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Stereochemistry of Nucleophilic Additions to 2,3-endo,endo-bridged-7-Ketonorbornanes [Tricyclo($5{\cdot}2{\cdot}1{\cdot}0^{2,6}$)decan-10-ones]· Observation of Long-range Electronic Effects

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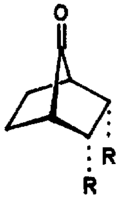
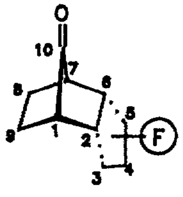
Key Words: π-Face Selectivity, Metal-hydride reduction, Remote electronic control.

Abstract: The diastereoselectivities exhibited by sterically unbiased endo-tricyclo($5.2.1.0^{2,6}$)decan-10-ones in nucleophilic additions can be modulated through substituents in the distal five membered ring.

The prediction and control of diastereoselectivity in nucleophilic additions to carbonyl group has been a subject of considerable scrutiny and intense debate in recent years.[1] Among the various experimental probes that have been devised to identify the various steric and electronic factors that influence π-facial selectivity in nucleophilic additions, sterically unbiased systems offer intrinsic advantage in isolating and evaluating electronic effects.[2] In a recent study,[2c,d] we have described the profound effect of remote substituents in controlling diastereoselectivity in sterically neutral 2,3-endo,endo-substituted-7-ketonorbornanes. In order to further assess the scope of this interesting observation, we have investigated the stereochemistry of nucleophilic additions to substituted Ⓕ endo-tricyclo($5.2.1.0^{2,6}$)decan-10-one derivatives 2. This tricyclic system was chosen because: (a) the two faces of the trigonal carbon at C_{10} are more or less sterically equivalent (MMX calculations), (b) the rigid tricyclic skeleton forestalls any ambiguity arising from the conformational uncertainty (cf. the unrestricted endo,endo-substituents in 1),[2c] and (c) the substitution on the endo-fused 5-ring provides a handle for electronic fine-tuning of the two faces of distal C_{10}-carbonyl group.



1



2

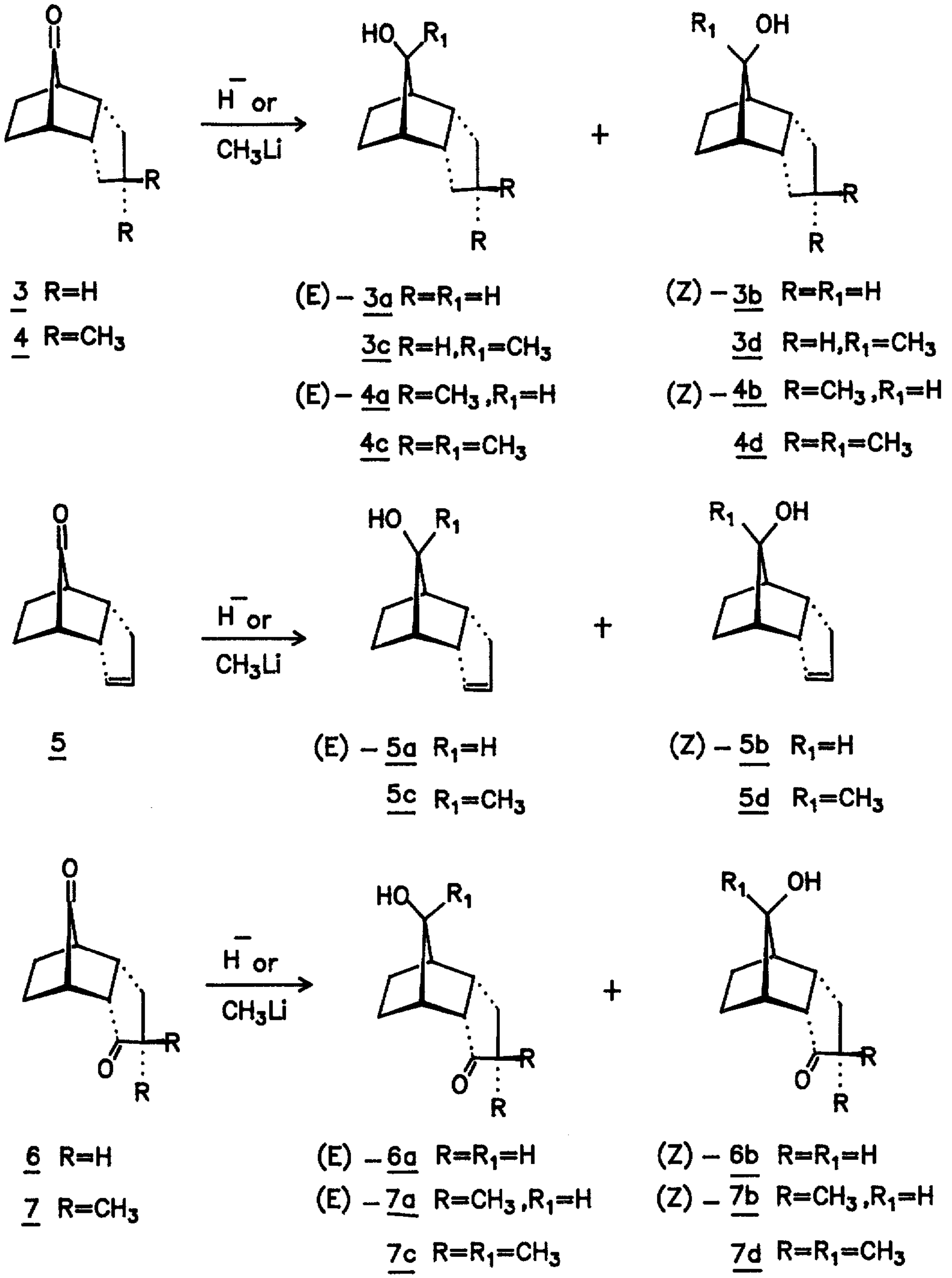
Five tricyclodecanones 3-7 were synthesised through unambiguous methods[3,4] and subjected to carbonyl reduction with hydrides ($NaBH_4$, LAH, DIBAL-H) of varying size and reactivity and methylation with CH_3Li to furnish (E)- and (Z)-alcohols 3a-d to 7a-d in near quantitative yield, Scheme 1.[6] The diastereoselectivities observed are presented in Table 1. The stereostructures of the diastereomers 3a-d to 7a-d are based on (a) the relative deshielding of C_2,C_6-exo-protons in (Z)-alcohols compared to the (E)-alcohols (confirmed by selective LIS studies),[2c,d] (b) greater deshielding of the proton and carbon attached to the hydroxyl group in the (Z)-series compared to (E)-series, and (c) chemical correlation with some of the known compounds.

Table 1: Product ratios in the metal hydride reduction and methylithium addition to 3-7.

Substrate	E : Z ratios[a]			
	$NaBH_4$[b,c]	$LiAlH_4$[b,d]	$[(CH_3)_2CHCH_2]_2AlH$[e,f]	CH_3Li[b,d]
3	24 : 76 (3a) (3b)	25 : 75 (3a) (3b)	25 : 75 (3a) (3b)	14 : 86 (3c) (3d)
4	28 : 72 (4a) (4b)	27 : 73 (4a) (4b)	27 : 73 (4a) (4b)	19 : 81 (4c) (4d)
5	37 : 63 (5a) (5b)	39 : 61 (5a) (5b)	40 : 60 (5a) (5b)	32 : 68 (5c) (5d)
6	45 : 55[f] (6a) (6b)			
7	56 : 44 (7a) (7b)	54 : 46 (7a) (7b)		53 : 47 (7c) (7d)

[a] Ratios based on ^1H NMR integration of the total mixture (± 5%). [b] Reductions were carried out at ~ 0-10°C for 10 min-30 min., till the starting ketone was fully consumed. Reactions were continuously monitored by TLC. [c] In methanol. [d] In dry diethyl ether. [e] In dichloromethane. [f] Reaction carried out at -78°C.

Several features of the results displayed in Table 1 deserve comment. The parent tricyclodecanone 3 itself exhibits significant selectivity (3 : 1) in favour of the approach of nucleophiles from the face opposite to the endo-cyclopentane ring, an observation reminiscent[2c] of the behaviour of endo,endo-diethyl-7-norbornanone 1 (R=Et). Thus, endo-alkyl substituents seem to favour the approach to 7-norbornanone from the anti-face irrespective of the conformational rigidity (in 3) or mobility (in 1, R=Et) of these substituents. That the anti-approach preference of 3 is not steric in origin is



3 R=H
4 R=CH_3

(E)-3a R=R_1=H
3c R=H,R_1=CH_3
(E)-4a R=CH_3,R_1=H
4c R=R_1=CH_3

(Z)-3b R=R_1=H
3d R=H,R_1=CH_3
(Z)-4b R=CH_3,R_1=H
4d R=R_1=CH_3

5

(E)-5a R_1=H
5c R_1=CH_3

(Z)-5b R_1=H
5d R_1=CH_3

6 R=H
7 R=CH_3

(E)-6a R=R_1=H
(E)-7a R=CH_3,R_1=H
7c R=R_1=CH_3

(Z)-6b R=R_1=H
(Z)-7b R=CH_3,R_1=H
7d R=R_1=CH_3

Scheme 1

supported by the fact that the placement of a bulky *gem*-dimethyl substitution at C_4 has little effect on the observed stereoselectivity. Also, the E : Z ratios reported here remain insensitive to the size of the hydride reducing agent. On the other hand, electronic perturbation in the *endo*-5 membered ring through introduction of electron-withdrawing groups as in 5, 6 and 7 results in an increase in *syn*-approach. Indeed, in 7a crossover is observed and the (E)-alcohol from *syn*-approach predominates. The preferred formation of (Z)-product in 3 and progressive increase in (E)-products in the series 3 ⟶ 5 ⟶ 6 ⟶ 7 is a result that is best interpreted in terms of the transition-state hyperconjugation model.[1d,e]

In short, we have demonstrated that π-face selectivities in sterically neutral tricyclodecanones 2 can be modulated through electronic changes in the remote *endo*-five-membered ring. These observations have a bearing on the currently debated models for diastereoselective nucleophilic additions to the carbonyl group.

Acknowledgements

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References and Notes:

1. For some of the leading recent references covering experimental and theoretical efforts, see: (a) R.R. Fraser and M. Stanciulescu, J. Am. Chem. Soc., 1987, 109, 1580. (b) E.P. Lodge and C.H. Heathcock, J. Am. Chem. Soc., 1987, 109, 3353. (c) T.B. Macauly and A.G. Fallis, J. Am. Chem. Soc., 1988, 110, 4074. (d) A.S. Cieplak, B.D. Tait and C.R. Johnson, J. Am. Chem. Soc., 1989, 111, 8447. (e) A.S. Cieplak, J. Am. Chem. Soc., 1981, 103, 4540. (f) S.S. Wong and M.N. Paddon-Row, Aus. J. Chem., 1991, 44, 765. (g) Y-D. Wu, J.A. Tucker and K.N. Houk, J. Am. Chem. Soc., 1991 113, 5018.
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3. While compound 3 was readily available through a known procedure,[5] 4-7 were prepared through new but unexceptional synthetic routes. Details will be published in a full paper.
4. All new compounds were characterised on the basis of their spectral/analytical data.
5. R.B. Woodward and T.J. Katz, Tetrahedron, 1959, 5, 70.
6. Regioselective addition of nucleophiles to the C_{10}-carbonyl group in the presence of C_3-carbonyl group in 6 and 7 is considered unexceptional as 7-ketonorbornanes are known to be reduced 2100 times faster than cyclopentanone by$NaBH_4$. See, H.C. Brown and J. Muzuo, J. Am. Chem. Soc., 1966, 88, 2811.

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