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Methyl Trideuteriomethyl (E)-(α-Bromoarylidene)malonates: Simple Stereochemical Probes in Nucleophilic Vinylic Substitution near the Retention/Stereoconvergence Borderline[1]

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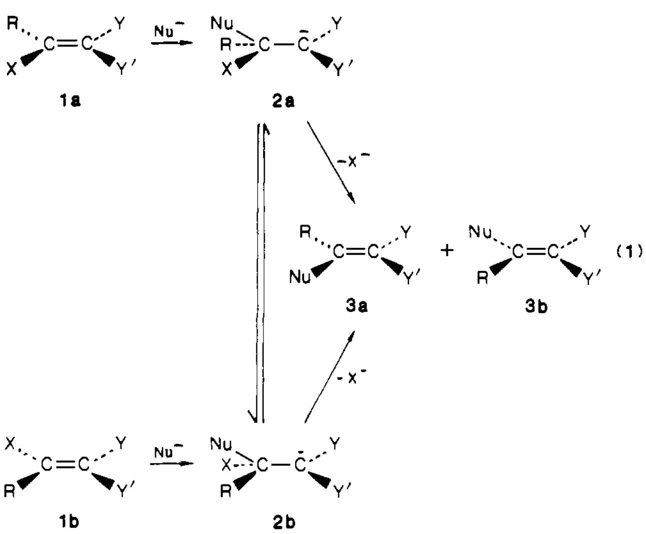
Abstract: Methyl trideuteriomethyl (E)-(α-bromo-p-methyl- and -p-nitrobenzylidene)malonates (**4** and **5**) were prepared. These electrophilic bromo olefins are activated to vinylic substitution by two chemically identical but isotopically distinguishable CO_2Me groups. The signal for the CO_2Me group cis to the aryl in the ^1H NMR is at a higher field than the signal for the other CO_2Me group in the unlabeled substitution products $ArC(Nu){=}C(CO_2Me)_2$. Hence, the stereochemistry of the substitution of **4** and **5** can be determined relatively rapidly and accurately in the NMR probe by studying only one isotopomeric vinyl bromide. The substitutions of **4** by four ArO^-, two ArS^-, and MeO^- ions and of **5** by three ArO^-, two ArS^-, and N_3^- ions in solvents such as DMSO-d_6 and 95:5 CD_3CN–DMSO-d_6 were studied. After corrections for postisomerization during the reaction and for isotopomeric impurity of **4** and **5**, it was found that all the reactions proceed with high preference for retention of configuration (i.e., partial stereoconvergence). The percentage of the retained product under kinetic control was between 81 and 97%; i.e., the diester-activated systems are still on the stereoconvergence side of the retention/stereoconvergence borderline. The change from **4** to **5** or of the nucleophile, the solvent, or the countercation of the nucleophile has only a small and unsystematic effect on the extent of retention. p-Toluidine gave complete stereoconvergence, SCN^- (but not Br^-) gave $E \rightleftharpoons Z$ bromide isomerization of **5** before the substitution, and BH_4^- reduced both the bromine and the double bond of **4**. Analysis of the results suggests that the reaction proceeds via intermediate carbanions and that the extent of stereoconvergence (the retention/inversion ratio) is determined by competition between rate-determining 60° and 120° internal rotations in the carbanion. The relative steric and hyperconjugative contributions to the barriers for these rotations are discussed, and the behavior is compared to that of other vinylic systems.

In nucleophilic vinylic substitution of highly activated halo olefins **1a** and **1b** (Y, Y′ = electron-withdrawing group, X = nucleofuge),[2] the stereochemical outcome is frequently partial or complete stereoconvergence; i.e., both isomeric products **3a** and **3b** are formed from either precursor (eq 1).[3]



At complete stereoconvergence, the initially formed [**3a**]/[**3b**] ratio formed from **1a** or **1b** is identical with the equilibrium [**3a**]/[**3b**] ratio under the same conditions. At partial stereoconvergence the two ratios differ.

Consequently, an analysis of the stereochemistry of the reaction with several nucleophiles requires preparation, separation, and characterization of both isomeric precursors **1a** and **1b** and of the products **3a** and **3b** as well as knowledge of the [**3a**]/[**3b**] equilibrium ratio. This is not always easy with the structurally similar tetrasubstituted reactants and products.

Moreover, analysis of the reaction mixture, which is usually performed by ^1H NMR, is frequently difficult due to overlap of reactant and product signals (e.g., a Me group when Y = COOMe) which are used for the analysis.

Since we experienced these difficulties in our previous stereochemical studies,[3] it became obvious that a study of a system where Y and Y′ are of similar bulk and only one of them shows an ^1H NMR signal would be beneficial since the [**3a**]/[**3b**] ratios would be close to unity in favorable cases: yet some of the problems mentioned above still remain. In an initial attempt to prepare such systems with Y = COMe and Y′ = $COCF_3$ the initial condensation of ArCHO with trifluoroacetylacetone took place mainly at the methyl rather than the methylene. We also prepared an E/Z mixture of $PhC(Cl){=}C(CO_2CH_2CH_3)CO_2CH_2CF_3$, but their separation was difficult. These systems were therefore abandoned.

A system where Y and Y′ are chemically identical but isotopically different and where the E and Z isomers of **1** and **3** are distinguishable by NMR would be ideal from the practical point of view. Chemically, it would be advantageous to study a system close to the borderline between those giving retention and those giving stereoconvergence since a change of R or the nucleophile may shift the stereochemistry from retention to stereoconvergence or vice versa.

We therefore prepared stereospecifically the two E diesters **4** and **5**, which have the following advantages: (a) There is no need to prepare and study the reaction of the Z isomers since the stereochemical outcome in the substitution of both E and Z isomers is expected to be very similar. (b) The E/Z equilibrium constants for the products will be practically unity under all conditions. (c) The ^1H NMR signals of the two COOMe groups in the unlabeled compounds **6** (Ar = p-MeC_6H_4, p-$O_2NC_6H_4$; X = Br, OAr, SAr,

(1) (a) Part 35 in the series "Nucleophilic Attacks on Carbon–Carbon Double Bonds". (b) Part 34: Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. *J. Am. Chem. Soc.* **1987**, *109*, 0000.

(2) (a) Patai, S.; Rappoport, Z. In *The Chemistry of Alkenes*; Patai, S. Ed.; Interscience: London, 1964; Chapter 8. (b) Rappoport, Z. *Adv. Phys. Org. Chem.* **1969**, *7*, 1. (c) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73. (d) Miller, S. I. *Tetrahedron* **1977**, *33*, 1211. (e) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (f) Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309. (g) Shainyan, B. A. *Usp. Khim.* **1986**, *55*, 942.

(3) (a) Rappoport, Z.; Topol, A. *J. Am. Chem. Soc.* **1980**, *102*, 406. (b) Rappoport, Z.; Avramovitch, B. *J. Org. Chem.* **1982**, *47*, 1397. (c) Rappoport, Z.; Gazit, A. *J. Org. Chem.* **1985**, *50*, 3184. (d) Rappoport, Z.; Gazit, A. *Ibid.* **1986**, *51*, 4112.

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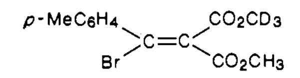
N_3) are at different positions. The CO_2Me signals of **4** and **5** are



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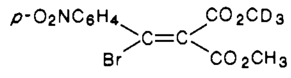

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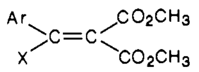
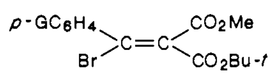
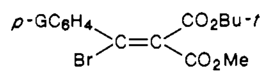


6a, Ar = p-MeC$_6$H$_4$, X = Br
b, Ar = p-O$_2$NC$_6$H$_4$, X = Br

sufficiently separated, and in relative positions which has enabled assignments in previous work.[3b–d] Consequently, analysis of the stereochemistry of the substitution by NMR without isolation of the products is feasible. (d) In most cases even small percentages of $E \rightleftharpoons Z$ isomerization of the precursors could be detected. Since inversion of configuration is usually not observed in substitution of electrophilic haloethylenes,[5] the ^{1}H NMR spectra of a substitution mixture immediately gives the ratio of retained to inverted substitution product. Finally, a recent study of the stereochemistry of the substitution of the analogues **7** and **8** had shown them to be close to the stereoconvergence/retention borderline.[3d] Consequently, it is possible that a change of the aryl group (from **4** to **5**) or of a nucleophile will change the stereochemistry from stereoconvergence to retention.



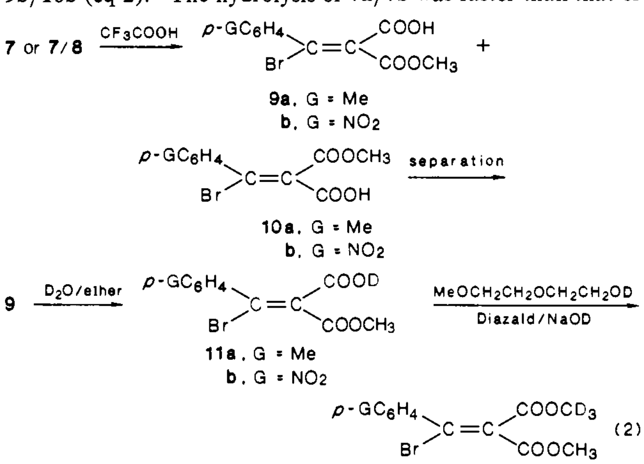
7a, G = Me
b, G = NO$_2$



8a, G = Me
b, G = NO$_2$

Results

Synthesis. (*E*)- and (*Z*)-*tert*-butyl methyl (α-bromo-*p*-methylbenzylidene)malonate (**7a** and **7b**) and the *p*-nitro analogues **8a** and **8b** were available from a previous study.[3c] Mild hydrolysis of the *tert*-butyl ester without double-bond isomerization followed by esterification with CD_2N_2 should therefore be a stereospecific route to both **4** and **5** and their *Z* isomers. However, mild hydrolysis of **7a** with dilute trifluoroacetic acid gave both acids **9a** and **10a**. Since conditions for *tert*-butyl ester hydrolysis without isomerization of the double bond could not be found, the pure *Z* isomers **7a** and **7b** or **7a**/**8a** and **7b**/**8b** mixtures were hydrolyzed with TFA to *E*/*Z* mixtures of the monomethyl esters **9a**/**10a** and **9b**/**10b** (eq 2). The hydrolysis of **7a**/**7b** was faster than that of



(2)

8a/**8b** under the same conditions. After 5 min in TFA **7a**/**7b** was hydrolyzed completely whereas only 15% of **8a**/**8b** was formed. After separation of the monoesters, the *Z* acids **9a**,**b** were separated (purity ≥90%) and after COOH → COOD exchange were esterified with CD_2N_2 (eq 2). The isomers **4** and **5** obtained were ≥91–95% geometrically pure by ^{1}H NMR.

Geometrical Assignment of Precursors and Products. The unlabeled esters **6a** and **6b** show two ester signals in the ^{1}H NMR in $CDCl_3$: at δ 3.57 and 3.86 for **6a** and at δ 3.63 and 3.94 for **6b**. Previous experience with many methyl cinnamate systems $ArC(R^1){=}C(R^2)CO_2Me$ showed that an ester group cis to the aryl group appears always at a higher field compared to the isomer where the two groups are in trans relationship,[3b–d] and this assignment was corroborated in the cases where we have X-ray diffraction data for one of the isomers.[3b–d] This is true also for **7** and **8** and their substitution derivatives. Likewise, pure (*E*)-*p*-$MeC_6H_4CH{=}C(CO_2CH_3)CO_2CD_3$, which was prepared for comparison, conforms to the generalization. Indeed, **4** and **5** showed main signals at δ 3.84 and 3.94, respectively, with signals at ≤5% intensity at δ 3.57 and 3.63, corroborating the generalization and indicating a geometrical purity of ≥95%.

The substitution products of the unlabeled **6a** and **6b** by various nucleophilic moieties showed two methyl ester signals. These were assigned similarly, and since the substitution products formed from **4** and **5** showed two signals (of different intensities; see below) at the same positions, the signal appearing at a lower field was ascribed to the substitution product with trans Ar and COOMe groups and the higher field signal was assigned to its cis isomer.[6] The NMR data used for the analysis are given in Table I together with data for a few structurally related compounds for comparison.

Substitution. The unlabeled bromo diester **6a** was substituted by several phenoxide and *p*-chlorobenzenethiolate ions in DMSO and by MeO^- in MeOH, giving the substitution products **12a–f** (eq 3). *p*-Nitrophenoxide ion did not react under the mild reaction

$$\underset{\textbf{6a}}{p\text{-}MeC_6H_4C(Br){=}C(CO_2Me)_2} + Nu^- \xrightarrow{\text{DMSO}} p\text{-}MeC_6H_4C(Nu){=}C(CO_2Me)_2 \quad (3)$$

12a, Nu = PhO
b, Nu = *p*-MeC$_6$H$_4$O
c, Nu = *p*-BrC$_6$H$_4$O
d, Nu = *p*-MeOC$_6$H$_4$O
e, Nu = MeO (in MeOH)
f, Nu = *p*-ClC$_6$H$_4$S

$$p\text{-}MeC_6H_4C(Cl){=}C(CO_2Me)_2 + p\text{-}MeC_6H_4S^- \xrightarrow{\text{DMSO}} \underset{\textbf{12g}}{p\text{-}MeC_6H_4C(SC_6H_4Me\text{-}p){=}C(CO_2Me)_2} \quad (4)$$

conditions, and *tert*-butoxide ion did not give a product with a *tert*-butyl signal. The chloro analogue of **6a** gave the product **12g** (eq 4). Reaction of **6a** with sodium borohydride in MeCN–MeOH did not show the formation of the substitution product **12h**, even when the reaction was incomplete. Instead, the double-bond reduction product of **12h**, i.e., **13**, was obtained (eq 5). Independently prepared **12h** gave **13** under the same reaction conditions.

$$\textbf{6a} \xrightarrow[\text{MeCN-MeOH}]{\text{NaBH}_4} \underset{\textbf{12h}}{p\text{-}MeC_6H_4CH{=}C(CO_2Me)_2} \rightarrow \underset{\textbf{13}}{p\text{-}MeC_6H_4CH_2CH(CO_2Me)_2} \quad (5)$$

Substitution of the unlabeled diester **6b** with three sodium phenoxides and two sodium thiophenoxides in DMSO gave the substitution products **14a–e**. In a slower reaction, *p*-toluidine gave **14f** (eq 6). In the reaction with sodium azide in acetonitrile, ^{1}H NMR showed that the substitution product **14g** was initially formed. However, **14g** was not isolated since it lost nitrogen and gave the rearranged ketene imine *p*-$O_2NC_6H_4N{=}C{=}C(CO_2Me)_2$. This reaction will be discussed elsewhere.

The reaction with potassium thiocyanate was slow at room temperature and gave four products (A–D) on reflux. The initial reaction product A is the substitution product **14h** and is the main product after 3 h. It is accompanied by product B, which is formed

(4) Gazit, A.; Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **1984**, 2863.
(5) For an exception due to a vinyl cation character of the substrate, see: Cappozi, G.; Luccini, V.; Modena, G.; Scrimin, P. *Tetrahedron Lett.* **1977**, 911.

(6) An exception where the assignments are apparently reversed are (*E*)- and (*Z*)-*p*-$MeC_6H_4CH{=}C(CO_2CH_3)CO_2CD_3$ in C_6D_6.

$$p\text{-}O_2NC_6H_4C(Br){=}C(CO_2Me)_2 \xrightarrow{Nu^- \text{ or } NuH} p\text{-}O_2NC_6H_4C(Nu){=}C(CO_2Me)_2 \quad (6)$$

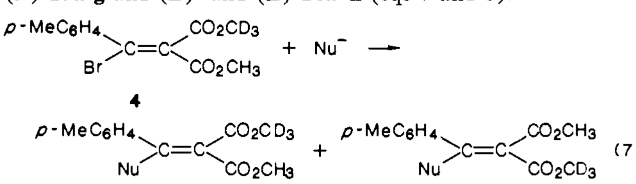
6b

14a, Nu = PhO (in DMSO)
b, Nu = p-MeC$_6$H$_4$O (in DMSO)
c, Nu = p-MeOC$_6$H$_4$O (in DMSO)
d, Nu = p-MeC$_6$H$_4$S (in DMSO)
e, Nu = p-ClC$_6$H$_4$S (in DMSO)
f, NuH = p-MeC$_6$H$_4$NH$_2$ (in MeCN)
g, Nu = N$_3$ (in MeCN)
h, Nu = SCN (in MeCN)

from A and is the main product after 16 h. B itself is converted to C, and product D is formed from either B or C. The structures of B–D are unknown. (See Experimental Section.) The analogous reaction with potassium cyanate was slower and required reflux for 17 h with excess nucleophile. The NMR, but not the mass spectrum, is consistent with an initial formation of the substitution product, and the reaction was not investigated further.

The reaction with KCN gave several products. Many CO$_2$Me signals were observed in the ^{1}H NMR. Since the main one is a singlet, a decarbomethoxylation probably took place.[7] **6b** was recovered unchanged from its reaction with a large excess of AgOMs at room temperature.

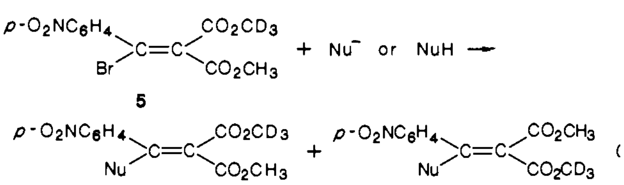
Stereochemistry of the Substitution. The methyl trideuteriomethyl bromoesters **4** and **5** were substituted by the nucleophiles used for the substitution of their unlabeled analogues in eq 3, 4, and 6. The reactions were followed by ^{1}H NMR, and two CO$_2$Me signals, which in nearly all cases were of different intensity, were observed at the positions of the two CO$_2$Me signals of the unlabeled products **12a–g** and **14a–h**. They were therefore ascribed to the (E)- and (Z)-methyl trideuteriomethyl analogues (E)- and (Z)-**15a-g** and (E)- and (Z)-**16a–h** (eqs 7 and 8).



(7)

(E)-**15a**, Nu = PhO; **b**, Nu = p-MeC$_6$H$_4$O; **c**, Nu = p-BrC$_6$H$_4$O; **d**, Nu = p-MeOC$_6$H$_4$O; **e**, Nu = MeO; **f**, Nu = p-ClC$_6$H$_4$S; **g**, Nu = p-MeC$_6$H$_4$S

(Z)-**15a**, Nu = PhO; **b**, Nu = p-MeC$_6$H$_4$O; **c**, Nu = p-BrC$_6$H$_4$O; **d**, Nu = p-MeOC$_6$H$_4$O; **e**, Nu = MeO; **f**, Nu = p-ClC$_6$H$_4$S; **g**, Nu = p-MeC$_6$H$_4$S



(8)

(E)-**16a**, Nu = PhO; **b**, Nu = p-MeC$_6$H$_4$O; **c**, Nu = p-MeOC$_6$H$_4$O; **d**, Nu = p-MeC$_6$H$_4$S; **e**, Nu = p-ClC$_6$H$_4$S; **f**, NuH = p-MeC$_6$H$_4$NH$_2$; **g**, Nu = N$_3$; **h**, Nu = SCN

(Z)-**16a**, Nu = PhO; **b**, Nu = p-MeC$_6$H$_4$O; **c**, Nu = p-MeOC$_6$H$_4$O; **d**, Nu = p-MeC$_6$H$_4$S; **e**, Nu = p-ClC$_6$H$_4$S; **f**, NuH = p-MeC$_6$H$_4$NH$_2$; **g**, Nu = N$_3$; **h**, Nu = SCN

The reactions were mostly conducted in CD$_3$CN or in 95:5 CD$_3$CN–DMSO-d_6, which were found to give convenient reaction rates. The addition of DMSO-d_6 to CD$_3$CN improved the solubility of the nucleophilic and product salts and increased somewhat the rate of substitution. Several reactions were conducted in DMSO-d_6. However, in this solvent a broad signal, which we ascribe to traces of water in the commercial DMSO-d_6, occassionally appeared at different positions in different reactions at δ ca. 3.35. Its position also changed during the reaction. In some cases, as in the reaction of **4** with PhO$^-$, it did not interfere, whereas in other cases, e.g., in the reaction of **4** with TolO$^-$, it overlapped the signal of the (Z)-**15b** product, and the reaction could not be followed. Careful drying of the solvent over molecular sieves eliminated this peak. The reaction of **5** with TolS$^-$ was also studied in (CD$_3$)$_2$CO and in 1:1 CD$_3$CN–CDCl$_3$, in which the reaction was the slowest of those studied.

The reactions with the phenoxy nucleophiles could be followed by NMR. For example, with a [PhO$^-$]/[**4**] ratio of 1.4 the half-life (τ) of the reaction was ca. 30 min, and with a [TolO$^-$]/[**5**] ratio of 1.3, $\tau \sim 10$ min in CD$_3$CN. The reactions with thiolate nucleophiles were much faster. E.g., in the addition of an unweighed amount of TolS$^-$Na$^+$ to **4** (see below) the same reaction percentage was obtained after 2 and 115 min; i.e., the reaction was complete at the first experimental point. The reactions with N$_3^-$, SCN$^-$, and especially p-toluidine were much slower.

Two problems were encountered in the calculation of the E/Z product ratios. First, in the stereospecific syntheses of **4** and **5**, these products were obtained together with small amounts of their Z isomers. **4** contained 6–7% of the Z isomer, and **5** contained 5% of the Z isomer, except in two preparations, when it contained 11% or 15% of the isomer. Elimination of these impurities is impossible by the usual purification techniques. Fortunately, when the E/Z precursor ratio is accurately known, an accurate correction for the presence of the Z isomer could be introduced since the E/Z product ratio from the E bromide is identical within experimental error with the Z/E product ratio from the Z bromide.

If x is the fraction of E bromide in the ($E + Z$) bromide mixture and y is the fraction of the E product obtained under kinetic control when starting from the pure E bromide, the *observed* fraction of E product in the ($E + Z$) products starting from the ($E + Z$) bromide mixture (f_{obsd}) is given by eq 9. The value of y is given by eq 10.

$$f_{obsd} = xy + (1 - x)(1 - y) \quad (9)$$

$$y = [f_{obsd} - (1 - x)]/(2x - 1) \quad (10)$$

Second, as with previous examples of substitutions of highly activated vinyl halides,[3b-d] the kinetically controlled E/Z product distribution changes with the progress of the reaction. This was previously ascribed to a reversible addition of the nucleophile to the double bond of the product, an intramolecular rotation in the formed intermediate carbanion, and nucleophile expulsion from a carbanionic conformer that leads to an isomer of the precursor. Two different approaches were used in order to overcome this problem. In the first, used for most reactions of **4**, the [Nu$^-$]$_{initial}$/[substrate] ratio was <1. Comparison of the E/Z product ratios obtained for the first and the last experimental points (when the nucleophile was mostly or completely consumed) shows (Table II) that the isomerization during the reaction is still extensive. Therefore, in most reactions of **5** and a few reactions of **4** the salt of the nucleophile was added portionwise, in proportions that ensured that the [Nu$^-$]/[substrate] ratio remained relatively small at each stage of the reaction. Since only the initial E/Z product distribution was desired, no attempt was made to determine accurately the amount of the nucleophile added in each portion. This procedure reduced appreciably the extent of isomerization during the reaction, especially in the fast reactions with ArS$^-$ ions, where the E/Z product ratios remained nearly constant during the reaction (cf. reactions 28 and 29 in Table II). However, isomerization was still important in the slower reactions with the oxygen and N$_3^-$ nucleophiles, as shown by comparison of the E/Z values at the first and at the last experimental point, which were closer to the 1:1 E/Z product equilibrium ratio (Table II).

When the E/Z ratios were changed during the reaction, they were extrapolated to zero reaction times by using plots of E/Z product ratios vs time. The first experimental point was mostly after 2–5 min, and the extrapolation was not extensive. The

(7) Halide ion promoted dechlorocarbomethoxylation of compounds RC(Cl)=C(CO$_2$Me)$_2$ to RC≡CCO$_2$Me (R = CN, CO$_2$Me) is known: Ykman, P.; Hall, H. K., Jr. *Tetrahedron Lett.* **1975**, 2429. (A related reaction is the formation of acetylenic esters from the reaction of RC(OSO$_2$Ar)=C(CO$_2$Et)$_2$ with base. E.g.: Fleming, I.; Owen, C. R. *J. Chem. Soc. B* **1971**, 1293.

Table I. δ(COOMe) Values for ArC(X)=C(COOMe)COOR (R = H, Me)[a]

Ar[b]	X[b]	R	substrate[c]	solvent	δ(COOMe) cis to Ar	δ(COOMe) trans to Ar	δ(Me)	Δδ(COOMe)[d]
Tol	H	H	*E* isomer	$CDCl_3$		3.88	2.38	0.01
	H	H	*Z* isomer	$CDCl_3$	3.87		2.38	
	Br	H	**9a**	$CDCl_3$		3.90	2.38	0.30
	Br	H	**10a**	$CDCl_3$	3.60		2.38	
	H	CD_3	*E* isomer	$CDCl_3$		3.83		
				C_6D_6		3.48		
	H	CH_3	**12h**	$CDCl_3$[e]	3.83	3.85	2.36	0.02
				C_6D_6[e]	3.38	3.50	1.96	0.12
	Cl	CH_3		$CDCl_3$[e]	3.61	3.88	2.38	0.27
	Br	CH_3	**6a**	$CDCl_3$[f]	3.59	3.89	2.38	0.30
				C_6D_6	3.10	3.48	1.92	0.36
				DMSO-d_6	3.53	3.82	2.34	0.29
	Br	CD_3	**4**	$CDCl_3$		3.89	2.38	0.30
	Br	CD_3	*Z* isomer	$CDCl_3$	3.59		2.38	
	PhO	CH_3	**12a**	$CDCl_3$	3.65	3.75	2.28	0.10
				DMSO-d_6	3.56	3.66	2.24	0.10
	TolO	CH_3	**12b**	$CDCl_3$	3.64	3.76	2.28, 2.20	0.12
				DMSO-d_6	3.52	3.66	2.25, 2.15	0.14
	p-BrC_6H_4O	CH_3	**12c**	$CDCl_3$	3.66	3.77	2.31	0.11
				DMSO-d_6	3.57	3.68	2.27	0.11
	AnO	CH_3	**12d**	$CDCl_3$	3.68	3.77	2.28, 3.63	0.09
				DMSO-d_6	3.54	3.68	2.25, 3.63	0.14
	MeO	CH_3	**12e**	$CDCl_3$	3.53	3.84	2.40, 3.52	0.31
	TolS	CH_3	**12g**	$CDCl_3$	3.43	3.83	2.19, 2.18	0.40
				DMSO-d_6	3.34	3.72	2.15	0.38
	p-ClC_6H_4S	CH_3	**12f**	$CDCl_3$	3.43	3.84	2.21	0.41
				DMSO-d_6	3.35	3.74	2.17	0.39
p-$O_2NC_6H_4$	Br	H	**9b**	$CDCl_3$		3.95		
				$(CD_3)_2CO$		3.90		
	Br	H	**10b**	$CDCl_3$	3.63			
				$(CD_3)_2CO$	3.60			
	Br	CD_3	**5**	$CDCl_3$		3.94		0.31
	Br	CD_3	*Z* isomer	$CDCl_3$	3.63			
	Br	CH_3	**6b**	$CDCl_3$	3.63	3.94		0.31
				DMSO-d_6	3.54	3.86		0.32
				95:5 CD_3CN–DMSO-d_6	3.55	3.88		0.33
	H	CH_3		$CDCl_3$[e]	3.85	3.89		0.04
				CD_3CN	3.82	3.84		0.02
	PhO	CH_3	**14a**	$CDCl_3$	3.66	3.80		0.14
				DMSO-d_6	3.59	3.73		0.14
				95:5 CD_3CN–DMSO-d_6	3.61	3.75		0.14
	TolO	CH_3	**14b**	$CDCl_3$	3.66	3.82	2.20	0.16
				DMSO-d_6	3.57	3.72	2.14	0.15
				95:5 CD_3CN–DMSO-d_6	3.59	3.75	2.18	0.16
	AnO	CH_3	**14c**	$CDCl_3$	3.65	3.83	3.68	0.18
				DMSO-d_6	3.56	3.74	3.63	0.18
				95:5 CD_3CN–DMSO-d_6	3.58	3.76	3.65	0.18
	TolS	CH_3	**14d**	$CDCl_3$	3.46	3.90	2.20	0.44
				DMSO-d_6	3.36	3.80	2.14	0.44
				95:5 CD_3CN–DMSO-d_6	3.39	3.83		0.44
	p-ClC_6H_4S	CH_3	**14e**	$CDCl_3$	3.60	4.05		0.45
				DMSO-d_6	3.52	3.95		0.43
				95:5 CD_3CN–DMSO-d_6	3.39	3.83		0.44
	SCN	CH_3	**14h**	$CDCl_3$	3.52	3.91		0.39
				CD_3CN	3.45	3.87		0.42
	N_3	CH_3	**14g**	$CDCl_3$	3.59	3.89		0.30
				CD_3CN	3.50	3.82		0.32
	OCN	CH_3	**14i**	$CDCl_3$	3.42	3.84		0.42
	p-MeC_6H_4NH	CH_3	**14f**	CD_3CN	3.36	3.83		0.47

[a]Values are reproducible to ±0.01 ppm. For comparison, δ ($CDCl_3$) for (*E*)-TolCH=CHCOOMe:2.36 (Me), 3.79 (COOMe). [b]Tol = *p*-MeC_6H_4; An = *p*-$MeOC_6H_4$. [c]The signals reported for the dimethyl esters **12a–g** and **14a–i** appear in the same positions also in the corresponding methyl trideuteriomethyl esters (*E*)- and (*Z*)-**15a–g** and (*E*)- and (*Z*)-**16a**–h formed in the substitutions of **4** and **5**. [d]Δδ(COOMe) = δ(COOMe trans to Ar) − δ(COOMe cis to Ar). [e]From ref 17. [f]Reported (footnote *e*): δ(COOMe) 3.57, 3.86 on a different spectrometer.

estimated error in the values is ±1–2%. In the few cases where the change in the *E*/*Z* ratios during the reaction was larger, the estimated error is ≤3%. By applying eq 10 to the extrapolated values, we obtained the kinetically controlled *E*/*Z* product ratios (Table II, last column). Table II also contains data on the product distributions at the first and the last experimental points, which serve as a measure of the extent of isomerization during the reaction. The column before the last shows that the equilibrium *E*/*Z* distribution was not achieved except in two reactions under the experimental conditions.

Monitoring the CO_2Me region of each reaction also enabled the detection of $E \rightleftharpoons Z$ isomerization of the precursor bromides **4** and **5** during the reaction. This was observed only in reactions 35 and 36 of Table II. In the substitution of **5** by KSCN in CD_3CN **5** was isomerized to a 1:1 mixture of **5** and its *Z* isomer before any substitution product was formed. The possibility that this is due to a photochemical isomerization is excluded since the **5** $\rightleftharpoons$ *Z* isomer isomerization was observed (although it was slower) also in the absence of light. Starting from a 92/8 ratio of **5**/*Z* isomer, 76/24 and 67/33 ratios were obtained after 16 and 45

Table II. Substitution of (*E*)-ArC(Br)=C(CO_2CH_3)CO_2CD_3 by Nucleophiles at Room Temperature

no.	substrate[a]	concn, M	Nu^-M^+ [b]	[Nu^-], M	[Nu^-]/[subs]	solvent	products	T_0,[c] min	% reactn[d]	E/Z product ratio[d]	T_∞,[e] min	% reactn[f]	E/Z product ratio[f]	kinetically controlled E/Z product ratio[g]
1	**6a**	0.087	PhO^-Na^+	0.138	1.6	DMSO-d_6	**12a**	2	12		3600	96		
2	**4**	0.030	PhO^-Na^+	0.015	0.5	CD_3CN	(*E*)- + (*Z*)-**15a**	15	8	79/21	65	29	58/42	93/7[h]
3	**4**	0.047	PhO^-Na^+	0.035	0.75	DMSO-d_6	(*E*)- + (*Z*)-**15a**	3	30	78/22	210	67	56/44	82/18[i]
4	**4**	0.070	PhO^-Na^+	0.129	1.8	DMSO-d_6	(*E*)- + (*Z*)-**15a**	5	45	91/9	30	97	70/30	97/3
5	**4**	0.030	$TolO^-Na^+$	0.010	0.33	CD_3CN	(*E*)- + (*Z*)-**15b**	20	6	75/25	120	21	57/43	85/15[h]
6	**4**	0.030	$TolO^-Na^+$	0.015	0.5	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**15b**	3	4	85/15	60	28	58/42	91/9
7	**4**	0.045	$TolO^-Na^+$	0.108	2.4	DMSO-d_6	(*E*)- + (*Z*)-**15b**	3	76	79/21	6	94	75/25	87/13
8	**4**	0.074	$TolO^-Na^+$	0.063	0.85	DMSO-d_6	(*E*)- + (*Z*)-**15b**	2	65	78/22	25	65	78/22	83/17
9	**4**	0.030	*p*-$BrC_6H_4O^-Na^+$	0.015	0.5	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**15c**	5	6	86/14	50	41	64/36[k]	92/8
10	**4**	0.030	AnO^-Na^+	0.015	0.5	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**15d**	6	7	87/13	51	43	67/33	96/4
11	**4**	0.057	AnO^-Na^+	0.090	1.6	DMSO-d_6	(*E*)- + (*Z*)-**15d**	8	42	85/15	80	46	60/40	96/4[h]
12	**4**	0.026	MeO^-Na^+	*m*	*m*	CD_3CN	(*E*)- + (*Z*)-**15e**[l]	3	0		60	*l*	*l*	*l*
13	**4**	0.030	*p*-$ClC_6H_4S^-Na^+$	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**15f**	3	17	84/16	*m*	75	65/35	91/9
14	**4**	0.030	$TolS^-Na^+$	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**15g**	2	24	82/18	*m*	87	77/23	88/12[h]
15	**4**	0.14	$TolS^-Na^+$	0.057	0.4	DMSO-d_6	(*E*)- + (*Z*)-**15g**	21	77	84/16				*n*
16	**5**	0.028	PhO^-Na^+	0.034	1.2	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16a**	2	22	75/25	40	80	55/45	81/19[h]
17	**5**	0.029	PhO^-Na^+	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16a**	3	17	86/14	*m*	81	53/47	90/10
18	**6b**	0.046	$TolO^-Na^+$	0.061	1.3	CD_3CN	**14b**	4	26		20	70		
19	**5**	0.074	$TolO^-Na^+$	0.063	0.9	DMSO-d_6	(*E*)- + (*Z*)-**16b**	2	65	78/22[o]	30	65	78/22[o]	81/19[o]
20	**5**	0.056	$TolO^-Na^+$	0.081	1.46	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16b**	2	66	62/38	15	97	51/49	68/32[h]
21	**5**	0.028	$TolO^-Na^+$	0.034	1.2	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16b**	2	22	75/25[o]	40	80	55/45	81/19
22	**5**	0.029	$TolO^-Na^+$	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16b**	2	4	83/17	*m*	52	62/38	97/3
23	**5**	0.035	$TolO^-Na^+$	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16b**	3	12	88/12	*m*	83	52/48	98/2[h]
24	**5**	0.030	$TolO^-K^+$	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16b**	2	12	85/15	*m*	72	81/19	90/10
25	**5**	0.030	$TolO^-K^+$	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16b**	2	33	82/18	*m*	100	60/40	86/14
26	**5**	0.030	$TolO^-Li^+$	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16b**	20	6	83/17	*m*	38	73/27	88/12
27	**5**	0.029	AnO^-Na^+	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16c**	5	7	90/10	*m*	54	68/32	95/5[h]
28	**5**	0.042	$TolS^-Na^+$	0.042	1.0	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16d**	1.5	77	85/15	50	81	85/15	89/11
29	**5**	0.040	$TolS^-Na^+$	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16d**	2	48	87/13	*m*	78	87/13	91/9
30	**5**	0.030	$TolS^-Na^+$	0.023	0.76	1:1 CD_3CN–$CDCl_3$	(*E*)- + (*Z*)-**16d**	5	31	86/14	45	47	86/14	90/10
31	**5**	0.035	$TolS^-Na^+$	*m*	*m*	$(CD_3)_2CO$	(*E*)- + (*Z*)-**16d**	3	15	90/10	*m*	100	55/45	94/6[h]
32	**5**	0.047	*p*-$ClC_6H_4S^-Na^+$	0.062	1.3	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16e**	2	100	84/16	50	100	52/48	90/10
33	**5**	0.040	*p*-$ClC_6H_4S^-Na^+$	*m*	*m*	CD_3CN–DMSO-d_6[j]	(*E*)- + (*Z*)-**16e**	3	16	92/8	*m*	95	85/15	96/4
34	**5**	0.026	$N_3^-K^+$ [p]	0.345	13.3	CD_3CN	(*E*)- + (*Z*)-**16g**	12	4	84/16	1440	94[q]	53/47	95/5
35	**5**	0.030	CNS^-K^+	0.180	6	CD_3CN	(*E*)- + (*Z*)-**16h**			*r*	1440	35	50/50	*r*
36	**5**	0.029	*p*-$MeC_6H_4NH_2$	0.065	2.2	CD_3CN	(*E*)- + (*Z*)-**16f**	40	15	50/50	*n*			50/50[n]

[a] **4** contained 6% of the *Z* isomer in experiments 3, 4, 6 and 7 and 7% of the *Z* isomer in the other experiments. **5** contained 5% of the *Z* isomer except in experiments 22 and 34, when the *Z* isomer consists of 15% and 11% of the mixture, respectively. [b] Tol = *p*-MeC_6H_4; An = *p*-$MeOC_6H_4$. [c] Time at which the first experimental point with reliable product distribution was measured. [d] At T_0. [e] Time of the last experimental point. [f] At T_∞. [g] Value at zero reaction time corrected for the presence of the *Z* isomer of reactants. It is obtained either from the constant ratio when this was time independent or by extrapolation when the measured *E*/*Z* ratio changed with time. Unless otherwise indicated, the estimated error is $\pm$1–2%. [h] A less reliable extrapolation than in other cases gives an estimated error of $\lesssim$3%. [i] Similar reaction percentages were obtained by integration of either the COOMe or the *Me*C_6H_4 signals of **4** and **15a**. [j] 95:5 ratio (v/v) of CD_3CN to DMSO-d_6. [k] A 69/31 *E*/*Z* ratio was obtained in DMSO-d_6 after 2 h (66% reaction) with a 1.3-fold excess of the nucleophile. [l] Apparent isomerization of the starting material (see text) prevented determination of the *E*/*Z* ratios. [m] The nucleophile was added portionwise to the reaction mixture, and the product distribution was determined one or more times until all the added nucleophile of each portion was consumed. [n] A one-point experiment. Extrapolation is meaningless. [o] Average of data for two similar experiments. [p] Not all the KN_3 was soluble in the reaction mixture. [q] The product rearranges slowly to the ketene imine. [r] The starting material isomerizes during the reaction so that the extrapolated *E*/*Z* product ratio cannot be obtained.

h in daylight, and 85/15 and 75/25 ratios were obtained after 24 and 40 h, respectively, in the dark. In both cases, the substitution products started to appear only when the E/Z bromide ratio was close to 1:1, and the observed (E)-**16**/(Z)-**16** ratio of 1:1 is due to precursor isomerization.

In the reaction of a 92/8 mixture of **5** and its Z isomer with p-toluidine in the dark at 60 °C for 40 min, 15% of a 1:1 (E)-**16f**/(Z)-**16f** mixture was formed. Concurrent isomerization gave an 84/16 mixture of **5** and its Z isomer.

Reaction of a 76/24 mixture of **4** and its Z isomer with MeO^-Na^+ in CD_3CN resulted in an apparent isomerization to a 1:1 (E)-**15e**/(Z)-**15e** mixture before the appearance of the substitution product. However, the COO*Me* signal of the Z isomer and the vinylic OMe signal of the products (E)- and (Z)-**12e** almost overlap, and this may be the reason for this observation. Although this overlap is removed in a 1:1 CD_3CN–C_6D_6 solvent, the possibility of a transesterification of the CO_2CD_3 group with the MeO^- cannot be excluded. This process can be independently monitored by comparing the intensities of the Me, MeO, and aromatic signals, but due to these complications, the stereochemistry was not studied.

Reaction of an 88/12 mixture of **4** and its Z isomer with a 2.5- and 5-fold excess of Bu_4NBr in $CDCl_3$ at room temperature showed no isomerization after 216 and 126 h, respectively. When the first mixture was kept in DMSO at 90 °C for 22 h, a new compound showing a single CO_2Me signal (which may be $TolC{\equiv}CCO_2Me$ formed by elimination)[7] was observed. When a mixture of **5** (containing 8% of its Z isomer) and 3.7 molar excess of Bu_4NBr was kept in CD_3CN at 20 °C in the dark for 160 h, no $E \rightleftharpoons Z$ isomerization was observed.

Discussion

Three aspects of the present work are of general interest. First, the use for sterochemical studies of a vinylic system with two chemically identical activating groups offers theoretical, but mostly practical advantages. Our systems are the first ones investigated belonging to this category and these advantages, as well as limitations, both general and unique to our systems, will be first discussed. Second, due to the advantages of the system, the number of nucleophile/solvent combinations used for stereochemical investigation is larger than those applied for previous systems. This enables generalizations concerning the structural and external parameters on the stereochemistry and placement of the diester-activated system in the stereoconvergence vs retention region. Third, interesting aspects related to several specific nucleophiles will be mentioned.

Mechanistic Advantages of the Use of Systems with Chemically Identical Activating Groups as Stereochemical Probes. A great advantage of stereochemical investigations at sp^3-hybridized carbon is the identical properties of two enantiomers in an achiral medium, except for their optical rotations. Consequently, it is sufficient to determine the stereochemical course of a reaction with only one enantiomer. The percentages of precursor racemization (an important parameter in determining ion pair return in solvolysis)[8] and of retention, inversion, or stereoconvergence in the process investigated (e.g., substitution) are immediately available from the observed rotation, provided that the rotations of a single enantiomer of the precursor and the product are known. This is a consequence of the fact that the thermodynamic equilibrium ratio of the d and l reactants or of the d and l product(s) is always unity when there is but one chiral center.

This advantage is not available for vinylic compounds.[9] For example, in the substitution of vinyl halides, the E and Z precursors differ in their chemical and physical properties and thus so do the E and Z products. If a single isomer is studied, the stereochemical outcome of the overall reaction is not established even if a single isomeric product is formed. For example, the retained Z substitution product is obtained exclusively from the precursor (Z)-$RC_\alpha(Br){=}CHR'$ (R = alkyl, Ar) by either a rate-determining nucleophilic attack on C_α or via an elimination (E2 or E1cB)–addition process.[2b,g] The E bromide should also be studied since it may give either the E product by reaction at C_α or the Z product by an elimination (E1cB)–addition route. When both E and Z products are formed from one isomeric precursor, it is impossible to predict if both will be formed, or their ratio, from the other isomeric precursor. Moreover, even when the E/Z product ratios from both processes are known, calculation of the extent of stereoconvergence requires the knowledge of the thermodynamic E/Z product equilibrium. (Complete stereoconvergence is defined as the formation of identical kinetic E/Z product ratios from both E and Z precursors. Partial stereoconvergence means that different E/Z product ratios are formed from the two precursors.[3])

These differences between substitutions at sp^3- and sp^2-hybridized carbon put a heavy experimental burden when stereochemistry is used as a mechanistic probe for substitution at sp^2-hybridized carbon. For each nucleophile studied both E and Z precursors and both E and Z products have to be prepared and identified. The equilibrium constant for each pair of E and Z products should be determined at the reaction temperature. The situation becomes simpler when both isomers give an exclusive retention, as is usually the case with slightly activated systems. The products could then be easily isolated and identified from these stereoselective and stereospecific reactions. However, most mechanistic information is obtained for the systems studied by us in recent years.[3] These systems give complete or partial stereoconvergence and are characterized by being diactivated. All these precursors were tetrasubstituted ethylenes for which separation and sometimes even assignment of the geometrical structure are not always easy.

For diactivated systems where the two activating groups are sterically similar (e.g., $COCF_3$ and $COCH_3$ or $CO_2CH_2CF_3$ and $CO_2CH_2CH_3$), the E/Z equilibrium ratios of reactants and products are likely to be near unity, but this conclusion should be confirmed for each system. In contrast, most of the abovementioned complications are removed when the two activating groups become chemically identical but isotopically distinguishable. If isotopic effects can be neglected when the isotopic change is remote from the reaction center as in our compounds, the symmetry imposed on the system confers on it a behavior similar to that described for reaction at sp^3-hybridized carbon. The E and Z isomers of the reactants and each isomeric E/Z pair of the product regardless of the nucleophile have identical energies, and the thermodynamic equilibrium constants for each E/Z isotopomeric pair will be therefore unity. The chemical behavior of the E and Z isotopomers will be identical, and it is sufficient to study the stereochemistry with only a single isotopomer. The problem is therefore reduced to the stereospecific preparation of a single isotopomer and to a rapid and reliable assignment of its configuration and of the configurations of the substitution products.

^1H NMR is an ideal probe for geometrical assignment since a CH_3 group gives a singlet whereas the CD_3 group is invisible. A CH_3 group can be easily introduced into activating groups such as $COCH_3$, CO_2CH_3, SO_2CH_3, etc. In view of the conformation-dependent shielding–deshielding effects caused by an aryl group on proximate and remote protons, an appreciable difference between the chemical shifts of groups cis and trans to the aryl group is expected.

These considerations were proven to be correct for our systems, where the following aspects demonstrate the advantages of our approach. (a) The feasibility of reaction with nucleophiles of interest is checked by reacting these nucleophiles with the easily prepared unlabeled **6a** and **6b**. (b) With those nucleophiles that give substitution there is no need to isolate the (relatively expensive) deuteriated derivative. Isolation of the nondeuteriated compounds **12a–g** and **14a–h** serve the same purpose. (c) There is no need to separate E and Z isomers of the products. (d) The ^1H NMR spectrum of the unlabeled products immediately shows

(8) For a review, see: Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley: London, 1974; Vol. 2, Chapter 3, pp 247–374.

(9) For a recent example of the use of an optically active (atropisomeric) vinyl halide in nucleophilic vinylic substitution, see: Cabaret, D.; Maigrot, N.; Welvart, Z.; Duong, K. N. V.; Gaudemer, A. *J. Am. Chem. Soc.* **1984**, *106*, 2870.

that NMR is applicable as a stereochemical probe. (e) The stereospecific synthesis of the E diesters **4** and **5** establishes their structure. This is important since a drawback of our approach is that X-ray diffraction cannot be used for structural assignment of our isotopomers. X-ray diffraction of our precursor monoacid monoesters **9** and **10** is unnecessary since the correlation between the positions of the CO_2Me groups and their δ's as given in Table I seems to us sufficiently unequivocal for the structural assignment. (f) The presence of a few percent of the Z isomer does not disturb the stereochemical studies due to the correction by using eq 9 and 10. Indeed, our systems seem to have an advantage over optically active sp^3-hybridized halides in this respect. The optical rotation probe used in studying the latter requires the knowledge of the rotation of the pure enantiomer. Since the optical activity of the whole solution is used for calculating the extent of retention, inversion, or racemization, the formation of optically active impurities or the racemization of the precursor halide will introduce an error into these calculations. In contrast, in our system the isomerization of the precursor halide, the E/Z ratio of the substitution product, and the formation of impurities are independently monitored without isolation of the various components. (g) The main generalization used for geometrical assignment and hence for the determination of the E/Z product ratios is that the ester group trans to the aryl appears in the ^1H NMR at a lower field than the CO_2Me cis to the aryl. Earlier studies on the positions of the COOR groups in (E)- and (Z)-ArC(X)=C(CO_2Me)R (R = CO_2Bu-t,[3d] CN,[3b] CHO,[3d] H),[10] which were occasionally corroborated by X-ray diffraction data,[3b,d] led, without exception, to this generalization. This is corroborated by comparison of the spectra of **6a** and **4** or of **6b** with **5**. The assignments in Table I are also consistent with the stereochemical results. In bimolecular nucleophilic vinylic substitutions studied so far the reactions proceeded with retention or with partial or complete stereoconvergence for reasons that are summarized below. However, a preferred inversion was never observed (except for a specific and irrelevant system).[5] In line with this, in the present study the E product was the one formed always in excess. The possibility that either all our reactions proceed with complete inversion or the assignment for **4** and **5** is opposite to those for all other compounds in Table I is highly unlikely. (h) Starting from the pure E bromide, only one product signal should be observed for complete retention, and two product signals of equal intensities will be observed for complete stereoconvergence. Since the CO_2Me signals are sharp singlets, even a casual glance at the spectrum will give the stereochemical outcome. It is clear that none of our reactions proceeds with complete retention, although for almost all of them the extent of the retention is high.

An interesting observation, reported also previously for the systems mentioned above,[3d] is that $\Delta\delta(CO_2Me)$ ($\Delta\delta$ of the two CO_2Me groups) is practically unaffected by changing the solvent from CD_3CN to DMSO-d_6. However, both $\delta(CO_2Me)$ and $\Delta\delta$-(CO_2Me) are strongly affected on changing the solvent to C_6D_6.

In addition, the $\Delta\delta(CO_2Me)$ values are strongly influenced by the α-substituent X. They are much higher for the sulfur-substituted systems (being 0.38–0.45) than for the phenoxide-substituted systems (0.09-0.18), although the values for the oxygen substituents OMe and OCN (3.31, 0.42) are higher. The highest value is for X = TolNH. There is also a trend for a higher $\Delta\delta(CO_2Me)$ value for the same X when the aryl is changed from p-tolyl to p-nitrophenyl. These generalizations could facilitate future planning of substrate/nucleophile/solvent systems for nucleophilic vinylic substitution.

Stereochemistry of the Substitution of Dimethyl (α-Bromoarylidene)malonates. Reactions at the Stereoconvergence Region. The extensive data of Table II lead to one general and qualitative conclusion: *the reactions of dimethyl (α-bromoarylidene)-malonates with nucleophiles proceed initially with high, but incomplete retention of configuration.* The stereochemical outcome involves partial stereoconvergence. This conclusion applies regardless of internal structural and external media changes. These include changes in the electronic effects from the electron-withdrawing α-p-$O_2NC_6H_4$ to the electron-donating α-p-tolyl and changes in the nucleophile from the moderately reactive phenoxide ions to the softer and more reactive arylthiolate ions, which also include changes within each series from electron-donating to electron-withdrawing para substituents, and the N_3^- nucleophile (an exception is the reaction with p-toluidine, which is discussed below). The external changes are in the cation in the series Li^+, Na^+, K^+ in the reaction of $TolO^-$ with **5** and in the solvent, mainly from CD_3CN to DMSO-d_6.

More quantitatively, in almost all the reactions the percentage of the retained E product is ≥80% and in half of them it is ≥90%. Since formation of a 50:50 E/Z product mixture is regarded as complete stereoconvergence, we can also define an "excess retention", i.e., the percentage of retained product in excess of its value at complete stereoconvergence. The percentages of "excess retention" and "stereoconvergence" are complementary, and almost all our reactions proceed with ≥60% excess retention (≤40% stereoconvergence) and half of them with ≥80% excess retention (≤20% stereoconvergence).

The analysis of differences in the percentage of stereoconvergence within this range depends on the accuracy of the determination of the E/Z ratios. The ratios depend on the activation free energies for the "retention route" and the "inversion route" (see below), and the differences in energies for, e.g., a 97/3 and a 90/10 distribution are much larger than the percentage difference in the E isomer in both cases. We estimated above that the error due to $E \rightleftharpoons Z$ isomerization in a single experiment is mostly 1–2%, but comparison of experiments under similar conditions (Table II, e.g., experiments 7 and 8, 16 and 17, 21 and 22, 24 and 25, 28 and 29, and 32 and 33) suggests a larger error in the ratio for each substrate/nucleophile/solvent system. A main reason is that the error in the NMR integration is usually a few percent and is larger when the inverted component is present in relatively low percentage. Hence, we did not take average values of the numbers in the last column of Table II. We will not regard differences up to 5% in the percentage of the E product as significant in the comparisons.

Within this limitation, in the reactions of **4**, a change in the para substituent in the phenoxide ion from MeO to Me, H, and Br in 95:5 CD_3CN–DMSO-d_6 and CD_3CN (experiments 4, 6, 9, and 10) did not affect the initial E/Z product ratios, which were 91/9 to 96/4. The limited data in DMSO-d_6 for PhO^- and AnO^- (experiments 4 and 11) show similar behavior, but $TolO^-$ gives a lower ratio (experiments 7 and 8). However, the first point in these experiments was already at ≥65% reaction. The ratios are also similar for p-$ClC_6H_4S^-$ and $TolS^-$ (experiments 13 and 14). Likewise in the reactions of **5** the ratios for PhO^-, AnO^-, p-$ClC_6H_4S^-$, $TolS^-$, and N_3^- (experiments 17, 27, 31, 33, and 34) are between 90/10 and 96/4, and the most reliable experiment with $TolO^-Na^+$ (experiment 22) gives a 97/3 ratio. In both series the differences between the ArS^- and the ArO^- nucleophiles are small and unsystematic.

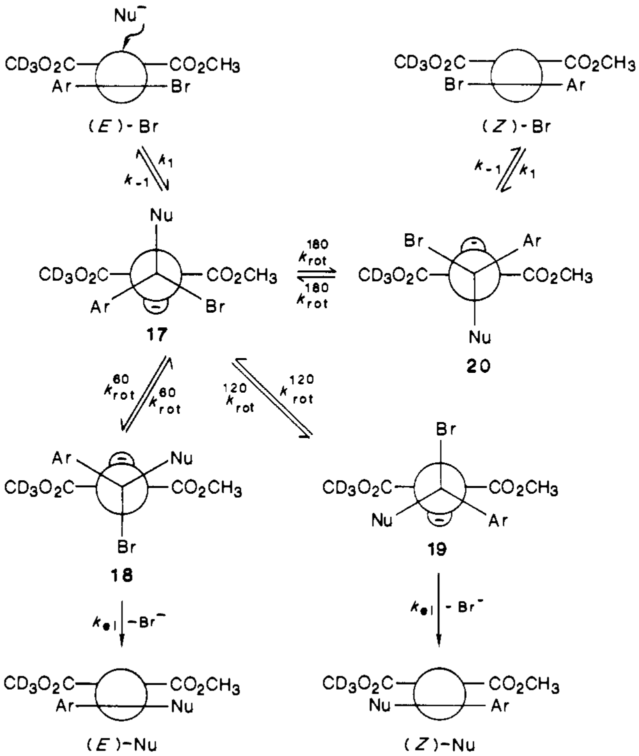
The solvent effect on the ratios is within experimental error. The ratios are 90/10 to 94/6 for the reaction of $TolS^-$ with **5** in CD_3CN, 1:1 CD_3CN–$CDCl_3$, and 95:5 CD_3CN–DMSO-d_6 (experiments 28–31) and for the reactions of **4** with AnO^- (experiments 10 and 11), $TolO^-$ (experiments 6 and 7), and PhO^- (experiments 2 and 4; see, however, experiment 3). The ratios do not change on changing the cation from Li^+ to K^+ in the reactions of **5** with $TolO^-M^+$, but it is difficult to compare them with those for the Na^+ salt since these show a large scatter and some are very inaccurate. $E \rightleftharpoons Z$ isomerizations may be responsible for this.

Finally, in the reactions of **4** and **5** in CD_3CN–DMSO-d_6 with PhO^- (experiments 2 (in CD_3CN) and 17), $TolS^-$ (experiments 14, 28, and 29), and p-$ClC_6H_4S^-$ (experiments 13, 32, and 33) the ratios are similar. With AnO^- (experiments 10 and 27) the ratio is somewhat higher for **5**, while comparison with $TolO^-$ (experiment 6 or 5 vs experiments 20–23) is again difficult.

The quantitative conclusion therefore resembles very much (although not for each case) the qualitative conclusion. The effect

(10) Hayashi, T. *J. Org. Chem.* **1966**, *31*, 3253.

Scheme I



of structural and external parameters on the ratios is minor.

It was suggested by us previously that a partial stereoconvergence argues strongly for a multistep substitution via an intermediate carbanion, and the same reasoning applies in the present case. The corresponding reaction scheme is simplified in the present case due to the chemical identity of the CO_2CH_3 and the CO_2CD_3 groups and is presented in Scheme I.

The nucleophilic attack on *E* bromide gives the carbanionic conformer **17**. Internal rotation in **17** of 60°, 120°, and 180° leads correspondingly to conformers **18**, **19**, and **20**. Expulsion of Br^- from **18** gives the retained *E* product, expulsion of Br^- from **19** gives the inverted product, and expulsion of Nu^- from **20** gives the isomeric *Z* precursor. Stereoconvergence is obtained from a combination of the "retention route" (**17** → **18** → (*E*)-Nu) and the "inversion route" (**17** → **19** → (*Z*)-Nu). A priori, either the rotation (k_{rot}) or the elimination (k_{el}) process can be rate determining. However, a unique characteristic of our system is that k_{el}(from **18**) = k_{el}(from **19**), neglecting isotope effects. If k_{el} were rate determining, an **18** ⇌ **19** equilibration would prevail before Br^- expulsion and the Curtin–Hammett principle will be applicable. The stereochemistry would then be a complete stereoconvergence, in contrast with the observation.

We therefore suggest that k_{rot} is rate determining in the formation of both (*E*)-Nu and (*Z*)-Nu. Since the stereochemical outcome is "excess retention" and (*E*)-Nu/(*Z*)-Nu = $k_{rot}^{60}/k_{rot}^{120}$, $k_{rot}^{60} > k_{rot}^{120}$. From the *E*/*Z* values of Table I, the difference in $\Delta G^{\ddagger}$, i.e., $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}$(inversion) − $\Delta G^{\ddagger}$(retention) = $\Delta G^{\ddagger}$(120° rotation) − $\Delta G^{\ddagger}$(60° rotation), is 1–2 kcal mol^{-1}.

The $\Delta G^{\ddagger}$ values for rotation can be artificially separated into two components, steric and hyperconjugative. In the 60° rotation only an eclipsing Ar/CO_2CD_3 interaction is encountered, whereas in the 120° rotation the two eclipsing interactions Nu/CO_2CD_3 and Br/CO_2CH_3 do not occur simultaneously and the larger of them will determine the steric barrier. The Ar/CO_2CD_3 and Nu/CO_2CD_3 interactions depend on the conformations of these multiatom groups, and it is likely that the least hindered conformations will be involved in the rotation process in order to minimize the eclipsing interactions. The Br/CO_2CH_3 interaction seems therefore the largest one.

The hyperconjugative contribution results from the overall stabilizing interaction between a carbanionic $2p(C^-)$ orbital and a neighboring C–X bond in $RR'\bar{C}-CH_2X$ (negative hyperconjugation).[11] It is maximal when the $2p(C^-)$ and the C–X orbitals are eclipsed and minimal when they are perpendicular. In carbanions of the type $YY'\bar{C}-CXY''Z$ such as conformers **17–20**, the interactions of $2p(C^-)$ with the C–X, C–Y″, and C–Z bonds should be considered. A rotation of 60° will be preferred when the interaction $2p(C^-)$/C–Br is larger than the $2p(C^-)$/C–Ar interaction, and 120° rotation will be preferred when the opposite is true. Gas-phase calculations show that a $2p(C^-)$/C–Cl interaction is much higher than a $2p(C^-)$/C–Ar interaction,[12a] and we suggested recently that the interactions with C–Cl and C–Br bonds are similar.[1b] Hence, 60° rotation will be hyperconjugatively preferred.[12a] The energy differences between the 60° and the 120° rotations in the gas phase for $\bar{C}H_2-CH_2Br$ can be estimated from the calculation to be >10 kcal mol^{-1}. The hyperconjugative interaction is strongly reduced by the presence of electron-withdrawing groups Y and Y′ on the carbanionic center.[12] Since both steric and hyperconjugative factors favor the 60° rotation, the hyperconjugative preference for the rotation is ≤2 kcal mol^{-1}. This conclusion suggests that the use of data on negative hyperconjugation, as calculated for closely related systems in the gas phase, should be restricted at most to semiquantitative conclusions.

The small effect of changes in the structure or the medium on the *E*/*Z* ratios is consistent with a rate-determining rotation. The rate of internal rotation and especially the rate difference between two such rotations should not be influenced appreciably by the medium. Likewise, since the loss of the $2p(C^-)$/C–Nu interaction is identical regardless of whether the rotation is clockwise or anticlockwise, it will be similar for the energetically important parts of the 60° and 120° rotations; i.e., the relative rotation rates should be independent of the nucleophilic moiety in **17**. The steric contribution should be manifested only in comparison of ArS^--, ArO^--, and N_3^--substituted **17**, since the para substituent in the ArO and ArS moieties in **17** should have no effect on the steric barrier. Apparently, the differential steric effect of these Nu moieties in **17** is minor. Likewise, no differential steric effect and a minor differential hyperconjugative effect is expected for the change of the p-MeC_6H_4 in **4** to the p-$O_2NC_6H_4$ in **5**.

One aim of our recent work on the stereochemistry of nucleophilic vinylic substitution is to define the structural range of the borderline between retention and stereoconvergence.[3] We have suggested that the main structural parameter influencing the stereochemistry is the negative charge delocalizing ability of the Y and Y′ activating substituents in ArC(Hal)=CYY′, which is directly related to the lifetime of the carbanion.[2e] The longer the lifetime of the carbanion, the larger the probability for stereoconvergence since both k_{rot} and k_{el} values are reduced. As a rough measure of the delocalizing ability of Y and Y′ we used the pK_a of CH_2YY'.[2e,3d] Study of the substitution of *E* and *Z* compounds **21–26** was in a qualitative agreement with this generalization.

PhC(X)=C(Ph)Y
21, X = I; Y = NO_2
22, X = Cl; Y = CHO

p-$O_2NC_6H_4C(Cl)=C(Y)CO_2Me$
23, Y = CN
24, Y = CHO

p-$GC_6H_4C(Br)=C(CO_2Me)CO_2Bu$-$t$
25, G = Me
26, G = NO_2

Since the appropriate comparisons were tabulated and the topic was discussed in detail,[3d] we will summarize here only the aspects relevant to the present work. (a) Complete stereoconvergence was achieved in the reactions of $TolS^-$ with systems **21–23**.[3a–c] (b) Complete retention was obtained in the reaction of $TolS^-$ with **25** and **26**, whereas very high (>95%) retention was observed with $TolO^-$.[3d] (c) For systems **21–26** there is a difference in the stereochemical outcome in reaction with ArO^- and ArS^- nucleophiles. In addition, retention is observed regardless of the nucleophile[2b]

(11) (a) Hoffmann, R.; Radom, L.; Pople, J. A.; Schleyer, P. v. R.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1972**, *94*, 6221. (b) Schleyer, P. v. R.; Kos, A. *Tetrahedron* **1983**, *39*, 1141. (c) For a recent review of anionic hyperconjugation, see: Nobes, R. H.; Poppinger, D.; Li, W.-H.; Radom, L. In *Comprehensive Carbanion Chemistry, Part C*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1987; pp 1–92.

(12) (a) Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* **1979**, *101*, 1343. (b) Apeloig, Y.; Karni, M.; Rappoport, Z. *Ibid.* **1983**, *105*, 2784.

(amines are excluded due to postisomerization)[13] for all singly activated systems.

The activation of compounds **4** and **5** is lower than that of **21–24** and, at least formally, is similar to that of the closely related diesters **25** and **26**. We therefore expected **4** and **5** to be close to the stereoconvergence/retention borderline, or even to cross it and to give retention. Experimentally, **4** and **5** are still on the stereoconvergence side of the border, and for the reasons discussed above, this conclusion is firmly established.

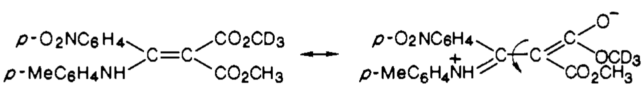
The difference between **4** and **5** on the one hand and **25** and **26** on the other[3d] is not very large. $TolO^-$ gives a high percentage of retained product in both cases, and we cannot say definitely that for **26** the stereochemistry is dependent on the nucleophile since with $TolS^-$ the retention/inversion ratios are 98/2 and 100/0 whereas with $TolO^-$ the ratio is >95/<5. Nevertheless, the higher retention observed for the *tert*-butyl methyl esters compared with the dimethyl esters is mechanistically significant. The difference cannot be electronic since the CO_2Me and CO_2Bu-*t* groups do not differ in their negative charge delocalizing ability, and their conjugative interactions with a double bond are similar.[14] However, they differ sterically and this difference is magnified in the tetrasubstituted systems. It is also reflected in the solid-state structures of (*E*)-**25** and of **6a** and **6b**.[15] It is not clear how relevant are these data, which may be due to crystal packing. More important, the stereochemistry is determined by the rotational processes in the anion and not by the structure of the halo ester. If we use our qualitative stereochemistry–pK_a correlation in reverse, we conclude that in carbanion *p*-$MeC_6H_4C(Br)(Nu)$–$\bar{C}(CO_2Me)CO_2Bu$-*t* (**27**) the negative charge is delocalized by the CO_2R groups less than in carbanion **17**. This is reasonable if steric effects increase the angle between the $2p(C^-)$ and the carbonyl COOR orbitals more for R = *t*-Bu in **27** than for R = Me in **17**.

***E* ⇌ *Z* Isomerization of the Bromides.** A corollary of the intermediacy of a carbanion in the substitution is the possibility of a nucleophilic Br^--catalyzed (*E*)-RBr ⇌ (*Z*)-RBr isomerization. The mechanism for this is the route (*E*)-Br → **17** → **20** → (*Z*)-Br (for Nu = Br) shown in Scheme I. It is expected to be slow compared with substitution by other nucleophiles for three reasons. First, halide ions are poor nucleophiles in bimolecular vinylic substitution;[16] i.e., k_1 is low and formation of **17** is slow. Second, Br^- is an excellent nucleofuge from carbanions $\bar{C}$–C–Br, and for systems such as **17** this is evident from our conclusion above that $k_{el} > k_{rot}$ in **18** or **19**. Since the hyperconjugative barrier for the **17** → **20** rotation is higher than in other systems due to the $2p(C^-)$/C–Nu stabilization, the k_{-1} process will be highly favored over rotation. Third, whereas 60° rotation with other nucleophiles gives substitution, it is degenerate with Br^-, and the expulsion of Br^- from **18** or **19** on the way to **20** will again reduce the substitution rate.

On the basis of these facts the lack of isomerization of **4** after 216 h in $CDCl_3$ or of **5** in CD_3CN after 160 h with Bu_4NBr should not be surprising. However, it should be accommodated with the fact that (*E*)-RCl ⇌ (*Z*)-RCl isomerization was observed for systems **22**,[3c] **23**,[3b] and **24**[3d] with Cl^-. We expect the isomerization to become slower when the hyperconjugative rotational barrier increases, i.e., with the decrease in the negative charge dispersal by Y and Y′. Hence, the lack of isomerization for **4**, **5**, and for **25** in the presence of Br^- in CD_3CN or $CDCl_3$[3d] is consistent with this conclusion. The long reaction times which do not lead to isomerization should not be deceiving: the "hidden" retention is expected to be 1–2 orders of magnitude faster than the isomerization, and the nucleophilicity difference between Br^- and $TolS^-$ is estimated to be 9 orders of magnitude,[2b] so that isomerization should be necessarily observed after these reaction times. Whether isomerization will be observed in another solvent,[17] or at a higher temperature, depends on the availability of competing reactions. The formation of an unidentified product with a single CO_2Me group at 90 °C in DMSO can be due to a competing Br^--promoted debromocarboalkylation.[7]

It was therefore surprising that thiocyanate ion in the dark led to an exclusive **5** ⇌ *Z* isomer isomerization which precedes the substitution. We know of one precedent for such a process.[18] In terms of Scheme I the (*E*)-Br → **17** → **20** → (*Z*)-Br process is faster than the (*E*)-Br → **17** → **18** or **19** → (*E*)-Nu or (*Z*)-Nu process. The consequent inequalities k_{rot}^{180} and/or k_{rot}^{60}, $k_{rot}^{120} > k_{el}(Br^-)$, and $k_{el}(SCN^-) = k_{-1}(Nu = SCN) > k_{el}(Br^-)$ are not easy to explain and are inconsistent with the suggestion above that $k_{el} > k_{rot}$ and with the better nucleofugality of Br^- compared with SCN^- in aliphatic substitutions. It seems that the hyperconjugative interaction $2p(C^-)$/C–SCN should be more stabilizing than the $2p(C^-)$/C–Br stabilization in order to start to explain this behavior. This question will be discussed elsewhere.

Complete Stereoconvergence with *p*-Toluidine. Only in the reaction of **5** with *p*-toluidine is the apparent stereochemical outcome complete stereoconvergence. This is the usual outcome in vinylic substitution by amines with no special constraints, such as *p*-toluidine.[2b] The suggestion that this is due to postisomerization in the product enamine by rotation around the C_α–C_β "partial" double bond seems equally applicable in our system (cf. **28b**). Such rotation leads usually to the more stable enamine,[2b]



28a **28b**

but this driving force is not present in our case, where a 1:1 mixture of (*E*)-**16f** and (*Z*)-**16f**, which are of equal energies, is formed. The rate of interconversion (*E*)-**16f** ⇌ (*Z*)-**16f** is sufficiently slow at room temperature on the NMR time scale, and the two CO_2Me groups appear as sharp singlets.[19] Consequently, it is possible that by using a more reactive amine at low temperature we will be able to observe the expected kinetically controlled excess retention[20] with our sensitive method and the isotopomeric probe.

Experimental Section

Elemental analyses were conducted by The Hebrew University of Jerusalem Microanalysis Laboratory. Melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected. UV spectra were determined with a Spectronics 2000 spectrometer, IR spectra were recorded with a Perkin-Elmer 157G spectrometer, and ^1H and ^{13}C NMR spectra were recorded on Bruker WH-300 and WP-200 pulsed FT spectrometers. Chemical shifts are reported ppm downfield from the internal Me_4Si signal. Electron impact mass spectra were recorded on a MAT 311 instrument. Chromatography columns were packed with Merck 35–70 silica gel or dry silica (Woelm-Pharma) and eluted with the solvents mentioned in each specific case. TLC was taken with Merck silica gel GF_{254} plates (0.25-mm thickness). Workup means diluting with H_2O, extracting with $CHCl_3$, drying the organic phase with $MgSO_4$, filtering, and evaporating the residue to dryness.

Solvents were obtained from Frutarom and were used without further purification. Preparation, X-ray diffraction, and spectral data of dimethyl (α-bromo-*p*-methylbenzylidene)malonate (**6a**) and dimethyl (α-bromo-*p*-nitrobenzylidene)malonate (**6b**) were previously reported.[15] The ^{13}C NMR data are as follows: **6a** in $CDCl_3$ (proton decoupled), δ 21.3 (Me, s), 52.4, 52.8 ($COOCH_3$, s), 127.9, 128.8 (C-2 and C-3, s), 128.0, 135.6, 139.7, 140.5 (C_α, C_β, C-1 and C-4, very weak; specific assignment within this group is tentative), 162.9, 164.4 ($COOCH_3$) (in the corresponding (*E*)-trideuteriomethyl ester **4** the signals at δ 52.4 and 162.9 were not observed); **6b** in CD_3CN (proton decoupled), δ 53.5, 53.7

(13) For references and review of this question, see: Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1000.

(14) Hine, J.; Kanagasabapathy, V. M.; Ng, P. *J. Org. Chem.* **1982**, *47*, 2745.

(15) Rappoport, Z.; Gazit, A. *J. Org. Chem.* **1986**, *51*, 4107.

(16) Rappoport, Z. *Adv. Chem. Ser.* **1987**, *No. 215*, 399.

(17) In DMF **8a** isomerizes slightly after a long reaction time.[3d]

(18) The reaction of pure (*E*)- or pure (*Z*)-2-methyl-3-chlorobutenal with KSCN gives initial partial stereoconvergence accompanied by *E* ⇌ *Z* isomerization of the precursor chloride (Korobov, M. S.; Nivorozhkin, L. E.; Minkin, V. I.; Levkovich, M. M.; Testoedova, S. I. *Zhur. Org. Khim.* **1978**, *14*, 788 (*Engl. Transl.* **1978**, 728). It is surprising that this paper apparently neglects a main reference in the field).

(19) For a review on rotation around the double bond of push–pull ethylenes, see: Sandström, J. *Top. Stereochem.* **1983**, *14*, 83.

(20) This possibility is suggested by the data of Le Guillanton et al. (Le Guillanton, G.; Cariou, M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 997).

($COOCH_3$), 124.4 (C-3), 130.0 (C-2), 132.4 (C_α), 136.3 (C_β), 145.5 (C-1), 149.4 (C-4), 162.7, 164.9 (COOMe).[21] Diazald was obtained from Aldrich. The ArO^- and ArS^- salts were prepared by dissolving the corresponding commercial ArOH and ArSH in ether, stirring with an equivalent amount of NaH until gas evolution ceased (15 min), adding hexane, filtering, washing with hexane, collecting, and drying the ArO^- and ArS^- salts.

(*Z*)-Methyl Hydrogen (*p*-Methylbenzylidene)malonate. (a) A 45:55 mixture of *tert*-butyl methyl (*p*-methylbenzylidene)malonates **7a**/**8a** (4 g, 14 mmol) and trimethylsilyl iodide (2.6 mL, 18 mmol) in CCl_4 (30 mL) was kept for 1 h at room temperature. Treatment of half of the mixture with aqueous sodium thiosulfate solution showed the presence of the precursor and a mixture of the monoacids. The other half was left overnight at room temperature and worked up as above, yielding an oil, which was crystallized from benzene-hexane, giving a white solid: mp 147 °C (0.29 g, overall 18%); R_f (95:5 CH_2Cl_2–MeOH) 0.2. ^1H NMR showed the presence of a 3:1 mixture of the (*Z*)- and (*E*)-methyl hydrogen (*p*-methylbenzylidene)malonates. ^1H NMR ($CDCl_3$): *Z* isomer, δ 2.38 (3 H, s, Me), 3.87 (3 H, s, COOMe), 7.21, 7.47 (4 H, AA'BB' q, J = 8.3 Hz, Ar), 7.88 (1 H, s, :CH); *E* isomer, δ 2.38 (3 H, s, Me), 3.88 (3 H, s, COOMe), 7.19, 7.35 (4 H, AA'BB' q, J = 8.3 Hz, Ar), 7.83 (1 H, s, :CH). Mass spectrum, m/z (relative abundance, assignment) 220 (75, M), 205 (12, M − Me), 189 (22, M − MeO), 160 (B, M − HCOOMe). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.47. Found: C, 65.74; H, 5.57.

(b) Exactly the same mixture was obtained sometimes in several attempted brominations of **7a**/**8a**, which usually give the dibromo derivative. The de-*tert*-butylation is probably due to traces of acid in the reaction mixture and was not investigated further.

(c) Chromatography of a 3:1 *Z*/*E* mixture of the monomethyl esters (6.3 g) on a silica gel column with $CHCl_3$ as the eluant gave pure (by ^1H NMR) (*Z*)-methyl hydrogen (*p*-methylbenzylidene)malonate: mp 152 °C (4.1 g, 65%); IR ($CHCl_3$) ν_{max} 3000–2400 (COOH), 1720–1680 (COOMe, COOH), 1600 cm^{-1}; mass spectrum, m/z (relative abundance, assignment), 220 (55, M), 205 (48, M − Me), 189 (40, M − MeO), 174 (42, M − HCOOH), 160 (61, M − HCOOMe), 143 (34, *p*-$MeC_6H_4C{\equiv}CCO$), 131 (11), 121 (21), 119 (11, *p*-MeC_6H_4CO), 115 (B, *p*-$MeC_6H_4C{\equiv}C$). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.45. Found: C, 65.67; H, 5.52.

(*E*)-Methyl Trideuteriomethyl (*p*-Methylbenzylidene)malonate. (*Z*)-Methyl hydrogen (*p*-methylbenzylidene)malonate (1 g, 4.5 mmol) was esterified with Diazald (2.5 g, 11.7 mmol) in carbitol-*O-d*/NaOD by a procedure identical with that described below for the preparation of the bromo analogue **4**. The white solid obtained (mp 50 °C (0.5 g, 47%)) was pure (by NMR) (*E*)-methyl trideuteriomethyl (*p*-methylbenzylidene)malonate: ^1H NMR ($CDCl_3$) δ 2.37 (3 H, s, Me), 3.83 (3 H, s, COOMe), 7.19, 7.32 (4 H, AA'BB' q, J = 8 Hz), 7.75 (1 H, s, :CH).

Reaction of (*E*)-Methyl Trideuteriomethyl (*p*-Methylbenzylidene)malonate with Tetrabutylammonium Bromide. A solution of (*E*)-methyl trideuteriomethyl (*p*-methylbenzylidene)malonate (14 mg, 0.063 mmol) and Bu_4NBr (47 mg, 0.15 mmol) in C_6D_6 (5 mL) was kept for 140 h at room temperature. Workup gave only the precursor.

(*Z*)-Methyl Hydrogen (α-Bromo-*p*-methylbenzylidene)malonate (10a). (a) To (*Z*)-*tert*-butyl methyl (α-bromo-*p*-methylbenzylidene)malonate (**7a**)[3d] (40 mg, 0.1 mmol) was added trifluoroacetic acid (1 mL, 15 mmol) ([TFA]/[**7a**] = 150). After 5 min at room temperature the mixture was poured into water, extracted with $CHCl_3$, washed three times with water, dried, and analyzed by NMR. The main product is a 55/45 mixture of the acids **10a**:**9a**: UV λ_{max} (EtOH) 274 nm (log ϵ = 4.28); IR ($CHCl_3$) ν_{max} 3500–2500 (COOH), 1730 (CO_2R), 1610 cm^{-1}; ^1H NMR ($CDCl_3$) **10a**, δ 2.38 (3 H, s, Tol), 3.60 (3 H, s, CO_2Me), 7.19, 7.30 (4 H, AB q, J = 8.0 Hz, Ar); **9a**, 2.38 (3 H, s, Tol), 3.90 (3 H, s, CO_2Me), 7.18, 7.30 (4 H, AB q, J = 8.0 Hz, Ar).

(b) To **7a** (20 mg, 0.05 mmol) in benzene (1 mL) was added TFA (0.05 mL, 0.75 mmol). After standing 2 min at room temperature and workup as in (a), only **7a** was isolated. In a similar reaction in $CDCl_3$ (0.5 mL) no hydrolysis or isomerization was observed by NMR after 0.5–130 h.

(c) A solution of **7a** (1.9 g, 53.5 mmol) in TFA (5 mL) was stirred for 5 min at room temperature and worked up as in (a). A white solid (1 g, 62%) of a 1:1 **9a**/**10a** mixture was obtained. Several crystallizations from hexane enriched the mixture to a 7:3 **10a**/**9a** mixture, mp 115 °C. Slow evaporation from benzene gave a 3:1 **9a**/**10a** mixture. Anal. Calcd for $C_{12}H_{11}BrO_4$: C, 48.16; H, 3.68; Br, 26.75. Found: C, 48.29; H, 3.75; Br, 26.70.

(d) A mixture of *tert*-butyl methyl (*p*-methylbenzylidene)malonate dibromide[3d] (12.1 g, 42 mmol), 2,6-di-*tert*-butylphenol (0.6 g, 3 mmol), and DBN (5.1 g, 42 mmol) in CH_2Cl_2 (150 mL) which was kept for 2 h at room temperature under argon and worked up as described above gave 9.5 g of a greenish oil. TFA (20 mL) was added, the mixture was stirred for 6 min at 25 °C, and the usual workup gave a green oil (6.5 g), which by NMR is a 40:30:30 mixture of **12h**:**10a**:**9a**. Separation by chromatography (order of elution **10a**, **12h**, **9a**) was poor but three chromatographies (98% $CHCl_3$–2% MeOH) followed by crystallization gave low yields of ≥95% pure **9a** and **10a**. (a) **10a** (96%, containing 4% **12h**): mp 125 °C from cyclohexane (0.3 g, 3.6% from the dibromide); IR ($CHCl_3$) ν_{max} 3000–2500 cm^{-1} (COOH), 1710(COMe), 1600; ^1H NMR ($CDCl_3$) δ 2.38 (3 H, s, Me), 3.90 (3 H, s, COOMe), 7.16, 7.28 (4 H, AA'BB' q, J = 8 Hz, Ar): mass spectrum, m/z (relative abundance, assignment) 300, 298 (8.5, 9, M), 285, 283 (6, 7, M − Me), 269, 267 (7, 8, M − MeO), 268, 266 (13, 13, M − MeOH), 253, 251 (6, 6, M − Me − MeOH), 219 (2, M − Br), 187 (2, M − Br − MeOH), 175 (60, M − Br − CO_2), 160 (4, M − Br − COOMe), 143 (B, $TolC{\equiv}CCO^+$), 119 (16, $TolCO^+$), 116 (35). (b) **9a** (95%, containing 5% **12k**): mp 112 °C from cyclohexane (0.25 g, 3% from the dibromide); IR ($CHCl_3$) similar to that of **10a**; ^1H NMR ($CDCl_3$) δ 2.38 (3 H, s, Me), 3.60 (3 H, s, COOMe), 7.19, 7.30 (4 H, AA'BB' q, J = 8.2 Hz, Ar).

Stability of 9a and 10a. A sample containing a 90:9:1 mixture of **10a**:**12h**:**9a** in $CDCl_3$ was kept for 5 days at room temperature. Analysis showed an 87:9:4 mixture; i.e., appreciable isomerization did not take place.

(*E*)-Methyl Trideuteriomethyl (α-Bromo-*p*-methylbenzylidene)malonate (4). Methyl deuterium (α-bromo-*p*-methylbenzylidene)malonate (220 mg, containing 5% methyl (*p*-methylbenzylidene)malonate) was obtained by dissolving **10a** in dry ether (5 mL) and shaking with D_2O (3 mL) four times, followed by separation each time. Carbitol-*O-d* (10 mL) was prepared by shaking carbitol (diethylene glycol monoethyl ether) three times with D_2O (5 mL) and evaporating the water.

In a 50-mL round-bottom flask NaOD (prepared from 350 mg of Na in 3 mL of D_2O) in carbitol (10 mL) was heated to 70 °C and Diazald (0.5 g) in dry ether (10 mL) was added in portions. The yellow solution of CD_2N_2 in ether was collected in an ice-cooled second flask. Additional ether (10 mL) was added and the distillation continued. When it was finished **10a-*O*-d** (220 mg) in ether (10 mL)–D_2O (2 mL) was added to the CD_2N_2 solution. The yellow color disappeared within 5 min. The mixture was stirred for 1 h at room temperature, and the organic phase was separated, dried, and evaporated. Chromatography on silica gel with 1:1 $CHCl_3$–hexane as eluant gave **4** as a viscous while oil (105 mg, 45%) containing 5% of its *Z* isomer): IR (neat) ν_{max} 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (3 H, s, Me), 3.89 (3 H, s, COOMe), 7.17, 7.28 (4 H, AA'BB' q, J = 8.1 Hz, Ar) (the sample also showed a δ 3.59 singlet and a δ 3.57 multiplet (with intensities of ca. 5% of that of the δ 3.89 signal), which are presumably due to the *Z* isomer and to a CD_2H species); mass spectrum m/z (relative intensity) 317, 315 (30, 31, M), 286, 284 (6, 7, M − OMe), 283, 281 (5.3, 4.4, M − OCD_3), 236 (B, M − Br), 192 (15, M − Br − CO_2), 168 (18), 143 (63, $TolC{\equiv}CCO^+$), 119 (18, $TolCO^+$), 115 (18, $TolC{\equiv}C^+$) (m/z 318/m/z 317 = 0.144; calcd 0.141).

(*E*)-Methyl Trideuteriomethyl (α-Bromo-*p*-nitrobenzylidene)malonate (5). (a) **(*Z*)-Methyl Hydrogen (α-Bromo-*p*-nitrobenzylidene)malonate (9b).** A 1:1 mixture of the (*E*)- and (*Z*)-*tert*-butyl methyl (α-bromo-*p*-nitrobenzylidene)malonates **7b**/**8b**[3d] (2.5 g, 6.5 mmol) in trifluoroacetic acid (5 mL) was stirred for 30 min at room temperature. A solid was formed. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (100 mL), and the organic phase was dried and evaporated, giving **9b** as a white solid (1.5 g) containing some impurities (by NMR). Trituration with warm $CHCl_3$, cooling, and filtering gave a white solid (0.7 g, 34%; mp 195 °C). NMR showed the solid to be 95% **9b**, containing **10b** and impurities that could be removed by chromatography on silica and elution with 2–15% MeOH. The compound is sparingly soluble in $CHCl_3$, moderately soluble in CH_2Cl_2, and soluble in EtOH and acetone. UV (EtOH) λ_{max} 278 nm (log ϵ = 4.23); ^1H NMR ($(CD_3)_2CO$) δ 3.90 (3 H, s, COOMe), 7.75, 8.32 (4 H, AA'BB' q, J = 9 Hz, Ar) ([**10b**]: δ 3.60 (COOMe)): ^1H NMR ($CDCl_3$) δ 3.95 (3 H, s, COOMe), 7.75, 8.26 (4 H, AA'BB' q, J = 8 Hz, Ar) ([**10b**]: δ 3.63 (COOMe), with 5% intensity); mass spectrum, m/z (relative intensity, assignment) 331, 329 (4.6, 4.8, M), 300, 298 (18, 17.5, M − OMe), 283, 281 (9, 9, M − MeO − OH), 250 (6, M − Br), 206 (51, M − Br − COO), 205 (76, M − Br − COOH), 174 (B, M − Br − COOH − MeO), 147 (70, M − Br − COO − COOMe), 128 (91, M − Br − COOH − OMe − NO_2), 116 (45, M − Br − COOH − COOMe − NO). Anal. Calcd for $C_{11}H_8BrNO_6$: C, 40.0; H, 2.42; N, 4.24. Found: C, 40.10; H, 2.67; N, 4.25.

(b) **(*E*)-Methyl Trideuteriomethyl (α-Bromo-*p*-nitrobenzylidene)malonate (5).** A solution of CD_2N_2 was prepared from Diazald (1.5 g) and NaOD solution (prepared from Na (1 g) and D_2O (10 mL)–

(21) For comparison with the ^{13}C spectrum of *p*-$O_2NC_6H_4CH{=}C(CO_2Et)_2$, see: Bottino, F. A.; Musumarra, G.; Rappoport, Z. *Magn. Reson. Chem.* **1986**, *24*, 31.

$MeOCH_2CH_2OCH_2CH_2OD$ (5 mL)) as described in the preparation of **4**. Since **9b** is insoluble in $CDCl_3$ and in ether, the H/D exchange of the COOH proton was conducted by dissolving **9b** in carbitol-*O-d* (10 mL), adding D_2O (5 mL), and evaporating. The exchange was repeated three times. To the formed solution of **9b**-*O-d* (0.65 g, 1.9 mmol) in carbitol-*O-d* (10 mL) was added dropwise at room temperature the CD_2N_2 solution in ether (40 mL). The yellow color disappeared after addition of ca. 90% of the CD_2N_2. After 30 min of stirring at room temperature and evaporation of the solvent, crystallization from EtOH gave white crystals, mp 92 °C, of (*E*)-methyl trideuteriomethyl (α-bromo-*p*-nitrobenzylidene)malonate (**5**) (0.41 g, 60%): ^{1}H NMR ($CDCl_3$) δ 3.94 (3 H, s, COOMe), 7.53, 8.26 (4 H, AA′BB′ q, J = 8.8 Hz, Ar) (δ 3.63 with 5% intensity of δ 3.94 is ascribed to 5% of the *Z* isomer); mass spectrum, m/z (relative abundance, assignment) 348, 346 (27, 28, M), 317, 315 (14, 16, M − MeO), 314, 312 (15, 13, M − OCD_3), 267 (B, M − Br), 223 (20, M − Br − CO_2), 174 (43, M − Br − CO_2CD_3 − MeO), 150 (11, $O_2NC_6H_4CO$), 128 (42, M − Br − $COOCD_3$ − OMe − NO_2).

When a solution of **5** (containing 5% of the *Z* isomer) in $CDCl_3$ stood for 100 h in the dark in an NMR tube, a 92:8 *E/Z* mixture was formed. When a similar solution was kept for 70 h without protection from light, the isomerization was much more extensive: a 57:43 *E/Z* mixture was obtained.

Reactions of Dimethyl (α-Bromo-*p*-methylbenzylidene)malonate with Nucleophiles in DMSO. (a) With Sodium Phenoxide. To a solution of **6a** (0.5 g, 1.6 mmol) in DMSO (10 mL) was added sodium phenoxide (240 mg, 2 mmol). A red color immediately developed. The mixture was stirred for 16 h at room temperature, poured into aqueous 0.1 N HCl solution (100 mL), and extracted with $CHCl_3$, and the organic phase was dried and evaporated. Chromatography on silica gel, using $CHCl_3$–hexane as the eluant, and crystallization from ethanol gave dimethyl (α-phenoxy-*p*-methylbenzylidene)malonate (**12a**) (100 mg, 19%) as a white solid: mp 104 °C; R_f 0.2 (1:1 hexane–$CHCl_3$); IR ($CHCl_3$) ν_{max} 1715 (CO_2Me), 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28 (3 H, s, Me), 3.65, 3.75 (6 H, 2 s, CO_2Me), 6.94, 7.31 (4 H, AA′BB′ *q*, J = 8.5 Hz, Ar), 7.08–7.19 (5 H, m, PhO); mass spectrum, m/z (relative abundance, assignment) 326 (2, M), 295 (6, M − MeO), 267 (24, M − CO_2Me), 266 (22, M − HCO_2Me), 235 (35, M − C_6H_4Me), 233 (17, M − OPh), 208 (2, M − 2 CO_2Me), 143 (33, *p*-$MeC_6H_4C{\equiv}CCO$), 119 (B, *p*-MeC_6H_4CO), 91 (30, $C_7H_7^+$). Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.83; H, 5.52. Found: C, 69.53; H, 5.64.

(b) With *p*-Cresolate Ion. Sodium cresolate (260 mg, 2 mmol) was added to a solution of **6a** (0.5 g, 1.6 mmol) in DMSO (10 mL), and the red solution was stirred for 16 h at room temperature. Workup as above gave a viscous oil which after chromatography on silica gel ($CHCl_3$–hexane as eluant) and crystallization from EtOH gave dimethyl (α-(*p*-methylphenoxy)-*p*-methylbenzylidene)malonate (**12b**) as large white crystals: mp 88 °C (80 mg, 15%); IR ($CHCl_3$) ν_{max} 1710 cm^{-1} (CO_2Me); ^{1}H NMR ($CDCl_3$) δ 2.20 (3 H, s, OC_6H_4Me?), 2.28 (3 H, s, C_6H_4Me?), 3.64 (3 H, s, COOMe), 3.76 (3 H, s, COOMe trans to *p*-tolyl), 6.82, 6.96 (4 H, AA′BB′ q, J = 8.6 Hz, TolO), 7.07, 7.30 (4 H, AA′BB′ q, J = 8.0 Hz, Tol); mass spectrum, m/z (relative abundance, assignment) 340 (12, M), 309 (5, M − MeO), 308 (3, M − MeOH), 281 (18, M − CO_2Me), 280 (18, M − HCO_2Me), 277 (8, M − MeO − MeOH), 249 (21, M − Tol), 233 (24, M − OTol), 189 (13, M − HCOOMe − Tol), 165 (15), 143 (38, TolC≡CCO), 119 (B, TolCO), 91 (17, $C_7H_7^+$). Anal. Calcd for $C_{20}H_{20}OS$: C, 70.59; H, 5.88. Found: C, 70.83; H, 6.11.

(c) With Sodium *p*-Bromophenoxide. A mixture of **6a** (0.3 g, 1 mmol) and sodium *p*-bromophenoxide (0.3 g, 1.5 mmol) in DMSO (20 mL) was stirred for 20 h at room temperature. The green color of the solution disappeared on workup with aqueous HCl. After extraction with $CHCl_3$, evaporation of the solvent, chromatography on silica gel, and crystallization from EtOH, dimethyl (α-(*p*-bromophenoxy)-*p*-methylbenzylidene)malonate (**12c**) was obtained as a white solid: mp 96 °C (110 mg, 28%); UV (EtOH) λ_{max} 278 nm (log ϵ = 4.26); IR ($CHCl_3$) ν_{max} 1720 cm^{-1} (CO_2Me); ^{1}H NMR ($CDCl_3$) δ 2.31 (3 H, s, Me), 3.66 (3 H, s, COOMe cis to Tol), 3.77 (3 H, s, COOMe trans to Tol), 6.82, 7.28 (4 H, AA′BB′ q, J = 9.0 Hz, OC_6H_4Br), 7.09, 7.28 (4 H, AA′BB′ q, J = 8 Hz, Tol); mass spectrum, m/z (relative abundance assignment) 406, 404 (9, 9, M), 375, 373 (5, 5, M − MeO), 347, 345 (11, 11, M − COOMe), 316, 314 (9, 9, M − COOMe − MeO), 233 (31, M − OC_6H_4Br), 189 (13, M − OC_6H_4Br − CO_2), 165 (16), 143 (46, TolC≡CCO), 119 (B, TolCO). Anal. Calcd for $C_{19}H_{17}BrOS$: C, 56.30; H, 4.20. Found: C, 56.40; H, 4.48.

(d) With Sodium *p*-Methoxyphenoxide. A solution of **6a** (0.3 g, 1.0 mmol) and sodium *p*-methoxyphenoxide (0.2 g, 1.3 mmol) in DMSO (20 mL) was stirred for 16 h at room temperature. After the usual workup, chromatography, and crystallization from EtOH, large white crystals of dimethyl α-(*p*-methoxyphenyl)-*p*-methylbenzylidene)malonate (**12d**) (mp 84 °C (160 mg, 47%)) were obtained: UV (EtOH) λ_{max} 280 nm (log ϵ = 4.21); IR ($CHCl_3$) λ_{max} 1720 (CO_2Me), 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28 (3 H, s, Me), 3.63 (3 H, s, MeO), 3.68 (3 H, s, COOMe cis to Tol), 3.77 (3 H, COOMe trans to Tol), 6.68, 6.86 (4 H, AA′BB′ q, J = 9.2 Hz, C_6H_4OMe), 7.07, 7.27 (4 H, AA′BB′ q, J = 8.2 Hz, Tol); mass spectrum, m/z (relative abundance, assignment) 356 (24, M), 325 (5, M − MeO), 297 (10, M − COOMe), 294 (10, M − 2 MeO), 266 (12, M − MeO − COOMe), 233 (36, M − *p*-$MeOC_6H_4O$), 189 (22, M − *p*-$MeOC_6H_4O$ − CO_2), 165 (36), 143 (B, M − *p*-$MeOC_6H_4O$ − COOMe − MeO), 119 (98, TolO), 101 (53, PhC≡C?). Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.61. Found: C, 67.25; H, 5.52.

(e) With Sodium *p*-Nitrophenoxide. To a solution of **6a** (0.35 g, 1.1 mmol) in DMF (10 mL) was added sodium *p*-nitrophenoxide (220 mg, 1.37 mmol), and the red solution was stirred for 20 h at room temperature. Workup as above, followed by chromatography on silica gel, gave a white solid (0.1 g, 53%), which was identified by ^{1}H NMR and mass spectra as *p*-nitrophenol.

(f) With Sodium Methoxide. A solution of **6a** (0.45 g, 1.5 mmol) in MeOH (10 mL) and a NaOMe solution (2.2 mmol) prepared from Na metal (50 mg) was stirred for 20 h at room temperature and worked up as above. Chromatography on silica gel gave **12e** as a viscous oil. Attempted crystallization from MeOH or hexane failed. R_f (4:1 $CHCl_3$–hexane) 0.2; IR ($CHCl_3$) ν_{max} 1720 cm^{-1} (CO_2Me); ^{1}H NMR ($CDCl_3$) δ 2.40 (3 H, s, Me), 3.53, 3.52 (6 H, 2 s, MeO and COOMe cis to Tol), 3.84 (3 H, s, CO_2Me trans to Tol), 7.25 (4 H, s, Ar); ^{1}H NMR (1:1 CD_3CN–C_6D_6 in the MeO region) δ 3.67, 3.35 (COOMe), 3.31 (OMe); mass spectrum, m/z (relative abundance, assignment) 264 (61, M), 249 (13, M − Me), 233 (70, M − MeO), 218 (5, M − Me − MeO), 205 (B, M − CO_2Me), 189 (16, M − CO_2 − OMe), 174 (35, M − CO_2Me − OMe), 165 (52), 143 (24, TolC≡CCO), 119 (69, TolCO), 91 (39, $C_7H_7^+$). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.06. Found: C, 63.51; H, 5.92.

(g) With Potassium *tert*-Butoxide. To a solution of **6a** (0.35 g, 1.1 mmol) in DMF (10 mL) was added potassium *tert*-butoxide (0.19 g, 1.7 mmol). After 20 h of stirring at room temperature, workup as above gave an oil, which according to TLC and ^{1}H NMR was a mixture that did not show a *tert*-butyl signal in the NMR, and its methyl ester signal was very weak. The reaction was not investigated further.

(h) With Sodium *p*-Chlorobenzenethiolate. To a solution of **6a** (0.6 g, 2 mmol) in DMSO (20 mL) was added sodium *p*-chlorobenzenethiolate (0.5 g, 3 mmol), and the mixture was stirred for 24 h at room temperature. Workup as above, followed by chromatography on silica gel, gave dimethyl (α-((*p*-chlorophenyl)thio)-*p*-methylbenzylidene)malonate (**12f**) as a white solid: mp 97 °C (50 mg, 7%); UV (EtOH) λ_{max} 266 (log ϵ = 4.09), 292 nm (4.14); IR ($CHCl_3$) ν_{max} 1715 cm^{-1} (CO_2Me); ^{1}H NMR ($CDCl_3$) δ 2.21 (3 H, s, Me), 3.43 (3 H, s, COOMe cis to Tol), 3.84 (3 H, s, COOMe trans to Tol), 6.90 (4 H, s, Ar), 7.06 (4 H, AA′BB′ q, J = 8.7 Hz, Tol); mass spectrum, m/z (relative intensity, assignment) 378, 376 (3, 8, M), 319, 317 (10, 28, M − COOMe), 287, 285 (13, 38, M − COOMe − MeOH), 233 (18, M − SAr), 189 (20, M − SAr − CO_2), 165 (28), 143 (B, TolC≡CCO), 115 (43). Anal. Calcd for $C_{19}H_{17}ClSO_4$: C, 60.40; H, 4.50. Found: C, 60.25; H, 4.41.

(i) With Sodium Borohydride. To a solution of **6a** (0.1 g, 0.3 mmol) in 1:1 MeCN–MeOH (20 mL) was added $NaBH_4$ (50 mg, 1.3 mmol), and the mixture was stirred at room temperature. After the usual workup, analysis by NMR after 5 and 24 days showed 70:30 and 90:10 mixtures of **13** (identified as described below) and **6a**, with no evidence for the vinylic hydrogen of **12h**. When the same concentration of **6a** was reacted with 1.0 mmol of $NaBH_4$ for 24 h, with 0.6 mmol of $NaBH_4$ for 3 h, and with 0.15 mmol of $NaBH_4$ for 1 h, 30:70, 17:83, and 5:95 [**13**]/[**6a**] ratios, respectively, were observed by NMR. Reflux for 16 h gave only unidentified decomposition products.

Reaction of Dimethyl (*p*-Methylbenzylidene)malonate (12h) with Sodium Borohydride. To a solution of **12h** (0.4 g, 1.7 mmol) in 1:1 MeCN–MeOH (60 mL) was added $NaBH_4$ (42 mg, 1.1 mmol), and the mixture was stirred for 16 h at room temperature. The mixture was poured into water (100 mL), extracted with $CHCl_3$ (3 × 40 mL), and dried ($MgSO_4$), and the solvent was evaporated, giving dimethyl (*p*-methylbenzyl)malonate as a white oil (0.3 g, 75%): IR ($CHCl_3$) ν_{max} 1730 cm^{-1} (COOMe); ^{1}H NMR ($CDCl_3$) δ 2.29 (3 H, s, Me), 3.17 (2 H, d, J = 8 Hz, CH_2), 3.66 (1 H, t, J = 8 Hz, CH; irradiation converts δ 3.17 to a singlet), 3.68 (3 H, s, COOMe), 7.04 (4 H, s, Ar). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.82. Found: C, 66.20; H, 5.86.

Reaction of Dimethyl (α-Chloro-*p*-methylbenzylidene)malonate with Sodium *p*-Toluenethiolate. (a) A mixture of dimethyl (α-chloro-*p*-methylbenzylidene)malonate[15] (0.35 g, 1.3 mmol) and sodium *p*-toluenethiolate (0.23 g, 1.6 mmol) in DMF (5 mL) was stirred at room temperature for 20 h. The solution was turned first red and then yellow. The mixture was poured into water (50 mL), extracted with CH_2Cl_2 (30 mL), washed with 0.1 N HCl solution (30 mL) and with water (50 mL), and dried, and the solvent was evaporated. Crystallization from hexane gave white crystals of dimethyl (α-(tolylthio)-*p*-methylbenzylidene)-

malonate (**12g**): mp 85 °C (120 mg, 26%); R_f (7:3 CH_2Cl_2–hexane) 0.2; UV (EtOH) λ_{max} 226 (log ϵ = 3.93), 261 (3.74), 296 nm (3.88); IR ($CHCl_3$) ν_{max} 1710 cm^{-1} (COOMe); ^1H NMR ($CDCl_3$) δ 2.18, 2.19 (6 H, s, 2 Tol), 3.43 (3 H, s, COOMe cis to tolyl), 3.83 (3 H, s, COOMe trans to tolyl), 6.88 (4 H, narrow AA′BB′ q, Ar), 6.85, 7.05 (4 H, AA′BB′ q, J = 8 Hz, Ar); mass spectrum, m/z (relative abundance, assignment) 356 (27, M), 325 (9, M – MeO), 296 (71, M – HCOOMe), 265 (B, M – HCOOMe – OMe), 238 (15, M – 2 COOMe), 233 (16, M – STol), 189 (15, M – STol – CO_2), 165 (18), 143 (41, TolC≡CCO). Anal. Calcd for $C_{20}H_{20}O_4S$: C, 67.41; H, 5.61; S, 8.99. Found: C, 67.52; H, 5.71; S, 8.95.

(b) When a mixture of dimethyl (α-chloro-*p*-methylbenzylidene)malonate (70 mg, 0.26 mmol) and sodium *p*-toluenethiolate (45 mg, 0.3 mmol) in MeCN (4 mL) was stirred for 20 h at 20 °C and worked up as above, the product consisted (by NMR) of a 2:1 mixture of the starting material and **12g**.

Reactions of Dimethyl (α-Bromo-*p*-nitrobenzylidene)malonate with Nucleophiles. (a) With Phenoxide Ion. To a solution of **6b** (0.3 g, 0.9 mmol) in DMSO (20 mL) was added sodium phenoxide (0.2 g, 1.7 mmol). The red solution was stirred for 40 h at room temperature, poured into a 0.1 N HCl solution (200 mL), extracted with $CHCl_3$, washed with water, and evaporated. Crystallization from EtOH gave dimethyl (α-phenoxy-*p*-nitrobenzylidene)malonate (**14a**): mp 109 °C (100 mg, 32%); UV (EtOH) λ_{max} 238 (log ϵ = 4.09), 285 nm (4.13); IR ($CHCl_3$) ν_{max} 1720 cm^{-1} (CO_2Me); ^1H NMR ($CDCl_3$) δ 3.66 (3 H, s, COOMe cis to Ar), 3.80 (3 H, s, COOMe trans to Ar), 6.9–7.13 (5 H, m, Ph), 7.59, 8.13 (4 H, AA′BB′ q, J = 8.9 Hz, $ArNO_2$); mass spectrum, m/z (relative abundance, assignment) 357 (13, M), 298 (B, M – COOMe), 297 (85, M – HCOOMe), 266 (62, M – COOMe – MeOH), 264 (9, M – PhO), 220 (M – COOMe – MeOH – NO_2), 174 (36, M – PhO – COOMe – OMe), 150 (82, *p*-$O_2NC_6H_4CO$), 128 (18, M – PhO – COOMe – MeO – NO_2). Anal. Calcd for $C_{18}H_{15}NO_7$: C, 60.50; H, 4.20. Found: C, 60.61; H, 4.54.

(b) With *p*-Cresolate Ion. To a solution of **6b** (0.3 g, 0.9 mmol) in DMSO (20 mL) was added sodium *p*-cresolate (0.22 g, 1.7 mmol). The solution turned reddish black. After 20 h of stirring at room temperature, the color of the solution was light red. Workup as above gave white crystals of dimethyl (α-(*p*-methylphenoxy)-*p*-nitrobenzylidene)malonate (**14b**): mp 120 °C (110 mg, 34%); UV (EtOH) λ_{max} 241 (log ϵ = 4.06), 287 nm (4.08); IR ($CHCl_3$) ν_{max} 1725 cm^{-1} (CO_2Me); ^1H NMR ($CDCl_3$) δ 2.20 (3 H, s, MeC_6H_4), 3.66 (3 H, s, COOMe cis to Ar), 3.82 (3 H, s, COOMe trans to Ar), 6.80, 6.97 (4 H, AA′BB′ q, J = 8.5 Hz, ArO), 7.55, 8.13 (4 H, AA′BB′ q, J = 8.7 Hz, $ArNO_2$); mass spectrum, m/z (relative abundance, assignment) 371 (27, M), 312 (63, M – COOMe), 311 (B, M – HCOOMe), 280 (69, M – COOMe – MeOH), 190 (52, M – Tol – COOMe – MeO), 174 (81, M – COOMe – OMe – TolO), 150 (96, *p*-$O_2NC_6H_4CO$), 128 (70, M – COOMe – OMe – TolO – NO_2). Anal. Calcd for $C_{19}H_{17}NO_7$: C, 61.45; H, 4.58. Found: C, 61.42; H, 4.86.

(c) With *p*-Methoxyphenoxide Ion. To a solution of **6b** (0.3 g, 0.9 mmol) in DMSO (20 mL) was added sodium *p*-methoxyphenoxide (0.2 g, 1.4 mmol). The dark red mixture was stirred for 70 h at room temperature, poured into dilute HCl solution, and worked up as above. The reaction was complete according to ^1H NMR. Crystallization from EtOH gave white crystals of dimethyl (α-(*p*-methoxyphenoxy)-*p*-nitrobenzylidene)malonate (**14c**): mp 120 °C (100 mg, 30%); UV (EtOH) λ_{max} 285 nm (log ϵ = 4.03); IR ($CHCl_3$) ν_{max} 1720 cm^{-1} (CO_2Me); ^1H NMR ($CDCl_3$) δ 3.65, 3.68 (6 H, 2 s, OMe and COOMe cis to Ar), 3.83 (3 H, s, COOMe trans to Ar), 6.68, 6.86 (4 H, AA′BB′ q, J = 9.1 Hz, OAr), 7.54, 8.13 (4 H, AA′BB′ q, J = 9.1 Hz, $ArNO_2$); mass spectrum, m/z (relative abundance, assignment) 387 (99, M), 328 (20, M – COOMe), 327 (28, M – HCOOMe), 297 (29, M – COOMe – OMe), 238 (B, M – 2 COOMe – MeO), 174 (46, M – COOMe – OMe – OAr), 150 (31, *p*-$O_2NC_6H_4CO$), 128 (32, M – COOMe – OMe – ArO – NO_2). Anal. Calcd for $C_{19}H_{17}NO_8$: C, 58.91; H, 4.39. Found: C, 58.61; H, 4.47.

(d) With *p*-Toluenethiolate Ion. To a solution of **6b** (0.3 g, 9 mmol) in DMSO (20 mL) was added sodium *p*-toluenethiolate (0.22 g, 1.5 mmol). The solution turned red, but the color became lighter with time. After 20 h of stirring at room temperature, the mixture was worked up as above, and NMR showed the presence of both the product and unreacted **6b**. Crystallization from EtOH gave dimethyl (α-(*p*-tolylthio)-*p*-nitrobenzylidene)malonate (**14d**): mp 119 °C (40 mg, 12%); UV (EtOH) λ_{max} 260 (sh) (log ϵ = 4.16), 277 nm (4.23); IR ($CHCl_3$) ν_{max} 1720 cm^{-1} (CO_2Me); ^1H NMR ($CDCl_3$) δ 2.19 (3 H, s, Me), 3.46 (3 H, s, COOMe cis to Ar), 3.90 (3 H, s, COOMe trans to Ar), 6.88, 7.06 (4 H, AA′BB′ q, J = 8 Hz, ArS), 7.19, 7.96 (4 H, AA′BB′ q, J = 8.8 Hz, $ArNO_2$); mass spectrum, m/z (relative abundance, assignment) 387 (28, M), 328 (30, M – COOMe), 327 (68, M – HCOOMe), 296 (B, M – COOMe – MeOH), 250 (16, M – Tol – NO_2), 174 (83, M – COOMe – OMe – TolS), 128 (89, M – COOMe – OMe – TolS – NO_2). Anal. Calcd for $C_{19}H_{17}NO_6S$: C, 58.91; H, 4.39. Found: C, 58.65; H, 4.45.

(e) With *p*-Chlorobenzenethiolate Ion. To a solution of **6b** (0.3 g, 0.9 mmol) in DMSO (20 mL) was added sodium *p*-chlorobenzenethiolate (0.25 g, 1.5 mmol). The solution became light red, and the color became lighter with the progress of the reaction. After 20 h of stirring at room temperature and workup as above, crystallization from EtOH gave white crystals of dimethyl (α-((*p*-chlorophenyl)thio)-*p*-nitrobenzylidene)malonate (**14e**): mp 142 °C (45 mg, 13%); UV (EtOH) λ_{max} 256 nm (log ϵ = 4.26); IR ($CHCl_3$) ν_{max} 1720 cm^{-1} (CO_2Me); ^1H NMR ($CDCl_3$) δ 3.60 (3 H, s, COOMe cis to Ar), 4.05 (3 H, s, COOMe trans to Ar), 7.46, 7.59 (4 H, AA′BB′ q, J = 8.8 Hz, ArS), 7.19, 8.15 (4 H, AA′BB′ q, J = 8.8 Hz, $ArNO_2$); mass spectrum, m/z (relative abundance, assignment) 409, 407 (4, 11, M), 377, 375 (5, 14, M – MeOH), 264 (B, M – ArS), 220 (36, M – ArS – CO_2), 174 (43, M – ArS – COOMe – MeO), 128 (25, M – ArS – COOMe – OMe – NO_2). Anal. Calcd for $C_{18}H_{14}ClNO_6S$: C, 53.0; H, 3.44. Found: C, 52.81; H, 3.40.

(f) With Potassium Cyanate. (a) A solution containing **6b** (300 mg, 0.9 mmol) and KOCN (500 mg, 6.2 mmol) in acetonitrile (50 mL) was refluxed for 17 h. The black reaction mixture was poured into dilute HCl solution, extracted with $CHCl_3$ (2 × 50 mL), dried, and evaporated. The ^1H NMR showed a 3:2 mixture of **6b** to a main new product, together with signals of lower intensity due to other products. Chromatography on silica gel with 4:1 hexane–$CHCl_3$ as the eluant gave **6b** and a yellow oil, which could not be purified by crystallization from cyclohexane or from ethanol. The ^1H NMR showed that the compound is not pure. For the main product: ^1H NMR ($CDCl_3$) δ 3.42, 3.84 (2 × 3 H, 2 s, COOMe), 7.52, 8.25 (4 H, AA′BB′ q, J = 8.5 Hz, Ar). However, the mass spectrum is inconsistent with a substitution product. Mass spectrum at 95 °C, m/z (relative abundance, assignment) 339 (51), 323 (17), 279 (19, m/z 339 – HCOOMe), 234 (9, *p*-$O_2NC_6H_4CH$=C(COOMe)-CO?), 174 (B, *p*-$O_2NC_6H_4C$≡CCO), 150 (51, *p*-$O_2NC_6H_4CO$), 128 (21, C_6H_4C≡CCO?); at 70 °C, 316 (B), 234 (17), 220 (72), 174 (68), 150 (91). The M for the substitution product is expected to be at m/z 306.

(b) The above-mentioned substitution is very slow. Reaction of a large excess of KOCN over **6b** in an NMR tube at room temperature for 4 days showed no product. Reflux of **6b** with a 6 molar excess of KOCN in $CDCl_3$ for 8 h gave only 13% of the substitution product, whereas reflux for 17 h with 7 molar equiv of KOCN in CH_3CN gave 40% reaction. The substitution product formed under these conditions was accompanied by other products, as shown by the presence of additional signals in the ^1H NMR.

(g) With Potassium Cyanide. (a) A solution of **6b** (0.7 g, 2 mmol) and KCN (0.15 g, 2.3 mmol) in MeCN (50 mL) was refluxed for 30 min and then worked up as above. TLC and NMR showed that only traces of a few products were formed.

(b) When **6b** (5 mg) and KCN (3 mg) in CD_3CN (0.5 mL) were kept for 3.5 h at 60 °C, only **6b** was recovered. After 7 h at 60 °C the solution was black. After workup TLC showed five spots in addition to that of **6b** and ^1H NMR showed eight singlets at δ 3.3–3.9, including a major one at δ 3.71. Consequently, the reaction was not investigated further.

(h) With Potassium Azide. To a solution of **6b** (0.9 g, 2.7 mmol) in dry MeCN (100 mL) was added KN_3 (2.1 g, 26 mmol). The solution turned yellow and then orange. The mixture was analyzed by NMR during 8 h and worked up when the mixture consisted of an 85:15 ratio of the vinyl azide **14g** to the ketene imine (whose isolation will be discussed elsewhere). For this mixture: IR ($CHCl_3$) ν_{max} 2150 cm^{-1} (N_3, s), 1730 (CO_2Me, s); ^1H NMR ($CDCl_3$) δ 3.59 (3 H, s, COOMe), 3.89 (3 H, s, COOMe), 7.61, 8.38 (4 H, AA′BB′ q, J = 8.8 Hz, Ar); ^1H NMR (CD_3CN) δ 3.50 (3 H, s, COOMe), 3.82 (3 H, s, COOMe), 7.66, 8.30 (4 H, AA′BB′ q, J = 8.8 Hz, Ar).

(i) With *p*-Toluidine. To **6b** (0.7 g, 2 mmol) in MeCN (50 mL) was added *p*-toluidine (0.55 g, 5.1 mmol). After 3 h at 25 °C no reaction took place. The mixture was then refluxed for 2.5 h. NMR showed a 4:6 ratio of **6b** to the substitution product **14f**. After an additional 2.5 h, 90% of **14f** was formed. On cooling, *p*-toluidine hydrobromide was formed and filtered. Evaporation of the solvent left an oil. Chromatography on silica gel followed by crystallization from cyclohexane gave **14f** as a white solid: mp 203 °C (0.36 g, 48%); IR ($CHCl_3$) ν_{max} 3300 (NH, w), 1720 (COOMe), 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (3 H, s, Me), 3.36 (1 H, s, COOMe), 3.83 (3 H, s, COOMe), 6.59, 6.91 (4 H, AA′BB′ q, J = 8.2 Hz, Tol), 7.42, 8.13 (4 H, AA′BB′ q, J = 9 Hz, $O_2NC_6H_4$), 11.14 (1 H, br, NH); ^1H NMR (CD_3CN) δ 2.18 (3 H, s, Me), 3.26 (3 H, s, COOMe), 3.75 (3 H, s, COOMe), 6.72, 6.94 (4 H, AA′BB′ q, J = 8.2 Hz, Tol), 7.46, 8.10 (4 H, AA′BB′ q, J = 9 Hz, $O_2NC_6H_4$), 10.9 (1 H, br, NH); mass spectrum, m/z (relative abundance, assignment) 370 (36, M), 338 (62, M – MeOH), 311 (36, M – COOMe), 279 (47, M – Tol), 239 (B, M – $CH(COOMe)_2$), 193 (99.5, M – $CH(COOMe)_2$ – NO_2), 190 (20), 178 (13, M – $CH(COOMe)_2$ –

NO_2 − Me), 128 (30), 106 (62, TolNH). Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.86; N, 7.57. Found: C, 61.65; H, 5.18; N, 7.00.

(j) With Potassium Thiocyanate. (a) To a solution of **6b** (0.3 g, 0.9 mmol) in acetonitrile (50 mL) was added potassium thiocyanate (0.6 g, 6.2 mmol). The mixture was refluxed for 6 h, poured into water (50 mL), and extracted with $CHCl_3$ (2 × 50 mL). The organic phase was washed with 10% aqueous HCl solution (50 mL), dried, and evaporated. Chromatography of the oil obtained on silica gel using 70:30 hexane–$CHCl_3$ as the eluant showed that a mixture of two compounds A and B was formed. The first fractions contained a 30:70 A/B mixture, and the following fractions were 70:30 A/B mixtures. The fractions richer in A were crystallized from ethanol, giving the substitution product dimethyl (α-thiocyanato-*p*-nitrobenzylidene)malonate (**14h**) as a white solid: mp 46 °C (40 mg, 15%); ^1H NMR ($CDCl_3$) δ 3.52 (3 H, s, COOMe), 3.92 (3 H, s, COOMe), 7.54, 8.34 (4 H, AA′BB′ q, J = 8.8 Hz, Ar); mass spectrum, m/z (relative abundance, assignment) 322 (5, M), 291 (9, M − OMe), 264 (10, M − SCN), 220 (18, M − SCN − CO_2), 205 (5, M − SCN − COOMe), 174 (66, M − SCN − COOMe − OMe), 128 (B, M − SCN − COOMe − NO_2 − OMe). Anal. Calcd for $C_{13}H_{10}N_2O_6S$: C, 48.44; H, 3.10. Found: C, 48.31; H, 2.95.

Attempts to crystallize compound B from its mixture with A was unsuccessful, and it was obtained only with 85% purity (according to the NMR): ^1H NMR ($CDCl_3$) δ 3.65 (3 H, s, COOMe), 3.91 (3 H, s, COOMe), 7.62, 8.30 (4 H, AA′BB′ q, J = 9.0 Hz, Ar); mass spectrum, m/z (relative abundance, assignment) 309 (30), 281 (37, m/z 309 − CO), 264 (26, $O_2NC_6H_4C{=}C(CO_2Me)_2$?), 220 (18, 264 − CO_2), 174 (84, $O_2NC_6H_4C{\equiv}CCO$?), 128 (B, $C_6H_4C{\equiv}CCO$).

(b) A solution of **6b** (190 mg, 0.55 mmol) and KSCN (340 mg, 35 mmol) in acetonitrile (50 mL) was refluxed for 16 h. After workup as in (a) above five compounds, including B as the major one, were observed by TLC. Two of them were separated by chromatography on silica gel, using 70:30 hexane–$CHCl_3$ as the eluant. Compound C was obtained first in 90% purity: ^1H NMR ($CDCl_3$) δ 3.44 (3 H, s, COOMe), 3.85 (3 H, s, COOMe), 7.58, 8.24 (4 H, AA′BB′ q, J = 8.8 Hz, Ar); mass spectrum, m/z (relative abundance) 309 (5), 281 (7), 264 (5), 234 (9), 205 (14), 174 (21), 166 (18), 150 (59), 149 (B), 128 (17).

From further fractions compound D was obtained after crystallization from ethanol as a white solid: mp 82 °C (45 mg); ^1H NMR ($CDCl_3$) δ 3.47 (3 H, s, COOMe), 3.93 (3 H, s, COOMe), 7.01, 7.98 (4 H, AA′BB′ q, J = 8.6 Hz, Ar); mass spectrum, m/z (relative abundance, assignment) 456 (42), 296 (34), 220 (17), 174 (75, ArC≡CCO), 150 (30, ArCO), 128 (B, $C_6H_4C{\equiv}CCO$?), 120 (41).

(c) A mixture of **6b** with 6 molar equiv of KSCN in acetonitrile was refluxed for 16 h, and the approximate product distribution of A, B, C, and D was determined by ^1H NMR after 3, 6, and 16 h. The respective percentages of A, B, C, and D were as follows: 33, 14, 0, 0; 40, 60, 0, 0; 0, 60, 25, 15. When the same reaction was repeated at room temperature, only the substitution product **14h** (A) was observed after 96 h.

Reaction of 4 with Sodium Methoxide. To a solution of **4** containing 26% of the Z isomer (4 mg, 0.013 mmol) in CD_3CN (0.5 mL) was added solid NaOMe portionwise. No change was observed up to 20 min, and after 60 min an apparent 56:44 E/Z bromide mixture was observed. The integral ratio of the Me to total MeO signals was at this time 1.56, compared with 1.36 at zero reaction time. The reaction was not investigated further.

General Procedure for Determination of the Stereochemistry of the Reactions. Two procedures were followed. (a) The solution of both the bromo ester (**4** or **5**) and the salt of the nucleophile in the appropriate deuteriated solvent (0.5 mL) was placed in an NMR tube and the reaction was followed as described below. (b) To a solution of **4** or **5** (several milligrams) in the deuteriated solvent (0.5 mL) in an NMR tube was added the nucleophile portionwise with vigorous shaking to ensure dissolution after the addition of each portion. The NMR spectrum was recorded once or several times after the addition of each portion.

In most cases the solution was homogeneous at the beginning of the reaction, although turbidity, probably due to incomplete dissolution, was sometimes observed. The reaction mixtures were visually homogeneous in the beginning of the reactions in most cases, at least during the determination of the first points, but turbidity due to the formation of NaBr was observed in later stages of the reaction.

The isomeric purity of **4** and **5** was determined before the addition of the first portion of nucleophile from the ratios of the two CO_2Me signals, using the assignments given in Table I for **6a** and **6b** or above for **4** and **5**. The spectra were taken in the CO_2Me region and occasionally over the full range at several intervals, and the first point was taken as early as possible. The identification of the CO_2Me signals of the E and Z products was based on the assignments of Table I. The E/Z ratio was based on integration of the two product signals, and the percentage of reaction was calculated from the ratio of the product CO_2Me signals to the precursor CO_2Me signals, and occasionally the value was confirmed by integration of other signals (e.g., the aromatic Me) in the reactants and products. The results are given in Table II. No isomerization of **4** or **5** to their isomers was observed, except for the cases described specifically below.

Reaction of 5 with *p*-Toluidine. To a light-protected solution of **5** (5 mg, 0.0144 mmol) (containing 8% of the Z isomer) in CD_3CN (0.5 mL) was added *p*-toluidine (3.5 mg, 0.0327 mmol). No reaction was observed after 3 days. After 40 min at 60 °C, 15% of the substitution products were formed. A broad signal centered at δ 3.60 overlapped the δ 3.55 CO_2Me signal of **5**, but it was shifted by adding D_2O. By integration of the CO_2Me signals, the (E)-**19f**:(Z)-**19f** ratio is 1:1, whereas the bromides consisted of an 84/16 ratio of **5** to its Z isomer.

Reaction of 4 with Tetrabutylammonium Bromide. An 88/12 mixture of **4** and its Z isomer (5.4 mg, 0.017 mmol) and tetrabutylammonium bromide (15 mg, 0.046 mmol) in $CDCl_3$ (0.5 mL) was kept at room temperature with the exclusion of light. No change in the composition was observed after 2, 24, 70, and 216 h. The solvent was evaporated, DMSO-d_6 was added, and the mixture was heated at 90 °C for 22 h. ^1H NMR showed the formation of a new compound with a single methoxy signal, which was not identified further.

The experiment in $CDCl_3$ was repeated with a 5:1 or a 4.2:1 ratio of Bu_4NBr to the mixture of the bromo diesters. No isomerization was observed after 126 h.

Reaction of 5 with Tetrabutylammonium Bromide. A light-protected mixture of **5** and its Z isomer (6.4 mg, 0.018 mmol) and Bu_4NBr (22.3 mg, 0.07 mmol) was kept in CD_3CN (0.5 mL) for 90 and 160 h. NMR analysis showed that no $E \rightleftharpoons Z$ isomerization took place within experimental error.

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Registry No. 4, 110242-24-5; **5**, 110242-25-6; **6a**, 103883-90-5; **6b**, 103883-91-6; **7a**, 106098-05-9; **7b**, 106098-07-1; **8a**, 106098-03-7; **8b**, 106098-06-0; **9a**, 110242-29-0; **9b**, 110242-33-6; **9b**-*O-d*, 110242-34-7; **10a**, 110242-30-3; **10a**-*O-d*, 110242-32-5; **12a**, 110242-35-8; **12b**, 110242-36-9; **12c**, 110242-37-0; **12d**, 110242-38-1; **12e**, 110242-39-2; **12f**, 110242-40-5; **12g**, 110242-41-6; **12h**, 59832-45-0; **13**, 49769-82-6; **14a**, 110242-42-7; **14b**, 110242-43-8; **14c**, 110242-44-9; **14d**, 110242-45-0; **14e**, 110242-46-1; **14f**, 110242-47-2; **14g**, 110242-48-3; **14g** (ketenimine), 110242-49-4; **14h**, 110242-50-7; **14i**, 110242-51-8; (E)-**15a**, 110242-67-6; (Z)-**15a**, 110242-68-7; (E)-**15b**, 110242-52-9; (Z)-**15b**, 110242-53-0; (E)-**15c**, 110242-54-1; (Z)-**15c**, 110242-55-2; (E)-**15d**, 110242-56-3; (Z)-**15d**, 110242-57-4; (E)-**15e**, 110242-58-5; (Z)-**15e**, 110242-59-6; (E)-**15f**, 110242-60-9; (Z)-**15f**, 110242-61-0; (E)-**15g**, 110270-81-0; (Z)-**15g**, 110242-62-1; (E)-**16a**, 110242-63-2; (Z)-**16a**, 110242-64-3; (E)-**16b**, 110242-65-4; (Z)-**16b**, 110242-66-5; (Z)-*p*-$MeC_6H_4CH{=}C(CO_2H)CO_2Me$, 110242-26-7; ($E$)-*p*-$MeC_6H_4CH{=}C(CO_2H)CO_2Me$, 110242-27-8; ($E$)-*p*-$MeC_6H_4CH{=}C(CO_2Me)CO_2CD_3$, 110242-28-9; *p*-$MeC_6H_4CH(Br)C(Br)(CO_2Me)CO_2Bu$-*t*, 110242-31-4; PhOH·Na, 139-02-6; *p*-MeC_6H_4OH·Na, 1121-70-6; *p*-BrC_6H_4OH·Na, 7003-65-8; *p*-$MeOC_6H_4OH$·Na, 1122-95-8; *p*-$NO_2C_6H_4OH$·Na, 824-78-2; MeOH·Na, 124-41-4; *t*-BuOH·K, 865-47-4; *p*-ClC_6H_4SH·Na, 18803-44-6; $NaBH_4$, 16940-66-2; *p*-$MeC_6H_4C(Cl){=}C(CO_2Me)_2$, 103883-89-2; *p*-$MeC_6H_4SH$·Na, 10486-08-5; KOCN, 590-28-3; KCN, 151-50-8; KN_3, 20762-60-1; *p*-$MeC_6H_4NH_2$, 106-49-0; KSCN, 333-20-0.