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Enantioselective Synthesis of Enantiomeric 1,3-Dideuteroallenes

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Abstract: (*R*)-1,3-$^2H_2$-Prop-2-yn-1-ol [(*R*)-**2**] was obtained by enzymatic deuteration of prop-2-yn-1-ol. Methoxymethylation and thermal rearrangement of (*R*)-**2** gave (*S*)-(1,3-$^2H_2$)allene (*S*)-**1**, while reaction of (*R*)-1-$^2H_2$-prop-2-yn-1-ol [(*R*)-**2a**] with MeOC$^2H_2$Cl followed by thermolysis afforded (*R*)-(1,3-$^2H_2$)allene (*R*)-**1**, the lightest chiral molecules composed of stable elements.
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1,3-Bis-substituted allenes possess axial chirality and are of theoretical interest.[1-6] The enantiomers of 1,3-dimethylallene have been known since 1968,[7-9] and have the lowest molecular mass among chiral allenes. Our interest in chemo-enzymatic synthesis and in chirality due to the isotopic substitution led us to undertake the synthesis of the title compounds which, to our knowledge hold the record as the lightest chiral molecules composed of stable elements.[10] Apart from being a laboratory curio the enantiomeric (1,3-$^2H_2$)allenes are of high interest in chiroptical studies. Their vibrational circular dichroism (VCD) spectrum[13] has already been predicted by theoretical calculations.[2-5] Mannschreck *et al.*[14,15] observed ^{1}H NMR signal separation of racemic chiral allenes in the presence of chiral lanthanide complexes and Ag(fod). Examination of racemic (1,3-$^2H_2$)allene would be of interest also in this respect.

Our strategy for the synthesis of the enantiomeric (1,3-$^2H_2$)allenes was the following: i) Generation of a chiral center of the type X–CHD–Y by a stereospecific enzymatic process and ii) conversion of the product to (1,3-$^2H_2$)allene by a concerted stereocontrolled reaction (Scheme 1).

Because of the volatile nature of allene (bp = –35 °C) it was necessary to optimize the last step using unlabelled material. Thus, for the pyrolysis of propargyl-methoxymethyl ether[16] and the capture of allene a special apparatus, equipped with heating, a glas tube filled with potassium hydroxide to trap methyl formate and finally a cold trap to collect allene, was constructed. The pyrolysis was conducted at 390°C and the procedure was then repeated with racemic (1,3-$^2H_2$)propargyl-methoxymethyl ether [(±)-**4**] (see below). The resulting racemic (1,3-$^2H_2$)allene (±)-**1** is important as reference for the infrared and VCD spectrum of its enantiomers.[17]

(1-^{2}H)propargyl alcohol [(±)-**2**] the starting material for the preparation of (±)-**4** was obtained earlier by a multistep procedure based on Li-^{2}H exchange in the corresponding aldehyde-thioacetal[18] or by reduction of

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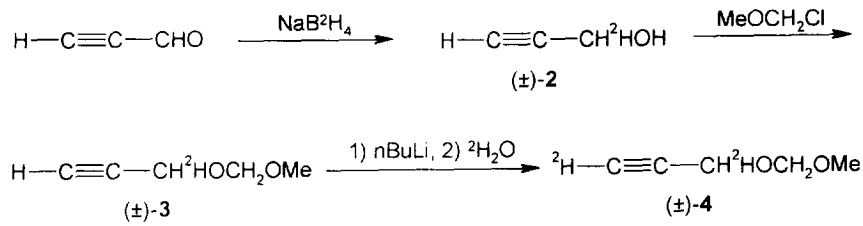
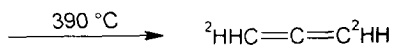
propargyl aldehyde with $LiAl^2H_4$.[19,20] In our hands the latter reaction was accompanied by partial reduction of the triple bond. The formation of overreduced products could not be avoided neither by reducing the reaction temperature nor by using mild reducing agents, such as AlH_3[21] or $Mg(AlH_4)$.[22] Selective reduction of the aldehyde group was finally achieved using NaB^2H_4 in water in 92% yield. The product [(±)-**2**] was converted into the corresponding methoxymethyl ether [(±)-**3**] by alkylation with methoxymethyl chloride in the presence of Na-Y Zeolite.[23] The second deuterium atom was introduced by treatment of (±)-**3** with butyl lithium followed by quenching with ^2H_2O to give (±)-**4**.





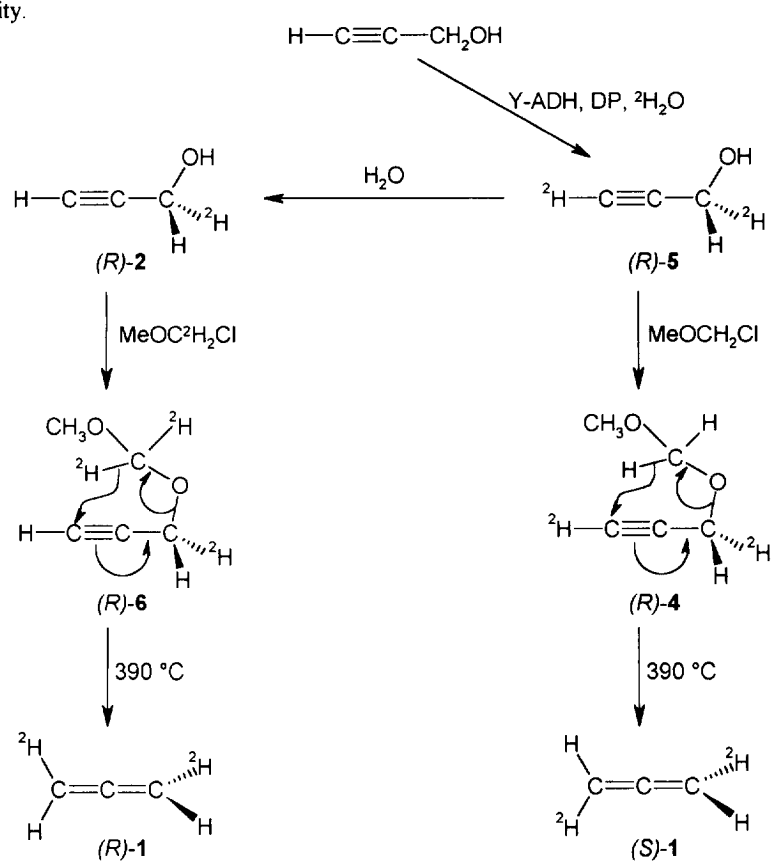
Scheme1 (±)-1

Experience gained with unlabelled and labelled but racemic materials encouraged us to start with the synthesis of the enantiomeric (1,3-$^2H_2$)allenes. Yeast alcohol dehydrogenase (YADH) served for the enantioselective introduction of deuterium into propargyl alcohol. Incubation of the latter with YADH, diaphorase and NAD in deuterium oxide led to stereospecific exchange of the 1-H_{Re} atom.[24] Alternatively, propargyl aldehyde[11] was reduced with YADH and (4-$^2H_1$)NADH the latter being regenerated *in situ* by formate dehydrogenase and sodium [$^2H_1$]formate.[25] For the preparation of (*R*)-(1,3-$^2H_2$)allene [(*R*)-**1**] a sample of (*R*)-(1,3-$^2H_2$)propargyl alcohol [(R)-**5**], obtained by the first described exchange procedure was incubated in excess water at pH 10 to exchange the deuterium in the acetylenic position. The recovered (*R*)-(1-$^2H_1$)propargyl alcohol [(*R*)-**2**] was then treated with methoxy-($^2H_2$)methyl chloride[26] to give methoxy-($^2H_2$)methyl-(1-$^2H_1$)propargyl ether [(*R*)-**6**].

Stereospecific thermally induced concerted sigmatropic shift in a propargyl-methoxymethyl ether was first exploited in an ingenious synthesis of chiral acetic acid by Townsend *et al.*[27] Later gas phase thermolysis of several propargylic amines[28,29] and ethers[30] was studied by Viola *et al.* They found that pyrolysis of (*R*)-3-phenylpropargyl alcohol ($^2H_2$)methyl ether led stereoselectively to (*S*)-3-phenyl-(1-$^2H_1$)allene.[31] To verify whether the methoxymethyl group was indeed the ideal group for the transfer of a hydrogen atom the mechanism of this acetylenic retro-ene rearrangement was studied by *ab initio* calculations and the transition state energies for the rearrangement of several propargylic ethers were obtained. In fact, the activation barrier was found to be the lowest for the reaction of the methoxymethyl ether (-7.49 kcal/mole relative to the corresponding methyl ether).[32]

Both (*R*)-**4** and (*R*)-**6** were pyrolyzed using the same method as described for the racemic (1,3-$^2H_2$)propargyl-methoxymethyl ether [(±)-**4**]. As shown in Scheme 2 pyrolysis of (*R*)-**4** and (*R*)-**6** leads to (*S*)- and (*R*)-(1,3-$^2H_2$)allene, respectively. The purity of the allenes was checked by absorbing a few bubbles of the gas in deuterochloroform and recording the ^1H NMR spectrum of the sample at 500 MHz. Geminal H–^2H coupling, estimated to be ≤0.3 Hz, was not observed, only a slight line broadening. Determination of the

deuterium content by mass spectrometry was severely limited by the fact that according both to the literature[33] and our own experience the base peak of allene was at *m/e* I=M-1. Thus the M-H peak of (1,3-$^2H_2$)allene would coincide with the M^+ peak of ($^2H_1$)allene. Fragmentation could, however, be almost totally suppressed by lowering the ionization voltage to 15 eV. Under these conditions an upper limit of 5% could be set for isotopic impurity.



Scheme 2

Isotopic purity of the end product was further confirmed by the ^{13}C NMR spectrum of its precursors showing only triplets for C-1, C-2 and C-3 ($^1J_{C-^2H}$ = 22, 7.3 and 38 Hz, respectively). There is no direct proof for the enantiomeric purity of our enantiomeric (1,3-$^2H_2$)allenes, but the optical purity of their precursors secured by the known stereospecificity of the enzymic reactions by which they were produced and the concerted nature of [1,5]-H sigmatropic shifts[34,35] by which the stereospecifically deuterated propargyl ethers were converted into (1,3-$^2H_2$)allenes permit the conclusion that also the latter were optically pure. Preliminary VCD measurements by Keiderling on one sample of our (*R*)-(1,3-$^2H_2$)allene showed a negative VCD effect between 900 and 800 cm^{-1} which would be in agreement with theoretical calculations (personal communication by Professor T. A. Keiderling, University of Illinois at Chicago). More exact VCD measurements on both enantiomers are in progress.

EXPERIMENTAL

General. ^{1}H NMR spectra were recorded with Bruker DRX-500, Bruker AC-250 and Varian VXR 400 spectrometers at 500, 250 and 400 MHz, respectively, on samples in C^2HCl_3 with TMS as an internal standard. Mass spectra were measured using a ZAB-2SEQ spectrometer. Optical rotations were determined in a Perkin-Elmer 241 polarimeter. NAD^+, NADH, yeast alcohol dehydrogenase (lyophilized, spec. activity 300 U/mg) and diaphorase from pig heart (lyophilized) were from Boehringer-Mannheim (Germany). Bovine serum albumin was from Sigma (St. Louis), ^{2}H-paraformaldehyde (98% ^{2}H) from Aldrich.

(±)-(1-$^2H_1$)Prop-2-yn-1-ol [(±)-2]: To a stirred solution of propargyl aldehyde[25] (2.0 g, 37 mmol) in distilled water (45 ml) NaB^2H_4 (0.6 g, 14.3 mmol) was added at 5 °C to the mixture and the stirring was continued for 30 min. After neutralization with 10% aqueous acetic acid the solution was continuously extracted with CH_2Cl_2 for 2 d. The extract was dried over Na_2CO_3 and the solvent was evaporated to yield (±)-**2** (1.94 g, 92%) as a colourless oil. ^{1}H NMR (250 MHz): δ 2.47 (d, J = 2.7 Hz, 1H, HC≡C), 4.26 (m, 1H, CH^2H).

(±)-1-Methoxymethoxy-(1-$^2H_1$)prop-2-yne [(±)-3]: A mixture of (±)-**2** (1.4 g, 25 mmol), methoxymethyl chloride (3.0 g, 37.5 mmol) and Na-Y Zeolite (0.35 g) in dry CH_2Cl_2 (50 ml) was refluxed with stirring for 4 h. Zeolite was filtered off and the filtrate washed with 10% aqueous $NaHCO_3$, water and brine. Finally the organic layer was separated and dried over Na_2SO_4. Evaporation of the solvent yielded (±)-**3** (2.4 g, 96%) as a colourless oil. ^{1}H NMR (250 MHz): δ = 2.43 (d, J = 2.7 Hz, 1H, HC≡C), 3.36 (s, 3H, OCH_3), 4.21 (m, 1H, CH^2H), 4.75 (s, 2H, OCH_2).

(±)-1-Methoxymethoxy-(1,3-$^2H_2$)prop-2-yne [(±)-4]: A stirred solution of (±)-**3** (0.85 g, 8.4 mmol) in dry diethyl ether (10 ml) was cooled to –78 °C and *n*-butyllithium (1.6 M in hexane, 5.6 ml) was added dropwise. After 2 min the mixture was allowed to warm to room temperature and quenched with ^2H_2O (98% ^{2}H, 4.0 ml). The organic layer was separated, dried over $MgSO_4$ and distilled under argon to give (±)-**3** (0.79 g, 90%) as a colourless oil. ^{1}H NMR (400 MHz): δ = 3.42 (s 3H, OCH_3), 4.25 (t, J = 2.7 Hz, 1H, CH^2H), 4.75 (s, OCH_2O).

(±)-(1,3-$^2H_2$)Allene (±)-1: (±)-**3** (0.4 g, 3.9 mmol) was pyrolyzed in a vapor-phase flow system in a slow flow of argon at 390 °C. The starting material was injected over a period of 20 min. The apparatus previously described by Viola *et al.*[34,35] was extended by three consecutive traps. The first trap was left at room temperature, the second at –20 °C (in order to retain methyl formate it was filled with beads of 4 Å molecular sieve onto which a layer of KOH was administered by evaporating a methanolic solution of KOH). Allene (0.14 g, 86%) was collected in the third trap kept at –78 °C, distilled over into a vial and then sealed. ^{1}H NMR (500 MHz): δ = 4.68 (s); MSEI + m/z 42.

(*R*)-(1,3-$^2H_2$)Prop-2-yn-1-ol [(*R*)-5]: K_2HPO_4 (3.48 g) was dissolved in ^2H_2O (20 ml) and the p^{2}H was brought to 8.3 by dropwise addition of a solution of KH_2PO_4 (1.36 g) in ^2H_2O (10 ml). The resulting solution was then evaporated and the residue dried over P_2O_5 under reduced pressure (5 Hgmm) to give a deuterated buffer-salt. This salt (637 mg), Na-EDTA (262 mg), NAD^+ (37 mg), bovine serum albumin (22 mg) YADH (500 mg) and diaphorase (50 mg) were dissolved in ^2H_2O (40 ml). To this solution prop-2-yn-1-ol (750 mg, 13.4 mmol) was added and the mixture was incubated for 10 d at 37 °C. The exchange process was monitored by recording ^{1}H NMR spectra from time to time. Finally the solution was centrifuged and continously extracted with CH_2Cl_2 for 2 d to yield (*R*)-**5** (690 mg, 92%) as a colourless oil. ^{1}H NMR (400 MHz) δ 4.20 (t, J = 2.6 Hz, 1H, CHD), $[\alpha]_D^{20}$ –0.214 (c = 5.0, H_2O).

(*R*)-(1-$^2H_1$)Prop-2-yn-1-ol [(*R*)-2]: (*R*)-**5** (0.74 g, 12.8 mmol) was dissolved in H_2O (20 ml) and the pH was adjusted to 9 by adding solid $NaHCO_3$. After incubation for 2 d and the usual work-up (*R*)-**2** (710 mg) was isolated as a colourless oil.

(*R*)-1-Methoxymethoxy-(1,3-$^2H_2$)prop-2-yne [(*R*)-4]: (*R*)-**5** (700 mg 12.0 mmol) was converted into (*R*)-**4** (1.10 g, 89%) as described for (±)-**3.** ^1H NMR (500 MHz): δ 3.29 (s, 3H, OCH_3), 4.25 (t, *J* = 2.7 Hz 1H, CH^2H), 4.77 (s, 2H, OCH_2O). ^{13}C NMR (125 MHz): δ 54,15 (t, *J* =22.3 Hz, C-1), 55.87 (s, OCH_3), 74.26 (t, *J* = 38 Hz, C-3), 79.29 (t, *J* = 7.3 Hz, C-2) , 95.18 (s, OCH_2O), $[\alpha]_D^{20}$ 0.175 (c=5.0, H_2O).

(*R*)-1-(^{2}H)-1-Methoxy-($^2H_2$)methoxy-prop-2-yne [(*R*)-6]: (*R*)-**2** (890 mg, 15.5 mmol) was converted into (*R*)-**6** as described for (±)-**3,** using methoxy-($^2H_2$)methyl chloride[26] (1.40g, 17.0 mmol) to give (*R*)-**6** (900 mg, 58%). ^1H NMR (250 MHz): δ 2.43 (d, *J* = 2.7 Hz, 1H, HC≡C), 3.29 (s, 3H, OCH_3), 4.25 (m, 1H, CH^2HO).

(*S*)-1,3-$^2H_2$)Allene [(*S*)-1]: (*R*)-**4** (400 mg, 3.9 mmol) was pyrolyzed as described for (±)-**1** to yield (*S*)-**1** (98 mg, 63%). ^1H NMR (500 MHz): δ=4.68; MS = EI + m/z 42.

(*R*)-(1,3-$^2H_2$)Allene [(*R*)-1]: (*R*)-**6** (700 mg, 6.8 mmol) was pyrolyzed as described for (±)-**1** to yield (*R*)-**1** (180 mg, 63%). ^1H NMR (500 MHz) and MS were identical to those of (*S*)-**1**.

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damped, the Cotton effect decreases dramatically. Because of the small size difference between protium and deuterium, in the case of (1,3-$^2H_2$)allene no appreciable bending and twisting which cause chiral torsions on the chromophore are expected. As a consequence, no UV-CD measurements are amenable for (1,3-$^2H_2$)allene.

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