hydroxy acids of opposite configuration,[28] the condensation of (−)-menthyl or (+)-bornyl acetates with aryl ketones gave β-hydroxy acids of the same configuration,[29,30] and the Darzens reaction of (−)-menthyl or (+)-bornyl chloroacetate with acetophenone gave glycidates in which the β-chiral centers had the same configuration.[31]
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Configuration and Conformation of Acyclic Keto Diesters

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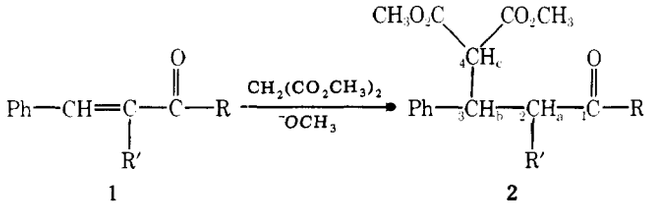
Conformational preferences in molecules such as 4,4-dicarbomethoxy-1,3-diphenyl-1-butanone are reported with special emphasis on the effect of the dicarbomethoxy group in comparison to other disubstituted carbon substituents on an ethanic skeleton. The diesters of interest are characterized by a low degree of conformational purity, especially in the threo isomers. The configuration of the keto diesters was proved by conversion into cyclopropanes, or into cyclic hemiacetals. The hemiacetals were characterized by a facile epimerization. The results of ^{13}C NMR determinations of conformation are compared to the usual ^1H determinations; the two forms are in reasonable agreement. T_1 measurements, however, were insensitive to segmental motion.

In the 1910's, Kohler and co-workers published convenient methods of synthesizing keto diesters of general structure **2**.[1] More important, methods for separating the pairs of diastereomers were given, usually a difficult task. The configuration of these diastereomers (e.g., **4** and **5**) remained unknown until the present study. These molecules are of interest with regard to their conformational preferences. In other work, compounds with the groups R_2CH or $RR'CH$ (e.g., isopropyl, cyclohexyl, cyclopentyl, $Ph(CH_3)CH$, etc.) have been thoroughly investigated.[2,3] These groups have a strong tendency to adopt a certain preferred conformation, and furthermore, they impart a strong degree of conformational purity elsewhere in the molecule. A possible exception is the benzhydryl group, which, despite a larger overall size, was not strongly determinative in the conformational sense.[4] Since benzhydryl has relatively few hydrogens at the periphery of the group which could interact with other vicinal substituents, the question arises as to the effect of a R_2CH group where R lacks interacting hydrogens altogether.[5] The diester function $(CH_3O_2C)_2CH$ is ideal for this investigation.

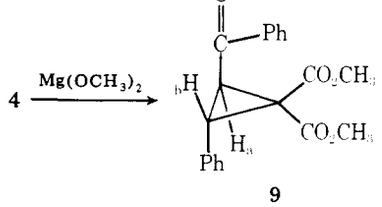


1 2

compd	isomer	R′	R	mp, °C
3		H	Ph	106–107
4	threo	Br	Ph	96–98
5	erythro	Br	Ph	108–109
6	threo	CH_3	Ph	88–90
7	erythro	CH_3	Ph	91–93
8	erythro	Ph	CH_3	118–119

In this study, NMR coupling constants will be used as a qualitative guide to conformation.[6] ^1H coupling constants of 11–13 Hz are indicative of trans protons, whereas values of 1–3 Hz indicate gauche protons. Intermediate values suggest weighted means of trans and gauche conformers. The ^1H NMR data will be compared to ^{13}C coupling constants to ^1H. A greater uncertainty prevails with regard to the $^3J_{CH}$ data, as relatively few cases have been studied. The ^{13}C data, in theory, are more useful, however, since many combinations of nuclei can be studied.[7] For anti $^{13}C_{(sp^3)}$ and ^1H nuclei, Chertkov and Sergeyev have found $^3J_{CH}$ to be 8 Hz, in a cyclohexane derivative, whereas for gauche nuclei $^3J_{CH}$ is ca. 2 Hz.[8] However, work in more complex systems by Perlin and co-workers[7b] and others[7c,d] (including this study) appeared to be consistent with smaller values. For sp^2 hybridized nuclei (e.g., COOH), $^3J_{CH}$ may be as high as 12 Hz.[7e,g] Lemieux has warned of substantial variations in $^3J_{CH}$ due to stereoelectronic effects,[7b] as well as due to the usual torsional variations. Thus, the ^1H--^1H data are regarded as the more important criteria in arriving at a decision with regard to molecular conformation.

Configuration of 4–8. The configuration of the low melting isomer of 2-bromo-4,4-dicarbomethoxy-1,3-diphenyl-1-butanone (**4**) was proved by base catalyzed conversion to the *trans*-cyclopropane **9** (J_{ab} = 7.8 Hz). The high-melting bromide **5** formed the *cis*-cyclopropane **10** ($^3J_{ab}$ = 10 Hz). A



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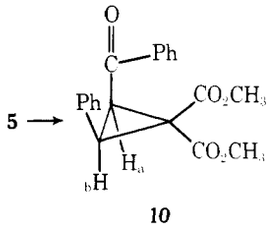

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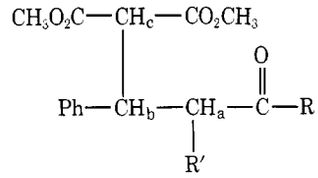
Table I. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz)



compd.	R	R′	δ_a	δ_b	δ_c	$^3J_{ab}$	$^3J_{bc}$	Other
3	Ph	$H_{a'}$[a]	3.48	4.21	3.88	4.8	9.4	
4 (threo)	Ph	Br	6.16	4.32	4.15	7.8	8.2	
5 (erythro)	Ph	Br	6.16	4.37	4.33	11.5	5.8	
6[b] (threo)	Ph	CH_3	4.06	3.67	3.89	7.6	8.3	δ_{CH_3} 1.01
7 (erythro)	Ph	CH_3	4.23	3.98	3.99	7.9	8.8	δ_{CH_3} 1.22
8 (erythro)	CH_3	Ph	4.75	4.31	3.52	11.5	6.3	δ_{CH_3} 1.88

[a] $\delta H_{a'}$ = 3.55 ppm, $^3J_{a'b}$ = 8.9; $^2J_{aa'}$ = −12.0 Hz. [b] In acetone-d_6 as solvent, $^3J_{ab}$ = 5.4; $^3J_{bc}$ = 9.1 Hz.

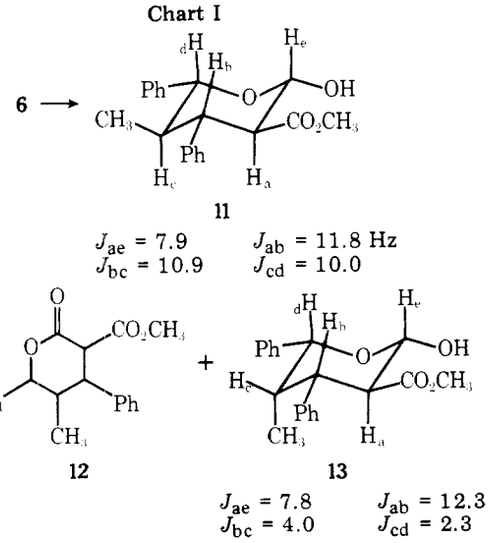
search of Bothner-By's compilation of authenticated coupling constants revealed no case in which a *trans*-cyclopropane had a larger ^3J value than the cis isomer (in the cis isomer, the dihedral angle between vicinal protons is ca. 0°, whereas in the trans isomer, this angle is ca. 120°).[9,10] Thus, **4** must be the threo isomer, and **5** the erythro isomer.

With regard to the α-methyl compounds **6** and **7**, it was hoped that configuration could be proved by reductive cyclization. The low-melting isomer **6** gave a hemiacetal **11** upon treatment with BH_4^- rather than the expected lactone.[11] The ^{1}H NMR coupling constants of **11** were very large (10–12 Hz), except for $^3J_{ae}$,[12] indicating several sets of trans diaxial hydrogens. The major substituents must therefore be equatorial. The configuration of **6** is thus threo.

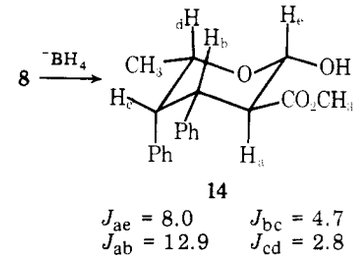
The high-melting isomer **7** gave the lactone **12**, as well as the hemiacetal, **13**, upon reduction. The configuration of the lactone **12** was unclear, perhaps due to conformational averaging.[13] However, the hemiacetal **13** exhibited a strong preference for the conformation indicated in Chart I. In **13**, C_4–CH_3 has the opposite configuration as **11**, consistent with the erythro configuration of **7**.

In the coupled ^{13}C spectrum, the methyl group of **13** was split into a rough quartet of quartets. This pattern is explicable in terms of a roughly equivalent coupling of CH_3 to H_c, H_d, and H_b of ca. 5 Hz. The splitting by H_b and H_d, though rather smaller than expected, is consistent with CH_3 trans to H_b and H_d. In **11**, the CH_3 was split into a doublet of quartets pattern (2 × 4). The doublet was due to $^2J_{CH_3\text{-}H_c}$ (ca. 4.4 Hz). Additional splittings of this resonance by H_b and H_d were barely visible, and of the same magnitude as the error in data collection, ±0.3 Hz. These small couplings are consistent with the gauche arrangement of CH_3 with H_b and H_d. Lack of solubility precluded the use of sufficiently high sample concentration to achieve better data collection statistics.

Chart I



By a similar procedure, 5,5-dicarbomethoxy-3,4-diphenyl-2-pentanone (**8**) was reductively cyclized to form the hemiacetal **14**, which is similar to **13**. Thus **8** is also an erythro isomer. The threo isomer could not be isolated.

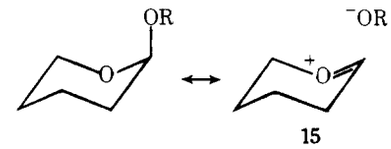


14

J_{ae} = 8.0 J_{bc} = 4.7
J_{ab} = 12.9 J_{cd} = 2.8

The hemiacetals **11**, **13**, and **14** each showed the presence of a second material in the ^{1}H and ^{13}C spectra. In neutral solvents, this second substance increased from an initial low level to ca. 20% of the overall quantity, and thereafter remained at a constant level. These minor components are believed to be the anomers (OH axial) of the parent compounds (OH equatorial). Attempts to isolate the anomers were unsuccessful. The $^3J_{ae}$ = 3 Hz observed for the anomer of **14** is consistent with equatorial He and an axial OH group.

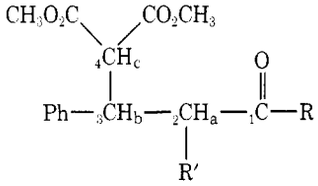
The low concentration of the presumed anomers is notable. In certain carbohydrates, the α anomer (OR axial) is dominant in many cases.[14] The reasons for the dominance of a seemingly sterically hindered axial OR group (the anomeric effect) have been extensively reviewed.[15] Eliel and co-workers, and others, have interpreted the anomeric effect in terms of a hyperconjugative interaction (i.e., as in **15**).[16] However, such stabilization is not apparent in the anomers of **11**, **13**, and **14**. Molecular models suggest that the hydrogen bond between hydroxyl and the C2-carbomethoxy group is more stable for an equatorial hydroxyl. The orientation of the carbonyl group (eclipsed with the C1–C2 bond) is favorable in such a case.[17] The orientation of carbonyl (not eclipsed) is less favorable, if hydrogen is bonded to an axial OH.



15

Acyclic Keto Diesters. Table I lists the ^{1}H NMR data, and Table II gives the ^{13}C data for **3**–**8**. Of these compounds, **3** alone lacks a substituent at C2. Compound **3**, however, is the most conformationally pure compound of this study with re-

Table II. ^{13}C NMR Chemical Shifts (ppm)[e] and Coupling Constants (Hz)



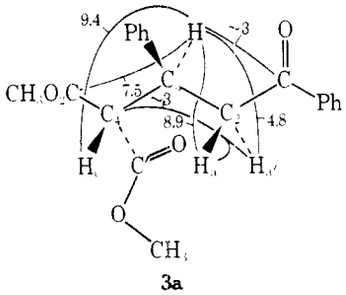
compd	δ_1	δ_2	δ_3	δ_4	$\delta_{R'}$	δ_{CO}[d]	$^3J_{C2-H_c}$	$^3J_{C4-H_a}$	$^3J_{CO-H_b}$[d]
3	197.0	42.0	40.6	57.1		168.4		2.8	2.6
						167.8			~7.5
4	191.4	52.5	46.8	55.2		167.8	3.4?	1.2	3.2
						167.2			8.0
5	191.5	47.9	46.9	54.9		168.2	2.8	~1	*a*
6	201.7	42.9	46.7	55.1	15.0	168.3	≤1	<2	~3
						167.9			~8
7	201.7	43.5	46.9	54.3	15.4	169.2	*b*	1.9	*b*
						167.8			
8[c]	205.7	61.8	46.8	54.8		168.2	2.0	≤1	*a*
						167.9			

[a] The two ester carbonyls were nearly superposed. Coupling constants could not be determined. [b] Several solutions of the spectrum are possible. [c] δ_{CH_3CO} = 30.2 ppm. [d] Ester carbonyl. [e] Me_4Si, at 0 ppm, is the standard.

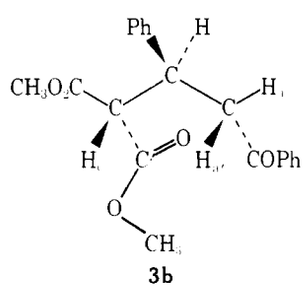
spect to rotation about the C3–C4 bond. Thus, $^3J_{bc}$ (9.4 Hz) indicates a 60–70% population of conformer(s) with anti H_b and H_c groups. However, somewhat less conformational purity is present at C2–C3 ($^3J_{ab}$ = 8.9 and $^3J_{a'b}$ = 4.8 Hz).

The ^{13}C coupling constants (to ^1H) are in reasonable agreement with ^1H data concerning conformation. Thus, $^3J_{C4-H_{a(a')}}$ appeared to be ca. 3 Hz, although this coupling was not adequately clarified by computer simulation. These values are midway between the 0 and 5 Hz values found for the rigid compounds **11** and **13**, and suggest considerable conformational averaging at C2–C3. Similarly, $^3J_{CO-H_b}$ (ca. 3 Hz) suggests more conformational averaging at C2–C3 than found in other compounds of this study.

Attempts to study $^3J_{CH}$ involving ester carbonyls were not generally successful due to small differences in chemical shift of the two ester carbonyls, extensive splitting of each resonance, and low signal intensity. However, in **3**, the ester carbonyl resonances were adequately separated (15 Hz). One solution of the splitting pattern is $^3J_{CO-H_b}$ = 7.5 Hz, and $^3J_{CO'-H_b}$ = 2.6 Hz. The former value is consistent with the ca.



3a

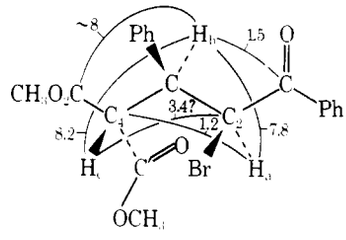


3b

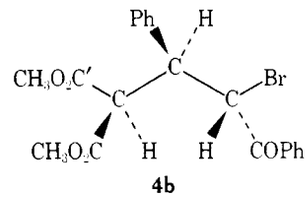
65% population of conformer with anti H_b and H_c only if the limiting value of ^3J is very high (ca. 16 Hz).[7g,18]

Structures such as *threo*-**4** are of interest with regard to the competition of groups at C2 (CO, Br, and H) vs. groups at C4 (CO, CO, and H) for the most comfortable orientation with respect to groups at C3 (Ph and H). Conformers **4a–c** illustrate possible conformations. The similarity of $^3J_{ab}$ and $^3J_{bc}$ (ca. 8 Hz) suggests that considerable conformational averaging is present, and that neither set of groups is dominant.

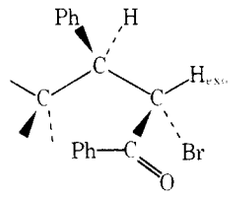
The ^{13}C coupling constants verify certain factors strongly suspected from ^1H work on other compounds.[3,4] An "exo" hydrogen as shown in **4c** is disfavored, as this would necessitate *two* large substituents extending toward the center of the



4a



4b



4c

molecule. Thus, $^3J_{CO-H_b}$ = 1.5 Hz suggests that the ketone carbonyl and H_b are gauche, as in **4a** or **4b**, and infrequently anti, as in **4c**. Similarly, $^3J_{C4-H_a}$ = 1.2 Hz is not in agreement with a major population of **4c**.

Diastereomers of the erythro configuration are frequently higher melting and more conformationally pure than their threo counterparts.[19] The ^1H NMR spectrum of **5** indeed indicates the existence of a strong preference for anti hydrogens a and b ($^3J_{ab}$ = 11.5 Hz). However, $^3J_{bc}$ is very unusual, namely 5.8 Hz. Usually, if a coupling constant between one set of protons is very large (i.e., $^3J_{ab}$ in **16**), the next set of protons shows a low value ($^3J_{bc}$ in **16**).[3,4] This alternation of coupling constants is a reflection of the preference for conformers in which 1,3 (eclipsing) interactions do not occur between large groups (e.g., **5a** or **16**). However, in **5**, the magnitude of $^3J_{bc}$ suggests that either: (1) a distorted propane skeleton exists for **5**, or (2) a sizable population of a conformer such as **5b** exists in which protons b and c, as well as a and b, are anti. If these protons are so oriented, eclipsing interactions, as between Br and CO_2CH_3 in **5b**, are inescapable. The chemical shifts indicate less distortion for **5** than for **4** (Table II).[20]

The ^{13}C coupling constants $^3J_{C4-H_a}$ (<1 Hz) are consistent with gauche nuclei, as in **5a** or **5b**. Similarly, $^3J_{C2-H_c}$ = 2.8 Hz precludes an "exo" hydrogen.

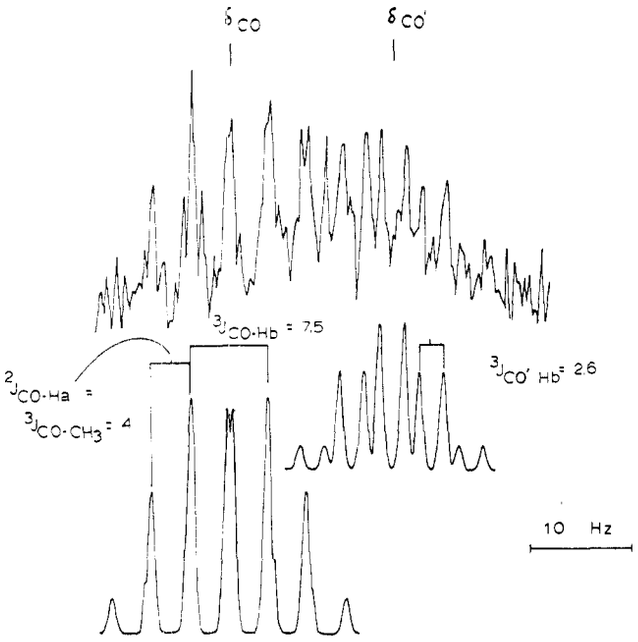
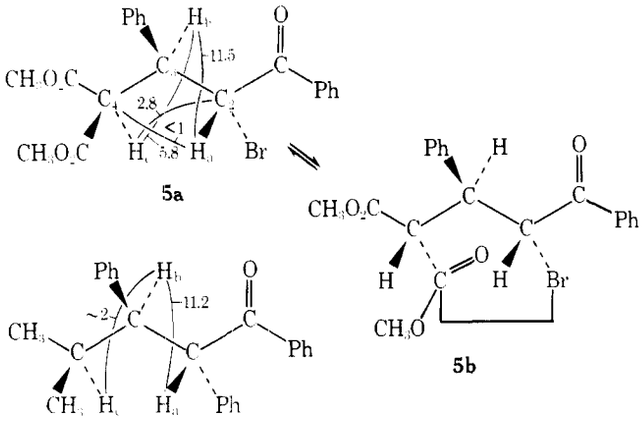
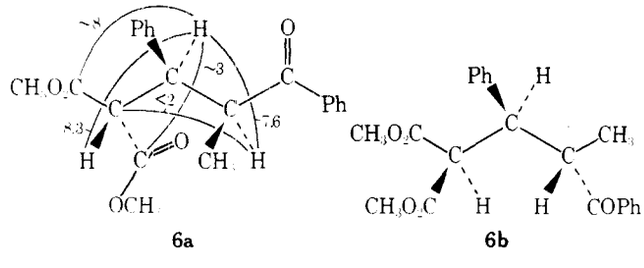


Figure 1. ^{13}C spectrum of the ester carbonyl region of **3**. The lower figures are computer simulations of the CO and CO' splitting patterns.



Moving from **4** to **6** involves a replacement of Br by a group of similar size, methyl. The ^1H spectrum of **6** at 100 MHz was extremely complex and uninterpretable. However, at 360 MHz the resonances were cleanly separated, and coupling constants, $^3J_{ab}$ = 7.6 Hz and $^3J_{bc}$ = 8.3 Hz, were derived by computer simulation. The simultaneous rather high magnitude of these ^3J values is quite unusual, but the high degree of conformational mixing does not permit unambiguous identification of eclipsed conformers.

As a consequence of the small separations of the ^1H resonances, the coupled ^{13}C spectra at 25 MHz were also very complex. A few approximate magnitudes of splittings are shown in structure **6a**. Selective decoupling permitted a relatively firm value for $^3J_{C2-Hc}$ (<1 Hz) to be obtained. Computer simulation indicated that the coupling constant between CH_3 and H_b is sizable (ca. 3 Hz), consistent with the ^1H indication of conformational mixing (**6a** ⇌ **6b**, in addition to other possible conformers).



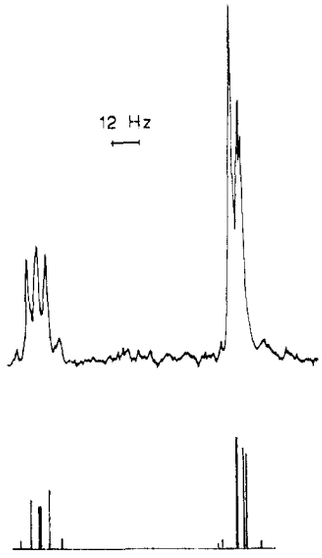
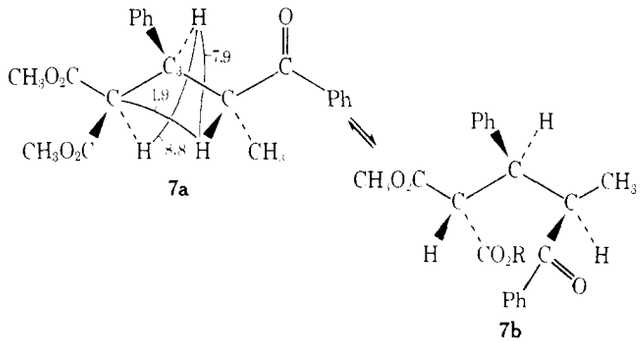


Figure 2. Portion of the ^1H NMR spectrum of **7**. Computer simulation of the spectrum is shown by means of the "stick" model in the lower trace.

erythro-**7** also showed a complex and uninterpretable ^1H spectrum at 100 MHz for protons a–c. The 360-MHz spectrum afforded some clarification, but even at this high field protons b and c were separated by only a few hertz. Similar to **5**, the spectrum resembled a common textbook example of an ABX pattern in which only one AB quartet and a singlet were visible in the AB region (Figure 2). Computer-assisted analysis of the splitting pattern indicated $^3J_{ab}$ = 7.9 Hz and $^3J_{bc}$ = 8.8 Hz. One interpretation of these data is a roughly equal mixture of conformers **7a** and **7b**. The level of conformational purity is much lower than for **5** despite the similarity of CH_3 and Br in size in **7** and **5**, respectively. Repulsion between protic groups, CH_3 and H_c, in **7a** is believed to provide a certain tendency for population of the alternate conformer, **7b**. However in **7b**, models suggest that C3–**Ph** is destabilized by its gauche orientation with respect to CH_3 and PhCO. In particular, one ortho hydrogen of C3–Ph lies near CH_3. Because of opposing influences, the molecule is conformationally mixed.

The ^{13}C coupling constant for CH_3 to H_b was not adequately clarified by attempted selective decoupling. However, computer simulation showed the general size of $^3J_{CH_3-H_b}$ to



be ca. 2.5 Hz. This value is somewhat larger than expected for a mixture of **7a** and **7b**, as CH_3 is gauche to H_b in both conformers.

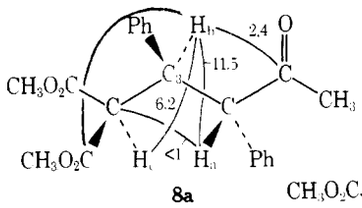
The final compound of interest, *erythro*-**8**, is highly conformationaly pure at C2–C3, similar to other erythro diastereomers with vicinal phenyl groups.[21] The $^3J_{ab}$ = 11.5 Hz indicates a strong conformational preference for the conformer with trans vicinal proton (~85%). On the other hand, $^3J_{bc}$ =

Table III. Temperature Effects on Vicinal Coupling Constants

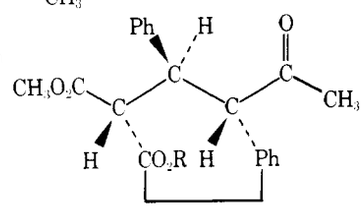
erythro-8			*threo*-4		
temp, °C[b]	$^3J_{ab}$, Hz	$^3J_{bc}$, Hz	temp, °C[b]	$^3J_{ab}$, Hz	$^3J_{bc}$, Hz
+160[a]	10.5	6.0	+54	7.7	7.8
+120[a]	11.0	6.2	+36	7.6	8.0
+80[a]	11.4	6.2	+25	7.4	8.2
+25	11.6	6.2	0	7.1	8.4
0	11.7	6.2	−30	6.4	8.8
−30	11.8	6.1	−50	5.8	9.4
−50	12.0	6.0			

[a] Solvent was benzonitrile; concentration 5% w/v. For all other experiments the solvent was $CDCl_3$ (5%). [b] Approximate range ±5 °C.

6.2 Hz, indicative of either a highly skewed conformation or, more likely, conformational mixing with respect to a C3–C4 bond, similar to **5**. Thus, one important contributor to the



8a



8b

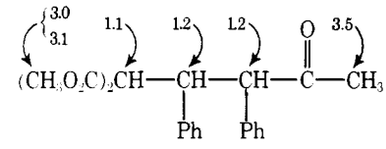
conformational equilibrium mixture would appear to be **8b**, in which eclipsed groups are present.

The ^{13}C data, in particular $^3J_{C4-H_a}$ (<1 Hz), are consistent with the dominance of **8a** and **8b**. Dissection of the ketone carbonyl splitting pattern yields, $^2J_{CO-CH_3}$ = 6 Hz, $^2J_{CO-H_a}$ = 4 Hz, and $^3J_{CO-H_b}$ = 2.4 Hz. The latter value, although somewhat large, is roughly consistent with gauche nuclei. Unlike hydrogen, carbonyl groups lack spherical symmetry, and the variation of the carbonyl coupling constants raises the question of the dependence of $^3J_{CH}$ on the orientation of carbonyl.

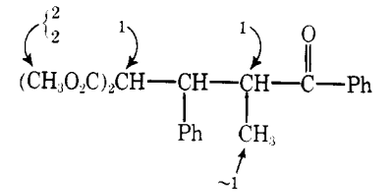
The effect of temperature on the ^1H coupling constants (Table III) was investigated to see if $^3J_{CH}$ responded in a manner consistent with the presumed **8a–b** conformational equilibrium.[22] The $^3J_{ab}$ value for **8** diminishes as temperature is increased in a purely normal manner. This observation is due to increased population at higher temperatures of conformers with gauche protons. On the other hand, $^3J_{bc}$ is virtually *invariant*.

There are two situations in which ^3J would show little response to temperature changes. In one case, a single very stable conformer might be present (say 99.99% of the total population). Raising the temperature might reduce the population to ca. 99.90%, but the effect of ^3J would be insignificant. In the second case, two or more conformers of similar enthalpy might be present. Since entropy differences are seldom large, these conformers would have similar populations resulting in an "averaged" ^3J value. Since there is little enthalpy difference, a change in temperature would not have much effect on the distribution of populations, or on ^3J. The second case is believed to be pertinent for **8** and **5**. The $^3J_{bc}$ is indeed suggestive of a lack of conformational preference. With regard to the alternative interpretation, it is difficult to believe that a single very stable conformation showing a ^3J = 6 Hz would be present. This ^3J would require a dihedral angle between protons of ca. 45° which would place two sets of large

Chart II. T_1 Values (s)



8



6

substitutents at C3–C4 at the same dihedral angle with respect of one another.

In contrast to **8**, **4** displays a normal temperature dependence for all sets of ^1H couplings. The ^3J values tend to equalize at higher temperature.

In **5** and **8**, the above analysis implies a high level of motion of C4 with respect to C2, C3. Relaxation measurements were performed on **8**, and on a model compound **6**, to attempt to identify the effects of segmental motion[23] in **8**. In **6** and **8**, C2, C3, and C4 each have a single attached proton and in **8**, C2 and C4 appear to be almost equivalent with regard to distance from other protons. Compound **5**, of course, would be inappropriate because of other relaxation mechanisms.[23] The masses of **6** and **8** are identical. Thus the contribution to T_1 of rotations of the molecule as a whole is likely to be similar. The data (Chart II) show that **6** and **8** are similar in T_1 for carbons along the propane backbone.

Two factors account for the lack of sensitivity of T_1 to internal rotation: (1) the fact that either C4 or C2–C3 may rotate if the other is held constant, or (2) the dominance of rotation of the entire molecule. Allerhand, Doddrell, and Komoroski have analyzed the overall rate of relaxation in terms of two components: τ_R^{-1} (rate of molecular rotation) and τ_G^{-1} (frequency of rotation of some particular group).[24] The overall relaxation is dominated by the fastest component. In molecules such as cholesterol, molecular rotation is moderately slow (τ_R ca. 10^{-10} s/rad), but individual methyl groups relax more slowly because of rapid internal rotation (τ_G ca. 5×10^{-12}).[23] The 20-fold difference in correlation times leads to an increase in T_1 from ca. 0.2 s for ring carbons to ca. 2 s for the side-chain methyls.

Similarly in **6** and **8**, the T_1 values for the backbone carbons are correlated with τ_R values of ca. 10^{-11}. It seems likely that a τ_G for some particular group of threefold more than τ_R would lead to a noticeable contribution to the overall correlation time τ_C ($\tau_C^{-1} = \tau_R^{-1} + \tau_G^{-1}$) and thus to T_1. If τ_G is ca. 3×10^{-11} s/rad, the inverse value may be considered to be a rate constant for internal rotation correlated with a rotation barrier of ca. 4 kcal/mol. Only rotations having this barrier or less would provide a contribution to T_1. In retrospect, it is not surprising that a supposedly conformationally mobile fragment of a molecule (i.e., C4 in **8**) shows little difference in T_1 than a conformationally pure segment (i.e., C2). The fact that C4 may occupy a variety of conformations, of course, does not require that conformational interconversion be rapid. For a tetrasubstituted ethane fragment, such as C3–C4, a barrier of 5–6 kcal/mol would be expected.

In conclusion, these data represent the first evidence, to the best of our knowledge, for the existence of 1,3 (eclipsing) interactions in acyclic molecules capable of eliminating these interactions by internal rotation.[25–27]

Experimental Section

Compounds. 4,4-Dicarbomethoxy-1,3-diphenyl-1-butanone (3). Compound 3 was prepared by the method of Kohler in 74% yield, mp 106–107 °C (lit.[1a] mp 107 °C).

2-Bromo-4,4-dicarbomethoxy-1,3-diphenyl-1-butanone (4 and 5). The lower melting compound, **4**, was prepared by essentially the method of Kohler. To a 250-mL Erlenmeyer flask fitted with a condenser, 20 g (0.059 mol) of **3**, 100 mL of dry methanol, and 9.8 g (0.061 mol) of bromine were added and the mixture was stirred vigorously for 20 h with irradiation by a 250-W Tungsten lamp. The mixture was cooled, solvent evaporated, and the product allowed to solidify. The product was recrystallized from hot methanol to give 24 g (94% yield) of a mixture of diastereomers, about 80% of which was **4**. Pure **4** was obtained by several recrystallizations from ether–methanol to give 17.3 g (70% yield) of **4**, mp 96–98 °C (lit.[1b] mp 93 °C).

The higher melting isomer **5** was obtained by placing 50 g (0.147 mol) of **3** dissolved in 300 mL of warm CCl_4 in a 500-mL flask equipped with a dropping funnel and condenser. The solution was gently warmed, and bromine was added dropwise until a permanent reddish color was apparent. However, this observation was made difficult by precipitation of the white product. The solvent was evaporated and the product filtered yielding 56 g (91%) of the crude product, which was about 90% **5**. Several recrystallizations from ether–methanol gave 41 g (67%) of white needles of **5**, mp 107.5–109 °C (lit.[1b] mp 113 °C). No impurities were evident in the NMR spectrum.

Compounds **4** and **5** were converted to the cyclopropanes (**9** and **10**) by dissolving 5.0 g (0.0012 mol) in 150 mL of methanol. A magnesium methoxide solution was prepared by placing a catalytic amount of $HgCl_2$ in 70 mL of methanol and then adding 1 g of magnesium metal. This solution was slowly added to the refluxing solution of **4** or **5** until faint yellow color persisted. The mixture was acidified to ca. pH 5 with acetic acid, and the solvent was evaporated. The residue was taken up in ether, extracted twice with water, and dried ($MgSO_4$), and the solvent was evaporated by rotary evaporation. Slow crystallization yielded **9** (3.0 g, 95% yield) as white cubes, mp 72–73 °C (lit.[1c] mp 72 °C), or **10** (3.4 g, 83% yield) as white needles, mp 91–92 °C (lit.[1c] mp 91–92 °C).

4,4-Dicarbomethoxy-2-methyl-1,3-diphenyl-1-butanone (6 and 7). These materials were prepared by the method of Kohler and Davis.[1d] To 40 g (0.18 mol) of 2-methyl-1,3-diphenyl-2-propen-1-one and 28 g (0.21 mol) of dimethyl malonate in an Erlenmeyer flask, a hot solution of sodium methoxide (prepared from 2.0 g of sodium metal dissolved in 50 mL of methanol) was added with stirring. The resulting reddish solution was stirred for 30 min without further heating. The mixture was allowed to cool and stand overnight, whereupon 42 g of crude products precipitated (about 50% each of **6** and **7**, by NMR analysis). The diastereomeric products were separated by slow crystallization from methanol–water. Compound **6** crystallizes as cubes, mp 88–89 °C (15 g, 24% yield), whereas **7** crystallizes as thin needles, mp 91–93 °C (19.5 g, 31% yield) (lit.[1d] mp 89–90 °C), respectively.

5,5-Dicarbomethoxy-3,4-diphenyl-2-pentanone (8). To a 250-mL flask was added 33.5 g (0.15 mol) of 3,4-diphenyl-3-buten-2-one and 24 g (0.18 mol) of dimethyl malonate. A solution of sodium methoxide was prepared from 200 g of sodium methanol. Both solutions were warmed and mixed with one another. The reaction proceeded without further heating. After 30 min, the reaction mixture was neutralized with acetic acid to ca. pH 5, and the solvent was removed by rotary evaporation, leaving a solid residue. The residue was taken up in 200 mL of hot methanol and allowed to slowly crystallize. This product was recrystallized from CH_3–OH/CH_2Cl_2 to give 46 g (72%) of compound **8**, mp 119–120 °C. A portion of the above was repeatedly recrystallized for analysis, mp 121–122 °C.

Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.16; H, 6.25. Found: C, 71.04; H, 6.32.

It was important not to let this reaction proceed for too long, as a side reaction, apparently cyclization, occurred. Repetition of this procedure on a smaller scale failed several times. Apparently a large scale run is necessary for unknown reasons. Attempts to isolate the minor isomer were not successful. The minor isomer could be seen by NMR, but it apparently isomerized to the major isomer more rapidly than it could be crystallized. Chromatography was likewise unsuccessful.

Procedure for the Reductive Cyclizations. To 5.0 g (0.014 mol) of **7** in 100 mL of unpurified tetrahydrofuran (THF), 1.0 g of sodium borohydride was added, and the resulting slurry was stirred for 40 h. The bulk of the solvent was removed by rotary evaporation, and finally, by passing a stream of nitrogen over the residue. To this residue, 50 mL of water was added and dilute HCl was added until an acidic test was obtained. The resulting mixture was extracted with 3 × 50 mL of ether. The combined ether layers were washed with water and dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica gel (Baker). The lactone **12** was eluted with 90% benzene–10% Skelly B, mp 139–140 °C (1.2 g, 27% yield): NMR (10% $CDCl_3$ using a 100-MHz instrument) δ 0.70 (d, 3, CH_3), 2.55 (ddq, 1, J_{bc} = 4.9, J_{cd} = 8.7 Hz, CH–CH_3), 3.65 (dd, 1, J_{ab} = 5.9 Hz, J_{bc} = 4.9 Hz, CH_b–Ph), 3.75 (s, 3, CH_3O_2C), 4.06 (d, 1, J_{ab} = 5.9 Hz, CH_3–O_2C–CH_a), 5.11 (d, 1, J_d = 8.7 Hz, H_d), plus aromatic absorptions.

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.04; H, 6.21. Found: C, 74.20; H, 6.29.

The hemiacetal, 3-carbomethoxy-2-hydroxy-5-methyl-4,6-diphenyltetrahydropyran (**13**), was obtained from the same chromatography using 10% ether–90% benzene as eluant, mp 178–179 °C (2.3 g, 51% yield): NMR (10% pyridine) δ 0.5 (d, 3, CH_3), 2.21 (ddq, 1, CH_c–CH_3), 3.50 (s, 3, CH_3O), 3.54 (dd, 1, H_a), 3.92 (dd, 1, H_b), 5.17 (d, 1, H_d), 5.59 (d, 1, H_3).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.59; H, 6.79. Found: C, 73.45, H, 6.78.

By the same procedure, 3-carbomethoxy-2-hydroxy-5-methyl-4,6-diphenyltetrahydropyran (**11**) was prepared. From 5.0 g (0.14 mol) of **6**, 2.5 g (55% yield) of **12** was formed, mp 180–181 °C: NMR (10% pyridine) δ 0.48 (d, 3, CH_3), 2.14 (ddq, 1, H_c), 3.08 (d, 1 H_d), 3.36 (dd, 1, H_b), 3.41, (s, 3, CH_3O_2C), 4.43 (dd, 1, H_a), 5.58 (d, 1, H_e), plus aromatic absorptions.

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.55, H, 6.79. Found: C, 73.73; H, 6.84.

By the same procedure, 3-carbomethoxy-2-hydroxy-6-methyl-4,5-diphenyltetrahydropyran (**14**) was formed. From 5.0 g (0.014 mol) of **8**, 2.1 g (46% yield) of **16** was obtained, mp 190–191.5 °C: NMR (10% pyridine) δ 1.09 (d, 3, CH_3), 2.78 (dd, 1, H_b), 3.33 (s, 3, CH_3O), 3.58 (dd, 1, H_a), 3.83 (dd, 1, H_c), 4.24 (dq, 1, H_d), 5.42 (d, 1, H_e), plus aromatic absorptions.

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.50; H, 6.79. Found: C, 73.76; H, 7.01.

NMR Analyses. The ^1H-NMR results were obtained on a Varian XL-100 instrument, or occasionally on a A-60D. The ^1H spectra were simulated using the LAOCON3 program adapted to provide a computer-generated plot of the spectrum. Parameters were varied until the simulated spectrum was superimposable on the original spectrum.[28] The spectra of **6** and **7** were run by Dr. W. Conover of the Stanford Magnetic Resonance Laboratory, using the 360-MHz instrument of that laboratory. Coupling constants were obtained by simulating expansions of the spectra region of interest (usually 100 Hz spectra width). However, the rather unusual spectral width (360 Hz) provided by the Stanford instrument was not compatible with the computer simulation program, and "stick" diagrams had to be drawn to compare with the observed spectrum.

The ^{13}C spectra were also obtained on the XL-100 instrument, operating at 25.2 MHz. First, a 5000-Hz spectral width was used to obtain chemical shifts, and then coupling constants were determined from 1000-Hz "windows" of the spectral regions of interest. Smaller "windows" were not generally successful in our hands. The error in the computer analysis of the data was ±1.25 Hz for the 5000-Hz runs, and ±0.25 Hz for the 1000-Hz runs. In the latter case, the gated mode of decoupler operation was used, along with a 4 s acquisition time, a 30–35 μs pulse width (tipping angle ca. 50–60°), and a 1.5–2.0 s pulse delay. From 5–10K of transients were collected depending upon sample concentration. A 500-Hz filter was used. The best results were obtained using a sample concentration of 0.33 g of substrate per milliliter of $CDCl_3$. The chemical shifts were determined relative to the center peak of $CDCl_3$, which was taken as 76.9 ppm from Me_4Si. The ^{13}C splittings were simulated using the LAOCON3 program, as before, using the ^1H data from simulations of the ^1H spectra.

In one case (**3**), the ketone CO splitting pattern was simplified by selective decoupling from the ortho phenyl protons. The line separations were obtained with approximately 0.6 W of decoupling power, and appeared to be independent of decoupler power at approximately that level. Selective decoupling was very expensive in terms of instrument time, and this technique was not used extensively.

The T_1 values were determined using the progressive saturation technique[29] (at UNL), and for **8** using the inversion-recovery technique[30] at the University of Iowa (UI). The samples were made up using approximately 0.5–0.7 g of substrate in 3 mL of $CDCl_3$ plus ca. 0.3 g of toluene as internal standard. The T_1 values found for the internal standard were acceptably close to literature values (UNL 12 s; UI 15 ± 3 s; lit.[31] 15 s) considering that data were taken at short intervals relative to this long T_1 in order to maximize the accuracy of the data given in Chart II. The UI sample was treated with decolorizing carbon and filtered several times; the UNL samples were

merely filtered. In both cases, a stream of filtered nitrogen was passed through the sample until approximately one-third of the solvent was evaporated, thus eliminating most of the oxygen, which was not expected to be a problem anyway because of the short relaxation times in the sample.[23] Approximately 8–10 spectra were taken in each determination using a variety of time delays. The UI calculation program used a weighted average infinity determined by extrapolation of the previous data. The UI calculation was performed using peak intensities rather than peak areas; use of the latter gave higher root mean square errors. The UNL calculation used peak intensities, and the usual graphical technique; however, computer calculation of the root mean square error was $<\pm 0.6$ s (usually ± 0.2 s) for the data for Chart II. The UI data (for 8 only) were in good agreement with the UNL data; the T_1 values were within ± 0.5 s of the values quoted in Chart II except for C_3 where a value of 1 s was found. The temperature was 25 ± 0.2 °C for the UI run, and 32 ± 1 °C for the UNL runs. The NOE η was between 1.5 and 2.1 for the carbons of major interest, showing that dipolar relaxation is the major mechanism.

Acknowledgments. The determination of T_1 values for 8 by Dr. Gerald Pearson of the University of Iowa is gratefully acknowledged. Dr. W. W. Conover and the Stanford Magnetic Resonance Lab are thanked for the timely 360-MHz determinations on their Bruker HXS 360 (enabled by Grants NSF No. GP 23633 and NIH No. RR0071). Partial funds for purchase of the UNL XL-100 instrument were supplied by NSF Grant GP 10293.

Registry No.—**3**, 67488-98-6; **4**, 67488-99-7; **5**, 67489-00-3; **6**, 67489-01-4; **7**, 67489-02-5; **8**, 67489-03-6; **8**, 67489-04-7; **10**, 67489-05-8; **11**, 67489-06-9; **12**, 67489-07-0; **13**, 67528-59-0; **14**, 67489-08-1; 2-methyl-1,3-diphenyl-2-propen-1-one, 4258-37-1; dimethyl malonate, 108-59-8; 3,4-diphenyl-3-buten-2-one, 1722-69-6.

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(25) The importance of eclipsing interactions was recognized at an early date by polymer chemists;[6a] cf. also (a) A. Dempster, K. Price, and N. Shepp. *Chem. Commun.*, 1457 (1968); (b) P. Corradini, T. Miyazawa, and V. Crecenzi in "The Stereochemistry of Polymers", A. Ketley, Ed., Marcel Dekker, New York, N.Y., 1976, p 150ff, 172ff, and 250ff.

(26) A few special cases have appeared in the literature in which acyclic compounds tolerate 1,3 interactions: R. Clifford, and D. Ewing, *Org. Magn. Reson.*, **4,** 473 (1972); P. McMahon and W. Tincher, *J. Mol. Spectrosc.*, **15,** 180 (1965) (certain 1,3-diols); L. Eberson and C. Kingsbury, unpublished work, *meso*-2,4-di-*tert*-butylpentanedioic acid.

(27) The referee has pointed out that attractive 1,3 interactions are well-known in cyclic compounds. Examples include: methoxycyclohexanones [R. Stolow and T. Giants, *J. Chem. Soc., Chem. Commun.*, 528 (1971)]; halocyclohexanones [M. Grenier-Loustalot, F. Metras, and J. Petrissans, *J. Mol. Struct.*, **24,** 261 (1975)]; silacyclohexanes, R. Ouellette, *J. Am. Chem. Soc.*, **96,** 2421 (1974); sulfoxides, sulfites, and phosphites (ref 14); phosphacyclohexanes [S. Featherman, S. Lee, and L. Quin, *J. Org. Chem.*, **39,** 2899 (1974)]. However, in some cases, it is not certain whether the axial conformational preference is the result of attractive dominance [cf. W. Jorgenson and L. Allen, *J. Am. Chem. Soc.*, **93,** 567 (1971), and related papers] or whether the equatorial conformers involve greater repulsive interactions. A case in point is 2,3-dichloro-1,4-dioxane [C. Altona, H. Giese, and C. Romers, *Recl. Trav. Chim. Pays. Bas,* **85,** 1197 (1966)] as well as the large number of 5-substituted 1,3-dioxanes reported by Eliel and co-workers (reviewed in ref 14), which may be regarded as special cases in view of the anomeric effect and dipole repulsions. The multiaxial substituents in the carbohydrate observed by X-ray crystallography reported by Luger, Kothe, and Paulsen, *Angew. Chem., Int. Ed. Engl.*, **16,** 52 (1977), appear to be an artifact of crystallization.

(28) J. Marshall and R. Seiwell, *Org. Magn. Reson.*, **8,** 419 (1976), report that a high degree of similarity exists between $^3J_{HH}$ and J_{CH} in sign (and to a certain extent, in magnitude). The simulations were performed on this basis.

(29) R. Freeman and H. Hill, *J. Chem. Phys.*, **54,** 3367 (1971).

(30) R. Vold, J. Waugh, M. Klein, and D. Phelps, *J. Chem. Phys.*, **48,** 3831 (1968).

(31) (a) C. Schmidt, Jr., and S. I. Chan, *J. Magn. Reson.*, **5,** 151 (1971); (b) G. Levy, J. Cargioli, and F. Anet, *J. Am. Chem. Soc.*, **95,** 1527 (1973).