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Effect of 2,6-Disubstituted Aryl Groups on Acyclic Conformation: Preference for an Antiperiplanar Orientation of the Geminal and Vicinal Hydrogens

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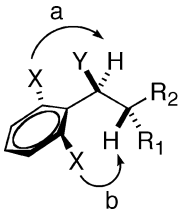

To minimize allylic 1,3-strain (a) and *syn*-pentane-like interactions (b), 2,6-disubstituted aryl groups induce the geminal and vicinal hydrogens to adopt an antiperiplanar orientation (X =F, Cl, Br, Me, Et)

Multiple X-ray crystallographic and ^{1}H NMR spectroscopic studies demonstrate that 2,6-disubstituted aryl groups exert a strong effect on acyclic conformation, inducing the geminal and vicinal hydrogens on the adjacent sp^3−sp^3 C−C bond to adopt an antiperiplanar orientation. Twenty-one examples comprising nitrile, ketone, and dithiane aldols are provided. A search of the Cambridge Structural Database uncovered an additional 11 examples of this effect. This preference causes some unanticipated remote effects on acyclic conformations: in *anti*-nitrile aldols, this effect causes 2,6-disubstituted aryls to generally prefer a gauche, rather than antiperiplanar, relationship to the largest vicinal groups. X-ray crystallography, ^{1}H−^{1}H NOESY spectroscopy, and computation demonstrate that minimization of allylic 1,3-strain and *syn*-pentane-like interactions work together in establishing this conformational preference.

Introduction

Control of conformational equilibria is critical in asymmetric synthesis,[1,2] lead compound optimization,[3,4] and supramolecular chemistry.[5] Conformational control of acyclic molecules is especially challenging,[6] and development of new strategies to achieve this goal would be welcome. During the course of our previous studies on the stereochemistry of the aldol reaction of arylacetonitriles, we characterized *anti*-**1**[7] and *anti*-**2**[8] by X-ray crystallography (Figure 1).

These compounds attracted our attention because in the solid state they adopt a conformation that places the large 2,6-disubstituted aryl ring in a gauche relationship to the largest vicinal group (aryl). Furthermore, this conformation is retained in solution: the large vicinal coupling constants (10.3, 9.3 Hz) establish an antiperiplanar orientation of H2 and H3.[10] Thus, the gauche orientation of the aryl rings observed in the solid state is not the result of crystal packing. Recently, Toru and co-workers reported the synthesis of dithiane-derived aldols *anti*-**3** and *syn*-**3**.[9,11] Although these compounds have not been

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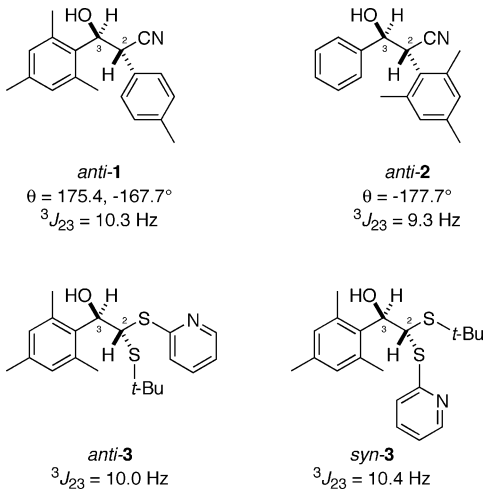

FIGURE 1. Solid state (X-ray) and solution (^{1}H NMR, $CDCl_3$) and evidence for an antiperiplanar orientation of H2 and H3 in previously published aldols.[7−9] Solid-state dihedral angles θ (H2C2C3H3) correspond to the depicted enantiomer; where two dihedral angles are given, two molecules were present in the asymmetric unit.

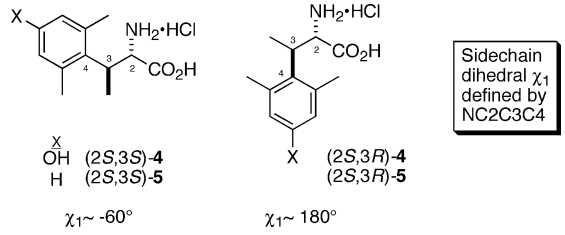

FIGURE 2. Preferred side-chain dihedrals χ_1 of 2,6-dimethyl-β-methyltyrosines **4**[12,13] and phenylalanines **5**.[14]

characterized by X-ray crystallography, similar conformational energetics appear to be operative. Based on the ^{1}H NMR vicinal coupling constants of 10.0 and 10.4 Hz, it is clear that in solution, H2 and H3 of *anti*- and *syn*-**3** are again in an antiperiplanar relationship. That the 2,6-disubstituted aryl ring is somehow responsible for the conformational preference of **1**−**3** is suggested by Hruby's studies of 2,6-dimethyl-β-methyltyrosines **4**[12,13] and phenylalanines **5**[14] (Figure 2).

With (2*S*,3*S*)-stereochemistry, it was noted that a side-chain dihedral χ_1 of $\sim -60°$ is preferred; with (2*S*,3*R*)-stereochemistry, the χ_1 side-chain dihedral of $\sim$180° is preferred.[13,14] This focus on the divergent χ_1 side-chain dihedrals is useful for peptide design, but potentially obscures a common feature of the stereoisomers: both adopt an antiperiplanar orientation of H2 and H3 in their preferred conformations. In this paper, we examine the generality of the effect of 2,6-disubstituted aryl groups on acyclic conformation, and its energetic origin.

Results and Discussion

To determine the generality of the conformational preference observed for the aldols in Figure 1, we used standard methods to prepare a number of nitrile and ketone aldols derived from

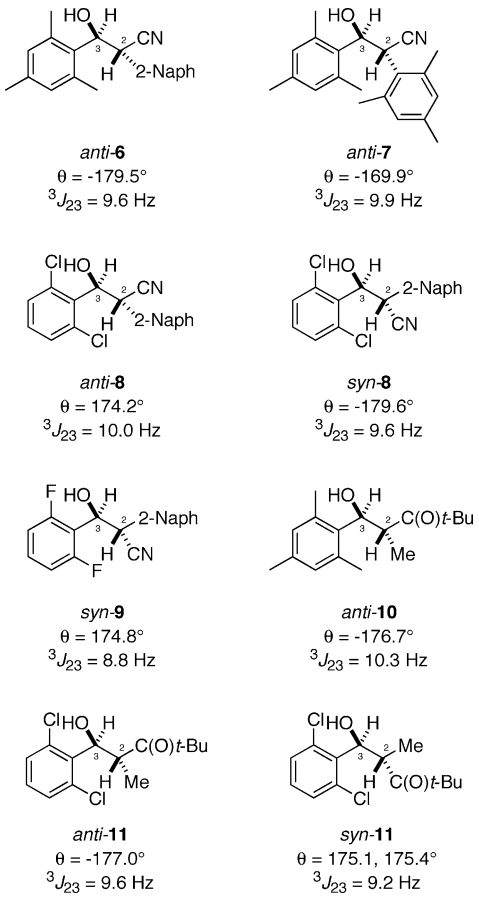

FIGURE 3. Solid-state dihedral angles θ (H2C2C3H3) and vicinal coupling constants ($CDCl_3$) of new nitrile and ketone aldols of 2,6-disubstituted benzaldehydes.

mesitaldehyde, 2,6-diethylbenzaldehyde, 2,6-difluorobenzaldehyde, 2,6-dichlorobenzaldehyde, and 2,6-dibromobenzaldehyde. All of the compounds examined gave evidence of similar conformational behavior in solution. Following separation of the diastereomeric aldols, eight gave crystals suitable for X-ray crystallography (Figure 3).

Aldols *anti*-**6** and -**7** are close analogues of *anti*-**1**; as the size of the 2-aryl group increases from 4-MeC_6H_4 to 2-naphthyl to mesityl, the preference for the 2- and 3-aryl groups to adopt a gauche orientation remains unchanged. Similarly, 2,6-dichlorobenzaldehyde aldol *anti*-**8** and mesitaldehyde aldol *anti*-**6** feature identical 2-naphthyl substituents at C2 and have nearly identical conformations in the solid state and solution. Examination of *syn*-**8** and *syn*-**9** indicates that they also exhibit an antiperiplanar relationship of H2 and H3 in solution and the solid state; note that for these *syn*-diastereomers, a gauche interaction between the C2- and C3-aryl groups is avoided. Although *syn*-**1**, *syn*-**2**, and *syn*-**6** were not characterized by X-ray crystallography, their vicinal coupling constants (9.3,[7] 8.8,[8] and 9.6 respectively) indicate that they also adopt an antiperiplanar orientation of H2 and H3.[15]

In contrast, aldols derived from benzaldehyde and arylacetonitriles lacking 2,6-disubstitution (e.g., Ar = Ph, 4-MeC_6H_4, 2-naphthyl) do not have a single preferred conformation along

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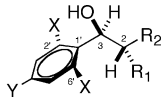
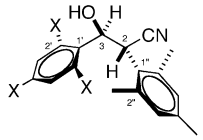
(15) Note that *syn*-**7** was not available for comparison, because the aldol reaction of mesitylacetonitrile and mesitaldehyde was completely *anti*-selective.



	R_1	R_2	X	Y	φ (H3C3C1'C2', °)
anti-**1**	4-MeC_6H_4	CN	Me	Me	6.8, -4.2
anti-**6**	2-Naph	CN	Me	Me	18.5
anti-**8**	2-Naph	CN	Cl	H	9.3
syn-**8**	CN	2-Naph	Cl	H	12.1
syn-**9**	CN	2-Naph	F	H	9.1
anti-**10**	Me	C(O)*t*-Bu	Me	Me	11.9
anti-**11**	Me	C(O)*t*-Bu	Cl	H	9.3
syn-**11**	C(O)*t*-Bu	Me	Cl	H	10.3



	X	φ (H3C3C1'C2', °)	τ (H2C2C1"C2", °)
anti-**2**	H	40.0	14.3
anti-**7**	Me	16.2	7.5

FIGURE 4. Orientation of 2,6-disubstituted aryl rings at C3 and C2 relative to their geminal hydrogens, as indicated by the dihedral angles φ and τ (X-ray).

the C2−C3 axis, as indicated by vicinal coupling constants that typically range from 5 to 6 Hz for the *anti*-diastereomer, and 6−7 Hz for the *syn*-diastereomer.[7] Thus, the conformational preference exhibited by the nitrile aldols in Figures 1 and 3 appears to be due to the 2,6-disubstituted aryl moiety. An antiperiplanar relationship between H2 and H3 is also seen in *anti*-**10**, *anti*-**11**, and *syn*-**11**, which are *tert*-butyl ethyl ketone aldols of mesitaldehyde and 2,6-dichlorobenzaldehyde, respectively (Figure 3). Thus, as was also demonstrated by dithiane aldols *anti*- and *syn*-**3**, the preference for an antiperiplanar orientation of H2 and H3 does not depend on the presence of a cyano or aryl group at C2. Finally, it is worth noting that, in each case, X-ray crystallography reveals intermolecular, not intramolecular, hydrogen bonding of the OH protons to basic nitrile, ketone, and hydroxyl moieties. Intramolecular hydrogen bonding in β-hydroxynitriles is known to be weak,[16,17] and we have earlier proposed that it does not play a major role in conformational energetics of β-hydroxynitriles.[7] In contrast, intramolecular hydrogen bonding in solution is commonly observed for ketone aldols;[18] however, in the solid-state structures of *anti*-**10**,**11** and *syn*-**11**, intermolecular hydrogen bonds are apparently preferred.

To determine how 2,6-disubstituted aryl rings at C3 and C2 might play a role in enforcing θ dihedral angles near 180°, we examined their solid-state orientations relative to H3 and H2 (Figure 4).

For the eight structured compounds bearing a 2,6-disubstituted aryl ring only at C3, dihedral angles φ (H3C3C1′C2′) are generally within 13°; the average dihedral for all eight compounds is 10.2°. Aldol *anti*-**7** bears 2,6-disubstituted aryl rings at C2 and C3; the dihedral of the C3 ring to its geminal hydrogen (φ) is 16.2°. Aldols *anti*-**2** and *anti*-**7** bear 2,6-disubstituted aryl rings at C2, and corresponding dihedrals τ to the geminal H (H2C2C1"C2") are 14.3° and 7.5°. This tendency of the 2,6-disubstituted aryl ring to nearly eclipse its geminal hydrogen derives from minimization of allylic 1,3-strain and is consistent with the conformational preference of similar sp^2-sp^3 bonds,[19] such as that in (*Z*)-4-methyl-2-pentene[20] and in constrained amino acids **4** and **5**.[13,14] Note that a near eclipsing interaction is not seen for the unsubstituted phenyl ring at C3 of *anti*-**2** (φ = 40.0°).

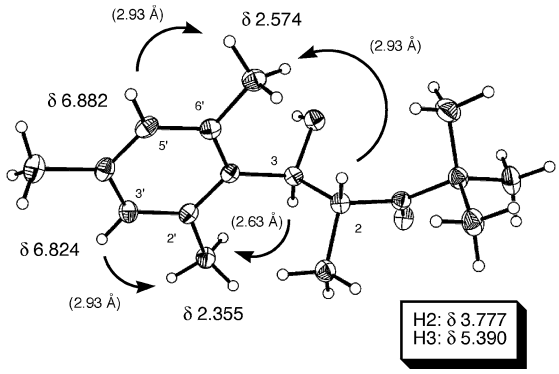


FIGURE 5. Thermal ellipsoid plot (50% probability) of *anti*-**10**, superimposed with select NOESY correlations at −33.4 °C ($CDCl_3$). Average H−H distances (X-ray) are given in parentheses.

Inspection of Figure 4 leads to the insight that small φ dihedral angles place the C6′−X group near H2. To provide evidence of this close contact in solution, we performed additional ^{1}H NMR spectroscopic studies on *anti*-**10**, because it showed nonequivalence of the mesityl *ortho*-methyl groups near room temperature (Figure 5).

The C2′ and C6′ methyl groups of *anti*-**10** coalesce at 21.5 °C, and the C3′ and C5′ protons coalesce at −1.3 °C, indicating barriers to rotation about the C1′−C3 bond of 14.2 and 13.7 kcal/mol at these temperatures, respectively.[21] ^{1}H−^{1}H NOESY NMR correlations at −33.4 °C revealed that, as predicted, H2 is near one of the mesityl methyl groups (C6′-Me) and that H3 is near the other (C2′-Me). Thus, the close proximity of H2 and H3 to the C6′ and C2′ substituents seen in the solid-state structure of *anti*-**10** is maintained in solution. In addition, inspection of the X-ray structure of *anti*-**10** indicates that the 2-methyl group lies within the shielding cone of the 2,6-disubstituted aryl group at C3. Consequently, an upfield shield (0.5 ppm) is observed by ^{1}H NMR for the 2-methyl groups in *anti*-**10** and *anti*-**11** relative to their *syn*-isomers. A similar upfield ^{13}C NMR shift (1.2−5.5 ppm) is seen for the cyano carbons in nitrile aldols *syn*-**6**−**8** relative to their *anti*-isomers.

The tendency of 2,6-disubstituted aryl rings to nearly eclipse their geminal hydrogens should have important consequences on the energies of conformations along the C3−C2 bond (Figure 6).

As can be seen, conformations 2 and 3 incur destabilizing steric interactions of the C6′−X group with the C2 substituent (R1 and R2, respectively): these interactions are somewhat

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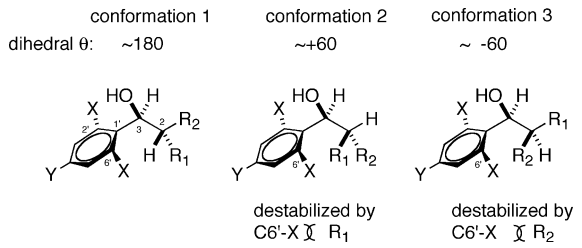
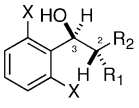


FIGURE 6. Steric effects in conformations along the C3−C2 axis; note the "*syn*-pentane"-like interactions in conformations 2 and 3.

remiscent of a "*syn*-pentane" interaction.[22,23] Conformation 1 is unique in placing a small H substituent proximal to the C6′−X group; thus it is lowest in energy. A similar analysis can be performed to show how a 2,6-disubstituted aryl group at C2 will also lead to dihedrals θ near 180°.

To assess the magnitude of the destabilizations suffered by conformations 2 and 3, we performed systematic conformational searches using the MMFF94 molecular mechanics method[24] and the conformer distribution module of Spartan '04 for Windows.[25] Although molecular mechanics-based procedures are strictly approximate, MMFF94 is particularly well parametrized to model acyclic conformations,[26] and the speed of the method allows sampling of the entire conformational space.[27] In this analysis, we also included aldols derived from 2,6-dibromobenzaldehyde and 2,6-diethylbenzaldehyde (**12** and **13**, respectively) that evidenced antiperiplanar orientations of H2 and H3 by ^{1}H NMR spectroscopy but have not yet yielded to X-ray crystallography.



	X	R_1	R_2
anti-**12**	Br	2-Naph	CN
syn-**12**	Br	CN	2-Naph
anti-**13**	Et	2-Naph	CN
syn-**13**	Et	CN	2-Naph

All conformers were examined and classified as conformation 1, conformation 2, or conformation 3, according to the dihedral θ. MMFF94 relative energies of the conformers were then used to calculate the summed Boltzmann weightings at 298 K for these conformations (Table 1).

In 18 of the 19 cases, Boltzmann weightings for conformation 1 are in the range 72−99%, consistent with the ^{1}H NMR observation that conformation 1 dominates in solution. We attribute the sole failure (entry 15) of molecular mechanics to approximate the solution conformation of these compounds to an overestimation of the intramolecular H-bonding stabilization of conformation 3 in *syn*-**11**.[28]

The excellent performance of the admittedly approximate molecular mechanics method to model the solution conformation of the aldols **1**, **2**, and **6**−**13** suggests a significant energetic preference for an antiperiplanar arrangement of H2 and H3. We have previously noted that, in this conformation, nitrile aldols *anti*-**1**, *anti*-**6**, *anti*-**7**, and *anti*-**8** place the C2-aryl group and the 2,6-disubstituted aryl group at C3 in a gauche relationship. Similarly, in *anti*-**2**, the mesityl group at C2 occupies a gauche relationship to the phenyl ring at C3, and in *anti*-**7**, the mesityl group at C2 occupies a gauche relationship to another mesityl ring at C3. If the C3 substituent in *anti*-**7** were to further increase in size, its gauche interaction with C2-mesityl group would become increasingly penalizing, and conformation 1 would no longer be favored. This threshold is reached in compound *anti*-**14**, which features a *tert*-butyl substituent at C3. X-ray crystallography reveals that, in the solid state, *anti*-**14** adopts conformation 3 ($\theta = -78.3°$), which places the large *tert*-butyl and mesityl substituents in a nearly antiperiplanar orientation (Figure 7).

Examination of the X-ray crystal structures of previously published[7] *tert*-butyl bearing aldols *anti*-**15** and *anti*-**16** also demonstrates adoption of conformation 3. In solution, the vicinal coupling constants for *anti*-**14**−**16** (<1−3.9 Hz) indicate a synclinal orientation of H2 and H3, also consistent with conformation 3. Preferential placement of *tert*-butyl antiperiplanar to the largest group is well known[29] and has been termed the "*tert*-butyl effect".[23] By comparison of *anti*-**14** with *anti*-**2** and *anti*-**7**, it can be seen that the 2,6-disubstituted aryl-induced preference for a 180° orientation of H2 and H3 does not overwhelm the "*tert*-butyl effect".[29] Nevertheless, in all of the other examples presented thus far, the presence of a 2,6-disubstituted aryl ring renders the adjacent sp^3-sp^3 bond "monoconformational", wherein the geminal and vicinal hydrogens adopt an antiperiplanar orientation.

To further test the generality of these findings, a search was conducted of the Cambridge Structural Database (CSD) using the query **A** (Figure 8).

Excluding compounds in which the ethane unit was embedded in a ring, 13 additional structures were retrieved, providing 15 independent measurements of the dihedral angle θ. Of these 13 structures, 11 displayed antiperiplanar arrangements of the geminal and vicinal hydrogens: θ ranged from −153° to +157°, with an unsigned mean of 173° (13 angles, see structures **17**−**27** in the Supporting Information).[30−40] The two CSD entries

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(28) Intramolecular hydrogen bonding is possible in conformation 3, due to the gauche arrangement of the C(O)*t*-Bu and OH groups; in conformer 1, intramolecular hydrogen bonding is precluded, because these groups are antiperiplanar. Note that the MMFF94 method correctly predicts that conformation 1 is preferred for *syn*-**10**, which is the mesityl analogue of *syn*-**11**.
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TABLE 1. MMFF94 Summed Boltzman Weightings of Conformations 1, 2, and 3 at 298 K

		summed Boltzmann weightings (number of conformers, θ dihedral range)[a]		
entry	compound	conformation 1	conformation 2	conformation 3
1	*anti*-**1**	74.3% (9, 170°−177°)	2.4% (8, 67°−79°)	23.3% (15, −68° to −82°)
2	*syn*-**1**	82.0% (8, 165°−177°)	1.5% (6, 68°−73°)	16.5% (12, −71° to −75°)
3	*anti*-**2**	71.6% (6, 166°−174°)	12.9% (4, 69°−70°)	15.5% (4, −68° to −86°)
4	*syn*-**2**	82.4% (8, 174°−175°, −173° to −177°)	14.4% (4, 72°−77°)	3.2% (6, −60° to −68°)
5	*anti*-**6**	73.5% (9, 170°−177°)	5.4% (8, 67°−79°)	21.0% (12, −68° to −82°)
6	*syn*-**6**	75.4% (9, 164°−177°)	1.0% (5, 68°−73°)	23.6% (12, −72° to −76°)
7	*anti*-**7**[b]	92.3% (8, 144°−149°, −167° to −169°)	4.4% (3, 60°−72°)	3.3% (4, −57° to −60°)
8	*anti*-**8**	96.9% (4, 158°−162°)	1.4% (2, 65°−66°)	1.7% (7, −66° to −77°)
9	*syn*-**8**	88.8% (6, 162°−171°)	0.3% (6, 67°−71°)	11.0% (4, −64° to −71°)
10	*anti*-**9**[c]	76.7% (7, 163° to −166°)	20.2% (6, 62°−77°)	3.1% (9, −66° to −73°)
11	*syn*-**9**	72.2% (6, 168°−176°)	2.5% (8, 66°−68°)	25.3% (5, −58° to −66°)
12	*anti*-**10**	99.8% (8, 160°−179°, −164° to −168°)	0% (0)	0.2% (4, −59° to −72°)
13	*syn*-**10**[d]	96.7% (9, −161° to −172°)	0% (2, 57°)	3.3% (6, −73° to −86°)
14	*anti*-**11**	97.9% (7, 159°−179°, −173°)	0.1% (2, 63°−64°)	2.1% (2, −68° to −69°)
15	*syn*-**11**	9.4% (4, 177°, −150° to −175°)	0.4% (2, 64°−65°)	90.3% (4, −54° to −89°)
16	*anti*-**12**[e]	96.9% (4, 160°−165°)	1.7% (4, 65°−71°)	1.4% (4, −66° to −77°)
17	*syn*-**12**[e]	87.1% (4, 161°−172°)	0.2% (5, 69°−73°)	12.8% (6, −68° to −73°)
18	*anti*-**13**[f]	77.8% (36, 164°−180°, −180° to −168°)	10.5% (14, 70°−86°)	11.7% (16, −68° to −83°)
19	*syn*-**13**[f]	80.6% (32, 157°−179°)	3.1% (10, 66°−71°)	16.3% (29, −69° to −75°)

[a] Dihedral angles reflect those of the depicted enantiomer. [b] Three members of an eclipsed conformer family were also found for *anti*-**7**; these were false minima that reverted to members of conformations 1−3 upon B3LYP/6-31G* optimization and were thus excluded from the MMFF94 Boltzmann weightings. Calculations for *syn*-**7** are not included because this diastereomer was not synthesized. [c] For reference, the vicinal coupling constant for *anti*-**9** ($CDCl_3$) is 8.8 Hz. [d] For reference, the vicinal coupling constant for *syn*-**10** ($CDCl_3$) is 9.2 Hz. [e] Vicinal coupling constants for *anti*- and *syn*-**12** are 10.0 and 9.2 Hz, respectively. [f] Vicinal coupling constants for *anti*- and *syn*-**13** are 9.6 Hz (both).

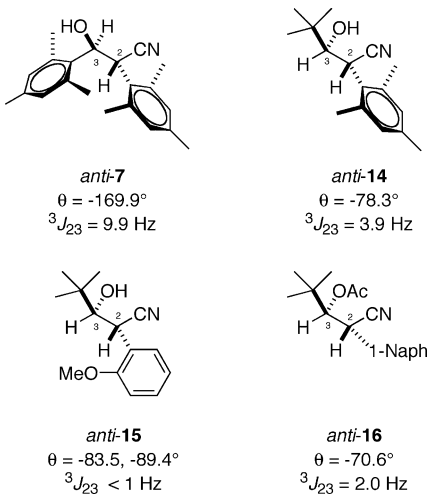

FIGURE 7. The effect of *tert*-butyl-substitution at C3 on nitrile aldol conformation along the C3−C2 axis in the solid state (θ) and solution ($^3J_{23}$).

retrieved in the search that do not follow this pattern are unusually crowded ethanes: (*RR*/*SS*)-1,2-di-*tert*-butyl-1,2-dimesitylethane[30] and 1,2,2-trimesitylethanol[41] (see structures **28** and **29** in the Supporting Information).

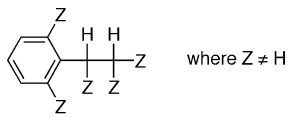

FIGURE 8. Query **A** used in a search of the Cambridge Structural Database (Allen, F. H. *Acta Crystallogr*. **2002**, *B58*, 380−388); see the Supporting Information for retrieved structures.

To conclude, we have shown that 2,6-disubstituted aryl rings exert steric effects on both the directly attached and the adjacent sp^3-carbons. Minimization of allylic 1,3-strain causes the 2,6-disubstituted ring to nearly eclipse the hydrogen on the directly attached carbon. To avoid *syn*-pentane-like interactions that might consequently emerge, the adjacent carbon rotates to place its hydrogen roughly within the plane of the 2,6-disubstituted aryl ring. When these geminal and vicinal carbons bear a single hydrogen each, an antiperiplanar orientation of the hydrogens is thus established. Mesityl, 2,6-diethylphenyl, 2,6-bromophenyl, 2,6-dichlorophenyl, 2,6-difluorophenyl, and pentafluorophenyl groups exert this effect: in total, X-ray crystallography and ^1H NMR spectroscopy provide 32 independent examples. The three exceptions found are limited to unusually crowded ethanes or cases in which the "*tert*-butyl effect" proves dominant. We believe that the findings reported here will prove useful for deducing the conformational preference of related acyclic molecules, and for conformational design of new hydrocarbon backbones.[23]

Experimental Section

General characterization and NMR spectroscopy protocols are described in the Supporting Information.

Computational Studies. Conformational searches were performed using the MMFF94 molecular mechanics method[24] and the conformer distribution module of Spartan '04 for Windows.[25]

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Conformers were examined and classified as conformation 1, 2, or 3 according to the dihedral angle θ. Boltzmann weightings were calculated at 298 K. All conformers were included in the analysis, except for *anti*- and *syn*-**13**, where their number exceeded 100; in this case, only conformers within 5.0 kcal/mol of the global minima were included. Energies and dihedral angles for these conformers, and Cartesian coordinates of the global minima, are reported in the Supporting Information.

General Procedure for Synthesis of Nitrile Aldols. An oven-dried 50 mL round-bottom flask equipped with stirring bar and septum was charged with nitrile (1 mmol) and fresh THF (10 mL), and cooled to −78 °C. The LDA (1.5 M, 0.7 mL, 1.05 mmol) was added via syringe, and the mixture was stirred at −78 °C for 30 min. Aldehyde (1 mmol) was added into the mixture. If mesitaldehyde was used, borontrifluoride etherate (1 mmol) was added to activate the aldehyde. After 30 min at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl and allowed to warm to room temperature. The 5 mL of 1 N HCl was poured into the reaction mixture and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give the crude product.

(2*RS*,3*RS*)-3-Hydroxy-3-(2,4,6-trimethylphenyl)-2-(2-naphthyl)propanenitrile (*anti*-6). Reaction of 2-naphthylacetonitrile (0.166 g, 1 mmol), mesitaldehyde (0.145 mL, 1 mmol), and boron trifluoride etherate (0.124 mL, 1 mmol) was performed as above. The initial ratio of *anti*- and *syn*-diastereomers was 2.3:1. The *anti*-diastereomer (0.115 g, 36.6%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:5). The crystals of *anti*-**6** were obtained from CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$): 2.13 (br, 6H), 2.20 (s, 3H), 2.83 (d, J = 3.5 Hz, 1H), 4.58 (d, J = 9.6 Hz, 1H), 5.25 (dd, J = 3.5, 9.6 Hz, 1H), 6.695−7.79 (m, 9H). ^{13}C NMR ($CDCl_3$): 20.7, 20.9, 44.4, 73.5, 120.4, 125.8, 126.64, 126.68, 127.71, 127.74, 128.0, 128.4, 129.6, 130.4, 131.4, 132.9, 133.0, 136.8, 138.0. HRMS (FAB): 298.15957 calcd for $C_{22}H_{20}N$, $[M - OH]^+$, found 298.15802 (−5.3 ppm, −1.6 mmu). Mp: 148.3−150.8 °C. X-ray structure obtained; thermal ellipsoid plot is in the Supporting Information.

(2*RS*,3*SR*)-3-Hydroxy-3-(2,4,6-trimethylphenyl)-2-(2-naphthyl)propanenitrile (*syn*-6). Data on *syn*-**6** were deduced by inspection of an anti:syn mixture (6:1) of **6**, obtained during isolation of *anti*-**6**. ^{1}H NMR ($CDCl_3$): 1.92 (d, J = 3.2, 1H), 2.26 (s, 3H), 2.52 (br, 6H), 4.49 (d, J = 9.6 Hz, 1H), 5.46 (dd, J = 3.0, 9.4 Hz, 1H), 6.88−7.92 (m, 9H). ^{13}C NMR ($CDCl_3$): 21.1, 43.6, 73.6, 119.0, 125.9, 127.06, 127.13, 128.1, 128.20, 128.25, 129.5, 131.2, 132.2, 133.38, 133.52, 136.9, 138.5. HRMS (FAB): 298.15957 calcd for $C_{22}H_{20}N$, $[M - OH]^+$, found 298.16141 (+6.1 ppm, +1.8 mmu). Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.52; H, 6.74; N, 4.51.

(2*RS*,3*RS*)-3-Hydroxy-2,3-di(2,4,6-trimethylphenyl)propanenitrile (*anti*-7). Reaction of mesitylacetonitrile (0.1601 g, 1 mmol), mesitaldehyde (0.145 mL, 1 mmol), and borontrifluoride etherate (0.124 mL, 1 mmol) was performed as above. The initial ratio of *anti*:*syn*-diastereomers was over 20:1. The *anti*-diastereomer (0.110 g, 35.5%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:4). ^{1}H NMR ($CDCl_3$): 1.31−2.85 (br, 6H), 1.58 (br, 3H), 2.20 (d, 6H), 2.69 (br, 3H), 4.82 (d, J = 9.9 Hz, 1H), 5.45 (d, J = 9.9 Hz, 1H), 6.61−6.87 (m, 4H). ^{13}C NMR ($CDCl_3$): 14.3, 19.7, 20.3, 20.9, 38.0, 69.4, 119.2, 125.7, 129.51, 129.72, 130.18 (br), 130.7, 132.7, 136.0, 137.18, 137.46, 137.90, 138.08. HRMS (FAB): 290.19087 calcd for $C_{21}H_{24}N$, $[M - OH]^+$, found 290.19293 (+7.0 ppm, +2.0 mmu). Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.89; H, 8.26; N, 4.47. Mp: 167.3−168.7 °C. X-ray structure obtained; thermal ellipsoid plot is in the Supporting Information.

(2*RS*,3*RS*)-3-(2,6-Dichlorophenyl)-3-hydroxy-2-(2-naphthyl)-propanenitrile (*anti*-8). Reaction of 2-naphthylacetonitrile (0.334 g, 2 mmol) and 2,6-dichlorobenzaldehyde (0.417 g, 2 mmol) was performed as above. The initial ratio of *anti*:*syn*-diastereomers was 1.8:1. The *anti*-diastereomer (0.223 g, 32.5%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:3). The crystals were obtained from CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$): 3.44 (d, J = 9.2 Hz, 1H), 4.95 (d, J = 10.0 Hz, 1H), 5.90 (dd, J = 9.2, 10.0 Hz, 1H), 7.02−7.74 (m, 10H). ^{13}C NMR ($CDCl_3$): 43.5, 73.7, 119.8, 125.4, 126.68, 126.77, 127.75, 127.91, 128.00, 128.7, 129.6, 130.3, 132.9, 133.0. HRMS (FAB): 342.04525 calcd for $C_{19}H_{14}{}^{35}Cl_2NO$, $[M + H]^+$, found 342.04266 (−7.5 ppm, −2.6 mmu). Mp: 154.0−155.2 °C. X-ray structure obtained; thermal ellipsoid plot is in the Supporting Information.

(2*RS*,3*SR*)-3-(2,6-Dichlorophenyl)-3-hydroxy-2-(2-naphthyl)-propanenitrile (*syn*-8). The *syn*-diastereomer (0.1572 g, 23.0%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:3). The crystals were obtained from CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$): 2.82 (d, J = 8 Hz, 1H), 4.85 (d, J = 9.6 Hz, 1H), 5.87 (dd, J = 8.0, 9.6 Hz, 1H), 7.02−7.94 (m, 10H). ^{13}C NMR ($CDCl_3$): 42.4, 73.7, 114.3, 125.7, 127.0, 127.9, 128.1, 128.41, 129.43, 130.2, 130.6, 133.39, 133.67, 135.4, 137.3. HRMS (FAB): 342.04525 calcd for $C_{19}H_{14}{}^{35}Cl_2NO$, $[M + H]^+$, found 342.04349 (−5.1 ppm, −1.8 mmu). Anal. Calcd for $C_{19}H_{13}Cl_2NO$: C, 66.68; H, 3.83; N, 4.09. Found: C, 66.58; H, 3.84; N, 4.06. Mp: 173.2−175.6 °C. X-ray structure obtained; thermal ellipsoid plot is in the Supporting Information.

(2*RS*,3*SR*)-3-(2,6-Difluorophenyl)-3-hydroxy-2-(2-naphthyl)-propanenitrile (*syn*-9). Reaction of 2-naphthylacetonitrile (0.334 g, 2 mmol) and 2,6-difluorobenzaldehyde (0.256 mL, 2 mmol) was performed as above. The initial ratio of *anti*:*syn*-diastereomers was 1.1:1. The *syn*-diastereomer (0.167 g, 29.9%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:3). The crystals were obtained from CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$): 2.71 (d, J = 7.1 Hz, 1H), 4.53 (d, J = 8.8 Hz, 1H), 5.44 (t, J = 8.0 Hz, 1H), 6.91−7.90 (m, 10H). ^{13}C NMR ($CDCl_3$): 44.4, 68.8, 112.15, 112.18, 112.32, 112.35, 118.2, 125.6, 127.00, 127.02, 127.89, 128.08, 128.36, 129.35, 129.65, 131.1, 133.3, 160.2, 162.1. HRMS (FAB): 310.10434 calcd for $C_{19}H_{14}F_2NO$, $[M + H]^+$, found 310.10535 (+3.0 ppm, +0.9). Mp: 156.7−157.9 °C. X-ray structure obtained; thermal ellipsoid plot is in the Supporting Information.

(2*RS*,3*RS*)-3-(2,6-Difluorophenyl)-3-hydroxy-2-(2-naphthyl)-propanenitrile (*anti*-9). Data on *anti*-**9** were deduced by inspection of an anti:syn mixture (1:1.8) of **9**, obtained during isolation of *syn*-**9**. ^{1}H NMR ($CDCl_3$): 3.23 (d, J = 7.8, 1H), 4.50 (d, J = 8.8 Hz, 1H), 5.49 (t, J = 8.2 Hz, 1H), 6.73−7.90 (m, 10H). ^{13}C NMR ($CDCl_3$): 45.0, 69.0, 111.87, 111.90, 112.03, 112.06, 119.4, 125.1, 126.78, 126.84, 127.78, 128.02, 129.03, 129.12, 130.8, 133.1, 160.1, 162.1. HRMS (FAB): 310.10434 calcd for $C_{19}H_{14}F_2NO$, $[M + H]^+$, found 310.10434 (−0.1 ppm, +0.0 mmu).

(2*RS*,3*RS*)-3-(2,6-Dibromophenyl)-3-hydroxy-2-(2-naphthyl)-propanenitrile (*anti*-12). Reaction of 2-naphthylacetonitrile (0.0671 g, 0.4 mmol) and 2,6-dibromobenzaldehyde[42] (0.1061 g, 0.4 mmol) was performed as above. The ratio of anti:syn diastereomers was 4:3. The *anti*-diastereomer (0.034 g, 13.6%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:9). Relative stereochemistry of *anti*- and *syn*-**12** was assigned on the basis of the ^{13}C NMR chemical shifts of the cyano carbons (see Results and Discussion). ^{1}H NMR ($CDCl_3$): 3.49 (d, J = 8.8 Hz, 1H), 5.10 (d, J = 10.0 Hz, 1H), 5.90 (dd, J = 9.0, 10.0 Hz, 1H), 6.86−7.75 (m, 10H). ^{13}C NMR ($CDCl_3$): 43.3, 76.9, 119.7, 125.62, 126.65, 126.75, 127.75, 128.01, 128.12, 128.60, 130.1, 130.9, 133.01, 133.04, 133.7 (br), 135.1. HRMS (FAB): 429.944211 calcd for $C_{19}H_{14}{}^{79}Br_2NO$, $[M + H]^+$, found 429.94525 (+2.3 ppm, +1.0 mmu).

(2*RS*,3*SR*)-3-(2,6-Dibromophenyl)-3-hydroxy-2-(2-naphthyl)-propanenitrile (*syn*-12). The *syn*-diastereomer (0.0235 g, 9.4%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:9). ^{1}H NMR

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($CDCl_3$): 2.85 (d, J = 8.0 Hz, 1H), 4.98 (d, J = 9.2 Hz, 1H), 5.88 (dd, J = 8.2, 9.8 Hz, 1H), 7.07−7.95 (m, 10H). ^{13}C NMR ($CDCl_3$): 42.1, 77.1, 118.0, 125.7, 127.0, 127.9, 128.1, 128.4, 129.4, 130.3, 131.3, 133.35, 133.39, 133.7, 134.8 (br), 135.9. HRMS (FAB): 429.944211 calcd for $C_{19}H_{14}{}^{79}Br_2NO$, $[M + H]^+$, found 429.94119 (−7.0 ppm, −3.0 mmu).

(2*RS*,3*RS*)-3-(2,6-Diethylphenyl)-3-hydroxy-2-(2-naphthyl)-propanenitrile (*anti*-13). 2,6-Diethylbenzaldehyde was synthesized from 1-bromo-2,6-diethylbenzaldehyde by lithium/bromine exchange and trapping with DMF;[43] the material obtained in this way was identical to the literature.[44] Reaction of 2-naphthylacetonitrile (0.1019 g, 0.6 mmol), 2,6-diethylbenzaldehyde (0.0976 g, 0.6 mmol), and borontrifluoride etherate (0.076 mL, 0.6 mmol) was performed as above. The ratio of *anti*:*syn*-diastereomers was 3:1. The *anti*-diastereomer (0.0451 g, 22.8%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl dichloromethane/hexane (1:1). Relative stereochemistry of *anti*- and *syn*-**13** was assigned on the basis of the ^{13}C NMR chemical shifts of the cyano carbons (see Results and Discussion). ^{1}H NMR ($CDCl_3$): 1.06 (br, 6H), 2.45 (br, 4H), 2.69 (d, J = 3.6 Hz, 1H), 4.55 (d, J = 9.6 Hz, 1H), 5.42 (dd, J = 3.6, 10.0 Hz, 1H), 6.91−7.73 (m, 10H). ^{13}C NMR ($CDCl_3$): 16.2 (br), 26.3, 45.7, 73.2, 120.2, 125.6, 126.63, 126.68, 127.68, 127.77, 127.89, 127.99, 128.4, 128.9, 129.5, 132.84, 132.97, 133.20, 143.4. HRMS (FAB): 312.175224 calcd for $C_{23}H_{22}N$, $[M - OH]^+$, found 312.17487 (−1.1 ppm, −0.4 mmu).

(2*RS*,3*SR*)-3-(2,6-Diethylphenyl)-3-hydroxy-2-(2-naphthyl)-propanenitrile (*syn*-13). The *syn*-diastereomer (0. 0115 g, 5.8%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl dichloromethane/hexane (1:1). ^{1}H NMR ($CDCl_3$): 1.29 (br, 6H), 2.01 (d, J = 3.2 Hz, 1H), 2.79−3.05 (br, 4H), 4.49 (d, J = 9.6 Hz, 1H), 5.50 (dd, J = 3.2, 10.0 Hz, 1H), 7.10−7.94 (m, 10H). ^{13}C NMR ($CDCl_3$): 16.1, 17.0, 26.2, 27.5, 44.7, 73.2, 118.9, 125.6, 126.84, 126.95, 127.02, 127.92, 128.08, 129.13, 129.32, 129.42, 131.2, 133.28, 133.41, 133.8, 142.7, 143.9. HRMS (FAB): 312.175224 calcd for $C_{23}H_{22}N$, $[M - OH]^+$, found 312.17490 (−1.1 ppm, −0.3 mmu).

(2*RS*,3*RS*)-3-Hydroxy-4,4-dimethyl-2-(2,4,6-trimethylphenyl)-pentanenitrile (*anti*-14). Reaction of mesitylacetonitrile (0.318 g, 2 mmol) and pivaldehyde (0.175 g, 2 mmol) was performed as above. The ratio of *anti*:*syn*-diastereomers was 35:1. The *anti*-diastereomer (0.424 g, 88%) was isolated from the crude product by recrystallization from CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$): 1.05 (s, 9H), 2.12 (d, J = 5.9 Hz, 1H), 2.26 (s, 3H), 2.50 (br, 6H), 3.60 (t, J = 4.6 Hz, 1H), 4.35 (d, J = 3.9 Hz, 1H), 6.88 (s, 2H). ^{13}C NMR ($CDCl_3$): 20.7, 21.3, 26.1, 34.7, 36.4, 80.0, 119.6, 128.6, 131 (br), 137.7. MS ($CI^+(NH_3)$): 263.21 calcd for $C_{16}H_{27}N_2O$, $[M + NH_4]^+$, found 263.3. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.37; H, 9.51; N, 5.72. Mp: 97.1−99.6 °C. X-ray structure obtained; thermal ellipsoid plot is in the Supporting Information.

General Procedure for Synthesis of Ketone Aldols. The 2,2-dimethyl-3-pentanone was obtained by the chromic acid oxidation of 2,2-dimethyl-pentan-3-ol (2.4 mL, 17 mmol).[45] An oven-dried 50 mL round-bottom flask equipped with stirring bar and septum was charged with fresh THF (10 mL), and cooled to −78 °C. The LDA (1.5 M, 0.7 mL, 1.05 mmol) was added via syringe, followed by 2,2-dimethyl-3-pentanone (1 mmol). The mixture was stirred at −78 °C for 30 min. Aldehyde (1 mmol) was added into the mixture. If mesitaldehyde was used, boron trifluoride etherate (1 mmol) was added. After 4 h at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl and allowed to warm to room temperature. The 5 mL of 1 N HCl was poured into the reaction mixture and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give the crude product.

(2*RS*,3*SR*)-5-Hydroxy-2,2,4-trimethyl-5-(2,4,6-trimethylphenyl)pentan-3-one (*anti*-10). Reaction of 2,2-dimethyl-3-pentan-3-one (0.117 g, 1 mmol), mesitaldehyde (0.145 mL, 1 mmol), and borontrifluoride etherate (0.125 mL, 1 mmol) was performed as above. The initial ratio of *anti*:*syn*-diastereomers was 1:1.25. The *anti*-diastereomer (26.5 mg, 10.0%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:10). The crystals were obtained from CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$): 0.78 (d, J = 6.9 Hz, 3H), 1.22 (s, 9H), 2.24 (s, 3H), 2.29−2.62 (br, 6H), 3.78 (dq, J = 10.2, 7.0, 1H), 5.40 (d, J = 10.3 Hz, 1H), 6.83 (s, 2H). ^{13}C NMR ($CDCl_3$): 15.8, 20.9, 26.4, 44.5, 45.0, 73.3, 129.4, 132.8, 134.4, 137.1, 220.2. HRMS (FAB): 245.19054 calcd for $C_{17}H_{25}$, $[M - OH]^+$, found 245.18999 (−2.2 ppm, −0.5 mmu). Mp: 106.0−106.8 °C. X-ray structure obtained; thermal ellipsoid plot is in the Supporting Information.

(2*RS*,3*SR*)-5-Hydroxy-2,2,4-trimethyl-5-(2,4,6-trimethylphenyl)pentan-3-one (*syn*-10). The *syn*-diastereomer (31.3 mg, 11.6%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:10). ^{1}H NMR ($CDCl_3$): 0.83 (s, 9H), 1.27 (d, J = 6.9 Hz, 3H), 2.20 (s, 3H), 2.40 (s, 6H), 3.68 (dq, J = 8.9, 6.8 Hz, 1H), 5.22 (d, J = 9.2 Hz, 1H), 6.75 (s, 1H). ^{13}C NMR ($CDCl_3$): 16.3, 20.81, 20.94, 25.9, 44.78, 44.83, 72.4, 130.3, 135.3, 136.7, 137.0, 218.8. HRMS (FAB): 245.19054 calcd for $C_{17}H_{25}$, $[M - OH]^+$, found 245.18940 (−4.6 ppm, −0.1 mmu). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.56; H, 9.98.

(2*RS*,3*SR*)-5-(2,6-Dichlorophenyl)-5-hydroxy-2,2,4-trimethylpentan-3-one (*anti*-11). Reaction of 2,2-dimethyl-3-pentan-3-one (0.340 g, 2.9 mmol) and 2,6-dichlorobenzaldehyde (0.825 g, 3.6 mmol) was performed as above. The initial ratio of *anti*:*syn*-diastereomers was 1:5. The *anti*-diastereomer (93.2 mg, 10.8%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:8). The crystals were obtained from CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$): 0.82 (d, J = 7.2, 3H), 1.16 (s, 9H), 2.67 (d, J = 8.4 Hz, 1H), 4.05 (dq, J = 10.3, 7.1 Hz, 1H), 5.74 (dd, J = 8.0 Hz, 9.6 Hz, 1H), 7.11−7.36 (m, 3H). ^{13}C NMR ($CDCl_3$): 15.6, 26.2, 43.6, 45.0, 76.9, 129.4, 136.0, 218.3. HRMS (FAB): 289.07621 calcd for $C_{14}H_{19}{}^{35}Cl_2O_2$, $[M + H]^+$, found 289.07760 (+4.8 ppm, +1.4 mmu). Mp: 119.3−123.2 °C. X-ray structure obtained; thermal ellipsoid plot is in the Supporting Information.

(2*RS*,3*SR*)-5-(2,6-Dichlorophenyl)-5-hydroxy-2,2,4-trimethylpentan-3-one (*syn*-11). The *syn*-diastereomer (0.475 g, 55.1%) was isolated from a mixture of *anti*- and *syn*-aldols by column chromatography with ethyl acetate/hexane (1:8). The crystals were obtained from CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$): 0.86 (s, 9H), 1.30 (d, J = 6.8, 3H), 2.84 (d, J = 9.2 Hz, 1H), 4.00 (dq, J = 9.6, 6.8 Hz, 1H), 5.51 (t, J = 9.2 Hz, 1H), 7.06−7.25 (m, 3H). ^{13}C NMR ($CDCl_3$): 16.6, 25.8, 44.56, 44.78, 73.1, 129.40, 129.52, 135.1, 136.7, 217.0. HRMS (FAB): 289.07621 calcd for $C_{14}H_{19}{}^{35}Cl_2O_2$, $[M + H]^+$, found 289.0767 (+1.7 ppm, +0.5 mmu). Anal. Calcd for $C_{14}H_{18}Cl_2O_2$: C, 58.14; H, 6.27. Found: C, 58.21; H, 6.42. Mp: 64.0−67.0 °C. X-ray structure obtained; thermal ellipsoid plot is in the Supporting Information.

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Supporting Information Available: Experimental procedures, characterization data, thermal ellipsoid plots, NOESY spectrum of *anti*-**10**, CSD search results, and a summary of the conformational searches. This material is available free of charge via the Internet at http://pubs.acs.org.

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