# FACILE SYNTHESIS OF [4-$^{13}$C]BUTANOIC ACID AND [4-$^{13}$C]BUTANOL

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## SUMMARY

Alkylation of the dianion of 3-(phenylsulfinyl)propanol with [$^{13}$C]iodomethane and subsequent reductive fission of the sulfoxides gave [4-$^{13}$C]butanol that was oxidized to give [4-$^{13}$C]butanoic acid.

Key words: [4-$^{13}$C]butanoic acid, [4-$^{13}$C]butanol, Carbon-13 labelling, 3-phenylsulfinyl[4-$^{13}$C]butanol

## INTRODUCTION

Mechanistic mass spectrometric studies in our laboratory (1-2) and elsewhere (3) with labelled butanoic acids focussed our interest on the synthesis of terminally labelled alkanoic acids. In spite of extensive literature on the preparation of labelled alkanoic acids (4-11), none of the published methods mentions a short and convenient synthesis of such terminally labelled compounds.
This communication describes a facile synthetic route to terminally labelled aliphatic alcohols and carboxylic acids proceeding via chain extension of ω-hydroxy sulfoxides with labelled iodomethane. The common applicability of this method is demonstrated by the synthesis of [4-$^{13}$C]butanoic acid.

## RESULTS AND DISCUSSION

The synthesis of [4-$^{13}$C]butanoic acid 8 is summarized in Scheme 1. Starting from commercially available ethyl 3-bromopropanoate 1 3-phenylsulfinylpropanol 4 was obtained in 57% overall yield. Preparation of the dilithio-anion of 4 with lithium diisopropylamide (12) and alkylation with $^{13}CH_3I$ gave the labelled alcohol 5 as a 60/40

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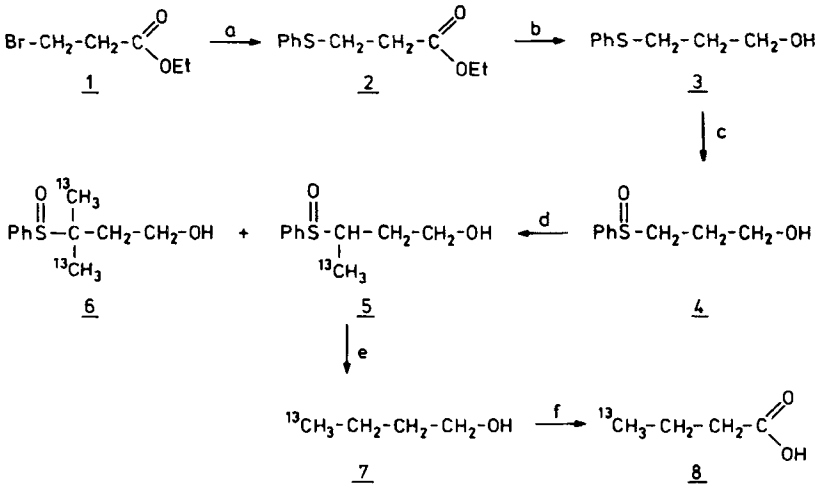


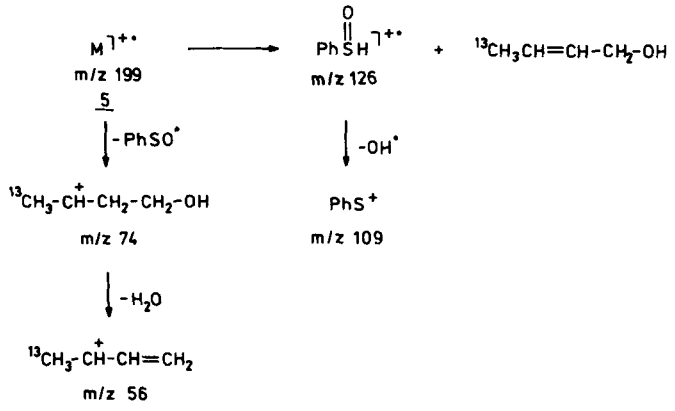

a) PhSH / $Et_3N$ , b) $LiAlH_4$ , c) m-CPBA , d) LDA ; $^{13}CH_3I$ , e) Li / $EtNH_2$ , f) $KMnO_4$

Scheme 1

mixture of the diastereomeric racemates and, to our surprise, the dialkylated product 6.

In our investigations on the substitution reaction of α-sulfinyl carbanions derived from β-hydroxy sulfoxides with various electrophiles (13-14), mono-alkylated sulfoxides were exclusively obtained, but dialkylated products could never be isolated. Thus the formation of 6 indicates the alkylation of the internal chelate of the dilithio derivative of the γ-hydroxy sulfoxides experiences less steric hindrance than the alkylation of the more crowded dilithio derivatives of the β-hydroxy sulfoxides.

Reduction of the phenylsulfinyl group with lithium in ethylamine afforded alcohol 7 that was oxidized with $KMnO_4$ to give [4-$^{13}$C]-butanoic acid 8 in high yield. The overall yield from the introduction of the label to the acid was 54%. Introduction of the label in a later stage of the reaction sequence is preferred to the known procedures for terminal labelling of aliphatic alcohols and




ELECTRON IMPACT IONIZATION

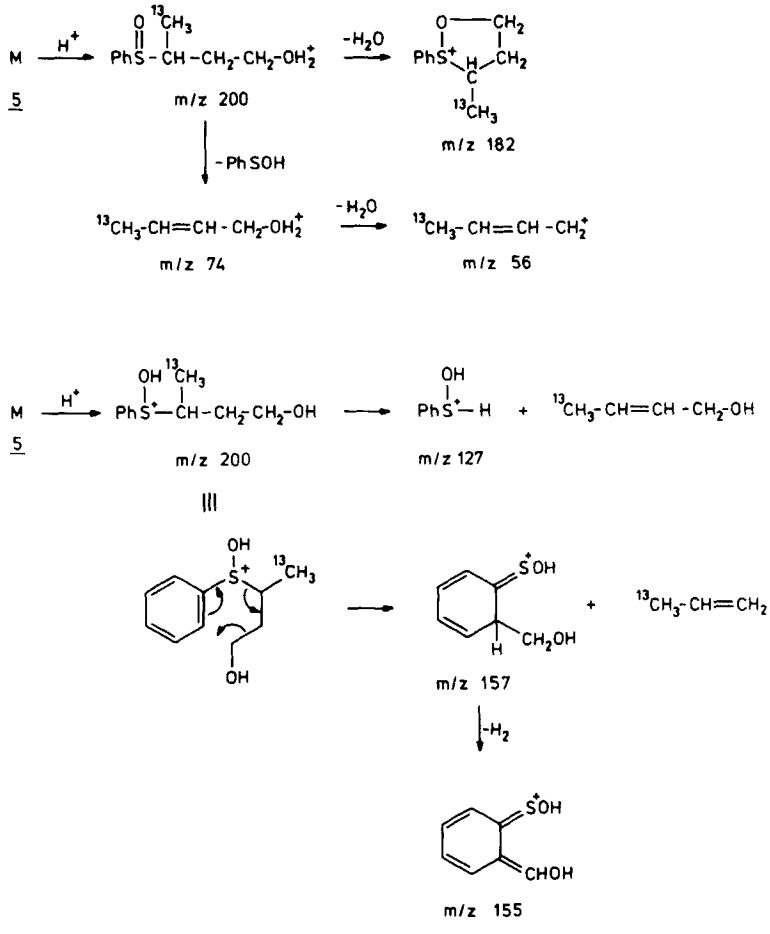
Scheme 2

carboxylic acids. Considering the results in the alkylation of various hydroxy sulfoxides (13-14), the synthetic sequence should be suitable for the preparation of other [ω-$^{13}$C]alkanoic acids. Detection of the $^{13}$C-label was performed with mass spectrometry: the fragmentation patterns of 5 with Electron Impact and Chemical Ionization techniques are presented in Schemes 2 and 3, respectively (15).

## EXPERIMENTAL

Materials: [$^{13}$C]Iodomethane (90 atom% $^{13}$C) was obtained from Merck, Sharpe and Dohme, Montreal, Canada; ethyl 3-bromopropanoate from Aldrich. Lithium diisopropylamide (LDA) was prepared by dissolving diisopropylamine (21 ml) in THF (29 ml), followed by addition of n-butyllithium (Merck, 100 ml 15% in hexane) under cooling in ice. The exact concentration was determined by titration with diphenylacetic acid (16). The solution usually contained 0,85-0,95 mmol per ml and could be stored in a refrigerator for months.

Methods: Column chromatography was performed through Merck Fertigsäule (Silicagel 60), elution with petroleum ether 60/80 and ethyl




Scheme 3

acetate (1:1). NMR spectra were recorded with Varian XL-100-15 and Bruker WM 250 spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were taken with a Varian Mat 711 Mass Spectrometer. Infrared spectra were measured with a Perkin Elmer Spectrophotometer, Model 298.

Ethyl 3-(phenylthio)propanoate 2

A solution of thiophenol (11.0 g, 0.1 mol) and triethylamine (11.1 g, 0.11 mol) in ether (100 ml) was cooled in ice and then ethyl 3-bromo-

propanoate (18.1 g, 0.1 mol) in ether (25 ml) was added. The mixture was refluxed for 2 hr and the white precipitate was filtered off. The filtrate was washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Distillation yielded 19.3 g (92%) of 2, colourless oil; bp. 97°/0.2 Torr. IR(liq.cap.): 2980, 1730, 1580, 1480, 1240, 1020, 740 and 690 $cm^{-1}$. $^1$H-NMR: 1.24 (t, 3H, J=7 Hz, $CH_2$-$CH_3$), 2.61 (t, 2H, J=7 Hz, $CH_2$), 3.17 (t, 2H, J=7 Hz, $CH_2S$), 4.14 (q, 2H, J=7 Hz, $OCH_2$), 7.1-7.6 (m, 5H, $C_6H_5$).

3-(Phenylthio)propanol 3

A solution of 2 (18.9 g, 0.09 mol) in THF (100 ml) was cooled to -60°C and then a suspension of $LiAlH_4$ (1.9 g, 0.05 mol) in THF (100 ml) was added slowly. During the addition the temperature of the mixture was kept below -40°C. After stirring overnight at room temperature, the mixture was cooled in ice, then water (10 ml) was carefully added, followed by an aqueous solution of NaOH (10 ml, 10%) and again water (30 ml). The precipitate was filtered off and washed with ether, the combined organic layers were dried over $MgSO_4$. Removal of the solvent and distillation gave 10.8 g (71%) of 3, colourless oil, bp. 90-92°/0.06 Torr. (Lit. (17) 130°/2 Torr.). IR(liq.cap.): 3340, 2940, 1580, 1480, 1050, 1020, 740 and 690 $cm^{-1}$. $^1$H-NMR: 1.87 (m, 2H, $CH_2$), 2.1 (br s, OH), 3.03 (t, 2H, J=7 Hz, $CH_2S$), 3.74 (t, 2H, J=7 Hz, $CH_2OH$), 7.1-7.5 (m, 5H, $C_6H_5$).

3-Phenylsulfinylpropanol 4

A solution of 3 (10.08 g, 60 mmol) in $CH_2Cl_2$ (200 ml) was cooled to -20°C and then m-chloroperbenzoic acid (12.2 g 85%, 60 mmol) was added in small portions under vigorous stirring. The mixture was subsequently stirred for 2 hr at -20°C and then filtered. The filtrate was washed three times with 5% $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated under reduced pressure leaving a light yellow oil. Column chromatography afforded 9.6 g of pure 4 (87%).

IR(liq.cap): 3380, 1580, 1480, 1440, 1020, 745 and 690 $cm^{-1}$.
$^1$H-NMR: 1.98 (m, 2H, $C\underline{H}_2$), 3.02 (m, 2H, $C\underline{H}_2SO$), 3.76 (t, 2H, J=7 Hz, $C\underline{H}_2OH$), 4.0 (br s, O$\underline{H}$), 7.4-7.7 (m, 5H, $C_6\underline{H}_5$); the NMR absorptions are not in agreement with those found in the literature (18).

3-Phenylsulfinyl[4-$^{13}$C]butanol 5

A solution of 4 (1.472 g, 8 mmol) in THF (75 ml) was cooled to -70°C. LDA (17.6 mmol) in THF was added and the solution was stirred for 15 min at -70°C. [$^{13}$C]Iodomethane (1.136 g, 8 mmol) was added at once. After stirring for 6 hr at -60°C, the reaction mixture was poured out into satd. brine (100 ml) to which conc. $H_2SO_4$ had been previously added. The water layer was extracted with ether (3x), the combined organic layers washed with brine containing a little $Na_2S_2O_3$ and dried over $MgSO_4$. Removal of the solvent followed by column chromatography gave 1.130 g (71%) of 5, colourless oil, as a 60/40 mixture of the RR/SS and the RS/SR racemates, (19) respectively, and 206 mg (12%) of 6, colourless oil.
$^1$H-NMR RR/SS-5: 1.05 (dd, 3H, J=7 Hz and $J_{C-H}$=130 Hz, $^{13}C\underline{H}_3$), 1.9 (m, 2H, $C\underline{H}_2$), 3.0 (m, 1H, C$\underline{H}$), 3.8 (m, 3H, $C\underline{H}_2O\underline{H}$), 7.4-7.7 (m, 5H, $C_6\underline{H}_5$). $^{13}$C-NMR: 10.0 ($C_4$), 33.4 ($C_2$), 55.7 (d, $C_3$), 58.5 ($C_1$), 124.4 ($C_m$), 128.5 ($C_o$), 130.4 ($C_p$), 140.7 ($C_i$). $^1$H-NMR RS/SR-5: 1.22 (dd, 3H, J=7 Hz and $J_{C-H}$=129 Hz, $^{13}C\underline{H}_3$), 1.8 (m, 2H, $C\underline{H}_2$), 2.8 (br s, O$\underline{H}$), 3.0 (m, 1H, C$\underline{H}$), 3.7 (m, 2H, $C\underline{H}_2OH$), 7.4-7.8 (m, 5H, $C_6\underline{H}_5$). $^{13}$C-NMR: 13.2 ($C_4$), 34.0 ($C_2$), 57.7 (d, $C_3$), 58.9 ($C_1$), 125.3 ($C_m$), 129.0 ($C_o$), 131.2 ($C_p$), 141.4 ($C_i$). $^1$H-NMR 6: 1.15 (dd, 3H, $^3J_{C-H}$=4 Hz, $J_{C-H}$=129 Hz, $^{13}C\underline{H}_3$), 1.27 (dd, 3H, $^3J_{C-H}$=4 Hz, $J_{C-H}$=129 Hz, $^{13}C\underline{H}_3$), 1.85 (m, 2H, $C\underline{H}_2$), 3.76 (t, 2H, $C\underline{H}_2OH$), 4.0 (br s, O$\underline{H}$), 7.4-7.8 (m, 5H, $C_6\underline{H}_5$). $^{13}$C-NMR: 20.6 and 21.7 (2 x $^{13}CH_3$), 39.7 ($C_2$), 57.9 ($C_3$), 59.0 ($C_1$), 126.9 ($C_m$), 128.5 ($C_o$), 131.4 ($C_p$), 138.6 ($C_i$).

[4-$^{13}$C]butanol 7

A solution of 5 (1.10 g, 5.53 mmol) in ethylamine (200 ml) was cooled to -70°C and reduced with lithium wire according to a literature procedure (20). Work-up gave 0.340 g (82%) of 7. $^{1}$H-NMR: 0.90 (dm, 3H, $J_{C-H}$=131 Hz, $^{13}C\underline{H}_3$), 1.1-1.7 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 3.49 (t, 2H, J=7 Hz, $C\underline{H}_2O$), 4.1 (br s, O$\underline{H}$).

[4-$^{13}$C]butanoic acid 8

Labelled 7 (0.340 g, 4.53 mmol) was oxidized with $KMnO_4$ (1.47 g, 9.3 mmol) in water (6 ml) via the method described by Saotome et al. (21). Work-up gave 0.383 g of 8. $^{1}$H-NMR: 0.90 (dt, 3H, J=7 Hz, $J_{C-H}$=131 Hz, $^{13}C\underline{H}_3$), 1.65 (m, 2H, $C\underline{H}_2$), 2.26 (t, J=7 Hz, $C\underline{H}_2CO$), 11.92 (s, COO$\underline{H}$).

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REFERENCES AND NOTES

1. Zwinselman J.J., Nibbering N.M.M., Hudson C.E. and McAdoo D.J. – Int.J.Mass.Spectrom.Ion.Phys. 47: 129 (1983)
2. Zwinselman J.J. – Ph.D. Thesis, University of Amsterdam, The Netherlands (1983)
3. McAdoo D.J. and Hudson C.E. – J.Amer.Chem.Soc. 103: 7710 (1981)
4. Koltai E. and Bánfi D. – J.Labell.Comp.Radiopharm. 18: 809 (1980)
5. Baretz B.H., Lollo C.P. and Tanaka K. – Ibid. 15: 369 (1978)
6. Fitzell D.L., Hsieh D.P.H., Reece C.A. and Seiber J.N. – Ibid. 11: 135 (1975)
7. Oae S., Redvanly C.S. and Wolf A.P. – Ibid. 4: 28 (1967)
8. Küng W., Faigle J.W., Kocher E. and Wirz B. – Ibid. 20:213 (1983)
9. Lee C.C., Kung F.L., Hahn B.S. and Robson A.J. – Ibid. 7: 46 (1970)
10. McAdoo D.J., Witiak D.N., McLafferty F.W. and Dill J.D. – J.Amer.Chem.Soc. 100: 6639 (1978)

11. McAdoo D.J., Witiak D.N. and McLafferty F.W. — Ibid. 99: 7265 (1977)
12. Use of n-butyllithium gave the desired products in poor yield
13. Van der Laan R. — Ph.D. Thesis, University of Amsterdam, The Netherlands (1983)
14. Van der Laan R., Moolenaar M.J. and De Koning H.— to be published
15. The dialkylated product 6 gave similar fragmentation patterns
16. Kofron W.G. and Baclawsky L.M. — J.Org.Chem. 41: 1879 (1976)
17. Fong H.O., Hardstaff W.R., Kay D.G., Langler R.F., Morse R.H. and Sandoval D.N. — Can.J.Chem. 57: 1206 (1979)
18. Durst T., Tin K-C. and Marcil M.J.V. — Can.J.Chem. 51: 1704 (1973)
19. Assignment of the relative configurations occurred on the ground of the NMR-spectra (see ref. 13 - 14)
20. Nederlof P.J.R., Moolenaar M.J., De Waard E.R. and Huisman H.O. — Tetrahedron 33: 579 (1977)
21. Saotome K. and Yamazaki T. — Bull.Chem.Soc.Japan 36: 1264 (1963)