PREPARATION OF VALERIC ACIDS, PENTENOIC ACIDS, AND γ-VALEROLACTONES LABELLED WITH DEUTERIUM

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SUMMARY

[2-$^2H_1$]-, [2,3-$^2H_2$]-, [2,2,3-$^2H_3$]-, and [4,4,5,5,5-$^2H_5$]Valeric acids, and *trans*- and *cis*-2-[2-$^2H_1$]pentenoic acid and 4-[4,5,5-$^2H_3$]pentenoic acid have been synthesized from 2-bromovaleric acid, *trans*-2-pentenoic acid, 2,3-dibromovaleric acid, and 4-pentynoic acid in 78% to 95% isotopic purity by employing Raney alloys or Aluminium powder in alkaline deuterium oxide. The reductions of *trans*-3- and 4-pentenoic acids, while smoothly proceeding with 10% Pd-C as an additive in the reaction system, resulted in the formation of deuteriated valeric acid with over-introduction of deuterium atoms. Use of 3,4-dibromo-valeric acid resulted in the dehydrobromination between C-2 and C-3 and the subsequent hydrolysis of the bromine at C-4, to provide γ-[2,3-$^2H_2$]-lactone, which was also prepared from 4-bromo-*trans*-2-pentenoic acid in higher purity. Levulinic acid involves the incorporation of deuterium atoms at C-3 and C-5 upon the treatment with 10% NaOD-D_2O, followed by Cu-Al alloy reduction, affording γ-[3,3,4,5,5,5-$^2H_6$]valero-lactone.

Key Words: Deuterium Labelling, Synthesis, Raney Alloy, Deuteriated Valeric Acid, Deuteriated Pentenoic Acid, Deuteriated γ-Valerolactone

INTRODUCTION

Selectively deuterium labelled aliphatic carboxylic acids have been attracting interest in metabolic investigation since many biologically important compounds possess straight-chain alkyl groups. It has been previously reported that the deuteriated phenols,[1] benzoic acids,[2] 1-phenylethanols,[3] and 2-thiophene-, furan-, and pyrrole-carboxylic acids,[4] salicylic acids,[5] and naphthalenes[6] were prepared in high isotopic purity by the hydrodehalogenation of the corresponding halo-compounds with Raney alloys in NaOD-D_2O. In our study on the reduction with Raney alloy in an alkaline solution, we have applied this method to the reductions of 2-

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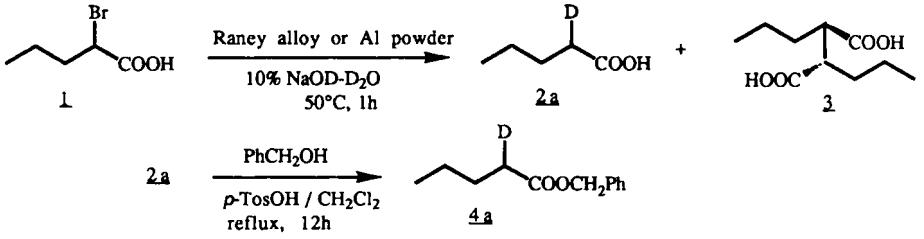
bromovaleric acid (1), 2,3-dibromovaleric acid (5), *trans*-2-pentenoic acid (9), *trans*-3-pentenoic acid (10), 4-pentenoic acid (11), and 4-pentynoic acid (12), to give valeric acid, *trans*- and *cis*-2-pentenoic acids, and 4-pentenoic acid in good yields.[7]

We report here that this procedure provides an useful method for the syntheses of the titled compounds in good yields and in high isotopic purity.

RESULTS AND DISCUSSION

Deuteriated Valeric Acids and Pentenoic Acids.

The reductions of 2-bromovaleric acid (1) by employing Raney alloys such as Ni-Al, Co-Al, and Cu-Al, and Aluminium powder were carried out in 10% NaOD-D_2O (Scheme 1 and Table 1). The isotopic purity of deuteriated acids obtained in this study was determined by mass spectra of the corresponding benzyl ester 4a.



Scheme 1

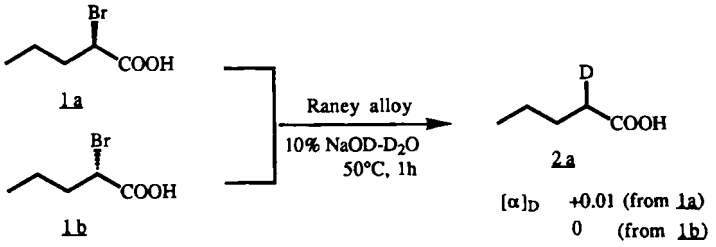
Table 1. Reduction of 2-bromovaleric acid (1).[a]

Run	Metal (g)	Product (%)[b]			Composition (%)[c] D_0	D_1	D_2	D_3
1[d]	Cu-Al (0.75)	2a (71)		4a (62)	11	83	5	1
2	Cu-Al (0.6)	2a (64)	3(16)	4a (66)	5	91	4	0
3	Co-Al (0.6)	2a (59)		4a (61)	9	86	5	0
4	Ni-Al (0.6)	2a (61)		4a (63)	10	85	5	0
5	Al (0.75)	2a (90)		4a (70)	5	95	0	0

a) Substrate: 11 mmol; alkali: 12 mL. b) Isolated yields are shown.
c) Determined by mass spectroscopic method. d) Alkali: 22.5 mL.
e) Stirring: 3 h.

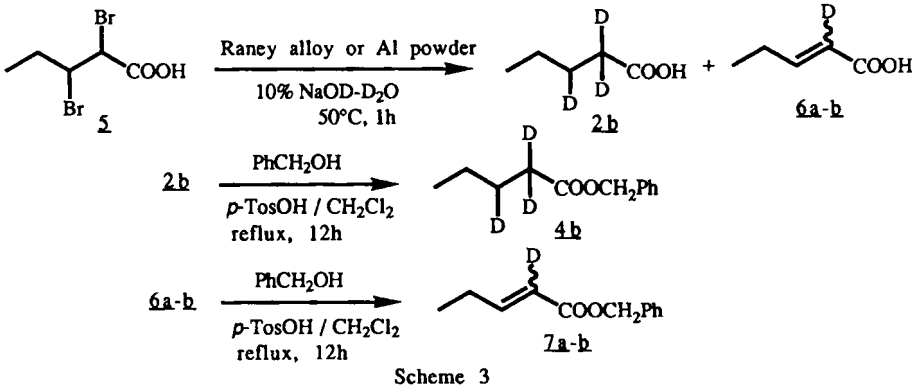
The bromo acid 1 was reductively hydrodebrominated with Raney alloys, to give [2-$^2H_1$]valeric acid (2a) in 59% to 70% yields and in 83% to 91% isotopic purity. It should be noted that treatment of 1 with powdered Aluminum resulted in the formation of 2a in a high yield (90%) and in an excellent isotopic purity (95%). This points to the high reactivity of the bromine atom adjoining the carboxyl group since brominated aromatic compounds can not be reduced under the same conditions. The employment of Cu-Al alloy gave Ulmann coupling dimer, *threo*-2,3-dipropylsuccinic acid (3) as a by-product (Run 2). Thus, it is postulated that the reduction employing Raney alloy in an alkaline deuterium oxide proceeds not concertedly as Pd-C reduction but, interestingly, stepwise. This is also

supported by the fact that the treatment of the optically active acids 1a-b[8] with Cu-Al alloy afforded the racemic acid 2a (Scheme 2).



Scheme 2

Next, we envisaged that if 2,3-dibromovaleric acid (5) could be reductively debrominated under the same conditions, [2,3-$^2H_2$]valeric acid might be generated in high isotopic purity. When compound 5 was reduced



Scheme 3

Table 2. Reduction of 2,3-dibromovaleric acid (5).[a]

Run	Metal (g)	Product (%)[b]		Composition (%)[c]					
				D_0	D_1	D_2	D_3	D_4	D_5
1	Cu-Al (1.2)	2b (83)	4b (67)	0	0	31	55	14	0
2	Ni-Al (1.2)	2b (74)	4b (70)	0	0	23	45	26	6
3	Cu-Al (0.6)	6a-b (75)	7a-b (41)	5	88	7	0	0	0
4[d]	Al (0.6)	6a-b (31)	7a-b (64)	2	91	4	3	0	0

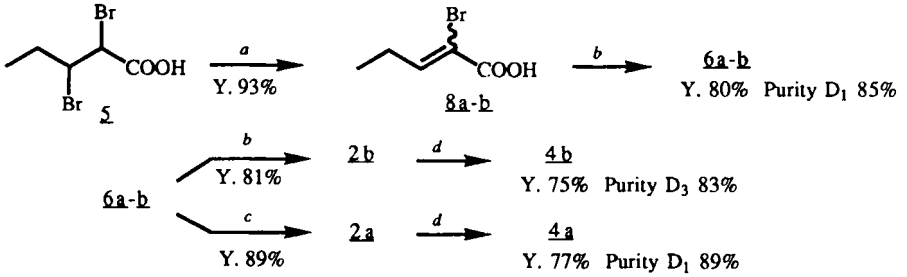
a) Substrate: 11 mmol; alkali: 12 mL. b) Isolated yields are shown.
c) Determined by mass spectroscopic method. d) Stirring: 3 h.

with Cu-Al alloy, unexpectedly, [2,2,3-$^2H_3$]valeric acid (2b) was formed in 55% isotopic purity. On the other hand, employment of Cu-Al alloy or Aluminium powder led to the formation of 2-[2-$^2H_1$]pentenoic

acids (6a-b) as a 3:1 mixture of the *trans* and *cis* isomers in 88% and 91% isotopic purity (Scheme 3 and Table 2).

The bromo acids 8a-b were treated with Cu-Al alloy or powdered Aluminum to give 6a-b, followed by reduction in 10% NaOD-D_2O, providing 2b of 81% isotopic purity. The reduction of 6a-b in 10% aqueous NaOH gave the [$^2H_1$]acid 2a of 89% isotopic purity (Scheme 4).

The above imply that 2b is formed *via* the reduction of 6a-b. In fact, the acid 2b of high isotopic purity was prepared from *E*- (8a) and Z-2-bromo-2-pentenoic acids (8b),[7] which were, upon the treatment with 10% aqueous NaOH at 50 °C for 1 h, obtained from 5 as 3:1 mixtures in 93% yield. The bromo acids 8a-b were treated with Cu-Al alloy or powdered Aluminum to give 6a-b, followed by reduction in 10% NaOD-D_2O, to provide 2b of 81% isotopic purity. The reduction of 6a-b in 10% aqueous NaOH gave the [$^2H_1$]acid 2a of 89% isotopic purity (Scheme 4).

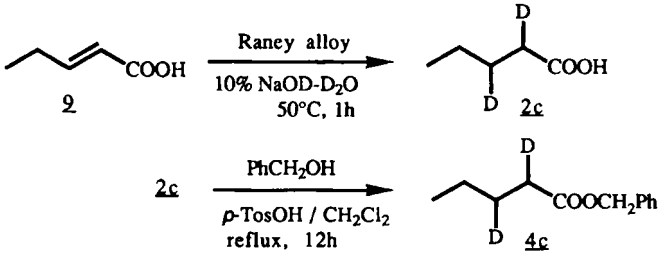


[a]Reagents and Conditions: (a) 10% aq. NaOH, 1h; (b) Cu-Al alloy/10% NaOD-D_2O, 50 °C, 1h; (c) Cu-Al alloy/ 10% aq. NaOH, 50 °C, 1h; (d) $PhCH_2OH$, *p*-TosOH/CH_2Cl_2, reflux, 12h.

Scheme 4[a]

[2,3-$^2H_2$]Valeric acid (2c), not directly prepared from 5, could be synthesized from *trans*-2-pentenoic acid (9) with Cu-Al alloy in 78% isotopic purity, although the use of Co-Al and Ni-Al alloys caused the hydrogen-deuterium exchange upon double bond, giving 2 in low isotopic purity (40% and 35%) (Scheme 5 and Table 3).

Since Aluminium powder did not reduce 9 under the same conditions, unequivocaly, the [$^2H_1$]acid 2a was directly obtained not *via* the reduction of 9 as an intermediate but the debromination of 1.



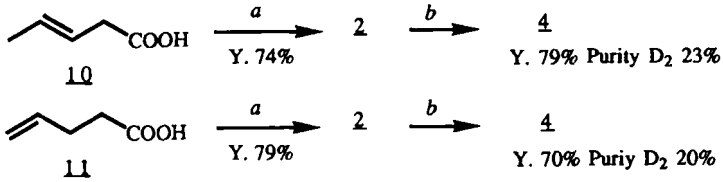
Scheme 5

Table 3. Reduction of *trans*-2-pentenoic acid (9).[a]

Run	Metal	Product (%)[b]		Composition (%)[c] D_1	D_2	D_3	D_4	D_5	D_6
1	Cu-Al	2c (79)	4c (72)	19	78	3	0	0	0
2	Co-Al	2c (76)	4c (70)	5	40	28	11	8	4
3	Ni-Al	2c (78)	4c (68)	7	35	41	20	3	2

a) Substrate: 9.8 mmol; alkali: 16 mL; alloy: 660 mg. b) Isolated yields are shown. c) Determined by mass spectroscopic method.

On the other hand, although the reductions of *trans*-3- (10) and 4-pentenoic acids (11) proceeded smoothly with 10% Pd-C as an additive (43% weight% upon the alloy), isotopic purity of 2 was lowered to 23% and 20% owing to hydrogen-deuterium exchange (Scheme 6).

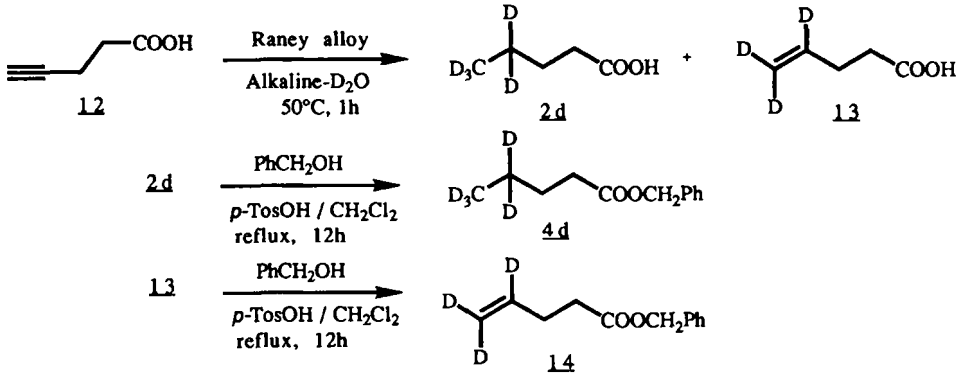


[a]Reagents and conditions: (a) Cu-Al alloy, 10% Pd-C/10% NaOD-D_2O, 50 °C, 1h; (b) $PhCH_2OH$, *p*-TosOH/CH_2Cl_2, reflux, 12h.

Scheme 6[a]

The reduction of 4-pentynoic acid (12) gave alternatively [4,4,5,5,5-$^2H_5$]valeric acid (2d) and 4-[4,5,5-$^2H_3$]pentenoic acid (13) depending upon the conditions (Scheme 7 and Table 4).

^1H n.m.r. spectra of 2d and 13 indicated that the hydrogen on the terminal acetylene moiety had been replaced by deuterium during the reduction under the basic conditions. It was found that [4,4,5,5,5-$^2H_5$]valeric acid (2d) was formed in 80% isotopic purity with a 1:1 (v/v) mixture of 10% NaOD-D_2O and 10% Na_2CO_3-D_2O (Run 2). Moreover, the treatment of the



Scheme 7

Table 4. Reduction of 4-pentynoic acid (12).[a]

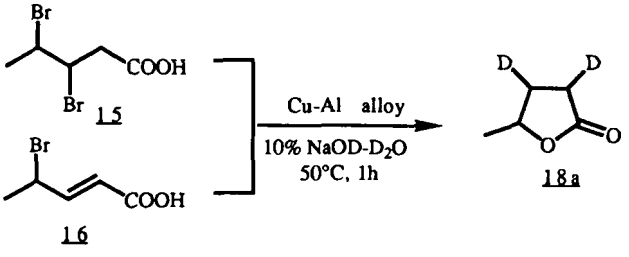
Run	Metal (g)	Alkali (mL)[b]	Product (%)[c]	Composition (%)[d] D_1 D_2 D_3 D_4 D_5 D_6 D_7
1	Cu-Al (0.3)	A (5.0)	2d (80) 4d (63)	0 2 10 15 58 10 5
2	Cu-Al (0.4)	A (5.0)	2d (75) 13 (+)[e] 4d (63)	0 0 3 10 80 7 0
3	Cu-Al (0.6)	B (15.0)	13 (80) 14 (67)	0 5 92 3 0 0 0
4	Fe-Al (0.3)	C (6.0)	2d (5) 13 (73) 14 (65)	6 10 79 5 0 0 0

a) Substrate: 4.1 mmol. b) A: 10% NaOD-D_2O; B: 10% Na_2CO_3-D_2O; C: 10% NaOD-D_2O + 10% Na_2CO_3-D_2O. C) Isolated yields are shown. d) Determined by mass spectroscopic method. e) + sign: below 1%.

acid 12 with Cu-Al alloy in 10% Na_2CO_3-D_2O or with Fe-Al alloy in 10% NaOD-D_2O afforded exclusively 4-[4,5,5-$^2H_3$]pentenoic acid (13) in 92% or 79% isotopic purity (Runs 3 and 4). Based on the above, it was revealed that the reduction of the acetylenic acid 12 does not proceed *via* the olefinic acid 13 since 13 is not reduced under the same conditions as mentioned above.

Deuteriated γ-Valerolactones.

The reductions of 3,4-dibromovaleric acid (15) and 4-bromo-*trans*-2-pentenoic acid (16) were carried out and the results are summarized (Scheme 8 and Table 5).



Scheme 8

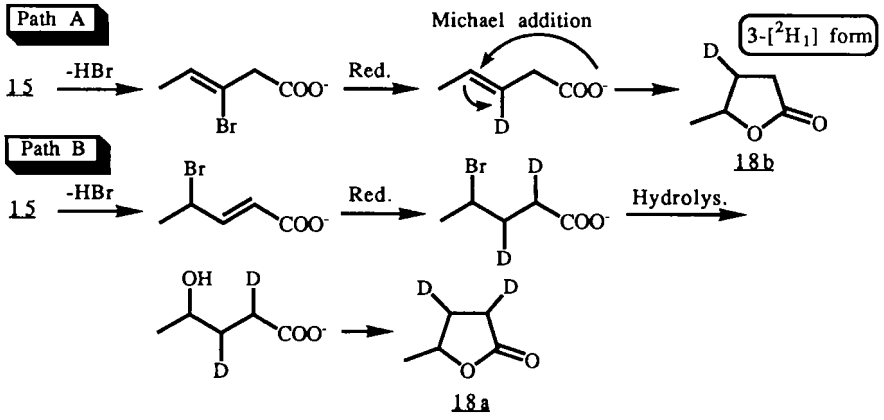
Table 5. Reduction of 3,4-dibromovaleric acid (15) and 4-bromo-*trans*-2-pentenoic acid (16).[a]

Run	Amount of alloy (mg)	Volume of alkali (mL)	Yield (%)[b]	Composition (%)[c] D_1 D_2 D_3 D_4 D_5
1	903	17.0	53	2 10 76 5 6
2	880	21.0	49	3 6 82 6 3

a) Substrate: 15, 1.2 mmol; 16, 7.4 mmol. b) Isolated yields are shown.
c) Determined by mass spectroscopic method.

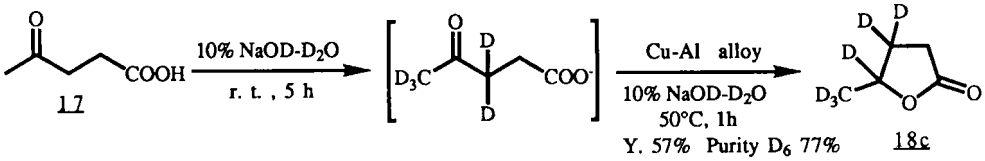
Reduction of 3,4-dibromovaleric acid (15) gave, interestingly, γ-[2,3-$^2H_2$]valerolactone (18a) in 53% yield (76% isotopic purity) instead of the expected [3,4-$^2H_2$]valeric acid. The [$^2H_2$]lactone 18a was also given *via* the reduction of 4-bromo-*trans*-2-pentenoic acid (16) in a higher isotopic purity

(83%). Thus, the reaction pathway to 18a is assumed as shown in Scheme 9. Dehydrobromination of 15 does not occur between C-3 and C-4 positions, followed by reductive debromination of the bromine at C-3 position and intramolecular Michael addition at C-4 position (Path A) but does between C-2 and C-3 positions and the bromine at C-4 position was hydrolysed under the basic conditions (Path B).



Scheme 9

Levulinic acid (17), on stirring at room temperature for 5 h, resulted in the incorporation of deuterium atoms at C-3 and C-5 positions, followed by Cu-Al alloy reduction, to generate γ-[3,3,4,5,5,5-$^2H_6$]valerolactone (18c) (Scheme 10).



Scheme 10

^2H and ^{13}C n.m.r. Spectra.

The positions, at which deuterium atoms were introduced, were confirmed on the basis of the ^2H and ^{13}C spectra. The representative ^2H and ^{13}C n.m.r. spectra are shown in Figures 1 and 2.

In ^2H n.m.r. spectra deuterium peaks of 2a-d having the desired integration intensity are observed at the expected positions.

^{13}C n.m.r. spectra in $CDCl_3$ indicate that carbon atoms, which bonded deuterium atoms, were revealed as triplets or quintets with coupling constants of 19.1-20.5 Hz at 0.29-0.35 ppm higher field than those of hydrogen-bonded carbons due to isotope effects.

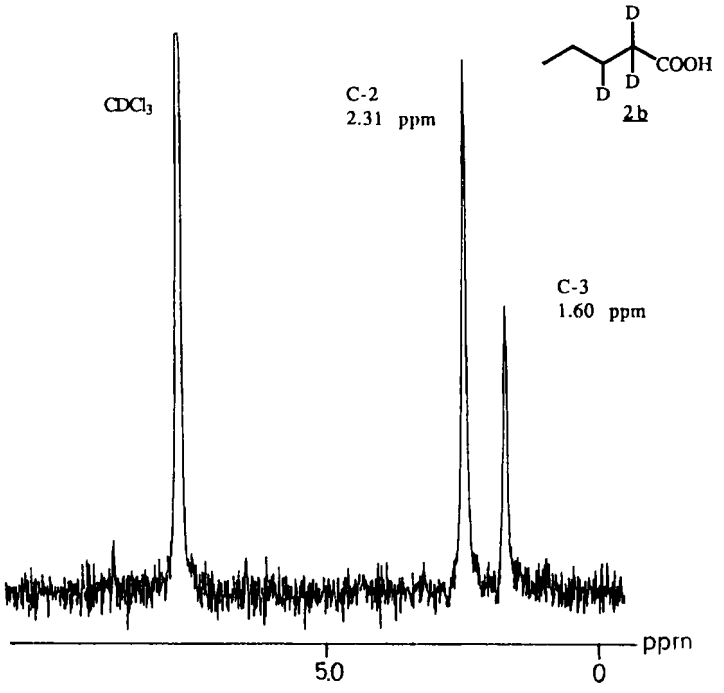


Figure 1 $^{2}H\{^{1}H\}$ of [2,2,3-$^{2}H_3$]valeric acid (2b) in $CDCl_3$.

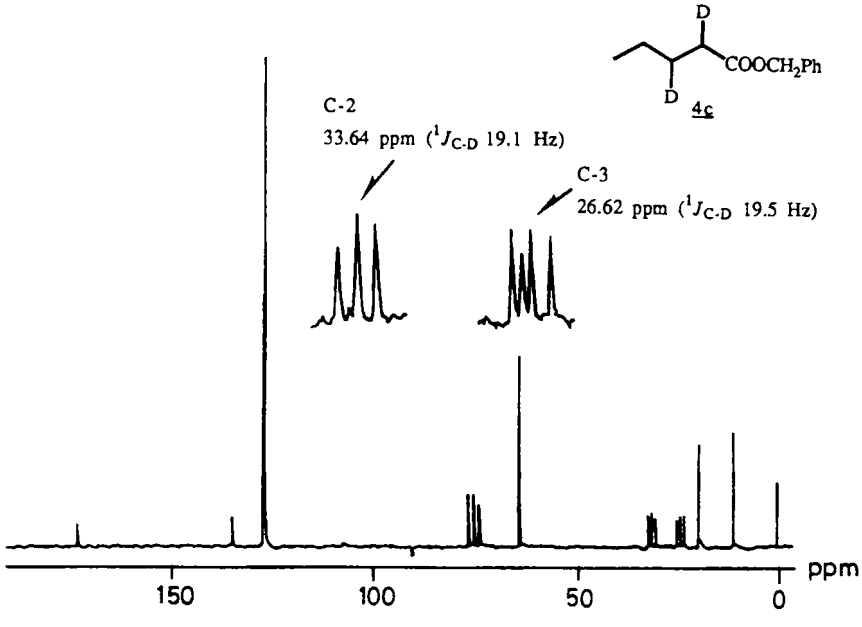


Figure 2 ^{13}C of benzyl [2,3-$^{2}H_2$]valerate (4c) in $CDCl_3$.

EXPERIMENTAL

D_2O (99.9 atom %D) was obtained from Division of Merck Frosst Canada inc. and 40% NaOD-D_2O (99.5 atom %D) from Merck & Co., Inc. All melting points were determined on a Yanagimoto micro-apparatus and are uncorrected. I.r. spectra were measured on a Nippon-bunko A-102 spectrophotometer as a liquid film with NaCl plates. Mass spectra were recorded on a Nippon Denshi JMS-01SG-2 mass spectrometer at 75 eV using a direct inlet system. Elemental analysis was carried out on a Yanaco MT-5 CHN corder. ^1H and ^{13}C n.m.r. were taken on a JEOL FX-100 n.m.r. spectrometer at 100 MHz and 25.05 MHz and $^2H\{^1H\}$ n.m.r. on a Hitachi R-90 H FT n.m.r. spectrometer in $CDCl_3$ with Me_4Si as an internal reference. Optical rotations were measured with an Union Model PM-101 apparatus at 26 °C.

Materials.

Compounds (11) and (17) were commercially available. Compounds (1), (5), (9), (10), (12), (15), and (16) were prepared following the reported or the modified method as previously described.[7] (±)-2-Bromovaleric acids (1a-b) were obtained following the reported method[8]; (1a): $[\alpha]_D$= +30.5 ° (ether), e.e. 98%, lit.,[8] $[\alpha]_D$= +31.0 °; (1b): $[\alpha]_D$= -22.4 ° (ether), e.e. 72%.

[2-$^2H_1$]Valeric acid (2a).

To a vigorously stirred mixture of 2.0 g (11 mmol) of 2-bromovaleric acid (1) and 12 mL of 10% NaOD-D_2O was added 600 mg of Cu-Al alloy in small portions to maintain the reaction temperature below 50 °C and the reaction mixture was stirred at 50 °C for 1 h. The above operation was carried out in a glove box under a nitrogen atmosphere. After cooling to room temperature, the reaction apparatus was taken out from a box, and the formed Cu powder and unreacted alloy were filtered off using celite as a filter aid and washed with a small amount of water. The filtrate combined with the washing was acidified with concentrated hydrochloric acid to pH.1 under ice-cooling and extracted with ether (30 mL x 10). The extracts were dried over $MgSO_4$ and evaporated *in vacuo* to leave a residue, which was distilled on a Kuhgel rohr apparatus (oven temperature: 99-102 °C) under a reduced pressure (13 Torr), to afford 720 mg (64%) of [2-$^2H_1$]valeric acid (2a) as colourless liquid (lit.,[9] b.p. 187-189 °C as for $^2H_0$ form). The residue was treated with hexane to afford white solids, followed by recrystallization from a mixture of benzene and petroleum ether, giving 180 mg (16%) of *threo*-2,3-dipropylsuccinic acid (3) as colourless needles, m.p. 185.5 °C (lit.,[10] m.p. 182-183 °C as for $^2H_0$ form).

[2,2,3-$^2H_3$]Valeric acid (2b).

To a vigorously stirred mixture of 2.0 g (7.7 mmol) of 2,3-dibromovaleric acid (5) and 12 mL of 10% NaOD-D_2O was gradually added 1.2 g of Cu-Al alloy to maintain the reaction temperature below 50 °C. Then, the reaction mixture was worked up as described above, and the distillation of the crude product by a Kuhgel rohr apparatus (oven temperature: 99-102 °C) under a reduced pressure (13 Torr) gave 671 mg (83%) of [2,2,3-$^2H_3$]valeric acid (2b) as colourless liquid (lit.,[9] b.p. 187-189 °C as for $^2H_0$ form).

***trans*- and *cis*-2-[2-$^2H_1$]Pentenoic acid (6a-b).**

To a vigorously stirred mixture of 400 mg (2.2 mmol) of *E*- and, *Z*-2-bromo-2-pentenoic acid (8a-b) and 2.5 mL of 10% NaOD-D_2O was added 123 mg of Cu-Al alloy in small portions to maintain the reaction temperature below 50 °C. The reaction mixture was worked up as previously described,

followed by distillation of the crude product by a Kuhgel rohr apparatus (oven temperature: 90-96 °C) under a reduced pressure (4 Torr), to give 178 mg (80%) of a 3:1 mixture of *trans*- and *cis*-2-[2-$^2H_1$]pentenoic acid (6a-b) as colourless liquid (lit.,[11] b.p. 105-108 °C/17 Torr as for *trans*-[$^2H_0$] form).

Reduction of *trans*-3-pentenoic acid (10).

To a vigorously stirred mixture of 1.0 g (10 mmol) of *trans*-3-pentenoic acid (10), 300 mg of 10% Pd-C, and 12 mL of 10% NaOD-D_2O was added 600 mg of Cu-Al alloy in small portions to maintain the reaction temperature below 50 °C. The reaction mixture was worked up as previously described, and the crude product was distilled on a Kuhgel rohr apparatus (oven temperature: 83-86 °C) under a reduced pressure (4 Torr) to afford 769 mg (74%) of deuteriated valeric acid (2) as colourless liquid (lit.,[9] b.p. 187-189 °C as for $^2H_0$ form).

4-[4,5,5-$^2H_3$]Pentenoic acid (13).

To a vigorously stirred mixture of 400 mg (4.1 mmol) of 4-pentynoic acid (12) and 15 mL of 10% Na_2CO_3-D_2O was added 600 mg of Cu-Al alloy in small portions to maintain the reaction temperature below 50 °C. The reaction mixture was worked up as previously described, and the crude product was distilled by a Kuhgel rohr apparatus (oven temperature: 110-115 °C) under a reduced pressure (6 Torr), giving 335 mg (80%) of 4-[4,5,5-$^2H_3$]pentenoic acid (13) as colourless liquid (lit.,[12] b.p. 186-188 °C/740 Torr as for $^2H_0$ form).

γ-[2,3-$^2H_2$]Valerolactone (18a).

To a vigorously stirred mixture of 1.33 g (7.4 mmol) of 4-bromo-*trans*-2-pentenoic acid (16) and 21 mL of 10% NaOD-D_2O was added 880 mg of Cu-Al alloy in small portions to maintain the reaction temperature below 50 °C. The reaction mixture was worked up as previously described, and the distillation of the crude product using a Kuhgel rohr apparatus (oven temperature: 152-155 °C) under a reduced pressure (30 Torr) gave 362 mg (49%) of γ-[2,3-$^2H_2$]valerolactone (18a) as colourless liquid (lit.,[13] b.p. 206-207 °C as for $^2H_0$ form).

γ-[3,3,4,5,5,5-$^2H_6$]Valerolactone (18c).

A mixture of 600 mg (5.2 mmol) of levlinic acid (17) and 8.4 mL of 10% NaOD-D_2O was vigorously stirred at room temperature for 5 h. To the mixture was gradually added 341 mg of Cu-Al alloy to maintain the reaction temperature below 50 °C, and then the whole mixture was worked up as previously described, followed by distillation of the crude product on a Kuhgel rohr apparatus (oven temperature: 150-157 °C) under a reduced pressure (33 Torr), to give 315 mg (57%) of γ-[3,3,4,5,5,5-$^2H_6$]valerolactone (18c) as colourless liquid (lit.,[13] b.p. 206-207 °C as for $^2H_0$ form).

Benzyl valerate.

A mixture of 10 g of (98 mmol) of valeric acid, 28.4 g (0.26 mol) of benzyl alchohol, and 666 mg of *p*-toluenesulphonic acid monohydrate in 100 mL of dichloromethane was heated under reflux for 12 h and the reaction mixture poured into water, and made alkaline (pH.9) with $NaHCO_3$. The mixture was extracted with ether (50 mL x 5) and the combined extracts were washed with water, dried over $MgSO_4$, and the ether evaporated off. The residue was chromatographed on sillica gel (Wakogel C-300) with dichloromethane as an eluent, followed by distillation, to give 14.0 g (75%) of benzyl valerate as colourless liquid; b.p. 258-258.5 °C; ν (NaCl) 1734 (C=O)

cm^{-1}; δ (CCl_4) 0.89 (3H, t, *J*6.5 Hz), 1.03-1.77 (4H, m), 2.32 (2H, t, *J*7.5 Hz), 5.05 (2H, s), 7.27 (5H, s); *m/z* (75 eV), 192 (M^+); (Found: C, 75.07; H, 8.40. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%).

Benzyl *trans*-2-pentenate.

A mixture of 5.0 g of (50 mmol) of *trans*-2-pentenoic acid (12), 14.2 g (0.13 mol) of benzyl alchohol, and 333 mg of *p*-toluenesulphonic acid monohydrate in 50 mL of dichloromethane was heated under reflux for 12 h, and the reaction mixture was worked up as described above to give 3.54 g (37%) of benzyl *trans*-2-pentenate as colourless liquid; b.p. 235-236 °C; ν (NaCl) 1721 (C=O) cm^{-1}; δ ($CDCl_3$) 1.04 (3H, t, *J*7.9 Hz), 1.97-2.38 (2H, m), 4.54 (2H, s), 5.86 (1H, dt, *J*15.8 Hz, *J*1.9 Hz), 7.11 (1H, dt, *J*15.8 Hz, *J*6.4 Hz), 7.31 (5H, s); *m/z* (75 eV), 190 (M^+); (Found: *m/z* 190.0995. Calcd. for $C_{12}H_{14}O_2$: 190.0993).

Benzyl 4-pentenate.

This ester was obtained in the similar manner as described above from 2.0 g of (20 mmol) of 4-pentenoic acid, 5.68 g (52 mmol) of benzyl alchohol, and 133 mg of *p*-toluenesulphonic acid monohydrate in 20 mL of dichloromethane as colourless liquid (3.24 g, 85%); b.p. 105-106 °C/4 Torr; ν (NaCl) 1740 (C=O) cm^{-1}; δ ($CDCl_3$) 2.17-2.50 (4H, m), 4.64-5.03 (2H, m), 5.07 (2H, s), 5.50-5.93 (1H, m), 7.29 (5H, s); *m/z* (75 eV), 190 (M^+); (Found: *m/z* 190.0993. Calcd. for $C_{12}H_{14}O_2$: 190.0993).

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