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Modulation Of π-Facial Selectivities In Nucleophilic Additions to 7-Norbornenones

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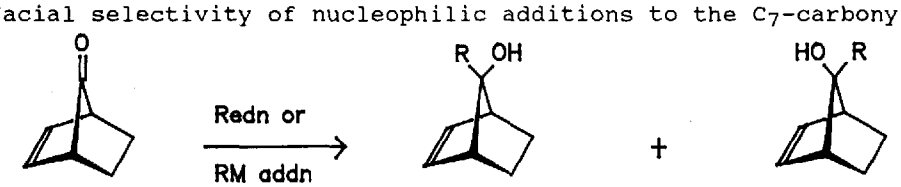
Key Words: 7-Norbornenone, $NaBH_4$ reduction, π-face-selectivity.
Abstract: The pronounced syn-face selectivity exhibited by 7-norbornenone in hydride reduction is dramatically altered (reversed) by the remote electron withdrawing substituents at the C_2,C_3-endo-position.

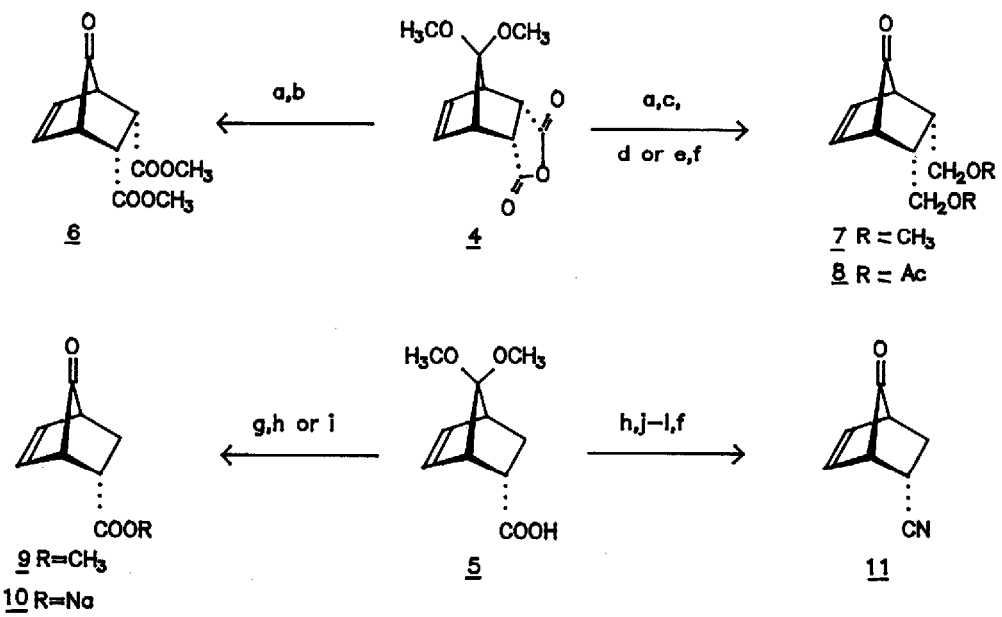
7-Norbornenone 1 is an intrinsically interesting substrate that has served as an important stereoelectronic probe in diverse organic reactions. In 1966, Brown and Muzzio[1] made the observation that sodium borohydride reduction of 1 proceeds predominantly from the double bond side to furnish 85 : 15 mixture of anti-2 (R=H) and syn-3 alcohols, respectively. Subsequently, Erman[2a] as well as Warkentin[2b,c] reported that CH_3Li and CH_3MgBr also exhibit marked preference for the syn-face addition to furnish 2 ($R=CH_3$) as the major product. However, Warkentin[2c] noted that in the case of vinyllithium and phenyllithium addition to 1, there was reversal in face-selectivity and 3 (R=vinyl or phenyl) was the major product. More recently, Gassman and O'Reilly[3] observed that C_2F_5Li and C_2F_5MgBr added to 1 almost exclusively from the anti-face to furnish 3 ($R=C_2F_5$). These intriguing results on the face-selectivity in nucleophilic additions to 1 have been interpreted in terms of one or more of the following factors: 1. preference for the approach from the sterically more accessible syn-face;[1,2b,c] 2. steric bulk of the reagent; 3. polar factors e.g., ion-pair formation through double bond participation at the C_7-electrophilic centre;[2,4] and 4. nucleophilicity of the attacking reagent.[3] While the above studies emphasize the reagent mediated alteration of face-selectivity in 1, complementary studies aimed at probing the effect of substrate modification on the face-selectivity have not been forthcoming.[5] In this letter, we disclose that distal electronic modifications in 1 through endo-substituents at C_2 and C_3, without accompanying perturbation in the steric environment, can cause alteration (reversal) in the π-facial selectivity of nucleophilic additions to the C_7-carbonyl of 1.



1 2 3

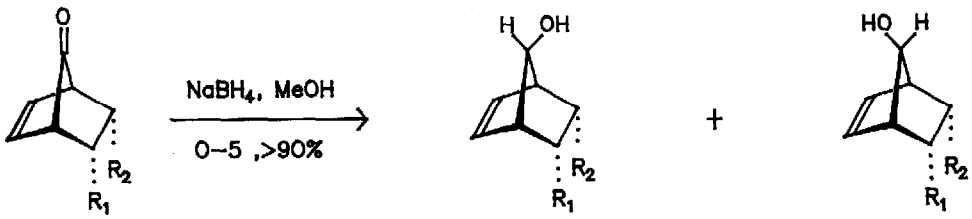
Six endo-substituted 7-norbornenones 6-11 were prepared through unambiguous but unexceptional routes from readily available 4[5] and 5,[6] Scheme 1.[7] In 6-11, the dangling endo-substituents differ in their inductive contributions (e.g., +I in 10 and -I in 11) but are sterically 'sterile', being on the 'blind-side' of the C_7-carbonyl and below the C_2, C_3, C_5, C_6 plane. Results of sodium borohydride reduction of 6-11 are summarised in Scheme 2.[7-9] In each case, the diastereomeric anti-alcohols 6a-11a and syn-alcohols 6b-11b were separated and the stereochemical assignments are based on (a) the relative deshielding (~0.1-0.15 ppm) of the C_5, C_6 olefinic protons in syn-alcohols (6b-11b) compared to anti-alcohols (6a-11a),[2b,c] (b) considerable deshielding (~0.3 ppm) of C_2,C_3-exo-protons in anti-(6a-11a) compared to syn-(6b-11b),[5] and (c) catalytic hydrogenation of 6a,b-11a,b to the known compounds prepared and characterised by us.[5]

A more notable result was obtained in the addition of methyl-lithium to 6, which furnished 6c and 6d in a ratio of 10 : 90, respectively. The methoxymethyl substituted 7 on the other hand displayed practically no change compared to 1, Scheme 3.



Reagents: (a) CH_3OH/H^+, Δ , 86%; (b) THF, 5% aq.H_2SO_4, Δ , 75%; (c) LAH, ether, 78%; (d) NaH, THF, CH_3I, 87%; (e) Ac_2O, DMAP, CH_2Cl_2, r.t., 95%; (f) Amberlyst-15, acetone-H_2O, Δ , 60-90%; (g) THF, 20% aq.HCl, Δ , 61%; (h) CH_2N_2, ether, 0-5 °C, 70%; (i) CH_3OH, aq.NaOH, quant.; (j) DIBAL-H, CH_2Cl_2, -78 °C, 65%; (k) $NH_2OH.HCl$, py., CH_2Cl_2, r.t., 90%; (l) TsCl, py., CH_2Cl_2, r.t., 65%.

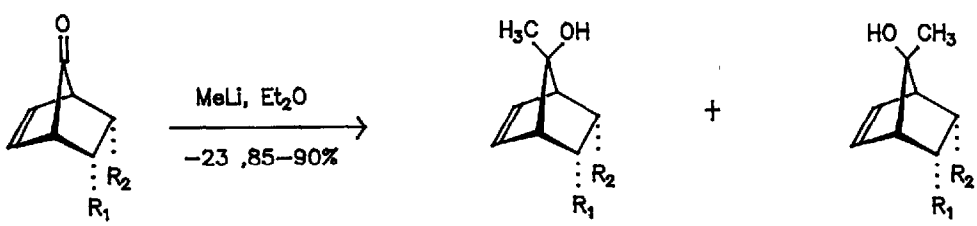
Scheme 1



			Ratio(%)	
1.	$R_1=R_2=R_3=H$	anti-2	85:15	syn-3
6.	$R_1=R_2=COOCH_3$	6a	45:55	6b
7.	$R_1=R_2=CH_2OCH_3$	7a	88:12	7b
8.	$R_1=R_2=CH_2OAc$	8a	87:13	8b
9.	$R_1=COOCH_3$, $R_2=H$	9a	68:32	9b
10.	$R_1=COONa$, $R_2=H$	10a	>90:10	10b
11.	$R_1=CN$, $R_2=H$	11a	44:56	11b

Scheme 2

The findings depicted in Scheme 2 and 3 demonstrate considerable variation in the face-selectivity as a function of the C_2,C_3-endo-substituent(s). The more significant cases being of diester 6 and cyano 11, where reversal is observed compared to 1 and the preferred addition is from the anti-face. This selectivity is much more pronounced in the case of methyllithium addition, wherein the syn-alcohol 6d is preponderant, Scheme3. Our results firmly indicate that electron withdrawing groups e.g., -CN, $-COOCH_3$ etc. at C_2, C_3 are particularly effective in directing the nucleophiles on the anti-face of the 7-norbornenones. While these substituent effects on the face selectivity can be accommodated in terms of the Cieplak hyperconjugation model[5,10] and/or the electrostatic effects,[11] the striking feature is that the endo-EWG's direct addition from the sterically less approachable anti-face.[12] Notably, the long-range electronic effects of the distal C_2,C_3-endo-substituents supersede the ground state geometrical features present in 7-norbornenones which would favour



1.	$R_1=R_2=H$	anti-2	74:26	syn-3
6.	$R_1=R_2=COOCH_3$	6c	10:90	6d
7.	$R_1=R_2=CH_2OCH_3$	7c	74:26	7d

Scheme 3

the syn-approach. Further studies on the response of new derivatives of **1** to diverse nucleophiles is currently under active investigation.[9,13]

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2. (a) W.F. Erman, J. Org. Chem., 1967, 32, 765. (b) J. Warkentin, Can. J. Chem., 1970, 48, 1391. (c) F.R.S. Clark and J. Warkentin, Can. J. Chem., 1971, 49, 2223.
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4. M.H. Lin, J.E. Silver and W.J. le Noble, J. Org. Chem., 1988, 53, 5155.
5. G. Mehta and F.A. Khan, J. Am. Chem. Soc., 1990, 112, 6140 and F.A. Khan unpublished results.
6. E. Gossinger and R. Muller, Tetrahedron, 1989, 45, 1377.
7. All new compounds reported here were characterised on the basis of their spectral (IR, ^{1}H and ^{13}C NMR) and analytical data.
8. The prefix syn- and anti- are with respect to the norbornene double bond. The diastereomer ratios were obtained by ^{1}H NMR integration and by GLC analysis (error ~5%) of the reaction mixture. ^{13}C NMR ($CDCl_3$, 25.0 MHz) data for some of the diastereomeric alcohols is as follows:-

   6a: δ 173.5, 133.5, 82.4, 51.7, 50.2, 45.5.
   6b: δ 172.0, 132.2, 85.7, 51.8, 51.7, 45.5.
   6c: δ 173.5, 134.7, 89.9, 54.6, 51.5, 46.9, 20.4.
   6d: δ 172.2, 134.3, 89.9, 55.0, 51.7, 46.1, 18.7.
   7a: δ 134.1, 82.9, 71.9, 58.7, 49.7, 38.2.
   7c: δ 135.1, 90.1, 72.2, 58.6, 54.1, 39.7, 20.9.
   7d: δ 134.8, 90.8, 71.9, 58.8, 55.2, 39.4, 18.6.
   9a: δ 176.1, 136.5, 131.6, 83.5, 51.7, 49.6, 46.3, 40.7, 25.9.
   9b: δ 174.4, 134.7, 129.7, 86.9, 51.8, 50.9, 48.2, 40.1, 26.8.
   11a: δ 137.8, 131.9, 123.4, 82.4, 49.7, 46.4, 29.5, 24.9.
   11b: δ 136.0, 129.9, 121.9,. 86.1, 50.5, 47.5, 29.7, 24.8.

9. Response of 6 and 7 to other nucleophiles, particularly organo lithium reagents is being investigated in collaboration with Prof. W.J. le Noble, S.U.N.Y., Stony Brook.
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11. Y-D. Wu, J.A. Tucker and K.N. Houk, J. Am. Chem. Soc., 1991, 113, 5018; S.S. Wong and M.N. Paddon-Row, Aust. J. Chem., 1991, 44, 765.
12. X-ray crystal structure determination of 6 has revealed that carbonyl bearing C_1-C_7-C_4 bridge is tilted away from the double bond, thus opening up the syn-face. See, V.A. Kumar, K. Venkatesan, B. Ganguly, J. Chandrasekhar, F.A. Khan and G. Mehta, accompanying communication.

13. We thank the CSIR for the financial support for this project.

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