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SYNTHESIS OF (2R)-[3,3,3-d_3] ISOBUTYRIC ACID, AMMONIUM SALT

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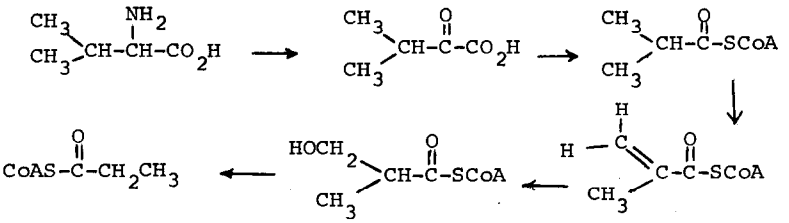
As part of a study on the stereochemical aspects of the metabolism of L-valine,[1] we investigated the fates of the diastereotopic methyls in the oxidative degradation pathway (Scheme I) occurring in mammalian systems and microorganisms.[2] For this purpose, we had synthesized[1]



Scheme I

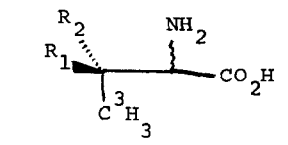
(2RS, 3R) and (2RS, 3S)-[4-^{3}H] valines, 1 and 2. We found,[3] however, that after incubation of 1 or 2 (with ^{14}C valine) in rat liver homogenates, the metabolites isobutyric, methacrylic, and propionic acids were isolated (as methyl esters by glc after addition of unlabelled carrier) having essentially the same ^{3}H/^{14}C ratios, whether the ^{3}H-valine used was 3R or 3S. This result could be interpreted in two ways: either the isobutyryl CoA dehydrogenase does not discriminate between enantiotopic methyls, or the configurational purity of the original valines was lost, possibly by enolization of the intermediate, α-ketoisovaleric acid.[4]

It appeared that a resolution of this ambiguity could be made by incubation of asymmetrically labelled isobutyryl CoA, rather than valine, thereby bypassing the labile α-ketoacid intermediate. We therefore developed a synthesis of ammonium (2R)-[3,3,3-d_3] isobutyrate 3 by a modification of our route[1] to chiral-valines.

Our task was simplified when it was found that isobutyraldehyde was oxidized rapidly at 20° with neutral $KMnO_4$ to isobutyric acid. When the reaction was conducted in D_2O, the isobutyric acid (isolated as the ammonium salt) contained no deuterium. Thus it seemed likely that if the reaction were performed on asymmetrically labelled isobutyraldehyde, the product would retain its configurational purity.

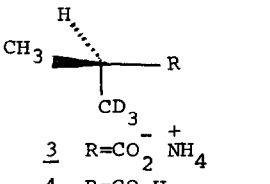
To obtain chiral-isobutyraldehyde, we used the synthetic route employed in our chiral-

valine synthesis.[1,5] Thus, (2S, 3R)-trans-2,3-epoxybutyric acid 7 was methylated (CH_2N_2) and reduced with sodium borohydride to (2R, 3R)-trans-2,3-epoxy-1-butanol 8, which with lithium iodide-free methyl-d_3 lithium gave (2S, 3R)-3-methyl-[4,4,4-d_3]butane-1,2-diol 6. Treatment of this with periodate gave (2R)-[3,3,3-d_3]isobutyraldehyde 5 (obtained only as an aqueous solution), oxidation of which with $KMnO_4$ gave (2R)-[3,3,3-d_3]isobutyric acid 4, isolated in good yield as the ammonium salt 3[6], after clarification with SO_2, low temperature distillation and neutralization with NH_4OH.



1 $R_1=CH_3$; $R_2=H$

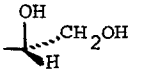
2 $R_1=H$; $R_2=CH_3$



3 $R=CO_2^- NH_4^+$

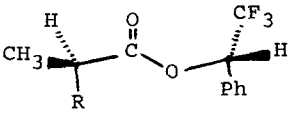
4 $R=CO_2H$

5 R=CHO

6 R= 

7 $R=CO_2H$

8 $R=CH_2OH$



9 $R=CD_3$

10 $R=CH_3$

A portion was esterified with S(+) phenyltrifluoromethyl carbinol, under mild conditions via the acid chloride. The nmr of the ester 9 showed a clean methyl doublet at δ 1.21, in contrast to the unlabelled ester 10 having δ 1.17 and 1.21. Thus, configurational homogeneity of the isopropyl was maintained throughout the sequence. The synthesis is now being extended to the ^{13}C analog of 3, which upon conversion to the CoA ester should allow a determination of the stereochemistry of its enzymatic dehydrogenation by nmr methods.[7]

References

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2. a. D. S. Kinnory, Y. Takeda, and D. M. Greenberg, J. Biol. Chem., 212, 385 (1955).
   b. M. J. Coon and W. G. Robinson, in "Methods in Enzymology", S. P. Colowick and N. O. Kaplan, Ed., Academic Press, New York, N.Y., 1962, vol V, p. 451.
3. D. J. Aberhart, unpublished work.
4. Chiral α-ketoisovaleric acid has been generated enzymatically in solution and converted without racemization into L-valine, but with purified enzymes rather than crude tissue cultures: R. K. Hill, S. Yan, and S. M. Arfin, J. Amer. Chem. Soc., 95, 7857 (1973).
5. We also attempted to generate chiral-isobutyraldehyde by Ag(II) Picolinate oxidation of valine: T. G. Clarke, N. A. Hampson, J. B. Lee, and J. R. Moreley, J. Chem. Soc. (C), 815 (1970). However, the yield was too low.
6. Compound 3 had $[\alpha]_D^{25}$-0.3° (c, 20, H_2O).
7. This work was supported by N.I.H. grant GM 18872.