Tetrahedron Letters,Vol.24,No.47,pp 5257-5260,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

METHOD FOR DETERMINATION OF ENANTIOMERIC COMPOSITION AND ABSOLUTE CONFIGURATION OF 2,3-DEUTERATED 3-ALKYLPROPANOLS

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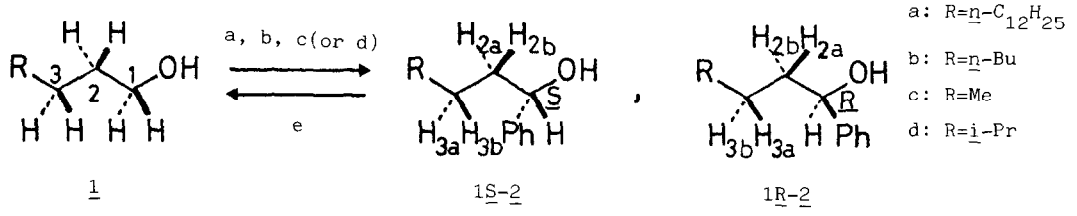
Summary: Assignments were made for diastereotopic methylene protons on C-2 and C-3 of 1-phenyl-3-alkylpropanols in $Eu(fod)_3$-enhanced ^{1}H-NMR spectra to develope a generally applicable method to determine enantiomeric composition and absolute configuration of 2 and/or 3-deuterated 3-alkylpropanols.

Determination of enantiomeric purity and absolute configuration of deuterium labeled chiral methylenes have great value for the study of mechanisms of chemical and biochemical reactions. It is known that enantiomeric purity and absolute configuration of 1-deuterated primary alcohols can be determined by the ^{1}H-NMR method using chiral lanthanide shift reagent[1], more generally, by the measurement of ^{1}H-NMR spectrum of (-)-camphanic esters of the alcohols in the presence of achiral shift reagent[2]. As for alcohols of the type 1 in which C-2 or C-3 methylene is stereospecifically substituted by deuterium, thus far no systematic research on determination of enantiomeric purity and absolute configuration by NMR method was reported.

In this report, we would like to describe a generally applicable method to determine absolute configurations of C-2 and C-3 position of 3-alkylpropanols 1 which are chiral due to deuterium substitution.

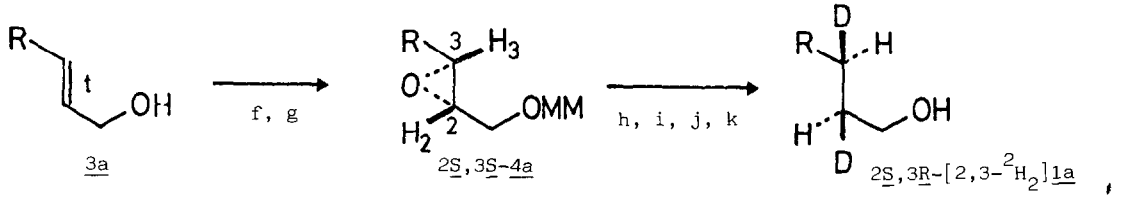
To defferentiate enantiotopic methylene protons of 3-alkylpropanol 1 in ^{1}H-NMR, the alcohol 1 was derivatized into 1-phenyl-3-alkylpropanol 2[4a] as shown in SCHEME 1. Because of the newly introduced chirality on C-1, methylene protons of 2 became diastereotopically non-equivalent. Indeed, diastereotopic methylene protons on C-2 and C-3 of 2 gave four multiplets in ^{1}H-NMR spectrum, but the separation of signals of H_{2a}[5], H_{2b}, H_{3a} and H_{3b} were small and the signals were partially overlapped with other signals even by 400 MHz ^{1}H-NMR spectrometer. To enhance the diastereotopic non-equivalence and to avoid the overlap with

SCHEME 1:



1 1S-2 1R-2

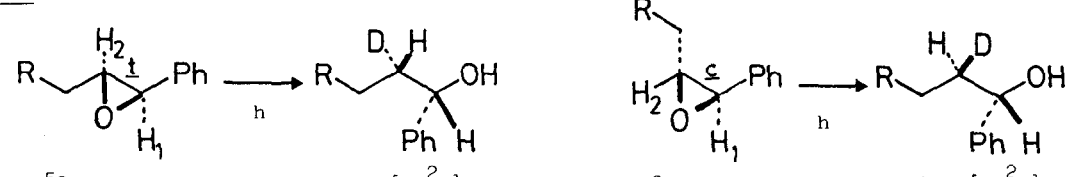
SCHEME 2:



3a 2S,3S-4a 2S,3R-[2,3-$^2H_2$]1a

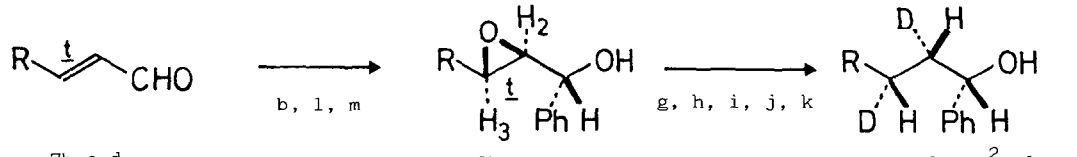
1S,2S,3R-[2,3-$^2H_2$]2a 1R,2S,3R-[2,3-$^2H_2$]2a

SCHEME 3:



5a (racemate) threo-[2-^2H]2a (racemate) 6a (racemate) erythro-[2-^2H]2a (racemate)

SCHEME 4:



7b,c,d 8b,c,d 1S,2S,3R/1R,2R,3S-[2,3-$^2H_2$]2b,c

1S,2S,3S/1R,2R,3R-[2,3-$^2H_2$]2d

a. PCC/AcONa/CH_2Cl_2. b. PhMgBr/Et_2O. c. Separation via (+)-MTPA Ester: (i) (+)-MTPA-Cl, (ii) HPLC: Silica Gel/CCl_4, (iii) LAH/Et_2O. d. Separation via R-(-)-Menthoxycarbonyl Deriv.: (i) (-)-Menthyl Chloroformate, (ii) Prep. GLC: 5% EGS, 1.5 m x 4 mmID, 160°C, (iii) LAH/Et_2O. e. (i) $RuO_4.2H_2O/NaIO_4/CH_2Cl_2-H_2O$, (ii) LAH/$Et_2O$. f. TBHP/Ti(OiPr)$_4$/L-(+)-Diethyltartarate. g. CH_3OCH_2Cl/iPr_2NEt. h. LAD/Et_2O. i. p-TsCl/Py. j. LAD/DME. k. HCl/MeOH. l. MCPBA/CH_2Cl_2. m. Silica Gel Column Chromatog./ CH_2Cl_2.

other signals, lanthanide shift reagent $Eu(fod)_3$ was added to the chloroform solution of 2 and 400 MHz ^{1}H-NMR spectra were taken at room temperature. In the $Eu(fod)_3$-shifted ^{1}H-NMR, the diastereotopic methylene protons on C-2 and C-3 of 2, i.e. H_{2a}, H_{2b}, H_{3a} and H_{3b} in the SCHEME 1, were clearly separated into four signals. Although many examples[6] were reported of this type of chemical shift non-equivalences among protons many bonds away from a site of asymmetry with or without lanthanide shift reagent, the separation of signals of H_{3a} and H_{3b} as well as H_{2a} and H_{2b} of 2 in $Eu(fod)_3$-shifted ^{1}H-NMR was not reported previously. Under the condition we employed in which equimolar amount of $Eu(fod)_3$ was added to 10 umol solution of 1-phenyl-3-alkylpropanols 2 in $CDCl_3$, chemical shift differences between diastereotopic methylene protons on C-2 and C-3 were found to be 0.6-0.7 ppm and 0.2-0.3 ppm respectively. And these diastereotopic differences exceeded 1.0 ppm for methylene protons on C-2 and 0.5 ppm for methylene protons on C-3 by a further addition of the lanthanide shift reagent.

To assign these signals unambiguously, stereospecifically deuterium labeled substrates[4] were prepared as follows. Chiral deuterium labeled alcohols mixture, 1S,2S,3R-[2,3-$^2H_2$]2a and 1R,2S,3R-[2,3-$^2H_2$]2a, were prepared via optically active epoxide 2S,3S-4a, as indicated in SCHEME 2. After the separation of isomeric alcohols via their (+)-MTPA esters, coupling constants between H_1 and H_2 of these alcohols were compared with those of threo-[2-^{2}H]2a and erythro-[2-^{2}H]2a which were prepared by LAD reduction of trans and cis epoxides, 5a and 6a to make clear which isomer had which configuration about C-1[7], i.e., 1S,2S,3R-[2,3-$^2H_2$]2a and threo-[2-^{2}H]2a had the same coupling constant, $J_{1,2}$=7.4 Hz, on the other hand, 1R,2S,3R-[2,3-$^2H_2$]2a and erythro-[2-^{2}H]2a showed smaller coupling constant, $J_{1,2}$=5.5 Hz.
For the same purpose to make assignments of the diastereotopic methylene protons on C-2 and C-3 of 1-phenyl-3-alkylpropanol 2, 2,3-deuterated 1-phenyl-3-alkylpropanols 2b, 2c and 2d with known relative configuration were also prepared as shown in SCHEME 4. These 2,3-deuterated compounds prepared above were racemic mixtures of 1S,2S,3R and 1R,2R,3S isomers and these were used for the following NMR measurement without optical resolution.

^{1}H-NMR spectra of the stereospecifically deuterated alcohols prepared above, 1S,2S,3R-[2,3-$^2H_2$]2a, 1R,2S,3R-[2,3-$^2H_2$]2a, threo-[2-^{2}H]2a, erythro-[2-^{2}H]2a, 1S,2S,3R/1R,2R,3S-[2,3-$^2H_2$]2b, 1S,2S,3R/1R,2R,3S-[2,3-$^2H_2$]2c and 1S,2S,3S/1R,2R,3R-[2,3-$^2H_2$]2d, were measured in the presence of $Eu(fod)_3$. The assignments for diastereotopic protons, H_{2a}, H_{2b}, H_{3a} and H_{3b} of the substrates (10 mM) shifted by $Eu(fod)_3$ (10 mM) in $CDCl_3$ were shown in TABLE 1. And

TABLE 1: Chemical shifts of diastereotopic protons of the 1-phenyl-3-alkylpropanol, 2 (10 mM) in the presence of $Eu(fod)_3$ (10 mM) in $CDCl_3$ at room temperature.

	H_{2a}	H_{2b}	H_{3a}	H_{3b}
2a: R=n-$C_{12}H_{25}$	5.1 ppm	5.7	3.4	3.6
2b: R=n-Bu	5.2	5.8	3.4	3.6
2c: R=Me	5.2	5.8	3.4	3.7
2d: R=i-Pr	5.2	5.9	3.4	3.7

these protons were found to keep their order in the spectra at every concentration of $Eu(fod)_3$, i.e. from higher to lower field, H_{3a}, H_{3b}, H_{2a} and H_{2b} resonated in this order.

This assignment of diastereotopic protons of 1-phenyl-3-alkylpropanol 2 will provide a new generally applicable method for determination of enantiomeric composition and/or absolute configuration of deuterium enriched chiral alkyl groups in a molecule when this part of the molecule can be derivatized to 1-phenyl-3-alkylpropanol 2. In this connection, it should be emphasized here that no loss of deuterium on C-2 was observed by GC-MS analysis in the derivatization of [2,3-$^2H_2$]1a to [2,3-$^2H_2$]2a, and in the reverse process in SCHEME 1 from [2,3-$^2H_2$]2a to the corresponding alkanol, [2,3-$^2H_2$]1a. The application of this method to a biosynthetic work on prochiral methylene protons of alkyl chain of a polyketide was investigated and was succesful. The result is in the following paper of this volume.

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2) H. Gerlach and B. Zagalak, J. C. S. Chem. Comm., 274 (1973).
3) J. M. Brown and D. Parker, Tetr. Lett., 2815 (1981).
4) a) ^{1}H-NMR (δ, $CDCl_3$) of 1-phenyl-3-alkylpropanols, 2a: 4.66(1H, ddd, J=7.4, 5.5, 3 Hz, H_1), 1.78(1H, d, J=3 Hz, OH), 1.71(1H, m, H_{2a}), 1.78 (1H, m, H_{2b}), 1.3(1H, m, H_{3a}), 1.40(1H, m, H_{3b}), 0.89(3H, t, J=7 Hz, CH_3), 1.25(24H, bs, CH_2x12), 7.2-7.4(5H, Ph). 1S,2S,3R-[2,3-$^2H_2$]2a: 4.66(1H, dd, J=7.4, 3 Hz, H_1), 1.78(1H, d, J=3 Hz, OH), 1.77(1H, H_{2b}), 1.40(1H, m, H_{3b}). 1R,2S,3R-[2,3-$^2H_2$]2a: 4.66(1H, dd, J=5.5, 3 Hz, H_1), 1.78(1H, d, J=3 Hz, OH), 1.69(1H, H_{2a}). threo-[2-^{2}H]2a: 4.66 (1H, dd, J=7.4, 3 Hz, H_1), 1.78(1H, d, J=3Hz, OH), 1.77(1H, m, H_{2a}). erythro-[2-^{2}H]2a: 4.66(1H, dd, J=5.5, 3 Hz, H_1), 1.78(1H, d, J=3 Hz, OH), 1.68(1H, m, H_{2b}). 2b: 4.65(1H, dd, J=7.4, 5.5 Hz, H_1), 1.78 (1H, bs, OH), 1.70(1H, m, H_{2a}), 1.78(1H, m, H_{2b}), 1.40(1H, m, H_{3b}), 0.88(3H, t, J=7 Hz, CH_3), 1.27(7H, bs, CH_2x3+H_{3a}), 7.2-7.4(5H, Ph). 1S,2S,3R/1R,2R,3S-[2,3-$^2H_2$]2b: 4.65(1H, d, J=7.4 Hz, H_1), 1.77(1H, H_{2b}), 1.39(1H, H_{3b}). 2c: 4.68(1H, dd, J=7.4, 5.5 Hz, H_1), 1.90(1H, bs, OH), 1.68(1H, m, H_{2a}), 1.78(1H, m, H_{2b}), 1.31(1H, m, H_{3a}), 1.42(1H, m, H_{3b}), 0.92(3H, t, J=7.4 Hz, CH_3), 7.2-7.4(5H, Ph). 1S,2S,3R/1R,2R,3S-[2,3-$^2H_2$]2c: 4.68(1H, d, J=7.4 Hz, H_1), 1.78(1H, bs, H_{2b}), 1.40(1H, m, H_{3a}), 0.92(3H, d, J=7.4 Hz, CH_3). 2d: 4.64 (1H, ddd, J=7.4, 5.5, 3 Hz, H_1), 1.8(1H, d, J=3 Hz, OH), 1.15(1H, m, H_{2a}), 1.32(1H, m, H_{2b}), 1.55(1H, m, H_{3a}), 1.73(1H, m, H_{3b}), 0.85(3H, d, J=2.3 Hz, CH_3), 0.87(3H, d, J=2.3 Hz, CH_3), 7.2-7.4(5H, Ph). 1S,2S,3S/1R,2R,3R-[2,3-$^2H_2$]2d: 4.64(1H, d, J=7.4 Hz, H_1), 1.32(1H, H_{2b}), 1.72(1H, H_{3b}).
b) Selected ^{1}H-NMR (δ, $CDCl_3$) data of synthetic intermediates, 2S,3S-4a: 2.84(1H, ddd, J=2.4, 5.4, 5.4 Hz, H_3), 2.93(1H, ddd, J=2.4, 3.1, 5.4 Hz, H_2), 3.54(1H, dd, 5.4, 11.7 Hz, H_1), 3.73(1H, dd, J=3.1, 11.7 Hz, H_1). 5a: 2.94(1H, ddd, J=2.1, 5.7, 5.7 Hz, H_2), 3.60(1H, d, J=2.1 Hz, H_1). 6a: 3.20(1H, ddd, J=4.3, 5.6, 5.6 Hz, H_2), 4.06(1H, d, J=4.3 Hz, H_1). 8c: 3.13(1H, dq, J=2.1, 5.4 Hz, H_3), 2.96(1H, dd, J=2.1, 5.0 Hz, H_2), 4.51(1H, d, J=5.0 Hz, H_1), 1.32(3H, d, J=5.4 Hz, CH_3), 2.47(1H. bs, OH). (+)-MTPA ester of 1S,2S,3R-[2,3-$^2H_2$]2a: 1.96(1H, dd, J=7.7, 5 Hz, H_{2b}), 3.54(3H, s, OCH_3), 5.87(1H, d, J=7.7 Hz, H_1). (+)-MTPA ester of 1R,2S,3R-[2,3-$^2H_2$]2a: 1.74(1H, dd, J=5.4, 5 Hz, H_{2a}), 3.44(3H, s, OCH_3), 5.95(1H, d, J=5.4 Hz, H_1).
5) Subscripts a and b were defined as in the SCHEME 1 to denote relative configurations to the asymmetry of C-1.
6) W. B. Jennings, Chemical Reviews, 75, 307 (1975); M. Schwarz, R. B. Bradley, H. M. MacIntyre, and E. D. Becker, Org. Mag. Resonance, 6, 625 (1974).
7) In other way, absolute configuration of C-1 of 1-phenyl-3-alkyl propanols, 1S,2S,3R-[2,3-$^2H_2$]2a and 1R,2S,3R-[2,3-$^2H_2$]2a as well as resolved 2a, 2b, 2c were asigned to be S or R from chemical shifts of OCH_3 and H_1 in the ^{1}H-NMR of their (+)-MTPA esters. The (+)-MTPA esters of 1S-2 showed OCH_3 signal around 3.54 and ^{1}H signal around 5.87 ppm, and the esters of 1R-epimers showed OCH_3 and H_1 signals around 3.44 and 5.95 respectively. These chemical shifts were coincident with the values reported by Yamaguchi; F. Yasuhara and S. Yamaguchi, Tetr. Lett., 21, 2827 (1980).

(Received in Japan 18 July 1983)