THE SYNTHESIS OF ESTRAGOLE LABELLED WITH DEUTERIUM IN SINGLE POSITIONS OF THE ALLYLIC SIDE CHAIN

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SUMMARY

[γ-$^2H_2$]Estragole was synthesized *via* vinylation of 4-methoxy-[methylene-$^2H_2$]-benzyl chloride; [β-^2H]estragole *via* reduction of 3-(*p*-anisyl)-propyne with bis-3-methyl-2-butylborane (obtained from $LiAl^2H_4$, BF_3 etherate and 2-methyl-2-butene); [α-^2H]estragole *via* reduction of the tosylhydrazone of 4-methoxy-[formyl-^2H]-cinnamaldehyde with $NaBH_3CN$.

Key Words: [γ-$^2H_2$]Estragole, [β-^2H]estragole, [α-^2H]estragole, vinylation, $NaBH_3CN$ reduction.

INTRODUCTION

Allylphenols and their methyl ethers, e.g. 1-5, are widely distributed in higher plants[1,2]. They are present in the higher boiling (aromatic) fractions of the most essential oils and flavoring agents with which individual have daily contact. Significant pharmacological activity has been shown for some of them[3], particularly for estragole[4], and in a few instances a carcinogenic character has been reported taking place through a "metabolic activation" of the allylic side chain. To study the metabolism of these compounds and their distribution *in vivo* allylbenzenes specifically labelled in the allyl group are desirable. Such tracer compounds are also required for biosynthetic

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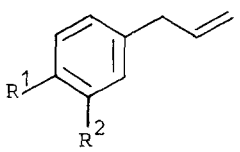
as well as enzymic studies.

In connection with our investigation on the biosynthesis of allylphenols in basil (Ocimum basilicum)[5] we needed estragole (2, p-allylmethoxybenzene) specifically labelled with isotopic hydrogen in each of the three position of the side chain. The synthesis of $[\gamma\text{-}^2H_2]$ (9), $[\beta\text{-}^2H]$ (13), $[\alpha\text{-}^2H]$ estragole[6] (17) are described here.



1	R^1=OH	R^2=H	chavicol
2	R^1=OMe	R^2=H	estragole
3	R^1=OH	R^2=OMe	eugenol
4	R^1=R^2=OMe		methyleugenol
5	R^1,R^2=OCH_2O		safrole

RESULTS AND DISCUSSION

$[\gamma\text{-}^2H_2]$Estragole (9) was prepared through route 1. The introduction of deuterium was performed by reduction of methyl-4-methoxy-benzoate (6) with $LiAl^2H_4$ to give a dideuterated 4-methoxybenzyl alcohol (7) which was then converted into the corresponding aralkyl chloride 8 by treatment with thionyl chloride. The allylic side chain was built up in one step exploiting a vinylation reaction. Dealing with this reaction, which was studied extensively for its general applicability to the synthesis of various substituted allylbenzenes,[7] we recommend: i) the use of the aralkyl chloride instead of the corresponding bromide to avoid polymerisation side-reactions, and ii) the use of THF as a solvent of choice at -65°C. The overall yield from the first deuterated intermediate was 51%.

The preparation of $[\beta\text{-}^2H]$estragole (13) was achieved according to route 2. 1-(p-anisyl)-propyne (11) was obtained instead of the expected 3-(p-anisyl)-propyne (12) by reaction of 4-methoxybenzyl chloride (10) with lithium acetylide, so that triple bond deconjugation was necessary. This was carried out by treatment of 11 with butyllithium in hexane[8]. Finally, deuterium was introduced in the last step via hydroboration of 12[8] employing bis-3-methyl-2-butylborane[9] (obtained by reaction of 2-methyl-2-butene with $LiAl^2H_4$ in the presence of BF_3 etherate) and acetic acid as solvolitic agent.

ROUTE 1

$$Ar\text{-}CO_2Et \xrightarrow{(a)} Ar\text{-}C^2H_2OH \xrightarrow{(b)} Ar\text{-}C^2H_2Cl \xrightarrow{(c)}$$

(6) (7) (8)

$$Ar\text{-}C^2H_2\text{-}CH{=}CH_2$$

(9)

(a) $LiAl^2H_4$; (b) $SOCl_2$; (c) $LiCH{=}CH_2$

ROUTE 2

$$Ar\text{-}CH_2Cl \xrightarrow{(a)} Ar\text{-}C{\equiv}C\text{-}CH_3 \xrightarrow{(b)} Ar\text{-}CH_2\text{-}C{\equiv}CH \xrightarrow{(c)}$$

(10) (11) (12)

$$Ar\text{-}CH_2\text{-}C^2H{=}CH_2$$

(13)

(a) $LiC{\equiv}CH$; (b) BuLi; (c) i) 2-methyl-2-butene, $LiAl^2H_4$, BF_3 eth. ii) CH_3CO_2H

ROUTE 3

$$Ar\text{-}CH{=}CH\text{-}CO_2Et \xrightarrow{(a)} Ar\text{-}CH{=}CH\text{-}C^2H_2OH \xrightarrow{(b)}$$

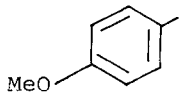
(14) (15)

$$Ar\text{-}CH{=}CH\text{-}C^2H{=}N\text{-}NH\text{-}Ts \xrightarrow{(c)} Ar\text{-}CH_2\text{-}CH{=}C^2HH$$

(16) (17)

(a) $LiAl^2H_4$; (b) i) MnO_2 ii) $Ts\text{-}NH\text{-}NH_2$; (c) $NaBH_3CN$

Ar =



The synthesis of [α-^{2}H]estragole (17) is shown in route 3. The dideuterated alcohol 15, formed by reduction of ethyl-(E)-4-methoxycinnamate (14) with $LiAl^2H_4$, was oxidised to the corresponding aldehyde by the method of Attenburrow et al.[10]. Treatment of the tosylhydrazone 16 of the deuterated aldehyde with $NaBH_3CN$ according to Hutchins et al.[11] afforded the expected estragole 17 monodeuterated at α-position (30% overall yield from 14). It can be noticed that the NMR spectrum of 17 was consistent with a pratically uniform isotopic substitution of the two hydrogen atoms of the terminal methylene group.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Model 257 spectrometer, NMR spectra on a Varian Model NV 14 spectrometer at 60 MHz using deuteriochloroform as solvent and tetramethylsilane as internal reference. Elemental analysis were consistent with the calculated values. TLC were carried out on silica gel HF_{254} plates; the products were visualized under UV light and by spraying with aqueous sulfuric acid. Gas-liquid chromathography (GLC) was carried out on a Carlo Erba Fractovap 2400 V instrument with nitrogen (1.5 atm) as carrier gas and 2 m glass columns (150°C) packed with neopentylglycole succinate (LAC 767) (3% w/w) on Chromosorb W silanized (80-100 mesh). GLC-MS was performed on LKB 9000 mass-spectrometer using a glass column as above.

4-methoxy-[methylene-$^2H_2$]benzylic alcohol (7). A suspension of $LiAl^2H_4$ (Merck 99% ^2H, 2.5 g) in dry ether (50 ml) was added slowly (1/2 hr) to a solution of methyl-4-methoxybenzoate (5 g) in dry ether (200 ml) under stirring and in Ar atmosphere. After refluxing for 3 hr, 15% aqueous solution of NaOH (3 ml) and successively water (9 ml) were added to the reaction mixture. The ethereal phase was washed twice with water (2 x 50 ml), dried over anhydrous magnesium sulfate and evaporated to dryness. The residue (4.2 g), exhibiting spectroscopic properties coherent with its structure, was shown by GLC to be pure enough to be used in the next step without further purification.

4-methoxy-[methylene-$^2H_2$]benzyl chloride (8). Thionyl chloride (3.6 ml) in $CHCl_3$ (30 ml) was added dropwise during 1 hr to a solution of 4-methoxy-[methylene-$^2H_2$]benzyl alcohol (4.2 g) in

$CHCl_3$ (100 ml). After keeping the reaction mixture under reflux for 8 hr, then at room temperature overnight, $CHCl_3$ was evaporated *in vacuo* and the residue treated with dry benzene (4 x 50 ml) till complete elimination of thionyl chloride. The crude product so obtained by bidistillation (140° C at 0.9 mmHg) afforded 3.8 g of an oil (79% yield from 6) which was found to be pure 4-methoxy-[methylene-$^2H_2$]-benzyl chloride on the basis of NMR, GLC-MS and elemental analysis.

[γ-$^2H_2$]Estragole (9). 4-methoxy-[methylene-$^2H_2$]benzyl chloride (2.12 g) in anhydrous THF (20 ml) was added dropwise to a 2 M solution of vinyllithium in THF (20 ml) cooled at -65° C. The reaction mixture was kept under stirring and in Ar atmosphere at -65° C for 3 hr and at room temperature overnight. After addition of ether (30 ml) and 5% HCl (30 ml) the organic layer was separated, washed with water (20 ml), then with 5% aqueous solution of $NaHCO_3$ (20 ml) and with water again. It was finally anhydrified with magnesium sulphate and evaporated to dryness *in vacuo* (20 mmHg at 30° C). The crude oil so obtained was purified by chromatography on a silica gel column. Fractions eluted with light petroleum (b.p. 40-70° C)-benzene (4:1) afforded by careful evaporation a product which was shown to be pure [γ-$^2H_2$]estragole (1.3 g, 65% yield, $^2H_2$-species>95%) by a comparison of its spectroscopic (NMR) and GLC-MS properties with those of an authentic sample of natural estragole.

NMR δ 3.68 (s, 3H, OCH_3), 5 (m, 2H, $=CH_2$), 5.95 (dd broad, J_{cis}=9 Hz, J_{trans}=17 Hz, 1H, -CH=), 6.78 (d, J=9 Hz, 2H, arom.), 7.08 (d, J=9 Hz, 2H, arom.).

GLC-MS m/e (I%): 150 (100, M^+), 149 (37), 119 (31), 123 (30), 135 (20), 107 (17), 93 (8), 92 (10), 80 (13), 79 (10), 78 (12).

3-(p-anisyl)-propyne (12). A solution of 4-methoxybenzyl chloride (1.6 g) in freshly distilled DMSO (10 ml) was added slowly and under magnetic stirring (Ar atmosphere) to a suspension of lithium acetylide (1.8 g) in DMSO (20 ml). After stirring at room temperature overnight, ether (40 ml) and 5% HCl (40 ml) were added to the reaction mixture, the organic layer was separated, washed with water (20 ml), then with 5% aqueous solution of $NaHCO_3$ (20 ml) and with water again (20 ml). It was finally anhydrified with magnesium sulphate and evaporated to dryness *in vacuo* giving crude 1-(p-anisyl)-propyne (11) (1.15 g). Its purification by

bidistillation in vacuo (120° C at 0.05 mmHg) gave a product (0.8 g, 54% yield) identical by TLC, GLC-MS, IR and NMR with a sample of 11 previously prepared through a different route[8]. A solution of 1-(p-anisyl)-propyne (540 mg) in n-hexane (15 ml) was treated with n-buyllithium (9 ml, 20-25% in hexane) and refluxed under Ar overnight. After addition of water with external cooling, extraction with ether, evaporation of the solvent and distillation (76-77° C at 0.1 mmHg) afforded pure 3-(p-anisyl)-propyne (325 mg, 60% yield).

[β-^{2}H]Estragole (13). BF_3 etherate (0.6 ml) in dry ether (5 ml) was added dropwise, at 0° C under Ar, to a suspension of $LiAl^2H_4$ (Merck 99% ^{2}H, 150 mg) in dry ether (20 ml). After keeping at 0° C for 8 hr, 3-(p-anisyl)propyne (300 mg) in ether (10 ml) was added to bis-3-methyl-2-butylborane. The reaction mixture was allowed to warm up to room temperature and stirred overnight. Excess deuteride was destroyed with acetone (2 ml). Glacial acetic acid (5 ml) was then added and the mixture left at room temperature for 4 hr. Usual work-up gave a crude product that by chromatography on silica gel column, as previously described, gave pure [β-^{2}H]estragole (165 mg, 54% yield, ^{2}H-species>95% by MS and NMR).
NMR δ 3.34 (s,2H, $-C\underline{H}_2-$), 3.78 (s, 3H, $OC\underline{H}_3$), 5.03 (m, 2H, $=C\underline{H}_2$), 6.82 (d, J=9 Hz, 2H, arom.), 7.11 (d, J=9 Hz, 2H, arom.).
GLC-MS m/e (I%): 149 (100, M^+), 148 (45), 134 (21), 121 (33), 118 (30), 106 (18) 92 (10), 91 (9), 78 (18), 77 (14).

4-methoxy-[α-$^2H_2$]cinnamyl alcohol (15). $LiAl^2H_4$ (Merck 99% ^{2}H, 1 g) was added slowly to a solution of ethyl-4-methoxy-cinnamate (14) (2.5 g) in dry ether (30 ml) cooled at -10° C. After addition was complete, H_2SO_4 (100 ml, 10%) was added and extraction was performed with ether. Evaporation of ethereal solution, after usual work-up, afforded pure 4-methoxy-[α-$^2H_2$]-cinnamyl alcohol (1.9 g, 95% yield).
IR (Nujol): 3270 (O-H), 2085 (C-^{2}H) and 1655 cm^{-1} (C=C).
NMR δ 1.9 (s, 1H, O$\underline{H}$), 3.75 (s, 3H, $OC\underline{H}_3$), 6.14 (d, J=16 Hz, 1H, C(β)-$\underline{H}$), 6.57 (d, J=16 Hz, 1H, C(γ)-$\underline{H}$), 6.82 (d, J=9 Hz, 2H, arom.), 7.29 (d, J=9 Hz, 2H, arom.), no signal corresponding to $C\underline{H}_2OH$.

4-methoxy-[α-^{2}H]cinnamaldehydetosylhydrazone (16). 4-methoxy-[α-^{2}H]cinnamyl alcohol (1 g) in CCl_4 (50 ml) was treated with "active" MnO_2 (15 g, prepared according to Attenburrow[10]) under stirring at room temperature for 2 hr. After filtering off the insoluble residue the solvent was evaporated to yield

the crude aldehyde [IR (liquid film): 2075 (C-^{2}H) and 1660 cm^{-1} (unsaturated C=O)], which was converted into the tosylhydrazone by treatment with p-toluensulphonylhydrazine in a minimum amount of absolute EtOH (5 ml) refluxing for 2 hr. Cooling the solution afforded cristalline product 16 (1.05 g, 53% yield).
NMR δ 2.35 (s, 3H, Ar-C$\underline{H}_3$), 3.75 (s, 3H, OC$\underline{H}_3$), complex pattern of signals between 6.6 and 8 (10 H, aromatic and olefinic protons), 8.5 (broad s, 1H, N$\underline{H}$).
MS m/e (I%): 331 (10%, M^+), 176 (100%, M^+- $CH_3C_6H_4SO_2$); [330 and 175 in MS of the non-deuterated compound].

[α-^{2}H]Estragole (17). To a solution of tosylhydrazone 16 (0.2 M) and $NaBH_3CN$ (0.8 M), in 1:1 DMF-sulfolane, hexane (5 ml) and a small amount of Bromcresol Green were added. Acidification was carried out by adding concentrated HCl dropwise through the top of the condenser until the blue-green color changed to tan. The reaction was heated at 110° C for 4 hr. Upon completion, the reaction was diluted with brine and extracted several times with benzene. The organic layer was dried and carefully evaporated. The residue was purified on silica gel column, as indicated above, to yield pure [α-^{2}H]estragole (60% yield, ^{2}H-species≅75±5% by MS).
NMR δ 3.31 (d, J=6.5 Hz, 2H, C$\underline{H}_2$), 3.74 (s, 3H, OC$\underline{H}_3$), 5.0 (m, 1-1.2 H, C=C$\underline{H}^2$H), 5.9 (m, 1H, C$\underline{H}$=C), 6.8 (d, J=9 Hz, 2H, arom.), 7.1 (d, J=9 Hz, 2H, arom.).
GLC-MS m/e (I%): 149 (100, M^+), 148 (54), 134 (22), 121 (33), 118 (33), 106 (20), 92 (12), 91 (12), 78 (20), 77 (17).

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