Unusual Stereospecificity in the Hydrogenation of an Isopropenyl Function with Wilkinson's Catalyst; A Route to Chiral Methyl Valine

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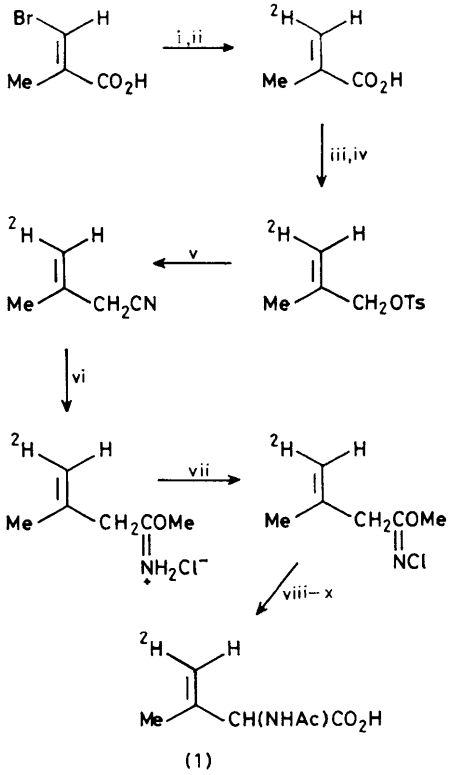
Summary Catalytic hydrogenation with H^3H in the presence of Wilkinson's catalyst of (2*RS*)-(*E*)-[4-^{2}H]-2-acetylamino-3-methylbut-3-enoic acid gave a mixture of (2*SR*, 3*SR*, 4*RS*)-[4-$^3H^2H$]-*N*-acetylvaline [(**8**) and (**9**)] and 2*SR*, 3*RS*, 4*SR*-[4-$^3H^2H$]-*N*-acetylvaline [(**6**) and (**7**)] in the ratio 19:1 by ^{3}H n.m.r. spectroscopy of the derived valines; a similar reduction with $^2H_2$ of 1,5-(*Z*)-4,7-diaza-7-[1-4-(nitrobenzyloxycarbonyl)-2-methylprop-2-enyl]-3-phenoxymethyl-2-thiabicyclo[3.2.0]hept-3-en-6-one gave a mixture of dideuterio-isomers (**11**) and (**12**), in the ratio 3:7 by ^{1}H n.m.r. spectroscopy of the derived valines.

DURING investigations on valine biosynthesis a sample of valine with stereospecifically labelled methyl groups ('chiral methyl valine') was required.† The route chosen (Scheme 2) was realised by catalytic reduction of *N*-acetylisodehydrovaline[1] (**1**) (Scheme 1) by an equilibrated mixture of hydro-



Ts = toluene-4-sulphonyl

SCHEME 1. *Reagents*. i, NaH; ii, Na–Hg/^2H_2O; iii, $LiAlH_4$; iv, TsCl, Et_3N; v, KCN, 18-crown-6; vi, MeOH–HCl; vii, NaOCl; viii, NaOMe, MeOH; ix, dil. HCl; x, Ac_2O, K_2CO_3.

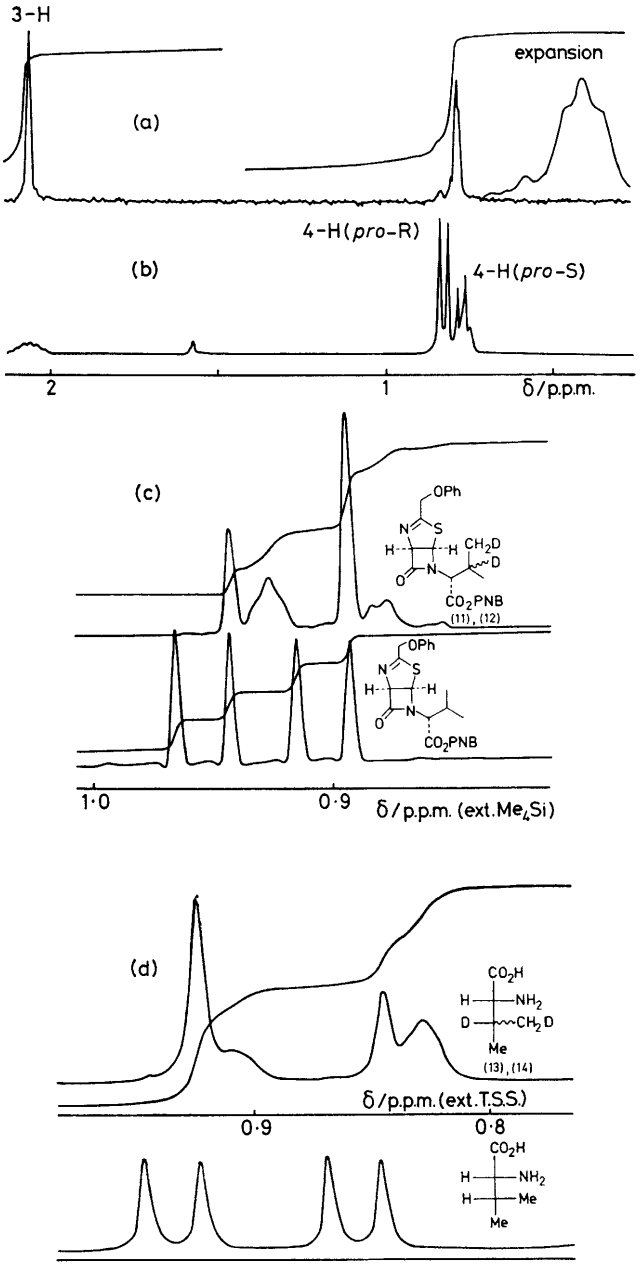
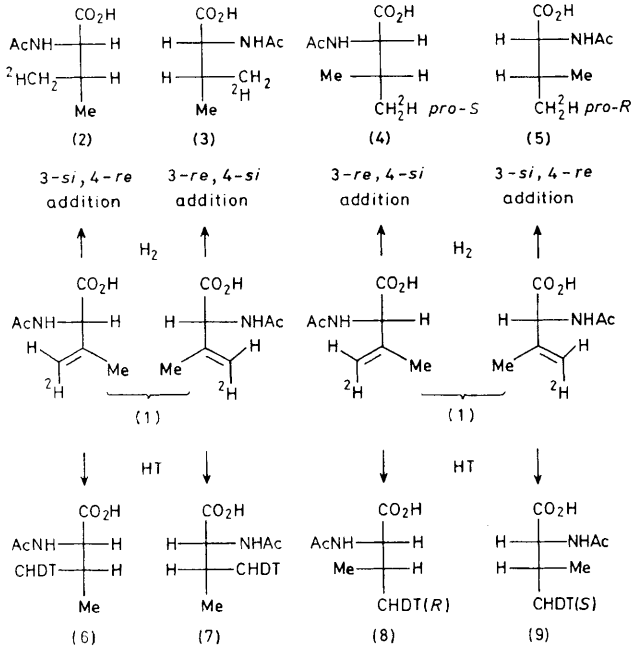


FIGURE. (a) ^{3}H N.m.r. spectrum; (b) ^{1}H n.m.r. spectrum of the valine produced by hydrogenation of (2*RS*)-(*E*)-[4-^{2}H]-2-acetylamino-3-methylbut-3-enoic acid [(**1**)] with an equilibrated mixture of H_2 and $^3H_2$ (7:1) in the presence of Wilkinson's catalyst. TSS = sodium 3-[2,2,3,3-^{2}H]trimethylsilylpropionate.

† The experiments on tritiation of dehydrovaline were carried out at Exeter and those on the penicillin-derived thiazoline at Oxford.

gen and tritium (7 : 1) in the presence of Wilkinson's catalyst, followed by hydrolysis, giving a mixture of labelled isomers of valine. The ^{1}H n.m.r. (300 MHz) spectrum (Figure, b) showed signals of unequal intensity for the diastereotopic methyl groups, from which it was concluded that the diastereomeric pairs [(**2**) and (**3**)] and [(**4**) and (**5**)] were formed in unequal amounts. Since the higher field methyl doublet in the ^{1}H n.m.r. spectrum of *S*-valine was assigned to the *pro-S* methyl group[2] [*cf.* (**4**)], then the observed intensity ratio (3 : 2) of low to high field methyl doublets indicated almost exclusive formation of the pair of diastereoisomers [(**4**) and (**5**)] (Scheme 2). This conclusion was

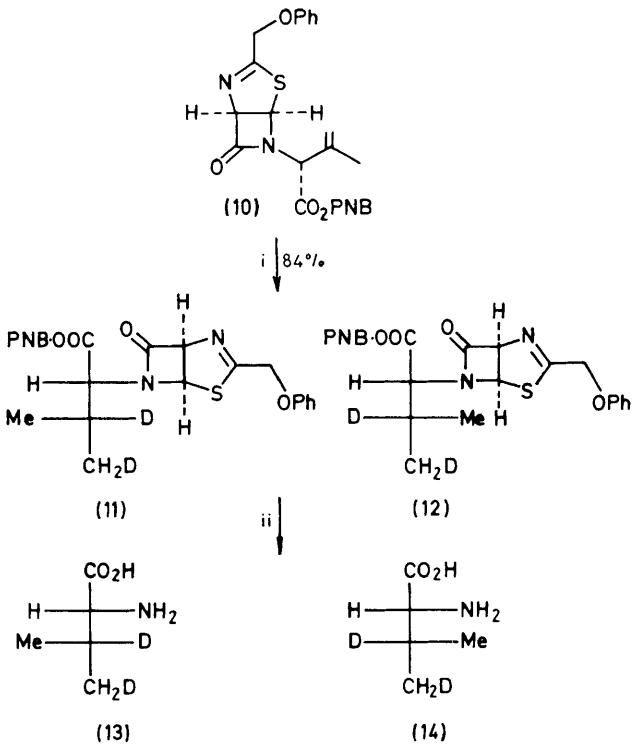


(plus corresponding 3-tritiated species)

SCHEME 2

supported by the noise-decoupled ^{3}H n.m.r. spectrum of the racemic valine so obtained which showed signals due to *pro-S* and *pro-R* methyl groups of the *S*-component [(**6**) and (**8**)] {which correspond respectively to the *pro-R* and *pro-S* methyl groups of the *R*-component [as (**7**) and (**9**)]} with relative intensity 19 : 1, and the expected ^{3}H^{2}H coupling (Figure, a).

Another example of this selectivity was found on catalytic deuteriation (Wilkinson's catalyst, 25 °C, 48 h) of the thiazoline azetidinone (**10**)[3] to the two dideuterio-isomers [(**11**) and (**12**), 30 : 70 respectively, 84%], (Figure, c). Their stereochemistry was determined by hydrolysis to the valines



PNB = 4-nitrobenzyl

SCHEME 3. *Reagents.* i, $^2H_2$, $(PPh_3)_3RhCl$, PhH, 48 h; ii, 6N-HCl, reflux, 24 h.

(**13**) and (**14**), (Scheme 3), the major component of which, (**14**), corresponds in its ^{1}H spectra (Figure, d) to the 2*R*, 3*R*-isomer.[2]

These results show that catalytic reduction by Wilkinson's catalyst occurs with a preference for 3-*re*, 4-*si* attack on the *S*-component and 3-*si*, 4-*re* attack on the *R*-component, for the dehydrovaline (**1**) and with 3-*re* attack for the 2*R*-thiazoline azetidinone (**10**). Whether this is a general result for $\beta\gamma$-unsaturated amino-acids and other $\beta\gamma$-unsaturated systems remains to be seen. However, regardless of the stereoselectivity and also regardless of the C-2 configuration of compound (**1**), the isotopically stereoisomeric chiral methyl valines produced from the *N*-acetyldehydrovaline (**1**) have methyl groups with the *R*-configuration in the *pro-S* position and the *S*-configuration in the *pro-R* position.‡

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‡ The isomeric valines with opposite configurations were synthesised from (*E*)-3-bromo-2-methylprop-2-enoic acid by a sequence initially involving metallation (BuLi) and deuteriation (^2H_2O) to (*E*)-3-[^{2}H]-3-bromo-2-methylprop-2-enoic acid, and subsequent processes as before, Scheme 1.

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