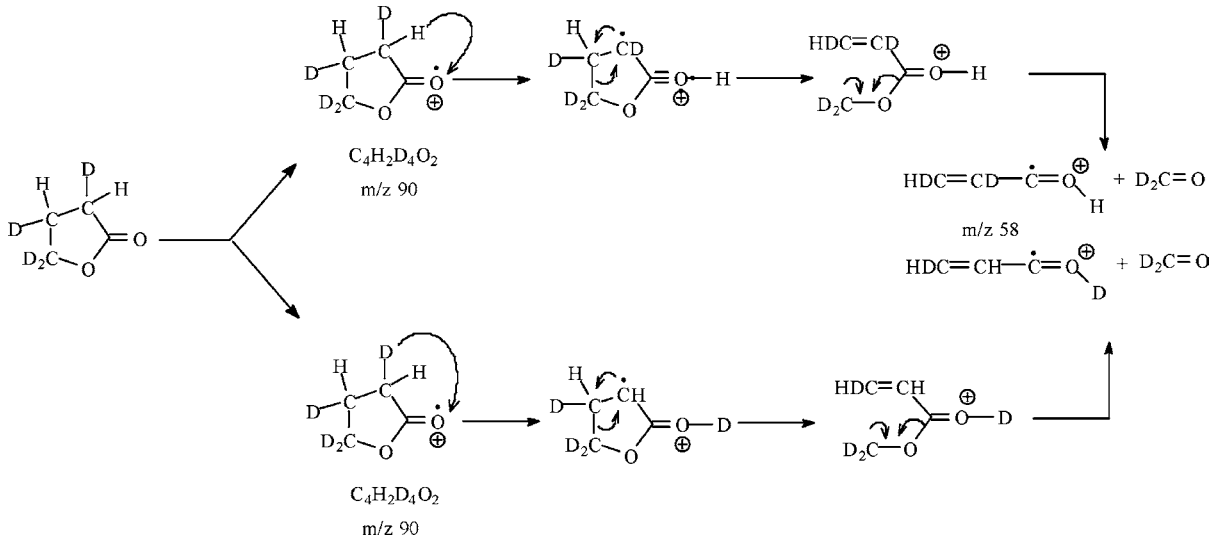
The presence of the deuterium atoms in position 5 of the ring is confirmed by the $^1$H NMR spectra of this compound: Peaks referred to as dihydro-2(3H)furanone-[5,5-$D_2$] are centered at 2.17 ppm ($-CH_2-CH_2-CO-$) and 2.45 ppm ($-CH_2-CH_2-CO-$), while the signal at 4.35 ppm almost disappeared. The amount of deuterium incorporation was evaluated by integration of the residual hydrogen signals with respect to those of the $CH_2-CH_2$ groups in the 3- and 4-positions. Integration of residual signal indicates a 96.3% incorporation of deuterium according to the relative intensities of peaks at *m*/*z* 88 and 86 in the mass spectrum.

*Dihydro-2(3H)furanone-[3,4,5,5-$D_4$] (5).* The GC-MS spectra of the product obtained from deuteration of fumaric or maleic acid show peaks at *m*/*z* 90 $[M]^{+\cdot}$, 58 $[CHD{=}CD{-}C{=}OH]^{+\cdot}$, and 46 $[CHD{-}CHD{-}CD_2]^{+\cdot}$ (100%). In this case also, the interpretation of the mass spectrum of **5** has been provided according to that of nondeuterated compound (*26*). The molecular ion peak is shown at *m*/*z* 90, indicating the incorporation of four deuterium atoms into the dihydro-2(3H)furanone ring. **Schemes 8** and **9** show two suggested fragmentations. The mass spectrum has a base peak at *m*/*z* 46 $[CHD{-}CHD{-}CD_2]^{+\cdot}$ given by a 1−4-bond splitting of **5**. Initial migration of a hydrogen of the alkyl chain followed by a loss of 32 ($D_2C{=}O$) leads to *m*/*z* 58 as the base peak $[CHD{=}CD{-}C{=}OH]^{+\cdot}$.

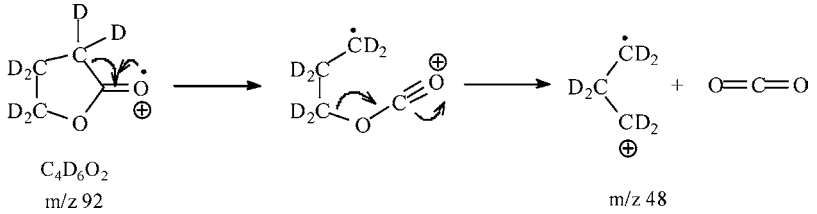
This interpretation is supported by the $^1$H NMR spectra of **5** obtained from deuteration of maleic acid: The insertion of deuterium in the position 3, 4, and 5 of the dihydro-2(3H)-furanone is shown by the practically complete disappearance of the signal at 4.35 ppm referred to $O-CH_2-$ group in the spectrum of nondeuterated dihydro-2(3H)furanone and collapse of the multiplets at 2.24 ($-CH_2-CH_2-CO-$) and 2.47 ($-CH_2-CH_2-CO-$) ppm into broaden singlets. Integration of residual signal indicates a 94.9% incorporation of deuterium when maleic acid or 98.7% when fumaric acid was employed as substrate. These data are in agreement with MS spectra.

*Dihydro-2(3H)furanone-[3,3,4,4,5,5-$D_6$] (6).* The GC-MS spectra of **6** obtained by deuteration of acetylenedicarboxylic acid shows peaks at *m*/*z* 92 $[M]^{+\cdot}$, 60 $[CD_2{=}CD{-}C{=}OD]^{+\cdot}$, and 48 $[CD_2{-}CD_2{-}CD_2]^{+\cdot}$ (100%). This spectrum has also been interpreted in agreement with that one of dihydro-furan-2-one (*26*). The molecular ion peak is present at *m*/*z* 92 ($C_4D_6O_2$), six mass units higher than the unlabeled compound, indicating the incorporation of six deuterium atoms into the dihydro-2(3H)-furanone ring. **Schemes 9** and **10** show two suggested fragmentations. The base peak at *m*/*z* 48 is attributed to $[CD_2-CD_2-CD_2]^{+\cdot}$ formed through a 3,5-bond splitting of **6** (**Scheme 10**). Initial migration of a deuterium on the alkyl chain of the molecular ion followed by a loss of 32 ($D_2C{=}O$) leads to a peak at *m*/*z* 60 $[CD_2{=}CD{-}C{=}OD]^{+\cdot}$ (**Scheme 11**). According to this interpretation, only very weak signals referred to the residual hydrogens of dihydro-2(3H)furanone were present in the $^1$H NMR spectrum of **6**, confirming the synthesis of fully

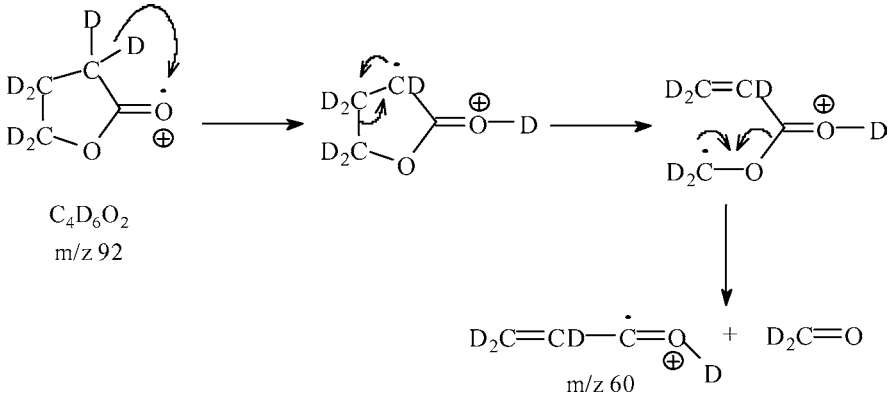
**Scheme 9.** H- or D-Rearrangement Followed by a 1,4-Bond Splitting of Dihydro-2(3H)furanone-[3,4,5,5-$D_4$] (**5**)




**Scheme 10.** 3,5-Bond Splitting of Dihydro-2(3H)furanone-[3,3,4,4,5,5-$D_6$] (**6**)




**Scheme 11.** D-Rearrangement Followed by a 1,4-Bond Splitting of Dihydro-2(3H)furanone-[3,3,4,4,5,5-$D_6$] (**6**)




deuterated dihydro-2(3H)furanone with a very high isotopic purity in agreement with the MS spectrum.

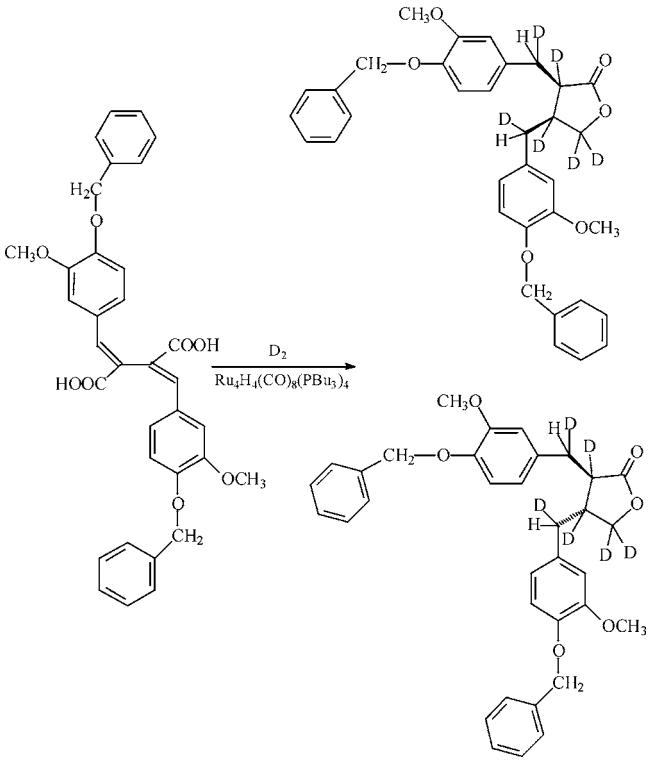
**Synthesis of 3,4-Bis{[3-methoxy-4-(phenylmethoxy)phenyl]-methyl}dihydro-2(3H)furanone-[7,7′,8,8′,9′,9′-$D_6$] and Its Conversion to Matairesinol-$D_6$.** The procedure for the synthesis of the furanoside-$D_6$ (**1**) is described in detail together with the full characterization of the product. The cluster ruthenium complex (**2**) successfully offered an efficient path to deuterium-labeled benzyl-protected matairesinol, simply by switching from $H_2$ to $D_2$ in the same operative conditions of the hydrogenation reaction.

In the deuteration step, the fulgenic acid was added to the cluster ruthenium complex in a 100/1 substrate/catalyst ratio. The reaction provides the simultaneous deuteration of the double bonds, the reduction of one carboxylic group, and the closure of the hydroxy acid to the furanoside moiety, giving rise to the benzyl-protected matairesinol-$D_6$ in a 10:1 *trans*:*cis* ratio (**Scheme 12**). The one-step conversion of the acid occurred in 48 h at 180 °C under a $D_2$ pressure of 120 bar (at room temperature). In this way, six deuterium atoms were introduced into the molecule (**Figure 1**) as confirmed by APCI-MS measurement (**Figure 2**) showing a molecular ion peak six mass units higher than the analogue nondeuterated dihydro-2(3H)-furanone derivative.

The benzyl protection remained unaffected by the deuteration. When required, the phenolic function may be easily restored by a conventional hydrogenolysis (Pd/charcoal), in order to obtain deuterated matairesinol to be used as an internal standard in MS isotope dilution assay for the quantification of naturally matairesinol occurring in food or drugs samples.

**MS and NMR Characterization of 3,4-Bis{[3-methoxy-4-(phenylmethoxy)phenyl}methyl]dihydro-2(3H)furanone-[7,7′,8,8′,9′,9′-$D_6$] (1).** Concerning the diastoisomeric isomers present in the deuterated isotopomeric product, we report the range of the chemical shift attributed to the nuclei at any time. The carbon numeration is reported in **Figure 1** where the trans form of **1** is represented.

**Scheme 12.** Deuteration of Fulgenic Acid in the Presence of $Ru_4H_4(CO)_8(PBu_3)_4$




$^1$H NMR (400 MHz, $CDCl_3$): 7.456 to 7.271 (10 H, m, nonequivalent aromatic protons of the benzyl groups), 6.867 to 6.439 (6 H, m, $C_2H$, $C_{2'}H$, $C_5H$, $C_{5'}H$, $C_6H$, $C_{6'}H$), 5.146 and 5.117 (4 H, two ps, Ph−C$H_2$O), 3.891 to 3.807 (6 H, m, OC$H_3$), and 3.217 to 2.228 (2 H, m, $C_7H$D and $C_{7'}H$D) ppm.

$^{13}$C NMR (400 MHz, $CDCl_3$): 178.7 and 178.0 (C═O), 149.9 to 149.7 ($C_4$ and $C_{4'}$), 147.1 to 147.0 ($C_3$ and $C_{3'}$), 137.1 (benzyl group), 131.8 to 131.5 and 131.0 to 130.8 ($C_1$ and $C_{1'}$), 128.5 to 127.2 (benzyl group), 121.3 to 120.3 ($C_6$ and $C_{6'}$), 114.4 to 114.1 ($C_2$ and $C_{2'}$), 112.9 to 112.3 ($C_5$ and $C_{5'}$), 71.2 to 71.1 (Ph−$CH_2$−Ph), 56.0 ($OCH_3$), 45.7 and 40.2 ($C_8$ and $C_{8'}$), 37.6 and 32.2 ($C_{7'}$), and 34.1 and 30.2 ($C_7$) ppm; the signal of $C_{9'}$ is overwhelmed by the signals of $CH_2$−Ph group in the range 71.2 to 71.1 ppm.

Confirmatory attribution of the signals for the couple $C_7$ and $C_{7'}$ came from gHMBC and gHSQC spectrum sequences. All attributions were in agreement with those reported by Chimichi et al. (*27*).

The MS spectrum of **1** was obtained by flow injection analysis (FIA) of a water:methanol 1:1 solution, containing about 10 ppm of analyte. The spectrum (**Figure 2**) shows $[MD_6H]^+$ as a base peak at 545 *m*/*z* and its adduct $[MD_6(NH_4)]^+$ at 562 *m*/*z*. Other minor signals were detected at 377 *m*/*z* (formed by loss of benzyl and phenyl groups), 279 *m*/*z* (formed by loss of 1-phenylmethoxy-2-methylbenzene group), and 214 *m*/*z* corresponding to the protonated 1-phenylmethoxy-2-methylbenzene group. Finally, the total conversion of the furanoside lignans to the trans form may be performed if required by treatment with methanolic potassium hydroxide solution (*28*).

**Conclusion**. A general procedure for the synthesis of differently isotopomeric dihydro-2(3H)furanones has been reported. The method is general, and it was easily applied to the synthesis of the hexadeuterated benzyl-protected matairesinol 3,4-bis{[3-methoxy-4-(phenylmethoxy)phenyl]methyl}dihydro-2(3H)furanone-[7,7′,8,8′,9′,9′-$D_6$] (**1**), a derivative of the natural lignans containing the dihydro-2(3H)furanone moiety. This product has been employed for isotopic dilution mass spectrometry analysis. This procedure could be worthy and extended to the synthesis of other furanoside lignans.

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