NOTE

SYNTHESIS OF HEXADEUTERATED HEXESTROL

(R,S)-3,4-DI-(4-HYDROXYPHENYL)HEXANE-1,1,1,6,6,6-$^2H_6$

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SUMMARY

A short and stereoselective synthesis of hexadeuterated hexestrol is described, involving catalytic hydrogenation of Z-3,4-di-(4-methoxyphenyl)hex-3-ene-1,1,1,6,6,6-$^2H_6$ followed by demethylation using sodium thioethoxide in dimethyl formamide.

KEY WORDS : $^2H_6$-hexestrol, deuterium labelling, isotope dilution gas chromatography/mass spectrometry.

RESULTS AND DISCUSSION

In a previous communication we described the 3-step synthesis of hexadeuterated diethylstilbestrol (4) starting from 1-(4-methoxyphenyl)propan-1-one-3,3,3-$^2H_3$ (1)[1]. The route

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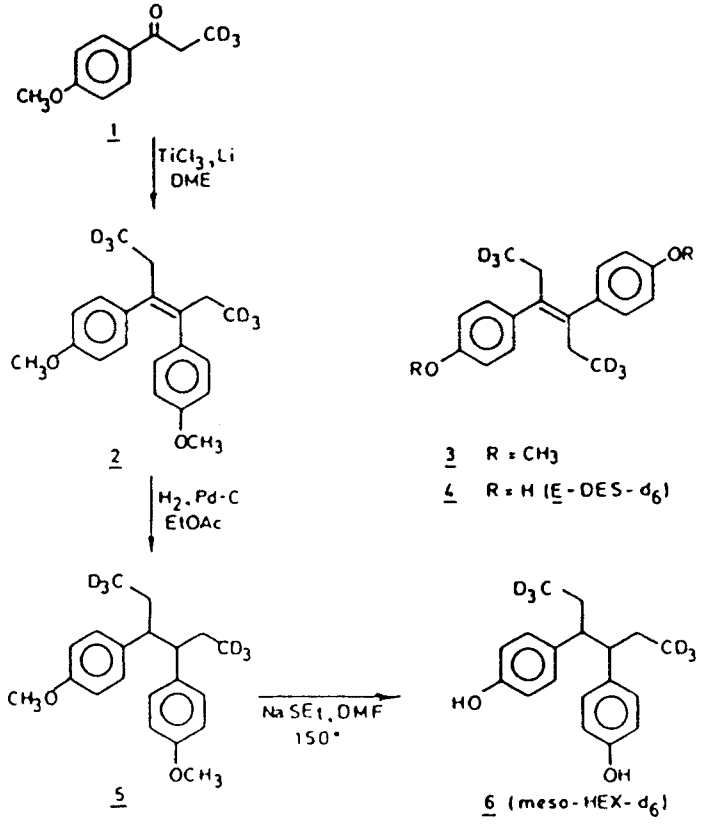
was based on the low valent titanium induced coupling of 1 (Li-$TiCl_3$ reagent)[2] which gave a mixture of olefins 2 and 3, largely in favor of the Z-isomer 2 (ratio 95:5, respectively)[3]. Subsequent treatment with trimethylsilyl iodide, followed by methanol, resulted in demethylation and concomitant isomerization to 4. In view of the predominant formation of the Z-isomer 2 in the reductive coupling reaction, the same route is ideally suited for the stereoselective production of (R,S-3,4-di-(4-hydroxyphenyl)hexane-1,1,1,6,6,6-$^2H_6$ (meso-HEX-d_6; 6) as shown below. The non-stereoselective synthesis of a tetradeuterated hexestrol derivative, i.e., (R,S)-3,4-di-(4-hydroxyphenyl)hexane-2,2,5,5-$^2H_4$,has been reported recently along different lines[4].



The catalytic hydrogenation of pure Z-3,4-di-(4-methoxyphenyl)hex-3-ene-1,1,1,6,6,6-$^2H_6$ (2)[1] with palladium on carbon (10 %) in ethyl acetate[5] gave the meso-derivative 5 as a single diastereomer in quantitative yield. Subsequent demethylation was performed using sodium thioethoxide in dimethyl formamide at 150°C (5 hrs)[6] and gave, after recrystallization from benzene, the desired hexadeuterated hexestrol 6 in 70 % overall yield. The product showed the same TLC behavior as authentic meso-hexestrol. Both labelled derivatives 5 (m.p. 138°C) and 6 (m.p. 186°C) were found isotopically pure by ^1H NMR (360 MHz). No significant amounts of non deuterated derivative could be observed as can be seen on Figure 1.

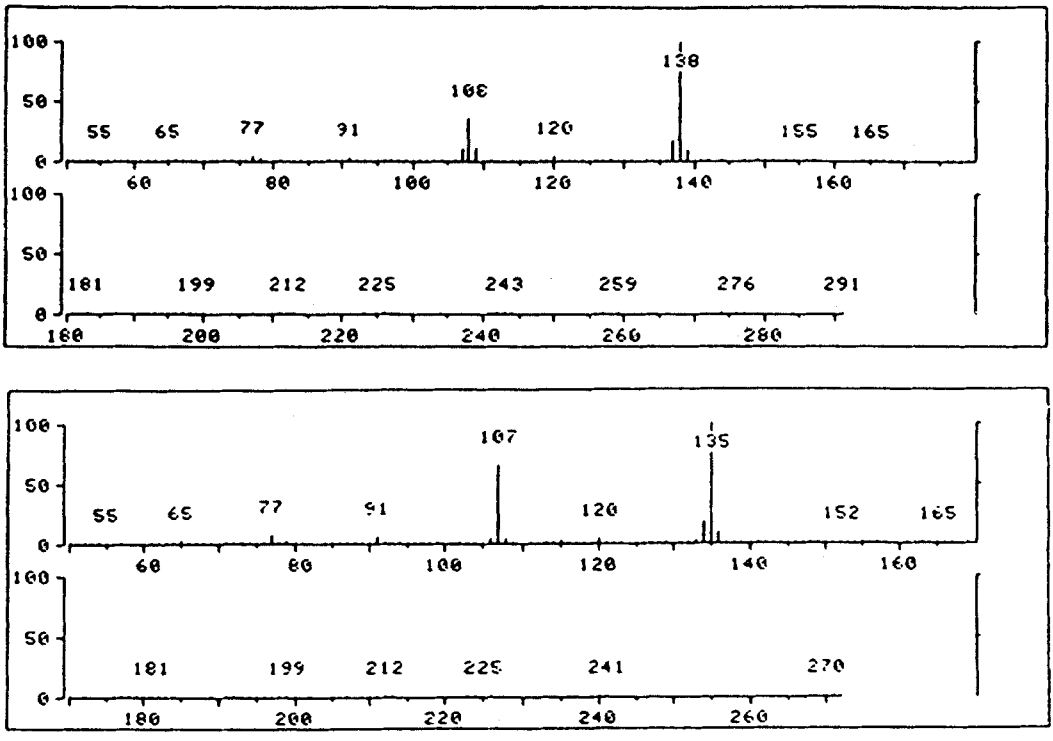


Figure 1 : Mass spectrum of the synthesized hexadeuterated hexestrol (6) (top) and of the unlabelled homologue (bottom).

EXPERIMENTAL

The melting points are uncorrected. The ^1H NMR spectra were recorded at 360 MHz (WH-Brucker) in chloroform-d with tetramethylsilane as internal standard ; chemical shifts (δ) are given in ppm.

Rf values are quoted for Merck silica gel 60 GF_{254} TLC plates of 0.25 mm thickness.

Palladium on carbon (10 %) was purchased from Merck. Ethyl acetate (Janssen Chimica) was distilled from diphosphorpentoxide and dimethyl formamide (Janssen Chimica) from calcium hydride. Sodium hydride (60 % in mineral oil) was purchased from Janssen Chimica. Ethanethiol (Janssen Chimica) was used without further purification. Authentic hexestrol was obtained from Sigma.

(R,S)-3,4-di-(4-methoxyphenyl)hexane-1,1,1,6,6,6- H_6 (5)

A solution of Z-olefin 2 (0.62 g ; 2.05 mmol) in ethyl acetate (15 ml) is hydrogenated over palladium on carbon (10 %, 0.15 g) at atmospheric pressure. After the hydrogen uptake has subsided, the solution is filtered over silica gel (elution with ethyl acetate) and concentrated in vacuo to yield crystalline meso-5 (625 mg), which is further used without purification. An analytical sample is obtained via recrystallization from benzene (m.p. 138°C). Rf (hexane-ethyl acetate, 95:5) : 0.31. ^1H NMR : 1.24 (2H, m), 1.37 (2H, m), 2.47 (2H, m), 3.81 (6H, s), 6.86 (4H, m), 7.09 (4H, m) ppm.

(R,S)-3,4-di-(4-hydroxyphenyl)hexane-1,1,1,6,6,6,- H_6 (6)

To a solution of sodium thioethoxide, prepared from sodium hydride (680 mg of a 60 % suspension in mineral oil ; 17 mmol) and ethanethiol (1.26 ml ; 17 mmol), in dimethyl formamide (10 ml) is added a suspension of meso-5 (0.517 g ; 1.7 mmol) in dimethyl formamide (15 ml). After stirring for 5 hrs at 150°C the reaction mixture is cooled to room temperature and acidified with 10 % hydrochloric acid (pH 1-2). After extraction

with 1:1 ether-hexane (5 times) the organic phases are extracted with 5 % sodium hydroxide solution (5 times) and the combined aqueous phases acidified with 10 % hydrochloric acid and extracted with 1:1 ether-hexane (5 times). The combined organic phases are washed with brine and dried over magnesium sulfate. After filtration and concentration in vacuo white crystalline material is obtained which, after two recrystallizations from benzene, gave pure meso-hexestrol-d_6 (6 ; 327 mg) in 70 % overall yield (m.p. 186°C). Rf (ethyl acetate-hexane, 2:8) : 0.11. ^{1}H NMR : 1.23 (2H, m), 1.38 (2H, m), 2.45 (2H, m), 4.62 (2H, br s), 6.78 (4H, m), 7.01 (4H, m).

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