Synthesis of [2,8-^{2}H$_2$]Oct-1-ene
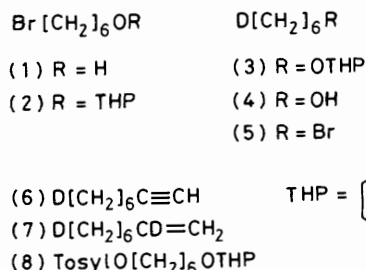
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[2,8-^{2}H$_2$]Oct-1-ene, with 98% and 93% deuterium incorporation at C-2 and C-8, respectively, is prepared from 6-bromohexan-1-ol in a six-step synthesis which offers access to a wide range of ω-labelled acyclic aliphatic compounds.

The application of deuterium- and tritium-labelling to bio-synthetic and mechanistic problems is common practice. However, the synthesis of compounds carrying singly labelled methyl groups at the ends of saturated aliphatic chains has received little attention. Sumitani and his co-workers [1] have described a specific route for ω-deuteriated-butanols, -pen-tanols, and -hexanols which involves aluminium cleavage of the corresponding cyclic ethers. Egyed and his co-workers [2] examined a more general method in which the hydroxy-group of an ω-halogeno-alcohol was protected by conversion into the magnesium halogen salt before the terminal halogen was displaced *via* the Grignard reagent. However, yields from this step were, in general, low. In some cases this was presumably due to the insolubility of the initial salts but competition for the active sites on the surface of the magnesium between the ionic centres of the alkoxide group and the carbon–halogen bond is another complicating factor. In both investigations, the isotopic purity of the product was dictated by the isotopic abundance in the deuteriated species used to hydrolyse the organometallic intermediate, and incorporations >90% were reported.

In connection with studies on alkene oxygenation at rho-dium complexes,[3] moderate quantities (10—30 g) of the alkene [2,8-^{2}H$_2$]oct-1-ene (7), with high isotopic abundances of deuterium, were required. Preliminary studies established that terminal alkenes specifically deuteriated at the 2-position could be more readily prepared from the corresponding al-kyne, using deuteriated disiamylborane,[4,†] than by treating the vinylic carbanion from base-promoted decomposition of a 2-tosylhydrazone with D$_2$O.[5] For the introduction of deuteri-um at the saturated centre, hydrolysis of a Grignard reagent with D$_2$O was preferred to deuteride displacement of a tosyl ester group, as the bromo-derivative (2) could be more easily obtained, in a pure form, from the readily available hexane-1,6-diol than could the alternative tosyl ester (8).[6]

Monobromination [7] of hexane-1,6-diol gave 6-bromo-hexan-1-ol (1) which was smoothly converted into the tetra-hydropyranyl derivative (2). Formation of the corresponding Grignard reagent proved to be more difficult than had been expected. In ethereal solution only low yields of product were formed, even in the presence of 1,2-dibromoethane, but by using tetrahydrofuran (THF) as solvent and 1-bromopropane as an entrainment agent, yields of the required [6-^{2}H$_1$]hexyl tetrahydropyran-2-yl ether (3) were obtained in >90% yield. The protecting group was cleanly removed using dilute H$_2$SO$_4$ in methanol. This reaction generates a second tetrahydro-pyran-2-yl ether which, for practical purposes, should have a boiling point well removed from that of the required alcohol. In this case methanol was the solvent of choice. In separating the products by fractional distillation, precautions had to be taken to ensure that no trace of acid was present to catalyse the back-reaction [equation (1)].

Br[CH$_2$]$_6$OR

(1) R = H
(2) R = THP

D[CH$_2$]$_6$R

(3) R = OTHP
(4) R = OH
(5) R = Br

(6) D[CH$_2$]$_6$C≡CH
(7) D[CH$_2$]$_6$CD=CH$_2$
(8) Tosyl O[CH$_2$]$_6$OTHP

THP =

Accurate deuterium-incorporation measurements, which were most readily made on 6-bromo[1-^{2}H$_1$]hexane (5), pre-pared from the alcohol by standard methods,[8] showed an incorporation of 92.9%. For this purpose the (C$_6$H$_{12}$D)$^+$ fragment (m/z = 86) was utilised. Treatment of the bromide with the ethylene diamine complex [9] of lithium acetylide gave [8-^{2}H$_1$]oct-1-yne (6) which was converted into the required alkene (7) with deuteriodisiamylborane using procedures adapted from those described by Brown and Zweifel.[4] In both stages yields were close to 90%. On the basis of a quantitative examination of the molecular ion, the octene was found to con-tain 8.9% of monodeuteriated material which, when taken with the incorporation at C-8, indicates a 98% incorporation of deuterium at C-2.

Experimental

I.r. spectra were measured on a Perkin-Elmer 357 grating spectrophotometer. ^{1}H N.m.r. spectra were determined in CDCl$_3$ solutions with a JEOL PFT 100 instrument using Me$_4$Si as the internal reference. For the mass spectra, samples were separated from trace impurities on a Pye 104 gas chroma-tograph (9 ft, 10% PEGA column) before being passed directly into a Micromass 16F instrument. Deuterium-incorporation figures were derived from 12 3-second scans over a range of ten mass units centred on the signals used for analysis. The scans were uniformly distributed over the length of the relevant g.l.c. peaks.

Nitrogen (B.O.C. White spot) was passed through concen-trated H$_2$SO$_4$ before use. THF (May & Baker) was purified by distillation from LiAlH$_4$ under nitrogen, and was stored under nitrogen in the dark. Dimethyl sulphoxide (DMSO) (Fisons) was purified by distillation from Ca$_2$H, and was stored under nitrogen in the dark. Diglyme [bis-(2-methoxyethyl) ether] was purified by distillation under reduced pressure from LiAlH$_4$ and stored at 5 °C in the dark under nitrogen. Light petroleum refers to that fraction boiling in the range 40—60 °C.

6-Bromohexyl Tetrahydropyran-2-yl Ether (2).—The tetra-hydropyranyl ether was prepared by the standard method from dihydropyran (55.35 g, 0.658 mol) and 6-bromohexan-1-ol (1) [7] (107.15 g, 0.592 mol) in chloroform with toluene-*p*-sulphonic

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† Deuteriobis-(1,2-dimethylpropyl)borane.

$$\text{(structure)} + \text{Me[CH}_2]_5\text{OH} \longrightarrow \text{(structure)} \quad + \text{ MeOH} \quad (1)$$
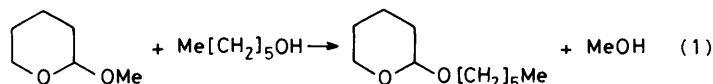
acid as catalyst. The distilled product, b.p. 102—107 °C at 0.02 mmHg, contained a small amount of parent alcohol which was removed by chromatography on basic alumina with 20% diethyl ether in light petroleum as eluant.

[6-^{2}H$_1$]*Hexyl Tetrahydropyran-2-yl Ether* (3).—This compound was prepared under dry nitrogen. After the initiation of reaction, a solution of 6-bromohexyl tetrahydropyran-2-yl ether (2) (57 g, 0.25 mol) and 1-bromopropane (28.7 g, 0.233 mol) in THF (150 cm^3) was added to magnesium turnings (14 g 0.576 mol) in THF (125 cm^3) at a rate which maintained a continuous, vigorous reaction. At the end of this period (*ca.* 90 min) the solution was refluxed and stirred for 5 h before being cooled to −40 °C. The organometallic complex was decomposed by cautious, dropwise addition of D$_2$O (45 cm^3) to the stirred solution. After a further 15 min at −40 °C the solution was kept overnight at room temperature before being worked up. G.l.c. analysis at this stage showed a >90% yield of the labelled hexyl ether as a pale, yellow oil which was used in the next stage without further purification.

[6-^{2}H$_1$]*Hexan-1-ol* (4).—2M H$_2$SO$_4$ (8 cm^3) was added to a solution of the monodeuteriated tetrahydropyranyl ether (3) (85 g, 0.455 mol) in methanol (400 cm^3). The slightly turbid solution was refluxed gently for 30 min after which time deprotection of the alcohol function was shown to be complete (g.l.c.). The cooled solution was diluted with saturated aqueous NaCl (200 cm^3) and was then extracted with diethyl ether (2 × 100 cm^3). The extracts were washed in turn with aqueous NaHCO$_3$ and water and were then dried (MgSO$_4$) and fractionally distilled over anhydrous K$_2$CO$_3$ (*ca.* 1 g) to give [6-^{2}H$_1$]hexan-1-ol, 30.5 g, 65% yield), b.p. 66—68 °C at 20 mmHg; n_D^{24} 1.4179; $\nu_{max.}$ (film) 2 175 cm^{-1} (C–D str.).

6-*Bromo*[1-^{2}H$_1$]*hexane* (5).—[6-^{2}H$_1$]Hexan-1-ol was converted into the bromide (5), b.p. 60—62 °C at 25 mmHg; n_D^{25} 1.4420; $\nu_{max.}$ 2 180 cm^{-1} (C–D str.), in 71% isolated yield by standard procedures.[8]

The mass spectrum of compound (5) showed peaks at m/z 167 and 165 (M^+), 137 and 135 (M^+ − 29), 109 and 107 (M^+ − C$_4$H$_8$D), 86 [(C$_6$H$_{12}$D)$^+$], and 85 [(C$_6$H$_{13}$)$^+$]. After correction for an abundance ratio m/z = 85: m/z = 84 of 1 : 0.02 in undeuteriated 1-bromohexane, the abundance ratio m/z = 86: m/z = 85, measured at slow scan rates for 12 separate scans, gave values of 92 and 93% for the deuterium incorporation in two separate preparations.

[8-^{2}H$_1$]*Oct*-1-*yne* (6).—Lithium acetylide–ethylenediamine complex [9] (Aldrich) (24.6 g, 0.256 mol) was added rapidly to vigorously stirred DMSO (100 cm^3) in a 250 cm^3 three-necked flask fitted with a nitrogen inlet, dropping funnel, condenser, and mechanical stirrer. The bromohexane (5) was added dropwise with the temperature maintained at 25—30°C. After the mixture had been stirred for 3 h, 5M HCl (100 cm^3) was added to decompose excess of the acetylide. The resulting two-phase mixture was poured into water (400 cm^3) and extracted with n-pentane (2 × 10 cm^3). G.l.c. analysis of the dried (MgSO$_4$) organic phase indicated an 87% yield of [8-^{2}H$_1$] oct-1-yne. Fractional distillation of this solution gave the

alkyne, b.p. 124—125 °C; n_D^{24} 1.4158; $\nu_{max.}$ 3 320 (≡C–H), 2 180 (C–D), and 2 130 cm^{-1} (C≡C).

[2,8-^{2}H$_2$]*Oct*-1-*ene* (7).—BF$_3$–Diethyl ether (12.49 g, 0.088 mol) was added dropwise, under nitrogen, to a stirred solution of 2-methylbut-2-ene (16.5 g, 0.23 mol) and NaBD$_4$ (3.7 g, 0.089 mol) in diglyme (50 cm^3) which was maintained at 0— 5 °C. After the mixture had been stirred at 0 °C for 2.5 h and then cooled to −5 °C, a solution of the oct-1-yne (6) (7.5 g, 0.068 mol) in diglyme (10 cm^3) was rapidly added. The solution and the gelatinous precipitate which formed were stirred for a further 0.5 h at 2 °C and for a further 2 h at room temperature.

Residual deuteride was decomposed by the slow addition of ethylene glycol (2.5 cm^3) in diglyme (4 cm^3). When effervescence had ceased the solution was again cooled to −5 °C and acetic acid (45 cm^3) was slowly added. The stirred solution was allowed to warm to room temperature over the next 2.5 h and was then poured into ice–water. The organic components were extracted into n-pentane (2 × 30 cm^3) and the extracts were washed in turn with dilute NaOH and saturated aqueous NaCl and were then dried (MgSO$_4$). G.l.c. analysis showed an 89% yield of the desired oct-1-ene (7). The solvent was removed and careful fractional distillation of the residue gave the title compound, b.p. 65—66 °C at 110 mm Hg; $\nu_{max.}$ 3 075 (=CH$_2$ str.), 2 225 (=CD str.), 2 180 (−H$_2$C−D str.), 995 (=CD bend), and 910 cm^{-1} (=CH$_2$ bend); δ_H 0.9 (2 H, m, DCH_2) and 4.9 (2 H, m, CH$_2$=). No signal at δ_H 5.75 (=CH−) could be detected.

The mass spectrum showed peaks at m/z 114 (M^+, C$_8$H$_{14}$D$_2$), 98 (C$_7$H$_{12}$D$^+$), and 84 (C$_6$H$_{10}$D$^+$). Slow-scan analysis, of the type outlined above, over the m/z 114 and very small 113 signal, showed a 98% incorporation of deuterium at C-2 when allowance for 93% incorporation at C-8 had been made.

References

1 M. Sumitani, K. Kanemitsuya, H. Yasuda, and H. Tani, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1511.
2 J. Egyed, A. Neszmélyi, I. Beke, and E. Baitz, *J. Labelled Compd.*, 1972, **8**, 607.
3 L. Carlton and G. Read, *J. Mol. Catal.*, 1981, **10**, 133 and papers cited therein.
4 H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1961, **83** 3834.
5 J. E. Stemke and F. T. Bond, *Tetrahedron Lett.*, 1975, 1815.
6 F. Bohlmann, R. Jenka, and R. Reinecke, *Chem. Ber.*, 1969, **102**, 3283.
7 E. F. Degering and L. G. Boatrigut, *J. Am. Chem. Soc.*, 1950, **72**, 5137.
8 O. Kamm and C. S. Marvel, *Org. Synth.*, 1958, Coll. Vol. I, p. 25.
9 R. E. A. Dear and F. L. M. Pattison, *J. Am. Chem. Soc.*, 1963, **85**, 621.