An NMR Method for Assigning Relative Stereochemistry to β-Hydroxy Ketones Deriving from Aldol Reactions of Methyl Ketones

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We describe a simple ^{1}H NMR analysis that permits the stereochemistry of β-hydroxy ketones to be assigned by visual inspection of the ABX patterns for the α-methylene unit of the β-hydroxy ketone in the ^{1}H NMR spectra. This method has been verified by application to a wide range of β-hydroxy ketones deriving from aldol reactions of chiral aldehydes with a variety of chiral and achiral methyl ketone enolates (see Tables 1 and 2). The stereochemistry of 54 of these compounds have been assigned by rigorous chemical methods.

The assignment of relative stereochemistry of conformationally flexible acyclic molecules remains a challenging problem in organic chemistry. NMR methods have been used extensively for these purposes, based on the recognition that the viscinal ^{1}H−^{1}H constants for protons on adjacent stereogenic centers typically fall in the range $J_{anti} > J_{syn}$.[3] However, the *J* analysis is not necessarily straightforward for molecules with three or more contiguous stereocenters (owing to the need to minimize gauche pentane interactions),[4] molecules with vicinal heteroatom substituents that prefer to adopt gauche relationships,[5,6] and molecules with functional groups that can participate in hydrogen-bonding networks.[7] These structural features may lead to perturbations of the conformational equilibrium distribution of the structure in question, and the $J_{anti} > J_{syn}$ "rule" may be violated in such cases. These issues have prompted several groups to develop empirical ^{13}C NMR methods for assignment of stereochemistry to α-substituted-β-hydroxy ketones,[8,9] 1,3-diol derivatives,[10] and secondary alcohols,[11] as well as the development of universal NMR databases for stereochemical assignment of structures with three or more stereocenters.[12,13] Alternative methods of stereochemical assignment involve conversion of the compound in question (or a segment of a compound) to a cyclic derivative for NMR stereochemical analysis.[14−18]

During the course of our studies of the fragment assembly aldol reactions of chiral aldehydes and methyl ketones, we faced the continual problem of assigning the stereochemistry of the newly introduced β-hydroxy group in the aldol products.[19−24] The stereochemistries of a significant number of the aldols generated in this study were assigned by ^{1}H NMR analysis of acetals prepared by appropriate chemical conversions of the aldol products. For example, aldols **3** and **4**, which derived from the aldol reaction of chiral methyl ketone **1** and chiral aldehyde **2**, were assigned following conversion to the corresponding *p*-methoxybenzylidene acetals **5** and **6** by DDQ oxidation of the PMB ethers.[25] In other cases where the chiral aldehyde contained a methoxymethyl (MOM) ether protectecting group for the β-alkoxy substituent, stereochemistry was assigned following conversion of the aldol products to the corresponding methylene acetals upon treatment with Me_2BBr and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (cf. **7** to **8**).[26] In still other cases (e.g., **9** to **11**),[23] silyl ether protecting groups were removed from

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Table 1. Selected ^{1}H NMR Data for 3,4-Syn (Felkin) Methyl Ketone Aldol Diastereomers[a]

compd	H_a (δ)	H_b (δ)	H_x (δ)	$J_{a,x}$ (Hz)	$J_{b,x}$ (Hz)	assgnt method[b]	lit. refs
3	2.66	2.46	4.47	8.4	4.3	A	19, 27
7	2.80	2.39	4.50	9.3	3.4	B	22, 28
9	2.72	2.39	4.55	9.3	3.5	D	23, 29
12a	2.77	2.40	4.54	9.0	3.5	B	28
12b	2.69	2.49	4.49	8.3	4.7	A	19, 27
13	2.68	2.57	4.50	6.8	5.6		27
14a	2.73	2.44	4.48	8.3	4.3		20, 27
14b	2.69	2.47	4.46	8.1	4.6	C	20, 27
14c	2.70	2.46	4.46	8.0	4.7	C	20, 27
15a	2.76	2.45	4.45	8.6	4.1		19, 27
15b	2.75	2.49	4.48	8.6	4.0	A	19, 27
15c	2.79	2.56	4.53	8.6	4.0	A	20, 27
16	2.67	2.46	4.48	8.0	4.8		27
17	2.71	2.46	4.44	8.4	4.2	A	27
18	2.69	2.40	4.56	8.7	3.8		30
19	2.77	2.55	4.56	8.1	4.2	C	31
20	2.80	2.52	4.57	8.4	4.4	*d*	31
21a	2.64	2.46	4.22	9.4	4.7	*c*	21, 32
21b	2.68	2.58	4.16	*e*	*e*	*c*	21, 32
22	2.62	2.52	4.56	*e*	*e*		33
23	2.71	2.45	4.54	9.1	4.9		33
24	2.68	2.52	4.53	9.1	4.4		33
25	2.75	2.52	4.55	7.8	5.4		33
26	2.82	2.36	4.57	9.0	2.3		33
27	2.71	2.22	4.26	9.3	3.4		33
28a	2.79	2.22	4.53	9.2	1.1	C	21, 32
28b	2.76	2.30	4.61	9.1	2.0	C	21, 32
28c[f]	2.87	2.32	4.57	9.7	2.5	B	21, 32
28d[f]	2.80	2.43	4.70	*e*	2.9	B	21, 32
28e	2.76	2.29	4.62	8.8	2.7	*c*	21, 34
28f	2.76	2.39	4.50	9.7	2.2		21, 34
28g	2.79	2.47	4.53	9.7	3.0		21, 34
29	2.82	2.36	4.55	9.8	2.3	C	33
30a	2.68	2.21	4.63	8.6	3.5		21, 32
30b	2.68	2.20	4.63	8.7	3.7	*c*	21, 32
30c	2.75	2.32	4.53	9.4	3.1	B	21, 32
31a	2.74	2.29	4.61	7.8	4.8		34
31b	2.79	2.38	4.51	9.1	3.2	B	34
32	2.77	2.36	4.53	10.0	3.1	B	22, 28
33a	2.67	2.24	4.31	9.3	3.4	B	22, 28
33b	2.78	2.46	4.46	8.3	4.4	A	22, 28
33c	2.81	2.41	4.49	9.3	3.7		22, 28
34a	2.75	2.37	4.49	10.0	4.0	*c*	28
34b	2.74	2.43	4.48	9.3	2.9	B	28
35a	2.77	2.38	4.48	9.9	2.8		23, 29
35b	2.72	2.45	4.48	9.2	3.5		23, 29
36	2.67	2.35	4.50	9.2	3.3		23, 29

[a] All NMR data are for spectra measured in $CDCl_3$ unless noted otherwise. [b] The relative stereochemistry of the β-hydroxy group was assigned by conversion of the aldol into the corresponding (A) *p*-methoxybenzylidene acetal (cf. **3** → **5**), (B) methylene acetal (cf. **7** → **8**), (C) hemiketal (cf. **9** → **10**), or (D) acetonide derivative (**9** → **11**). If no assignment method is indicated, the stereochemistry of the aldol was assigned by application of the ABX NMR method described in this paper. [c] The stereochemistry in this case was assigned by process of elimination, since the corresponding 3,4-anti (anti-Felkin) aldol diastereomer was rigorously assigned (see Table 2). [d] The stereochemistry of **20** was confirmed by elaboration to synthetic (−)-bafilomycin A_1 (see ref 24). [e] Coupling constants could not be measured due to overlap with other resonances in the ^{1}H NMR spectrum. [f] ^{1}H NMR spectra of **28c,d** were measured in C_6D_6.

Table 2. Selected ^{1}H NMR Data for 3,4-Anti (Anti-Felkin) Methyl Ketone Aldol Diastereomers[a]

compd	H_a (δ)	H_b (δ)	H_x (δ)	$J_{a,x}$ (Hz)	$J_{b,x}$ (Hz)	assgnt method[b]	lit. refs
4	2.68	2.55	4.21	2.3	9.6	A	27
37a	2.76	2.53	4.25	2.0	9.5	B	28
37b	2.69	2.56	4.23	2.5	9.5	A	19, 27
38	2.77	2.55	4.15	2.0	9.4		27
39a	2.75	2.54	4.23	2.3	9.7		20, 27
39b	2.74	2.52	4.22	2.3	9.6	*c*	20, 27
39c	2.75	2.52	4.22	2.3	9.7	*c*	20, 27
39a	2.79	2.56	4.32	2.0	9.7		19, 27
40b	2.73	2.62	4.29	2.1	9.7	A	19, 27
40c	2.76	2.65	4.27	2.2	9.4	*c*	20, 27
41	2.69	2.50	4.06	2.4	9.4		27
42	2.70	2.54	4.22	2.4	9.2	*c*	27
43	2.71	2.54	4.27	1.8	9.8		30
44a	2.75	2.48	4.09	2.2	9.4	C	21, 32
44b	2.65	2.52	4.40	*e*	*e*	B	21, 32
45	2.74	2.52	4.11	*e*	*e*		33
46	2.66	2.52	4.09	2.3	*e*		33
47	2.71	2.53	4.07	2.4	9.5		33
48	2.64	2.53	4.07	2.2	9.2	C	33
49	2.79	2.64	4.05	*e*	*e*		33
50a	2.79	2.54	4.04	2.0	9.4	C	21, 32
50b	2.75	2.57	4.08	2.0	9.4	*c*	21, 32
50c[f]	2.72	2.16	4.39	*e*	*e*	*c*	21, 32
50d[f]	2.75	2.16	4.39	*e*	*e*	*c*	21, 32
50e	2.79	2.55	4.04	1.9	9.7	d	21, 34
50f	2.72	2.56	4.07	2.1	9.7		21, 34
51a	2.76	2.49	4.07	1.9	9.7		21, 32
51b	2.76	2.47	4.17	2.0	9.9	C	21, 32
51c	2.71	2.52	4.18	2.2	9.7	*c*	21, 32
52a	2.84	2.50	4.08	1.9	9.7		34
52b	2.77	2.55	4.19	1.8	9.9	*c*	34
53	2.70	2.52	4.18	2.2	9.9	B	22, 28
54a	2.72	2.57	4.10	2.2	9.8	*c*	22, 28
54b	2.73	2.57	4.07	*e*	10.0	A	22, 28
54c	2.74	2.58	4.15	*e*	12.5		22, 28
54d	2.70	2.57	4.14	2.0	10.0	B	22, 28
55a	2.70	2.60	4.17	1.5	9.5	B	28
55b	2.71	2.62	4.07	2.8	9.2	*c*	28
56a	2.72	2.53	4.13	2.2	9.2		23, 29
56b	2.68	2.54	4.1	*e*	*e*		23, 29
56c	2.61	2.51	4.14	E	9.3	*c*	23, 29

[a] All NMR data are for spectra measured in $CDCl_3$ unless noted otherwise. [b] See footnotes to Table 1. [c] The stereochemistry in this case was assigned by process of elimination, since the corresponding 3,4-syn (Felkin) aldol isomer was rigorously assigned (see Table 1). [d] The stereochemistry of **50e** was assigned by conversion to the corresponding spiroketal, following removal of the TES (R_1) and PMB (R_3) protecting groups. [e] Coupling constants could not be measured due to overlap with other resonances in the ^{1}H NMR spectrum. [f] ^{1}H NMR spectra of **50c,d** were measured in C_6D_6.

the δ-alkoxy group of the aldol products, and the resulting hemiacetal (**10** in this example) was subjected to NMR analysis or was converted to the corresponding acetonide for ^{13}C NMR analysis according to Rychnovsky's method.[14,16−18]

After accumulating a considerable amount of data on fragment assembly methyl ketone aldol reactions, we noticed a striking correlation between the rigorously assigned aldol stereochemistry and the ^{1}H NMR ABX pattern for the three spin system consisting of the α-methylene unit between the ketone and the methine of the β-hydroxyl bearing carbon. Selected ^{1}H NMR data for 47 methyl ketone aldols with 3,4-syn (or Felkin; see **A**) stereochemistry are summarized in Table 1, while data for 41 aldols with 3,4-anti (or anti-Felkin; see **B**) stereochemistry are provided in Table 2. The stereochemistry of 23 of the compounds in Table 1 and 14 of the compounds in Table 2 were assigned by rigorous chemical

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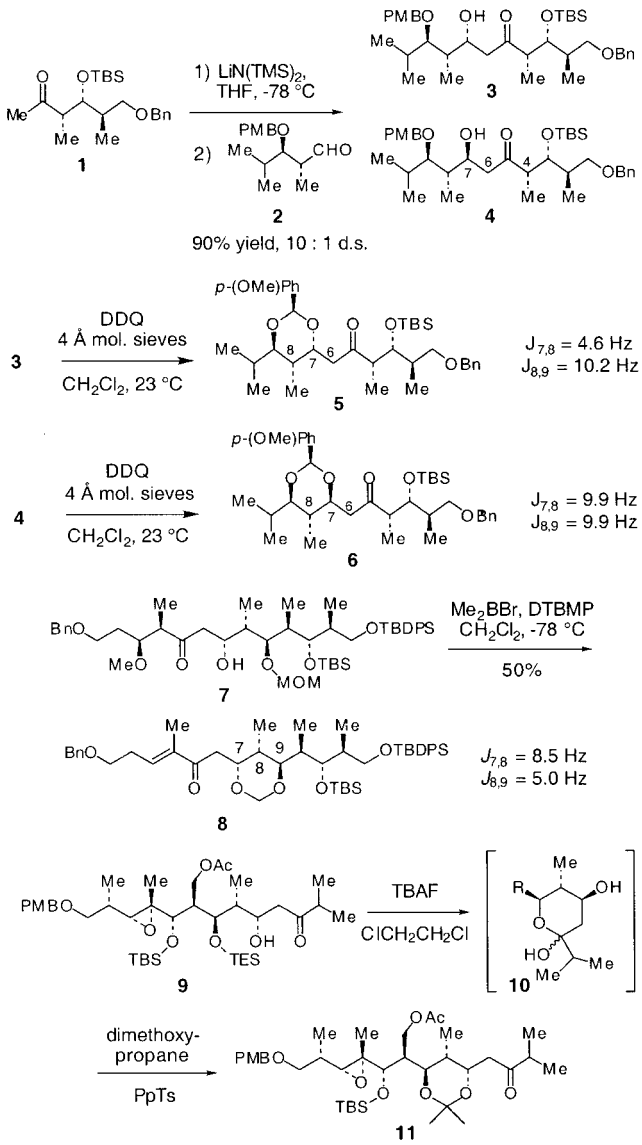
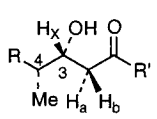
methods. The stereochemistry of another 5 of the compounds in Table 1 and an additional 12 entries in Table 2 can be assigned with certainty, since the corresponding aldol diastereomers were rigorously assigned by chemical means (see footnote *c* to Tables 1 and 2).



In all 63 of these rigorously assigned cases, the ^{1}H NMR spectra (measured in $CDCl_3$ or C_6D_6) of aldols with 3,4-syn (or Felkin) stereochemistry as in **A** exhibit a characteristic doublet of doublet for H_a with a large $J_{a,x}$ downfield of the resonance for H_b which displays a small $J_{b,x}$ coupling constant (see Table 1). However, in the NMR spectra ($CDCl_3$ or C_6D_6) of the anti-Felkin aldols **B** (with 3,4-anti stereochemistry), the downfield resonance H_a has the smaller $J_{a,x}$ coupling constant, and the higher field resonance for H_b has the larger coupling constant for $J_{b,x}$ (see Table 2). These coupling constants are consistent with the aldols adopting the internally hydrogen bound conformations indicated below.[8] The stereochemistry of all other compounds in Tables 1 and 2 were assigned by application of the ABX NMR analysis that is the subject of this paper.

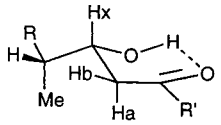
3,4-*syn* β-hydroxy ketones, or Felkin aldols



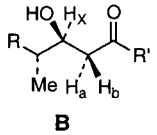
H_a, δ 2.64-2.88
H_b, δ 2.20-2.52
H_x, δ 4.26-4.80

$J_{a,x}$ = 7.8-10.0 Hz
$J_{b,x}$ = 1.1-5.4 Hz

A



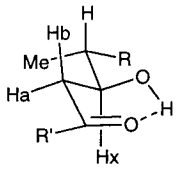
3,4-*anti* β-hydroxy ketones, or "anti-Felkin" aldols



H_a, δ 2.58-2.84
H_b, δ 2.16-2.65
H_x, δ 4.02-4.40

$J_{a,x}$ = 1.5-2.8 Hz
$J_{b,x}$ = 9.2-12.5 Hz

B



Portions of the ^{1}H NMR spectra of aldol diastereomers **25** and **47** which illustrate the appearance of the H_a and H_b resonances of the 3,4-syn and 3,4-anti *β*-hydroxy ketones are provided in Figures 1 and 2. H_b of the anti-Felkin diastereomers **B** typically appears downfield from H_b of the Felkin diastereomer **A**, while H_a of the Felkin aldols **A** typically appears downfield of the corresponding signal in the anti-Felkin diastereomer **B**. In the vast majority of cases, these differences in chemical shift are sufficient to permit NMR integration to be used to quantitate the mixture of diastereomers obtained in the methyl ketone aldol reactions. Characteristic differences also occur in the chemical shifts of H_x, the proton on the hydroxyl-bearing carbon, with the H_x resonance for the Felkin aldols **A** appearing downfield of H_x in the corresponding anti-Felkin diastereomers **B**.

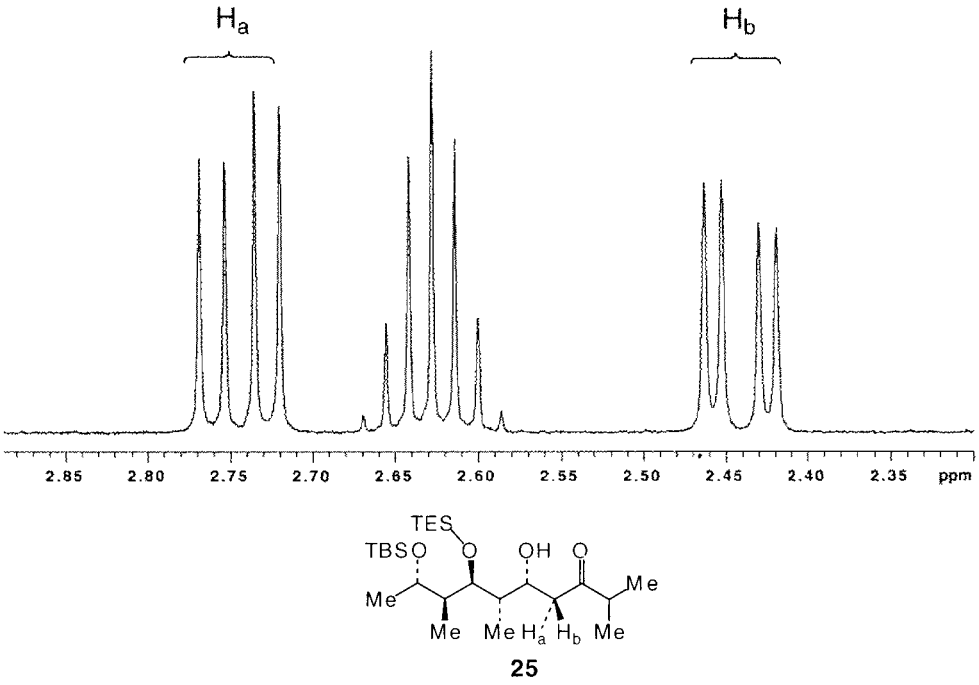
These characteristic ABX patterns are observed in a variety of NMR solvents (see Tables 3 and 4). While the chemical shifts for H_a and H_b vary with the NMR solvent, there are not significant changes in the coupling constants, except for the NMR spectrum of **47** in DMSO-d_6 in which case H_a and H_b collapsed into a single broad resonance. Moreover, the chemical shifts and coupling constants for the H_a and H_b protons in the ^{1}H NMR spectra of **25** and **47** are concentration independent in $CDCl_3$, an observation that is consistent with the hydrogen-bonded conformations **A** and **B** indicated above. The latter conclusion is reinforced by the IR spectra for these compounds measured in CCl_4 at a range of concentrations, which again suggest that these compounds adopt the hydrogen bound conformations indicated in the generalized structures **A** and **B**. Finally, we note that the characteristic ABX pattern for the aldol H_a and H_b resonances changes substantially when the hydroxyl

Table 3. Selected ^{1}H NMR Data for 3,4-Syn (Felkin) Diastereomer 25 in Various NMR Solvents

solvent	H_a (δ)	H_b (δ)	$J_{a,x}$ (Hz)	$J_{b,x}$ (Hz)
$CDCl_3$	2.75	2.46	7.8	4.9
$CDCl_3$−D_2O	2.75	2.46	7.8	4.9
C_6D_6	2.61	2.24	7.8	4.9
DMSO-d_6	2.62	2.48	8.3	4.6
CD_3OD	2.74	2.59	8.1	4.9

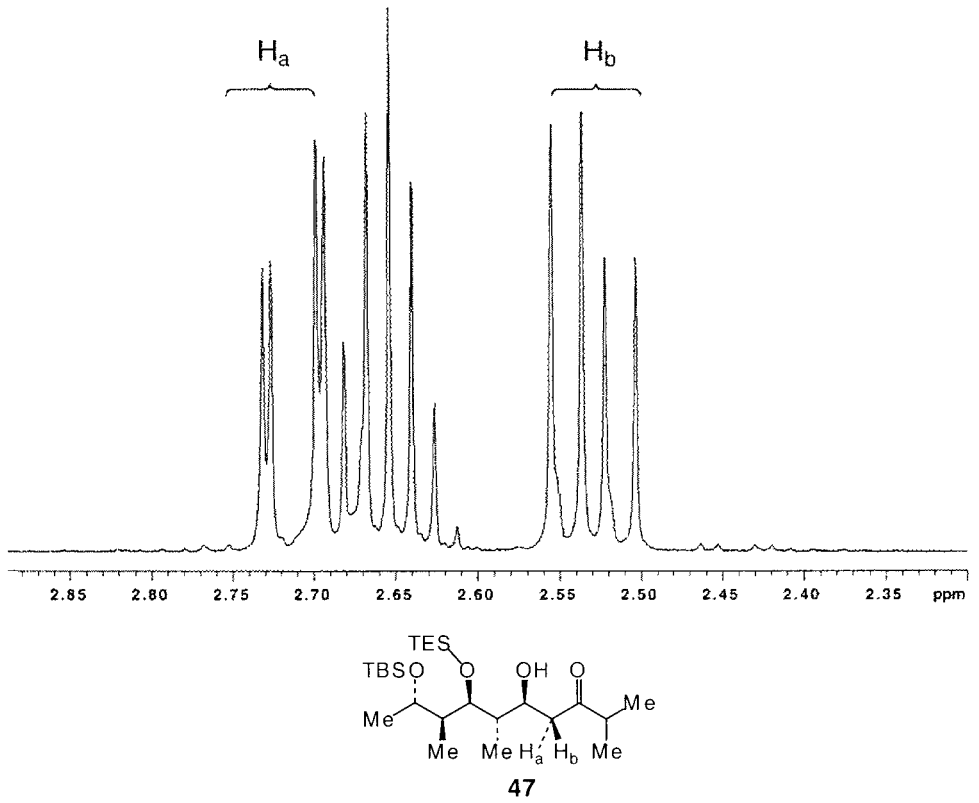
Table 4. Selected ^{1}H NMR Data for 3,4-Anti (Anti-Felkin) Diastereomer 47 in Various NMR Solvents

solvent	H_a (δ)	H_b (δ)	$J_{a,x}$ (Hz)	$J_{b,x}$ (Hz)
$CDCl_3$	2.71	2.53	2.4	9.5
$CDCl_3$−D_2O	2.71	2.53	2.4	9.5
C_6D_6	2.49	2.36	2.4	9.3
DMSO-d_6	2.49	2.49		
CD_3OD	2.72	2.59	2.4	9.8



25

Figure 1. Partial 500 MHz ^{1}H NMR spectrum of **25** (in $CDCl_3$) showing the characteristic patterns for H_a and H_b of 3,4-syn (Felkin) aldol diastereomers.



47

Figure 2. Partial 500 MHz ^{1}H NMR spectrum of **47** (in $CDCl_3$) showing the characteristic patterns for H_a and H_b of 3,4-anti (anti-Felkin) aldol diastereomers.

group is protected or derivatized in any way. This point is amply demonstrated by the NMR data provided in the Supporting Information for the *p*-methoxybenzylidene acetals and methylene acetals of type **5**, **6**, and **8**.

The NMR method for assignment of β-hydroxy ketone stereochemistry is applicable to the products of aldol reactions of chiral aldehydes with both chiral and achiral methyl ketone enolates (cf. **12** vs **3** or **14**). Moreover, this NMR correlation is independent of the chirality of the methyl ketone component (cf. **14** vs **15** and **54** vs **55**), it is independent of the 2,3-stereochemistry of the original chiral aldehyde fragment (cf. **21** vs **30** and **43** vs **51**), and it is also independent of the protecting groups present in these complex structures.

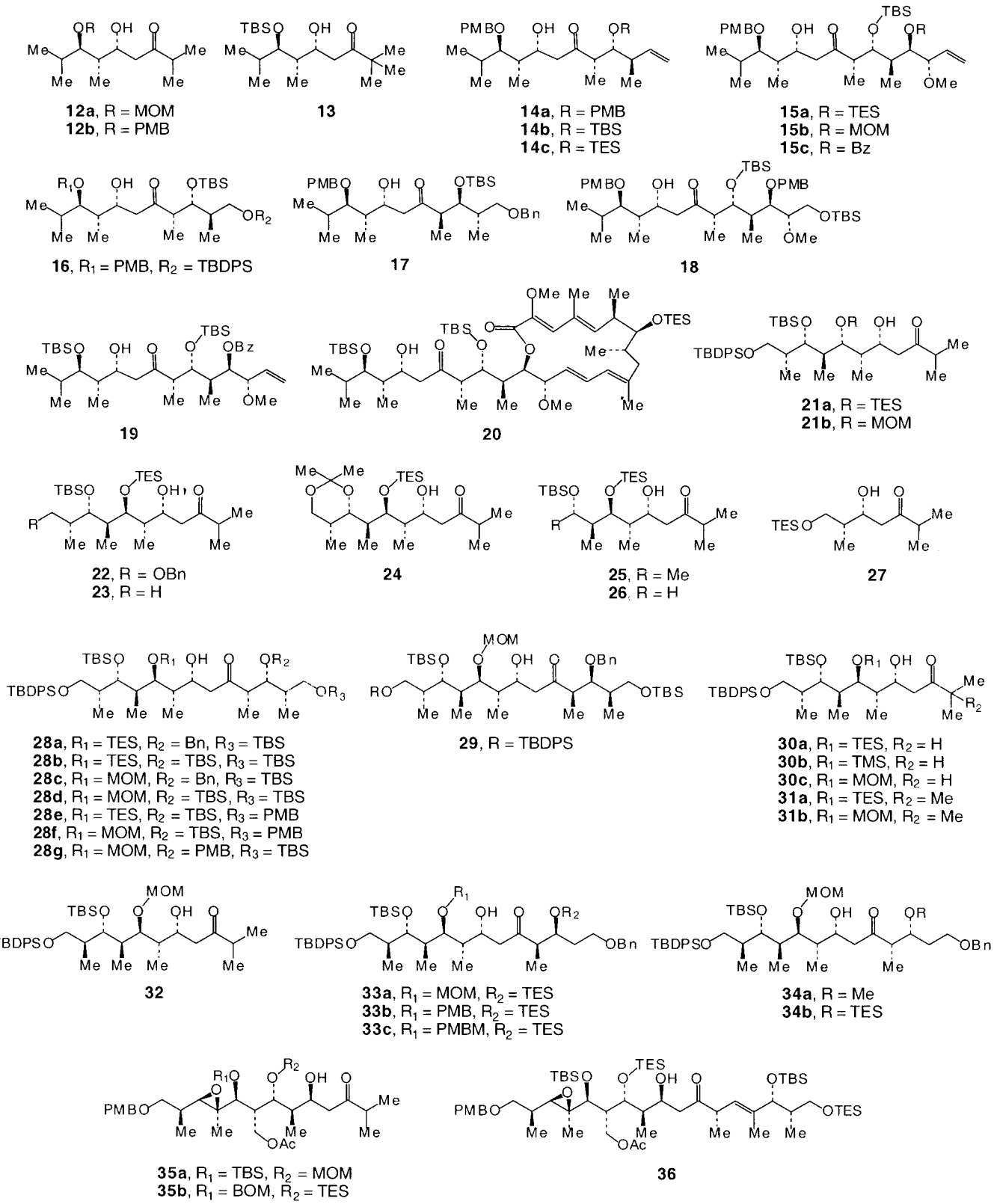


Figure 3. Felkin aldol diastereomer products of methyl ketone aldol reactions.

In summary, this simple NMR analysis permits the stereochemistry of β-hydroxy ketones deriving from methyl ketone aldol reactions to be assigned simply by visual inspection of the ABX patterns for the α-methylene of the β-hydroxy ketone in the ^{1}H NMR spectra. We have demonstrated that this method has considerable generality and believe that it should also be useful for the assignment of stereochemistry to α-unsubstituted, β-hydroxy ketones that derive from other preparative methods or which are found in nature as structural units of natural products. This simple visual analysis for β-hydroxy ketone stereochemistry assignment should also

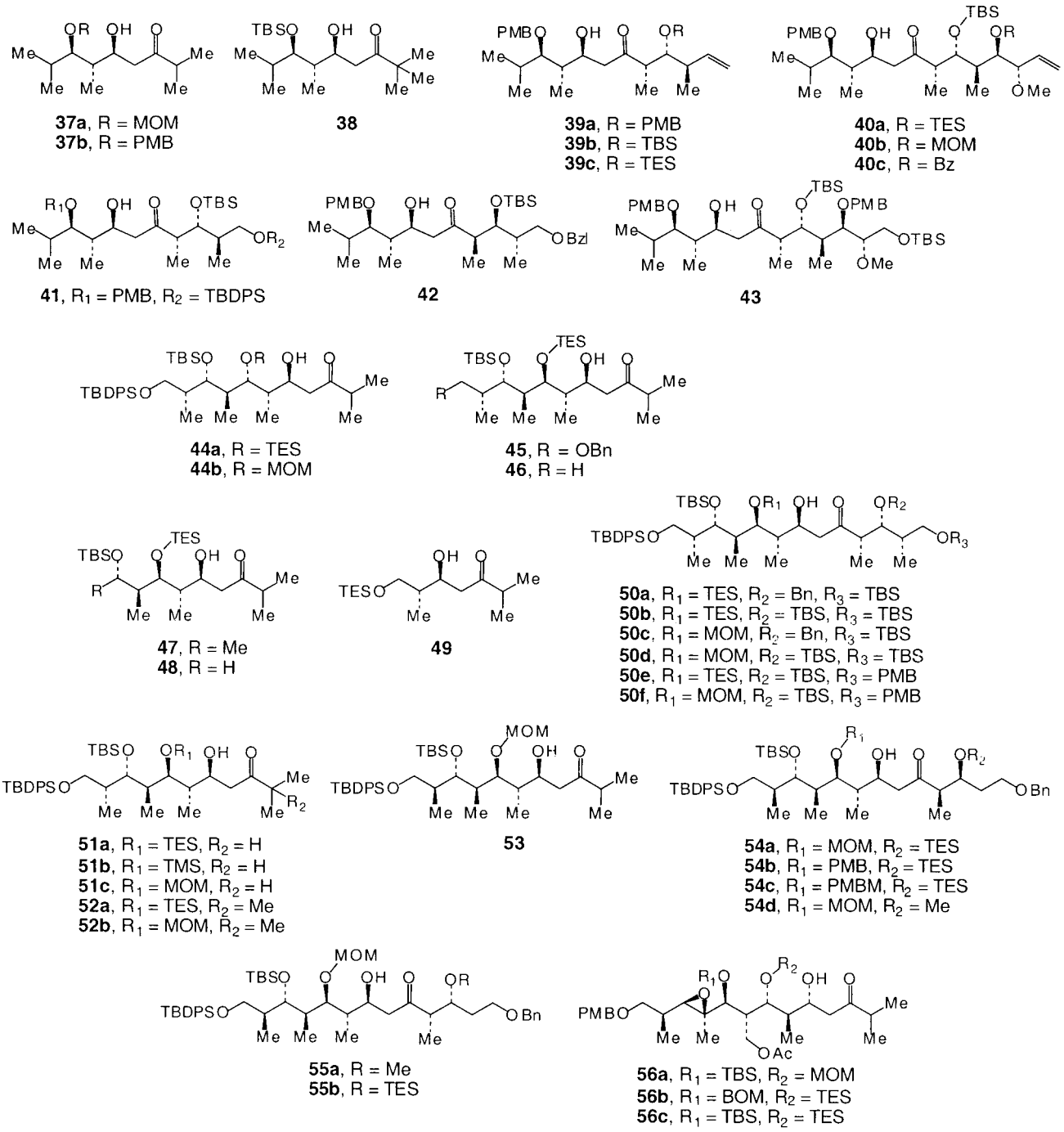


Figure 4. Anti-Felkin aldol diastereomer products of methyl ketone aldol reactions.

prove useful in combination with universal NMR databases for more complex stereochemical problems in natural products chemistry.[12,13]

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Supporting Information Available: Tabulated spectroscopic data and stereochemical assignments for β-hydroxy ketones listed in Tables 3 and 4 and selected ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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