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STEREOCHEMISTRY AND ISOTOPE EFFECTS IN THE DEUTERIATION OF HINDERED 2,3-DIHYDROFURANS

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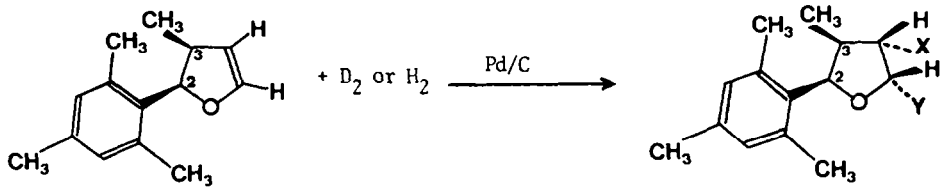
Abstrat - Reductions by deuterium over Pd/C were carried out on a series of dihydrofuran compounds. A stereoselective cis hydrogenation is observed in all cases. The stereochemistry of the dideuteriated products was determined by NOE measurements. According to the steric hindrance of the substituents, deuterium entry is found on the α face or the β face of dihydrofuran ring. The formation of mono- or trideuteriated products may occur from an exchange reaction between adsorbed hydrogenated and semi-hydrogenated species. An unexpected reverse kinetic isotope effect at C4 is observed, showing a very low vibrationnal energy of atomic hydrogen dissolved in the metal lattice.

INTRODUCTION

Our search for determining comparative parameters for exchange rates and barriers to rotation in phenyl dihydro- and tetrahydrofuran products,[1] leads us to synthesize the deuteriated compounds 2a or 2c.



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2a X = Y = D
2c X = D, Y = H
2d X = Y = H

Scheme 1

Effectively, this study requires accurate ^{1}H NMR line-width or line-shape measurements for the two ortho-methyl groups but these groups and the H4α proton (X in scheme 1) have chemical shifts which are very close. However replacement of this proton by deuterium in 2a or 2c should allow an easy analysis of the methyl signals. The reduction of the dihydrofuran compound 1 with deuterium was carried out on Pd/C and the product 2a was obtained as the major product of the reaction, in addition to 5% of 2c. Therefore, in this case, the approach of 1 to the surface of the catalyst occurs only by the α face, opposite to the bulky aromatic group. Moreover, there is no evidence for isotopic exchange as predicted by the Polanyi and Horiuti mechanism[2] (e.g. exchange of H3α which could invert the methyl group configuration). This work shows the influence of the size of the substituents on the selectivity of this reduction. The kinetic isotope effects of deuterium on C4 and on C5 will be discussed.

RESULTS

As shown in Table 1, variation in the steric hindrance of the substituents on the dihydrofuran ring leads to entry of the deuterium from the α face (cis to R) or from the β face (cis to Ar). The stereochemistry of the reaction was studied by ^{1}H NMR at 250 MHz or 500 MHz and mass spectroscopy.

Each of the dideuteriated products of a- or b-type, gives for its 5α or 5β proton a characteristic doublet with a classical α-isotope shift of about -0.02 to -0.025 ppm, owing to the geminal deuterium[3]. Decoupling experiments, analysis of coupling constants and nuclear Overhauser effect measurements were used to determine the position α or β of the two remaining H4 and H5 protons. As an example, for 2a, the rotation of the aromatic ring at-70°C was slow enough that selective irradiation of the two ortho-methyl groups was possible without any noticeable saturation transfer between them[4]. The NOE values allow the distinction between the syn (2.39 ppm) and the anti[5] (2.19 ppm) methyl groups (fig. 1a), as well as the unambiguous determination of the β position of the two protons H4 and H5 in 2a. The null effect observed at room temperature for H2α by irradiation of the CH_3 doublet at 0.66 ppm (fig. 1b) proved a predominant axial character for these two substituents H2α and CH_3-3β.

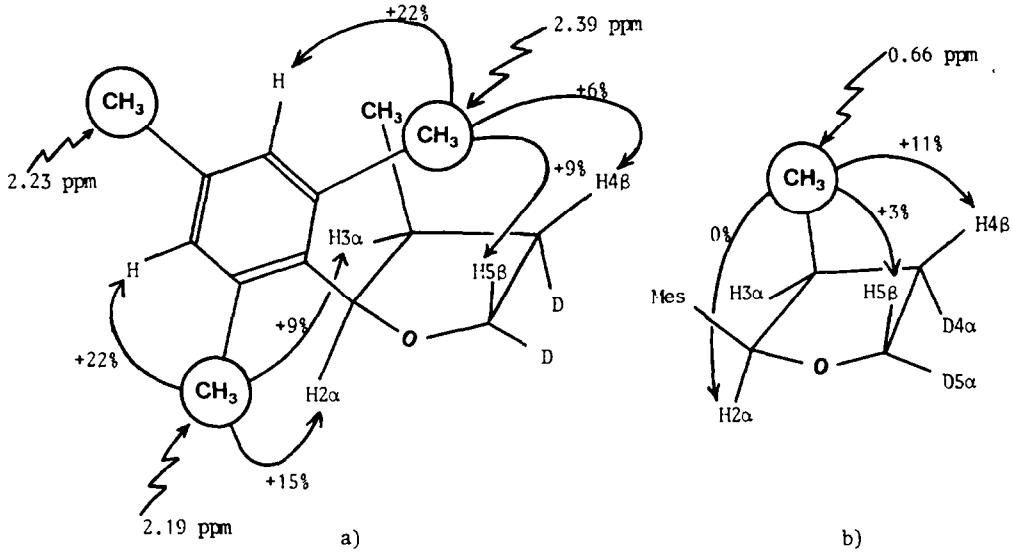
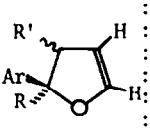
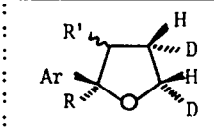
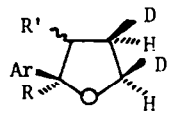


fig. 1 - NOE in the molecule 2a ($CDCl_3$ solution)
a) measured at -70°C on the aromatic methyl groups
b) measured at room temperature, on the 3β-methyl group

In some cases, a small amount (<8%) of the C4-monodeuteriated products is formed (c-type with D4α or e-type with D4β). These species are detected by two small signals in the ^1H NMR spectrum at lower field (+ 0.02 ppm) with respect to the H5 doublets corresponding to the dideuteriated products. The amount of these compounds is evaluated by analysis of the isotopic cluster of a characteristic ion (the molecular ion when possible) in mass spectroscopy. In the reduction of 1, 3, 7, 13 and 19, the absence of the 4β,5β-dideuteriated products (b-type) allows a straightforward NMR analysis of the H5α signals in the monodeuteriated products. Decoupling experiments and comparison of J values show that these monodeuteriated products are of c-type (with D4α). The amount of these monodeuteriated products is slightly solvent dependent. For 3, NMR integration indicates 4 to 5% of 4c when the reduction is performed in benzene or hexane and 7% in ethanol. A special mention is required for the reduction of 19. In hexane, 10% of 20c and 7% of a trideuteriated product (probably D4α, D5α, D5β as determined by mass and NMR spectroscopy) are formed in addition to 20a. In all other cases, the proportion of these trideuteriated products was 0 to 2%. In absolute ethanol or methanol, a small amount (13% and 17% respectively) of the 4β,5β-dideuteriated product 20b is also found.

This formation of C4-monodeuteriated compounds indicates an important difference in kinetic-isotope effects for deuterium entry at C5 and C4 (scheme 2). An evaluation of these effects is possible by using a mixture H_2 + D_2 (50 : 50) followed by analysis by mass spectroscopy and 250 or 500 MHz ^1H NMR : this was done with 3 and 19. In the case of 19, the 250 MHz NMR spectra showed

Table 1. Influence of the substitution on the stereochemistry of the dideuteriated products.

Ar	R	R'			
Mes	H	$CH_3(\beta)$	1	2a : 100%	2b : 0%
Mes	H	H	3	4a : 100%	4b : 0%
Mes	H	$CH_3(\alpha)$	5	6a : 96%	6b : 4%
Mes	CH_3	$CH_3(\beta)$	7	8a : 100%	8b : 0%
Mes	CH_3	H	9	10a : 56%	10b : 44%
Mes	CH_3	$CH_3(\alpha)$	11	12a : 41%	12b : 59%
Ph	H	$CH_3(\beta)$	13	14a : 100%	14b : 0%
Ph	H	H	15	16a : 92%	16b : 8%
Ph	H	$CH_3(\alpha)$	17	18a : 80%	18b : 20%
Ph	CH_3	$CH_3(\beta)$	19	20a : 100%	20b : 0%
Ph	CH_3	H	21	22a : 44%	22b : 56%
Ph	CH_3	$CH_3(\alpha)$	23	24a : 15%	24b : 85%
Ph	*i*Pr	$CH_3(\beta)$	25	26a : 66%	26b : 34%
Ph	*i*Pr	H	27	28a : 24%	28b : 76%
Ph	*i*Pr	$CH_3(\alpha)$	29	30a : 10%	30b : 90%

Mes = $(CH_3)_3C_6H_2$- ; Ph = C_6H_5- ; *i*Pr = $(CH_3)_2CH$-

$CH_3(\beta)$ is cis with Ar ; $CH_3(\alpha)$ is cis with R.

clearly the presence of only three species : 20a, 20c and 20d. In mass spectroscopy, the analysis of the isotopic cluster of the (M-15) peak at 11eV led to the following composition : 26% d_o, 51% d_1, 21% d_2, and 2% d_3. Correction, for the formation of d_1 and d_3 products in the deuteriation gives the values used for the calculation of the kinetic isotope effects (table 2). A similar analysis of the reduction products of 3 gave the composition : 16% d_o, 48% d_1, 35% d_2 and 1% d_3. The 500 MHz NMR spectra confirmed the presence of the three species 4a, 4c and 4d, possibly with a small amount of a C5-monodeuteriated compound (5 to 10%). These results show that the substitution of H_2 by D_2 produces a rate depression at C5 and an inverse effect on C4. The kinetic-isotope effects are calculated (table 2) as the ratio k_H/k_D for C5 (Σ products with two H on C5/Σ products with one D on C5) and as k_D/k_H for C4 (inverse effect) (Σ products with one D on C4/Σ products with two H on C4).

Table 2. Kinetic isotope effects

	d_o	d_1(C4)	d_1(C5)	d_2	k_D/k_H(C4)	k_H/k_D(C5)
3[a]	16%	48%	--	35%	5.5	1.8
3[a]	16%	40%	8%	35%	3.2	1.3
19	26%	49%	--	21%	2.7	3.6

a) two alternative values, according to the hypothesis of the amount of the C5-monodeuteriated product.

DISCUSSION

The reaction is an obvious case of a steric-approach control[6,7] in the *cis*-addition of hydrogen to a double bond, without any evidence for the reverse reactions of the Polanyi and Horiuti mechanism[2,7]. In the following discussion, the bulky aromatic group is assumed to be equatorial and, as a result of the envelope conformation of the dihydrofuran ring, R' is equatorial in position 3α or axial in position 3β (fig.2a, 2b).

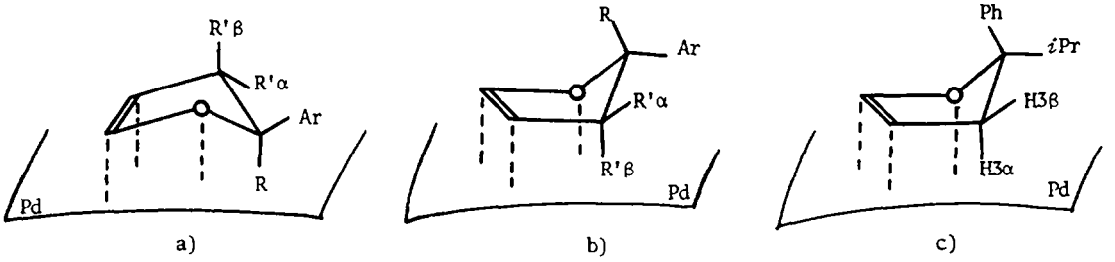


fig. 2 - the envelope conformation of the 2,3-dihydrofuran compounds and their absorption
a) by the α face with R ≠ *i*Pr
b) by the β face
c) by the α face with R = *i*Pr (compound 27)

The influence of a methyl group on the stereochemistry of the reaction is observed to be very different according to its position on C2 or C3 (table 1). As an example, with 3 (Ar = mesityl) the deuterium entry occurs only from the α face whereas very different amounts of the α and β dideuteriated products are obtained when a methyl group is introduced at the 2α position (9) or at the 3α position (5). This may be explained by the orientation of the methyl groups, which is axial at 2α but equatorial at 3α. Similar variations are observed by adding a second methyl group (11 compared to 5 or 9). In general, the presence of a 3β-methyl group leads to deuterium entry from the α face, as observed for 7, 13 and 19. In the case of 19, the formation of the isomer 20b is detected when alcohols are used as solvents (13 to 17%) : this may be explained by hydrogen bonding with the solvent on the less hindered α face of the dihydrofuran. Thus, the approach of deuterium by the β face is made more competitive (fig. 3).

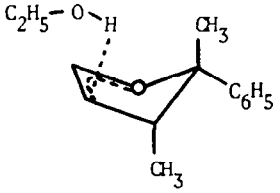


fig. 3 - Steric hindrance of the α-face of 19 by hydrogen bonding with ethanol.

The situation is probably different for 25, 27, 29 with R = *i*Pr. As a result of a similar steric hindrance of the phenyl and isopropyl groups, a facile conformational interconversion of the dihydrofuran ring may occur and so neither of these substituents is locked in an axial position (fig. 2c).

The formation of the monodeuteriated products of c-type is probably an indication of initial attack of deuterium at C4. The resulting monoadsorbed species are stabilized by the neighbouring heteroatom[8,9,10]. The structure of this intermediate does not allow for epimerisation[11] or isotopic exchange at C3. Only two reactions are then possible, the first leading to starting material, the second to the *cis*-dihydrogenated product (Scheme 2).

The reverse kinetic-isotope effect observed at C4 (table 2) is an unexpected result for a primary kinetic effect[12]. A possible explanation may be found in the small vibrational energy of H or D atoms dissoved in the metal lattice (the atomic hydrogens are not tightly bonded to the metal). The difference between the vibrational energies of the two dissolved species (... H or ...D) is small compared to the difference between the transition states where C-H and C-D bonds are partially

formed. Thus with a late transition state, the activation energy would be greater for C-H than for C-D bond formation (fig. 4).

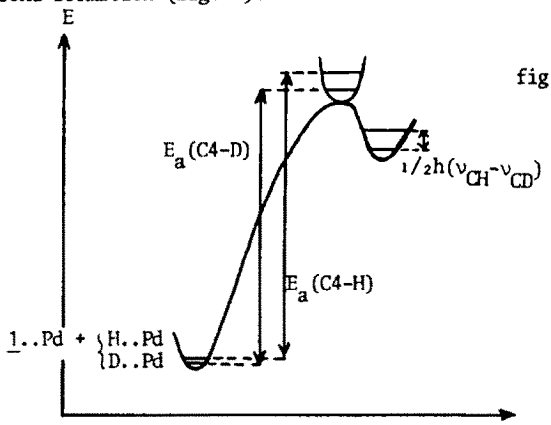
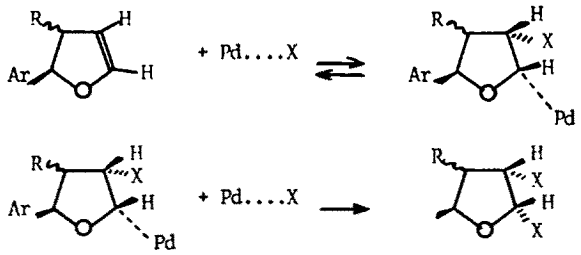


fig. 4 - Change of the zero-point energy as an interpretation of the unexpected inverse C4-isotope effect.
The loosely bonded hydrogen have low frequency vibrations. These frequencies increase in the transition state as C-H covalent bond formation occurs.



Scheme 2 (X = H or D)

Concerning the formation of a small amount of a trideuteriated product, it may result from an exchange reaction as shown in fig. 5, which would lead to an equivalent amount of the trideuteriated and the C4-monodeuteriated product. The latter product is assumed to be formed by two independent pathways : the "normal" pathway described above which results in the reverse kinetic isotope effect on C4 (concentration of the H impurities on C5) and the "bimolecular" pathway illustrated in fig. 5.

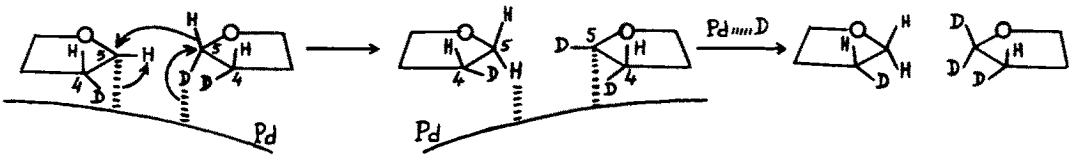


fig. 5 - Simultaneous formation of the trideuteriated and C-4 monodeuteriated products.

EXPERIMENTAL AND NMR DATA

The NMR spectra were recorded on Bruker WM 250 or WM 500 Spectrometers (Centre de Spectrochimie de l'Université Pierre et Marie Curie, Paris) on 0.1 to 0.2 M solutions in $CDCl_3$ (TMS as internal reference) (s, singlet ; d, doublet ; t, triplet ; qt, quartet ; qp, quintuplet ; hx, hexuplet ; hp heptuplet ; m, massif).

The values fHx{Hy} represent the nuclear Overhauser effects (NOE) observed on Hx by irradiation of Hy.

The 2,3-dihydrofuran coupounds were synthetized by the previously published methods[1,13]. All the natural hydrogenated products were prepared as analytic, chromatographic and NMR references.

4α,5α-dideuterio 3β-methyl 2β-mesityl tetrahydrofuran, 2a.
NMR at-70°C (δ, ppm) : 6.8 (H3', H5', s) ; 5.21 (H2α, d, 7.4 Hz) ; 4.12 (H5β, d, ≈7 Hz) ; 2.65 (H3α, hx) ; 2.39 (CH_3-2' *syn*, s) ; 2.24 (CH_3-4', s) ; 2.19 (CH_3-6' *anti*, s) ; 1.69 (H4β, ≈m) ; 0.65 (CH_3-3β, d, 7.3 Hz). In the natural product 2d, H5α and H4α appeared at 3.73 ppm and 2.25 ppm. The NOE results, measured at-70°C or at room temperature are given in fig.1 .

In the monodeuteriated product 2c (≈ 5%) H5α proton is at 3.72 ppm (H5α, ≈ t, 7.6 and 8.3 Hz).

4α,5α-dideuterio 2β-mesityl tetrahydrofuran, 4a.
NMR (δ, ppm) : 6.8 (H3', H5', s) ; 5.14 (H2α, dd, 6.4 and 9.7 Hz) ; 4.07 (H5β, d, ≈7 Hz) ; 2.33 (CH_3-2' and 6', s) ; 2.21 (CH_3-4', s) ; 2.1 (H3α and H4β, m) ; 1.83 (H3β, m). In the natural product 4d, H5α is at δ = 3.92 ppm and H4α in the massif at 2.1 ppm.
The monodeuteriated product 4c (5%) gives a signal at 3.92 ppm (H5α, dd, 5.6 and 8.1 Hz).

4α,5α-dideuterio 3α-methyl 2β-mesityl tetrahydrofuran, 6a.
NMR (δ, ppm) : 6.80 (H3' and H5', s) ; 4.76 (H2α, d, 9.5 Hz) ; 4.06 (H5β, d, ≈7 Hz) ; 2.40 (H3β, m) ; 2.35 (CH_3-2' and 6', s) ; 2.25 (CH_3-4' and H4β) ; 1.02 (CH_3-3α, d, 6.5 Hz). In the natural product 6d, H5α and H4α are at 3.93 ppm and 1.71 ppm. In the product obtained by deuteriation, we observe a complex signal near 3.92 ppm (9%) corresponding to the monodeuteriated product 6c and the stereoisomeric dideuteriated product 6b. This last product 6b was evaluated by integration of the signal of H4α at 1.70 ppm (4%).

4α,5α-dideuterio 2α, 3β-dimethyl 2β-mesityl tetrahydrofuran 8a.
NMR (δ, ppm) : 6.80 (H3' and H5', s) ; 3.90 (H5β, d, 7.6 Hz) ; 2.71 (H3α, qt, 7 Hz, JH3αH4β< 1 Hz); 2.25, 2.36 and 2.21 (CH_3-2', 4' and 6') ; 1.60 (H4β, d, 6.5 Hz) ; 1.46 (CH_3-2α, s) ; 0.67 (CH_3-3β, d, 6.8 Hz). In the natural product, H5α is very close to H5β. On the other hand, H4α is at 2.30 ppm between two aromatic methyl groups and shows the coupling constant JH3αH4α = 7.1 Hz. This signal is completely cancelled in the deuteriated product and the remaining coupling constant JH3H4< 1 Hz shows that H3 and H4 are trans and bi-equatorial in the dideuteriated product.

4α,5α-dideuterio- and 4β,5β-dideuterio 2α-methyl 2β-mesityl tetrahydrofuran, 10a *and* 10b.
NMR of the two mixed isomers (δ, ppm) : 6.79 (H3' and H5', s) ; 3.88 (H5α, d, 7.4 Hz, 44% of 10b) ; 3.45 (H5β, d, 6 Hz, 56% of 10a) ; 2.45 (CH_3-2' and 6', s) ; 2.26 (H3α and H3β, m) ; 2.21 (CH_3-4', s) ; 1.87 (H4α, m) and 1.81 (H4β, m) ; 1.52 (CH_3-2α, s). The two signals of H4α (10b, a large signal) and H4β (10a, a narrow signal) are not completely resolved at 250 MHz but are well assigned by selective decoupling of H5α and H5β and belong to distinct molecules. NOE : fH5α{CH_3-2α} = +6% ; fH5β{CH_3-2α} = 0% ; fH3',5'{CH_3-2',6'} = +26% ; fH5α{CH_3-2',6'} = +1% ; fH5β{CH_3-2',6'} = +9%.

4α,5α-dideuterio and 4β,5β-dideuterio 2α,3α-dimethyl 2β-mesityl tetrahydrofuran, 12a *and* 12b.
NMR of the two mixed isomers (δ, ppm) : 6.79 (H3' and H5', s) ; 3.83 (H5α, d, 7.3 Hz, 59% of 12b); 3.59 (H5β, d, 8.4 Hz, 41% of 12a) ; 2.74 (H3β, m) ; 2.43 (CH_3-2' and 6', s) ; 2.20 (CH_3-4', s) ; 1.85 (H4β, m) ; 1.52 (CH_3-2α, s) ; 1.47 (H4α, m) ; 1.10 (CH_3-3α, d, 7.2 Hz). A double irradiation of H4α (or H4β) gives a selective decoupling of H5α (or H5β). NOE : fH3',5'{CH_3-2',6'} = +25% ; fH5β{CH_3-2',6'} = +21% ; fH5α{CH_3-2',6'} = +2% ; fH5α{CH_3-2α} = +5% ; fH5β{CH_3-2α} = +1%.

4α,5α-dideuterio 3β-methyl 2β-phenyl tetrahydrofuran, 14a.
NMR (δ, ppm) : 7.2 (C_6H_5, m) ; 4.89 (H2α, d, 6.4 Hz) ; 4.10 (H5β, d, 7.6 Hz) ; 2.46 (H3α,≈hx, 6-7 Hz) ; 1.65 (H4β,≈t) ; 0.56 (CH_3-3β, d, 7 Hz). In the natural product 14d, two other signals are observed at 3.86 ppm (H5α) and 2.11 ppm (H4α). The monodeuteriated product 14c gives a little signal (3-4%) at 3.86 ppm (≈t, 6.8 and 8 Hz). NOE : fH2α{C_6H_5} = +4% ; fH5β{C_6H_5} = +5% ; fH4β{C_6H_5} = 0% ; fH4β{CH_3-3β} = 8.5% ; fH5β{CH_3-3β} = +3% ; fH2α{CH_3-3β} = 0%.

4α,5α-dideuterio and 4β,5β-dideuterio 2β-phenyl tetrahydrofuran, 16a *and* 16b
NMR (δ, ppm) : 7.2 - 7.4 (C_6H_5, m) ; 4.9 (H2α, t, 6.9 and 7.4 Hz) ; 4.08 (H5β, d, 7.2 Hz,≈92% of 16a) ; 3.92 (H5α, d, ≈7 Hz, ≈8% of 16b) ; 2.32 (H3α, m) ; 2.0 (H4β of 16a and H4α of 16b, m) ; 1.81 (H3β, m). The signal H5α of the monodeuteriated product 16c is mixed to the doublet of the same signal in 16b. In the signal of H3β (1.81 ppm), a coupling constant JHD = 1-1.1 Hz is observed. NOE : fH2α{C_6H_5} = +10% ; fH3α{C_6H_5} = +7% ; fH3β{C_6H_5} = 13% ; fH4β{C_6H_5} = +12% ; fH5β{C_6H_5} = +6%.
In mass spectrography, the MIKE spectrum of the natural product 16d shows only two signals at z/e = 148($M^{\cdot+}$) and 147 (M-1). A similar doublet is obtained with the deuteriated product at z/e = 150 and 149 and about 4% of monodeuteriated product is detected.

4α,5α-dideuterio and 4β,5β-dideuterio 3α-methyl 2β-phenyl tetrahydrofuran, 18a *and* 18b .
NMR of the two mixed isomers (δ, ppm) : 7.2.-7.4 (C_6H_5, m) ; 4.29 (H2α, d, 8.2 Hz) ; 4.09 (H5β, d, 7 Hz, 80% of 18a) ; 4.01 (H5α, d, 8.6 Hz, 20% of 18b) ; 2.18 (H4β, t, ≈7.2 Hz, 80% of 18a) ; 2.06 (H3β, hx, ≈7 Hz) ; 1.68 (H4α, ≈t, 20% of 18b) ; 1.09 (CH_3-3α, d, 6.5 Hz). NOE : fH2α{CH_3-3α} = 16% ; fH5β{CH_3-3α} = 1,5% ; fH5α{CH_3-3α} = +10% ; fH4β{CH_3-3α} = +9% ; fH4α{CH_3-3α} = +7% ; fH2α{C_6H_5}=17% fH5β{C_6H_5} = +6% ; fH3β{C_6H_5} = +7% ; fH5α, H4α, H4β{C_6H_5} = 0%. The methyl group is equatorial.

4α,5α-dideuterio 2α,3β-dimethyl 2β-phenyl tetrahydrofuran, 20a.
NMR at 250 MHz of the mixture 85% 20a and 15% 20c (δ, ppm) : 7.3 (4H, C_6H_5 *ortho* and *meta*, m) ; 7.2 (1H, C_6H_5 *para*, m) ; 4.12 (H5β, d, 8.4 Hz, overlapping a triplet at 4.14 ppm of 20c) ; 3.99 (H5α of 20c, t, 8.2 Hz) ; 2.20 (H3α, qt, 7.0 Hz) ; 1.56 (CH_3-2α and H4β, s and m) ; 0.69 (CH_3-3β, d, 7 Hz). In the natural product 20d, H4α is at 2.09 ppm.

4α,5α-dideuterio and 4β,5β-dideuterio 2α-methyl 2β-phenyl tetrahydrofuran, 22a *and* 22b.
NMR of the two mixed isomers (δ, ppm) : 7.4 (2H, C_6H_5 *ortho*, m) ; 7.31 (2H, C_6H_5 *meta*, m) ; 7.21 (1H, C_6H_5 *para*, m) ; 3.98 (H5α, d, 6.3 Hz, 56% of 22b) ; 3.85 (H5β, d, 7.8 Hz, 44% of 22a) ; 2.19 and 2.0 (H3α and H3β, m) ; 1.95 (H4α, m) ; 1.76 (H4β, m) ; 1.53 (CH_3-2α, s). NOE : fH5β{*H ortho*} = +5% ; fH5α{ *H ortho*} = 0% ; fH5β{CH_3-2α} = 1% ; fH5α{CH_3-2α} = 4%.

4α,5α-dideuterio and 4β,5β-dideuterio- 2α,3α-dimethyl 2β-phenyl tetrahydrofuran, 24a *and* 24b.
NMR of the two mixed isomers (δ, ppm) : 7.41 (2H, C_6H_5 *ortho*, m) ; 7.3 (2H, C_6H_5 *meta*, m) ; 7.2 (1H, C_6H_5 *para*) ; 4.02 (H5α, d, 8.2 Hz, 87% of 24b) ; 3.9 (H5β, d, 7.9 Hz, 13% of 24a) ; 2.3 (H3β, qt, 7.1 Hz) ; 1.99 (H4β, t, 7 Hz), 1.64 (H4α, m) ; 1.39 (CH_3-2α, s) ; 1.11 (CH_3-3α, d, 7.0 Hz). NOE : fH5β{*H ortho*} = +8% ; fH5α{CH_3-2α} = +6% ; fH5α{CH_3-3α} = +4% ; fH5β{CH_3-3α} = +2%.

4α,5α-dideuterio and 4β,5β-dideuterio 2α-isopropyl 3β-methyl 2β-phenyl tetrahydrofuran, 26a *and* 26b.
NMR of the two mixed isomers (δ, ppm) : 7.18-7.35 (C_6H_5, m) ; 4.10 (H5β, d, 8.2 Hz, 64% of isomer 26a) ; 3.86 (H5α, d, 7 Hz, 36% of isomer 26b) ; 2.52 (H3α, m) ; 2.24 (H-*i*Pr, hp, 6.8 Hz) ; 1.94 (H4α, t, 6.5 Hz, 26b) ; 1.43 (H4β, t, 8.8 Hz, 26a) ; 1.0 and 0.70 (Me-*i*Pr, two d, 6.8 Hz) ; 0.75 (Me-3β, d, 6.8 Hz). NOE : fH4α,4β,5α,5β (CH_3(*i*Pr) at 1 and 0.70 ppm) = 0% ; fH4β(CH_3-3β) = +7% ; fH4α, H5α, H5β(CH_3-3β) = 0% ; fH3α(CH_3, at 1 ppm) = +9%.

4α,5α-dideuterio and 4β,5β-dideuterio 2α-isopropyl 2β-phenyl tetrahydrofuran, 28a *and* 28b.
NMR of the two mixed isomers (δ, ppm) : 7.28-7.40 (4H, C_6H_5 *ortho* and *meta*, m) ; 7.21 (1H, *para*, m) ; 3.90 (H5α, d, 7.4 Hz, 77% of 28b) ; 3.73 (H5β, d, 7.9 Hz, 23% of 28a) ; 2.07 and 2.21 (H3α and H3β, m) ; 2.0 (H-*i*Pr, hp, 6.5 Hz) ; 1.84 (H4α, m, 28b) ; 1.68 (H4β, m, 28a) ; 0.80 and 0.90 (CH_3-*i*Pr, d and d, 6.8 Hz).
The stereochemical assignment of the two isomers 28a and 28b is well established by the regular decrease of the amounts of 16a (92%)- 22a (44%)- 28a (23%) with the increasing hindrance of R (H, Me, *i*Pr).

4β,5β-dideuterio 3α-methyl 2α-isopropyl 2β-phenyl tetrahydrofuran, 30b.
The main product 30b (about 78%) is formed with 7-8% of 30a and the monodeuteriated derivatives as by-products (≈14%).
NMR (δ, ppm) : 7.2-7.4 (5H, C_6H_5, m) ; 3.94 (H5α, d, 8 Hz) ; 2.65 (H3β, dd, 6.9 Hz and 2.1 Hz) ; 2.11 (H-*i*Pr, hp, 6.9 Hz) ; 1.48 (H4α, dd, 8 and 2.1 Hz) ; 1.13 (CH_3-3α, d, 6.9 Hz) ; 0.72 and 0.83 (CH_3-*i*Pr, d, and d, 6.9 Hz). In the natural product, H5β and H4β appeared at 3.72 and 1.68 ppm.
The stereochemistry of this product is well deduced from inspection of the series 26b - 28b - 30b. As a matter of fact, the coupling JH3βH4α = 2.1 Hz shows that these protons are trans and bie-quatorial.

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