JOC Note

Investigation of the Diastereoselectivity of Tricyclo(5.2.1.$0^{2,6}$)decan-10-ones: Controversies and Agreements

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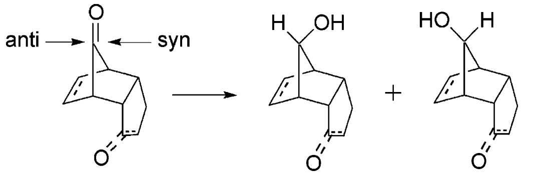

The diastereoselectivities of tricyclo(5.2.1.$0^{2,6}$)decan-10-one and its derivatives are controlled by antiperiplanar and vicinal $\sigma \rightarrow \pi^*_{C=O}$ interactions rather than the hyperconjugation effects as reported previously.

Introduction

7-Norbornanones have been the subject of intense experimental and theoretical investigations for their π-selectivities caused by the *endo*-substituents at positions 2 and 3.[1] The *endo*-tricyclo(5.2.1.$0^{2,6}$)decan-10-one, **1**, *endo*-tricyclo(5.2.1.$0^{2,6}$)dec-3-en-10-one, **4**, and *endo*-tricyclo(5.2.1.$0^{2,6}$)decan-3,10-dione, **7**, undergo preferred anti attack by hydride ion when treated with $NaBH_4$ in MeOH (Scheme 1). The anti/syn selectivity that decreased from 76:24 for **1** to 63:37 for **4** to 55:45 for **7** was interpreted by Mehta and Praveen[2] to follow Cieplak's hyperconjugation model[3] that envisages $\sigma_{\mathrm{vicinal}} \rightarrow \sigma^{*}\#$ interaction in the transition state. Interestingly, a σ_{C-H} is hyperconjugatively more electron donating than σ_{C-C}, $\sigma_{C=C}$, or $\sigma_{C-C(=O)}$.[4] The endo hydrogens on C_8 and C_9 will, therefore, support syn attack to all these molecules in strict compliance with Cieplak's hyperconjugation hypothesis. However, it contradicts the above experimental findings. It is significant to note the increase in syn selectivity from 24% for **1** to 37% for **4** to 45% for **7** for presumably the increasing electron-withdrawing abilities of σ_{C-C}, $\sigma_{C=C}$, or $\sigma_{C-C(=O)}$, in that order, in apparent compliance with the hyperconjugation hypothesis. A suitable explanation for the preferred anti selectivity is, therefore, desirable.

We considered applying the cation complexation approach[5] to understand the origin of observed anti preferences. We demonstrate in this manuscript that (a) the cation-complexation approach predicted the experimental selectivity throughout, (b) antiperiplanar effects[6] rather than hyperconjugation effects determined the electron-donating and electron-withdrawing abilities of $\sigma_{C1-C2}/\sigma_{C6-C7}$, on one hand, and $\sigma_{C1-C9}/\sigma_{C7-C8}$, on the other hand, which, in turn, controlled the experimental selectivity, and (c) the observed erosion in the anti selectivity of **7** is likely to be due to the preferred syn selectivity of the species in which both the carbonyl functions have been subjected to cation complexation. We also explored the related substrates **10** and **12** and commented on the origin of their selectivities. It is important to note that whereas the hyperconjugation effect is independent of orientation,[7] the antiperiplanar effect is fully dependent on it.

SCHEME 1. Experimentally Observed Diastereoselectivities of 1, 4, and 7

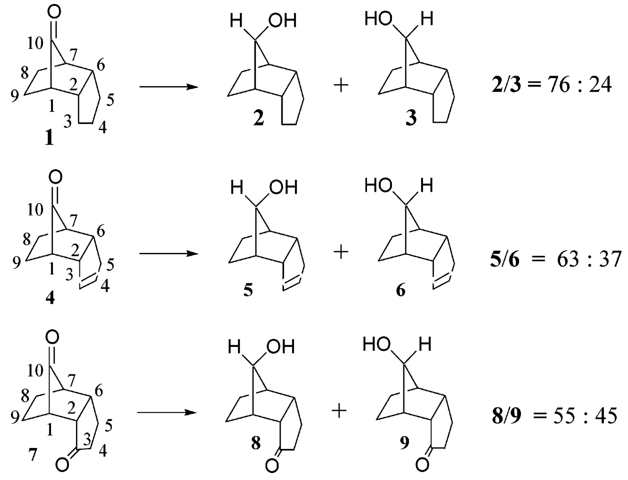

TABLE 1. Calculated Geometrical Parameters of Tricyclo(5.2.1.$0^{2,6}$)decan-10-ones and Their Complexes with Na^+ (D_1 = O−C_{10}−C_1−C_2; D_2 = O−C_{10}-C_1−C_9; D_3 = O−C_{10}−C_7−C_6; D_4 = O−C_{10}−C_7−C_8; D_5 = C_7−C_{10}−O−C_1)

	D_1	D_2	D_3	D_4	D_5
1	121.30	−124.90	−121.30	124.90	−178.80
1−Na^+	119.50	−127.00	−119.50	127.00	−177.20
4	123.00	−124.60	−120.40	126.10	−178.90
(**4**−Na^+)[a]	122.00	−126.20	−118.90	127.80	−177.80
(**4**−Na^+)[b]	121.50	−126.60	−118.50	128.30	−177.40
7	123.00	−124.60	−120.80	125.70	−179.10
(**7**−Na^+)[a]	121.10	−126.80	−118.40	128.40	−177.20
(**7**−Na^+)[b]	121.10	−126.80	−118.40	128.40	−177.20
(**7**−2Na^+)[c]	125.90	−121.90	−123.80	122.80	−181.90
(**7**−2Na^+)[d]	125.70	−122.00	−123.60	122.90	−181.80

[a] Complexation was allowed syn to C_7. [b] Complexation was allowed syn to C_1. [c] C_{10}=O was complexed syn to C_7, and C_3=O was complexed anti to C_2. [d] C_{10}=O was complexed syn to C_1, and C_3=O was complexed anti to C_2.

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TABLE 2. Calculated Antiperiplanar Interactions in Tricyclo(5.2.1.0^{2,6})decan-10-ones and in the Complexes with Na$^+$ [a]

	interaction energy (kcal mol^{-1})						
substrate	$\sigma_{C1-C2} \rightarrow \pi^*_{C10=O}$	$\sigma_{C1-C9} \rightarrow \pi^*_{C10=O}$	$\sigma_{C6-C7} \rightarrow \pi^*_{C10=O}$	$\sigma_{C7-C8} \rightarrow \pi^*_{C10=O}$	$\pi_{C3=C4} \rightarrow \sigma^*_{C1-C2}$	$\sigma_{C5-H} \rightarrow \sigma^*_{C6-C7}$	$\pi_{C3=O} \rightarrow \sigma^*_{C1-C2}$
1	3.37	3.18	3.37	3.18			
1-Na$^+$	5.22	4.12	5.22	4.12			
4	3.36	3.31	3.51	2.99	4.27	1.66	
(**4**−Na$^+$)^a	5.15	4.49	5.28	3.93	4.95	1.84	
(**4**−Na$^+$)^b	5.24	4.40	5.37	3.86	4.96	1.82	
7	3.46	3.13	3.57	2.89		2.41	1.43
(**7**−Na$^+$)^a	5.27	4.10	5.44	3.68		2.52	1.36
(**7**−Na$^+$)^b	5.27	4.10	5.44	3.68		2.52	1.36
(**7**−2Na$^+$)^c	3.85	4.29	4.53	4.25		2.52	1.19
(**7**−2Na$^+$)^d	3.86	4.28	4.55	4.24		2.52	1.19

[a] The superscripts carry the same expansion as those given in Table 1.

Results and Discussion

In application of the cation complexation approach, we calculated the dihedral angles D_1 ($O-C_{10}-C_1-C_2$), D_2 ($O-C_{10}-C_1-C_9$), D^3 ($O-C_{10}-C_7-C_6$), D_4 ($O-C_{10}-C_7-C_8$), and D_5 ($C_7-C_{10}-O-C_1$) both before and after cation complexation to assess the degree and direction of carbonyl pyramidalization.[8,9] We term the pyramidalization 'anti' when D_1 and D_3 are smaller than D_2 and D_4 and 'syn' when D_1 and D_3 are larger than D_2 and D_4, respectively. Anti pyramidalization leads to anti selectivity, and syn pyramidalization leads to syn selectivity. The changes in D_5 may also be used to discern anti/syn pyramidalization. A decrease in D_5 suggests anti pyramidalization. Likewise, an increase in D_5 suggests syn pyramidalization. Since **4** and **7** are unsymmetrical about $\pi_{C10=O}$, cation complexation syn to both C_1 and C_7 was considered. For reasons of steric interactions, cation complexation of C_3-carbonyl in **7** was allowed only anti to C_2. Further, since the experimental results were obtained from reduction with $NaBH_4$, we considered it prudent to use the Na$^+$ cation for complexation. Selected geometrical parameters and relevant (to selectivity) antiperiplanar and vicinal $\sigma \rightarrow \pi^*_{C=O}$ interactions (threshold = 0.50 kcal/mol)[10] are collected in Tables 1 and 2, respectively.

Smaller D_1 and D_3 in comparison to D_2 and D_4, respectively, favor anti selectivity for **1** and **4**. This is supported by the antiperiplanar interactions as well. The sum of the interactions of σ_{C1-C2} and σ_{C6-C7} with $\pi^*_{C10=O}$ is superior to the sum of the interactions of σ_{C1-C9} and σ_{C7-C8} with $\pi^*_{C10=O}$ in both **1** and **1**−Na$^+$. Likewise, the sum of the interactions of σ_{C1-C2} and σ_{C6-C7} with $\pi^*_{C10=O}$ is superior to the sum of the interactions of σ_{C1-C9} and σ_{C7-C8} with $\pi^*_{C10=O}$ in both **4** and **4**−Na$^+$. In **1** and **1**−Na$^+$, one of the two σ_{C-H} bonds on C_3 and C_5 are nearly antiperiplanar to σ_{C1-C2} and σ_{C6-C7} ($H-C_3-C_2-C_1$ and $H-C_5-C_6-C_7$ = 144−145°), respectively. Their interactions ($\sigma_{C3-H} \rightarrow \sigma^*_{C1-C2}$ = 2.80 kcal/mol in **1**, $\sigma_{C5-H} \rightarrow \sigma^*_{C6-C7}$ = 3.04 kcal/mol in **1**−Na$^+$) make σ_{C1-C2} and σ_{C6-C7} more electron rich than σ_{C1-C9} and σ_{C7-C8}, which, in turn, supports anti pyramidalization and, hence, anti selectivity.

TABLE 3. Calculated NBO Charges on Selected Atoms in 1, 4, 7, 10, and 12

substrate	C2	C6	C8	C9
1	−0.2581	−0.2581	−0.4660	−0.4660
4	−0.2786	−0.2510	−0.4661	−0.4639
7	−0.3557	−0.2585	−0.4690	−0.4695
10	−0.2845	−0.2602	−0.4638	−0.4670
12	−0.3492	−0.2542	−0.2292	−0.2276

The major factor that supports anti pyramidalization in **4** is the $\pi_{C3=C4} \rightarrow \sigma^*_{C1-C2}$ interaction that is 4.27 and 4.96 kcal/mol in **4** and **4**−Na$^+$, respectively. The $\pi_{C3=C4}$ bond is held in an orientation that it is nearly parallel to the σ_{C1-C2} bond to allow the above interactions. The possibility of such an interaction has been contemplated earlier by Mehta and Khan[11] and proved later by us.[12] It is interesting to note that the contribution from the $\sigma_{C5-H} \rightarrow \sigma^*_{C6-C7}$ interaction in **4** is reduced to 1.84 kcal/mol as compared to 2.80 kcal/mol in **1**. This is likely to be due to relatively inferior antiperiplanar relationship of σ_{C5-H} with σ_{C6-C7} in **4** ($H-C_5-C_6-C_7$ = 131°) as compared to that in **1** ($H-C_5-C_6-C_7$ = 145°).

The diketone **7** is particularly interesting because arguments as stated above favor better anti selectivity for it than for **4**. The sum of the antiperiplanar interactions of σ_{C1-C2} and σ_{C6-C7} with $\pi^*_{C10=O}$ is 1.01 kcal/mol larger than the sum of the antiperiplanar interactions of σ_{C1-C9} and σ_{C7-C8} with $\pi^*_{C10=O}$ in **7**. In comparison, this difference is 0.57 kcal/mol only in **4**. However, it contradicts the experimental finding. It was, in fact, **4** that exhibited higher anti selectivity (anti/syn = 63:37) than **7** (anti/syn = 55:45). The larger interactions of σ_{C1-C2} and σ_{C6-C7} in comparison to those of σ_{C1-C9} and σ_{C7-C8} with $\pi^*_{C10=O}$ in **7** are supported by $\sigma_{C5-H} \rightarrow \sigma^*_{C6-C7}$, 2.41 kcal/mol, and $\pi_{C3=O} \rightarrow \sigma^*_{C1-C2}$, 1.43 kcal/mol, interactions.

We envisioned the above discrepancy in the level of observed selectivity of **7** for a supposedly valid reason. Why must only the C_{10}-carbonyl be allowed for cation complexation when the C_3-carbonyl has a similar charge distribution?[5i] Natural bond orbital (NBO)[8] analysis at the B3LYP/6-31G* level showed the charges on the oxygen atoms as −0.5150 and −0.5290, respectively. Consequently, on allowing the additional complexation of C_3=O, the situation changed in support of syn selectiv-

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TABLE 4. Product Distribution from the Reaction of 7 with Selected Hydride Agents

entry	hydride	solvent	temp	time	yield %	products	anti/syn
1	$NaBH_4$	MeOH	−78 °C	30 min	85	**8** + **9**	55:45
2	DIBAL-H	CH_2Cl_2	−78 °C	100 min	75	**8** + **9**	65:35
3	$NaCNBH_3$	MeOH, pH 3−4	−78 °C	50 min	80	**10**:**11**= 10:1	**11a**:**11b** = 85:15

ity. The dihedral angles D_1 and D_3 increased and the dihedral angles D_2 and D_4 decreased in **7**−2Na^+ in comparison to the dihedral angles in **7**. Alternatively, the sum of the antiperiplanar interactions of σ_{C1-C2} and σ_{C6-C7} with $\pi^*_{C10=O}$, 8.38−8.41 kcal/mol, was inferior to the sum of the antiperiplanar interactions of σ_{C1-C9} and σ_{C7-C8} with $\pi^*_{C10=O}$, 8.52−8.54 kcal/mol, by an average of 0.14 kcal/mol, which supports syn pyramidalization. The selectivity of **7** will, therefore, be compromised and the observed selectivity will depend on the progress of double-level complexation under the given reaction conditions.

It is important to note that the reaction of **7** was carried out at −78 °C and **8,** and **9** were obtained directly from the reaction.[2] In our hands, also, **8** and **9** were formed predominantly along with small amounts of diols. The reported anti/syn (55:45) selectivity, therefore, is truly the selectivity of reduction of C_{10}=O in the presence of C_3=O. The concentration of the doubly cation-complexed species is, therefore, a likely limiting factor in determining the observed selectivity. This, in turn, will depend on the reaction conditions, including the solvent and source of the nucleophile. The C*H*OH resonates at a lower field in **8** (δ 4.33, s) than in **9** (δ 4.11, s).[2]

In the application of the cation-complexation model to substrates **1**, **4,** and **7**, use of H^+ performed similar to the use of Na^+. The changes in dihedral angles on carbonyl protonation followed a trend similar to that on complexation with Na^+. However, the changes on protonation were larger than the changes on complexation with Na^+. This demonstrates the significance of the cation and its possible effect on the observed selectivity.[13]

In the application of Houk's electrostatic model,[14] the sum of the charges on C_2 and C_6, on one hand, and those on C_8 and C_9, on the other hand, will be considered for the prediction of selectivity. The sum of the NBO charges on C_2 and C_6 and C_8 and C_9 in **1**, **4,** and **7** are, respectively, −0.5162 and −0.9320, −0.5296 and −0.9300, and −0.6143 and −0.9385 (Table 3). These charges predict syn attack throughout that contradicts the experimental finding. The electrostatic model, therefore, is not suitable to predict the selectivity of these substrates.

TABLE 5. Calculated Geometrical Parameters for 3-*endo*-Hydroxytricyclo(5.2.1.0^{2,6})decan-10-one 10 and Its Complexes with H^+ (D_1 = O−C_{10}−C_7-−$_6$; D_2 = O−C_{10}−C_7−C_8; D_3 = O−C_{10}−C_1−C_2; D_4 = O−C_{10}−C_1−C_9; D_5 = H−C_1−C_{10}−O; D_6 = H−C_7−C_{10}−O)

substrate	D_1	D_2	D_3	D_4	D_5	D_6
10	120.8	−125.3	−120.7	123.3	−1.35	1.35
10−H^+	114.0	−132.8	−114.7	129.7	−8.79	9.51[a]
10−H^+	115.4	−131.5	−114.6	129.7	−8.79	9.51[b]

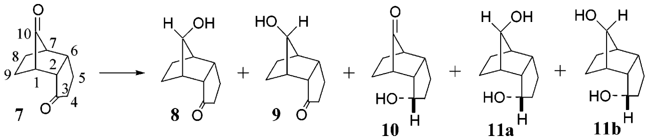
[a] Complexation was syn to C_7. [b] Complexation was syn to C_1.

TABLE 6. Antiperiplanar Interactions (kcal/mol) in 3-*endo*-Hydroxytricyclo(5.2.1.0^{2,6})decan-10-one, 10, and Its Complexes with H^+

substrate	$\sigma_{C1-C2} \rightarrow \pi^*_{C10=O}$	$\sigma_{C1-C9} \rightarrow \pi^*_{C10=O}$	$\sigma_{C6-C7} \rightarrow \pi^*_{C10=O}$	$\sigma_{C7-C8} \rightarrow \pi^*_{C10=O}$
10	3.10	3.43	3.45	2.98
10−H^+	7.74	6.06	9.15	4.98[a]
10−H^+	7.63	6.00	8.95	5.26[b]

[a] Protonation was syn to C_7. [b] Protonation was syn to C_1.

The preferential reduction of C_{10}=O in the presence of C_3=O in **7** is interesting but not new. Brown and Muzo observed that 7-ketonorbornanones reduced 2100 times faster than cyclopentanone by $NaBH_4$.[15] We wished to explore this reactivity profile further and, thus, repeated the reduction of **7** not only with $NaBH_4$ but also with other reducing agents such as DIBAL-H and $NaCNBH_3$. Under the conditions of reduction with $NaCNBH_3$ at pH 3−4, an enhanced syn selectivity was expected on account of possible protonation of both the carbonyl functions, provided the C10-carbonyl reacted chemoselectively.



In the event that we conducted the reductions, the anti/syn (55:45) selectivity reported by Mehta and Praveen[2] on reduction with $NaBH_4$ at −78 °C was reproduced. The reduction with DIBAL-H exhibited somewhat enhanced anti selectivity (anti/syn = 65:35). This is possibly due to stronger complexation of Al with the ketone than with Na^+ and, hence, larger carbonyl pyramidalization leading to greater discrimination of the two faces. The reduction with $NaCNBH_3$ was highly chemoselective. However, it was rather the C_3=O that reacted in preference to C_{10}=O as **8** and **9** had not formed. The products **10** and **11** were formed in a 10:1 ratio, estimated from the relative weights of **10** and the mixture of **11a** and **11b**. The selectivity of reduction of **10** with $NaCNBH_3$, established from a separate experiment under identical conditions, was anti/syn = 85:15, estimated from the relative ^{1}H

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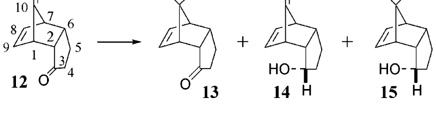
TABLE 7. **π- and Chemoselectivities of the Reduction of 12 by Selected Hydride Agents**

entry	hydride	solvent	temp	time (min)	yield (%)	product(s)	composition anti:syn
1	$NaBH_4$	MeOH	−78 °C	20	85	**14**:**15** = 1:1	**15** (>99:1)
2	DIBAL-H	CH_2Cl_2	−78 °C	60	75	14	
3	$NaCNBH_3$	MeOH pH 3−4	−78 °C	300	80	**13**, **14**, **15** **13**:**14** = 2:3	**13** (>99:1) **15** (>99:1)

integrals of C10-*H*. The said proton in **11a** resonated downfield (δ 4.20, s) compared to the proton in **11b** (δ 4.08, s) in keeping with the arguments used previously for such a characterization.[2] The ratio estimation was also possible from the relative integrals of C_3−H as the same in **11a** appeared downfield (δ 4.50−4.43, q, $J = 8.4$ Hz) compared **11b** (δ 4.34−4.27, q, $J = 8.4$ Hz). These results are collected in Table 4.

How do we account for the observed anti preference of **10**? A comparison of the dihedral angles D_1/D_3 vs D_2/D_4 collected in Table 5 supports anti selectivity. D_1 and D_3 have decreased and D_2 and D_4 increased on carbonyl protonation.[16] The relevant antiperiplanar interactions are collected in Table 6. The difference of the sum of the interactions of σ_{C1-C2} and σ_{C6-C7} and σ_{C1-C9} and σ_{C7-C8} with $\pi^*_{C=O}$ is 0.14 kcal/mol in **10** itself. Though this is in favor of the observed anti selectivity, its level may not be predicted to be as high as observed. However, this energy difference increased to 5.91 kcal/mol on carbonyl protonation. The sum of the NBO charges on C_2 and C_6 and C_8 and C_9 in **10** are, respectively, −0.545 and −0.931, which will predict syn selectivity in keeping with Houk's electrostatic model. This, however, contrasts the experimental results. The NBO charges in **10** are collected in Table 3.

In the course of the above investigations we had easy access to tricyclo(5.2.1.0^{2,6})dec-8-en-3,10-dione, **12**, and were interested in studying its selectivity for hydride additions to C_{10}=O under the influence of C_3=O on one side of the bridge and π-bond on the other side. To our knowledge, such a combination of functional-group discrimination of a carbonyl group has not been explored previously. In addition, **12** presented an opportunity to study the chemoselectivity of reduction of one carbonyl over the other as well. The $\pi_{C=C} \rightarrow \pi^*_{C10=O}$ interaction, 4.15 kcal/mol, should render C_{10}=O less reactive, and thus, a chemoselective reduction of C_3=O appeared to be a possibility. The sum of the NBO charges on C_2 and C_6, −0.6033, and C8 and C9, −0.4568, predict syn-to-olefin selectivity as indeed observed. The NBO charges in **12** are collected in Table 3.



NaBH$_4$ furnished a 1:1 mixture of **14** and **15** (determined from the isolated weights) and none of **13**. We take it to understand that the chemoselectivity of C_3=O reduction over C_{10}=O was exclusive and that **15** was formed from **14** on further reduction that entailed exclusive hydride attack from syn to the π bond. This was confirmed separately from the reduction of **14** under identical conditions when only **15** had formed. DIBAL-H was highly chemoselective as it reduced only C_3=O to generate **14** as the sole product. Further reduction of **14** into **15** did not occur. The reaction with NaCNBH$_3$ at pH 3−4 was less chemoselective as both **13** and **14** (**13**/**14** = 2:3) were formed. The product **15**, formed from either **13** or **14**, was also formed in trace amounts. Irrespective of the hydride reagent used and irrespective of whether it was C_3=O as in **13** or C3-*endo*-OH as in **14**, C_{10}=O was reduced exclusively syn to the π bond. This was secured from separate experiments with **13** and **14** when only **15** had formed from each. The results are collected in Table 7.

The faster reduction of C_3=O over C_{10}=O in **12** suggests lower reactivity of the latter function due possibly to $\pi_{C=C} \rightarrow \pi^*_{C10=O}$ interaction. We indicated in a previous publication that vicinal effects did not predict the selectivities of bicyclo[2.2.1]hept-2-en-7-ones well and that the observed selectivity was modulated probably by the acid−base interaction of the olefin and the cation end of the nucleophile, allowing the nucleophile to be delivered to C_{10}=O exclusively syn to the olefin.[5h]

Conclusions

Antiperiplanar and $\sigma \rightarrow \pi^*_{C=O}$ effects controlled the selectivities of **1**, **4**, **7**, **10,** and **12**. The ground-state conformers are possibly less important than the conformers generated on cation complexation in the determination of diastereoselectivity. The species **7** is inherently anti selective for the vicinal effects arising from $\pi_{C3=O} \rightarrow \sigma^*_{C1-C2}$ interaction. Its poor anti selectivity in comparison to **4** is possibly a consequence of competitive cation complexation of C_3-ketone vs C_{10}-ketone, which favored syn selectivity. The species **10** exhibits high anti selectivity in comparison to **7**. This can be explained by considering vicinal effects in the cation-complexed species. Species **12** exclusively undergoes syn-to-olefin reduction of the C_{10}-ketone. This is possibly due to the acid−base-like coordination of the cation end of the nucleophile with the olefin, and thus, the nucleophile is delivered to C_{10}-ketone syn to the olefin. Houk's electrostatic model predicts the incorrect selectivity for several of the compounds.

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Supporting Information Available: Spectroscopic data, experimental details for the preparation of new substrates and their reduction, and Cartesian coordinates of substrates and their cation complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Since the dihedral angle changes on protonation are similar to the changes on complexation with a metal cation such as Na$^+$, only protonation of **10** was studied. Alternatively, under the conditions of reduction with NaCNBH$_3$ at pH 3−4, protonation is more likely than complexation with Na$^+$.