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Observations on the Stereochemistry of Aldol Reaction Products. Crystal and Molecular Structure of *erythro*-4-(Benzoyloxy)-3-*tert*-butyl-4-phenylbutan-2-one

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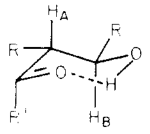
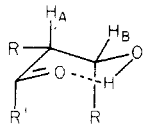
The crystal and molecular structure of the title compound **3a** has been determined from X-ray diffractometer data by direct methods. Crystals are triclinic, space group $P\bar{1}$, with $a = 8.562$ (2) Å, $b = 18.722$ (3) Å, $c = 6.107$ (1) Å, $\alpha = 93.45$ (2)°, $\beta = 110.0$ (1)°, $\gamma = 90.97$ (1)°, and $z = 2$. The structure was refined by full-matrix least-squares methods to $R = 0.071$ for 1906 observed reflections and confirmed that **3a** is the erythro isomer. The stereochemical assignments for the β-hydroxy ketones **1a** and **1b** based on ^{1}H NMR vicinal coupling constants are incorrect and caution is advised in assigning β-hydroxy ketone stereochemistry only on the basis of coupling constants especially in situations where the chiral α-carbon contains a bulky substituent.

The aldol reaction has long been recognized as a potentially valuable method for carbon–carbon bond formation.[1] Recent improvements in synthetic methodology have made this reaction an attractive, high-yield sequence, and subsequent activity has focussed on the stereoselectivity accompanying the carbon–carbon bond formation step. Considerable stereoselectivity has been noted by using various enolates[2] and related[3,4] species, but an inherent problem in these studies is the determination of the relative stereochemistry of the aldol product.

The most quoted method[5] of stereochemical assignment has used the ^{1}H NMR vicinal coupling constants between the protons attached to the adjacent chiral centers with J_{AB} (threo) > J_{AB} (erythro). This analysis is based on hydrogen-bonded structures with chair conformations having the minimum number of substituents R axial. In this arrangement the threo isomer has a diaxial relationship between H_A and H_B which leads to a larger coupling (J_{AB}) than for the erythro isomer where H_A and H_B have an axial-equatorial disposition.

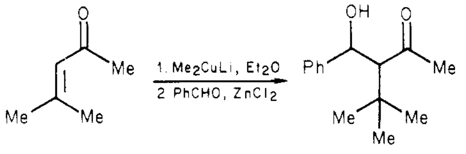


threo



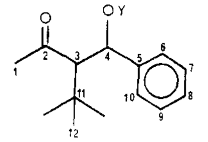
erythro

We have previously reported[6] aldol reactions using the enolates created from organocuprate conjugate additions to α,β-unsaturated ketones and noted the formation of diastereoisomers in some cases. In particular, reaction of mesityl oxide with lithium dimethylcuprate followed by trapping with benzaldehyde in the presence of zinc chloride gave a separable mixture of β-hydroxy ketones **1a** and **1b**.[7]



1a,b

Table I. Selected ^{1}H NMR Resonances for β-Hydroxy Ketones 1a,b and Derivatives



1 Y = H
2 Y = OCOMe
3 Y = OCOPh

compd[a]	δ (H-1)	δ (H-3)	δ (H-4)	$J_{3,4}$, Hz	δ (H-12)
1a	1.56	2.90	4.90	10	1.13
1b	1.84	2.86	5.07	3.5	1.09
2a	1.62	3.17	5.93	10.5	1.09
2b	1.92	3.08	6.03	9.5	0.98
3a	1.57	3.17	6.13	10.5	1.08
3b	1.95	3.03	6.21	6.8	0.93

[a] **a** series, erythro; **b** series, threo.

The stereochemical relationship between **1a** and **1b** was established by oxidation of each diastereoisomer to the same β-diketone.[6] The ^{1}H NMR spectra for **1a** and **1b** (Table I) showed considerably different J_{34} values and **1a** and **1b** were initially assigned[6] as threo (3*RS*,4*SR*)[7] and erythro (3*RS*,4*RS*),[7] respectively, by using the previously mentioned method.[5] However, an alternative synthesis of **1b** has been reported[3] and it has been assigned as threo on the basis of infrared, ^{1}H NMR, and conformational considerations (vide infra). We now report our efforts to resolve this stereochemical dilemma.

Results

Acetylation (Ac$_2$O/py) and benzoylation (PhCOCl/py) of the individual β-ketol diastereoisomers **1a** and **1b** gave

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(1) A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968); H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Menlo Park, CA, 1972, pp 629–682.

(2) J.-E. Dubois and M. Dubois, *Tetrahedron Lett.*, 4215 (1967); J.-E. Dubois and P. Fellman, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **274**, 1307 (1972); J.-E. Dubois and P. Fellman, *Tetrahedron Lett.*, 1225 (1975); C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

(3) E. A. Jeffery, A. Meisters, and T. Mole, *J. Organomet. Chem.*, **74**, 373 (1974).

(4) J. Mulzer, J. Segner, and G. Bruntrup, *Tetrahedron Lett.*, 4651 (1977); A. I. Meyers and P. J. Reider, *J. Am. Chem. Soc.*, **101**, 2501 (1979); S. Masamune, S. Mori, D. Van Horn, and D. W. Brooks, *Tetrahedron Lett.*, 1665 (1979); D. A. Evans, E. Vogel, and J. V. Nelson, *J. Am. Chem. Soc.*, **101**, 6120 (1979).

(5) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).

(6) K. K. Heng and R. A. J. Smith, *Tetrahedron*, **35**, 425 (1979).

(7) All compounds in this paper are racemic although enantiomers are given in structural formulas.

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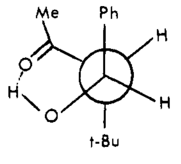
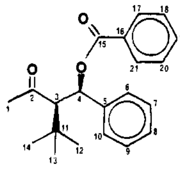
the corresponding acetates **2a** and **2b** and benzoates **3a** and **3b** whose ^{1}H NMR (Table I) showed considerable change in $J_{3,4}$ for the **b** series but little change for the **a** series following esterification. The solid diastereoisomer (**1a**) showed a considerably higher field shift for the H-1 protons compared with those of **1b**, and this relative shielding was retained throughout the **a** series. These results indicate intramolecular hydrogen bonding in **1b** which is removed on esterification, but this feature is not apparent in **1a**. Dilute solution infrared studies supported this premise. A previous stereochemical analysis[3] of **1** had recognized that the most favorable arrangement for intramolecular hydrogen bonding for **1** was in the threo conformer **4** which places the bulky *tert*-butyl and phenyl groups far apart avoiding a gauche interaction. The H–C–C–H dihedral angle (60°) would lead to a small vicinal coupling constant (~3 Hz) similar to the observed value, and hence **1b** was proposed to be threo. Consideration of all possible conformations for the erythro diastereomer indicates that intramolecular hydrogen bonding must be accompanied by an unfavorable gauche interaction between bulky groups.



4 (threo)

X-ray structure analysis of **3a** was carried out and the results are shown in Figure 1. From this structure, **3a** and hence **1a** are unequivocally erythro, in contrast to the assignment based on vicinal coupling constants.[5] The conformation of crystalline **3a** shows a large H_3–C–C–H_4 dihedral angle (177.2°) and the H-1 protons spatially close to the shielding area of the phenyl ring which correlates well with the solution ^{1}H NMR (J_{34} large, H-1 deshielded). This may indicate that **3a** adopts similar solution and solid-state conformations, and extrapolation to a similar conformation for **1a** in solution gives a result that is consistent with the spectral observations.



3a (erythro)

Recently ^{13}C NMR has been proposed[8] as a useful method for assignment of stereostructure of *β*-hydroxycarbonyl compounds; however, direct application to **1a** and **1b** gave incorrect assignments. Reconsideration of possible conformations for **1** with preference for arrangements avoiding gauche interactions of bulky groups (e.g., **4**) gave results compatible with the ^{13}C NMR data (cf. Experimental Section).

Conclusion

These results indicate that *β*-hydroxy ketones with bulky groups on the *α* and *β* chiral carbons may not necessarily always adopt an intramolecularly hydrogen bonded chair conformation. Stereochemical assignments of these types of compounds based on ^{1}H and ^{13}C NMR measurements using the chair conformational scheme could lead to incorrect conclusions and should not be regarded as definitive. In some cases involving *β*-hydroxy ketones similar to **1** (e.g., compounds **4** and **6–8** quoted in ref 6) the assigned stereochemistries should probably be reversed.

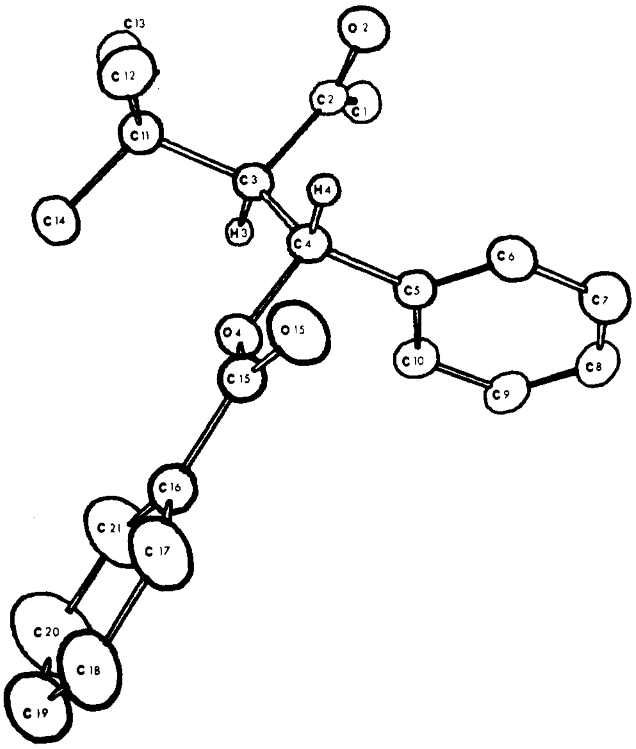


Figure 1. Computer-generated perspective drawing of **3a**.[7,11]

Experimental Section

Melting points were determined on a Reichert apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 357 or 137 spectrophotometer in Nujol mulls.

Proton magnetic resonance spectra were obtained on Varian T-60 and HA-100 spectrometers. Chemical shifts are reported as *δ* values in parts per million relative to tetramethylsilane (*δ* 0.00) as an internal standard. Multiplicities are reported as follows: s, singlet; d, doublet; q, quartet; m, multiplet.

Carbon magnetic resonance spectra were obtained on a JEOL FX-60 FT spectrometer in deuteriochloroform solution. Chemical shifts are given as *δ* values relative to tetramethylsilane (*δ* 0.0) taken as 77.1 ppm upfield from the center of the deuteriochloroform signal. The letter following each peak indicates the appearance under single-frequency proton off-resonance decoupling conditions.

Mass spectra were recorded by using a Varian MAT CH-7 mass spectrometer with an ionizing voltage of 70 eV.

Analytical thin-layer chromatography (TLC) was carried out on Merck TLC aluminum roll silica gel 60 F_{254} strips with a layer thickness of 0.2 mm. Preparative layer chromatography (PLC) was achieved on glass plates (20 × 20 cm) coated with Merck silica gel $PF_{254+366}$ with a layer thickness of 1.25 mm.

Elemental microanalyses were carried out by Professor A. D. Campbell and associates of this department. ***erythro*-3-*tert*-Butyl-4-hydroxy-4-phenylbutan-2-one (1a)** and ***threo*-3-*tert*-butyl-4-hydroxy-4-phenylbutan-2-one (1b)** were available from previous studies.[6]

For **1a**: ^{13}C NMR 29.2 (q, C-12), 34.2 (s, C-11), 34.6 (q, C-1), 67.7 (d, C-3), 75.0 (d, C-4), 127.3 (d, C-6), 127.9 (d, C-8), 128.4 (d, C-7), 143.7 (s, C-5), 211.8 (s, C-2).

For **1b**: ^{13}C NMR 28.9 (q, C-12), 34.1 (s, C-11), 35.7 (q, C-1), 66.5 (d, C-3), 72.7 (d, C-4), 125.3 (d, C-6), 127.1 (d, C-8), 128.2 (d, C-7), 144.1 (s, C-5), 215.6 (s, C-2).

The assignments of C-3 and C-4 were confirmed by specific ^{1}H heteronuclear decoupling.

***erythro*-4-Acetoxy-3-*tert*-butyl-4-phenylbutan-2-one (2a).** A stirred solution of **1a** (96 mg) in dry pyridine (15 mL) was

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(8) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, *J. Org. Chem.*, **44**, 4294 (1979).

Table II. Selected Interatomic Distances[a] (Å) and Bond Angles (deg) for 3a

Distances

C1-C2	1.490 (6)	C11-C12	1.529 (5)
C2-C3	1.535 (5)	C11-C13	1.540 (6)
C3-C4	1.542 (5)	C11-C14	1.537 (5)
C3-C11	1.563 (5)	C15-C16	1.483 (4)
C4-C5	1.516 (4)	C16-C17	1.369 (7)
C5-C6	1.370 (5)	C16-C21	1.343 (6)
C5-C10	1.395 (4)	C17-C18	1.404 (7)
C6-C7	1.392 (6)	C18-C19	1.308 (8)
C7-C8	1.367 (7)	C19-C20	1.345 (10)
C8-C9	1.371 (7)	C20-C21	1.387 (8)
C9-C10	1.386 (6)	C3-H3	1.000 (4)
C2-O2	1.208 (4)	C4-H4	1.000 (4)
C4-O4	1.449 (4)		
C15-O4	1.344 (5)		
C15-O15	1.202 (5)		

Angles

C1-C2-C3	117.6 (3)	C15-C16-C17	118.6 (3)
C2-C3-C4	105.2 (3)	C15-C16-C21	122.7 (4)
C2-C3-C11	111.0 (2)	C17-C16-C21	118.7 (4)
C4-C3-C11	116.8 (3)	C16-C17-C18	119.2 (5)
C3-C4-C5	112.3 (3)	C17-C18-C19	121.9 (6)
C4-C5-C6	120.4 (3)	C18-C19-C20	118.4 (5)
C4-C5-C10	120.5 (3)	C19-C20-C21	121.9 (6)
C6-C5-C10	119.1 (3)	C16-C21-C20	119.7 (6)
C5-C6-C7	120.5 (4)	C4-O4-C15	117.4 (3)
C6-C7-C8	120.2 (4)	O2-C2-C1	121.2 (3)
C7-C8-C9	119.8 (4)	O2-C2-C3	121.2 (3)
C8-C9-C10	120.5 (4)	O4-C4-C3	108.1 (3)
C9-C10-C5	119.8 (4)	O4-C4-C5	108.3 (2)
C3-C11-C12	112.2 (3)	O4-C15-C16	111.9 (3)
C3-C11-C13	108.9 (3)	O4-C15-O15	123.3 (3)
C3-C11-C14	109.5 (3)	O15-C15-C16	124.8 (4)
C12-C11-C13	109.8 (3)		
C12-C11-C14	110.4 (4)		
C13-C11-C14	106.0 (4)		

[a] Shortest intermolecular nonbonded distance not involving hydrogen atoms was O2· · ·C9 3.495 Å.

treated dropwise with acetic anhydride (0.57 mL), and the mixture was stirred at room temperature for 48 h. Dilution with water and ether extraction afforded TLC pure ester **2a** (85 mg) which on crystallization from pentane had the following: mp 75 °C; IR 1745 (OC═O), 1710 (C═O), 1235, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9 H, *t*-Bu), 1.62 (s, 3 H, H-1), 2.00 (s, 3 H, $OCOCH_3$), 3.17 (d, 1 H, J = 10.5 Hz, H-3), 5.93 (d, 1 H, J = 10.5 Hz, H-4), 7.25 (s, 5 H, Ph); ^{1}H NMR (C_6D_6) δ 1.09 (s, 9 H, *t*-Bu), 1.39 (s, 3 H, H-1), 1.63 (s, 3 H, $OCOCH_3$), 3.00 (d, 1 H, J = 11 Hz, H-3), 6.20 (d, 1 H, J = 11 Hz, H-4), 7.20 (s, 5 H, Ph); mass spectrum, m/e 262 (M^+), 105 (base peak).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.45; H, 8.13.

***threo*-4-Acetoxy-3-*tert*-butyl-4-phenylbutan-2-one (2b).** Repetition of the reaction as outlined above for **2a** with **1b** (48 mg) gave TLC pure **2b** (48 mg) which crystallized from hexane: mp 55 °C; IR 1735 (OC═O), 1695 (C═O), 1230, 775, 763, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 9 H, *t*-Bu), 1.92 (s, 3 H, H-1), 2.15 (s, 3 H, $OCOCH_3$), 3.08 (d, 1 H, J = 9.5 Hz, H-3), 6.03 (d, 1 H, J = 9.5 Hz, H-4), 7.30 (s, 5 H, Ph); ^{1}H NMR (C_6D_6) δ 0.75 (s, 9 H, *t*-Bu), 1.52 (s, 3 H, H-1), 1.93 (s, 3 H, $OCOCH_3$), 2.93 (d, 1 H, J = 9 Hz, H-3), 6.23 (d, 1 H, J = 9 Hz, H-4), 7.25 (s, 5 H, Ph); mass spectrum, m/e 262 (M^+), 145 (base peak).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.14; H, 8.19.

***erythro*-4-(Benzoyloxy)-3-*tert*-butyl-4-phenylbutan-2-one (3a).** A mixture of **1a** (70 mg) and benzoyl chloride (1 mL) in pyridine (5 mL) was heated under reflux for 1 h. The product was isolated by dilution with water and ether extraction. PLC in benzene gave pure **3a** (63 mg) which recrystallized from hexane: mp 150 °C; IR 1712 (C═O), 1275, 1110, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9 H, *t*-Bu), 1.57 (s, 3 H, H-1), 3.17 (d, 1 H, J = 10.5 Hz, H-3), 6.13 (d, 1 H, J = 10.5 Hz, H-4), 7.1–8.2 (m, 10 H, Ph).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.91; H, 7.64.

***threo*-4-(Benzoyloxy)-3-*tert*-butyl-4-phenylbutan-2-one (3b).** Repetition of the reaction as outlined above for **3a** with **1b** (57 mg) gave **3b** (48 mg) after PLC with benzene. Recrystallization from hexane followed by sublimation [100 °C (0.03 mmHg)] gave pure **3b**: mp 133 °C; IR 1715 (C═O), 1710 (C═O), 1280, 1110, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9 H, *t*-Bu), 1.95 (s, 3 H, $COCH_3$) 3.03 (d, 1 H, J = 6.8 Hz, H-3), 6.21 (d, 1 H, J = 6.8 Hz, H-4) 7.1–8.3 (m, 10 H, Ph).

Anal. Calcd for $C_{21}H_{24}O_3$; C, 77.75; H, 7.46. Found: C, 77.55; H, 7.54.

X-ray Structure Determination of 3a. The compound **3a** crystallized from hexane solution as colorless prisms, and a single crystal with dimensions 1.5 × 0.4 × 0.4 mm was used for the X-ray measurements. Crystal data: $C_{21}H_{24}O_3$, M_r = 324.42, triclinic, a = 8.562 (2) Å, b = 18.722 (3) Å, c = 6.107 (1) Å, α = 93.45 (2)°, β = 110.0 (1)°, γ = 90.97(1), V = 917.33 Å^3, $F(000)$ = 348.00, Cu Kα radiation λ = 1.5418 Å, μ = 5.39 cm^{-1}, d_m = 1.10 g cm^{-3}, d_c = 1.17 g cm^{-3}, Z = 2. Precession photography indicated the space group to be $P\bar{1}$. A θ–2θ scanning mode with nickel-filtered Cu Kα radiation was used to collect the intensities of 2253 independent reflections with a Hilger and Watts four-circle, computer-controlled diffractometer. The intensities were corrected for Lorentz and polarization effects, but no absorption corrections were applied. Of the 2253 reflections collected, 1906 had values of F_o^2 that were greater than three times their estimated standard deviations, and these were used in the final refinement of structural parameters.

Structure Solution and Refinement. The structure was solved by direct methods using the program MULTAN.[9] The E map revealed the location of all carbon and oxygen atoms. The positional and isotropic thermal parameters were refined by full-matrix least-squares methods to R ($\sum||F_o| - |F_c||/|F_o|$) = 0.169 by using the program SHELX.[10] A difference Fourier synthesis revealed electron density maxima in reasonable locations for the hydrogen atoms. These were input in idealized positions for all subsequent least-squares cycles with a C–H distance of 1.00 Å, but their coordinates and isotropic temperature factors were not refined. All nonhydrogen atoms were assigned anisotropic thermal parameters, and weights derived from counting statistics were applied. The final conventional R factor was 0.071 and the weighted R factor 0.089, and a final difference Fourier synthesis revealed no peaks higher than those earlier assigned to hydrogen atoms. The weighting scheme appeared reasonable, and no abnormal discrepancies were found between observed and calculated structure factors for those reflections not used in the refinement. The final bond lengths and angles together with their standard deviations are listed in Table II.

Table III (supplementary material), containing refined atomic parameters, reveals no anomalous atomic thermal vibrations though, as can be seen from Figure 1, the thermal ellipsoids associated with the carbon atoms of the benzoate phenyl group indicate greater thermal motion in this ring than in the other phenyl ring in the molecule.

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Registry No. (±)-**1a**, 77320-82-2; (±)-**1b**, 77320-83-3; (±)-**2a**, 77320-84-4; (±)-**2b**, 77320-85-5; (±)-**3a**, 77320-86-6; (±)-**3b**, 77320-87-7.

Supplementary Material Available: Table 3 lists the final positional and thermal parameters for all nonhydrogen atoms and Table 4 the corresponding data for the hydrogen atoms (2 pages). Ordering information is given on any current masthead page.

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[9] P. Main, M. M. Woolfson, and G. Germain, "MULTAN, a Computer for the Automatic Solution of Crystal Structures", University of York, York, England, 1971.

[10] Refinement was performed by using the program system SHELX written by G. M. Sheldrick, Univerity of Göttingen.

[11] C. K. Johnson, "ORTEP", Report 3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1974.