# Methyl Trideuteriomethyl (E)- $(\alpha$ -Bromoarylidene)malonates: Simple Stereochemical Probes in Nucleophilic Vinylic Substitution near the Retention/Stereoconvergence Borderline<sup>1</sup>

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Abstract: Methyl trideuteriomethyl (E)-( $\alpha$ -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<sub>2</sub>Me groups. The signal for the CO<sub>2</sub>Me group cis to the aryl in the <sup>1</sup>H 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<sup>-</sup>, two ArS<sup>-</sup>, and MeO<sup>-</sup> ions and of 5 by three ArO<sup>-</sup>, two ArS<sup>-</sup>, and N<sub>3</sub><sup>-</sup> ions in solvents such as DMSO- $d_6$  and 95:5 CD<sub>3</sub>CN-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<sup>-</sup> (but not  $Br^-$ ) gave  $E \rightleftharpoons Z$  bromide isomerization of 5 before the substitution, and BH<sub>4</sub> 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),<sup>2</sup> the stereochemical outcome is frequently partial or complete stereoconvergence; i.e., both isomeric products 3a and **3b** are formed from either precursor (eq 1).<sup>3</sup>



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 <sup>1</sup>H 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,<sup>3</sup> it became obvious that a study of a system where Y and Y' are of similar bulk and only one of them shows an  ${}^{1}H$ 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<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)CO<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, 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 <sup>1</sup>H NMR signals of the two COOMe groups in the unlabeled compounds 6 (Ar = p-MeC<sub>6</sub>H<sub>4</sub>, p-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>; X = Br, OAr, SAr,

<sup>(1) (</sup>a) Part 35 in the series "Nucleophilic Attacks on Carbon-Carbon Double Bonds". (b) Part 34: Avramovitch, B.; Weyerstahl, P.; Rappoport,

<sup>Double Bonds". (b) Part 34: Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. J. Am. Chem. Soc. 1987, 109, 0000.
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(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. Ibid.</sup> 

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sufficiently separated, and in relative positions which has enabled assignments in previous work.<sup>3b-d</sup> 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  $E \Rightarrow Z$  isomerization of the precursors could be detected. Since inversion of configuration is usually not observed in substitution of electrophilic haloethylenes,<sup>5</sup> the <sup>1</sup>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.<sup>3d</sup> 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.

 $\begin{array}{ccc} & \rho \ -GC_6H_4 \\ & Br \end{array} > C = C < CO_2Me \\ & Br \end{array} > C = C < CO_2Bu \ -t \\ & Br \end{array} > C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & 7a, G = Me \\ & b, G = NO_2 \\ \end{array} > C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & Br \\ & C = C < CO_2Bu \ -t \\ & CO_2Me \\ & Br \\ & C = C < CO_2Bu \ -t \\ & CO_2Me \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & CO_2Me \\ \hline & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C < CO_2Bu \ -t \\ & C = C$ 

#### Results

Synthesis. (E)- and (Z)-tert-butyl methyl ( $\alpha$ -bromo-pmethylbenzylidene)malonate (7a and 7b) and the p-nitro analogues 8a and 8b were available from a previous study.<sup>3c</sup> 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



**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  $\geq$ 90%) and after COOH  $\rightarrow$  COOD exchange were es-

terified with  $CD_2N_2$  (eq 2). The isomers 4 and 5 obtained were  $\ge 91-95\%$  geometrically pure by <sup>1</sup>H NMR.

Geometrical Assignment of Precursors and Products. The unlabeled esters 6a and 6b show two ester signals in the <sup>1</sup>H NMR in CDCl<sub>3</sub>: at  $\delta$  3.57 and 3.86 for 6a and at  $\delta$  3.63 and 3.94 for 6b. Previous experience with many methyl cinnamate systems ArC(R<sup>1</sup>)=C(R<sup>2</sup>)CO<sub>2</sub>Me 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,<sup>3b-d</sup> and this assignment was corroborated in the cases where we have X-ray diffraction data for one of the isomers.<sup>3b-d</sup> This is true also for 7 and 8 and their substitution derivatives. Likewise, pure (*E*)-*p*-MeC<sub>6</sub>H<sub>4</sub>CH=C(CO<sub>2</sub>CH<sub>3</sub>)CO<sub>2</sub>CD<sub>3</sub>, which was prepared for comparison, conforms to the generalization. Indeed, 4 and 5 showed main signals at  $\delta$  3.84 and 3.94, respectively, with signals at  $\leq$ 5% intensity at  $\delta$  3.57 and 3.63, corroborating the generalization and indicating a geometrical purity of  $\geq$ 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.<sup>6</sup> 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<sup>-</sup> in MeOH, giving the substitution products 12a-f(eq 3). *p*-Nitrophenoxide ion did not react under the mild reaction

$$p-\text{MeC}_{6}\text{H}_{4}\text{C}(\text{Br}) = C(\text{CO}_{2}\text{Me})_{2} + \text{Nu}^{-} \xrightarrow{\text{DMSO}} 6a$$

$$p-\text{MeC}_{6}\text{H}_{4}\text{C}(\text{Nu}) = C(\text{CO}_{2}\text{Me})_{2} (3)$$

$$12a, \text{Nu} = \text{PhO}$$

$$b, \text{Nu} = p-\text{MeC}_{6}\text{H}_{4}\text{O}$$

$$c, \text{Nu} = p-\text{MeC}_{6}\text{H}_{4}\text{O}$$

$$d, \text{Nu} = p-\text{MeC}_{6}\text{H}_{4}\text{O}$$

$$e, \text{Nu} = \text{MeO} (\text{in MeOH})$$

$$f, \text{Nu} = p-\text{ClC}_{6}\text{H}_{4}\text{S}$$

$$p-\text{MeC}_{6}\text{H}_{4}\text{C}(\text{Cl}) = C(\text{CO}_{2}\text{Me})_{2} + p-\text{MeC}_{6}\text{H}_{4}\text{S}^{-} \xrightarrow{\text{DMSO}} p-\text{MeC}_{6}\text{H}_{4}\text{C}(\text{SC}_{6}\text{H}_{4}\text{Me}-p) = C(\text{CO}_{2}\text{Me})_{2} (4)$$

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.

12g

$$6a \xrightarrow{\text{NaBH}_4} p \cdot \text{MeC}_6\text{H}_4\text{CH} = C(\text{CO}_2\text{Me})_2 \rightarrow 12h \\ p \cdot \text{MeC}_6\text{H}_4\text{CH}_2\text{CH}(\text{CO}_2\text{Me})_2 \quad (5) \\ 13$$

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, <sup>1</sup>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

<sup>(4)</sup> 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.

<sup>(6)</sup> An exception where the assignments are apparently reversed are (E)-and (Z)-p-MeC<sub>6</sub>H<sub>4</sub>CH=C(CO<sub>2</sub>CH<sub>3</sub>)CO<sub>2</sub>CD<sub>3</sub> in C<sub>6</sub>D<sub>6</sub>.

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

$$p-O_2NC_6H_4C(Nu) = C(CO_2Me)_2 \quad (6)$$

$$14a, Nu = PhO (in DMSO)$$

$$b, Nu = p-MeC_6H_4O (in DMSO)$$

$$c, Nu = p-MeC_6H_4O (in DMSO)$$

$$d, Nu = p-MeC_6H_4S (in DMSO)$$

$$e, Nu = p-CIC_6H_4S (in DMSO)$$

$$f, NuH = p-MeC_6H_4NH_2 (in MeCN)$$

$$g, Nu = N_3 (in MeCN)$$

$$h, Nu = SCN (in MeCN)$$

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  $CO_2Me$  signals were observed in the <sup>1</sup>H NMR. Since the main one is a singlet, a decarbomethoxylation probably took place.<sup>7</sup> **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 <sup>1</sup>H NMR, and two CO<sub>2</sub>Me signals, which in nearly all cases were of different intensity, were observed at the positions of the two CO<sub>2</sub>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).



The reactions were mostly conducted in  $CD_3CN$  or in 95:5  $CD_3CN-DMSO-d_6$ , which were found to give convenient reaction rates. The addition of  $DMSO-d_6$  to  $CD_3CN$  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  $\delta$  ca. 3.35. Its position also changed during the reaction. In some cases, as in the reaction of 4 with PhO<sup>-</sup>, it did not interfere, whereas in other cases, e.g., in the reaction of 4 with TolO<sup>-</sup>, 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<sup>-</sup> was also studied in (CD<sub>3</sub>)<sub>2</sub>CO and in 1:1 CD<sub>3</sub>CN-CDCl<sub>3</sub>, 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<sup>-</sup>]/[4] ratio of 1.4 the half-life ( $\tau$ ) of the reaction was ca. 30 min, and with a [TolO<sup>-</sup>]/[5] ratio of 1.3,  $\tau \sim 10$  min in CD<sub>3</sub>CN. The reactions with thiolate nucleophiles were much faster. E.g., in the addition of an unweighed amount of TolS<sup>-</sup>Na<sup>+</sup> 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<sub>3</sub><sup>-</sup>, SCN<sup>-</sup>, 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.

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

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

Second, as with previous examples of substitutions of highly activated vinyl halides,<sup>3b-d</sup> 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/Zproduct 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<sup>-</sup>]/[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/Zvalues 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/Zproduct ratios vs time. The first experimental point was mostly after 2-5 min, and the extrapolation was not extensive. The

<sup>(7)</sup> Halide ion promoted dechlorocarbomethoxylation of compounds RC-(Cl)=C(CO<sub>2</sub>Me)<sub>2</sub> to RC=CCO<sub>2</sub>Me (R = CN, CO<sub>2</sub>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<sub>2</sub>Ar)=C(CO<sub>2</sub>Et)<sub>2</sub> with base. E.g.: Fleming, L; Owen, C. R. J. Chem. Soc. B **1971**, 1293.

					δ(C0	DOMe)		
Ar <sup>b</sup>	$\mathbf{X}^{b}$	R	substrate <sup>c</sup>	solvent	cis to Ar	trans to Ar	δ(Me)	Δδ(COOMe) <sup>6</sup>
Tol	H	Н	E isomer	CDCl <sub>3</sub>		3.88	2.38	0.01
	Н	Н	Z isomer	CDCl <sub>3</sub>	3.87		2.38	
	Br	H	9a	CDCl <sub>3</sub>		3.90	2.38	0.30
	Br	H	10a	CDCl <sub>3</sub>	3.60		2.38	
	н	$CD_3$	E isomer	CDCl <sub>3</sub>		3.83		
	TT	CU	136	$C_6 D_6$	202	3.48	2.26	0.02
	п	СП3	120	$CDCl_3$	3.83	3.83	2.30	0.02
	CI	СЧ			3.30	3.20	1.90	0.12
	Br	CH.	69	CDCl <sup>3</sup>	3.59	3.80	2.38	0.27
	DI	C113	0a	C.D.	3.10	3 48	1.92	0.36
				DMSO-d	3.53	3.82	2 34	0.29
	Br	CD <sub>2</sub>	4	CDCl <sub>2</sub>	0.00	3.89	2.38	0.30
	Br	CD <sub>2</sub>	Z isomer	CDCh	3.59	2107	2.38	0.00
	PhO	CH <sub>2</sub>	12a	CDCl	3.65	3.75	2.28	0.10
		5		DMSO-d	3.56	3.66	2.24	0.10
	TolO	CH1	12b	CDCl	3.64	3.76	2.28, 2.20	0.12
		,		DMSO-d <sub>6</sub>	3.52	3.66	2.25, 2.15	0.14
	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> O	CH <sub>3</sub>	12c	CDCl <sub>3</sub>	3.66	3.77	2.31	0.11
	1 0 4	2		$DMSO-d_6$	3.57	3.68	2.27	0.11
	AnO	$CH_3$	12d	CDCl <sub>3</sub>	3.68	3.77	2.28, 3.63	0.09
		-		$DMSO-d_6$	3.54	3.68	2.25, 3.63	0.14
	MeO	CH3	12e	CDCl <sub>3</sub>	3.53	3.84	2.40, 3.52	0.31
	TolS	$CH_3$	12g	CDCl <sub>3</sub>	3.43	3.83	2.19, 2.18	0.40
				DMSO-d <sub>6</sub>	3.34	3.72	2.15	0.38
	p-ClC <sub>6</sub> H₄S	CH3	12f	CDCl <sub>3</sub>	3.43	3.84	2.21	0.41
				DMSO-d <sub>6</sub>	3.35	3.74	2.17	0.39
$p-O_2NC_6H_4$	Br	Н	9b	CDCl <sub>3</sub>		3.95		
	_			$(CD_3)_2CO$		3.90		
	Br	н	10b	CDCl <sub>3</sub>	3.63			
	<b>P</b>	<b>CD</b>	-	$(CD_3)_2CO$	3.60			
	Br	$CD_3$	5	CDCl <sub>3</sub>		3.94		0.31
	Br D-	$CD_3$	Z isomer	CDCl <sub>3</sub>	3.63	2.04		0.21
	Dr	СП3	OD		3.03	3.94		0.31
				05.5 CD CN-DMSO d	3.34	3.80		0.32
	ч	CH		$GDC1^{\ell}$	3.33	3.00		0.33
	11	C113		CD CN	3.85	3.89		0.04
	PhO	CH.	149	CDC1.	3.62	3.80		0.02
	1110	0113	144	DMSO-d	3 59	3 73		0.14
				95.5 CD-CN-DMSO-d	3 61	3.75		0.14
	TolO	CH-	14b	CDCh	3.66	3.82	2 20	0.14
	1010	<i></i> ,	- 10	DMSO-de	3.57	3.72	2.20	0.15
				95:5 CD <sub>2</sub> CN-DMSO-d <sub>4</sub>	3.59	3.75	2.18	0.16
	AnO	$CH_1$	14c	CDCl <sub>1</sub>	3.65	3.83	3.68	0.18
		-		DMSO-d <sub>6</sub>	3.56	3.74	3.63	0.18
				95:5 $CD_3CN-DMSO-d_6$	3.58	3.76	3.65	0.18
	TolS	CH3	14d	CDCl <sub>3</sub>	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 <sub>6</sub> H <sub>4</sub> S	CH3	14e	CDCl <sub>3</sub>	3.60	4.05		0.45
				$DMSO-d_6$	3.52	3.95		0.43
				95:5 CD <sub>3</sub> CN–DMSO- $d_6$	3.39	3.83		0.44
	SCN	CH3	14h	CDCl <sub>3</sub>	3.52	3.91		0.39
				CD <sub>3</sub> CN	3.45	3.87		0.42
	N <sub>3</sub>	CH3	14g	CDCl <sub>3</sub>	3.59	3.89		0.30
				CD <sub>3</sub> CN	3.50	3.82		0.32
	OCN	CH,	14i	CDCl <sub>3</sub>	3.42	3.84		0.42
	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> NH	СН₃	14f	CD <sub>3</sub> CN	3.36	3.83		0.47

**Table I.**  $\delta$ (COOMe) Values for ArC(X)=C(COOMe)COOR (R = H, Me)<sup>a</sup>

<sup>a</sup>Values are reproducible to  $\pm 0.01$  ppm. For comparison,  $\delta$  (CDCl<sub>3</sub>) for (E)-TolCH=CHCOOMe:2.36 (Me), 3.79 (COOMe). <sup>b</sup>Tol = p-MeC<sub>6</sub>H<sub>4</sub>; An = p-MeOC<sub>6</sub>H<sub>4</sub>. <sup>c</sup>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**. <sup>d</sup> $\Delta\delta$ (COOMe) =  $\delta$ (COOMe trans to Ar) -  $\delta$ (COOMe cis to Ar). <sup>e</sup>From ref 17. <sup>f</sup>Reported (footnote e):  $\delta$ (COOMe) 3.57, 3.86 on a different spectrometer.

estimated error in the values is  $\pm 1-2\%$ . In the few cases where the change in the E/Z ratios during the reaction was larger, the estimated error is  $\leq 3\%$ . 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/Zisomer, 76/24 and 67/33 ratios were obtained after 16 and 45

										i.				kinetically
										E/Z			E/Z	E/Z
		concn,		[Nu <sup>_</sup> ],	[Nu <sup>-</sup> ]/			$T_{0,}^{c}$	₽°	product	T'	<i>6</i> %	product	product
no.	substrate <sup>a</sup>	Σ	Nu <sup>+</sup> M <sup>+</sup>	M	[sqns]	solvent	products	min	reactn <sup>a</sup>	ratio <sup>d</sup>	min	reactn'	ratio'	ratio
	6a	0.087	PhO-Na <sup>+</sup>	0.138	1.6	DMSO-d <sub>6</sub>	12a	2	12		3600	96		
7	4	0.030	PhO-Na <sup>+</sup>	0.015	0.5	<b>CD</b> <sup>3</sup> <b>CN</b>	(E) - + (Z) - 15a	15	8	79/21	65	29	58/42	93/7#
e.	4	0.047	PhO-Na <sup>+</sup>	0.035	0.75	DMSO-d <sub>6</sub>	(E) - + (Z) - 15a	e.	30	78/22	210	67	56/44	82/18 <sup>i</sup>
4	4	0.070	PhO-Na <sup>+</sup>	0.129	1.8	DMSO-d <sub>6</sub>	(E) - + (Z) - 15a	2	45	6/16	30	67	70/30	97/3
s	4	0.030	TolO-Na <sup>+</sup>	0.010	0.33	CD <sub>3</sub> CN	(E) - + (Z) - 15b	20	9	75/25	120	21	57/43	85/15#
9	4	0:030	TolO-Na <sup>+</sup>	0.015	0.5	CD <sub>3</sub> CN-DMSO-d <sub>6</sub> <sup>j</sup>	(E) - + (Z) - 15b	£	4	85/15	60	28	58/42	91/9
7	4	0.045	TolO-Na <sup>+</sup>	0.108	2.4	DMSO-d <sub>6</sub>	(E) - + (Z) - 15b	ę	76	79/21	9	94	75/25	87/13
×	4	0.074	TolO-Na <sup>+</sup>	0.063	0.85	DMSO-de	(E) - + (Z) - 15b	2	65	78/22	25	65	78/22	83/17
6	4	0:030	p-BrC <sub>6</sub> H <sub>4</sub> O <sup>-</sup> Na <sup>+</sup>	0.015	0.5	CD <sub>3</sub> CN-DMSO-d <sub>6</sub> <sup>j</sup>	(E) - + (Z) - 15c	S	9	86/14	50	41	$64/36^{k}$	92/8
10	4	0:030	AnO-Na <sup>+</sup>	0.015	0.5	CD,CN-DMSO-d	(E) - + (Z) - 15d	9	7	87/13	51	43	67/33	96/4
Π	4	0.057	AnO <sup>-</sup> Na <sup>+</sup>	0.090	1.6	DMSO-d <sub>6</sub>	(E) - + (Z) - 15d	×	42	85/15	80	46	60/40	96/4*
12	4	0.026	McO-Na <sup>+</sup>	ш	ш	<b>CD</b> <sup>3</sup> <b>CN</b>	(E) - + (Z) - 15e'	e	0		60	1	1	. 1
13	4	0.030	p-CIC <sub>6</sub> H₄S <sup>-</sup> Na <sup>+</sup>	m	ш	CD <sub>3</sub> CN–DMSO-d <sub>6</sub> <sup>j</sup>	(E) - + (Z) - 15f	ŝ	17	84/16	ш	75	65/35	6/16
14	4	0.030	TolS-Na <sup>+</sup>	ш	ш	CD <sub>3</sub> CN–DMSO-d <sub>6</sub>	(E) - + (Z) - 15g	7	24	82/18	ш	87	77/23	88/12 <sup>h</sup>
15	4	0.14	TolS-Na <sup>+</sup>	0.057	0.4	DMSO-d <sub>6</sub>	(E) - + (Z) - 15g	21	77	84/16			•	, u
16	v	0.028	PhO-Na <sup>+</sup>	0.034	1.2	CD <sub>3</sub> CN-DMSO-d <sub>6</sub> <sup>j</sup>	(E) - + (Z) - 16a	7	22	75/25	40	80	55/45	$\frac{10}{10}$
17	Ś	0.029	PhO-Na <sup>+</sup>	ш	ш	CD <sub>3</sub> CN-DMSO-d <sub>6</sub> <sup>1</sup>	(E) - + (Z) - 16a	ŝ	17	86/14	ш	81	53/47	90/10
18	49	0.046	TolO-Na <sup>+</sup>	0.061	1.3	CD <sub>3</sub> CN	14b	4	26	•	20	70	•	
61	Ś	0.074	TolO-Na <sup>+</sup>	0.063	0.9	$DMSO-d_6$	(E) - + (Z) - 16b	7	65	78/22°	30	65	78/22°	$81/19^{o}$
20	ŝ	0.056	TolO <sup>-</sup> Na <sup>+</sup>	0.081	1.46	CD <sub>3</sub> CN-DMSO-d <sub>6</sub> <sup>j</sup>	(E) - + (Z) - 16b	2	99	62/38	15	97	51/49	68/32 <sup>h</sup>
21	ŝ	0.028	TolO-Na <sup>+</sup>	0.034	1.2	CD <sub>3</sub> CN-DMSO-d <sub>6</sub> <sup>j</sup>	(E) - + (Z) - 16b	2	22	75/250	40	80	55/45	81/19
22	ŝ	0.029	TolO <sup>-</sup> Na <sup>+</sup>	ш	ш	CD <sub>3</sub> CN-DMSO-d <sub>6</sub> <sup>j</sup>	(E) - + (Z) - 16b	2	4	83/17	т	52	62/38	97/3
23	ŝ	0.035	TolO-Na <sup>+</sup>	ш	т	CD <sub>3</sub> CN-DMSO-d <sub>6</sub>	(E) - + (Z) - 16b	÷	12	88/12	т	83	52/48	98/24
24	ŝ	0.030	TolO <sup>-</sup> K <sup>+</sup>	ш	ш	CD <sub>3</sub> CN-DMSO-d <sub>6</sub>	(E) - + (Z) - 16b	7	12	85/15	ш	72	81/19	90/10
25	ŝ	0.030	TolO-K <sup>+</sup>	ш	т	CD <sub>3</sub> CN-DMSO-d <sub>6</sub>	(E) - + (Z) - 16b	7	33	82/18	ш	100	60/40	86/14
26	ŝ	0.030	TolO-Li <sup>+</sup>	ш	ш	CD <sub>3</sub> CN-DMSO-d <sub>6</sub>	(E) - + (Z) - 16b	20	9	83/17	т	38	73/27	88/12
27	ŝ	0.029	AnO <sup>-</sup> Na <sup>+</sup>	ш	ш	$CD_3CN-DMSO-d_{\delta'}$	(E) - + (Z) - 16c	Ś	L	90/10	ш	54	68/32	95/5#
28	ŝ	0.042	$TolS^{-}Na^{+}$	0.042	1.0	CD <sub>3</sub> CN-DMSO-d <sub>6</sub>	(E) - + (Z) - 16d	1.5	<i>LL</i>	85/15	50	81	85/15	89/11
29	ŝ	0.040	TolS-Na <sup>+</sup>	т	ш	CD <sub>3</sub> CN–DMSO-d <sub>6</sub>	(E) - + (Z) - 16d	7	48	87/13	ш	78	87/13	6/16
30	ŝ	0.030	TolS-Na <sup>+</sup>	0.023	0.76	1:1 CD <sub>3</sub> CN-CDCl <sub>3</sub>	(E) - + (Z) - 16d	S	31	86/14	45	47	86/14	90/10
31	ŝ	0.035	TolS <sup>-</sup> Na <sup>+</sup>	ш	ш	$(CD_3)_2CO$	(E) - + (Z) - 16d	÷	15	90/10	ш	100	55/45	94/6"
32	ŝ	0.047	p-CIC <sub>6</sub> H <sub>4</sub> S-Na <sup>+</sup>	0.062	1.3	CD <sub>3</sub> CN-DMSO-d <sub>6</sub>	(E) - + (Z) - 16e	7	001	84/16	50	100	52/48	90/10
33	Ś	0.040	p-CIC <sub>6</sub> H <sub>4</sub> S <sup>-</sup> Na <sup>+</sup>	ш	ш	$CD_3CN-DMSO-d_6'$	(E) - + (Z) - 16e	<b>~</b>	16	92/8	ш	95	85/15	96/4
34	S	0.026	$N_{3}K^{+}p$	0.345	13.3	CD <sub>3</sub> CN	(E) - + (Z) - 16g	12	4	84/16	1440	949	53/47	95/5
35	ŝ	0:030	CNS-K <sup>+</sup>	0.180	9	<b>CD</b> <sup>3</sup> <b>CN</b>	(E) - + (Z) - 16h			r	1440	35	50/50	r
36	ŝ	0.029	p-MeC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	0.065	2.2	CD <sub>3</sub> CN	(E) - + (Z) - 16f	40	15	50/50	u	I		50/50"
. 4 C	intained 6% (	of the Z is $\frac{1}{2}$	omer in experiments	3, 4, 6 an	7 and 7	% of the Z isomer in the	e other experiments	. 5 con	tained 5%	of the $Z$ is	omer exc	cpt in exp	beriments 2	2 and 34, when
une z 1	somer consist	T (T 15%)	and 11% of the mixth s of the lost experime	rre, respect	nively. 1	0I = p-MeC <sub>6</sub> H <sub>4</sub> ; AII = $g$ Value at zero reaction	p-MeUC <sub>6</sub> H <sub>4</sub> . 111 a time corrected fo	ne at wi	ncn the In	st experim	entat por	nt with re	illable prou	uct distribution aither from the
Constan	t ratio when	this was 1	time indenendent or	by extranc	dation who	and the measured $E/Z$ r	atio changed with 1	time. U	inless other	rwise indic	ated the	estimated	lerror is ±	1-2% <sup>h</sup> A less
reliable	extrapolation	than in c	other cases gives an e	stimated e	rror of ≲3	%. 'Similar reaction pe	rcentages were obt	ained by	integratio	n of either	the COC	Me or the	e MeC.H.	signals of 4 and
15a. /5	15:5 ratio (v/1	v) of CD <sub>3</sub> (	CN to DMSO-d6. * /	V 69/31 E	/Z ratio w	as obtained in DMSO-6	16 after 2 h (66% re	action)	with a 1.3-	-fold excess	of the n	ucleophile	. 'Apparer	it isomerization
of the s	tarting mater	ial (see te	xt) prevented determ	ination of	the $E/Z$ I	atios. "The nucleophile	c was added portion	nwise to	the reactic	on mixture,	and the	product di	istribution	was determined
one or I	nore times ur	ntil all the	added nucleophile of	each porti	on was cor	isumed. "A one-point et	xperiment. Extrapc	lation is	meaningle	ss. <sup>o</sup> Avera	ige of dat	a for two	similar exp	eriments. <sup>p</sup> Not
all the	KN <sub>3</sub> was solt	the in the	creaction mixture.	The prod	uct rearrai	iges slowly to the keten	e imine. 'The star	ting ma	terial isom	erizes duri	ng the re	action so	that the ex	trapolated $E/Z$
produc	t ratio cannot	be obtair	ied.											

Table II. Substitution of (E)-ArC(Br)=C(CO<sub>2</sub>CH<sub>3</sub>)CO<sub>2</sub>CD<sub>3</sub> by Nucleophiles at Room Temperature

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 COOMe 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<sup>-</sup> 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 stereo-chemistry was not studied.

Reaction of an 88/12 mixture of 4 and its Z isomer with a 2.5and 5-fold excess of Bu<sub>4</sub>NBr in CDCl<sub>3</sub> 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<sub>2</sub>Me signal (which may be TolC==CCO<sub>2</sub>Me formed by elimination)<sup>7</sup> was observed. When a mixture of 5 (containing 8% of its Z isomer) and 3.7 molar excess of Bu<sub>4</sub>NBr was kept in CD<sub>3</sub>CN 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<sup>3</sup>-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)<sup>8</sup> 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.<sup>9</sup> 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 stereo-

chemical 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<sub> $\alpha$ </sub>(Br)=CHR' (R = alkyl, Ar) by either a rate-determining nucleophilic attack on  $C_{\alpha}$  or via an elimination (E2 or E1cB]addition process.<sup>2b,g</sup> The E bromide should also be studied since it may give either the E product by reaction at  $C_{\alpha}$  or the Z product by an elimination (E1cB)-addition route. When both E and Zproducts 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.<sup>3</sup>)

These differences between substitutions at sp<sup>3</sup>- and sp<sup>2</sup>-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 Zproducts 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.<sup>3</sup> 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<sub>3</sub> and COCH<sub>3</sub> or CO<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub> 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.

<sup>1</sup>H NMR is an ideal probe for geometrical assignment since a CH<sub>3</sub> group gives a singlet whereas the CD<sub>3</sub> group is invisible. A CH<sub>3</sub> group can be easily introduced into activating groups such as COCH<sub>3</sub>, CO<sub>2</sub>CH<sub>3</sub>, SO<sub>2</sub>CH<sub>3</sub>, 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 <sup>1</sup>H NMR spectrum of the unlabeled products immediately shows

<sup>(8)</sup> 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.

<sup>(9)</sup> 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<sub>2</sub>Me groups and their  $\delta$ '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<sup>3</sup>-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 <sup>1</sup>H 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<sub>2</sub>Me)R (R =  $CO_2Bu-t$ ,<sup>3d</sup> CN,<sup>3b</sup> CHO,<sup>3d</sup> H),<sup>10</sup> which were occasionally corroborated by X-ray diffraction data,<sup>3b,d</sup> 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).<sup>5</sup> In line with this, in the present study the Eproduct 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 Ebromide, 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<sub>2</sub>Me 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,<sup>3d</sup> is that  $\Delta\delta(CO_2Me)$  ( $\Delta\delta$  of the two  $CO_2Me$  groups) is practically unaffected by changing the solvent from CD<sub>3</sub>CN to DMSO- $d_6$ . However, both  $\delta(CO_2Me)$  and  $\Delta\delta$ -(CO<sub>2</sub>Me) are strongly affected on changing the solvent to C<sub>6</sub>D<sub>6</sub>.

In addition, the  $\Delta\delta(CO_2Me)$  values are strongly influenced by the  $\alpha$ -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 ( $\alpha$ -Bromoarylidene)malonates. Reactions at the Stereoconvergence Region. The extensive data of Table II lead to one general and qualitative conclusion: the reactions of dimethyl ( $\alpha$ -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  $\alpha$ -*p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub> to the electron-donating  $\alpha$ -*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<sub>3</sub><sup>-</sup> nucleophile (an exception is the reaction with *p*-toluidine, which is discussed below). The external changes are in the cation in the series Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup> in the reaction of TolO<sup>-</sup> with **5** and in the solvent, mainly from CD<sub>3</sub>CN to DMSO-*d*<sub>6</sub>.

More quantitatively, in almost all the reactions the percentage of the retained *E* product is  $\geq 80\%$  and in half of them it is  $\geq 90\%$ . 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  $\geq 60\%$  excess retention ( $\leq 40\%$  stereoconvergence) and half of them with  $\geq 80\%$  excess retention ( $\leq 20\%$  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  $E \rightleftharpoons Z$  isometization 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<sub>3</sub>CN-DMSO- $d_6$  and CD<sub>3</sub>CN (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<sup>-</sup> and AnO<sup>-</sup> (experiments 4 and 11) show similar behavior, but TolO<sup>-</sup> gives a lower ratio (experiments 7 and 8). However, the first point in these experiments was already at  $\geq 65\%$  reaction. The ratios are also similar for p-ClC<sub>6</sub>H<sub>4</sub>S<sup>-</sup> and TolS<sup>-</sup> (experiments 13 and 14). Likewise in the reactions of 5 the ratios for PhO<sup>-</sup>, AnO<sup>-</sup>, p-ClC<sub>6</sub>H<sub>4</sub>S<sup>-</sup>, TolS<sup>-</sup>, and N<sub>3</sub><sup>-</sup> (experiments 17, 27, 31, 33, and 34) are between 90/10 and 96/4, and the most reliable experiment with TolO<sup>-</sup>Na<sup>+</sup> (experiment 22) gives a 97/3 ratio. In both series the differences between the ArS<sup>-</sup> and the ArO<sup>-</sup> 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<sup>-</sup> with 5 in CD<sub>3</sub>CN, 1:1 CD<sub>3</sub>CN-CDCl<sub>3</sub>, and 95:5 CD<sub>3</sub>CN-DMSO- $d_6$ (experiments 28-31) and for the reactions of 4 with AnO<sup>-</sup> (experiments 10 and 11), TolO<sup>-</sup> (experiments 6 and 7), and PhO<sup>-</sup> (experiments 2 and 4; see, however, experiment 3). The ratios do not change on changing the cation from Li<sup>+</sup> to K<sup>+</sup> in the reactions of 5 with TolO<sup>-</sup>M<sup>+</sup>, but it is difficult to compare them with those for the Na<sup>+</sup> 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<sup>-</sup> (experiments 2 (in  $CD_3CN$ ) and 17), TolS<sup>-</sup> (experiments 14, 28, and 29), and *p*-ClC<sub>6</sub>H<sub>4</sub>S<sup>-</sup> (experiments 13, 32, and 33) the ratios are similar. With AnO<sup>-</sup> (experiments 10 and 27) the ratio is somewhat higher for 5, while comparison with TolO<sup>-</sup> (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

<sup>(10)</sup> Hayashi, T. J. Org. Chem. 1966, 31, 3253.





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<sup>-</sup> from 18 gives the retained E product, expulsion of Br<sup>-</sup> from 19 gives the inverted product, and expulsion of Nu<sup>-</sup> from 20 gives the isomeric Z precursor. Stereoconvergence is obtained from a combination of the "retention route"  $(17 \rightarrow 18 \rightarrow (E)$ -Nu) and the "inversion route"  $(17 \rightarrow 19 \rightarrow (Z)$ -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  $\approx$  19 equilibration would prevail before Br<sup>-</sup> expulsion and the Curtin-Hammett principle will be applicable. The stereochemistry would then be a complete stereo-convergence, in contrast with the observation.

We therefore suggest that  $k_{\rm rot}$  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 =  $k_{\rm rot}^{60}/k_{\rm rot}^{20}$ ,  $k_{\rm rot}^{60} > k_{\rm rot}^{20}$ . From the E/Z values of Table I, the difference in  $\Delta G^*$ , i.e.,  $\Delta \Delta G^* = \Delta G^*$ (inversion) –  $\Delta G^*$ (retention) =  $\Delta G^*$ (120° rotation) –  $\Delta G^*$ (60° rotation), is 1–2 kcal mol<sup>-1</sup>.

The  $\Delta G^{\dagger}$  values for rotation can be artificially separated into two components, steric and hyperconjugative. In the 60° rotation only an eclipsing Ar/CO<sub>2</sub>CD<sub>3</sub> interaction is encountered, whereas in the 120° rotation the two eclipsing interactions Nu/CO<sub>2</sub>CD<sub>3</sub> and Br/CO<sub>2</sub>CH<sub>3</sub> do not occur simultaneously and the larger of them will determine the steric barrier. The Ar/CO<sub>2</sub>CD<sub>3</sub> and Nu/CO<sub>2</sub>CD<sub>3</sub> 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<sub>2</sub>CH<sub>3</sub> 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'C-CH<sub>2</sub>X (negative hyperconju-

gation).<sup>11</sup> 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'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  $2p(C^{\text{-}})/C\text{-}Ar$  interaction,  $^{12a}$  and we suggested recently that the interactions with C-Cl and C-Br bonds are similar.<sup>1b</sup> Hence, 60° rotation will be hyperconjugatively preferred.  $^{12a}$  The energy differences between the 60° and the 120° rotations in the gas phase for  $\bar{C}H_2\text{-}CH_2Br$  can be estimated from the calculation to be >10 kcal mol<sup>-1</sup>. The hyperconjugative interaction is strongly reduced by the presence of electron-withdrawing groups Y and Y' on the carbanionic center.<sup>12</sup> Since both steric and hyperconjugative factors favor the 60° rotation, the hyperconjugative preference for the rotation is  $\leq 2$  kcal mol<sup>-1</sup>. 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<sup>-</sup>-, ArO<sup>-</sup>-, 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<sub>6</sub>H<sub>4</sub> in 4 to the p-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub> 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.<sup>3</sup> 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.<sup>2e</sup> 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<sub>2</sub>YY'.<sup>2e,3d</sup> Study of the substitution of E and Z compounds **21–26** was in a qualitative agreement with this generalization.

PhC(X)=C(Ph)Y 
$$p$$
-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>C(Cl)=C(Y)CO<sub>2</sub>Me  
21, X = I; Y = NO<sub>2</sub> 23, Y = CN  
22, X = Cl; Y = CHO 24, Y = CHO  
 $p$ -GC<sub>6</sub>H<sub>4</sub>C(Br)=C(CO<sub>2</sub>Me)CO<sub>2</sub>Bu-t  
25, G = Me  
26, G = NO<sub>2</sub>

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

<sup>(11) (</sup>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.

<sup>(12) (</sup>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)<sup>13</sup> 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<sup>3d</sup> is not very large. TolO<sup>-</sup> 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<sub>2</sub>Me and CO<sub>2</sub>Bu-t groups do not differ in their negative charge delocalizing ability, and their conjugative interactions with a double bond are similar.<sup>14</sup> 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.<sup>15</sup> 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  $p-MeC_6H_4C(Br)$ - $(Nu)-\tilde{C}(CO_2Me)CO_2Bu-t$  (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.

 $E \rightleftharpoons Z$  Isomerization of the Bromides. A corollary of the intermediacy of a carbanion in the substitution is the possibility of a nucleophilic Br<sup>-</sup>-catalyzed (E)-RBr  $\rightleftharpoons$  (Z)-RBr isomerization. The mechanism for this is the route (E)-Br  $\rightarrow$  17  $\rightarrow$  20  $\rightarrow$  (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;<sup>16</sup> i.e.,  $k_1$  is low and formation of 17 is slow. Second, Br<sup>-</sup> is an excellent nucleofuge from carbanions C-C-Br, and for systems such as 17 this is evident from our conclusion above that  $k_{\rm el} > k_{\rm rot}$  in 18 or 19. Since the hyperconjugative barrier for the 17  $\rightarrow$  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<sup>-</sup> 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<sub>3</sub> or of 5 in CD<sub>3</sub>CN after 160 h with Bu<sub>4</sub>NBr should not be surprising. However, it should be accommodated with the fact that (E)-RCl  $\rightleftharpoons$  (Z)-RCl isomerization was observed for systems  $22^{3c} 23^{3b}$  and  $24^{3d}$  with Cl<sup>-</sup>. 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<sup>-</sup> and TolS<sup>-</sup> is estimated to be 9 orders of magnitude,<sup>2b</sup> so that isomerization should be necessarily observed after these reaction times. Whether isomerization will be observed in another solvent,<sup>17</sup> 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<sup>-</sup>-promoted debromocarboalkylation.<sup>7</sup>

It was therefore surprising that thiocyanate ion in the dark led to an exclusive  $5 \rightleftharpoons Z$  isomer isomerization which precedes the substitution. We know of one precedent for such a process.<sup>18</sup> In terms of Scheme I the (E)-Br  $\rightarrow 17 \rightarrow 20 \rightarrow (Z)$ -Br process is faster than the (E)-Br  $\rightarrow 17 \rightarrow 18$  or  $19 \rightarrow (E)$ -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<sup>-</sup> compared with SCN<sup>-</sup> 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.<sup>2b</sup> The suggestion that this is due to postisomerization in the product enamine by rotation around the  $C_{\alpha}-C_{\beta}$  "partial" double bond seems equally applicable in our system (cf. **28b**). Such rotation leads usually to the more stable enamine,<sup>2b</sup>



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  $\rightleftharpoons (Z)$ -16f is sufficiently slow at room temperature on the NMR time scale, and the two CO<sub>2</sub>Me groups appear as sharp singlets.<sup>19</sup> 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<sup>20</sup> 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 <sup>1</sup>H and <sup>13</sup>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<sub>4</sub>Si 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<sub>254</sub> plates (0.25-mm thickness). Workup means diluting with H<sub>2</sub>O, extracting with CHCl<sub>3</sub>, drying the organic phase with MgSO<sub>4</sub>, 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 ( $\alpha$ -bromo-*p*-methylbenzylidene)malonate (**6a**) and dimethyl ( $\alpha$ bromo-*p*-nitrobenzylidene)malonate (**6b**) were previously reported.<sup>15</sup> The <sup>13</sup>C NMR data are as follows: **6a** in CDCl<sub>3</sub> (proton decoupled),  $\delta$  21.3 (Me, s), 52.4, 52.8 (COOCH<sub>3</sub>, s), 127.9, 128.8 (C-2 and C-3, s), 128.0, 135.6, 139.7, 140.5 ( $C_{\alpha}$ ,  $C_{\beta}$ , C-1 and C-4, very weak; specific assignment within this group is tentative), 162.9, 164.4 (COOCH<sub>3</sub>) (in the corresponding (*E*)-trideuteriomethyl ester **4** the signals at  $\delta$  52.4 and 162.9 were not observed); **6b** in CD<sub>3</sub>CN (proton decoupled),  $\delta$  53.5, 53.7

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

<sup>(14)</sup> Hine, J.; Kanagasabapathy, V. M.; Ng, P. J. Org. Chem. 1982, 47, 2745.

<sup>(15)</sup> Rappoport, Z.; Gazit, A. J. Org. Chem. 1986, 51, 4107.
(16) Rappoport, Z. Adv. Chem. Ser. 1987, No. 215, 399.

<sup>(17)</sup> In DMF 8a isomerizes slightly after a long reaction time.<sup>3d</sup>

<sup>(18)</sup> The reaction of pure (E)- or pure (Z)-2-methyl-3-chlorobutenal with KSCN gives initial partial stereoconvergence accompanied by  $E \rightleftharpoons Z$  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).

<sup>(19)</sup> For a review on rotation around the double bond of push-pull ethylenes, see: Sandström, J. Top. Stereochem. 1983, 14, 83.

<sup>(20)</sup> 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).

## Methyl Trideuteriomethyl (E)- $(\alpha$ -Bromoarylidene)malonates

(COOCH<sub>3</sub>), 124.4 (C-3), 130.0 (C-2), 132.4 (C<sub>a</sub>), 136.3 (C<sub>b</sub>), 145.5 (C-1), 149.4 (C-4), 162.7, 164.9 (COOMe).<sup>21</sup> Diazald was obtained from Aldrich. The ArO<sup>-</sup> and ArS<sup>-</sup> 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<sup>-</sup> and ArS<sup>-</sup> 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<sub>4</sub> (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<sub>2</sub>Cl<sub>2</sub>-MeOH) 0.2. <sup>1</sup>H NMR showed the presence of a 3:1 mixture of the (Z)- and (E)-methyl hydrogen (p-methylbenzylidene)malonates. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 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,  $\delta$  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<sub>12</sub>H<sub>12</sub>O<sub>4</sub>: 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<sub>3</sub> as the eluant gave pure (by <sup>1</sup>H NMR) (Z)-methyl hydrogen (*p*-methylbenzylidene)malonate: mp 152 °C (4.1 g, 65%); IR (CHCl<sub>3</sub>)  $\nu_{max}$  3000-2400 (COOH), 1720-1680 (COOMe, COOH), 1600 cm<sup>-1</sup>; 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<sub>6</sub>H<sub>4</sub>C=CO), 131 (11), 121 (21), 119 (11, *p*-MeC<sub>6</sub>H<sub>4</sub>CO), 115 (B, *p*-MeC<sub>6</sub>H<sub>4</sub>C=C). Anal. Calcd for C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>: 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: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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 ( $\alpha$ -Bromo-*p*-methylbenzylidene)malonate (10a). (a) To (Z)-tert-butyl methyl ( $\alpha$ -bromo-*p*-methylbenzylidene)malonate (7a)<sup>3d</sup> (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<sub>3</sub>, washed three times with water, dried, and analyzed by NMR. The main product is a 55/45 mixture of the acids 10a:9a: UV  $\lambda_{max}$  (EtOH) 274 nm (log  $\epsilon$ = 4.28); IR (CHCl<sub>3</sub>)  $\nu_{max}$  3500–2500 (COOH), 1730 (CO<sub>2</sub>R), 1610 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 10a,  $\delta$  2.38 (3 H, s, Tol), 3.60 (3 H, s, CO<sub>2</sub>Me), 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<sub>2</sub>Me), 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<sub>3</sub> (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<sup>3d</sup> (12.1 g, 42 mmol), 2,6-di-tert-butylphenol (0.6 g, 3 mmol), and DBN (5.1 g, 42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>-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<sub>3</sub>) v<sub>max</sub> 3000-2500 cm<sup>-1</sup> (COOH), 1710(COMe), 1600; <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 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<sub>2</sub>), 160 (4, M - Br - COOMe), 143 (B, TolC=CCO<sup>+</sup>), 119 (16, TolCO<sup>+</sup>), 116 (35). (b) 9a (95%, containing 5% 12k): mp 112 °C from cyclohexane (0.25 g, 3% from the dibromide); IR (CHCl<sub>3</sub>) similar to that of 10a; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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 ( $\alpha$ -Bromo-p-methylbenzylidene)malonate (4). Methyl deuterium ( $\alpha$ -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<sub>2</sub>O (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<sub>2</sub>O (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<sub>2</sub>O) 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<sub>2</sub>N<sub>2</sub> 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<sub>2</sub>O (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 CHCl3-hexane as eluant gave 4 as a viscous while oil (105 mg, 45%) containing 5% of its Z isomer): IR (neat) v<sub>max</sub> 1725 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) § 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  $\delta$  3.59 singlet and a  $\delta$  3.57 multiplet (with intensities of ca. 5% of that of the  $\delta$  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<sub>3</sub>), 236 (B, M - Br), 192 (15, M - Br - CO<sub>2</sub>), 168 (18), 143 (63, TolC≡CCO<sup>+</sup>), 119 (18, TolCO<sup>+</sup>), 115 (18, TolC=C<sup>+</sup>) (m/z 318/m/z 317 = 0.144; calcd 0.141).

(E)-Methyl Trideuteriomethyl (a-Bromo-p-nitrobenzylidene)malonate (5). (a) (Z)-Methyl Hydrogen ( $\alpha$ -Bromo-p-nitrobenzylidene)malonate (9b). A 1:1 mixture of the (E)- and (Z)-tert-butyl methyl ( $\alpha$ -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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>, 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<sub>3</sub>, moderately soluble in CH<sub>2</sub>Cl<sub>2</sub>, and soluble in EtOH and acetone. UV (EtOH)  $\lambda_{max}$  278 nm (log  $\epsilon$  = 4.23); <sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>CO)  $\delta$  3.90 (3 H, s, COOMe), 7.75, 8.32 (4 H, AA'BB' q, J = 9 Hz, Ar) ([10b]: δ 3.60 (COOMe)): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.95 (3 H, s, COOMe), 7.75, 8.26 (4 H, AA'BB' q, J = 8 Hz, Ar) ([10b]:  $\delta$  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 - NO2), 116 (45, M - Br - COOH - COOMe - NO). Anal. Calcd for C11H8BrNO6: C, 40.0; H, 2.42; N, 4.24. Found: C, 40.10; H, 2.67; N, 4.25.

(b) (*E*)-Methyl Trideuteriomethyl ( $\alpha$ -Bromo-*p*-nitrobenzylidene)malonate (5). A solution of CD<sub>2</sub>N<sub>2</sub> was prepared from Diazald (1.5 g) and NaOD solution (prepared from Na (1 g) and D<sub>2</sub>O (10 mL)-

<sup>(21)</sup> For comparison with the <sup>13</sup>C spectrum of p-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CH=C-(CO<sub>2</sub>Et)<sub>2</sub>, see: Bottino, F. A.; Musumarra, G.; Rappoport, Z. Magn. Reson. Chem. **1986**, 24, 31.

MeOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OD (5 mL)) as described in the preparation of 4. Since 9b is insoluble in CDCl<sub>3</sub> 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 ( $\alpha$ -bromo-p-nitrobenzylidene)malonate (5) (0.41 g, 60%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.94 (3 H, s, COOMe), 7.53, 8.26 (4 H, AA'BB' q, J = 8.8 Hz, Ar) ( $\delta$  3.63 with 5% intensity of  $\delta$  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<sub>3</sub>), 267 (B, M - Br), 223  $(20, M - Br - CO_2), 174 (43, M - Br - CO_2CD_3 - MeO), 150 (11, 100)$  $O_2NC_6H_4CO$ , 128 (42, M – Br – COOCD<sub>3</sub> – OMe – NO<sub>2</sub>)

When a solution of 5 (containing 5% of the Z isomer) in CDCl<sub>3</sub> 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 (a-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<sub>3</sub>, and the organic phase was dried and evaporated. Chromatography on silica gel, using CHCl<sub>3</sub>hexane as the eluant, and crystallization from ethanol gave dimethyl ( $\alpha$ -phenoxy-p-methylbenzylidene)malonate (12a) (100 mg, 19%) as a white solid: mp 104 °C;  $R_{f}$  0.2 (1:1 hexane–CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>)  $\nu_{max}$ 1715 (CO<sub>2</sub>Me), 1620 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.28 (3 H, s, Me), 3.65, 3.75 (6 H, 2 s, CO<sub>2</sub>Me), 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<sub>2</sub>Me), 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<sub>6</sub>H<sub>4</sub>C=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<sub>3</sub>-hexane as eluant) and crystallization from EtOH gave dimethyl ( $\alpha$ -(*p*-methylphenoxy)-*p*-methylbenzylidene)malonate (12b) as large white crystals: mp 88 °C (80 mg, 15%); IR (CHCl<sub>3</sub>)  $\nu_{max}$  1710 cm<sup>-1</sup> (CO<sub>2</sub>Me); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.20 (3 H, s, OC<sub>6</sub>H<sub>4</sub>Me?), 2.28 (3 H, s, C<sub>6</sub>H<sub>4</sub>Me?), 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<sub>2</sub>Me), 280 (18, M – HCO<sub>2</sub>Me), 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<sub>7</sub>H<sub>7</sub><sup>+</sup>). Anal. Calcd for C<sub>20</sub>H<sub>20</sub>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<sub>3</sub>, evaporation of the solvent, chromatography on silica gel, and crystallization from EtOH, dimethyl ( $\alpha$ -(*p*-bromophenoxy)-*p*-methylbenzylidene)malonate (12c) was obtained as a white solid: mp 96 °C (110 mg, 28%); UV (EtOH)  $\lambda_{max}$  278 nm (log  $\epsilon$  = 4.26); IR (CHCl<sub>3</sub>)  $\nu_{max}$  1720 cm<sup>-1</sup> (CO<sub>2</sub>Me); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>6</sub>H<sub>4</sub>Br), 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<sub>6</sub>H<sub>4</sub>Br), 189 (13, M – OC<sub>6</sub>H<sub>4</sub>Br – CO<sub>2</sub>), 165 (16), 143 (46, TolC $\equiv$ CCO), 119 (B, TolCO). Anal. Calcd for C<sub>19</sub>H<sub>17</sub>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  $\alpha$ -(*p*-methoxyphenyl)-*p*-methylbenzylidene)malonate (12d) (mp 84 °C (160 mg, 47%)) were obtained: UV (EtOH)  $\lambda_{max}$  280 nm (log  $\epsilon$  = 4.21); IR (CHCl<sub>3</sub>)  $\lambda_{max}$  1720 (CO<sub>2</sub>Me), 1630 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)

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<sub>6</sub>H<sub>4</sub>OMe), 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<sub>6</sub>H<sub>4</sub>O), 189 (22, M – p-MeOC<sub>6</sub>H<sub>4</sub>O – CO<sub>2</sub>), 165 (36), 143 (B, M – p-MeOC<sub>6</sub>H<sub>4</sub>O) – COOMe – MeO), 119 (98, TolO), 101 (53, PhC=C). Anal. Calcd for C<sub>20</sub>H<sub>20</sub>O<sub>6</sub>: 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 <sup>1</sup>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<sub>3</sub>-hexane) 0.2; IR (CHCl<sub>3</sub>)  $\nu_{max}$  1720 cm<sup>-1</sup> (CO<sub>2</sub>Me); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>Me trans to Tol), 7.25 (4 H, s, Ar); <sup>1</sup>H NMR (1:1 CD<sub>3</sub>CN-C<sub>6</sub>D<sub>6</sub> in the MeO region)  $\delta$  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<sub>2</sub>Me), 189 (16, M – CO<sub>2</sub> – OMe), 174 (35, M – CO<sub>2</sub>Me – OMe), 165 (52), 143 (24, TolC=CCO), 119 (69, TolCO), 91 (39, C<sub>7</sub>H<sub>7</sub><sup>+</sup>). Anal. Calcd for C<sub>14</sub>H<sub>16</sub>O<sub>5</sub>: 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 <sup>1</sup>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 ( $\alpha$ -((*p*-chlorophenyl)thio)-*p*-methylbenzylidene)-malonate (12f) as a white solid: mp 97 °C (50 mg, 7%); UV (EtOH)  $\lambda_{max}$  266 (log  $\epsilon$  = 4.09), 292 nm (4.14); IR (CHCl<sub>3</sub>)  $\nu_{max}$  1715 cm<sup>-1</sup> (CO<sub>2</sub>Me); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>), 165 (28), 143 (B, TolC=CCO), 115 (43). Anal. Calcd for C<sub>19</sub>H<sub>17</sub>ClSO<sub>4</sub>: 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<sub>4</sub> (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<sub>4</sub> for 24 h, with 0.6 mmol of NaBH<sub>4</sub> for 3 h, and with 0.15 mmol of NaBH<sub>4</sub> 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<sub>4</sub> (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<sub>3</sub> (3 × 40 mL), and dried (MgSO<sub>4</sub>), and the solvent was evaporated, giving dimethyl (*p*methylbenzyl)malonate as a white oil (0.3 g, 75%): IR (CHCl<sub>3</sub>)  $\nu_{max}$ 1730 cm<sup>-1</sup> (COOMe); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.29 (3 H, s, Me), 3.17 (2 H, d, J = 8 Hz, CH<sub>2</sub>), 3.66 (1 H, t, J = 8 Hz, CH; irradiation converts  $\delta$  3.17 to a singlet), 3.68 (3 H, s, COOMe), 7.04 (4 H, s, Ar). Anal. Calcd for C<sub>13</sub>H<sub>16</sub>O<sub>4</sub>: C, 66.08; H, 6.82. Found: C, 66.20; H, 5.86.

Reaction of Dimethyl ( $\alpha$ -Chloro-*p*-methylbenzylidene)malonate with Sodium *p*-Toluenethiolate. (a) A mixture of dimethyl ( $\alpha$ -chloro-*p*methylbenzylidene)malonate<sup>15</sup> (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<sub>2</sub>Cl<sub>2</sub> (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 ( $\alpha$ -(tolylthio)-*p*-methylbenzylidene)-

#### Methyl Trideuteriomethyl (E)- $(\alpha$ -Bromoarylidene)malonates

malonate (12g): mp 85 °C (120 mg, 26%);  $R_f$  (7:3 CH<sub>2</sub>Cl<sub>2</sub>-hexane) 0.2; UV (EtOH)  $\lambda_{max}$  226 (log  $\epsilon$  = 3.93), 261 (3.74), 296 nm (3.88); IR (CHCl<sub>3</sub>)  $\nu_{max}$  1710 cm<sup>-1</sup> (COOMe); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>), 165 (18), 143 (41, TolC=CO). Anal. Calcd for C<sub>20</sub>H<sub>20</sub>O<sub>4</sub>S: 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 ( $\alpha$ -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 **12**g.

Reactions of Dimethyl ( $\alpha$ -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<sub>3</sub>, washed with water, and evaporated. Crystallization from EtOH gave dimethyl (a-phenoxy-p-nitrobenzylidene)malonate (14a): mp 109 °C (100 mg, 32%); UV (EtOH)  $\lambda_{max}$  238 (log  $\epsilon$  = 4.09), 285 nm (4.13); IR  $(CHCl_3) \nu_{max} 1720 \text{ cm}^{-1} (CO_2Me); {}^{1}\text{H} \text{ NMR} (CDCl_3) \delta 3.66 (3 \text{ H}, s, s)$ 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<sub>2</sub>); 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<sub>2</sub>), 174 (36, M -PhO - COOMe - OMe), 150 (82, p-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CO), 128 (18, M - PhO - COOMe – MeO – NO<sub>2</sub>). 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 ( $\alpha$ -(*p*-methylphenoxy)-*p*-nitrobenzylidene)malonate (14b): mp 120 °C (110 mg, 34%); UV (EtOH)  $\lambda_{max}$  241 (log  $\epsilon$  = 4.06), 287 nm (4.08); IR (CHCl<sub>3</sub>)  $\nu_{max}$  1725 cm<sup>-1</sup> (CO<sub>2</sub>Me); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>); 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<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CO), 128 (70, M - COOMe - OMe - TolO - NO<sub>2</sub>). Anal. Calcd for C<sub>19</sub>H<sub>17</sub>NO<sub>7</sub>: 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 <sup>1</sup>H NMR. Crystallization from EtOH gave white crystals of dimethyl ( $\alpha$ -(p-methoxyphenoxy)-p-nitrobenzylidene)malonate (14c): mp 120 °C (100 mg, 30%); UV (EtOH)  $\lambda_{max}$  285 nm (log  $\epsilon$  = 4.03); IR (CHCl<sub>3</sub>)  $\nu_{max}$  1720 cm<sup>-1</sup> (CO<sub>2</sub>Me); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>2</sub>); 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<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CO), 128 (32, M - COOMe - OMe - ArO - NO<sub>2</sub>). Anal. Calcd for C<sub>19</sub>H<sub>17</sub>NO<sub>8</sub>: 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 ( $\alpha$ -(*p*-tolylthio)-*p*-nitrobenzylidene)malonate (14d): mp 119 °C (40 mg, 12%); UV (EtOH)  $\lambda_{max}$  260 (sh) (log  $\epsilon$  = 4.16), 277 nm (4.23); IR (CHCl<sub>3</sub>)  $\nu_{max}$ 1720 cm<sup>-1</sup> (CO<sub>2</sub>Me); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>); 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<sub>2</sub>), 174 (83, M - COOMe - OMe - TolS), 128 (89, M - COOMe - OMe - TolS - NO<sub>2</sub>). 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 ( $\alpha$ -((*p*-chlorophenyl)thio)-*p*-nitrobenzylidene)-malonate (14e): mp 142 °C (45 mg, 13%); UV (EtOH)  $\lambda_{max}$  256 nm (log  $\epsilon$  = 4.26); IR (CHCl<sub>3</sub>)  $\nu_{max}$  1720 cm<sup>-1</sup> (CO<sub>2</sub>Me); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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, ArS), 20 (36, M - ArS - CO<sub>2</sub>), 174 (43, M - MeOH), 264 (B, M - ArS), 220 (36, M - ArS - COOMe - OMe - NO<sub>2</sub>). Anal. Calcd for C<sub>18</sub>H<sub>14</sub>ClNO<sub>6</sub>S: 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 <sup>1</sup>H 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<sub>3</sub> as the eluant gave 6b and a yellow oil, which could not be purified by crystallization from cyclohexane or from ethanol. The <sup>1</sup>H NMR showed that the compound is not pure. For the main product: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CH=C(COOMe)-CO?), 174 (B, p-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>C $\equiv$ CCO), 150 (51, p-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CO), 128 (21, C<sub>6</sub>H<sub>4</sub>C $\equiv$ 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/z306

(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<sub>3</sub> for 8 h gave only 13% of the substitution product, whereas reflux for 17 h with 7 molar equiv of KOCN in CH<sub>3</sub>CN 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 <sup>1</sup>H 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<sub>3</sub>CN (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 <sup>1</sup>H NMR showed eight singlets at  $\delta$  3.3–3.9, including a major one at  $\delta$  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<sub>3</sub> (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<sub>3</sub>)  $\nu_{max}$  2150 cm<sup>-1</sup> (N<sub>3</sub>, s), 1730 (CO<sub>2</sub>Me, s); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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); <sup>1</sup>H NMR (CD<sub>3</sub>CN)  $\delta$  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<sub>3</sub>)  $\nu_{max}$  3300 (NH, w), 1720 (COOMe), 1710 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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); <sup>1</sup>H NMR (CD<sub>3</sub>CN)  $\delta$  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)<sub>2</sub>), 193 (99.5, M - CH(COOMe)<sub>2</sub> - NO<sub>2</sub>), 190 (20), 178 (13, M - CH(COOMe)<sub>2</sub> -

 $NO_2$  – 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<sub>3</sub> 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 ( $\alpha$ -thiocyanato-p-nitrobenzylidene)malonate (14h) as a white solid: mp 46 °C (40 mg, 15%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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); massspectrum, m/z (relative abundance, assignment) 322 (5, M), 291 (9, M - OMe), 264 (10, M - SCN), 220 (18, M - SCN - CO<sub>2</sub>), 205 (5, M - SCN - COOMe), 174 (66, M - SCN - COOMe - OMe), 128 (B, M - SCN - COOMe - NO<sub>2</sub> - 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): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>), 174 (84,  $O_2NC_6H_4C=CCO$ ?), 128 (B,  $C_6H_4C=CCO$ ).

(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<sub>3</sub> as the eluant. Compound C was obtained first in 90% purity: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>6</sub>H<sub>4</sub>C=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 <sup>1</sup>H 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<sub>3</sub>CN (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<sub>2</sub>Me 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<sub>2</sub>Me 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<sub>2</sub>Me 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<sub>2</sub>Me signals to the precursor CO<sub>2</sub>Me 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<sub>3</sub>CN (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  $\delta$  3.60 overlapped the  $\delta$  3.55 CO<sub>2</sub>Me signal of **5**, but it was shifted by adding D<sub>2</sub>O. By integration of the CO<sub>2</sub>Me 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<sub>3</sub> (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. <sup>1</sup>H 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<sub>3</sub>CN (0.5 mL) for 90 and 160 h. NMR analysis showed that no  $E \rightleftharpoons Z$  isomerization took place within experimental error.

Acknowledgment. We are indebted to Dr. D. Elmaleh for preliminary experiments. The work was supported by the Israel Commission for Basic Research, The Israel Academy for Sciences and Humanities, to which we are indebted.

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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<sub>6</sub>H<sub>4</sub>CH=C-
(CO_2H)CO_2Me, 110242-26-7; (E)-p-MeC<sub>6</sub>H<sub>4</sub>CH=C(CO<sub>2</sub>H)CO<sub>2</sub>Me,
110242-27-8; (E)-p-MeC<sub>6</sub>H<sub>4</sub>CH=C(CO<sub>2</sub>Me)CO<sub>2</sub>CD<sub>3</sub>, 110242-28-9;
p-MeC<sub>6</sub>H<sub>4</sub>CH(Br)C(Br)(CO<sub>2</sub>Me)CO<sub>2</sub>Bu-t, 110242-31-4; PhOH·Na,
139-02-6; p-MeC<sub>6</sub>H<sub>4</sub>OH·Na, 1121-70-6; p-BrC<sub>6</sub>H<sub>4</sub>OH·Na, 7003-65-8;
p-MeOC<sub>6</sub>H<sub>4</sub>OH·Na, 1122-95-8; p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OH·Na, 824-78-2;
MeOH·Na, 124-41-4; t-BuOH·K, 865-47-4; p-ClC<sub>6</sub>H<sub>4</sub>SH·Na, 18803-
44-6; NaBH<sub>4</sub>, 16940-66-2; p-MeC<sub>6</sub>H<sub>4</sub>C(Cl)=C(CO<sub>2</sub>Me)<sub>2</sub>, 103883-89-2;
p-MeC<sub>6</sub>H<sub>4</sub>SH·Na, 10486-08-5; KOCN, 590-28-3; KCN, 151-50-8; KN<sub>3</sub>,
20762-60-1; p-MeC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>, 106-49-0; KSCN, 333-20-0.
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