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STEREOSELECTIVITY IN THE HYDROBORATION OF CHIRAL CYCLOHEXANE-DERIVED ALLYLIC ALCOHOLS

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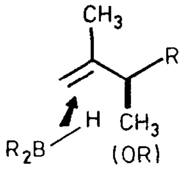
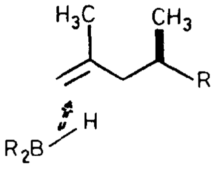
Summary The isomeric 2-ethylidenecyclohexanols are hydroborated by t-hexylborane with weak stereoselectivity whilst 1-(1'-hydroxyalkyl)cyclohexenes show up to 50:1 discrimination.

Several examples of diastereoselective hydroboration of acyclic chiral olefins exist. These include the generation of adjacent[1] and non-adjacent[2] carbon atoms with alkyl groups in stereochemically defined orientation, and the synthesis of compounds with three contiguous asymmetric centres,[3] as shown in A - C. Hydroboration of cyclic olefins may be stereoselective, although largely controlled by steric factors in most published examples.[4] We were interested in discovering whether the reaction could be utilised for preparation of cyclic 1,3-diols of general structure D. There are several routes for the elaboration of a cyclohexane side-chain with defined stereochemistry at the α-position, but none appeared to be suitable for the problem in hand.[5]



A



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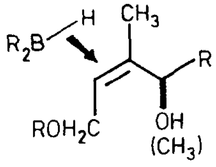

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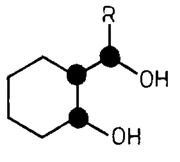
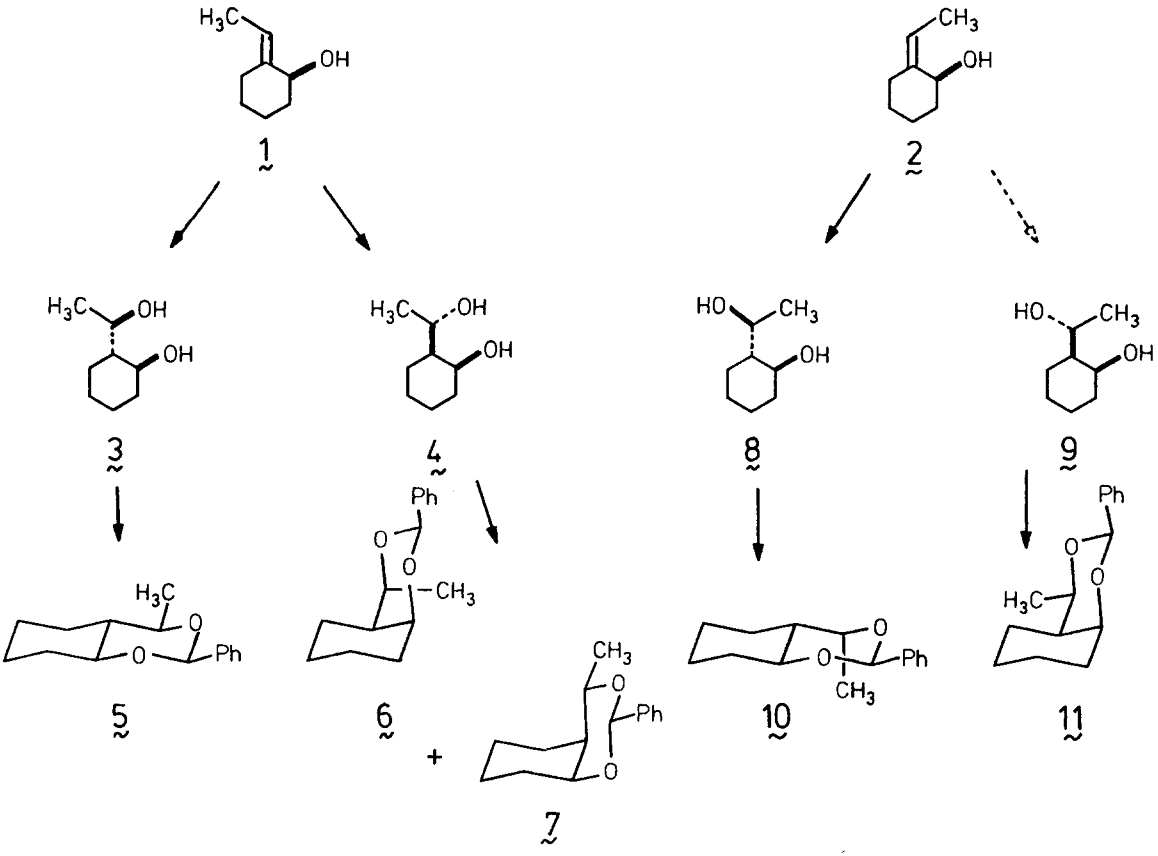


D-stereochemistry at ● defined

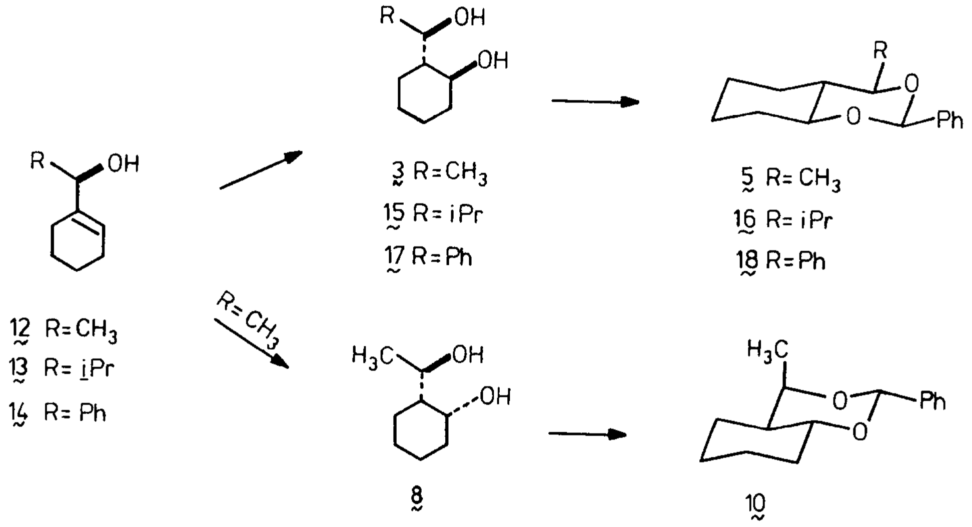
Both E and Z-2-ethylidenecyclohexanol were prepared as described[6] from ketone precursors separated by preparative g.l.c. (carbowax 20M, 170°). It was noted that the chemical shift and vicinal coupling constants for H_a in 1 (δ = 4.07 p.p.m., ^3J = 8Hz) were comparable to the values observed for 2-methylenecyclohexanol, but the corresponding proton in 2 is strongly deshielded with no large coupling constant (δ = 4.88 p.p.m, ^3J = 3Hz). These observations suggest that the hydroxyl-group in 2 is substantially axial to alleviate the effects of A(1,3)-strain.[7]

Hydroboration of alcohol 1 under standard conditions[8] gave a 50:50 mixture of diastereomeric 1,3-diols 3 and 4 not separable by chromatography or preparative g.l.c.. Conversion into the corresponding benzylidene derivatives 5 and 6 (PhCHO, 5 mol % p-TsOH, C_7H_8, 50°) was effected[9] and these were readily separated by preparative g.l.c. (OV17, 250°). The structure and stereochemistry followed from analysis of their ^1H N.m.r. spectra.[10] Small quantities of a diastereomeric benzylidene compound 7 were formed from cis-isomer 4.

Hydroboration of alcohol 2 gave rise to a mixture of 1,3-diols 8 and 9 with the former predominating by 75:25. The structures were again proved by N.m.r. analysis of the corresponding benzylidene derivatives 10 and 11. Assuming that the conformation with axial-OH predominates, the major isomer 10 is the product of equatorial B-H approach. The level of stereoselectivity is comparable to that observed in hydroboration of conformationally fixed methylenecyclohexanes.[4]



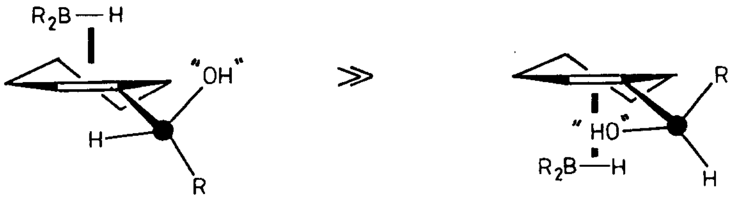
The isomeric 1'-(hydroxyethyl) cyclohex-1-ene 12 was prepared (cyclohex-1-enecarboxaldehyde,[11] CH_3Li, Et_2O, 0°) and subjected to standard hydroboration conditions. The crude mixture of 1,3-diols 3 and 8 was converted into cyclic benzylidene derivatives 5 and 10 which were separated by preparative g.l.c. and analysed as before. The 87:13 predominance of the *eq eq*-isomer 5 reflects substantial selectivity in the addition step. Consequently the 1-hydroxy-2-methylpropyl analogue 13 and the hydroxybenzyl analogue 14 were prepared (cyclohex-1-enecarboxaldehyde, RMgBr, Et_2O, 0°) and subjected to hydroboration. The former compound reacted to give a single diastereomer 15 whose stereochemistry was proved *via* 2D-COSY and nOe ^1H N.m.r. experiments on the benzylidene derivative 16. Hydroboration of the hydroxybenzylcyclohexene 14 was also highly stereoselective, and in each case the major diastereomer had the same relative configuration of adjacent chiral centres.



Thus allylic exocyclic alcohols undergo stereoselective hydroboration, but allylic endocyclic alcohols do not. In ^{11}B N.m.r. experiments it was observed that t-hexylborane (δ = 24 ppm,[12] generated in situ from fresh H_3B; thf) reacted rapidly with alcohol 12 to give a product (δ = 53 p.p.m), which parallel t.l.c. studies indicate not to be associated with hydroboration of the olefin. Heating to 45° for 2h. results in consumption of a further equivalent of t-hexylborane (δ = 57 p.p.m, broad) accompanied by hydroboration. The sequence shows that formation of a borate is much more rapid than addition to the olefin.

In acyclic cases, an empirical model for stereoselectivity in hydroboration has been presented[2] and reinforced by theoretical studies.[13] The model appears to have considerable generality for electrophilic additions to olefins and enolates.[14] When applied to 1'-hydroxyalkylcyclohexenes it fits well, and predicts increasing diastereoselectivity with increasing size of the alkyl side-chain. The steric order H < OR < R', placing C-H synclinal to C=C, is in accord with microwave spectroscopic studies on but-3-en-2-ol and with ab initio calculations.[15]

The threo-selectivity obtained in hydroboration of alcohols 12, 13 and 14 compares well with that observed in aldol approaches to related structures.[5]



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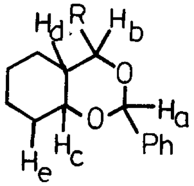
8. Hydroborations were carried out in t.h.f. at reflux using t-hexylborane prepared in situ, and oxidation effected with H_2O_2/OH^-. Reactions with 9-BBN were much slower, and often less stereospecific.
9. New compounds were fully characterised by spectroscopic methods and analysis.
10. ^1H N.m.r. data for benzylidene derivatives 300 MHz, $CDCl_3$).
    - 5: δ: H_a 5.623 s, H_b 3.60 dq, H_c 3.47 ddd, CH_3 1.3 d, p.p.m. J_{bd} 10, $J_b(CH_3)$ 6, J_{cd} = J_{ce} 11 Hz. nOe: (H_a^*) H_b 8.1, H_c 11.4, (H_b^*) H_a 9.9, (H_c^*) H_a 13.1%.
    - 6: δ: H_a 5.84 s, H_b 4.03 brq, H_c 4.32 br, CH_3 1.52 d, p.p.m. $J_b(CH_3)$ 7 Hz. nOe (H_a^*) H_b 10.5, CH_3 2.0, (H_c^*) H_a 12.8, H_d 2.0, CH_3 3.0 %.
    - 7: δ: H_a 5.95 s, H_b 4.26 dq, H_c 4.15 ddd, CH_3 1.33 d, p.p.m. J_{bd} 11, $J_b(CH_3)$ 7, J_{ce} 11 Hz.
    - 10: δ: H_a 5.90 s, H_b 4.26 dq, H_c 3.78 ddd, CH_3 1.40 d p.p.m., J_{bd} 6, $J_b(CH_3)$ 6, J_{cd} 11, J_{ce} 11, $J_{ce'}$ 3Hz.
    - 11: δ: H_a 5.60 s, $H_{b,c}$ 4.1-4.0 brm, CH_3 1.56 d p.p.m. $J_b(CH_3)$ = 7 Hz.
    - 16: δ: H_a 5.65 s, H_b 3.40 dd, H_c 3.48 ddd, CH_3 1.07, 0.96 d,d p.p.m. J_{bd} 10, $J_{b(CH)}$ 2, J_{cd} 10, J_{ce} 10, $J_{ce'}$ 4 Hz. nOe (H_a^*) [H_b + H_c] 21.8%; spectrum fully assigned by 2D-COSY at 500 MHz.
    - 18: δ: H_a 5.80 s, H_b 4.59 dd, H_c 3.68 ddd p.p.m. J_{bd} 10, J_{cd} = J_{ce} 10, $J_{ce'}$ 3 Hz. nOe (H_a^*) H_b 11.6 H_c 12.6, (H_b^*) H_a 17.8, H_c 7.0 (+ o aryl) (H_c^*) H_b 6.9 H_z 16.4%.



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