Asymmetric Induction in the Addition of Chiral Carbalkoxycarbenoids to Styrene

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The diazoacetic esters of (−)-borneol, (+)-borneol, (−)-menthol, and (−)-2-methyl-1-butanol were prepared and allowed to decompose in styrene (50 °C) in the presence of a catalytic amount of copper(I) chloride (homogeneous solution). The resulting esters were quantitatively saponified (no epimerization) and treated with diazomethane to give chiral methyl *cis*- and *trans*-2-phenylcyclopropanecarboxylates with a trans to cis ratio of 2–3 (starting chiral group, percent optical purity, and sign of *cis*-methyl ester: percent optical purity and sign of *trans*-methyl ester): (−)-bornyl, 4.63 ± 0.18 (−), 1.23 ± 0.07 (+); (+)-bornyl, 4.52 ± 0.19 (+), 1.40 ± 0.10 (−); (−)-menthyl, 11.7 ± 0.4 (−), 0.33 ± 0.04 (−); (−)-2-methyl-1-butyl, inactive, 0.37 ± 0.02 (−). The value of $[\alpha]^{25}_{D}$ −51.0° (*c* 1.74; 95% EtOH) was established for optically pure methyl (1*R*,2*S*)-*cis*-2-phenylcyclopropanecarboxylate.

The additions to simple olefins by carbalkoxycarbenoids from copper and copper salt catalyzed decompositions of diazoacetic esters are well known and synthetically useful.[1,2] Relative rate studies have shown that these reactive intermediates behave as electrophiles with reasonably low discriminatory ability among various alkenes.[3] The addition of carbalkoxycarbenoids to olefins has been found to be stereospecific. Although there is evidence that carbene, catalyst, and olefin are all involved in the transition state for the addition step,[4,5] other studies have led to the suggestion that the reaction of catalyst with diazoester might be the overall rate-determining step.[6] More recent information has provided further speculation on the mechanism of these reactions.[7]

The induction of chirality in the formation of cyclopropanes from olefins is well recognized and has been used to obtain mechanistic information on such reactions.[8] However, the studies of the catalyzed reactions of diazoesters with olefins have been limited to the homogeneous decomposition of ethyl diazoacetate in the presence of styrene and either bis(*N*-(*R*)-α-phenethylsalicyladiminato)copper(II)[5] or (tri-*l*-bornyl phosphite)copper(I).[4,9]

In the study to be described, alkyl diazoacetates in which the alkyl groups were chiral were decomposed in styrene in the presence of copper(I) chloride.

Results

The diazoacetates of (−)-borneol. (+)-borneol, (−)-menthol, and (−)-2-methyl-1-butanol were prepared by the method of House[11] and completely characterized (Experimental Section). The decompositions were carried out at 50 °C in styrene with a catalytic amount of copper(I) chloride as an apparently homogeneous solution (ca. 0.02 M in catalyst).[12] Mixtures of alkyl *cis*- and *trans*-2-phenylcyclopropanecarboxylates were formed in yields (before purification) as high as 97%. The sequence of steps used to convert these esters to the corresponding methyl esters is outlined in Scheme I.

Although the saponification of *cis*-esters **2a–d** was somewhat slower than that for the trans esters, controlled reaction conditions and careful monitoring with GLC allowed essentially quantitative conversion of esters **2** to acids **3** without any epimerization (as evidenced by the virtually identical cis–trans ratios of esters **2** and **4**). Control reactions indicated that rather harsh conditions were required to effect cis–trans interconversion.

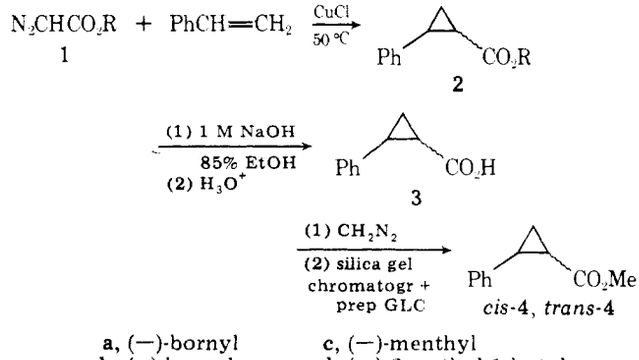
Prior to rotational measurements, acids **3** were converted to methyl esters **4** which can be conveniently purified by column chromatography with nonpolar solvents and by preparative GLC, methods which will not alter the optical purity. In addition, the smaller rotation of *cis*-acid **3** (compared to the trans acid) is enhanced by conversion to *cis*-ester **4**. It was estimated that purified samples of *cis*-ester **4** contained ≤1% *trans*-ester **4** and that samples of *trans*-ester **4** contained ≤0.5% *cis*-ester **4**. The starting chiral alcohols, which can be detected by GLC, could not have been present in amounts sufficient to cause any significant variation in the observed rotations for esters **4** (see Experimental Section).

Only in the absence of more favored reactions (such as additions to olefins) or in the presence of weak allylic bonds have carbon–hydrogen insertion reactions been observed to occur during the catalyzed decompositions of diazoacetic esters.[7,14–16] Spectroscopic and GLC techniques failed to detect any impurities (in the methyl esters **4**) which might be present if chiral lactones had been formed initially by intramolecular carbon–hydrogen insertion.[17]

The absolute configurations of (−)-borneol,[18] (−)-menthol,[18] and (−)-2-methyl-1-butanol[19] are summarized in the left column of Table I. Rotations for the optically pure alcohols are referenced in the Experimental Section.

With regard to the products of the reactions depicted in Scheme I, the geometric configurations of the 2-phenylcyclopropanecarboxylic acids (**3**) have been established by epimerization of the cis acid,[20a] ozonolysis to the corresponding dicarboxylic acids,[20b] and the correlation of acid dissociation constants[20b,c] as well as NMR,[20d] IR,[20e,f] and UV[20g] spectral properties. The absolute configuration and maximum rotation of *trans*-acid **3** are known through ozonolysis to the dicarboxylic acid.[21] More recently partially resolved (+)-*cis*-acid **3** was converted to (−)-(1*R*:2*R*)-*trans*-1,2-diphenylcyclopropane of known optical purity by a free-radical reaction in which the complete absence of phenyl migration was assumed.[22] Because even a small amount of phenyl migration could affect the value thus obtained for the maximum rotation of chiral *cis*-**3** (and the corresponding methyl ester **4**), we carried out the transformations indicated in Scheme II in which epimerization of the partially resolved cis acid chloride

Scheme I. Decomposition Sequence for Chiral Alkyl Diazoacetates



a, (−)-bornyl **c**, (−)-menthyl
b, (+)-bornyl **d**, (−)-2-methyl-1-butyl

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Table I. Decompositions of Chiral Diazoacetic Esters in Styrene (50 °C) in the Presence of Copper(I) Chloride

chiral R in esters 1 and 2[a]	registry no.	trans/cis ratio of esters 2[b]	% optical purity and sign of rotation of esters 4 cis	trans	runs
(−)-(1*S*:2*R*:4*S*)-bornyl (**1a**)	67528-60-3	2.88 ± 0.27	4.63 ± 0.18 (−)[f]	1.23 ± 0.07 (+)[h]	5
(+)-(1*R*:2*S*:4*R*)-bornyl (**1b**)	67528-61-4	2.79 ± 0.24	4.52 ± 0.19 (+)[g]	1.40 ± 0.10 (−)[i]	6
(−)-(1*R*:3*R*:4*S*)-menthyl (**1c**)	63254-50-2	2.15 ± 0.20	11.7 ± 0.4 (−)	0.33 ± 0.04 (−)	3
			0.7 ± 0.6 (−)[d]	1.1 ± 0.9 (−)[d]	3
(−)-(*S*)-2-methyl-1-butyl (**1d**)	67489-28-5	2.70 ± 0.06	inactive[e]	0.37 ± 0.02 (−)	4

[a] Signs are those of the corresponding alcohols; rotations of chiral diazoesters were not recorded. [b] Essentially identical to that of ester **4**. [c] Values of optical purity for each run were averaged over seven wavelengths from 300–589 nm; errors expressed as ±0.5 (range) for the average value from the specified number of runs. [d] Photolysis, 50 °C; no catalyst present. [e] Induced chirality equal in percent to that of the trans ester could have been detected. [f] Registry no. 67528-62-5. [g] Registry no. 67528-63-6. [h] Registry no. 16205-72-4. [i] Registry no. 10488-03-6.

Table II. Specific Rotations for Optically Pure Methyl 2-Phenylcyclopropanecarboxylates (25 °C, 95% EtOH)[a]

(1*R*:2*S*)-cis (*c* 1.74)				(1*S*:2*S*)-trans (*c* 1.97)			
nm	[α]	nm	[α]	nm	[α]	nm	[α]
300	−660	500	−84.2	300	2963	500	499
365	−255	546	−63.3	365	1294	546	398
400	−176	589	−51.0	400	954	589	330
436	−130			436	733		

[a] Cary Model 60 spectropolarimeter.

at 120°[23] followed by treatment with methanol produced *trans*-**4** of known optical purity. The value of $[\alpha]^{25}_{D}$ −51.0° (*c* 1.74; 95% EtOH) was obtained for optically pure methyl (1*R*:2*S*)-*cis*-ester **4**. The specific rotations for optically pure methyl *cis*- and *trans*-esters **4** in 95% ethanol at the seven wavelengths used in establishing the amount of induced chirality in the reaction sequence of Scheme I are in Table II (Experimental Section).

The results for the decompositions of chiral diazoacetic esters in styrene are summarized in Table I.

Discussion

One notes from the summary of results that the trans to cis ratio ranges from 2 to 3 and shows no trend with respect to the size of the starting chiral group. The catalyzed decomposition of ethyl diazoacetate in styrene gave trans and cis adducts in the ratio of 2.14, and similar values have been found for the catalyzed decompositions of alkyl diazoacetates with other substituted olefins.[7,24]

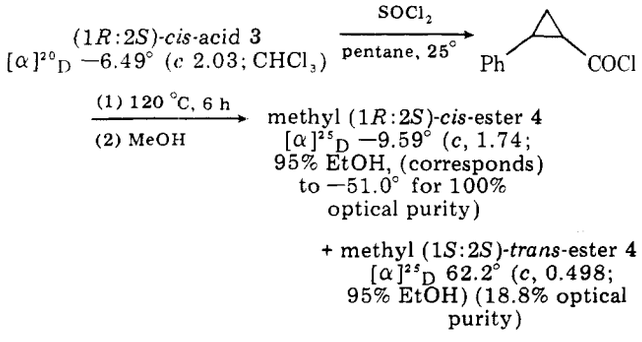
Except for the case of amyl diazoester **1d**, where induced chirality in both the cis and trans products is negligible or quite small (consistent with the substantial four-bond distance between the nearest chiral center of the alkyl group and the developing carbenoid), the other diazoesters exhibited greater induced chirality in the cis product than in the trans product. Similar behavior has been observed in the reactions of achiral diazoalkanes[10,25,26] and diazoesters[10] with chiral α,β-unsaturated esters, and in the reaction of styrene with ethyl diazoacetate in the presence of chiral copper complexes.[4,5]

A comparison of the signs of induced chirality in the various product esters **4** provides an interesting example of factors other than the configuration of the chiral center nearest the reaction site controlling the configuration of the product. Although the chiral carbinol atoms of (−)-menthol and (−)-borneol have the same absolute configuration (and ordering of groups relative to size), the trans products resulting from the catalyzed decompositions of diazoesters **1a** and **1c** have opposite chirality[27] while the cis products from the reactions have the same chirality. Nozaki and co-workers[31] have suggested that for certain reactions involving (−)-menthyl and (−)-bornyl compounds, it may be the respective β-chiral atoms (which have the opposite configuration and ordering of groups relative to size) which are most important in determining the induced chirality in the product.

The fact that products resulting from the decomposition of (+)- and (−)-bornyl diazoesters **1a** and **1b** had a comparable magnitude of induced chirality but were of opposite sign provides evidence that the activity of the products was not an artifact caused by an extraneous contaminant.

Although models can be devised to explain the relationship between the observed configurations of chiral centers in product **4** relative to those in diazoacetate **1**, such models are highly speculative and unwarrented until further details of the mechanism have been uncovered.

Scheme II. Optical Purity of Chiral Methyl *cis*-Ester 4



Experimental Section

Elemental analyses were performed either on an F & M, C, H, N Analyzer, Model 185 or a Hewlett-Packard Analyzer, Model 185B. Melting points are uncorrected. IR spectra were recorded on either a Beckman IR-8, IR-10, or IR-33. Ultraviolet spectra were recorded in a Cary-14 spectrophotometer. NMR spectra were recorded either on a Varian A-60 or T-60 spectrometer with an internal Me_4Si standard. Mass spectra were run on a Varian MAT CH-5 single-focusing instrument with peak matching capability. Polarimetric measurements were made with a Perkin-Elmer Model 141 polarimeter (10-cm cell), and optical rotatory dispersion measurements were made with a Cary Model 60 spectropolarimeter (1-cm cell); unless otherwise noted the solvent was 95% ethanol. An F & M Model 700 Chromatograph (thermal conductivity detector) with a Model 240 power proportioning temperature programmer was used for GLC analyses with

the following columns: 6 ft × ¼ in. (glass), 10% OV-210 on gas Chromosorb Q (100/200); 8 ft × ¼ in, 10% HI-EFF-8AP on gas Chromosorb Q (60/80).

Materials. The silicic acid used for column chromatography was Silicar CC-7 (Mallinkrodt) (10% slurry is ca. pH 7). (*S*)-2-Methyl-1-butanol (Eastman) had $[\alpha]^{26}_D$ −5.66° (neat; 1 dm) (lit.[32] $[\alpha]^{27.5}_D$ −5.86° (neat, 1 dm)) and was 98% pure by GLC (OV-210, 45°). (−)-Menthol (Aldrich, Eastman) had mp 42–44 °C, $[\alpha]_D$ −49.1° (*c* 10; 95% EtOH) (lit.[33] mp 43 °C, $[\alpha]^{19}_D$ −49.44° and lit.[34] mp 42 °C, $[\alpha]^{17}_D$ 49.8 (*c* 2.0; alcohol)). (−)-Borneol (Aldrich) had mp 206–207.5 °C, $[\alpha]^{20}_D$ −36.5° (*c* 5.32; 95% EtOH) (lit.[35] mp 208.5 °C, $[\alpha]_D$ −37.92° (*c* 11.5; toluene)). Styrene (Baker, stabilized with *tert*-butylpyrocatechol) was distilled with bp 45 °C (15 Torr) immediately prior to use, passed through basic alumina, and stored (N_2, −20 °C) for no more than 24 h.

Copper(I) chloride was prepared,[36a] washed,[36b] and dried under nitrogen to give a faintly blue-grey solid stored in wax-sealed vials in a dark desiccator.

(+)-Borneol was prepared by adaptation of the method of Huffman and Charles[37] from 152 g (1.0 mol) of (+)-camphor. After removal of the (−)-isoborneol[38] from the crude product, the (+)-borneol was sublimed and recrystallized (hexane) to give white, hexagonal plates, mp 204–206 °C. Recrystallization of a chromatographed sample from hexane gave mp 205–206 °C: IR spectrum identical to that of (−)-borneol; $[\alpha]^{25}_D$ 35.9 (*c* 5.6; 95% EtOH).

(−)-Menthyl Diazoacetate. (−)-Menthol (43 g, 0.274 mol) in dry methylene chloride was added dropwise (25 min) to a cold (0 °C), vigorously stirred (Morton flask) solution of 70 g (0.268 mol) of glyoxylyl chloride *p*-toluenesulfonyl hydrazone[11] (mp 106–108 °C) in methylene chloride, followed by dropwise addition (25 min; 0–5 °C) of triethylamine (ca. 54 g, 0.53 mol). The mixture was stirred for 3 h at 0–5 °C and then was concentrated in vacuo (in a 15 °C bath) to give a dark, orangish mixture of solid and oil (159 g). The mixture was taken up in benzene, slurried with 200 g of Florisil, and poured onto a 4 × 30 cm column of Florisil. Two fractions were collected and concentrated in vacuo (25 °C bath) to give a yellow oil (44.3 g; UV max 248 nm (ε 9660)) and a red brown oil (37 g), respectively, both of which contained diazoester (IR_{max} 2110 cm^{-1}). The red brown oil was chromatographed on a column 4 × 38 cm of 200 g of silicic acid and eluted with benzene–cyclohexane (1:1); 60 mL of bright yellow eluant were concentrated in vacuo (30 °C bath) to give 18.6 g of yellow oil (IR 2120 cm^{-1}; UV max 248 nm (ε 12 572)). Thus, based on the purity determined by UV (vida infra), the combined yield of diazoester is ca. 40.7 g (68%). The combined fractions of diazoester were crystallized from 15 mL of cold (−20 °C) pentane to give 35.3 g of yellow crystals (mp 38–46 °C).

Recrystallization of (−)-menthyl diazoacetate (95% ethanol) gave yellow crystals: mp 48.5–49.5 C: IR (CCl_4) 2110 (s), 1690 cm^{-1} (s); UV max (95% EtOH) 248 nm (ε 16 059), 216 (4000); UV max (hexane) 244 nm (ε 12 311), 226 (7386); NMR ($CHCl_3$) δ 0.73, 0.85, and 0.93 (3 singlets, ca. 9 H, 3 CH_3), 0.65–2.43 (m, ca. 9 H), 4.60–5.00 (m, 1 H), 4.73 (s, 1 H, N_2CHCO_2); MS (70 eV, 15°) *m/e* (rel intensity) 81 (100), 224.1593 (0.71; M^+, calcd for $C_{12}H_{20}N_2O_2$, 224.1524),[39] 225 (0.14).

(−)-Bornyl diazoacetate was prepared from (−)-borneol (41 g) by the previously described method to give 58.8 g of yellow oil which contained 36.1 g (61% yield) of (−)-bornyl diazoacetate based on ultraviolet spectroscopic analysis. Crystallization gave 18.2 g of yellow solid, mp 33–38 °C.

Recrystallization gave (−)-bornyl diazoacetate as light-yellow crystals: mp 39–40.5 °C; IR (CCl_4) 3140 (w), 2100 (vs), 1690 (s), (CS_2) 1375 (s), 1345 (s), 1230 (s), 1170 (s), and 720 cm^{-1} (m); UV max (95% ethanol) 248.5 nm (ε 17 295 ± 245), 215 (4804 ± 57); UV max (hexane) 245 nm (ε 12 259 ± 111), shoulder 220 (7503 ± 187); NMR ($CDCl_3$) δ 0.87, 0.90, and 0.93 (3 singlets, 9 H, 3 CH_3), 1.12–2.67 (complex multiplets, 7 H), 4.73 (s, 1 H, N_2CHCO_2), 4.90–5.13 (a doublet of multiplets, 1 H, CO_2CH); MS (70 eV; 15°) *m/e* (rel intensity) 95 (100), 222.13681 av (18.5; M^+, calcd for $C_{12}H_{18}N_2O_2$, 222.136 820), 223 (2.94), 224 (0.41).

(+)-Bornyl diazoacetate was prepared from (+)-borneol (49 g) by the previously described method to give 13.3 g (18.7%) of yellow crystals: mp 35–39.5 °C; UV max (95% ethanol) 249 nm (ε 17 644 ± 149), 213 (4980 ± 86); infrared spectrum (CCl_4) identical to that of *l*-bornyl diazoacetate.

(*S*)-2-Methyl-1-butyl diazoacetate was prepared from 2-methyl-1-butanol (26 g) by the procedure of House and Blankley,[11] in the manner described for (−)-menthyl diazoacetate. Distillation yielded 26 g (56.5%) of yellow oil: bp 36 °C (0.33 torr) to 30 °C (0.13 torr); IR (CCl_4) 3140 (w), 2105 (s), 1695 (vs); IR (CS_2) 1385 (s), 1225 (s), 1170 (s), and 720 cm^{-1} (m); UV max (95% ethanol) 248 nm (ε 17 400), 213 (ε 4546); NMR ($CDCl_3$) δ 0.87, 0.90, and 0.92 (the three peaks total ca. 2 H), 0.98 (ca. 4 H), 0.98–1.93 (complex multiplet, ca. 4.5 H), 3.97 and 4.07 (a pair of doublets, 2 H, *J* = 1 Hz, OCH_2), and 4.73 (s, 1 H, N_2CHCO_2); MS (70 eV, 71° inlet, 83° transfer tube) *m/e* (rel intensity) 70 (100), 128.08352 av (4.30; calcd for $C_7H_{12}O_2$ ($M - N_2$), 128.08372), 129 (1.23) but no molecular ion at *m/e* 156. (The compound probably decomposed prior to entering the source.)

It should be noted that the 2-methyl-1-butanol (Eastman 10919) is ca. 98% pure by GLC (OV-210, 45°) but is described in Kodak Catalog No. 46 as 83% min by NMR. The integration of the NMR spectrum of the alcohol is consistent with ca. 2 methylene protons (1–2δ) "too many" and thus is consistent with the integration obtained for the NMR of the diazoester. A mass spectrum (70 eV, 101°) of the alcohol failed to show a peak at *m/e* 102 (M^+, $C_6H_{14}O$) for a contaminating homologue but showed a weak peak (0.18%) at *m/e* 84 ($C_6H_{14}O - 18$), a weak peak (0.15) at *m/e* 88 (M^+, $C_5H_{12}O$), and a strong peak (36.2%) at *m/e* 70 ($C_5H_{12}O - 18$). A satisfactory elemental analysis of the alcohol was obtained.

Copper(I) Chloride Catalyzed Decomposition of (−)-Bornyl Diazoacetate in Styrene General Procedure. The reaction apparatus used for the catalyzed thermal decompositions consisted of a 100-mL jacketed flask (Ace 9266) and a four-necked head (Ace 9267) equipped with a thermometer, serum cap, vibromixer, and a condenser fitted with a gas inlet tube, which could be connected to a nitrogen source vacuum system or gas burettes.

The flask was flushed with nitrogen and then copper(I) chloride (96.7 mg, 0.97 mmol) and styrene (55 mL) were added. The mixture was placed under a nitrogen atmosphere (attained by successive evacuations of the apparatus followed by addition of N_2), and stirred for 20 min prior to circulating warm (50 °C) water through the jacket of the flask. Only after at least 10 min (reaction mixture at 49–50 °C) and disappearance of all (occasionally all but a trace) of the copper(I) chloride was (−)-bornyl diazoacetate (2.137 g, 9.61 mmol, dissolved in 15 mL of styrene) added via syringe over a period of about 30 s. Within 15–20 s after beginning the addition of diazoester, the reaction mixture changed from light-yellow to a yellowish-brown and nitrogen evolution began. The temperature reached a maximum of about 53.5 °C in 1–2 min, and nitrogen evolution continued smoothly and rapidly over the next 10 min.

Concentration of the reaction mixture in vacuo gave 3.10 g of dark brown, viscous oil; GLC (6 ft, 10% OV-210, 194 °C isothermal for 27 min, to 240 °C at 10 °C/min, helium at 50 mL/min) showed (−)-bornyl *cis*-2-phenylcyclopropanecarboxylate (15.5 min) and the trans ester (20.5 min) in the appropriate ratio of 37:100. These compounds represented 90% of the volatile components in the oil.

Identical procedures were used for the decompositions of (+)-bornyl, (−)-menthyl, and (−)-2-methyl-1-butyl diazoacetates. The yields of (−)-menthyl 2-phenylcyclopropanecarboxylate ranged from 75 to 88%. In each case the corresponding maleate and fumarate esters constituted only a minor portion of the byproducts formed. All byproducts were removed in subsequent conversion to the methyl esters, vide infra.

Saponification of (−)-Bornyl *cis*- and *trans*-2-Phenylcyclopropanecarboxylates. Conversion to the Methyl Esters. General Procedure. The concentrated residue from the diazoester decomposition mixture was treated with 10 equiv of 1 M NaOH in 85% ethanol (N_2) at reflux with stirring for ca. 48 h. Benzophenone (51.4 mg, 0.282 mmol) was added and an aliquot of a methylene chloride extract was checked by GLC (10% OV-210, 200 °C) to assay reaction progress.

The reaction mixture was concentrated in vacuo to remove the ethanol and the residue was taken up in 100 mL of water–methylene chloride (1:1). The phases were separated, the aqueous phase was extracted with methylene chloride (3 × 50 mL), and the combined methylene chloride extracts were washed with 20 mL of water followed by 20 mL of saturated sodium chloride solution (brine), dried ($MgSO_4$), and concentrated in vacuo to give 1.51 g of yellow solid whose GLC (OV-210) showed the presence of (−)-borneol (≤1 min) and benzophenone (4–5 min) but no starting esters.

The aqueous phase was acidified to about pH 1 (pHydrion paper) by the dropwise addition of about 9 mL of concentrated hydrochloric acid with stirring and then extracted with methylene chloride (3 × 50 mL). The combined extracts were washed with 15 mL of water followed by 15 mL of brine, dried ($MgSO_4$), then concentrated in vacuo to give 0.970 g (5.98 mmol, 62%) of *cis*- and *trans*-2-phenylcyclopropanecarboxylic acids as brown-yellow crystalline solid. (Control experiments indicated no cis–trans isomerization of the starting esters or the acids occurs under the reaction conditions.)

The crude cis and trans acids (0.970 g, 5.98 mmol) were dissolved in ether (20 mL) and diazomethane solution (25 mL, an excess) was added dropwise with swirling. The solution, which may contain a light flocculent precipitate, was allowed to stand for several minutes and then was concentrated in vacuo to give 1.05 g (100%) of the methyl

esters as a yellow oil (trans/cis = 3.0). This trans/cis ratio is comparable to that of the *l*-bornyl esters (trans/cis = 2.9–2.8).

The methyl cis and trans esters (1.05 g) were chromatographed on a 2 × 15 cm column of silicic acid (20 g) with cyclohexane and benzene–cyclohexane mixtures. Fractions of cis–trans mixtures containing <70% of one isomer were combined and chromatographed in the same manner. Fractions containing predominately methyl cis ester were subjected to preparative GLC and the cis ester was collected as 115 mg of colorless liquid, the GLC (OV-210, 140 °C and Hi-EFF-8AP, 190 °C) of which showed >99% methyl cis ester: $[\alpha]^{27}_D$ −2.72° (*c* 2.02). Similarly, methyl trans ester was collected as 116 mg of colorless liquid, the GLC of which showed >99% methyl trans ester: $[\alpha]^{27}_D$ 4.17° (*c* 2.01).

Saponification of the (+)-bornyl *cis*- and *trans*-2-phenylcyclopropanecarboxylates was carried out in the same manner. Sublimation (ca. 40°, 0.1 torr) of the nonacidic fraction (1.27 g) obtained from saponification of crude (+)-bornyl esters (3.04 g) gave 0.927 g of white crystals which after recrystallization (hexane) gave *d*-borneol, mp 205–206 °C, $[\alpha]^{25}_D$ 36.9° (*c* 5.61).

(−)-Menthyl *cis*- and *trans*-2-phenylcyclopropanecarboxylates were saponified and converted to the methyl esters as previously described. GLC of the crude methyl ester mixture showed a trans/cis = 2.16 comparable to the ratio of 2.10 for the (−)-menthyl esters. GLC (HI-EFF-8AP; 190 °C) assay of the methyl ester sample for ORD is capable of detecting the presence of 0.3% (by weight) of (−)-menthol (ca. 3 min) in cis (ca. 8 min) or trans (ca. 10 min) esters. If (−)-menthol were present at this level in the ORD sample, then the specific rotation due to (−)-menthol would account for ca. 3% of that observed for cis ester (ca. 6 °C) and ca. 15% of that observed for trans ester (ca. 1 °C).

Photolysis of (−)-Menthyl Diazoacetate in Styrene. The apparatus was the same as that used in the thermal decompositions but with an aluminum foil reflector behind the flask. After the system was purged with nitrogen 1.655 g (7.38 mmol) of (−)-menthyl diazoacetate (UV max (95% ethanol) 249 nm (ε ~15 250)) and 50 mL (435 mmol) of styrene (bp 32–33 °C (8 torr)) were added; the stirred solution was warmed to 50 °C (or cooled to 0 °C) and irradiated with a 275 W G. E. Sunlamp for a period of ca. 5 h and then was concentrated in vacuo to give 3.2 g of a pale-orange oil: IR (film) 3120, 3100, 3060 (w–m), 2120 (w), 1800 (m), 1750, 1740, and 1725 cm^{-1} (ms).

As a check for possible photoisomerization of the esters during photolysis, a solution of ethyl *cis*-2-phenylcyclopropanecarboxylate (187 mg (0.98 mmol)), cis/trans (97.3), in 10 mL of styrene (bp 34–35 °C (10 torr)) was irradiated during a period of 4 h. GLC (HI-EFF-8AP) failed to show any change in the cis–trans ratio and only one additional peak, presumably polystyrene; the solution seemed to become more viscous as irradiation progressed.

Gas chromatograms (OV-210) of the crude reaction mixtures from photolysis at 50 and 0 °C showed only minor differences. In two instances the (−)-menthyl esters were partially purified by column chromatography and shown to contain different compounds with identical retention times on the GLC columns used, a result different from that from the catalyzed decompositions.

Saponification of the (−)-menthyl esters was carried out by the method described for the (−)-bornyl esters to give 643 mg (3.96 mmol; 53.6% yield based on diazoester) of crude acids. Esterification via diazomethane gave crude methyl esters (trans/cis = 1.0) which were chromatographed on silicic acid to give 330 mg (1.87 mmol; 27%) of the methyl esters, which were separated partially by column chromatography and then were purified by preparative GLC. The nonacidic material obtained from saponification was chromatographed on silicic acid in each case to isolate unsaponified (−)-menthyl esters; a small amount (<2% of the total theoretical yield of (−)-menthyl esters) of cis (−)-menthyl esters was recovered in each instance. (GLC was not a reliable means to assay the saponification because of similarity in the retention times of several of the components.)

(±)-*cis*- and *trans*-2-phenylcyclopropanecarboxylic acids were obtained by adaption of the method of Walborsky and Plonsker.[40] Partial saponification of 18 g (9.46 mmol) of ethyl *cis*- and *trans*-2-phenylcyclopropanecarboxylate (42:58), prepared by the method of DePuy and co-workers[41] (modified by use of copper(I) chloride and a lower reaction temperature), with 0.58 equiv of sodium hydroxide gave 9.7 g of crude trans acid, mp 77–83 °C (lit.[18a] mp 93 °C). The unsaponified fraction (5.37 g) was >99% cis ester by GLC (10% HI-EFF-8AP).

Saponification of cis ester (9.76 g, 51.3 mmol) was accomplished in the same manner using an excess of sodium hydroxide to give 7.99 g of crude cis acid (mp 98–104.5 °C) which was recrystallized (benzene–pentane) to give 7.26 g (87.5%) of white crystals: mp 104–106 °C (lit.[18a] mp 106–107 °C); IR (CS_2) 3500–2300 (ms), 1700 (vs), 1220 (s), 950 (m), 900 (w–m, shoulder), 770 (w), 740 (w), 725 (m), 680 cm^{-1} (ms); UV max (95% ethanol) 260–255 nm (ε 210), 216 (7688), 210 (8056).

Recrystallization of (±)-trans acid from benzene–pentane gave fine, white needles: mp 105–106 °C; IR (CS_2) 3400–2300 (ms), 1695 (vs), 1320 (m), 1288 (m), 1230 (s), 1200 (ms, shoulder), 933 (ms, broad), 750 (s), 694 cm^{-1} (s); UV max (95% ethanol) 260 nm (ε 316), 220 (10 272); (lit.[42] UV max 220 nm (ε 10 060), shoulder 204 (9078)).

Methyl (±)-*cis*-2-Phenylcyclopropanecarboxylate. Racemic cis acid was dissolved in ether and treated with an excess of diazomethane solution. The reaction mixture was concentrated in vacuo to give an oil which was distilled (short-path) to afford *cis*-methyl ester as a colorless liquid, bp 78–80 °C (0.5 torr, bath 97 °C) (lit.[20] bp 83 °C (4 torr)). Preparative GLC (8 ft, 10% HI-EFF-8AP on gas Chromosorb Q, 60/80, 190 °C) of part of the oil gave a colorless liquid which was assayed by GLC as >99.9% *cis*-methyl ester: IR ($CHCl_3$) 1725 (vs), 1440 (ms), 1385 (s), (CS_2) 1195 (vs), 1172 (vs), 1160 (vs), 920 (ms), 788 cm^{-1} (ms); UV max (95% ethanol) 209.5 nm (8391 ± 215), 216 (8121 ± 161), 254.5 (178), 260 (206), 265 (167, shoulder); NMR ($CDCl_3$) δ 1.00–2.83 (4–5 H, complex multiplet, cyclopropyl ring protons), 3.38 (3 H, CO_2CH_3), 7.20 (5 H, C_6H_5); MS (70 eV, 83 °C) *m/e* (rel intensity) 117 (100), 176 (25; M^+), 177 (3.1), 178 (0.55).

Methyl (±)-*trans*-2-Phenylcyclopropanecarboxylate. The *trans*-methyl ester was prepared in the same manner as the (±)-*cis*-methyl ester. Distillation (short-path) gave *trans*-methyl ester as a colorless liquid, bp 80–82 °C (0.5–0.6 torr, bath 97 °C) (lit.[20] bp 100 °C (3 torr)). Preparative GLC (9 ft, 10% HI-EFF-8AP on gas Chromosorb Q, 60/80, 190 °C) of part of this oil gave a colorless liquid which was assayed by GLC as >99.9% *trans*-methyl ester: IR ($CHCl_3$) 1725 (vs), 1455 (ms), 1440 (s), 1340 (s); IR (CS_2) 1000 (w), 990 (w–m), 906 cm^{-1} (m); UV max (95% ethanol) 220 nm (ε 10 606 ± 235), 253 (233, shoulder), 259 (314), 265 (355), 272 (235); NMR ($CDCl_3$) δ 1.03–2.06 (3 H, complex multiplet), 2.36–2.70 (H, complex multiplet, PhC**H**), 3.68 (3 H, CO_2CH_3), 7.00–7.33 (5 H, C_6H_5); MS (70 eV, 78 °C) *m/e* (rel intensity) 176 (24; M^+), 177 (4.5).

Base-Catalyzed Epimerization of Methyl (±)-*cis*-2-Phenylcyclopropanecarboxylate. Deuterium Labeling. Methanol-*O*-*d* (25 mL) over magnesium turnings (120 mg) was allowed to reflux gently for 7 days, and then was distilled (bp 66 °C) from the turnings and collected over 3A molecular sieves.

Sodium (852 mg, 37 mmol) was placed into a dry, three-necked, round-bottomed flask equipped with a connecting tube with a stopcock, condenser (stoppered), and a serum cap, Methanol-*O*-*d* (9 mL) was added rapidly via syringe. After the sodium had dissolved, the solution was warmed to reflux and *cis*-methyl ester (90.0 mg, 0.516 mmol), which had been collected by GLC (>99% pure), in methanol-*O*-*d* (3.5 mL) was added via syringe. The reaction (N_2 atm) was allowed to reflux 24 h and then to stand 7 days at 45–50 °C.

The light-yellow reaction solution was poured into ice–water (100 mL) and the solution was extracted with methylene chloride (4 × 50 mL). The combined extracts were washed with water (2 × 25 mL) and brine (20 mL) and then dried ($MgSO_4$) and concentrated in vacuo to give a yellow, oily residue (6 mg). The aqueous phase was acidified (pH 1) by addition of 6 N hydrochloric acid (ca. 9 mL) and extracted with methylene chloride (3 × 50 mL). The combined extracts were washed with water (25 mL) and brine (20 mL) and then dried ($MgSO_4$) and concentrated in vacuo to give 75 mg of light-yellow oil, the GLC (HI-EFF-8AO; 230 °C) of which showed two peaks 16.3 and 18.8 min consistent with cis and trans acids.

The oily mixture of cis and trans acids was dissolved in ether (ca. 1 mL) and an excess of diazomethane solution was added. The ether and diazomethane were allowed to evaporate under a stream of nitrogen to give an amorphous residue (ca. 59 mg) which was chromatographed on a 0.9 × 14-cm column of silicic acid (4.5 g). The esters (49 mg) were collected in fractions eluted by 30% benzene–cyclohexane (v/v). A sample of trans ester was collected by GLC as a colorless oil: MS (70 eV, 75 °C) *m/e* (rel intensity) 118 (100), 177 (21.5; (M+), 178 (2.7); NMR ($CDCl_3$) δ 1.18–1.68 (septet 2 H), 2.40–2.67 (doublet of doublets, 1 H, PhC**H**), 3.70 (s, 3 H, CO_2CH_3), 7.00–7.30 (m, 5 H, C_6H_5).

Partial Resolution of (+)-*cis*-2-Phenylcyclopropanecarboxylic Acid. Method A. Acetyl Cellulose (Woelm) (100 g) was soaked in 400 mL of benzene for about 14 h; this slurry formed a 3.3 × 50-cm column which was washed with three volumes (ca. 430 mL each) of benzene. A benzene solution of racemic cis acid (504 mg) was placed on the column and elution with benzene was continued. The combined levorotatory fractions (231 mg, 46%) were approximately 9.7% optically pure, $[\alpha]_D$ −3.1° (*c* 0.478; $CHCl_3$). The 243 mg (48%) of dextrorotatory material $[\alpha]_D$ 2.52° (*c* 0.673; $CHCl_3$)) obtained by combining dextrorotatory fractions was about 8% optically pure.

Method B. Partial resolution via the quinine salt was also accomplished by the method of Aratani, Nakanisi, and Nozaki.[20] Fractional recrystallization of the salt from methanol–water (3:1) gave a sample

of white needles, mp 150–151 °C. Treatment of this salt with an excess of 6 N hydrochloric acid and extraction with methylene chloride gave the cis acid as white crystals: mp 71–77 °C; $[\alpha]^{21}_D$ 19.3° (*c* 1.5) (lit.[40] mp 78–98 °C, $[\alpha]^{23}$D −20°). Other fractions (88% recovery) yielded levorotatory cis acid of about 14% optical purity.

A sample of (±)-cis acid (ca. 10% optical purity) was partially resolved in the same manner. One fraction of quinine salt (mp 150–153 °C, $[\alpha]^{25}_D$ −124° (*c* 0.7)) gave (+)-cis acid (mp 74–77 °C, $[\alpha]_D$ 23° (*c* 0.8; $CHCl_3$)).

The IR spectrum was identical to that of racemic cis acid. The use of the cinchonine salt proved to be far less effective than the use of the quinine salt.

(1*S*:2*R*)-Methyl *cis*-2-phenylcyclopropanecarboxylate was prepared by addition of excess ethereal diazomethane to 91.6 mg (0.56 mmol) of (+)-cis acid ($[\alpha]^{20}_D$ 22.9° (*c* 2.03; $CHCl_3$)) in ether (10 mL). Concentration of the reaction mixture in vacuo afforded 104 mg of colorless, cloudy liquid which was distilled in a modified Hickman still (bath 60–85 °C, 0.2 torr) to give 62 mg (62%) of a clear, colorless liquid: $[\alpha]^{20}_D$ 32.8° (*c* 1.99, $CHCl_3$). GLC (HI-EFF-8AP, 195 °C) of this liquid showed >99% purity with a retention time (6.6 min) identical to that of (±)-cis ester.

(1*R*:2*S*)-Methyl *cis*-2-phenylcyclopropanecarboxylate was prepared by addition of excess ethereal diazomethane to 90.8 mg (0.56 mmol) of (−)-cis acid $[\alpha]^{20}_D$ −6.49° (*c* 2.03; $CHCl_3$)) in ether (10 mL). Concentration of reaction mixture in vacuo gave 108 mg of a cloudy, colorless oil which was distilled in a modified Hickman still (bath 60–85 °C, 0.2 torr) to yield 86 mg (87%) of a clear, colorless liquid: $[\alpha]^{25}_D$ −10.0° (*c* 2.80); GLC (HI-EFF-8AP, 195 °C) showed >99% purity with a retention time (6.6 min) identical to that of (±)-cis ester.

Partial resolution of (±)-*trans*-2-phenylcyclopropanecarboxylic acid was accomplished by recrystallization of the brucine salt from acetone[40] followed by recrystallization of the quinine salt from methanol–water (3:1).[19] One fraction of quinine salt (mp 146–152 °C, $[\alpha]_D$ −20.5° (*c* 0.96)) gave (+)-trans acid with $[\alpha]_D$ 301° (*c* 1.0) whereas another fraction of the quinine salt (mp 82–93 °C, $[\alpha]_D$ −148° (*c* 1.0)) gave (−)-trans acid with $[\alpha]_D$ −166° (*c* 1.2).[21] The IR spectrum was identical to that of the racemic trans acid.

(1*S*:2*S*)-Methyl *trans*-2-phenylcyclopropanecarboxylate was prepared from 341 mg (2.1 mmol) of (+)-(1*S*:2*S*)-trans acid (97.4% optical purity)[21] in ether by addition of an excess of ethereal diazomethane; concentration in vacuo gave 331 mg of a colorless oil. Distillation of the oil in a modified Hickman still (bath 65–75 °C; 0.15 torr) gave (+)-*trans*-methyl ester as 259 mg (70%) of colorless liquid: $[\alpha]^{20}_D$ 324.7° (*c* 1.24; $CHCl_3$). GLC (HI-EFF-8AP, 183 °C) of this (+)-trans-methyl ester showed ca. 99.5% purity with retention time (12 min) the same as that of (±)-*trans*-methyl ester.

Epimerization of (−)-*cis*-2-phenylcyclopropanecarboxylic acid via the acid chloride was performed by adaptation of the method of Smejkol and Farkas.[21] (−)-*cis* acid (278 mg, 1.71 mmol, $[\alpha]^{20}_D$ −6.49° (*c* 2.03; $CHCl_3$)) was added to a solution of freshly distilled (bp 75 °C) thionyl chloride (9.1 g, 76 mmol) in dry pentane (10 mL) and the solution was allowed to stand overnight at room temperature. Concentration at 50 °C in vacuo gave a light-yellow oil (IR (CCl_4) 1850 (m), 1800 (vs), 1360 (ms), 980 cm^{-1} (vs)) which was distilled in a modified Hickman still (65°–90 °C bath, 0.25 torr) to afford the acid chloride as 234 mg of a faintly yellow liquid.

The acyl chloride was sealed in a glass ampule and heated (120 °C) for a period of 6 h. A solution of the moderately red-brown oil in carbon tetrachloride (0.5 mL) was poured into methanol (3 mL) and the resultant solution was concentrated in vacuo to give 219 mg of a red-brown oil (IR ($CHCl_3$) 3550 (vw), 1730 (vs), 1490 (s), 1190 (ms), 1170 cm^{-1} (vs)), the GLC (HI-EFF-8AP, 185°) of which showed two peaks (1:1.25) with retention times (8.8 and 11.4 min) consistent with those of authentic *cis*- and *trans*-methyl esters.

The oily mixture of methyl esters was chromatographed on a 1.2 × 15-cm column of silicic acid (8 g). *trans*-Methyl ester was collected predominately in fractions eluted by 2–7.5% benzene–cyclohexane while *cis*-methyl ester was eluted by 7.5–30% benzene–cyclohexane.

The combined fractions containing only *trans*-methyl ester were heated under a stream of nitrogen to evaporate solvent (some loss of ester) and gave 50 mg of a faintly yellow liquid, $[\alpha]^{25}_D$ 60.4° (*c* 1.48; $CHCl_3$). Distillation of this oil in a modified Hickman still gave ca. 33 mg of clear, colorless liquid (>99% *trans*-methyl ester by GLC) (HI-EFF-8AP, 190°) $[\alpha]^{25}_D$ 62.2° (*c* 0.49; 95% ethanol); ORD ([α]) 589 (62.2), 546 (73.4), 500 (91.3), 436 (133), 400 (174), 365 (237), 300 mm (544).

The combined fractions containing only *cis*-methyl ester were concentrated in vacuo to give a yellow oil (ca. 65 mg) which was distilled in a modified Hickman still (bath 60–80 °C, 0.2 torr) to afford *cis*-methyl ester as a clear, colorless oil (47 mg). This oil was subjected to preparative GLC (OV-210) to give *cis*-methyl ester as a faintly pink oil (25 mg), $[\alpha]^{25}_D$ −9.59° (*c* 1.74).

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Registry No.—(−)-*cis*-**2a**, 67489-29-6; (+)-*trans*-**2a**, 67528-64-7; (+)-*cis*-**2b**, 67528-65-8; (−)-*trans*-**2b**, 67528-66-9; (−)-*cis*-**2c**, 67489-30-9; (−)-*trans*-**2c**, 67528-67-0; (−)-*trans*-**2d**, 67489-31-0; (±)-*cis*-**3**, 67528-68-1; (±)-*trans*-**3**, 42916-14-3; (+)-*cis*-**3**, 23020-18-0; (−)-*cis*-**3**, 48126-51-8; (+)-*trans*-**3**, 23020-15-7; (+)-*cis*-**3** quinine salt, 67596-33-2; (+)-*trans*-**3** brucine salt, 67596-35-4; (+)-*trans*-**3** quinine salt, 76596-34-3; (±)-*cis*-**4**, 67528-69-2; (±)-*trans*-**4**, 67528-70-5; (−)-menthol, 2216-51-5; glyoxylyl chloride *p*-toluenesulfonyl hydrazine, 14661-69-9; (−)-borneol, 464-45-9; (+)-borneol, 464-43-7; (*S*)-2-methyl-1-butanol, 1565-80-6; styrene, 100-42-5; ethyl *cis*-2-phenylcyclopropene carboxylate, 63038-63-1; ethyl *trans*-2-phenylcyclopropane carboxylate, 63038-62-0.

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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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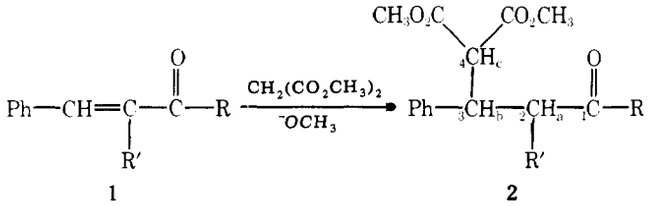
Conformational preferences in molecules such as 4,4-dicarbomethoxy-1,3-diphenyl-1-butanone are reported with special emphasis on the effect of the dicarbomethoxy group in comparison to other disubstituted carbon substituents on an ethanic skeleton. The diesters of interest are characterized by a low 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.

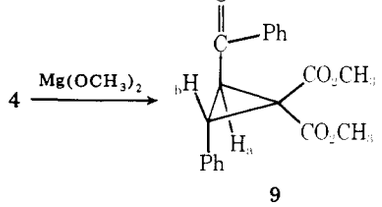


1 2

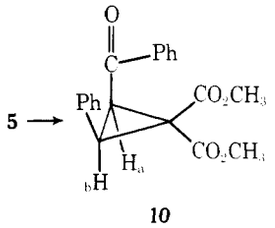
compd	isomer	R′	R	mp, °C
3		H	Ph	106–107
4	threo	Br	Ph	96–98
5	erythro	Br	Ph	108–109
6	threo	CH_3	Ph	88–90
7	erythro	CH_3	Ph	91–93
8	erythro	Ph	CH_3	118–119

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



9



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