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REARRANGEMENTS OF (*E*,*Z*)-4-ACETYL[^{17}O]OXYHEPTA-2,5-DIENE CATALYSED BY Pd^0 AND Pd^{II}: MECHANISTIC DEDUCTIONS FROM OBSERVATIONS BY ^{17}O NMR SPECTROSCOPY

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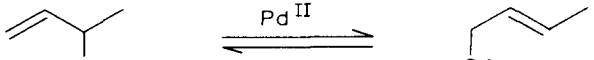
Summary

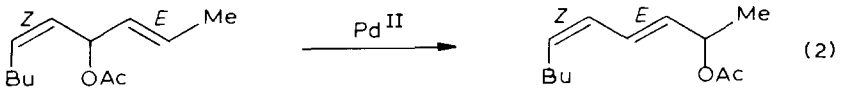
(*E*,*Z*)-4-Acetyl[^{17}O]oxyhepta-2,5-diene [$MeCH\overset{E}{=}CHCH(^{17}OCOMe)CH\overset{Z}{=}CHMe$] has been synthesised and rearranged under Pd^0- and Pd^{II}-catalysis. The distribution of ^{17}O in the products of these rearrangements has been determined by ^{17}O NMR spectroscopy. With Pd^0 catalyst the product is a 1:1 mixture of $MeCH\overset{E}{=}CHCH\overset{E}{=}CHCH(^{17}OCOMe)Me$ and $MeCH\overset{E}{=}CHCH\overset{E}{=}CHCH(OC^{17}OMe)Me$ formed from an intermediate Pd-coordinated pentadienyl species and ^{17}O-acetate. With Pd^{II} catalyst the product is $MeCH\overset{Z}{=}CHCH\overset{E}{=}CHCH(OC^{17}OMe)Me$ formed via an intermediate acetoxonium ion.

Introduction

The synthetic value of the Pd^{II}-catalysed rearrangement of allylic acetates [1] (eq. 1) has been demonstrated with prostaglandins [2]. We have exploited this reaction by using $(RCN)_2Pd^{II}Cl_2$ (R = Me or Ph) as a catalyst for effecting rapid isomerisations of 3-acetoxy-1,4-dienes to 1-acetoxy-2,4-dienes [3]. These reactions occur with high regio- and stereo-selectivity (e.g. eq. 2). Thus (*E*,*Z*)-4-acetoxyhepta-2,5-diene (**1a**)



(1)



(2)

rearranges predominantly to (3*E*,5*Z*)-2-acetoxy-hepta-3,5-diene (**2a**) when treated with a catalytic quantity of $(RCN)_2Pd^{II}Cl_2$ (R = Me or Ph). In contrast, catalytic

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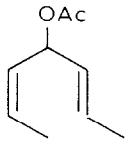
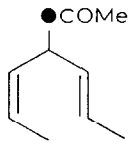
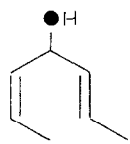


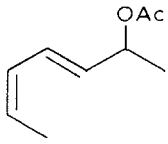
(1a)



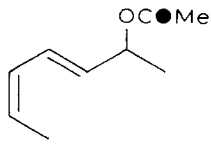
(1b)



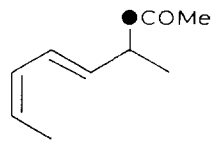
(1c)



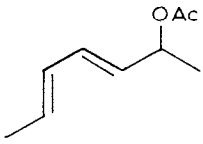
(2a)



(2b)



(2c)



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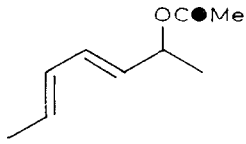
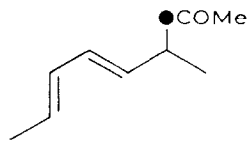
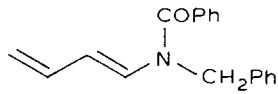


(3b)



(3c)

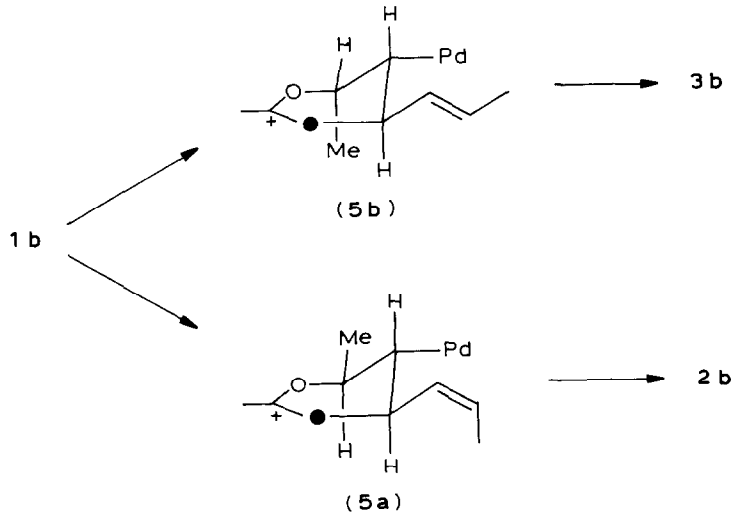
● = ^{17}O



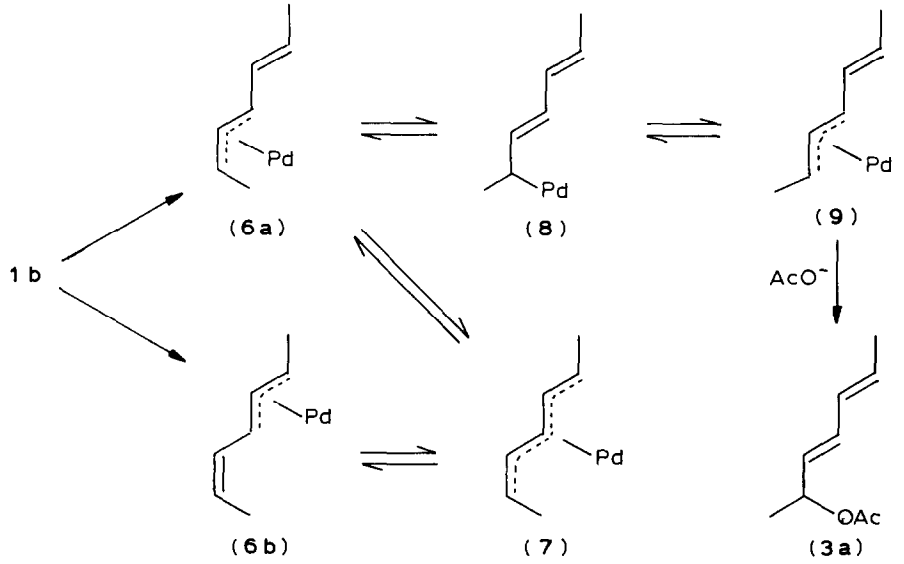
(4)

$(Ph_3P)_4Pd^0$ causes isomerisation of (*E*,*Z*)-diene (**1a**) to (3*E*,5*E*)-2-acetoxyhepta-3,5-diene (**3a**).

In further studies of these rearrangements using (*E*,*Z*)-4-acetyl[^{17}O]oxyhepta-2,5-diene (**1b**) and ^{17}O NMR spectroscopy, [4,5] we have found that the diene (**2b**) derived from (**1b**) by Pd^{II}-catalysed rearrangement contains ^{17}O exclusively in its carbonyl oxygen, whereas a 1 : 1 mixture of dienes (**3b**) (^{17}O in carbonyl oxygen) and (**3c**) (^{17}O in alkyl oxygen) is obtained from Pd^0-catalysed rearrangement of **1b**. These results enable the mechanisms in the Schemes to be proposed for the Pd^{II}- (Scheme 1) and Pd^0-catalysed (Scheme 2) rearrangements of dienes **1a** and **1b** (cf. Discussion below).



SCHEME 1



SCHEME 2

Results and discussion

N-Benzoyl-*N*-benzyl-1-aminobuta-1,3-diene (**4**) was prepared essentially as described [6], although considerable experimentation was needed to define a reproducible method for obtaining pure **4**. Acid-catalysed hydrolysis [7] of this diene in ether containing 1 mol equiv [^{17}O] water (11.0 atom % ^{17}O) per mol diene gave [^{17}O]but-2-enal. Condensation of this aldehyde * with (*Z*)-propenylmagnesium bromide gave

* 5.5 atom% ^{17}O because of dilution with unlabelled but-2-enal.

(*E*,*Z*)-[^{17}O]-4-hydroxyhepta-2,5-diene (**1c**) which was acetylated (acetic anhydride in pyridine) to give (*E*,*Z*)-4-acetyl[^{17}O]oxyhepta-2,5-diene (**1b**). The ^{17}O NMR spectrum of ester **1b** showed a resonance at δ 193.3 (cf. Fig. 1a). Almost no absorption was observed ca. δ 360 (characteristic of ester carbonyl oxygen [4]) showing that ester **1b** is specifically labelled at its alkyl oxygen.

Following treatment of ester **1b** with $(MeCN)_2PdCl_2$ in tetrahydrofuran in the manner described, [3] the isolated (3*E*, 5*Z*)-2-acetoxyhepta-3,5-diene was examined by ^{17}O NMR spectroscopy. This showed (cf. Fig. 1b) a major resonance at δ 359.2, proving that ^{17}O in the alkyl oxygen of **1b** is quantitatively transferred to the carbonyl oxygen of **2b**. A mechanism for the Pd^{II}-catalysed isomerisation of **1** to **2**, consistent with this result, is shown in Scheme 1. The preference for rearrangement via the *E* double-bond of **1b** can be explained by comparing the intermediate **5a** (cf. Scheme 1) with the intermediate **5b** for rearrangement via the *Z* double-bond. The species **5a**, with all substituents quasi-equatorial, is likely to be more stable than **5b** which possesses a 1,3-diaxial Me–H interaction. Intramolecular coordination of the *Z*-double-bond to Pd may also favour **5a** over **5b**. Thus, conversion of **1b** into **2b** is a kinetically controlled process in which the transition state leading to **5a**, and hence **2b**, is preferred over that giving **5b** and hence, the thermodynamically more stable **3b**.

The mechanistic proposal (Scheme 1) is similar to that made [1] for Pd^{II}-catalysed isomerisations of allylic acetates and for Pd^{II}-catalysed Cope rearrangements [8]. However, an experiment performed with [^{18}O]crotyl propionate for the demonstration of intramolecular $-O \rightarrow C{=}O$ transfer was imperfect, because a mass spectral analysis was used on a substrate and product labelled, albeit differentially, with very low levels of ^{18}O in both alkyl oxygen and carbonyl oxygen [1].

In contrast to the result described for Pd^{II}-catalysed isomerisation of ester **1b**, treatment of this diene with $[(Ph)_3P]_4Pd^0$ gave (3*E*, 5*E*)-2-acetoxyhepta-3,5-diene, which is a 1 : 1 mixture of the isomers **3b** and **3c** according to its ^{17}O NMR spectrum (Fig. 1c). One isomer is labelled with ^{17}O in the alkyl oxygen (**3c**), δ 193.5, whereas the other is labelled in the carbonyl oxygen (**3b**), δ 358.7. Pd^0-assisted ionisation of **1b** could lead to either π-allyl **6a** or **6b**, depending on which double-bond is initially coordinated to Pd. These species might interconvert, possibly via the pentadienyl complex **7**. If π-allyl **6a** can be converted into the σ-allyl complex **8**, then formation of π-allyl **9** could follow. Finally, return of acetate would lead to the observed product mixture. It is significant that under the conditions used **2b** does not readily isomerise to **3b**/**3c**. Remarkably, $[(Ph)_3P]_4Pd^0$-catalysed isomerisation of **2b** to a 1 : 1 mixture of **3b** + **3c** (cf. Fig. 1d) required > 100 h/r.t. It was important to conduct this experiment anaerobically, otherwise rapid oxidation of Ph_3P to Ph_3PO occurred, with quenching of catalytic activity [9].

Experimental

The ^{17}O NMR spectra were obtained on a Bruker WH400 spectrometer operating at 54.24 MHz. A typical sample contained acetoxydiene (0.2 g, 5.25% ^{17}O) in CD_2Cl_2(0.3 cm^3) in a 5 mm diameter NMR tube. All spectra were run locked. Chemical shifts are reported in ppm relative to external dioxan (CD_2Cl_2) at $\delta = 0$. The spectral width was 50,000 Hz and free induction decays were stored in 2048 data points and zero filled 8192 data points. Pulse angles of 90° were used with no

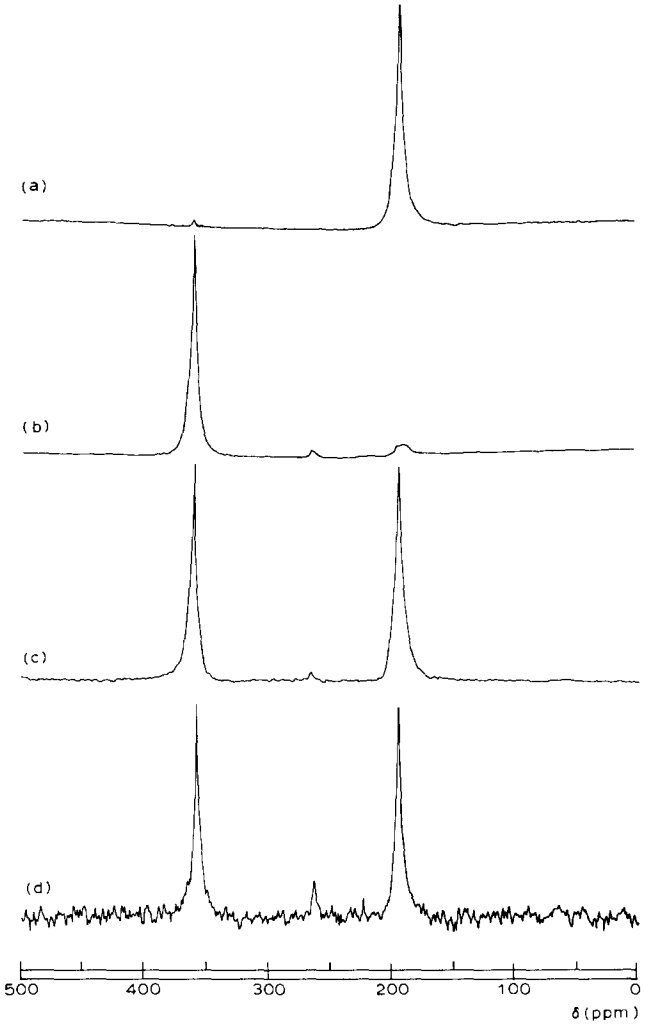


Fig. 1. ^{17}O NMR spectra of: (a) (*E*,*Z*)-4-Acetyl[^{17}O]oxyhepta-2,5-diene (**1b**). (b) (3*E*,5*Z*)-[^{17}O-Acetyl]-2-acetoxyhepta-3,5-diene (**2b**) from Pd^{II}-catalysed isomerisation of **1b**. (c) Mixture (1 : 1) of (*E*,*E*)-2-acetyl[^{17}O]oxyhepta-3,5-diene (**3c**) and (*E*,*E*)-[^{17}O-acetyl]-2-acetoxyhepta-3,5-diene (**3b**) from Pd^0-catalysed isomerisation of **1b**. (d) Mixture (1 : 1) of **3c** and **3b** from Pd^0-catalysed isomerisation of **2b**.

delay between successive acquisitions. Low power ^1H decoupling was employed. Temperatures were monitored and held constant ($\pm 1°C$) with a standard Bruker control unit. For the ^{17}O-labelled acetoxydienes spectra were obtained as shown (cf. Figs. 1a–1d) in < 5 min accumulation. Natural abundance spectra of the corresponding unlabelled acetoxydienes required > 45 min accumulation. ^1H NMR spectra were recorded on a Perkin–Elmer R34 spectrometer at 220 MHz with chemical shifts reported in ppm relative to TMS at $\delta = 0$.

Mass spectra were recorded on a Kratos (Model MS80) spectrometer; oxygen isotopic abundances for both labelled and unlabelled acetoxydiene were calculated from data obtained from six consecutive spectra, using M^+ 154, 155, 156. IR spectra

were recorded on a Perkin–Elmer (Model 580B) spectrometer with internal reference.

All chemicals used were of the highest available purity. Diethyl ether and tetrahydrofuran were dried by boiling with lithium aluminium hydride, followed by distillation under nitrogen and storage over activated 4A molecular sieves. *N*-Benzoyl-*N*-benzyl-1-aminobuta-1,3-diene was prepared essentially by a published procedure [6]. [^{17}O] water was obtained from Prochem and analysed as 11.0 atom % ^{17}O.

(E)-[^{17}O]but-2-enal

N-benzoyl-*N*-benzyl-1-aminobuta-1,3-diene (2.5 g, 9.5 mmol) was dissolved in dry diethyl ether (20 cm^3) and treated with [^{17}O] H_2O (0.18 g, 9.5 mmol) and 0.05 mol equivalents of HCl in dry ether. The resulting solution was stirred at room temperature under nitrogen, and the hydrolysis was monitored by ^{1}H NMR spectroscopy. After 4 h hydrolysis was complete and anhydrous Na_2CO_3 (0.2 g) was added. The mixture was swirled for ca. 2 min and the whole was poured into pentane (20 cm^3). The precipitate was removed by filtration. The filtrate was carefully concentrated and then flash-distilled to give an ether/pentane solution (10 cm^3) containing (*E*)-[^{17}O]but-2-enal (0.5 g, 7.1 mmol, 75%). ^{1}H NMR $\delta(CCl_4)$: 2.05 (3H, d, Me), 6.14 (1H, dd, H-2), 6.90 (1H, dq, H-3), 9.50 (1H, d, H-1) ppm.

(Z)-1-bromopropene

(*R,S/S,R*)-α,β-dibromobutyric acid * (60 g, 0.24 mol) was dissolved in cyclohexanone (250 cm^3) and stirred during the addition of sodium hydrogen carbonate (102.6 g, 1.2 mol). The resulting suspension was heated at 100°C for 8 h, and then fractionally distilled (fraction 40–90°C collected). Careful redistillation in darkness gave (*Z*)-1-bromopropene (14.2 g, 0.12 mol, 48%) b.p. 58–60°C. ^{1}H NMR δ (CCl_4): 1.76 (3H, Me, d), 6.14 (2H, m, H-1 and H-2) ppm. IR (thin film): 3080, 3010, 2918, 1640, 1444, 1370, 1300, 932, 660 cm^{-1}.

(E,Z)-[^{17}O]hepta-2,5-dien-4-ol

Magnesium turnings (0.69 g, 28.4 mmol), iodine (1 crystal) and (*Z*)-1-bromopropene (3 drops) were warmed in dry THF (15 cm^3) until the iodine colour was discharged and reaction commenced. A solution of (*Z*)-1-bromopropene (3.45 g, 28.4 mmol) in dry THF (10 cm^3) was then added dropwise over 20 min and the solution stirred for a further 10 min. (*E*)-[^{17}O]but-2-enal (1.0 g, 14.2 mmol) ** in ether/pentane was then added dropwise, followed by stirring at RT for 2 h. Diethyl ether (25 cm^3) was then added, followed by 15% NH_4Cl (aq) (25 cm^3). The aqueous phase was separated, extracted with diethyl ether (3 × 10 cm^3), and the combined ethereal extracts were dried ($MgSO_4$). Filtration, concentration and distillation (Kugelrohr apparatus) gave (*E,Z*)-[^{17}O]-hepta-2,5-dien-4-ol (1.15 g, 10.3 mmol), b.p. 76–78°C (14 mmHg), in 72.5% yield. ^{1}H NMR δ (CCl_4): 1.65 (3H, d, Me), 1.67 (3H, d, Me), 3.10 (1H, s, O–*H*), 4.75 (1H, t, H-4), 5.41 (4H, m, =C–*H*) ppm.

*Prepared from (*E*)-crotonic acid and bromine in CH_2Cl_2.

**At this point [^{17}O]but-2-enal (0.5 g) was diluted with unlabelled but-2-enal (0.5 g).

(E,Z)-4-acetyl[^{17}O]oxyhepta-2,5-diene

(*E*,*Z*)-[^{17}O]hepta-2,5-dien-4-ol (1.1 g, 9.8 mmol), and acetic anhydride (2.0 g, 19.6 mmol) were dissolved in dry pyridine (15 cm^3) and stirred at room temperature for 8 h. The solution was poured into water (20 cm^3), acidified (5 *M* HCl (aq)) and extracted with ether (4 × 25 cm^3). The combined ethereal extracts were washed with 5 *M* HCl (aq), 10% Na_2CO_3 (aq), dried ($MgSO_4$), filtered, concentrated and distilled (Kugelrohr apparatus) to give (*E*,*Z*)-4-acetyl[^{17}O]oxyhepta-2,5-diene (1.23 g, 8.0 mmol, 82%) b.p. 45–47°C (0.5 mmHg). ^{1}H NMR $\delta(CCl_4)$: 1.70 (3H, d, Me), 1.71 (3H,d, Me), 1.96 (3H, s, Me), 5.50 (4H, m, =C–*H*), 5.86 (1H, t, H-4) ppm. ^{17}O NMR $\delta(CD_2Cl_2)$: 193.3 ppm. (cf. Fig. 1a).

Isomerizations

(a) [P(Ph)$_3$]$_4$Pd^0. (*E*,*Z*)-4-acetyl[^{17}O]oxyhepta-2,5-diene (0.2 g, 1.3 mmol) was dissolved in dry benzene (2 cm^3) with 5 mol% $[P(Ph)_3]_4$ Pd^0 (75 mg, 65 μmol). ^{1}H NMR indicated immediate reaction and the solution was poured into pentane. The precipitated catalyst was removed by filtration, and concentration followed by distillation (Kugelrohr apparatus) gave (*E*,*E*)-[^{17}O]-2-acetoxyhepta-3,5-diene (0.175 g, 1.14 mmol, 88%) b.p. 85–87°C (2 mmHg). ^{1}H NMR $\delta(CCl_4)$: 1.28 (3H, d, *J* 6 Hz, H-1), 1.75 (3H, d, *J* 7.5 Hz, H-7), 1.97 (3H, s, Me), 5.28 (1H, m, $J_{1,2}$ 6 Hz, $J_{2,3}$ 6 Hz, H-2), 5.34 (1H, dd, $J_{3,4}$ 15.5 Hz, H-3), 5.70 (1H, m, H-6), 5.93 (1H, dd, $J_{4,5}$ 10.5 Hz, $J_{5,6}$ 15.5 Hz, H-5), 6.10 (1H, dd, H-4) ppm. ^{17}O NMR $\delta(CD_2Cl_2)$: 193.5, 358.7 ppm (cf. Fig. 1c). MS (EI): % ^{16}O (85.11), ^{17}O (5.25), ^{18}O (9.64).

(b) (CH$_3$CN)$_2$PdCl$_2$. (*E*,*Z*)-4-acetyl[^{17}O]oxyhepta-2,5-diene (0.2 g, 1.3 mmol) was dissolved in dry THF (2 cm^3) with 5 mol% $(CH_3CN)_2PdCl_2$ (16.8 mg, 65 μmol). ^{1}H NMR indicated immediate reaction and the solution was poured into pentane. The catalyst was removed by filtration, and concentration followed by distillation (Kugelrohr apparatus) gave (*E*,*Z*)-[^{17}O-acetyl]-2-acetoxyhepta-3,5-diene (0.194 g, 1.26 mmol), b.p. 84–86°C (2 mmHg) in 97% yield. ^{1}H NMR $\delta(CCl_4)$: 1.30 (3H, d, *J* 6 Hz, H-1), 1.76 (3H, d, *J* 6.5 Hz, H-6), 1.98 (3H, s, Me), 5.33 (1H, m, H-2), 5.49 (1H, dd, $J_{3,4}$ 15.5 Hz, H-3), 5.58 (1H, m, H-6), 5.90 (1H, dd, $J_{5,6}$ 11 Hz, $J_{4,5}$ 10.5 Hz, H-5), 6.45 (1H, dd, *J* 15.5 Hz and 10.5 Hz, H-4) ppm. ^{17}O NMR $\delta(CD_2Cl_2)$: 359.2 ppm (cf. Fig. 1b).

(c) [P(Ph)$_3$]$_4$Pd^0. Compound **2b** (0.1 g, 0.65 mmol) was dissolved in dry degassed benzene-d_6 and $[P(Ph)_3]_4Pd^0$ (37.5 mg, 33 μmol) was added. The resulting solution was kept under nitrogen and monitored periodically. ^{1}H NMR spectroscopy indicated essentially complete reaction after 110 h. The product was isolated as described in section (a) and was found to be spectroscopically identical to (*E*,*E*)-[^{17}O]-2-acetoxyhepta-2,5-diene.

^{17}O NMR $\delta(CD_2Cl_2)$: 193.5, 358.7 ppm (cf. Fig. 1d).

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