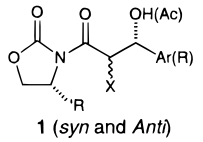
Reliable ^{13}C NMR Method of Making Relative Stereochemical Assignments to Certain *N*-[α-Hetero-*β*-hydroxy(acetoxy)-*β*-(substituted phenyl)-1′-oxopropyl]-2-oxazolidinones

Lendon N. Pridgen* and Charlie De Brosse†

Synthetic Chemistry Department, Chemical, R&D,
SmithKline & Beecham Pharmaceuticals
Post Office Box 1539, King of Prussia, Pennsylvania 19406

Received October 3, 1995 (Revised Manuscript Received November 11, 1996)

Facile establishment of relative stereochemistry for juxtapositioned polar functionalities has long been the object of intense scrutiny by organic chemists employing a variety of physical organic methods. The method most often quoted for establishing stereochemical assignments is ^{1}H NMR vicinal coupling constants between the protons attached to the adjacent stereogenic centers with $J_{2',3'}$ (*anti*) > $J_{2',3'}$ (*syn*).[1] In work recently reported from this laboratory,[2ab] several *N*-[α-hetero-*β*-hydroxy(acetoxy)-*β*-(substituted phenyl)-1′-oxopropyl]-2-oxazolidinones **1** were synthesized, but all attempts to apply this principle in making relative stereochemical assignments were unsuccessful. This ^{1}H NMR analysis was based on the



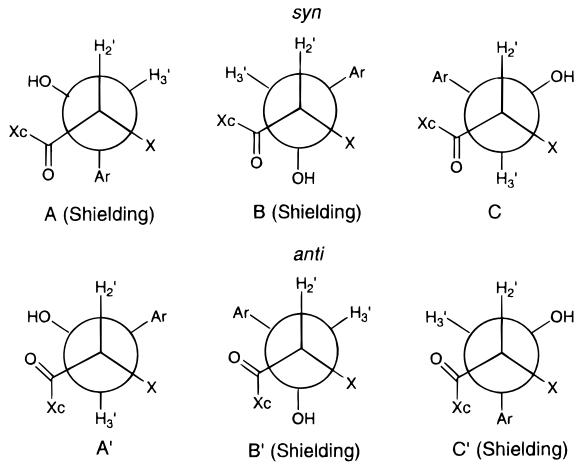
1 (*syn* and *Anti*)

Ar(R) = Substituted phenyls or alkyls
R' = ^{i}Pr or phenyl
X = F, Cl, Br, N_3

structures as depicted in Scheme 1 by analogy to Heathcock's treatise on the topic.[1a] In the arrangement (A′) for the *anti* isomer, there is a diaxial relationship between $H_{2'}$ and $H_{3'}$ that leads to a larger coupling constant than for the *syn* isomer (A) where $H_{2'}$ and $H_{3'}$ exist in an axial−equatorial disposition. This analysis is highly dependent on the sizes of the substituents Xc, X, and Ar. As the steric size of X or Ar increases, the conformation C becomes most important for the *syn* isomer, while conformation B′ becomes more important for the *anti* isomer.

In extreme cases, the *syn* isomer shows no evidence of intramolecular hydrogen bonding. Such was the case in our study where we were not able to detect any evidence of intramolecular hydrogen bonding in either the *syn* or *anti* isomers except for extremely dilute concentrations (*vide infra*). As pointed out by Heathcock,[1a] such a system would lead to ambiguous assignments when attempting to use vicinal proton coupling constants alone

Scheme 1



in establishing relative stereochemistry. Alternatively, conversion of these same halohydrin adducts to their respective epoxides followed by the more reliable ^{1}H NMR analysis was invariably consistent but time consuming. Finally, X-ray crystallography proved to be the most definitive tool at our disposal but suffers from the disadvantage of being applicable only to crystalline materials. Therefore, it was recognized that a single spectroscopic analysis tool would be invaluable in making relative stereochemical assignments of halohydrins or other adjacent heteroatoms.

Chemical shift differences (^{13}C and/or ^{1}H NMR) have previously been found in compounds possessing two adjacent chiral centers and has been used in attempts to elucidate their conformational preferences.[3] Examples of such diastereomeric ^{13}C chemical shift differences have been reported to include α-methylidene-*β*-hydroxy-*γ*-alkoxy esters,[4b] dihalogenated esters,[3b,4c,5] halohydrin chalcones,[6] and 2-(alkylsulfinyl)-1-arylethanols.[7] Heathcock[8] in 1979 reported the first use of ^{13}C NMR to make stereochemical assignments of α-methyl-*β*-hydroxycarbonyl compounds by noting the consistent upfield shift (5−2 ppm) of the α-methyl substituent for the *syn* (erythro) isomer relative to the *anti* (threo). This upfield shift was attributed to two additional gauche shieldings between the methyl and C_β−O bond in one hydrogen bonded conformer and between the R substituent and the C_α−C═O bond in another hydrogen-bonded conformer. Since that report, other laboratories[4] have utilized that method of spectral analysis to corroborate their configu-

† Analytical Services Department.

(1) (a) Heathcock, H. C. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, 1984; Vol. 3, Part B, pp 111−212. (b) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(2) (a) Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I.; Eggleston, D. S.; Shilcrat, S. *J. Org. Chem.* **1993**, *58*, 5107. See that report for complete synthesis details and full spectral characterization of all the compounds cited in this work excepting compound **2**. (b) Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I. *Tetrahedron Lett.* **1989**, *30*, 5539. (c) Abdel-Magid, A. F.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595. (d) Abdel-Magid, A. F.; Lantos, I.; Pridgen, L. N. *Tetrahedron Lett.* **1984**, *25*, 3273.

(3) (a) Prashad, M.; Séth, M; Bhaduri, A. P.; Banerji, A. *Org. Magn. Reson.* **1980**, *14*, 74. (b) Schneider, H.-J.; Lonsdorfer, M. *Ibid.* **1981**, *16*, 133 and references therein. (c) Alvarez-Ibarra, C.; Arias-Perez, M. S.; Moya, E. *Magn. Reson. Chem.* **1990**, *28*, 617. (d) Knupp, G.; Frahm, A. W. *Ibid.* **1988**, *26*, 37. (e) Levy, G. C.; Pehk, T.; Lippmaa, E. *Org. Magn. Reson.* **1980**, *14*, 214.

(4) (a) Heng; K. K.; Simpson, J.; Smith, R. A. J.; Robinson, W. T. *J. Org. Chem.* **1981**, *46*, 2932. (b) Banfi, L.; Potenza, D.; Ricca, G. S. *Org. Magn. Reson.* **1984**, *22*, 224. (c) Pitkänen, M. *Org. Magn. Reson.* **1984**, *22*, 434. (d) Welch, J. T.; Seper, K.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720. (e) Gould, T. J.; Balestra, M. D.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889.

(5) For a ^{13}C NMR study of conformationally restricted vicinal dihaloalkanes see: Schneider, H.-J.; Becker, G.; Freitag, W.; Hoppen, V. *J. Chem. Res.* **1979**, 14.

(6) Weber, F. G.; Kaatz, C.; Radeglia, R.; Köppel, H. *Monatsch. Chem.* **1992**, *123*, 18.

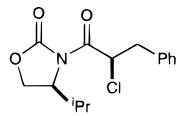
(7) Alcudia, F.; Fernández, I.; Llera, J. M.; Trujillo, M.; Zorilla, F. *Magn. Reson. Chem.* **1988**, *26*, 687.

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

S0022-3263(95)01798-1 CCC: $14.00

rational assignments, but no one has yet reported the use of ^{13}C NMR as a primary tool for establishing relative stereochemistry when the α-methyl group is absent. In such cases, one still has to rely on one of the aforementioned methods.

In compiling data for a related publication,[2a] we observed a reliable and consistent upfield shift of about 6.0−2.2 ppm (Δ ppm = δ *syn* − δ *anti*) being exhibited by the α-heteromethine carbon for all *anti* isomers **1** (R′ = ^{i}Pr or Ph, Ar = Ph or substituted phenyl, and X = Br, Cl, F, N_3) (Table 1). We are able to conclude that this is an upfield shift of the α-carbon and not a downfield shift of the *β*-carbon by synthesizing the deshydroxy chloro analog of **1**, (4*S*,2*R*)-3-(2′-chloro-3′-phenyl-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (**2**).[9] Its ^{13}C NMR spectrum exhibited the α-chloromethine chemical shift at 54.15 ppm. On the basis of chemical shift differences between the halomethylene of chloro and bromoethane versus chloro and bromoethanol,[10,11,12b] the expected deshielding contribution on the α-halo methine from the *β*-hydroxy is ∼+6.75 ppm. The summation of these two values, 60.9 ppm, would be the expected absorption value for **1** when X = chloro. The observed values of 59.8 ppm for the two *syn* chloro isomers of 1 (Table 1, entries 1 and 2) and ∼55.0 ppm for the *anti* (Table 1, entries 26 and 27) suggest that a shielding mechanism is operative for both but is more pronounced for the *anti* isomer.



2

Upon further examination of Table 1, *one notes that the α-bromomethine carbon (CHX) for syn isomers of β-hydroxy α-bromo compounds (Table 1, entries 9−25), absorbs within a 50.3−48.7 ppm range. The corresponding signal for the anti isomers (Table 1, entries 32−56) is found within a 45.3−42.9 ppm range, which does not overlap the syn chemical shift range.* Acetylating the hydroxyl (compare entries 8 and 31 of Table 1) diminished but did not eliminate the chemical shift differences. The α-chloromethine carbon (*C*HX) for *syn* isomers of *β*-hydroxy compounds (Table 1, entries 1−4) absorbs within a 59.8−57.9 ppm range. The corresponding signal for the *anti* chloro isomers (Table 1, entries 26 and 27) absorbs within a 55.3−54.8 ppm range. *Again, there was no overlap between ranges.* For the chloro examples, a possible source of interference could come from the nearby absorbing aminomethine (*C*HN) signal that is normally in the 60.0−57.5 ppm range (Table 1). The azido and fluoro isomers behave similarly (compare entries 5−7 and 28−30 of Table 1), although, in these latter two examples, the ^1H NMR coupling constant data were diagnostic enough for establishing the *syn*/*anti* relationship (4.8−2.2 and 8.5−7.4 Hz for the *syn* and *anti* isomers, respectively). The relative stereochemistry for all the isomers discussed herein, as well as all carbon assignments, were unambiguously established by using either X-ray crystallography, $^1H/^{13}C$ correlation experiments, conversion of certain halohydrins to epoxides, and proton NMR spectroscopy as reported in ref 2a or 2c (see also Table II in the Supporting Information). It should be noted that the observed chemical shift differences are independent of the configuration of the chiral auxiliary. Each partner of the diastereomeric pairs utilized throughout this study exhibited similar spectral characteristics that were consistent with all the above discussion.

A solvent study (see Table III in the Supporting Information) was conducted wherein the dielectric constants (ϵ) ranged from 4.26 to 42.4. No readily discernible solvent-related differences were detected in the ^{13}C NMR spectral data. Throughout the range of solvent polarities, all ^{13}C absorption signals remained relatively constant, to include the consistent ∼5.0 Δ ppm for the *syn*/*anti* *C*HBr absorption signals. However, ^1H NMR vicinal coupling constants for both isomers tended to increase slightly with solvent polarity, thereby indicating a slight shift toward an increase in the rotameric contributions of the type C and A′ depicted in Scheme 1.

The precise origin of the observed ^{13}C chemical shift of the α-heteromethine carbon is not entirely clear. Aromaticity and/or its accompanying π cloud interaction may be discounted since re-examination of the ^{13}C NMR spectral data for aliphatic bromo- and chlorohydrins prepared earlier show a similar pattern as that observed above.[16] Likewise, the 2-oxazolidine *syn*/*anti* pairs, now with the C_2 carbonyl absent, exhibited similar chemical shift differences for the α-chloromethine carbon.[17] Relief of steric strain through distortion in the vicinal dihedral angles between the halogen and hydroxyl most probably plays a role, but because the ^{13}C chemical shift differences are still substantial for the sterically small azido and fluoro groups, reasons other than simply steric have to be more important.

Because ^{13}C NMR shifts are known to be particularly sensitive to local electron density variations, the observed chemical shift difference could be due to through-bond dipolar interactions or linear or square electric field effects (LEF), which influence shielding at the α- and

(9) The configuration at the 2′ carbon for the major isomer was determined to be *R* by converting it to (*S*)-L-phenylalanine in unpublished work done in this laboratory by Dr. Ahmed Abdel-Magid in 1985. Proton and carbon assignments were made using $^{13}C/^1H$ correlation experiments.

(10) It is interesting to note that the ^{13}C NMR chemical shift of the methine carbon in isopropyl halides more closely resembles that of the *anti* isomer (Tables I and II), although this is probably fortuitous given all the other functionality on both the α- and *β*-carbons of **1**; see: Kalinowski, H.-O.; Berger, S.; Braun, S. In *^{13}C-NMR-Spektroskopie*; Georg Thieme Verlag: Stuttgart, 1984. Table 3.29 in this reference shows the following ^{13}C NMR (δ, ppm) for C-1: 87.3, 53.6, and 44.8 for C−F, C−Cl, and C−Br, respectively.

(11) For a relevant ^{13}C NMR study of methylcyclohexanes and cyclohexanols, see: (a) Grant, D. M.; Dalling, D. K. *J. Am. Chem. Soc.* **1967**, *89*, 6612. (b) Grant, D. M.; Cheney, B. V. *Ibid.* **1967**, *89*, 5319. (c) Buchanan, G. W.; Stothers, J. B.; Wu, S.-T. *J. Can. Chem.* **1969**, *47*, 3113 and references therein.

(12) (a) Wehli, F. W.; Wehli, S.; Marchand, A. P. In *Interpretation of Carbon-13 Spectra*, 2nd ed.; Wiley: Chichester, 1988. (b) Stothers, J. B. In *Carbon-13 NMR Spectroscopy*; Blomquist, A. T., Wasserman, H., Eds.; Academic: New York, 1972; Vol. 24, Chapter 5.

(13) Bock, K.; Lundt, I.; Pederson, C. *Tetrahedron* **1973**, *13*, 1037.

(14) Cyr, N.; Hamer, G. K.; Perlin, A. S. *Can J. Chem.* **1978**, *56*, 297.

(15) Parella, T.; Sanchez, F.; Virgili, A. *Magn. Reson. Chem.* **1994**, *32*, 657.

(16) (a) The previously unreported ^{13}C NMR spectral data for the aliphatic *anti* **7a** as referenced in 2c are as follows: δ 168.9, 153.7, 73.5 (*C*HOH), 63.9 (*C*H_2O), 59.3 (*C*HN), 56.2 (*C*HCl), 33.4, 31.6, 28.5, 24.7, 22.6, 17.9, 14.8, 14.0; therefore, Δ ppm, for the α-chloromethine carbon is ∼2.35 ppm. (b) ^{13}C NMR spectral data for the aliphatic *anti* **7f** as referenced in 2c are as follows: δ 169.6, 153.4, 76.3 (*C*HOH), 63.7 (*C*H_2O), 59.3 (*C*HN), 43.1 (*C*HBr), 29.4, 28.5, 19.9, 17.9, 24.7, 14.9, 14.8; therefore, Δ ppm for the α-bromomethine carbon is ∼6.05 ppm.

(17) From the previously reported ^{13}C NMR spectral data for the *syn* and *anti* (4*S*)-3-(2′-chloro-3′-hydroxy-4′-methylpentanoyl)-4-(1-methylethyl)-2-oxazolidines (**10**, **11**, **12**, and **13**) in ref 2c, Δ ppm for the α-chloromethine carbons is 1.8 ppm. These *syn* and *anti* signals absorb on the average at δ 56.3 and 54.5, respectively.

Table 1. Relevant ^{1}H and ^{13}C NMR Spectral Data for *N*-[2′-Substituted-3′-hydroxy-3′-(substituted phenyl)-1′-oxopropyl)]-2-oxazolidinones (1)[a]

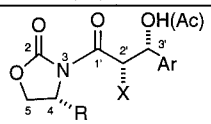
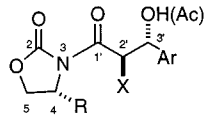
Entry	Cpd#	X	Ar	R	^{1}H δ (ppm) $C_{2'}HX$	$C_{3'}H$OH	$J_{2',3'}$ (Hz)	Misc.	^{13}C δ (ppm) $C_{1'}$=O	C_2=O	$C_{2'}$HX	C_4HN	C_5H_2O	$C_{3'}$HOH
														
					syn –**3**									
1	**7**	Cl	Ph	^{i}Pr	6.00	5.17	6.23	-	167.9	152.8	59.8	58.6	63.6	74.3
2[b,c,e]	**8**	"	"	"	6.08	5.25	6.45	-	167.1	153.0	59.8	58.5	63.5	74.5
3	**9**	Cl	C_6H_{11}	"	5.94	3.80	2.50	-	168.1	153.5	58.7	60.0	64.0	76.0
4[e]	**10**	"	"	"	5.87	3.75	2.20	-	168.8	153.1	57.9	58.7	63.6	75.1
5[b]	**11**	F	Ph	"	6.22	5.17	3.38	-	167.1	153.7	91.0	59.0	64.3	73.5
6[e]	**12**	"	"	"	6.12	5.25	2.20	-	167.2	154.1	91.1	58.9	64.9	73.0
7[c]	**13**	N_3	"	"	5.35	5.17	4.80	-	168.5	153.4	65.5	59.0	63.8	74.5
8[d]	**14**	Br	"	"	6.30	6.20	9.30	δ 2.08(CH_3CO)	166.5	152.9	45.8	58.4	63.4	74.6
9	**15**	"	"	"	6.05	5.06	7.00	-	168.5	152.6	**50.3**	58.4	63.5	73.5
10[e]	**16**	"	"	"	6.16	5.25	8.00	-	167.6	152.8	**49.6**	58.5	63.2	75.3
11	**17**	"	*o*-[Ph(CH_2)$_8$]C_6H_4	"	6.32	5.42	8.60	-	167.7	152.8	**48.7**	58.3	63.3	70.6
12[e]	**18**	"	"	"	6.21	5.40	7.33	-	168.1	152.6	**49.3**	57.9	63.1	69.5
13	**19**	"	"	Ph	6.33	5.27	8.60	*o*-(Ar*H*), δ 6.6 (d, *J* = 8.6 Hz)	167.1	152.5	**48.7**	57.5	69.7	70.0
14[e]	**20**	"	"	"	6.20	5.34	7.08	-	167.6	152.4	**49.5**	57.4	69.4	69.8
15	**21**	"	Ph	"	6.01	5.11	6.30	-	167.4	160.0	**50.2**	57.3	69.7	72.8
16[b,e]	**22**	"	"	"	6.09	5.05	7.20	*o*-(Ar*H*), δ 6.82 (d, *J* = 7.3 Hz)	167.3	152.6	**49.1**	57.5	69.9	73.8
17	**23**	"	*o*-(Bu)C_6H_4	Ph	6.33	5.25	8.37	*o*-(Ar*H*) δ 6.63 (d, *J* = 8.37 Hz)	167.3	152.5	**48.7**	57.5	69.8	70.0
18[e]	**24**	"	"	"	6.22	5.35	7.09	-	167.7	159.8	**49.5**	57.5	69.9	69.4
19	**25**	"	*p*-(Ph)C_6H_4	"	6.15	5.11	7.45	*o*-(Ar*H*) δ 6.83 (d, *J* = 8.57 Hz)	167.4	152.6	**49.4**	57.6	70.0	73.7
20[e]	**26**	"	"	"	6.05	5.15	6.43	-	167.6	152.4	**50.3**	57.6	69.9	72.9
21[b]	**27**	"	*p*-(Br)C_6H_4	"	5.94	5.08	5.84	-	167.8	152.4	**50.0**	57.6	70.0	72.2
22[e]	**28**	"	"	"	6.00	5.02	7.44	*o*-(*Ar*) δ 6.87 (d, *J* = 8.30 Hz)	167.2	152.5	**49.1**	57.6	70.1	73.4
23	**29**	"	*p*-(^{t}Bu)C_6H_4	"	6.02	5.24	6.60	-	167.4	152.3	**50.3**	57.2	69.7	72.6
24	**30**	"	*p*-(MeO)C_6H_4	"	5.98	5.02	6.97	*o*-(*Ar*) δ 6.83 (d, *J* = 8.63 Hz)	167.5	159.8	**50.3**	57.6	69.9	72.9
25	**31**	"	*p*-(NO_2)C_6H_4	"	5.93	5.23	4.43	*o*-(Ar*H*) δ 8.24 (d, *J* = 8.77 Hz) and δ 7.63 (d, *J* = 8.69 Hz)	168.2	152.4	**49.6**	57.7	71.5	70.1
														
					anti – **4**									
26[b,c]	**32**	Cl	Ph	^{i}Pr	6.01	5.05	7.88	-	168.9	153.4	54.8	59.0	68.6	75.9
27[f]	**33**	"	"	"	5.88	5.06	8.32	-	168.8	153.2	55.3	58.5	63.7	75.3
28[b]	**34**	F	"	"	6.25	4.94	7.35	-	168.1	154.5	88.4	58.8	64.5	74.2
29[f]	**35**	"	"	"	6.30	4.98	7.40	-	168.3	154.0	88.8	58.9	64.2	74.0
30	**36**	N_3	"	"	5.37	4.94	8.50	-	169.9	154.0	62.8	59.0	63.7	74.8
31[d]	**37**	Br	"	"	6.20	6.05	10.39	δ 1.94 (CH_3CO)	167.4	153.2	42.6	59.0	63.7	75.6
32[b]	**38**	"	"	"	6.09	5.15	7.00	-	169.1	153.0	**44.3**	59.0	63.5	75.4
33[f]	**39**	"	"	"	5.93	5.17	8.40	-	169.0	152.9	**44.9**	58.2	63.5	74.7
34	**40**	"	"	Ph	6.03	5.07	7.55	*o*-(Ar*H*) δ 7.17 (m)	168.8	152.7	**44.5**	57.7	70.3	75.2
35[b,f]	**41**	"	"	"	5.92	5.12	8.20	-	168.5	152.6	**45.1**	57.8	70.1	74.8
36	**42**	"	*o*-[Ph(CH_2)$_8$]C_6H_4	"	6.02	5.47	9.00	-	168.5	153.2	**44.6**	57.8	70.0	70.4
37	**43**	"	"	^{i}Pr	6.10	5.46	8.30	-	169.0	153.2	**43.9**	59.0	63.4	71.1
38[c,f]	**44**	"	"	"	6.04	5.53	8.79	-	169.0	153.1	**44.5**	58.4	63.5	70.1
39[c]	**45**	"	*o*-(Ph)C_6H_4	Ph	5.97	5.31	8.95	-	168.3	152.7	**44.1**	57.7	70.0	70.7
40[b]	**46**	"	*o*-(Br)C_6H_4	"	6.20	5.52	6.46	-	168.8	152.4	**42.1**	57.8	70.1	74.1
41[b]	**47**	"	"	"	6.13	5.43	7.10	-	168.2	152.4	**43.2**	57.6	70.0	73.6

Table 1 (Continued)

Entry	Cpd#	X	Ar	R	^{1}H δ (ppm) $C_{2'}HX$	$C_{3'}HOH$	$J_{2',3'}$ (Hz)	Misc.	^{13}C δ (ppm) $C_{1'}=O$	$C_2=O$	$C_{2'}HX$	C_4HN	C_5H_2O	$C_{3'}HOH$
42	**48**	"	*o*-(Bu)C_6H_4	"	6.03	5.49-5.44	9.10	-	168.5	152.8	**44.5**	57.8	70.1	70.2
43	**49**	"	*o*-(MeO)C_6H_4	"	6.39	5.20	7.16	-	169.3	152.8	**42.4**	58.0	70.1	75.0
44[f]	**50**	"	"	"	6.31	5.22	8.06	-	168.5	156.9	**43.0**	57.6	69.9	73.2
45	**51**	"	*o*-(^{t}Bu)C_6H_4	"	6.24	6.05	9.60	-	168.6	156.0	**44.0**	58.0	70.1	69.8
		"	*o*-(NO_2)C_6H_4	"	6.16	5.82	7.09	-	168.3	152.6	**42.9**	57.9	70.2	70.3
47[f]	**52**	"	"	"	6.08	5.84	8.24	-	167.8	152.7	**43.7**	57.8	70.2	69.7
48	**53**	"	*p*-(Ph)C_6H_4	"	6.08	5.45	7.50	-	169.0	152.7	**44.3**	57.9	70.1	75.0
49[b]	**54**	"	"	"	5.96	5.17	8.03	-	168.5	152.6	**45.0**	57.7	70.1	74.6
50	**55**	"	*p*-(Br)C_6H_4	"	5.95	5.01	7.17	-	168.7	152.6	**44.0**	57.8	70.1	74.5
51	**56**	"	*p*-(Bu)C_6H_4	"	5.91	5.08	8.29	-	168.5	152.7	**45.1**	57.7	70.0	74.7
52	**57**	"	*p*-(^{t}Bu)C_6H_4	"	5.98	5.00	7.87	-	169.3	153.0	**44.9**	58.2	70.4	75.4
53[f]	**58**	"	"	"	5.91	5.10	8.20	-	168.5	152.7	**45.2**	57.8	70.1	74.7
54	**59**	"	*p*-(MeO)C_6H_4	"	5.88	5.07	8.61	-	168.4	159.7	**45.3**	57.6	70.0	74.3
55	**60**	"	*p*-(NO_2)C_6H_4	"	5.82	5.22	8.08	-	168.1	152.9	**44.5**	57.7	70.1	73.8
56	**61**	"	*o*-(Br)C_6H_4	^{i}Pr	6.12	5.60	7.10	-	168.4	152.7	**43.3**	58.0	63.4	72.9

[a] The synthesis of all compounds reported herein is described in ref 2a. Spectral data were determined in $CDCl_3$ and measured downfield from TMS. [b] This structural assignment is supported by X-ray crystallographic data. [c] ^{1}H NMR resonance assignments were made using ^{13}C/^{1}H correlation experiments. [d] An acetoxy derivative. [e] This *syn* isomer is enantiomeric to *syn*-**3** at $C_{2'}/C_{3'}$ as shown. [f] This *anti* isomer is enantiomeric to *anti*-**4** at $C_{2'}/C_{3'}$ as shown.

β-carbon.[18,19] Heteroatom-induced steric and electric field effects (linear and square) on chemical shifts have been known for quite some time, ever since the advent of the proposed Grant−Cheney mechanism involving deshielding by steric interactions.[11,12,15,16] A study reported by Schneider to correlate the ^{13}C NMR chemical shift differences of equatorial- and axial-substituted cyclohexanes to increased bond angle widening for the axial conformation[18c] appears to be relevant to this work. Heteroatom substitution results in β-carbon electron cloud distortion (as well as other α and γ effects) by its interaction with the fluctuating dipole of the C_α−X bond. Such substitution produces steric compression, which in turn causes bond angle widening that is felt more strongly when the substituent is in an axial orientation. The usual β-deshielding effect found in cyclohexanes, 3−14 ppm, is 3−4 ppm less for axially oriented substituents than equatorial ones, thereby producing a stereochemical significant difference.[18a−c] *The α-methine carbon in the Heathcock study, now with a nonpolar methyl group attached, did not exhibit a consistently different syn/anti chemical shift pattern.*[8]

After considering ^{13}C NMR chemical shifts (SCS) differences in terms of van der Waals and electrostatic intramolecular nonbonded interactions energies[20] and possible dipole−dipole interactions resulting from the introduction of two adjacent heterosubstituents,[3b,5,21] we were drawn to the discussions of Duddeck[19a] (pp 276−282) and Abraham.[22] In Duddeck's review, a summary of work by several laboratories[23] was presented wherein a difference in α-substituent-induced ^{13}C NMR chemical shift (SCS) values was noted for equatorial- and axial-positioned α-bromocyclohexanones. These results were essentially explained in terms of differing degrees of nπ^*, $\pi\sigma^*$, and nσ^* orbital interactions between the α-halogen and the carbonyl resulting in decreased inductive effects, particularly for the axial isomer. An orientation where the halogen was in an *anti* relationship with the carbonyl allowed for the most favorable (overlap) interaction. A *syn* orientation was not nearly as effective. In fact, it was suggested by Salem[23a] that obtaining maximum orbital interaction plays a large role in determining conformational preferences.

In order to probe for conformational preferences about the halohydrin C−C bond that might explain the *syn*/*anti* differences in ^{13}C chemical shift at the α-carbon, we measured variable-temperature ^{1}H and ^{13}C NMR spectra for *syn* isomer **7** and *anti* isomer **32** in deuteriomethylene chloride from 32 to −67 °C. The *syn* compound showed pronounced broadening at −67 °C for the halohydrin methine ^{13}C signals, as well as for their attached protons. ^{1}H spectra for the *syn* compound at still lower temperature (to ca. −120 °C) in deuterioethanol showed continued broadening for all resonances but never resolved into patterns for which coupling constants could be extracted.

(18) (a) Schneider, H.-J.; Buchheit, U.; Hoppen, V.; Schmidt, *Chem. Ber.* **1989**, *122*, 321. (b) Schneider, H.-J.; Weigand, E. F.; Becker, N. *J. Org. Chem.* **1988**, *53*, 3361. (c) Schneider, H.-J.; Weigand, E. F. *J. Am. Chem. Soc.* **1977**, *99*, 8362. (d) Schneider, H.-J.; Freitag, W. *Ibid.* **1977**, *99*, 8363. (e) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866. (f) Rajan, K. P.; Manimekalai, A. *Magn. Reson. Chem.* **1991**, *29*, 904.

(19) For reviews, see: (a) Dubbeck, H. *Top. Stereochem.* **1986**, *16*, 219. (b) Wilson, N. K.; Stothers, J. B. *Ibid.* **1974**, *47*, 8, 1. (c) Sergeev, N. M.; Subbotin, O. A. *Russ. Chem. Rev. (Engl. Transl.)* **1978**, *47*, 265. (d) Eliel, L. E.; Pietrusiemicz, K. M. *Top. Carbon-13 NMR Spectrosc.* **1979**, *3*, 171.

(20) Pachter, R.; Wessels, P. L. *J. Mol. Struct.* **1988**, *178*, 323.

(21) (a) Carman, C. J.; Tarpley, A. R., Jr.; Goldstein, J. H. *J. Am. Chem. Soc.* **1971**, *93*, 2864. (b) Ernst, L.; Trowitzsch, W. *Chem. Ber.* **1974**, *107*, 3771.

(22) Abraham, R. J.; Bretschneider, E. In *Internal Rotations in Molecules*; Orville-Thomas, W. J., Ed.; Wiley: New York, 1974; Chapter 13.

(23) (a) Eisenstein, O.; Trong Anh, N.; Jean, Y.; Devaquet, A.; Cantacuzène, J.; Salem, L. *Tetrahedron* **1974**, *30*, 1717. (b) Jantzen, R.; Tordeux, M.; de Villardi, G.; Chachaty, C. *Org. Magn. Reson.* **1976**, *8*, 183. (c) Reisse, J.; Piccini-Leopardi, C.; Zahra, J. P.; Waegell, B.; Fournier, J. *J. Org. Magn. Reson.* **1977**, *9*, 512. (d) Metzger, P.; Casadevall, E.; Casadevall, A.; Pouet, M.-J. *Can. J. Chem.* **1980**, *58*, 1503. (e) Loudet, M.; Metras, F.; Petrissans, J.; Pfister-Guillouzo, G. *J. Mol. Struct.* **1975**, *29*, 263.

(24) Bellamy, L. J. In *The Infrared Spectra of Complex Molecules*; Bellamy, L. J., Ed.; Chapman and Hall: New York, 1980; Vol. 2, pp 148−149.

The corresponding signals for the *anti* compound remained sharp over the 32 °C through −67 °C temperature range. We interpret this behavior as representing a preferred conformer for the *syn* with contributions from other conformers separated by barriers of < ca. 8 kcal/mol. The *anti* behavior seems to reflect a preferred conformation for this compound, which is probably close to one of the two staggered rotamers possessing ca. 60° angle between the methine protons.

Further evidence for the conformational restriction of **1** rests on the fact that the deshydroxy compound **2** shows no significant difference in the ^{13}C NMR absorption signal (54.2 ppm) for the α-chloromethine carbon and the methine coupling constants, which are time-averaged triplets ($J = \sim 7.5$ Hz) for both diastereomeric isomers. In addition, X-ray crystallography and low-temperature IR indicate very strong intermolecular O−H/amide carbonyl bonding for *syn* isomer **7**. Interestingly, for *syn* **7**, at a very low concentration, 1.9×10^{-4} M in CH_2Cl_2, an intermolecular O−H stretching bond at 3570 cm^{-1} was replaced by two O−H bands at 3683 and 3614 cm^{-1}. Even more significantly, the amide C═O stretching bond is altered dramatically from 1708 to 1723 and 1605 cm^{-1} (broad), thereby revealing evidence of intramolecular bonding at this very low concentration. In any event, molecular motion appears to be restricted. Although we expected to see other consistent differences in amide carbonyl IR absorption frequencies between *syn* and *anti* isomers based on literature precedent for α-halogenated ketones,[24,2a] such was not the case.

It was beyond the scope of this study to determine if a variety of vicinal groups of the same or similar polarities exhibited similar ^{13}C spectral differences as presented by Metzger.[23d] Hopefully, sufficient data will be generated through practical utility to ascertain if this method will be a general one for making relative stereochemical assignments of *syn*/*anti* pairs of many other adjacent α-heteroatom keto-substituted entities.

In summary, we have have demonstrated how one may routinely determine the relative stereochemistry of *syn* and *anti* isomers of certain conformationally restricted *N*-[α-hetero-*β*-hydroxy(acetoxy)-*β*-(substituted phenyl)-1′-oxopropyl]-2-oxazolidinones **1** by simply examining the 92−42 ppm region in the ^{13}C NMR spectrum. As an example, for the α-bromomethine carbon (*C*HBr), within the 45−42 ppm chemical shift range is representative of the *anti* isomer, while a 50−47 ppm chemical shift range is representative of the *syn* isomer. The chloro, fluoro, and azidohydrins' α-methine carbon follow a similar pattern but in different spectral regions. This method is solvent independent for ^{13}C NMR but solvent dependent for proton spectra. We caution that since our empirical observations are limited to primarily *N*-acyl-2-oxazolidinone and 2-oxazolidine systems, prudence should be exercised when this method is applied to other keto functionalities, cyclic or acyclic. Replacement of any of the juxtapositioned substituents above with another functionality could either change or reverse the observed chemical shift differences observed above. Both stereoisomers should be on hand before conclusions are drawn, and the stereochemistry should be verified when possible with other supporting data.[25]

Experimental Section[2a]

NMR Methods. ^1H NMR and ^{13}C NMR spectra routinely were recorded on a Bruker AMX 400 or a WM 360 spectrometer operating at 400.13 or 360.13 MHz for ^1H and 100.62 or 90.56 MHz for ^{13}C and measured downfield from TMS. All routine solution ^{13}C NMR spectra were obtained using a GASPE pulse sequence. $^{13}C/^1H$ correlation experiments were done as noted in Table 1 using a JEOL GX 270 spectrometer at 67.8 MHz for ^{13}C and 270.15 MHz for ^1H. Low-temperature NMR studies were done in CD_2Cl_2 using a Bruker WM 360.13 MHz for proton and 90.56 MHz for carbon. Spectra were measured at ambient (25 °C) temperature or regulated *via* liquid nitrogen boiloff for low-temperature measurements. ^{13}C satellite frequencies were measured accurately *via* a 1D inverse ^1H-detected experiment. Low temperature infrared spectra were recorded on a Nicolet 800 Fourier transform infrared spectrometer with a MC detector.

Acknowledgment. The author is indebted to Mr. G. Zuber for low dilution infrared studies. The author also wishes to acknowledge the synthesis contributions of Dr. Ahmed Abdel-Magid and Ms. S. Shilcrat for some of the compounds studied. We thank Dr. Lloyd Jackman for his many helpful discussions thoughout this study and for his attempt to employ solid-state ^{13}C NMR techniques to help us determine most stable ground-state configurations.

Supporting Information Available: Experimental data for **2a** and **2b**, copies of ^1H and ^{13}C spectra for **2a** and **2b**, Table II, which contains ^1H and ^{13}C spectral data for selected syn/anti pairs, and Table III, which contains spectral data from the solvent study (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951798L

(25) Using the information provided in a preprint from us, Prof. F. Davis of Drexel University reported the utilization of this procedure to substantiate his stereochemical assignments of a *syn*/*anti* pair of α-fluoro-*β*-benzamidophenylpropanoates: Davis, F. A.; Reddy, R. F. *Tetrahedron: Asymmetry* **1994**, *5*, 955.