Synthesis of (3*R*,4*S*)- and (3*R*,4*R*)-[4-^{2}H,^{3}H]Valine. Preparation of Compounds containing Chiral Methyl Groups with an Adjacent Asymmetric Centre

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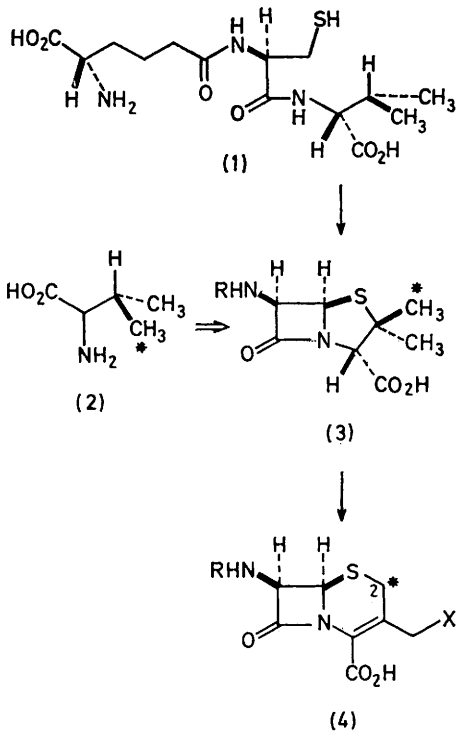
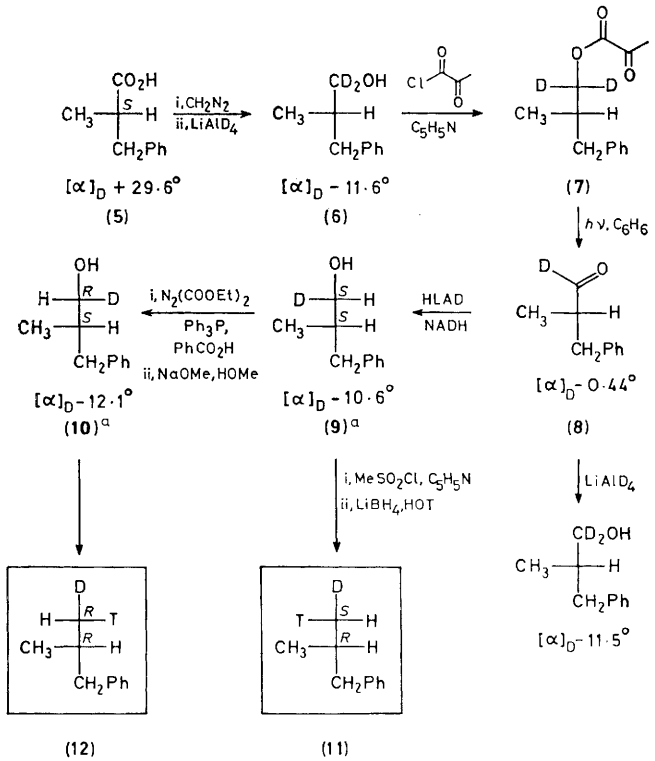
The general problem of the synthesis of compounds containing chiral methyl groups adjacent to an asymmetric centre is addressed for the specific case of valine having such groups exclusively at the 3-*pro*(*R*) position.

The formation of the penam and cephem ring systems from the Arnstein tripeptide (**1**) remains a classic problem in bioorganic chemistry.[1] It now appears certain,[2] however, that penicillin N [**3**, R = δ-(D-α-aminoadipyl)] in protoplast lysate systems of *Cephalosporium acremonium* is the direct precursor of deacetoxycephalosporin C [**4**, R = δ-(D-α-aminoadipyl), X = H]. In an attempt to understand more fully the details of the *in vivo* ring expansion, we have sought to examine the stereochemical fate of specimens of valine bearing chiral methyl groups in the 3-*pro*(*R*) position (**2**, * = CHDT) in conversion into the β methyl group[3] of penicillin N (**3**) and into the C-2 methylene group[3] of cephalosporin (**4**) (Scheme 1). A number of approaches to the synthesis of compounds containing chiral methyl groups have been described in the last decade,[4-6] but the additional synthetic problem of an adjacent asymmetric centre presented by the required valine (**2**) has not been addressed previously.

(*S*)-(+)-α-Methyldihydrocinnamic acid (**5**), $[\alpha]_D^{22}$ +29.6° (*c* 5.78, $CHCl_3$), [lit.,[7] +27.7° (*c* 3.28, $CHCl_3$)] was chosen to establish the correct absolute configuration at what was to become the β carbon atom of valine (Scheme 2). Treatment afforded (*S*)-(−)-[1-$^2H_2$]-2-methyl-3-phenylpropanol (**6**) (95% yield). Oxidation of the [$^2H_2$]-alcohol (**6**) to the [$^2H_1$]-aldehyde (**8**) using a variety of chromium(VI)-based reagents proved difficult owing in part to partial racemization of the product, but most particularly to a marked primary isotope effect[8] and



Scheme 1



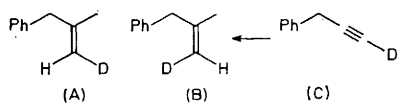
Scheme 2. [a] Mass spectrometry showed the presence of > 99% of the [$^2H_1$]-alcohol.

further to disproportionation of the aldehyde to the alcohol of the acid (**5**) with diazomethane and reduction of the resulting ester with lithium aluminium deuteride (Fluka) and carboxylic acid. These problems were solved by photochemical decomposition[9] of the pyruvyl ester (**7**) under essentially neutral conditions to afford (**8**) smoothly as a volatile oil in 60% isolated yield after silica gel chromatography. Re-reduction of (**8**) with lithium aluminium deuteride gave the [$^2H_2$]-alcohol (**6**) having, within experimental error, the *same* specific rotation as the starting material. The pure [$^2H_1$]-aldehyde (**8**) was immediately and readily reduced using horse liver alcohol dehydrogenase (HLAD), NAD^+, and ethanol as the coupled hydride donor to give the (1*S*,2*S*)-alcohol† (**9**), 94% after kugelrohr distillation. Complete inversion at the carbinol centre was achieved using the Mitsunobu[10] procedure followed by methanolysis of the intermediate benzoate to afford the (1*R*,2*S*)-alcohol (**10**) (80%).

Repetitive mass spectral analyses of the diastereomeric alcohols (**9**) and (**10**) showed each to be labelled with one deuterium atom to an extent of > 99%. Their specific rotations bracket the value observed for the starting [$^2H_2$]-alcohol (**6**) having a single chiral centre. The high stereochemical purity of both asymmetric centres was unambiguously shown by inspection of the slightly broadened (geminal coupling to deuterium) doublets for the carbinol hydrogen atoms in the ^1H n.m.r. spectra of (**9**) and (**10**) in the presence of 40 mole % of tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]europium(III). No trace of stereoisomeric impurities could be detected in either specimen of alcohol.‡

The stereochemical integrity of the two asymmetric centres having been introduced and preserved, reaction of the methanesulphonates of (**9**) and (**10**) with lithium borohydride that had been pre-equilibrated with tritiated water in dry tetrahydrofuran[11] cleanly afforded the desired chiral-methyl isobutylbenzenes (**11**) and (**12**), respectively.§ No hydrolysis or reduction to alcohol or elimination to olefinic products was detectable. The isobutylbenzenes (**11**) and (**12**) were separately adsorbed on to silica gel and treated with an excess of precooled ozone at −78 °C.[12] Elution of the silica gel at room temperature with chloroform containing several drops of 1 M-hydrochloric acid gave the corresponding *pure* isovaleric acids, 75—85% (Scheme 3). These chiral, doubly labelled acids

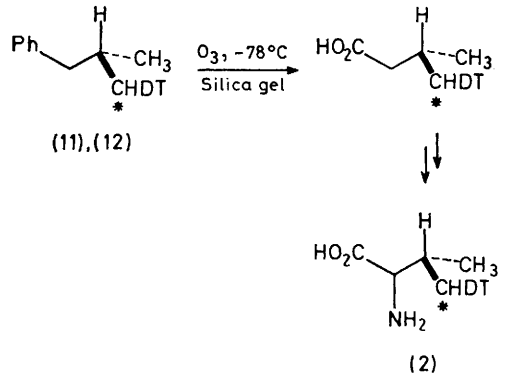
† The configuration at the carbinol centre may be declared with some assurance to be (*S*) on the basis of considerable precedent (J. B. Jones and J. F. Beck in 'Applications of Biochemical Systems in Organic Chemistry,' Part I, eds. J. B. Jones, C. J. Sih, and D. Perlman, Wiley-Interscience, New York, 1976, pp. 107—401; R. Bentley, 'Molecular Asymmetry in Biology,' Vol. 2, Academic Press, New York, 1970, pp. 1—86; G. Popják, in 'The Enzymes,' Vol. 2, ed. P. D. Boyer, Academic Press, New York, 1970, pp. 115—215). However, to prove the point we converted (**9**) stereospecifically into the (*E*)-olefin (A) by selen-



oxide elimination of the arylselenide derived from the reaction of (**9**) with *o*-nitrophenyl selenocyanate (P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, 1976, **41**, 1485; M. A. Adams, A. J. Duggan, J. Smolanoff, and J. Meinwald, *J. Am. Chem. Soc.*, 1979, **101**, 5364). The isomeric (*Z*)-olefin (B) was synthesized regiospecifically by the addition of dimethylcuprate–dimethyl sulphide complex to [1-^{2}H]-3-phenylpropyne (C); see A. B. Theis and C. A. Townsend, *Synth. Commun.*, 1981, **11**, 157.

‡ Control experiments using a sample obtained by reduction of the racemic [$^2H_1$]-aldehyde (**8**) with sodium borohydride gave a mixture of all four possible stereoisomeric [$^2H_1$]-alcohols whose ^1H n.m.r. spectra were distinguishable under the conditions of the chiral shift-reagent study. The high stereochemical purities of (**9**) and (**10**) are further borne out in the experiment described in footnote †.

§ Assuming a statistical distribution of tritium between the water and the borohydride,[11] the specific incorporation of radioisotope over several trials fell in the range 15—50% of that theoretically possible. These values may be compared with 45—70% of theoretical observed by Cornforth in analogous reductions of carbonyl functions.[11]



Scheme 3

were converted according to known procedures[13] into D,L-(3*R*,4*S*)- and (3*R*,4*R*)-[4-^{2}H,^{3}H]valine, respectively. That the labelled methyl groups indeed possessed the expected absolute configurations was demonstrated by Kuhn–Roth degradation[14] of the valines and submission of the respective chiral acetates to the established Cornforth–Arigoni[4,5] assay.

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