Conformational Analysis in the Directed Hydrogenation of Homoallylic Alcohols

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The stereochemical course of homogeneous hydrogenation of 2-(β-hydroxyalkyl)-*N*-methylacrylamides is in accord with steric effects in a simple model.

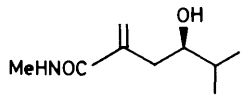
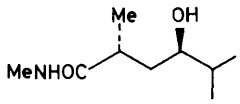
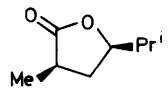
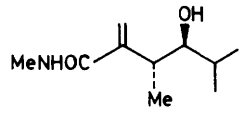
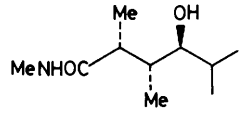
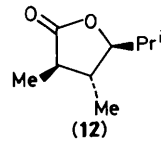
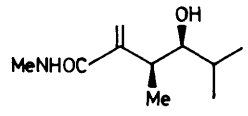
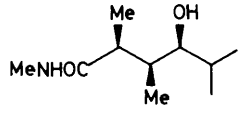
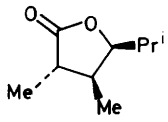
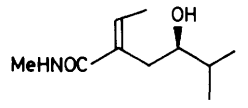
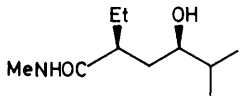
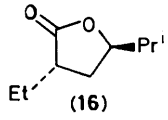
Hydrogenation of chiral allylic alcohols, esters, and amides proceeds with high diastereoselectivity when catalysed by cationic rhodium catalysts.[1] The *anti*-predominance can be explained by minimisation of steric effects in a chelate-co-ordinated alkene complex; this model is supported by *X*-ray structural evidence.[2] For homoallylic alcohols the selectivity of hydrogenation is lower, and interpretation less clear-cut. Depending on the substitution pattern, either *syn*- or *anti*-isomer of the product may predominate.[1,3]

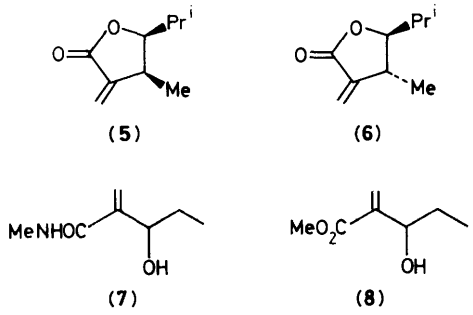
We have examined the stereochemical course of H_2 addition to a series of alcohols (**1**)—(**4**), differing only in the siting of one Me-group. The first of these was prepared in moderate yield by reacting the dilithium salt of *N*,2-dimethylpropenamide[4] with 2-methylpropanal in tetrahydrofuran (THF) (−70 to 0 °C) and purification by flash chromatography. Reaction of the homologous dilithium salt from (*E*)-*N*,2-dimethylbutenamide with 2-methylpropanal gave a 2 : 1 : 4 mixture of hydroxyamides (**2**), (**3**), and (**4**), which was separated by preparative h.p.l.c. (CH_2Cl_2, MeCN, 4 : 1, silica). When this condensation reaction was carried out in the presence of $ZnCl_2$, the predominant product was (**3**), with linear isomer (**4**) effectively absent.†

The relative configuration of compounds (**2**) and (**3**) was determined as follows. Methyl (*Z*)-(2-bromomethyl)prop-2-enoate was added to activated Zn powder[6] and excess 2-methylpropanal in THF, giving a mixture of methylenelactones (**5**) and (**6**) directly. These were separated by preparative g.l.c. (15% OV 225 15′, 180 °C) and the stereochemistry of the more retained isomer shown to be (**5**) by nuclear Overhauser enhancement (n.O.e.) analysis. The same two lactones were formed when a mixture of hydroxyamides (**2**)

† Presumably this is due to tight chelation of aldehyde to a primary zinc allyl with C–C bond formation occurring by an intracomplex S_E2' reaction. Crotylzinc compounds react with carbonyl compounds preferentially *via* the more substituted carbon.[5]

Table 1. Hydrogenation of homoallylic alcohols. Reactions were carried out at 20 °C and 1 atm in MeOH solution, typically with 5 mol % of $Ph_2P(CH_2)_4PPh_2Rh^+(C_7H_8)CF_3SO_3^-$ as catalyst for 20 h.

Reactant	Major product		Lactone
 (1)	 (9)	92 %	 (10)
 (2)	 (11)	91 %	 (12)
 (3)	 (13)	67 %	 (14)
 (4)	 (15)	89 %	 (16)



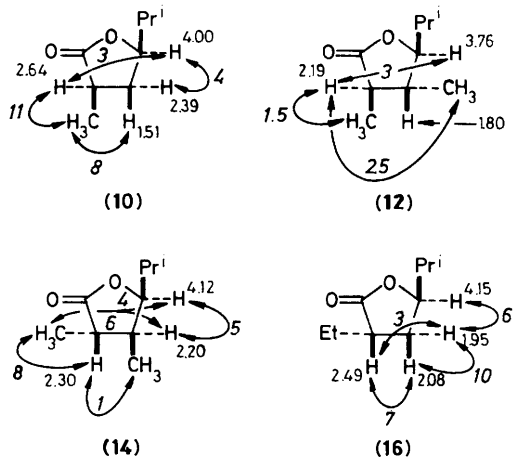


Figure 1. Configurational assignment of alkylbutyrolactones. Chemical shifts (δ) and % n.O.e.s are given.

and (**3**) was subjected to preparative g.l.c. at 180 °C, providing samples from which an assignment was made by direct comparison.

Hyrogenations were carried out as indicated in Table 1. All were relatively slow; it was confirmed that amides are reduced less rapidly than esters through competitive experiments involving (**7**) and (**8**). In all cases, product isomer ratios were determined directly from their 500 MHz spectra, analysing the 4-H signals. Configurational assignments were made by cyclisation through preparative g.l.c. (15% OV 225, 15′, 180 °C) with n.m.r. spectroscopic identification of the major component in each case, and comparison with closely related compounds (Figure 1).[7]

For the unsubstituted case (**1**), the preferred reduction product (**9**) is of *anti*-configuration. This is in accord with a chelated intermediate which has the configuration (**A**) rather than (**B**) (Figure 2). Inspection of molecular models indicates that in the conformations which minimise non-bonded interactions, the C=C double-bond in (**A**) is more nearly perpendicular to the co-ordination plane and hence better disposed for Rh–H transfer. In accord with this model, the *anti*-methyl diastereoisomer (**2**) gave a very similar result to compound (**1**) on hydrogenation; the C(3)-methyl group is remote from steric clashes in both (**A**) and (**B**). With *syn*-diastereoisomer (**3**), reaction is slower and much less selective, the major product being formed *via* (**B**). The 2-methyl group experiences a serious non-bonded interaction with $C{=}CH_2$ [in (**B**)] or with MeNHCO [in (**A**)]. In (**B**), but not in (**A**), torsional movement of C(2)–C(3)–C(4) relieves the repulsion and at the same time improves overlap of the double bond with Rh.

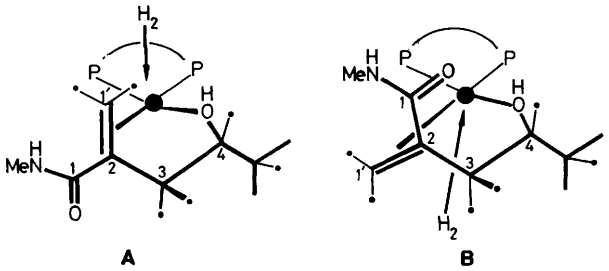


Figure 2. Structure and steric interactions in diastereoisomeric chelate intermediates.

The most striking result was obtained with ethylideneamide (**4**), since the *syn*-hydrogenation product predominates. In structure (**A**), the vinylic methyl-group is in enforced proximity to the pseudo-axial 4-H. In structure (**B**) this methyl group experiences a less serious interaction from 2-H, and hence this configuration is preferred.

Taken together, the results demonstrate that the directed hydrogenation of homoallylic alcohols may be rationalised by a simple steric model. In this chelate structure (**A**) [torsion angle C(4)–C(3)–C(2)–C(1′) ≃ 30°] is intrinsically preferred over alternative (**B**) [torsion angle C(4)–C(3)–C(2)–C(1′) ≃ 120°] by *ca.* 5 kJ mol^{-1} at the rate-determining transition-state.[8] An alkyl substituent at C(3) (*syn*) negates this preference, whilst an (*E*)-methyl group at C(1′) tips the balance in favour of (**B**) by *ca.* 5 kJ mol^{-1}.

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References

1 J. M. Brown, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 191, and references therein; J. M. Brown and A. P. James, *J. Chem. Soc., Chem. Commun.*, 1987, 181; J. M. Brown, A. P. James, and L. M. Prior, *Tetrahedron Lett.*, 1987, 2179; J. M. Brown, I. Cutting, and A. P. James, *Bull. Soc. Chim. Fr.*, 1988, 211.
2 N. W. Alcock, J. M. Brown, and A. P. James, to be published.
3 J. M. Brown and R. G. Naik, *J. Chem. Soc., Commun.*, 1982, 348; D. A. Evans, M. M. Morrissey, and R. L. Dow, *Tetrahedron Lett.*, 1985, **26**, 6005; D. A. Evans and S. L. Bender, *ibid.*, 1986, **27**, 799; D. A. Evans and D. di Mare, *J. Am. Chem. Soc.*, 1986, **108**, 2476.
4 D. J. Kempf, *J. Org. Chem.*, 1986, **51**, 3921; P. Beak, D. J. Kempf, and K. D. Wilson, *J. Am. Chem. Soc.*, 1985, **107**, 4745.
5 Y. Yamamoto and K. Maruyama, *J. Organomet. Chem.*, 1985, **284**, C45.
6 *Cf.* M. F. Semmelhack and E. S. C. Wu, *J. Am. Chem. Soc.*, 1976, **98**, 3384; G. P. Boldrini, L. Lodi, E. Tagliavini, C. Tarasco, C. Trombini, and A. Umani-Rouchi, *J. Org. Chem.*, 1987, **52**, 5447; K. Uneyama, K. Ueda, and S. Torii, *Chem. Lett.*, 1986, 1201.
7 C. Jaime, R. M. Ortuno, and J. Font, *J. Org. Chem.*, 1986, **51**, 3946, and references therein.
8 C. R. Landis and J. Halpern, *J. Am. Chem. Soc.*, 1987, **109**, 1746.