Nucleophilic Attacks on Carbon-Carbon Double Bonds. 33.[1,2] Approaching the Retention Region from the Stereoconvergence Region in Nucleophilic Substitution of (*E*)- and (*Z*)-Methyl *p*-Substituted α-Formyl- and α-(*tert*-Butoxycarbonyl)-β-halocinnamates

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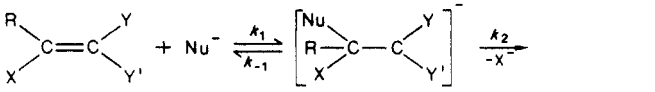
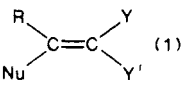
Received February 12, 1986

The three *E*/*Z* pairs of the highly electrophilic vinyl halides β-chloro-α-(methoxycarbonyl)-*p*-nitrocinnamaldehydes (**6**), *tert*-butyl methyl β-bromo(*p*-methylbenzylidene)- (**21**) and β-bromo(*p*-nitrobenzylidene)malonates (**26**) were prepared and separated. The structures of (*E*)-**6** and (*E*)-**21** and of intermediates in their synthesis were determined by X-ray crystallography. The stereochemistry of the substitution of the halogen by *p*-toluenethiolate ($TolS^-$) and *p*-cresolate ($TolO^-$) ions was investigated by using ^1H NMR as the stereochemical probe. Substitution of **6** in Me_2SO-d_6 by $TolS^-$ proceeds with nearly complete stereoconvergence, whereas substitution by $TolO^-$ proceeds with high extent of, but not complete, retention of configuration. Cl^--assisted (*E*)-**6** ⇌ (*Z*)-**6** isomerization was observed. The substitution of (*E*)- and (*Z*)-**21** in Me_2SO-d_6 and of (*E*)- and (*Z*)-**26** in 95:5 CD_3CN-Me_2SO-d_6 by $TolS^-$ proceeds with complete retention of configuration and by $TolO^-$ with nearly complete retention. The results are discussed in terms of the multistep route of vinylic substitution via an intermediate carbanion. They corroborate the predictions of the variable transition-state theory in nucleophilic vinylic substitution that stereoconvergence will be observed for highly activated systems and that the stereochemistry should be gradually changed to retention when the electrophilicity of the vinyl halide is decreased and near the borderline when the nature of the nucleophile is changed. Comparison with other systems for which stereoconvergence was observed raises the question of the structural borderline between stereoconvergence and retention, and predictions for the stereochemical outcome in substitutions of systems not yet studied are given. Some stereochemical aspects of the condensation, bromine addition, and HBr elimination in the reactions leading to **21** and **26** are briefly discussed.

The main progress in our understanding of the mechanistic details of vinylic substitution (via addition–elimination) of halosubstituted electrophilic olefins (**1**, Y and/or Y′ = electron-withdrawing groups, X = nucleofuge, e.g., Cl, Br) by nucleophiles (eq 1)[3] comes from studies of highly activated systems.[4] Singly activated systems (Y′ = H or



1 **2**



(1)

alkyl) (a) usually give retention of configuration of **1**, (b) react with second-order kinetics, and (c) give element effects k_{Br}/k_{Cl} around unity.[3-5] From the "normal" kinetic behavior it is impossible to distinguish between the alternatives whether the negatively charged species (**2**) on the reaction coordinate between reactants and products is a transition state or an intermediate. The stereochemistry is intuitively more consistent with **2** being a transition state (the "single step" route), whereas the element effect is more consistent with **2** being an intermediate (the "multistep" route).[4] MO calculations show a relatively high hyperconjugative rotational barrier in carbanionic **2**, X = Cl, R = Y = Y′ = H,[6] suggesting the feasibility of retention via short-lived carbanions. The calculations also show that the barrier is reduced when Y and Y′ are strongly electron withdrawing due to their ability for charge dispersal. The expectation is that if the reaction indeed proceeds via carbanions, the stereochemistry of **1** will be partially or completely lost, at least with some systems ("stereoconvergence"). The charge delocalization to Y, Y′ should increase the lifetime of an intermediate carbanion and deviations from second-order kinetics, and element effects different from unity might also be observed. Indeed, the approach of the variable transition-state theory in vinylic substitution[4] is to show first that **2** is a discrete carbanionic intermediate when Y and Y′ are strongly electron withdrawing and then to try to extrapolate to less activated systems.

The appearance of a third-order term in the substitution of systems **1** by amines ("amine catalysis") when Y = Y′ = CN or COR was indeed used as evidence for intermediacy of carbanions.[7] However, it is limited to reactions of amines. The similarity of the element effects for highly, moderately, and slightly activated systems[4,8] reduces the utility of this mechanistic tool.

The stereochemical probe seems to be the most versatile so far. We have shown that systems **1** activated by Y = NO_2 and Y′ = Ph,[9] Y = CHO and Y′ = Ph,[10] and Y = CN and Y′ = CO_2Me[11] groups, i.e., **3**, **4**, and **5**, showed partial or complete stereoconvergence with several nucelophiles. In each case both geometrical isomers have to be studied. We believe that this serves as the strongest evidence that

(1) For part 32, see: Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309.
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PhC(I)=C(Ph)NO_2 (3) PhC(Cl)=C(Ph)CHO (4)

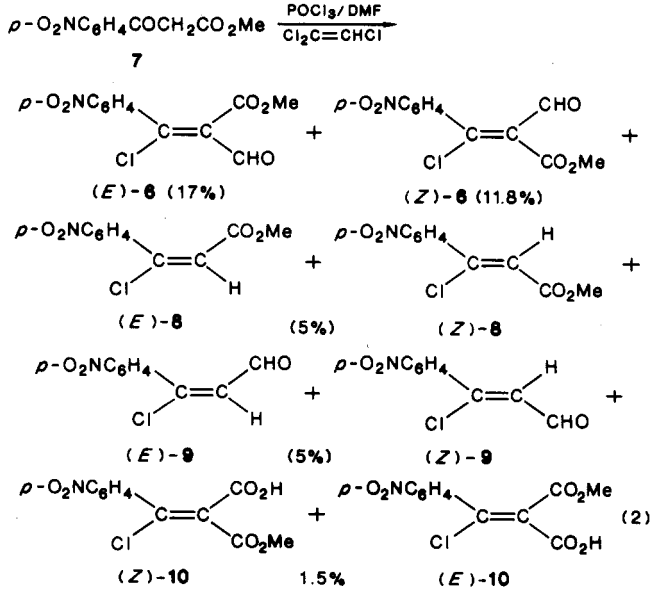
p-$O_2NC_6H_4C(Cl)=C(CN)CO_2Me$ (5)

2 is an intermediate rather than a transition state in most vinylic substitutions. However, there are several open questions that require studies of the stereochemistry of the substitution of additional systems. (a) Where is the structural transition between partial stereoconvergence and retention? This mainly relates to variations in groups Y and Y′, but the effect of R may also be important. (b) Are there regular differences in the effect of different nucleophiles on the extent of stereoconvergence? (c) Are the extents of stereoconvergence similar for the E and Z isomers of each pair or are they dependent on Y, Y′, R, and Nu?

Since the lifetime of 2 depends on the charge dispersal ability of Y and Y′ we use the relative acidities of the carbon acids CH_2YY' as rough measures for the relative lifetimes of the intermediate carbanions. This seems preferable over the use of some combination of σ_I and σ_R of Y and Y′ since the steric interaction between Y and Y′ which reduces the lifetime of 2 is reflected in the pK_a of CH_2YY'. The systems studied so far (3–5 and ArC(X)=CYY′, Y = Y′ = CN, COR) have $pK_a(CH_2YY') < 12$. For answering question a by a gradual increase of pK_a we used a diester activated system, Y = Y′ = COOR, whereas for collecting more data on questions b and c and for evaluating the effect of Y′ when Y = COOMe, a "formally" more activated system, by both a formyl and a methoxycarbonyl group, was investigated.

Results

Preparation and Reactions of (E)- and (Z)-β-Chloro-α-(methoxycarbonyl)-p-nitrocinnamaldehydes ((E)-6 and (Z)-6). Synthesis. A Vilsmeier reaction of methyl (p-nitrobenzoyl)acetate (7) gave several products which were identified as (E)- and (Z)-β-chloro-α-(methoxycarbonyl)-p-nitrocinnamaldehydes ((E)-6 and (Z)-6), (E)- and (Z)-methyl β-chloro-p-nitrocinnamates ((E)-8 and (Z)-8) and the corresponding cinnamaldehydes ((E)-9 and (Z)-9), and acids which are probably (E)- and (Z)-β-chloro-α-(methoxycarbonyl)-p-nitrocinnamic acids (10) (eq 2).



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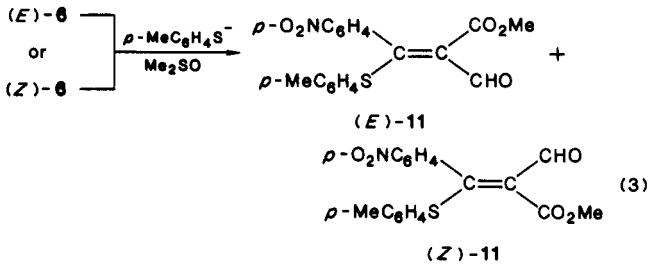
Only (E)-6 and 96% of pure (Z)-6 (admixed with 4% of (E)-6) were isolated from the mixture by crystallization. Their structural assignments are discussed below. We were unable to separate them by HPLC. The other structures were assigned from the ^1H NMR of fractions rich in (E)-8/(Z)-8 or (E)-9/(Z)-9, and the solubility of (E)-10/(Z)-10 in aqueous $NaHCO_3$ identified them as acids. The E vs. Z assignment was based on the relative positions of the CHO or the CO_2Me groups (cf. Experimental Section).

The (E)-6/(Z)-6 ratio of ca. 60:40 obtained from chromatography differs slightly from the E/Z ratio of 58:42 obtained for the phenyl analogues (see below). However, in a different reaction the (E)-6/(Z)-6 ratio was 1:1 and since some of the products may arise by decomposition of (E)-6 and (Z)-6, no importance is attributed to the differences.

The assignment of configuration for the tetrasubstituted ethylenes (E)-6 and (Z)-6 is based on the X-ray diffraction of (E)-6. The data are in Table I. A stereoscopic view is given in Figure S1 (supplementary material), and additional crystallographic data are given in Tables S1–S4 (supplementary material). Their UV spectra differ both in λ_{max} and in the ϵ values, but it is not clear what chromophore is responsible for the absorption. The assignment of configuration of their substitution products is based mainly on the characteristic differences in the positions of the ^1H NMR signals of the CHO and the CO_2Me groups; the aromatic signals also differ. The assignment is based on the assumption (corroborated for (E)-6 and (Z)-6) that when either a CHO or a COOMe group is trans to the p-nitrophenyl group it absorbs at a lower field than in the isomer where the group is cis to the aryl group (Table II). This analogy extends to compounds 4 and their TolS-, TolO-, and MeO-substitution products, where the CHO groups cis to a phenyl is always at a higher field than the group trans to the aryl. This result was also corroborated by X-ray diffraction for several derivatives.[10] Both the δ(CHO) values and the $\Delta\delta = \delta(E) - \delta(Z)$ values do not differ much between systems 4 and system 6 and its β-substitution products.

Substitution by Nucleophiles. (a) By p-Toluenethiolate Ion. Reaction of either (E)-6 or (Z)-6 with sodium p-toluenethiolate in DMF or Me_2SO gave a mixture of (E)- and (Z)-α-(methoxycarbonyl)-p-nitro-β-tolylthiocinnamaldehydes (E)-11 and (Z)-11 (eq 3). The reaction is very



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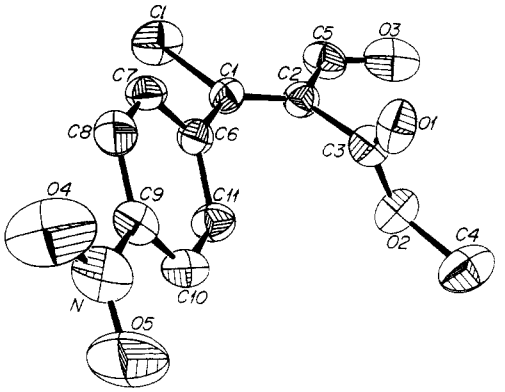
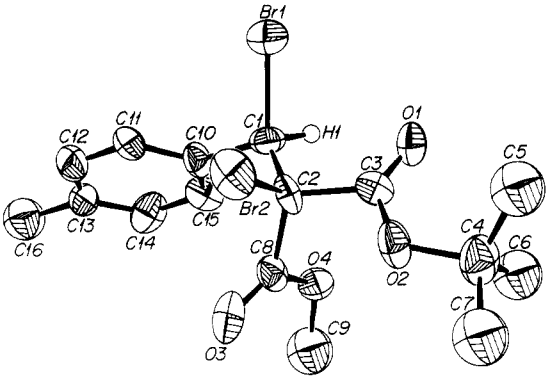
fast and the (E)-11/(Z)-11 ratio after 2.5 h in DMF is 55:45. In order to obtain the kinetically controlled ratio, the substitution was followed in Me_2SO-d_6 in the NMR probe at intervals of 2–3 min at the beginning of the reaction. In all cases the reaction at $[ArS^-]/[6]$ ratios ranging from 0.53 to 1.1 was complete within <2 min, and the initially obtained (E)-11/(Z)-11 ratio changed only slightly with time. The assignment of the structure is based on Table II.

The extrapolated product distribution from the reaction of (E)-6 to $t = 0$ is 48:52 (E)-11/(Z)-11 with excess ArS^- and the ratio after 60 h is 40:60 (E)-11/(Z)-11. At an $[ArS^-]/[6] = 0.53$ the ratio observed is 52:48, but since the error in the NMR ratios is estimated as ±5%, the difference is not considered to be significant. Starting from

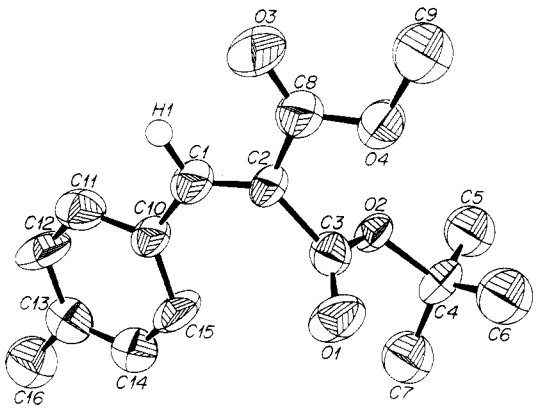
Table I. Important Crystallographic Data for (*E*)-6, (*Z*)-19, (*RR*)-20, and (*E*)-21



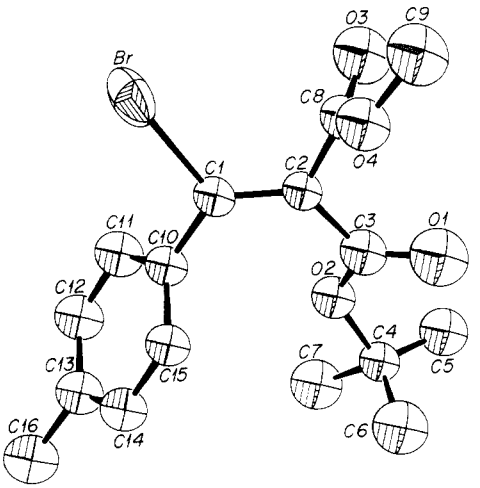
(*E*)-6



(*RR*)-20



(*Z*)-19



(*E*)-21

compd	bond	length, Å	angle	deg.
(*E*)-6[a]	C(1)–Cl	1.726 (2)	C(1)C(2)C(3)	120.0 (3)
	C(1)–C(2)	1.331 (4)	C(1)C(2)C(5)	124.1 (3)
	C(1)–C(6)	1.489 (3)	C(5)C(2)C(3)	115.8 (3)
	C(2)–C(3)	1.500 (4)	C(2)C(1)Cl	121.0 (3)
	C(2)–C(5)	1.484 (4)	C(2)C(1)C(6)	125.4 (3)
	C(5)–O(3)	1.197 (4)	ClC(1)C(6)	113.6 (2)
	C(3)–O(1)	1.191 (4)	O(1)C(3)O(2)	124.7 (3)
	C(3)–O(2)	1.326 (3)	O(1)C(3)C(2)	124.6 (3)
	C(4)–O(2)	1.449 (4)	C(3)O(2)C(4)	116.2 (3)
			ClC(1)C(6)–Ar[b]	128.76
			ClC(1)C(6)–C(2)C(5)C(3)[b]	3.37
(*Z*)-19[c]	C(1)–H(1)	1.00 (7)	H(1)C(1)C(10)	111.0 (4)
	C(1)–C(2)	1.33 (1)	H(1)C(1)C(2)	117.6 (4)
	C(1)–C(10)	1.45 (1)	C(1)C(2)C(3)	126.4 (8)
	C(2)–C(8)	1.49 (1)	C(1)C(2)C(8)	118.0 (8)
	C(2)–C(3)	1.51 (1)	C(3)C(2)C(8)	115.5 (7)
	C(8)–O(3)	1.20 (1)	C(2)C(1)C(10)	131.4 (8)
	C(8)–O(4)	1.33 (1)	C(2)C(8)O(3)	125.2 (9)
	C(9)–O(4)	1.44 (1)	C(2)C(8)O(4)	111.7 (8)
	C(3)–O(1)	1.20 (1)	C(8)O(4)C(9)	116.2 (7)
	C(3)–O(2)	1.325 (9)	C(2)C(3)O(1)	123.1 (8)
	C(4)–O(2)	1.493 (9)	C(2)C(3)O(2)	110.4 (8)
			C(3)O(2)C(4)	122.0 (6)
			O(1)C(3)O(2)	126.5 (8)
			H(1)C(1)C(10)–C(8)C(2)C(3)[b]	1.59
			H(1)C(1)C(10)–Ar[b]	168.89 (8)
			H(1)C(1)C(10)C(2)C(8)C(3)–Ar[b]	9.44
			C(8)C(2)C(3)–C(2)C(3)O(1)O(2)[b]	86.02 (8)
			C(8)C(2)C(3)–C(2)C(8)O(3)O(4)[b]	178.81 (9)
(*RR*)-20[d]	C(1)–C(2)	1.54 (1)	Br(1)C(1)C(2)	111.9 (7)
	C(1)–Br(1)	1.97 (1)	Br(1)C(1)C(10)	110.6 (7)
	C(2)–Br(2)	1.941 (8)	Br(2)C(2)C(1)	113.6 (7)
	C(1)–C(10)	1.53 (1)	Br(2)C(2)C(3)	108.3 (6)
	C(2)–C(3)	1.54 (1)	Br(2)C(2)C(8)	108.5 (6)
	C(2)–C(8)	1.55 (1)	C(3)C(2)C(8)	107.3 (8)

Table I (Continued)

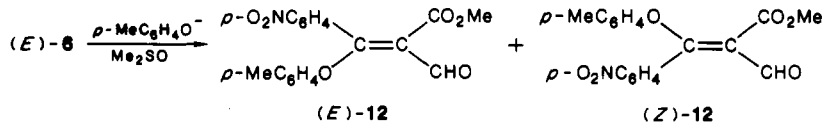
compd	bond	length, Å	angle	deg.
	C(3)–O(2)	1.32 (1)	C(1)C(2)C(3)	110.9 (8)
	C(4)–O(2)	1.48 (1)	C(1)C(2)C(8)	107.9 (7)
	C(8)–O(4)	1.33 (1)	Br(1)C(1)C(2)Br(2)[e]	49.6 (8)
	C(9)–O(4)	1.44 (1)	C(3)C(2)C(1)H(1)[e]	30 (6)
			C(8)C(2)C(1)C(10)[e]	43 (1)
(*E*)-21[f]	C(1)–C(2)	1.33 (1)	C(1)C(2)C(3)	123 (1)
	C(1)–Br	1.914 (9)	C(1)C(2)C(8)	122.4 (9)
	C(1)–C(10)	1.47 (1)	C(3)C(2)C(8)	114.5 (9)
	C(2)–C(8)	1.45 (1)	C(2)C(1)Br	117.5 (8)
	C(2)–C(3)	1.46 (1)	BrC(1)C(10)	113.4 (7)
	C(8)–O(4)	1.30 (1)	C(2)C(1)C(10)	129.1 (9)
	C(9)–O(4)	1.46 (1)	C(2)C(3)O(1)	121 (1)
	C(3)–O(2)	1.31 (1)	C(2)C(3)O(2)	117 (1)
	C(4)–O(2)	1.50 (1)	C(2)C(8)O(3)	123 (1)
			C(2)C(8)O(4)	115 (1)
			BrC(1)C(10)–C(3)C(2)C(8)[b]	176.12 (9)
			BrC(1)C(10)–Ar[b]	110.77 (9)
			BrC(1)C(10)C(3)C(2)C(8)–C(2)C(3)O(1)O(2)[b]	158.52 (9)
			BrC(1)C(10)C(3)C(2)C(8)–C(2)C(8)O(3)O(4)[b]	89.32 (9)

[a] Aromatic bond lengths are 1.365 (4)–1.387 (4) Å; aromatic bond angles are 118.4 (3)–122.6 (3)°. [b] Dihedral angle. [c] Aromatic bond lengths are 1.36 (1)–1.39 (1) Å; aromatic bond angles are 116.8 (8)–123.1 (9) Å. [d] Aromatic bond lengths are 1.36 (1)–1.40 (1) Å; aromatic bond angles are 118.6 (9)–122.9 (1)°. [e] Torsional angle. [f] Aromatic bond lengths are 1.36 (1)–1.39 (1) Å; aromatic bond angles are 118 (1)–122 (1)°.

Table II. ^{1}H NMR Data (δ Values in $CDCl_3$) for β-X-α-(Methoxycarbonyl)-*p*-nitrocinnamaldehydes

		E isomer				*Z* isomer			
X	compd	CO_2Me	CHO	Me	Ar[a]	CO_2Me	CHO	Me	Ar[a]
Cl	6	3.68	10.18		7.73, 8.30	3.96	9.40		7.74, 8.37
TolS	11	3.53	10.21	2.19	6.93, 7.08;[b] 7.26, 8.04	3.94	9.30	2.22	6.92, 7.04;[b] 7.17, 7.98
TolO	12	3.67	10.17	2.25	6.76, 7.05;[b] 7.65, 8.28	3.80	9.40	2.22	6.86, 7.05;[b] 7.68, 8.22
OMe	13	3.74	10.19	3.40	7.7, 8.3	3.96	9.38	3.53	7.7, 8.3

[a] Centers of the two halves of the aromatic *p*-$O_2NC_6H_4$ quartet are given, unless otherwise stated. [b] For the Tol quartet.



(4)

$\frac{[ArO^-]}{[6]}$			
1.6	70	t = 0	30
	45	t = 37 min	55
1.1	92	t = 0	8
	82	t = 30 min	18
(*Z*)-6 $\xrightarrow[Me_2SO]{p\text{-}MeC_6H_4O^-}$			
1.1	12	t = 0	88
	45	t = 30 min	55

(*Z*)-6, (*E*)-11/(*Z*)-11 ratios of 50:50 or 45:55 and "infinity" values of 46:54 were obtained. Consequently, the ratios obtained from (*E*)-6 and (*Z*)-6 are within ±5% of one another and of the equilibrium ratio. The outcome is therefore a nearly complete stereoconvergence, with a possibility of a contribution of ≤10% retention.

In a single experiment which was conducted with an excess of freshly prepared ArS^- in the NMR probe, the signals for the two products were broadened in the first 12 min of the reaction, but sharp signals at δ 2.17 (CH_3), 3.35 (COOMe), 8.13, 8.16 (Ar), and 9.43 (CHO) [in Me_2SO] were also observed. In addition, a signal at 0.74 ppm appeared after 3.5 and 10.1 min in the absorption mode and after 5.7 and 12.3 min in the emission mode. After 1 h, all the signals were sharp, the signal at 0.74 ppm disappeared, the (*E*)-11/(*Z*)-11 ratio was 48:52, and several new CHO signals at δ 10.04, 9.11, and 9.08 which integrate to 5%, 20%, and 11% of the total CHO signals were observed. When the experiment was repeated with (*Z*)-11 using the same sample of ArS^-, peak broadening was not observed, but the emission–absorption phenomenon of the singlet at δ 0.74 was again observed. The new signal at δ 9.4 consisted of 22% of the product, the extrapolated (*E*)-11/(*Z*)-11 ratio to t = 0 was 51:49, and after 60 h it was 46:54. These new phenomena were not observed in other experiments and were not investigated further.

A search for an ESR signal in the reaction mixture of (*E*)-6 with relatively old ArS^- showed no signal.

(b) By *p*-Cresolate Ion. When either (*E*)-6 or (*Z*)-6 was substituted by *p*-cresolate ion in Me_2SO a mixture of (*E*)- and (*Z*)-α-(methoxycarbonyl)-*p*-nitro-β-(tolyloxy)-cinnamaldehydes [(*E*)-12 and (*Z*)-12] was obtained (eq 4). Their assignment is based on the δ(CHO) and δ(COOMe) as shown in Table I. The NMR shows the formation of a few small signals that were not identified. Initial experiments showed that an extensive (*E*)-12 ⇌ (*Z*)-12 isomerization whose extent was dependent on the ArO^- concentration took place during the reaction. The reaction was therefore followed in the probe of the NMR instrument in Me_2SO-d_6, and readings were taken every 2–3 min.

Table III. Stereochemistry of the Substitution of (*E*)-6 and (*Z*)-6 by Nucleophiles at Room Temperature

substrate	Nu⁻[a]	[Nu⁻], M	[Nu⁻]/[Sub]	solvent	t_{init},[b] min	% reacn at t_{init}	stereochem at t_{init}	t_∞,[c] min	% reacn at t_∞	stereochem at t_∞	stereochem[d] at t_0
(*E*)-6	TolS⁻[e]	0.112	0.53	Me_2SO-d_6	4	25	56*E*/44*Z*	13	30	66*E*/34*Z*	52*E*/48*Z*
	TolS⁻[e]	0.084	1.1	Me_2SO-d_6	2	100	47*E*/53*Z*	38	100	46*E*/54*Z*	48*E*/52*Z*
	TolS⁻[e,f]	0.053	1.18	Me_2SO-d_6	1.7	100	47*E*/53*Z*	60	100	40*E*/60*Z*	47*E*/53*Z*
	TolS⁻[e]	0.37	1.35	DMF				120	100	55*E*/45*Z*[g]	
(*Z*)-6	TolS⁻[e]	0.112	0.53	Me_2SO-d_6	1	26	46*E*/54*Z*	10	29	35*E*/65*Z*	46*E*/54*Z*
	TolS⁻[e]	0.120	1.2	Me_2SO-d_6	2	100	51*E*/49*Z*	48	100	46*E*/54*Z*	50*E*/50*Z*
(*E*)-6	TolO⁻	0.084	1.1	Me_2SO-d_6	2	35	91*E*/9*Z*	30	55	82*E*/18*Z*	92*E*/8*Z*
	TolO⁻	0.074	1.6	Me_2SO-d_6	5	60	66*E*/34*Z*	37	100	45*E*/55*Z*	72*E*/28*Z*
	TolO⁻	0.16	1.25	DMF				1800	100	45*E*/55*Z*[g]	
(*Z*)-6	TolO⁻	0.084	1.1	Me_2SO-d_6	2	30	17*E*/83*Z*	30	100	45*E*/55*Z*	10*E*/90*Z*
(*E*)-6	MeO⁻		1.1	Me_2SO-d_6	20	0[h]		3120			
	MeO⁻		1.0	MeOH				90		35*E*/65*Z*[g]	
(*Z*)-6	MeO⁻		1.3	Me_2SO-d_6	15	0[h]		240			

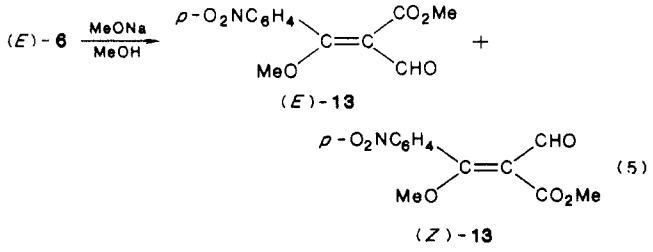
[a] The nucleophiles were studied as the sodium salts (TolS⁻, TolO⁻). [b] t_{init} = time of the first measured point. [c] t_∞ = time of the last measured point. [d] Extrapolated from *E*/*Z* vs. time ratios to zero reaction time. [e] Red color was formed on mixing the reactants. [f] Fresh sodium *p*-toluenethiolate was prepared 90 min before the experiment. [g] Products observed under synthetic conditions. [h] See text.

The relative yields and the (*E*)-12/(*Z*)-12 ratios were calculated from the relative intensities of the COOMe and CHO signals, and the relatively fast isomerization is exemplified in the Experimental Section. The kinetically controlled (*E*)-12/(*Z*)-12 ratios were obtained by extrapolation of the ratios vs. time curves and are probably accurate to ±5%. Typical (*E*)-12/(*Z*)-12 ratios at $t = 0$ (extrapolated) and at the end of the reaction are shown in eq 4. It is clear that the isomerization rate is higher when the [ArO^-]/[(*E*)-6] ratio is higher, and hence the (*E*)-12/(*Z*)-12 ratio at lower [ArO^-]/(*E*)-6 ratio is more accurate and was taken as the kinetically controlled ratio.

The stereochemical outcome shows high preference, although not complete, for retention of configuration starting from either isomer. Both extrapolated (*E*)-12/(*Z*)-12 values give 90 ± 2% retained product.

For calculating the percentage of retention more accurately the thermodynamically controlled (*E*)-12/(*Z*)-12 ratio is required. At long reaction times, the (*E*)-12/(*Z*)-12 ratios obtained from both (*E*)-6 and (*Z*)-6 converge to the values of 45:55. This ratio is also obtained after 30 h in DMF, in an experiment from which (*E*)-12 was isolated, and we believe that this is the thermodynamic equilibrium ratio of the vinyl ethers. By using this value, the products from (*E*)-6 and (*Z*)-6 are ≥85% and 78% retained, respectively.

(c) By Methoxide Ion. The reaction of (*E*)-6 with sodium methoxide in MeOH gave a mixture which according to the NMR consisted of a 35:65 ratio of (*E*)- to (*Z*)-β-methoxy-α-(methoxycarbonyl-*p*-nitrocinnamaldehydes [(*E*)-13 to (*Z*)-13] whose structures were assigned according to Table II (eq 5). The products are



(5)

apparently unstable, since on chromatography new signals were developed. When the reaction was investigated in an NMR tube, the CHO signal disappeared slowly, but no new signals were observed. This may be due to formation of "hydrate" by traces of water in the MeOH, but the reaction was not investigated further.

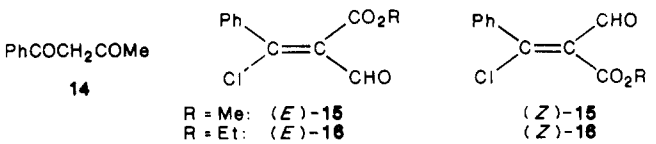
(d) By Chloride Ion. Solutions of (*E*)-6 in $CDCl_3$ or in DMF were stable to isomerization even after long reaction times at room temperature. However, in $CDCl_3$ (*E*)-6 isomerizes slowly to (*Z*)-6 in the presence of tetrabutylammonium chloride at room temperature (eq 6).

$$(E)\text{-}6 \xrightarrow[\text{room temperature}]{Bu_4NCl/CDCl_3} \underset{52\%}{(E)\text{-}6} + \underset{48\%}{(Z)\text{-}6} \qquad (6)$$

The isomerization was followed (cf. Experimental Section) until a 52:48 (*E*)-6/(*Z*)-6 mixture was obtained after 130 h and did not change after 170 h. Consequently, this ratio should be close to the equilibrium (*E*)-6/(*Z*)-6 ratio.

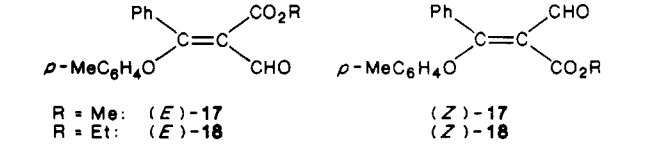
The stereochemistries of all the substitution reactions are summarized in Table III.

Substitution of Other β-Chloro-α-(alkoxycarbonyl)cinnamaldehydes. In analogy to the preparation of (*E*)-6 and (*Z*)-6, Vilsmeier reactions of methyl (14) or ethyl benzoylacetate with $POCl_3$ and DMF gave *E*/*Z* mixtures of β-chloro-α-(methoxycarbonyl)cinnamaldehydes [(*E*)-15 and (*Z*)-15] and the α-ethoxycarbonyl analogue ((*E*)-16 and (*Z*)-16].[12] The *Z* isomers were slightly preferred, consisting of 53–65% of the crude *E*/*Z* products.



Separation of the mixtures to the pure *E* and *Z* isomers was unsuccessful, and the substitution reactions had to be conducted on *E*/*Z* mixtures rich in one of the isomers.

Substitution of a 20:80 (*E*)-15/(*Z*)-15 mixture by a *p*-cresolate ion in DMF for a long time gave a 33:67 mixture of the tolyl ethers (*E*)-17 to (*Z*)-17. Substitution of a 40:60



(*E*)-16/(*Z*)-16 mixture by *p*-cresolate ion in DMF gave a 1:1 mixture of the ethers (*E*)-18 and (*Z*)-18. In each case the products were not separated and their composition was determined from the δ values of the CO_2Me and CHO groups, which followed the behavior recorded in Table II.

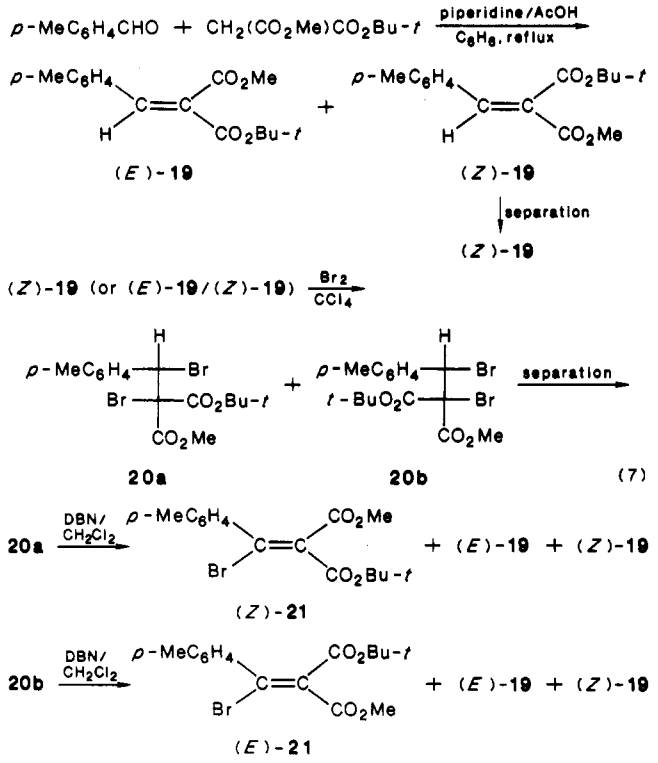
Synthesis and Reactions of (*E*)- and (*Z*)-*tert*-Butyl Methyl β-Bromo-(*p*-methylbenzylidene)malonates

(12) Gagan, J. M. F.; Lloyd, D. *J. Chem. Soc. C* **1970**, 2488.

[(*E*)-21 and (*Z*)-21]. Condensation of *p*-tolualdehyde with *tert*-butyl methyl malonate was not stereospecific and gave a 45:55 mixture of (*E*)- and (*Z*)-*tert*-butyl methyl (*p*-methylbenzylidene)malonates [(*E*)-**19** and (*Z*)-**19**]. The *Z* isomer was obtained in a pure form and its structure was determined by X-ray crystallography. The data are in Table I. A stereoscopic view is given in Figure S2 (supplementary material), and additional crystallographic data are given in the Tables S5–S8 (supplementary material). In the ^{1}H NMR spectrum in $CDCl_3$ the CO_2Me and CO_2Bu-*t* signals of the two isomers appear at almost the same positions, but in C_6D_6 $\delta(CO_2Bu\text{-}t)$ is at 0.09 ppm higher field in (*E*)-**19** compared with (*Z*)-**19**, whereas $\delta(CO_2Me)$ is shifted 0.12 ppm to lower field.

(*Z*)-**19** is isomerized rapidly by 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) in CH_2Cl_2, by piperidine/AcOH in benzene, or by HCl in CH_2Cl_2 to a (57 ± 3):(43 ± 3) (*E*)-**19**/(*Z*)-**19** mixture.

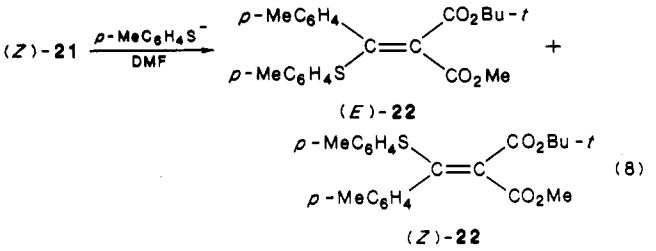
Bromination of (*E*)-**19** or of (*Z*)-**19** with bromine in CCl_4 is not stereospecific and gives 45:55 and 66:34 of the diastereomeric (1*R*,2*R*/1*S*,2*S*)**20a** and (1*R*,2*S*/1*S*,2*R*)**20b**, respectively (eq 7). A pure *d*,*l* mixture of **20a** was crystallized and its structure was determined by X-ray crystallography. The data are in Table I. A stereoscopic view is given in Figure S3 (supplementary material), and additional crystallographic data are given in the Tables S9–S12 (supplementary material).



The reaction of the dibromides **20a** and **20b** with DBN in CH_2Cl_2 results in both dehydrobromination to the bromo diesters (*E*)-**21** and (*Z*)-**21** and debromination to (*E*)-**19** and (*Z*)-**19**. Whereas the debromination is not stereospecific, the dehydrobromination shows high trans stereospecificity. Reaction of a 90:10 **20a**/**20b** mixture with DBN gave a 67:33 mixture of (*E*)-**21**/(*Z*)-**21** to (*E*)-**19**/(*Z*)-**19** in which the (*Z*)-**21**/(*E*)-**21** ratio is 90:10 and the (*E*)-**19**/(*Z*)-**19** ratio is 30:70. Other **20a**/**20b** mixtures gave results with similar stereospecificities. By taking advantage of the stereospecificity, (*Z*)-**21** was prepared starting from pure **20a**. Since pure **20b** was not available a 9:1 **20b**/**20a** mixture was used, giving a 9:1 mixture of (*E*)-**21** to (*Z*)-**21**. Separation of the two isomers was difficult, but a low yield of (*E*)-**21** was obtained after chromatography and crystallization.

The assignments of (*E*)-**21** and (*Z*)-**21** were based on NMR ($CDCl_3$): $\delta(CO_2Me)$ 3.60 and $\delta(CO_2Bu\text{-}t)$ 1.57 for (*Z*)-**21**, and $\delta(CO_2Me)$ 3.76 and $\delta(CO_2Bu\text{-}t)$ 1.26 for (*E*)-**21**. The differences are in the same direction but larger in C_6D_6: $\Delta\delta(CO_2Me)$ 0.39, $\Delta\delta(CO_2Bu\text{-}t)$ 0.40. The values are consistent with the generalization of Table II: the CO_2R group trans to the aryl absorbs at a lower field (Table IV). Since this conclusion is used for assignment of configuration of the substitution products, it was corroborated by X-ray diffraction of (*E*)-**21**. The data are given in Table I. A stereoscopic view is given in Figure S4 (supplementary material), and additional crystallographic data are given in Tables S12–S16 (supplementary material).

Substitution by Nucleophiles. (a) By *p*-Toluenethiolate Ion. Reaction of (*Z*)-**21** with excess sodium *p*-toluenethiolate in DMF gave the two thioethers (*E*)-**22** and (*Z*)-**22** in a 45:55 ratio (eq 8). Crystallization gave a 90:10 (*E*)-**22**/(*Z*)-**22** sample which was not purified further.



The reaction of either (*E*)-**21** or (*Z*)-**21** with a slight molar excess of sodium *p*-toluenethiolate in Me_2SO or 1:1 Me_2SO–$CDCl_3$ was followed by ^{1}H NMR in the probe of the instrument. The reactions were rapid ($T_{1/2}$ = 1–36 min at our concentrations), and after 2 min the *E*/*Z* product distributions could be determined. The reactions were found to be completely stereospecific, the products from both isomers being 100% retained (eq 9). No isomerization was observed after long reaction times. However, when (*Z*)-**21** was reacted with a large excess of the thiolate for a long reaction time in Me_2SO-d_6 in an NMR tube, new peaks appeared [e.g., at δ 1.42 (*t*-Bu) and 3.16 (Me)]. The product (40%) was not investigated further, but it may be the adduct of *p*-toluenethiol to **22**. It is noteworthy that the reactions did not always go to completion even when the thiolate concentration was higher than that of **21**. The results are given in Table V.

$$\text{(E)-21} \xrightarrow{p\text{-}MeC_6H_4S^-} \text{(E)-22}$$
$$\text{(Z)-21} \xrightarrow{p\text{-}MeC_6H_4S^-} \text{(Z)-22} \qquad (9)$$

Configuration assignment was based on comparison of the $\delta(CO_2Me)$ and $\delta(CO_2Bu\text{-}t)$ values with those of (*E*)-**21** and (*Z*)-**21**, as well as with those in the analogous methyl trideuteriomethyl β-arylthio esters (cf. ref 18).

(b) By *p*-Cresolate Ion. Reaction of (*Z*)-**21** with excess sodium *p*-cresolate in Me_2SO for 23 hrs at room temperature gave a mixture of ca. 1:1 of the ethers (*E*)-**23** and (*Z*)-**23** (eq 10). The stereochemistry in Me_2SO was followed by ^{1}H NMR in the NMR probe. The reaction was slower than that with the *p*-toluenethiolate ion (Table V), but after 2 min, the product distribution could be deter-

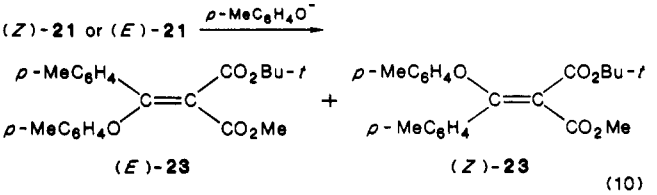


Table IV. $\delta(CO_2R)$ Values (in ppm) for ArC(X)=C(CO_2Me)CO_2Bu-*t*

Ar[a]	X	substrate	solvent	$\delta(CO_2Me)$	$\delta(CO_2Bu\text{-}t)$	$\delta(Me)$	$\Delta\delta(CO_2R)$[b]	R
Tol	H	(*E*)-**19**	$CDCl_3$	3.83	1.53	2.36	0.00	Me
			C_6D_6	3.51	1.38	1.94	−0.12	Me
		(*Z*)-**19**	$CDCl_3$	3.83	1.54	2.37	0.01	*t*-Bu
			C_6D_6	3.39	1.46	1.96	−0.08	*t*-Bu
Tol	Br	(*E*)-**21**	$CDCl_3$	3.76	1.26	2.31	0.16	Me
			C_6D_6	3.51	1.10	1.92	0.39	Me
			Me_2SO-d_6	3.80	1.17	2.34	0.25	Me
		(*Z*)-**21**	$CDCl_3$	3.60	1.57	2.37	0.31	*t*-Bu
			C_6D_6	3.12	1.50	1.91	0.40	*t*-Bu
			Me_2SO-d_6	3.55	1.50	2.35	0.37	*t*-Bu
Tol	TolS	(*E*)-**22**	$CDCl_3$	3.82	1.19	2.18	0.37	Me
			Me_2SO-d_6	3.72	1.05	2.14	0.34	Me
		(*Z*)-**22**	$CDCl_3$	3.45	1.55	2.18	0.36	*t*-Bu
			Me_2SO-d_6	3.38	1.46	2.14	0.41	*t*-Bu
Tol	TolO	(*E*)-**23**	$CDCl_3$	3.75	1.33	2.28	0.09	Me
			Me_2SO-d_6	3.66	1.25	2.25	0.08	Me
		(*Z*)-**23**	$CDCl_3$	3.66	1.41	2.28	0.08	*t*-Bu
			Me_2SO-d_6	3.58	1.33	2.25	0.08	*t*-Bu
p-$O_2NC_6H_4$	Br	(*E*)-**26**	$CDCl_3$	3.92	1.26		0.29	Me
			Me_2SO-d_6	3.84	1.15		0.27	Me
		(*Z*)-**26**	$CDCl_3$	3.63	1.59		0.33	*t*-Bu
			Me_2SO-d_6	3.57	1.55		0.40	*t*-Bu
p-$O_2NC_6H_4$	TolS	(*E*)-**27**	$CDCl_3$	3.88	1.13		0.40	Me
			Me_2SO-d_6	3.78	1.05		0.39	Me
		(*Z*)-**27**	$CDCl_3$	3.48	1.58		0.45	*t*-Bu
			Me_2SO-d_6	3.39	1.51		0.46	*t*-Bu
p-$O_2NC_6H_4$	TolO	(*E*)-**28**	$CDCl_3$	3.82	1.34		0.19	Me
			Me_2SO-d_6	3.72	1.23		0.13	Me
		(*Z*)-**28**	$CDCl_3$	3.63	1.46		0.12	*t*-Bu
			Me_2SO-d_6	3.59	1.36		0.13	*t*-Bu

[a] Tol = *p*-MeC_6H_4. [b] $\Delta\delta = \delta(CO_2R$ trans to Ar) − $\delta(CO_2R$ cis to Ar).

Table V. Stereochemistry of the Substitution of *tert*-Butyl Methyl β-Bromoarylidenemalonates by Nucleophiles at Room Temperature

substrate[a]	Nu^-[b]	[sub], M	[Nu^-], M	[Nu^-]/[sub]	solvent	t_{init},[c] min	% reacn at t_{init}	stereochem at t_{init}	$t_{1/2}$,[d] min	stereochem at $t_{1/2}$	t_∞,[e] h	% reacn at t_∞	stereochem at t_∞
(*E*)-**21**	$TolS^-$	0.118	0.137	1.15	Me_2SO-d_6	1.5	49	100*E*	3	100*E*	40	55	100*E*
(*E*)-**21**	$TolS^-$	0.052	0.075	1.4	1:1 Me_2SO-d_6/$CDCl_3$	2	24	100*E*	12	100*E*	30	61	100*E*
(*Z*)-**21**	$TolS^-$	0.034	*h*	*h*	Me_2SO-d_6			100*Z*		100*Z*	40		100*Z*
(*Z*)-**21**	$TolS^-$	0.076	0.109	1.45	Me_2SO-d_6	2	67	100*Z*	~1	100*Z*	16	84	100*Z*
(*Z*)-**21**	$TolS^-$	0.088	0.105	1.25	1:1 Me_2SO-d_6/$CDCl_3$	2	25	100*Z*	36	100*Z*	28	58	100*Z*
(*E*)-**21**	$TolO^-$	0.091	0.100	1.1	Me_2SO-d_6	2	16	94*E*/6*Z*	30	90*E*/10*Z*	26	77	51*E*/49*Z*
(*E*)-**21**	$TolO^-$	0.039	0.108	2.7	Me_2SO-d_6	2	19	85*E*/15*Z*	~10	85*E*/15*Z*	1	93	76*E*/24*Z*
(*Z*)-**21**	$TolO^-$	0.079	0.092	1.1	Me_2SO-d_6	2	12	92*Z*/8*E*	13	89*Z*/11*E*	25	73	51*Z*/49*E*
(*Z*)-**21**	$TolO^-$	0.039	0.108	2.7	Me_2SO-d_6	1.5	14	78*Z*/22*E*	~8	78*Z*/22*E*	0.9	90	77*Z*/23*E*
(*E*)-**26**	$TolS^-$[f]	0.055	0.082	1.5	Me_2SO-d_6	2.5	68	72*E*/28*Z*					
(*E*)-**26**	$TolS^-$	0.032	*h*	*h*	95:5 CD_3CN/Me_2SO-d_6		83	83*E*/17*Z*				100	66*E*/34*Z*[i]
(*E*)-**26**	$TolS^-$	0.032	*h*	*h*	95:5 CD_3CN/Me_2SO-d_6		8	94*E*/6*Z*				100	64*E*/36*Z*
(*Z*)-**26**	$TolS^-$	0.035	*h*	*h*	95:5 CD_3CN/Me_2SO-d_6		50	6*E*/94*Z*				100	16*E*/84*Z*
(*E*)-**26**	$TolO^-$[f]	0.055	0.077	1.4	Me_2SO-d_6	g	g	50*E*/50*Z*					
(*E*)-**26**	$TolO^-$	0.072	0.101	1.4	1:1 Me_2SO-d_6/$CDCl_3$	2.0	20	87*E*/13*Z*			0.7	31	80*E*/20*Z*
(*E*)-**26**	$TolO^-$	0.026	*h*	*h*	95:5 CD_3CN/Me_2SO-d_6		8	88*E*/12*Z*				71	60*E*/40*Z*
(*Z*)-**26**	$TolO^-$	0.026	*h*	*h*	95:5 CD_3CN/Me_2SO-d_6		3	4*E*/96*Z*				44	28*E*/72*Z*

[a] (*E*)-**26** means a 96:4 (*E*)-**26**/(*Z*)-**26** mixture. (*Z*)-**26** means a 91:9 (*Z*)-**26**/(*E*)-**26** mixture. [b] Introduced as a sodium salt. [c] Time of the first measurement. [d] Interpolated approximate half-life of the reaction at the conditions specified. [e] Time of the last measurement. [f] Violet color was formed on mixing the reagents (see text). [g] Reaction is complete in <2 min. [h] Portionwise addition of the nucleophile. [i] The product slowly isomerizes on standing.

mined. Only a slight change in the product composition in the direction of the equilibrium composition was obtained after 8–13 min (Table V) so that only small correction was required for obtaining the kinetically controlled product distribution. The reaction was found to proceed with preferential retention of about the same magnitude: 94:6 (*E*)-**23**/(*Z*)-**23** from (*E*)-**21** and 92:8 (*Z*)-**23**/(*E*)-**23** from (*Z*)-**21**.

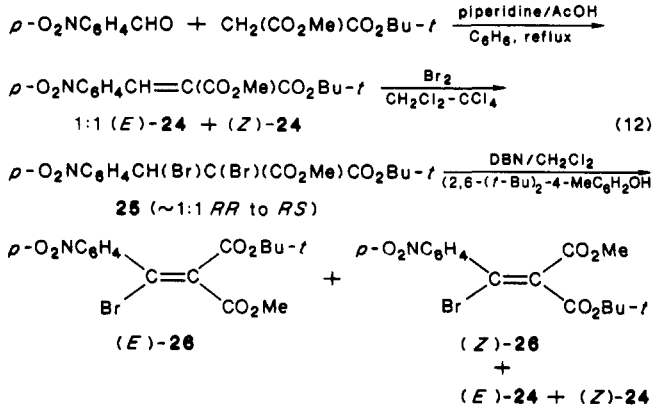
Higher concentrations of nucleophile and longer reaction times resulted in (*E*)-**23** ⇌ (*Z*)-**23** isomerization, since values of ca. 1:1 (*E*)-**23**/(*Z*)-**23** were obtained starting from both isomeric precursors, the reactions proceed with 84–88% retention of configuration.

(c) By Bromide Ion. When (*Z*)-**21** reacted with Bu_4NBr in DMF for 240 h at room temperature, partial isomerization to a 80:20 (*Z*)-**21**/(*E*)-**21** mixture took place (eq 11). In contrast, no isomerization was observed on reflux of (*Z*)-**21** for 4 h with Bu_4NBr in acetonitrile or when (*E*)-**21** or (*Z*)-**21** reacted with Bu_4NBr for 126 h at room temperature in the absence of light in $CDCl_3$.

$$(Z)\text{-}\mathbf{21} \xrightarrow[DMF]{Bu_4NBr} (E)\text{-}\mathbf{21} + (Z)\text{-}\mathbf{21} \qquad (11)$$

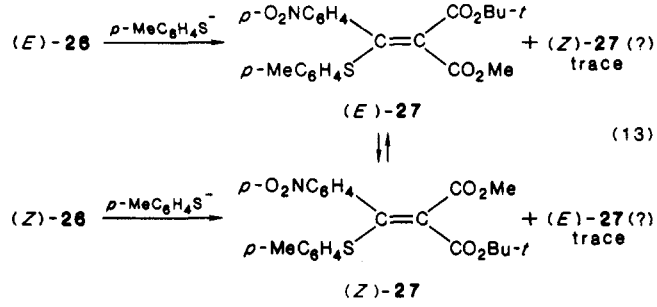
Synthesis and Reactions of (*E*)- and (*Z*)-*tert*-Butyl Methyl β-Bromo-(*p*-nitrobenzylidene)malonates [(*E*)-26 and (*Z*)-26]. The synthesis of the *p*-nitro ana-

logue of (*E*)-21 and (*Z*)-21 was similar to that of (*E*)-21 and (*Z*)-21. Condensation of *p*-nitrobenzaldehyde with *tert*-butyl methyl malonate gave a ca. 1:1 ratio of the *p*-nitrobenzylidene diesters (*E*)-24/(*Z*)-24, from which only (*Z*)-24 was obtained as a stereochemically pure isomer. Bromination of the mixture in 4:1 CCl_4–CH_2Cl_2 gave a mixture (1:1 by ^1H NMR) of the *RR* and *RS* dibromides **25**. This, on treatment with DBN with or without 2,6-di-*tert*-butyl-4-methylphenol gave *E*/*Z* mixtures of both the debromination [(*E*)-24)/(*Z*)-24] and the desired dehydrobromination [(*E*)-26/(*Z*)-26] products. Separation by repeated crystallization gave 96% stereochemically pure (*E*)-26 and 91% stereochemically pure (*Z*)-26 (eq 12), which were used for the stereochemical studies.



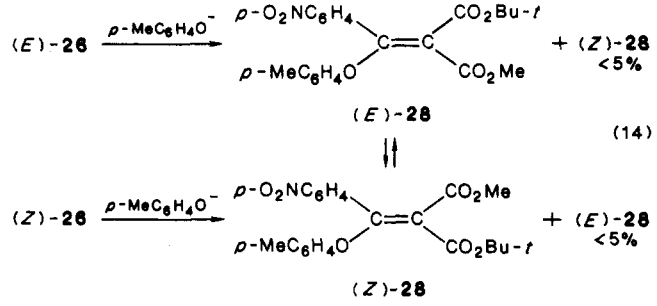
Reaction of (*E*)-26 and (*Z*)-26 with Nucleophiles. The reaction of a 1:1 (*E*)-26/(*Z*)-26 mixture with sodium *p*-toluenethiolate and *p*-methylphenolate gave *E*/*Z* mixtures of the corresponding vinyl thiolates ((*E*)-27 and (*Z*)-27) and cresolates ((*E*)-28 and (*Z*)-28), respectively.

The stereochemistry of the substitution with 96:4 and 9:91 (*E*)-26 to (*Z*)-26 ratios, respectively, was followed in an NMR tube in the probe of the NMR spectrometer. Since postisomerization of the products by excess nucleophile or at high reaction percentages is expected to be easier than for the less activated (*E*)- or (*Z*)-24, attempts to obtain the initial, kinetically controlled distribution of the substitution products by measuring them at the earliest convenient reaction time possible or by portionwise addition of the nucleophiles were made. The results under various conditions in several solvents are given in Table V. In Me_2SO, the reaction is homogeneous, but it is so rapid that it is practically completed before the first experimental point is taken. Moreover, a peak which we attribute to traces of water (in spite of repeated drying) sometimes overlaps the peaks used for the stereochemical analysis. Hence, the reaction was slowed down by either working in 1:1 Me_2SO–$CDCl_3$ or by working in 95:5 CD_3CN–Me_2SO-d_6, where no interference from water signal was observed. The 5% Me_2SO was necessary for a rapid dissolution of the sodium salts of the nucleophiles. On portionwise addition of the nucleophile, the *E*/*Z* product distribution was followed both immediately on addition of each portion and between the additions in order to evaluate semiquantitatively both the initial product ratio and the effect of the change in the ratio due to $E \rightleftharpoons Z$ isomerization. The results are given in Table V. The following conclusions can be drawn from the data presented in Table V and from the extent of change in the ratios, which is not given in Table V. (a) No isomerization of either (*E*)-26 or (*Z*)-26 was observed during the substitution. (b) With *p*-toluenethiolate ion (*E*)-27/(*Z*)-27 mixtures are obtained even at an early stage of the reaction, but in 95:5 CD_3CN–Me_2SO at an early reaction time the extrapolated value, corrected for the presence of the minor isomer, indicates nearly complete retention. Considering the limitation of the NMR method, we believe that in this solvent the reaction proceeds with ≥98% retention for both isomers (eq 13). (c) On standing (*E*)-27 ⇌ (*Z*)-27 isomerization takes place. No attempt was made to determine the equilibrium ratio, which is ca. 1:1 (*E*)-27/(*Z*)-27 under the synthetic conditions.



When (*E*)-26 reacted with a large excess of TolS$^-$Na$^+$ in 95:5 CD_3CN–Me_2SO-d_6 for a long time, the signals of 27 were gradually replaced by those of a new compound (presumably the adduct of TolSH and 27) which was not investigated further.

The reaction with *p*-methylphenolate ion was slower than with the thiolate ion, and the products distributions after few percent reaction could be measured. Here again, mixtures of (*E*)-28 and (*Z*)-28 were obtained, with preferred retention. From the reported ratios (corrected for the presence of the isomeric bromide) and the rate of isomerization in the portionwise addition, the reaction proceeds again with a high extent of retention of configuration, ≥96% in 95:5 CD_3CN–Me_2SO for both isomers (eq 14). Isomerization probably leads to ca 1:1 (*E*)-28/



(*Z*)-28 ratios as found in their synthesis, and a 60:40 (*E*)-28 to (*Z*)-28 ratio was already obtained after 2 h in 95:5 CD_3CN–Me_2SO even when a free nucleophile was apparently not present in the reaction mixture (i.e., in a portionwise addition when the reaction was incomplete).

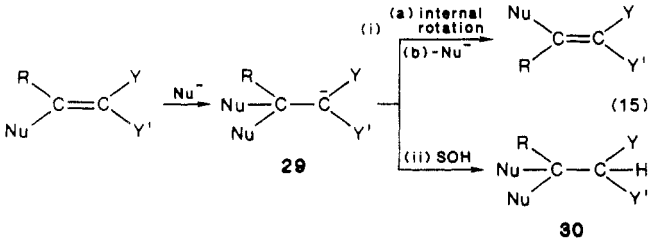
Violet colors appeared occasionally on addition of the nucleophile salts in some of these reactions. The sodium salts were prepared from the free thiol or phenol with NaH, and the possibility that the color is due to traces of NaH cannot be excluded. When care was taken to avoid these traces the violet color was not observed.

Discussion

The substitutions of the more activated β-chloro aldehydo ester system **6** proceeds with a much higher stereoconvergence than those of the β-bromo diesters **21** and **26**, as expected. Indeed, the latter systems are at the structural crossover region between retention and stereoconvergence. However, before discussing the mechanistic implications of these results to nucleophilic vinylic substitution, general comments concerning (a) the reliability and accuracy of the products distributions and practical

problems related to the extent of retention and (b) the possibility that the substitution proceeds by a different route than eq 1 should be discussed.

Sources of Problems with and Reliability of the Products Distributions. The systems studied by us now (**6**, **21**, **26**) and previously (**3**–**5**),[9-11] regardless of whether complete or partial stereoconvergence or retention was observed, are all highly activated for nucleophilic attack. The advantage in using these systems is that substitution proceeds at room temperature when thermal isomerization of both precursors and products are reduced. However, there are several disadvantages relevant to our study due to the high reactivity with nucleophiles. The main one is that a nucleophilic attack on the substitution product by excess nucleophile is possible. This would give carbanion **29**, which can either (i) undergo an internal rotation followed by nucleophile expulsion or (ii) be captured by the solvent to give the adduct **30** (eq 15). Process i is relevant



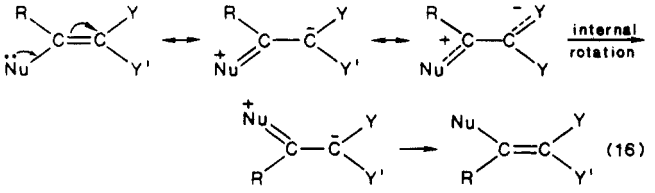
to vinylic substitution since the nucleophiles usually studied (ArO^-, ArS^-) are relatively poor nucleofuges so that internal rotation in **29** is faster than their expulsion. The outcome will be an (*E*)-RNu ⇌ (*Z*)-RNu postisomerization. Vinylic substitutions of poor nucleofuges with stereoconvergence are known.[13] We ascribe the relatively rapid change from the kinetically controlled product compositions toward the equilibrium ratios to this reason. The rate of such process is dependent on the relative concentrations of the Nu^-, the RX and the RNu as well as on the relative rate $k(RX)/k(RNu)$. The presence of the formerly nucleophilic moiety with nonbonded electron pair (O, S) may increase the electrophilicity of C_β (cf. eq 16), and the latter ratio may be higher than unity. There are scarce data corroborating this conclusion[14] which is also consistent with the isomerization accompanying the substitution which was observed even when the initial $[RX]/[Nu^-]$ ratio is >1. We reduced this problem now (see Tables III and V) and previously[11] by a portionwise addition of the nucleophile, so that $[RX]/[Nu^-] \gg 1$ at the beginning of the reaction when [RX] > [RNu], thus increasing the reliability of the extrapolated [(*E*)-RNu]/[(*Z*)-RNu] values. In contrast, the formation of close to equilibrium [(*E*)-RNu]/[(*Z*)-RNu] ratios under the synthetic conditions (excess nucleophile, relatively long reaction time) are ascribed to this postisomerization.

Addition of a proton from the medium to **29** to form the adduct **30** poses an additional problem, since the rates of loss of (*E*)-RNu and (*Z*)-RNu will usually differ, thus distorting the kinetically controlled ratio in an unknown direction. We encountered this problem previously when using MeO^- in MeOH,[11] and the loss of (*Z*)-**22** and (*E*)-**27** in the presence of a high excess of $TolS^-$ may be due to this reaction. The proton source is either the protic solvent or traces of moisture in the aprotic solvent (as observed in "dry" Me_2SO-d_6).

The number of nucleophiles available for stereochemical studies is reduced by side reactions. A previous example is the reaction of ON_3^- with **5**, which gave *p*-$O_2NC_6H_4NHC(OMe)=C(CN)CO_2Me$ by a sequence of consecutive nucleophilic addition, nitrogen loss, aryl migration, and addition of MeOH.[11] Likewise, the reaction of (*E*)- and (*Z*)-**6** with MeO^- in Me_2SO results in loss of the CHO signal before the substitution process. Regardless of the nature of the species formed[15] the interpretation of the (*E*)-**13**/(*Z*)-**13** ratios formed under synthetic conditions is doubtful since both RX and the new species may form the product, each giving a different (*E*)-**13**/(*Z*)-**13** ratio.

The true stereochemistry can also be distorted by a preisomerization of the precursor RX. The initially formed anion **2** may undergo rotation, followed by loss of Nu^- to give the isomeric RX in preference to substitution. The Cl^- formed from **6** or the Br^- formed from **21** or **26** may be the isomerizing nucleophile. This aspect is discussed further below, but it is sufficient to mention that (*E*)-RX ⇌ (*Z*)-RX (X = Cl, Br) isomerization was not observed during any of our substitutions. The Cl^--catalyzed (*E*)-**6** ⇌ (*Z*)-**6** isomerization which was independently monitored was many orders of magnitude slower than substitutions by $TolS^-$ and $TolO^-$.

The stereochemistry of the products may be also lost if their C_α–C_β bond has a partial single bond character. The products are push-pull ethylenes with an electron-withdrawing moiety on C_α and a resonatively electron-donating substituent (Nu) on C_β. This will reduce the rotational barrier around the C_α–C_β bond and facilitate the (*E*)-RNu ⇌ (*Z*)-RNu postisomerization (eq 16). This



process is responsible for the loss of stereochemistry in substitution by amines.[16] The rapid rotation around the formal double bond in push–pull ethylenes was studied extensively by Sandström and co-workers,[17] We previously[9-11] excluded such rotation for **3**–**5**, and the present results which show that the (*E*)-RNu ⇌ (*Z*)-RNu isomerization is slow in the absence of nucleophiles suggest that it does not contribute to isomerization in our systems. The data on this question for the case of compounds (*E*)- and (*Z*)-**11** are insufficient.

Three practical problems are important in our study. First the salts $TolS^-Na^+$ and $TolO^-Na^+$ are sparingly soluble in $CDCl_3$, and the reaction is heterogeneous, whereas in Me_2SO-d_6 where the solubility is much better the reactions are frequently so rapid that even the first experimental point is often already at >90% reaction. We achieved homogeneity by using 1:1 Me_2SO-d_6–$CDCl_3$ or 95:5 CD_3CN–Me_2SO-d_6 mixtures, although in the latter case, the reaction is still fast. We found no appreciable

(13) (a) Marchese, G.; Modena, G.; Naso, F. *J. Chem. Soc. B* **1969**, 290. (b) van der Sluijs, M. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2*, 1974, 1968.

(14) In the substitution of excess (p-$O_2NC_6H_4)_2C$=C(Cl)Br with $TolO^-$ the disubstitution product is obtained even at early reaction time, suggesting that the TolO moiety activates the systems similarly or even more than an halogen (Avramovitch, B., unpublished results).

(15) The only information on the product is that no new Ar and COOMe signals are observed during its formation; i.e., these signals are at approximately the same positions in the precursor and the product. Formation of hydrate of the CHO group by traces of water in the Me_2SO-d_6 is a possibility, but other products can also be envisioned.

(16) E.g.: Modena, G.; Todesco, P. E.; Tonti, S. *Gazz. Chim. Ital.* **1959**, *89*, 878. For an extensive list of references, see ref 9 in: Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1000.

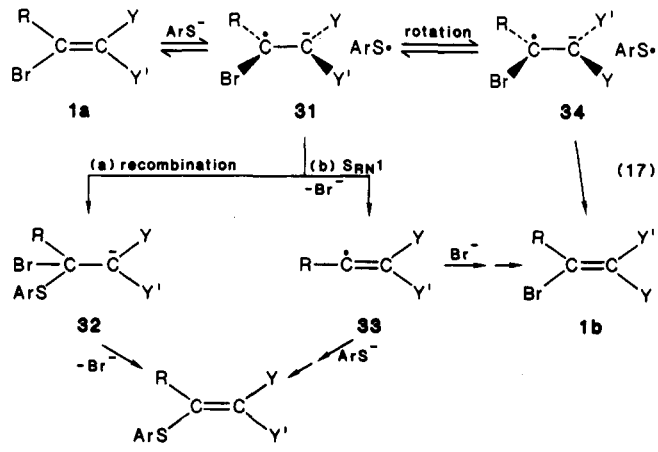
(17) Sandström (Sandström, J. *Top. Stereochem.* **1983**, *14*, 83) reviewed his and other work in the field.

differences in the kinetically controlled products distributions as a function of the solvent or the homogeneity, and we consider these factors to be unimportant in affecting the stereochemistry in our systems. Second, our analytical method is ^{1}H NMR, which enables analysis at room temperature without workup, detection of both precursor and product isomerization, and several consecutive measurements on the same sample. However, the method has two limitations. (a) It is sensitive to small impurities, e.g., traces of water in the Me_2SO-d_6 sometimes overlapped a product COOR signal and prevented the analysis. (b) The accuracy of signal integrations is not better than ±2% as judged by repeated integrations or by using different probes (COOMe/COOBu-*t* or the CHO/COOMe). This is a significant problem when the extent of retention is high and the absolute and relative percentage of the inverted product is low at the more important initial points. Since the precursors vinyl halides sometimes contain ≥4% of the isomeric halide, and unequivocal differentiation between 98% retained and 100% retained product, i.e., between complete retention and small percentage of stereoconvergence is difficult. Third, for a complete analysis of the substitution both isomers should be studied, and the (*E*)-RNu/(*Z*)-RNu should be known. The preparation and separation of isomeric pairs of precursors and products is frequently difficult and always time-consuming and is the main reason why a relatively small number of nucleophiles was studied for each system. The amount of work will be appreciably reduced if one isotopomer of **1** where Y and Y′ are chemically similar and isotopically different will be studied. Our efforts in this direction will be reported elsewhere.[18]

Single Electron Transfer as a Mechanistic Possibility. Our highly electrophilic vinyl halides **1a** are low LUMO substrates and are very prone to a single electron transfer (SET). This is especially true for systems **6** and **26**, which are substituted *p*-nitrobenzyl halides, substrates which are known to react via a mechanism involving an initial SET,[19] especially with nucleophiles such as $TolS^-$. Competing substitution routes to that depicted in eq 1 proceeding via initial formation of the radical anion–radical pair **31** are given in eq 17. Route a which involves recombination of the pair to give the anion **32** is a modification of eq 1. Route b is an $S_{RN}1$ process via the radical **33**, and if **33** is linear (or a pair of rapidly interconverting sp^2-hybridized radicals) it should lead to stereoconvergence.

If the electron transfer is reversible and if internal rotation in **31** to form **34** is faster than routes a and b, (*E*)-RBr ⇌ (*Z*)-RBr (i.e., **1a** ⇌ **1b**) isomerization should be observed during the substitution. Moreover, since Br^- is formed during the substitution its capture by **33** should give **1a** and **1b**, i.e., lead to precursor isomerization. In spite of our search for precursor halide isomerization in all our reactions none was observed. Consequently, unless the reversal of electron transfer is relatively slow, this route and especially subroute b is excluded.

According to our discussion below the stereochemistry is determined by intramolecular processes in the carbanion



2 (formed by eq 1). Obviously, although our results do not unequivocally distinguish between the different first steps of eqs 1 and 17(a) our conclusions are valid regardless of whether **2** (=**32**) is formed by an initial SET or by a nucleophilic attack.

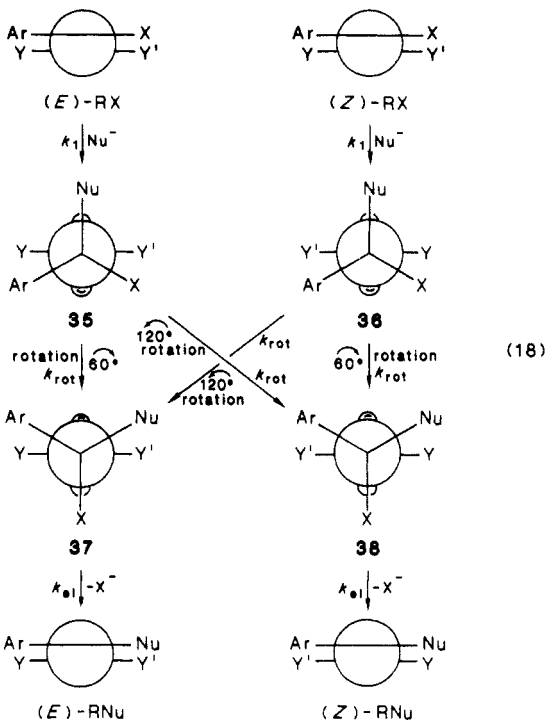
Radicals are formed during our reaction with the *p*-toluenethiolate ion. Their dimerization accounts for the lower yield than that calculated from the stoichiometric ArS^- concentration. The disulfide was previously detected in related reactions.[11] Formation of strong colors in the synthetic runs with **6** and **26** may also indicate an initial electron-transfer process, and in the reactions of **6** we detected and described briefly above a CIDNP behavior. However, granted that a SET is a likely process, the anion radical is not necessarily on the reaction coordinate. Since precursors' isomerization was not detected and the stereoconvergence that may be associated with a SET is more pronounced for $TolO^-$ than for $TolS^-$, which is a better SE donor, the evidence that the kinetically controlled stereochemical outcome is determined by reaction of the anion **2** is strong.

Stereochemistry of the Substitution: From Complete Stereoconvergence to Complete Retention. Our analysis of the details of the mechanism of nucleophilic vinylic substitution (cf. the introduction) suggests that with highly activated systems the reaction proceeds via the intermediacy of carbanion **2**.[4] The stereochemistry of the process which serves as a strong support to the theory is best discussed in terms of eq 18. Attack on (*E*)-RX gives intially the carbanionic conformer **35** which by 60° clockwise rotation gives conformer **37** and by 120° anticlockwise rotation gives conformer **38**. Expulsion of X^- from **37** gives the retained product and from **38** the inverted product. A parallel scheme applies when starting from (*Z*)-RX. A 60° clockwise rotation is favored over 120° anticlockwise rotation[6] and if leaving group expulsion (k_{el}) is faster than the rotation (k_{rot}) once conformer **37** is formed from **35** (or **38** from **36**) expulsion of X^- will take place, giving the retained product. In the other extreme $k_{rot} \gg k_{el}$ and both **37** and **38** (obtained formally via 120° anticlockwise or 240° clockwise rotation) will be formed from (*E*)-RX or from (*Z*)-RX, and expulsion of X^- will give the same (*E*)-RNu/(*Z*)-RNu ratios, i.e., stereoconvergence. When $k_{el} \sim k_{rot}$, partial stereoconvergence, i.e., formation of nonidentical mixtures starting from (*E*)-RX and (*Z*)-RX will be obtained. When X is a good nucleofuge, e.g., Cl or Br as in our systems, $k_{rot} \geq k_{el}$ only when the negative charge in the carbanion is highly delocalized on Y and Y′, since then k_{rot} is increased and k_{el} is reduced. The observation of a partial or complete stereoconvergence for systems **3–5** supports the prediction of the variable transition-state theory,[4] and the present results corroborate another pre-

(18) The systems that we investigated are $ArC(Br)=C(CO_2Me)\cdot CO_2CD_3$ where one stereoisomer was prepared in a stereospecific way (Gazit, A.; Rappoport, Z., unpublished results).

(19) (a) Kornblum, N. In *The Chemistry of Functional Groups*; Patai, S., Ed.; Wiley: Chichester, 1982; Suppl. F, p 361. (b) For a recent review of the $S_{RN}1$ reaction, see: Norris, R. K. In *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Supplement D, p 681. (c) For general recent references concerning SET, see: Chanon, M.; Tobe, M. L. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 1. Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212.

(20) Avramovitch, B.; Rappoport, Z., unpublished results.



(18)

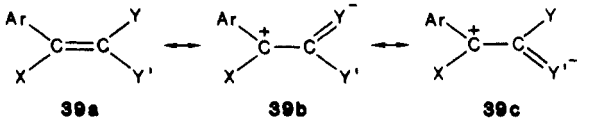
a, Ar = Tol; X = Cl; Y = CO_2Me; Y' = CHO
b, Ar = Tol; X = Br; Y = CO_2Bu-*t*; Y' = CO_2Me
c, Ar = *p*-$O_2NC_6H_4$; X = Br; Y = CO_2Bu-*t*; Y = CO_2Me
d, Ar = *p*-$O_2NC_6H_4$; X = Cl; Y = CO_2Me; Y' = CN
e, Ar = Ph; X = Cl; Y = CHO; Y' = Ph
f, Ar = Ph; X = I; Y = NO_2; Y' = Ph

diction that with the decreasing negative charge delocalizing ability of Y and Y' k_{rot}/k_{el} will gradually decrease until a complete retention will be observed. Table VI summarizes the stereochemical results for systems **6**, **21**, and **26** studied in the present work together with similar results for systems **3–5** studied previously.[9-11] Only reactions with $TolS^-$ and the oxygen nucleophiles $TolO^-$ and MeO^- are compared. From comparison of the (*E*)-RNu/(*Z*)-RNu ratios obtained from both precursors and the ratios obtained under thermodynamic control or ratios approaching thermodynamic control the kinetically controlled stereochemistry was deduced.

For system **6** with $TolS^-$ as the nucleophile a nearly complete stereoconvergence is deduced from the closely similar (*E*)-**11**/(*Z*)-**11** ratios. In each case the retained product predominates by a few percent over the equilibrium ratio. In contrast, with the $TolO^-$ analogue the reaction proceeds with much lower degree of stereoconvergence. Although the preference for retention (based on the equilibrium ratio) differs for (*E*)-**6** (≥85%) and (*Z*)-**6** (78%), the differences are not large enough in view of the combined experimental errors to warrant discussion.

The situation is different with the β-bromo arylidene diester systems **21** and **26**. The thio nucleophile gave almost complete retention in both cases, whereas the oxygen nucleophile gave a high degree of retention (≥84% in both cases).

The activation by the two ester groups of **21** and **26** is expected to be lower than by the formyl and the ester groups of **6**. This prediction is consistent with our previous tentative "activation guide", which assumes that the order of activation by Y,Y' is roughly in the inverse order of the pK_a's of CH_2YY'.[4] We do not have data for $pK_a(CH_2(CO_2Me)CO_2Bu\text{-}t)$, but it should not differ much from that of $CH_2(CO_2Me)_2$ (pK_a = 15.8 in Me_2SO).[21] The pK_a of $CH_2(CO_2Me)CHO$ is again unknown, but since σ_R^0 (0.24) and σ_p^- (1.00) of CHO are higher than those of CO_2R (0.16 and 0.64),[22] CHO/CO_2Me should activate a double bond to nucleophilic attack much more than $CO_2Me/CO_2Bu\text{-}t$. An important deviation from this pK_a guide should result from steric effect between Y,Y' and the β-carbon substituents. The electrophilicity of C_β is largely due to the conjugation of Y,Y' with the double bond (cf. valence bond structure **39b**, **39c**). From the dihedral angles of Table



39a **39b** **39c**

I it is clear that in **6** both groups are nearly coplanar with the C=C bond, thus exerting their maximum influence. For (*E*)-**21** the $CO_2Bu\text{-}t$ group is almost perpendicular to the C=C plane and the CO_2Me group is partially twisted from the plane, so that the contributions of hybrid **39b** are negligible and of **39c** are less than in **6**. We expect that similar interactions will operate in the same direction, although not to the same extent, in the carbanions **35a–c** to **38a–c**, and the stereochemical outcome is thus consistent with the predictions.

Comparison is possible now also with systems **4** and **5**. If we disregard the small difference between a β-phenyl and a β-tolyl group the difference in activation is that the Ph group of **4** is replaced by the CO_2Me of **6**. The latter group is usually regarded as a better carbanion stabilizer[23] and is therefore predicted to give a higher extent of stereoconvergence. Table VI shows that both systems behave similarly: complete or nearly complete stereoconvergence with $TolS^-$ and high extent of retention for $TolO^-$. Again the differences are too small to warrant discussion.

Another interesting comparison is between systems **5** and **26**. The prediction is that due to the higher coplanarity of the double bond with the CN of **5** compared with the $CO_2Bu\text{-}t$ of **26**, and assuming, as is customary, that Br and Cl have similar effects,[24] **5** will show a higher extent of stereoconvergence. This is indeed observed with both nucleophiles.

We expected system **5** to show more stereoconvergence than system **6**. With $TolS^-$ both systems are at the stereoconvergence region, but with $TolO^-$ system **5** shows more stereoconvergence. We do not know if this is a failure of the theory or if this is a case when the change of solvent affects the stereochemistry, when the differences are not large.

An important comparison is between systems **21** and **26** which differ only in the β-aryl substituent. The prediction is that **26** should show a higher extent of stereoconvergence, although the differences should be smaller than for a change in the α-activating group. Table VI shows that this prediction cannot be adequately investigated since both systems are already at the "complete retention" end of the stereochemical spectrum with $TolS^-$, whereas the differences between the extents of retentions for $TolO^-$ are not considered to be significant. The prediction should be checked either with a system more on the stereocon-

(21) Bordwell, F. G., personal communication. This is a widely circulated list of pK_a's of hundreds carbon acids in Me_2SO.

(22) Exner, O. In *Correlation Analysis in Chemistry. Recent Advances*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978; p 439. This chapter gives a critical compilation of various substituent constants. The σ_p^- values are based on the pK_a's of substituted phenols. The σ_R^0 values are based on IR.

(23) This is deduced, for example, from the higher reactivity toward nucleophilic attack of ethyl cinnamate compared to stilbene.

(24) The assumption is based on the small difference in the inductive and resonative substituent constants for both halogens. It serves as the basis for the use of the "element effect" as a mechanistic probe.

Table VI. Stereochemistry of Vinylic Substitution of Highly Activated Systems ArC(X)=CYY′ by Nucleophiles at Room Temperature

system	Ar	X	Y	Y′	Nu⁻	solvent	% (*E*)-RNu/% (*Z*)-RNu at $t = 0$[a]	% (*E*)-RNu/% (*Z*)-RNu at $t = \infty$[b]	kinetically controlled stereochem[c]	ref
(*E*)-**3**	Ph	I	NO_2	Ph	$TolS^-$	EtOH	100*E*[d]	100*E*[d]	complete S.C.	9
(*Z*)-**3**					$TolS^-$	EtOH	100*E*[d]	100*E*[d]		9
(*E*)-**3**					MeO^-	6:100 MeOH–MeCN (v/v)	30*E*/70*Z*[e]	40*E*/60*Z*[f]	partial S.C.	10
(*E*)-**4**	Ph	Cl	CHO	Ph	$TolS^-$	DMF	100*E*	100*E*[d]	complete S.C.	10
(*Z*)-**4**					$TolS^-$	DMF	100*E*	100*E*[d]		10
(*E*)-**4**					$TolO^-$	DMF	100*E*	100*E*[d]	preferred R.	10
(*Z*)-**4**					$TolO^-$	DMF	70*E*/30*Z*	100*E*		10
(*E*)-**4**					MeO^-	MeOH	90*E*/10*Z*	90*E*/10*Z*[g]		10
(*Z*)-**4**					MeO^-	MeOH	96*E*/4*Z*		high R.	10
(*E*)-**5**	*p*-$O_2NC_6H_4$	Cl	CO_2Me	CN	$TolS^-$	CD_3CN	31*E*/69*Z*[h]	100*Z*	complete S.C.	11, 20
(*Z*)-**5**					$TolS^-$	CD_3CN	30*E*/70*Z*[h]	100*Z*		11, 20
(*E*)-**5**					$TolO^-$	CD_3CN	68*E*/32*Z*	75*E*/25*Z*	high S.C.	11
(*Z*)-**5**					$TolO^-$	CD_3CN	40*E*/60*Z*	79*E*/21*Z*		11
(*E*)-**5**					MeO^-	4:1 CD_3CN–CD_3OD (v/v)	67*E*/33*Z*	93*E*/7*Z*		11
(*Z*)-**5**					MeO^-	4:1 CD_3CN–CD_3OD (v/v)	33*E*/67*Z*	93*E*/7*Z*	partial S.C.	11
(*E*)-**6**	*p*-$O_2NC_6H_4$	Cl	CO_2Me	CHO	$TolS^-$	Me_2SO-d_6	52*E*/48*Z*	40*E*/60*Z*		*i*
(*Z*)-**6**					$TolS^-$	Me_2SO-d_6	46*E*/54*Z*	50*E*/50*Z*	nearly complete S.C.	*i*
(*E*)-**6**					$TolO^-$	Me_2SO-d_6	92*E*/8*Z*	45*E*/55*Z*	high R.	*i*
(*Z*)-**6**					$TolO^-$	Me_2SO-d_6	10*E*/90*Z*	45*E*/55*Z*		*i*
(*E*)-**21**	Tol	Br	CO_2Bu-*t*	CO_2Me	$TolS^-$	Me_2SO-d_6 or 1:1 Me_2SO-d_6–$CDCl_3$	100*E*	45*E*/55*Z*[j]	complete R.	*i*
(*Z*)-**21**					$TolS^-$	Me_2SO-d_6	100*Z*			*i*
(*E*)-**21**					$TolO^-$	Me_2SO-d_6	94*E*/6*Z*	51*E*/49*Z*	high R.	*i*
(*Z*)-**21**					$TolO^-$	Me_2SO-d_6	8*E*/92*Z*	49*E*/51*Z*		*i*
(*E*)-**26**	*p*-$O_2NC_6H_4$	Br	CO_2Bu-*t*	CO_2Me	$TolS^-$	95:5 CD_3CN–Me_2SO-d_6 (v/v)	98*E*/2*Z*[k,l]	64*E*/36*Z*	complete R.	*i*
(*Z*)-**26**					$TolS^-$	95:5 CD_3CN–Me_2SO-d_6 (v/v)	100*Z*[l]			*i*
(*E*)-**26**					$TolO^-$	95:5 CD_3CN–Me_2SO-d_6 (v/v)	>95*E*/<5*Z*[l]	60*E*/40*Z*	nearly complete R.	*i*
(*Z*)-**26**					$TolO^-$	95:5 CD_3CN–Me_2SO-d_6 (v/v)	<5*E*/>95*Z*[l]			*i*

[a] Extrapolated from (*E*)-RNu/(*Z*)-RNu ratios vs. time to zero reaction time. [b] (*E*)-RNu/(*Z*)-RNu ratios obtained after long reaction time, which reflect approach to the thermodynamically controlled ratio or this ratio itself. [c] R. = retention; S.C. = stereoconvergence. [d] Isolated product. No evidence for the isomer was observed. [e] Ratio obtained in a single experiment after 140 h. [f] Ratio obtained after chromatography of the reaction mixture. [g] In view of the results for (*Z*)-**4** the equilibrium ratio should be either close to this value or consists more of the (*E*)-RNu. [h] Differs from a value which was reported in ref 11 and based on reanalysis of the data. [i] This work. [j] From a synthetic experiment in DMF. [k] Due to the error in determining low percentages of product, the value could be 100*E*. [l] Corrected for the isomeric impurity in the precursor.

vergence side of the spectrum, e.g., with the β-tolyl analogue of **5** or with a nucleophile more prone to stereoconvergence.[25]

The effect of the nucelophile was previously discussed for $TolS^-$ and $TolO^-$,[11] by evaluating their effects on the calculated rotational barriers (k_{rot}) and on k_{el} taking the S_N1 reaction as a model for this step. The calculated gas phase rotational barrier for SH is lower by 2.3 kcal mol^{-1} than for OH,[6] and this would favor stereoconvergence for SH compared with OH. The comparison of the abilities of Nu = STol and Nu = OTol in **37a–f** to assist k_{el} is less straightforward since $k_{el(O)}/k_{el(S)}$ ratios between 2000 and 0.08 are known for S_N1 processes.[26] However, although a priori predictions are difficult a generalization emerges from Table VI. The extent of stereoconvergence is higher for the thio than for the oxygen nucleophile(s). Systems **21** and **26** are, however, exceptions since the thio nucleophile gives complete retention and the oxygen nucleophile gives high extent of retention, but with a small stereoconvergence component. We intend to investigate whether this is a single deviation or a beginning of a trend for the less activated systems. We note that for less activated systems both thio and oxygen nucleophiles give complete retention.[3,27]

The importance of Table VI is not merely that it corroborates the predictions of the variable transition-state theory for vinylic substitution[4] and by doing so strengthens it but that it also shows the structural range at which stereoconvergence is the expected stereochemical outcome. To the extent that the pK_a guide applies beyond the structures of Table VI we predict that systems **1** where $pK_a(CH_2YY')$ in Me_2SO is <12.8 (the pK_a of $CH_2(CN)$-CO_2Me in Me_2SO)[21] will show stereoconvergence or other evidence for intermediate carbanions if the stereochemical probe is not available to them. Examples are the stereoconvergence observed for **3** ($pK_a(PhCH_2NO_2)$ = 12.2 in Me_2SO)[21] and the amine catalysis observed for β-haloarylidenemalononitriles[7a–c,e] (pK_a $CH_2(CN)_2$ = 11.15 in Me_2SO).[21] We therefore predict that compound **39**, Y = COMe, Y′ = COPh, will give stereoconvergence since $pK_a(MeCOCH_2COPh)$ = 12.7 in Me_2SO.[21]

The present results brought us from the stereoconvergence region to the retention region, which now seems to

(25) Both approaches are presently under investigation with the ArC(Br)=C(CO_2Me)CO_2CD_3 system.

(26) (a) Modena, G.; Scorrano, G.; Venturello, P. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1. (b) Chwang, W. K.; Kresge, A. J.; Wiseman, J. R. *J. Am. Chem. Soc.* **1980**, *101*, 6972. (c) For a recent reference, see: Hoz, S.; Aurbach, D. *J. Org. Chem.* **1984**, *49*, 3285.

(27) (a) Maioli, L.; Modena, G. *Gazz. Chim. Ital.* **1959**, *89*, 854. (b) Modena, G.; Todesco, P. E. *Ibid.* **1959**, *89*, 866.

include even apparently rather highly activated systems such as **21** and **26**. Retention is usually observed with singly activated systems such as **39**, Y = COR,[28a] CN,[28b] CO_2R,[28c] or SO_2Ar,[27] Y′ = H or Me. However, we do not know if with **21** and **26** we are at the borderline between stereoconvergence and retention or if we are deeply within the retention region. This is due to two reasons. First, the pK_a's for the formyl derivatives $CH_2(Ph)CHO$ and $CH_2(CO_2Me)CHO$ are unknown, and even if we assume that $pK_a(CH_2(CO_2Me)CO_2Bu\text{-}t) = pK_a(CH_2(CO_2Me)_2) = 15.8$ in Me_2SO[21] there is still a 3 pK_a unit gap between the derived compounds **39** in the stereoconvergence (system **5**) and the retention (**21** and **26**) regions. Second, it is not clear whether the use of the pK_a guide should be extended to the *tert*-butoxycarbonyl derivatives for steric reasons. Indeed, the crystallographic data which indicate an extensive deconjugation between the $CO_2Bu\text{-}t$ and the C=C bond suggest that the appropriate pK_a for compounds **21** and **26** will be between that for dimethyl malonate and a much less activated ester system, e.g., $PhCH_2CO_2Et$ (pK_a = 22.7 in Me_2SO).[21] This reservation suggests that at least one less sterically hindered diester should be studied before defining more precisely the $pK_a(CH_2YY')$ for which **39** will be in the borderline between retention and stereoconvergence.

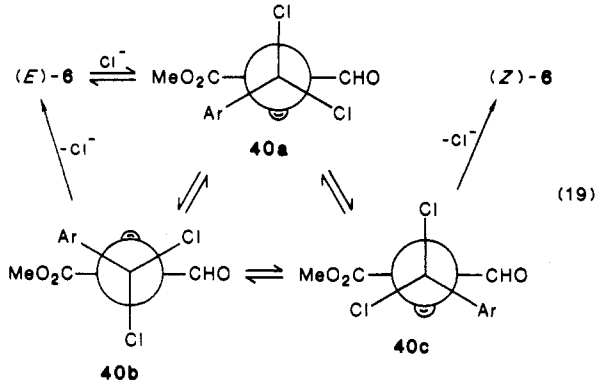
Our guess at present is that compounds **39**, Y = COMe, Y′ = CO_2Et ($pK_a(MeCOCH_2CO_2Et) = 14.37$ in Me_2SO)[21] and **39**, Y = SO_2Me, Y′ = SO_2Et ($pK_a(CH_2(SO_2Et)_2 = 14.4$ in Me_2SO)[21] will be in the stereconvergence region. It would be of interest to find out whether nitro-activated systems such as **39**, Y = NO_2, Y′ = H, Me ($pK_a(MeNO_2)$ = 17.2, $pK_a(EtNO_2) = 16.7$, in Me_2SO)[21] will be in the retention region or will still behave like compound **3**.

It is interesting to compare the stereochemical probe for the intermediacy of carbanions in the substition of highly activated system with the amine-catalyzed probe.[7] Both are complementary since the stereochemistry is lost in the substitution by amines due to intramolecular rotation in the product, of the type depicted in eq 16. Both probes compare k_{el} with another process that the intermediate undergoes. This is k_{rot} in the stereochemical probe, and bimolecular proton expulsion by another amine molecule in the amine-catalysis probe. A priori the later process is much more limited since it is applicable only to amines and since the intermediate is a zwitterion rather than a carbanion. Comparison of the results of Table VI with those of amine catalysis investigated previously[7] show that the scope of the stereochemical probe is larger. Amine catalysis was observed only with the very highly activated systems,[7,29] whereas stereoconversion was also observed for somewhat less activated systems. Moreover, k_{rot} should be much less sensitive to external (e.g., solvent) effects than the deprotonation of the zwitterion.

An unfortunate deficiency of the stereochemical probe is that the extent of stereoconvergence enables the estimation of only the k_{rot}/k_{el} ratios. The desired parameters for locating the region where the multistep route is converted to the single-step route is k_{el} and its structural dependence.[4] Although k_{rot} values could be estimated in the gas phase for model carbanionic systems[6,30] they are not available as yet to our systems in solution, and hence the magnitude of k_{el} is unknown.

Halide Ion Catalyzed Isomerization. The stereochemical results for $TolS^-$ and $TolO^-$ are supplemented by those obtained in the presence of halide ion X^-. There are three special characteristics of the reaction of X^- with a vinyl halide RC(X)=CYY′. First, the nucleophilicities of halide ions toward electrophilic olefins are orders of magnitude lower than those of $TolS^-$ and $TolO^-$.[31] Second, substitution with retention is a degenerate process and will not be observed unless conducted with an isotopically labelled halide. Third, substitution via a long-lived carbanionic intermediate, i.e., when $k_{rot} \lesssim k_{el}$ will be detected as an (*E*)-**RX** ⇌ (*Z*)-**RX** isomerization. Consequently, the absence of an (*E*)-**RX** ⇌ (*Z*)-**RX** isomerization in the presence of X^- can be ascribed either to an absence of reaction or to substituion with retention. In contrast, if isomerization is obtained and other isomerization routes, e.g., photochemical,[32] are excluded, its observation serves as a strong argument for an intermediate carbanion, i.e., for a multistep substitution.

Since (*E*)-**6** was found to be stable to thermal isomerization the Cl^--catalyzed (*E*)-**6** ⇌ (*Z*)-**6** isomerization in the absence of light indicates that internal rotation in the carbanionic conformer **40a** takes place to give conformer **40c** (either by a direct 120° anticlockwise rotation or by a 180° rotation in **40b**), followed by Cl^- expulsion (eq 19). Note that since the retention process is hidden there is no way to estimate the k_{rot}/k_{el} ratio in our experiment.



(19)

The reaction of (*E*)- and (*Z*)-**21** with Br^- in $CDCl_3$ showed no isomerization in the absence of light after 126 h. Likewise no isomerization of (*Z*)-**21** was observed in refluxing acetonitrile. However, in a single experiment in DMF some isomerization was obtained. Whether it is a solvent effect on the reaction or a slow (*E*)-**6** ⇌ (*Z*)-**6** isomerization due to impurities in the solvent is unknown. In view of the larger number of cases where isomerization was not observed we consider the reaction as proceeding without isomerization.

Chloride ion catalyzed isomerizations were previously observed for systems **4**[10] and **5**.[11] The present results show that the stereochemical outcome with Cl^- parallels the

(28) (a) E.g.: Angeletti, E.; Montanari, F. *Boll. Sci. Fac. Chim. Ind. Bologna* **1958**, *16*, 140. (b) E.g.: Biougne, J.; Thêron, F.; Vessière, R. *Bull. Soc. Chim. Fr.* **1975**, 2703. (c) E.g.: Pizey, J. S.; Truce, W. E. *J. Org. Chem.* **1965**, *30*, 4355.

(29) Amine catalysis with the poor RO nucleofuge was observed also for singly carbonyl-activated systems: Lartey, P. A.; Fedor, L. *J. Am. Chem. Soc.* **1975**, *101*, 7385. Ritchie, C. D.; Kawasaki, A. *J. Org. Chem.* **1981**, *46*, 4704. Stereoconvergence with thio and oxygen nucleophiles are expected for these systems in view of the results of ref 13.

(30) From the rotational barrier for internal rotation which was calculated for the analogous intermediate formed in nucleophilic epoxidation of an electrophilic olefin, an approximate k_{rot} value was calculated (Apeloig, Y.; Karni, M.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 2784).

(31) Estimated ratios were calculated in ref 3a from the data of: Miller, S. I.; Yonan, P. K. *J. Am. Chem. Soc.* **1957**, *79*, 5931. Beltrame, P.; Bellobono, I. R.; Fère, A. *J. Chem. Soc. B* **1966**, 1165. Beltrame, P.; Pitea, D.; Simonetta, M. *Ibid.* **1967**, *1108*.

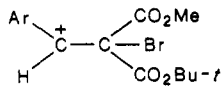
(32) For example, (*Z*)-**4** was prepared from (*E*)-**4** by irradiation.[10]

(33) (a) Zabicky, J. *J. Chem. Soc.* **1961**, 683. (b) Tanikaga, R.; Konya, N.; Kaji, A. *Chem. Lett.* **1985**, 1583. (c) For a review of Knoevenagel reaction, including several references to the stereochemistry, see: Jones, G. *Org. React. (N.Y.)* **1967**, *15*, 204.

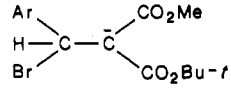
behavior of the $TolS^-$ and $TolO^-$ nucleophiles.

Comments on the Stereochemistry of the Reaction Leading to 21 and 26. Information on the stereochemistries of the Knoevenagel condensation, of bromine addition to the electrophilic olefins (*E*)- and (*Z*)-**19** and on the DBN-promoted dehydrobromination of the dibromides **20** and **25** was gathered in the present study. The condensations of *p*-methyl- and *p*-nitrobenzaldehydes with *tert*-butyl methyl malonate gave under the synthetic conditions, which are likely to lead to thermodynamic controlled products, ca. 1:1 (*E*)/(*Z*) mixtures of the olefins **19** and **24**. The stereochemistry of the Knoevenagel reaction is controlled by the relative bulk of Y and Y′ in CH_2YY', and the sterically less hindered product is usually formed.[33] Our conclusion is that the *E* and the *Z* products have similar stabilities, and in both, one CO_2R group is extensively twisted from the plane of the double bond while the other is nearly coplanar with it, in line with the X-ray data.

The addition of bromine to (*E*)- or (*Z*)-**19** is nonstereospecific, giving mixtures of cis and trans adducts. Consequently, bromonium ions are not (the major) intermediates in these reactions. This is not surprising since the α-substituents are incapable to delocalize the positive charge in such species. Initial formation of the open carbenium ion **41** by electrophilic addition or initial nucleophilic addition to form the carbanion **42**, which is trapped by bromine[34] are both feasible.



41



42

There is nothing special about the base-promoted trans elimination of HBr from the dibromides. An interesting (and synthetically disturbing) feature of the reaction is that an extensive debromination accompanies the dehydrobromination. We encountered a similar behavior previously[35] and we ascribe it to a combination of electronic and steric reasons. The electrophilicity of the α-bromine which is geminal to two electron-withdrawing groups may exceed that of the β-hydrogen which is vicinal to these groups. Moreover, in crowded pentasubstituted ethane derivatives approach of the base to the bulky bromine may be less hindered than to the hydrogen, and the elimination of the two bulky bromines relieves more strain than elimination of HBr.

Interesting Features of the Solid-State Structures. The X-ray data of Table I reveal four interesting features. (i) The double bond is not exactly planar. The dihedral angles between the $ArC_\beta X$ and the $YC_\alpha Y'$ planes are 3.37°, 1.59°, and 3.88° for (*E*)-**6**, (*Z*)-**19**, and (*E*-**21**, respectively. Twisted double bonds are found for other heavily substituted ethylenes.[36] (ii) In (*Z*)-**19** the COOMe group is almost coplanar and the Ar group is slightly twisted (by 11.11°) from the double bond plane. In contrast, the COOBu-*t* group is almost perpendicular. When Br replaces the β-H (in (*E*)-**21**) the COOMe group cis to the Br is almost perpendicular, the Ar group is highly twisted (by 69.23°) and the COOBu-*t* group is less twisted (by 21.48°) from the C=C plane. (iii) The O-Bu-*t* bonds (O(2)–C(4)) (1.49 Å in (*Z*)-**19**, 1.48 Å in (*RR*)-**20**, and 150 Å for (*E*)-**21**) are consistently longer than the O–Me bonds (O(4)–C(9)) which are 1.44, 1.44, and 1.46 Å in (*Z*)-**19**, (*RR*)-**20** and (*E*)-**21**, respectively. Precedents are known and the average O-Bu-*t* bond length for 43 compounds from the literature is 1.480 ± 0.016 Å.[37] (iv) Solid (*RR*)-**20** has a gauche conformation with a Br(1)C(1)C(2)Br(2) dihedral angle of 49.6°. This is in contrast with the conformation of 1,2-dibromoethane.[38]

Experimental Section

Elemental analyses were conducted by The Hebrew University of Jerusalem Microanalysis Laboratory. Melting points were taken on Fischer-Johns melting point apparatus and are uncorrected. UV spectra were determined with a Spectronics 2000 spectrometer, IR spectra with Perkin-Elmer 157G spectrometer, and ^1H NMR spectra were recorded on Bruker WH-300 and WP-200 pulsed FT spectrometers in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in ppm downfield from internal Me_4Si signal. Electron impact mass spectra were recorded on MAT 311 instrument.

Chromatography columns were packed with Merck 35-70 silica gel or dry silica (Woelm-Pharma) and eluted with hexane, hexane–CH_2Cl_2, CH_2Cl_2, and CH_2Cl_2–MeOH successively. Solvents obtained from Frutarom were used without purification. TLC was taken with Merck silica gel GF_{254} plates (0.25-mm thickness). *tert*-Butyl methyl malonate and ethyl (*p*-nitrobenzoyl)acetate were purchased from Fluka.

Workup means diluting with H_2O, extracting with $CHCl_3$, drying the organic phase with $MgSO_4$, filtering, and evaporating to dryness.

X-ray Crystal Structure Analysis. Data for (*E*)-**6**, (*Z*)-**19**, and (*RR*)-**20** were collected on a PW1100/20 Philips four-circle computer-controlled diffractometer at room temperature. Mo Kα (γ = 0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. The unit cell dimensions were obtained by a least-squares fit of 20 centered reflections in the range of $10° \le \theta \le 14°$. Intensity data were collected by using the $\omega - 2\theta$ technique to a maximum 2θ of 50°. The scan width, $\Delta\omega$, for each reflection was 1° with a scan time of 20 s. Background measurements were made for another 20 s at both limits of each scan. Three standard reflections were monitored every 60 min. No systematic variations in the intensities were found.

Intensities were corrected for Lorentz and polarization effects. All nonhydrogen atoms were found by using the results of the Multan direct method analysis.[39] After several cycles of refinements[40] the positions of the hydrogen atoms were calculated and introduced with a constant isotropic temperature factor of 0.5 Å^2 to the refinement process. Refinement proceeded to convergence by minimizing the function $\sum w(|F_o| - |F_c|)^2$, where the weight, w, is $\sigma(F)^{-2}$.

The discrepancy indices $R = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|]^{1/2}$ are presented below.

Data for *R* of (*E*)-**21** were measured on an Enraf-Nonius CAD-40 automatic diffractometer, Mo Kα (λ = 0.71069 Å) ra-

(34) For a clear-cut example of Cl^--catalyzed addition of Cl_2 to the double bond of the highly electrophilic tricyanoethylene, see: Dickinson, C. L.; Wiley, D. W.; McKusick, B. C. *J. Am. Chem. Soc.* **1960**, *82*, 6132.

(35) Rappoport, Z.; Apeloig, Y.; Greenblatt, J. *J. Am. Chem. Soc.* **1980**, *102*, 3837. For a recent reference on 1,2-dehalogenations, including nucleophile-promoted processes, see: Baciocchi, E. In *The Chemistry of Functional Groups*; Patai, S.; Rappoport, Z., Eds.; Wiley: Chichester, 1983; Supplement D, p 161.

(36) (a) Sandström, J.; Wennerbeck, I. *J. Chem. Soc., Chem. Commun.* **1971**, 1088. Abrahamsson, S.; Rehnberg, T.; Liljefors, T.; Sandström J. *Acta Chem. Scand., Ser. B* **1974**, *28*, 1109. (b) Kaftory, M.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 1701.

(37) The values were taken from the Cambridge Structural Data Base. Only two O-Bu-*t* bonds in this list are longer than 1.495 Å. We are indebted to Prof. M. Kaftory for his help in obtaining the list.

(38) For a recent discussion on the conformations of organohalogen compounds including 1,2-dihaloethanes, see: Meyer, A. Y. In *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Supplement D, p 1.

(39) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. Multan 78, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data, Universities of York, England, and Louvain, Belgium.

(40) All crystallographic computing was done on a Cyber 74 computer at the Hebrew University of Jerusalem, by using the Shelx 1977 structure determination package.

diation with a graphite crystal monochromator in the incident beam was used. The standard CAD-4 centering, indexing, and data collection programs were used. The unit cell dimensions were obtained by a least-squares fit of 24 centered reflections in the range of $11 \leq \theta \leq 15°$.

Intensity data were collected using the ω–2θ technique to a maximum 2θ of 45°. The scan width, $\Delta\omega$, for each reflection was $0.80 + 0.35 \tan \theta$. An aperture with a height of 4 mm and a variable width, calculated as $(2 + \tan \theta)$ mm, was located 173 mm from the crystal. Reflections were first measured with a scan of 8.24°/min. The rate for the final scan was calculated from the preliminary scan results so that the ratio $I/\sigma(I)$ would be at least 40 and the maximum scan time would not exceed 60 s. If in a preliminary scan $I/\sigma(I) < 2.5$, this measurement was used as the datum. Scan rates varied from 1.26 to 8.24°/min. Of the 96 steps in the scan, the first and the last 16 steps were considered to be background. During data collection the intensities of three standard reflections were monitored after every hour of X-ray exposure. No decay was observed. In addition, three orientation standards were checked after 100 reflections to check the effects of crystal movement. If the standard deviation of the h, k, and l values of any orientation reflection exceeded 0.08, a new orientation matrix was calculated on the basis of the recentering of the 24 reference reflections.

Intensities were corrected for Lorentz and polarization effects. The structure was solved by the Patterson method. After several cycles of refinements[40] the positions of the hydrogen atoms were found and added with a constant isotropic temperature factor of 0.05 Å^2 to the refinement process. Refinement proceeded to convergence by minimizing the function $\sum w(|F_o| - |F_c|)^2$. A final difference Fourier synthesis map showed several peaks less than 0.5 e Å^{-3} scattered about the unit cell without a significant feature.

The discrepancy indices, $R = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ are presented with other pertinent crystallographic data in Table I. Changing x,y,z coordinates of all atoms into $-x, -y, -z$, resulted after refinement in $R = 0.0535$; $R_w = 0.0720$.

Crystallographic Data. (*E*)-**6**: $C_{11}H_8ClO_5N$, space group $P2_1/c$, $a = 13.203$ (2) Å, $b = 11.987$ (2) Å, $c = 7.860$ (2) Å, $\beta = 104.75$ (5)°, $V = 1203.0$ (5) Å^3, $Z = 4$, $\rho_{calcd} = 1.489$ g cm^{-3}; μ(Mo Kα) 2.78 cm^{-1}; collection range $3 \leq 2\theta \leq 45°$; no. of unique reflections = 1567, reflections with $I \geq 3\sigma(I) = 1289$; $R = 0.043$; $R_w = 0.072$.

(*Z*)-**19**: $C_{16}H_{20}O_4$, space group $P2_1/c$, $a = 15.457$ (2) Å, $b = 9.276$ (2) Å, $c = 11.175$ (2) Å, $\beta = 98.19$ (5)°, $V = 1585.9$ (6) Å^3, $Z = 4$, $\rho_{calcd} = 1.16$ g cm^{-3}; μ(Mo Kα) 0.49 cm^{-1}; collection range $3 \leq 2\theta < 45°$; no. of unique reflections = 1966, reflections with $I \geq 1.5\sigma(I) = 1.38$; $R = 0.099$; $R_w = 0.091$.

(*RR*)-**20**: $C_{16}H_{20}Br_2O_4$, space group $P2_12_12_1$, $a = 27.987$ (7) Å, $b = 10.596$ (3) Å, $c = 6.291$ (2) Å, $V = 1865.0$ (8) Å^3, $Z = 4$, $\rho_{calcd} = 1.55$ g cm^{-3} μ(Mo Kα) = 42.53 cm^{-1}; collection range $3 \leq 2\theta \leq 55°$; no. of unique reflections = 2420, reflection with $I \geq 2\sigma(I) = 1568$; $R = 0.057$; $R_w = 0.053$.

(*E*)-**21**: $C_{16}H_{19}BrO_4$, space groups $Pna2_1$, $a = 31.736$ (7) Å, $b = 8.624$ (1) Å, $c = 6.128$ (1) Å, $V = 1677.2$ (1) Å^3, $Z = 4$, $\rho_{calcd} = 1.407$ g cm^{-3}, μ(Mo Kα) = 23.84 cm^{-1}; collection range $3 \leq 2\theta \leq 55$; no. of unique reflections = 1102, reflections with $I \geq 2\sigma(I) = 850$; $R = 0.0496$; $R_w = 0.0672$; $w = (\sigma_F^2 + 0.000929\ F^2)^{-1}$.

(*E*)- and (*Z*)-β-Chloro-α-(methoxycarbonyl)-*p*-nitrocinnamaldehydes [(*E*)-6 and (*Z*)-6]. (a) Methyl (*p*-Nitrobenzoyl)acetate (7). (i) A mixture of ethyl (*p*-nitrobenzoyl)acetate (35 g, 0.15 mol) and concentrated H_2SO_4 (1 mL) in MeOH (300 mL) was refluxed for 22 h. After pouring into water (300 mL), extraction with $CHCl_3$ (2 × 100 mL) and evaporation of the solvent, methyl (*p*-nitrobenzoyl)acetate (30 g, 91%) was obtained as a pale yellow solid. Crystallization from MeOH gave a pure sample, mp 110 °C, which gave red-violet color with $FeCl_3$: R_f (CH_2Cl_2) 0.65; UV (EtOH) λ_{max} 243 nm (ϵ 16100), 311 (7800); IR ($CHCl_3$) ν_{max} 1740 (CO_2R), 1690, 1650 (C=O), 1625, 1590 cm^{-1}; ^{1}H NMR [shows a 7:3 enol/ketone mixture] ($CDCl_3$) δ [keto form] 3.77 (3 H, s, CO_2Me), 4.07 (2 H, s, CH_2), 8.12, 8.34 (4 H, AB q, $J = 9.0$ Hz, Ar); [enol form] 3.84 (3 H, s, CO_2Me), 5.78 (1 H, s, CH=), 7.95, 8.27 (4 H, AB q, $J = 9$ Hz, Ar). Anal. Calcd for $C_{10}H_9NO_5$: C, 53.81; H, 4.03; N, 6.28. Found: C, 53.96; H, 4.04; N, 6.48.

(ii) Ethyl (*p*-nitrobenzoyl)acetate (25 g, 0.107 mol) in methanol (300 mL) containing H_2SO_4 (2 mL) was refluxed for 16 h. After neutralization with NaOMe and evaporation, a light yellow solid (23 g) containing (by NMR) 70% of the enol/ketone mixture of (*p*-nitrobenzoyl)acetate and 30% of a new compound, presumably the dimethyl acetal of methyl (*p*-nitrobenzoyl)acetate [($CDCl_3$) δ 3.03 (2 H, s, CH_2CO_2Me), 3.25 (6 H, s, MeO), 3.47 (3 H, s, CO_2Me), 7.69, 8.22 (4 H, AB q, $J = 8.2$ Hz, Ar)] were formed.

(b) (*E*)-6 and (*Z*)-6. (i) Methyl (*p*-nitrobenzoyl)acetate (30 g, 135 mmol) was added to a Vilsmeier reagent which was prepared from $POCl_3$ (29 g, 190 mmol) and DMF (19 g, 260 mmol) dissolved in trichloroethylene (200 mL). After being heated with stirring for 20 h at 95 °C the mixture was poured into water (150 mL) containing NaOAc (60 g, 0.75 mol), extracted with $CHCl_3$ (2 × 50 mL), washed with water, dried, and evaporated, giving 25 g of a black oil. After two chromatographies over silica, extraction of the acidic fraction with aqueous $NaHCO_3$ and crystallization, the five fractions obtained were purified as described below and gave five compounds.

(a) (*E*)-6 [4.7 g (13%), 95% pure]. Crystallization from benzene–hexane gave 3.7 g (10.1%) of 97% pure (by NMR) (*E*)-**6**: mp 140 °C; R_f (CH_2Cl_2) 0.5; t_r (HPLC) 4.2 min (RP-18, $F = 1.0$, UV 254); UV (EtOH) λ_{max} 250 sh nm (ϵ 5000), 284 (7500); IR ($CHCl_3$) ν_{max} 1735 (CO_2Me), 1685 (C=O), 1590, 1350, 1300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.68 (3 H, s, CO_2Me), 7.73, 8.30 (4 H, AB q, $J = 9.0$ Hz, Ar), 10.18 (1 H, s, CHO); MS, m/z (relative intensity) [no molecular peak] 239, 237 (18, 49, M – MeOH), 220 (22, M – Cl – CH_2), 211, 209 (12, 33, M – HCOOMe), 206 (72, M – Cl – CO), 193, 191 (13, 37, M – MeOH – NO_2), 174 (100, M – HCl – CO_2Me), 160 (12, M – Cl – CO – NO_2), 128 (34, M – HCl – CO_2Me – NO_2). Anal. Calcd for $C_{11}H_8ClNO_5$: C, 48.99; H, 2.97; N, 5.19; Cl, 13.16. Found: C, 48.85; H, 3.10; N, 4.88; Cl, 12.78.

(b) (*Z*)-6. A yellow oily solid fraction containing 4:1 (*Z*)-**6**/(*E*)-**6** (5 g, 13.8%) was crystallized from MeOH, giving a yellow solid (0.3 g, 0.8%) of 96% pure (by NMR) (*Z*)-**6**; mp 82 °C; R_f (CH_2Cl_2) 0.4; t_r (HPLC) 4.2 min (conditions as for (*E*)-**6**); UV (EtOH) λ_{max} 244 nm (ϵ 6900), 275 (16600), 335 sh (1600); IR ($CHCl_3$) ν_{max} 1730 (CO_2Me), 1685 (CHO), 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.96 (3 H, s, CO_2Me), 7.74, 8.37 (4 H, AB q, $J = 9.0$ Hz, Ar), 9.40 (1 H, s, CHO). Anal. Calcd for $C_{11}H_8ClNO_5$: C, 48.99; H, 2.97; N, 5.19. Found: C, 48.73; H, 3.01; N, 4.97.

(c) Methyl β-Chloro-*p*-nitrocinnamates [(*E*)-8 and (*Z*)-8]. A third fraction (3.9 g, 10%) is 85% of a 1:1 (*E*)-/(*Z*)-**8** mixture (by NMR). After chromatography on silica and crystallization from EtOH, light yellow crystals (0.7 g, 2%); mp 45–55 °C, of 6:4 (*E*)-/(*Z*)-**8** were obtained: t_r (HPLC) 4.5, 6.0 min (conditions as for (*E*)-**8**); UV (EtOH) λ_{max} 285 nm (ϵ 8800); IR ($CHCl_3$) ν_{max} 1740 (CO_2R) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ [*E* isomer] 3.60 (3 H, s, CO_2Me), 7.35 (1 H, s, =CH), 7.60, 8.23 (4 H, AB q, $J = 9$ Hz, Ar); [*Z* isomer] 3.86 (3 H, s, CO_2Me), 7.29 (3 H, s, =CH), 7.60, 8.23 (4 H, AB q, $J = 9$ Hz, Ar).

(d) (*E*)- and (*Z*)-β-Chloro-*p*-nitrocinnamaldehydes [(*E*)-9 and (*Z*)-9]. A fraction containing 50% of a mixture of ca. 1:1 (*E*)-**9** to (*Z*)-**9** (3 g, 5.3%) admixed with 40% of (*E*)-**8** and (*Z*)-**8** and 10% of (*E*)-**6** was assigned by NMR and was not purified further: NMR ($CDCl_3$) δ [(*E*)-**9**] 6.77 (1 H, s, =CH), 7.95, 8.31 (4 H, AB q, $J = 9$ Hz, Ar), 10.23 (1 H, s, CHO); [(*Z*)-**9**] 6.75 (1 H, s, =CH), 7.95, 8.31 (4 H, AB q, $J = 9$ Hz), 10.26 (1 H, s, CHO).

(e) (*E*)- and (*Z*)-β-Chloro-α-(methoxycarbonyl)-*p*-nitrocinnamic Acids (10). The last fractions from the chromatography were black oils (3 g) which showed CHO and COOH absorptions in the IR and the NMR. Extraction with aqueous $NaHCO_3$ (100 mL) followed by acidification with aqueous HCl and extraction with $CHCl_3$ (50 mL) gave light yellow solid (0.5 g, 1.5%). Crystallization from benzene followed by recrystallization from EtOH gave needles, mp 214 °C (70 mg, 0.2%), which were tentatively assigned as (*Z*)-β-chloro-α-(methoxycarbonyl)-*p*-nitrocinnamic acid (*Z*)-**10**, on the basis of the spectral properties and the solubility in $NaHCO_3$, although a good analysis was not yet obtained: R_f (85:15 CH_2Cl_2–MeOH) 0.5; t_r (HPLC) 2.8 min (conditions as above); UV (EtOH) λ_{max} 288 nm (ϵ 8100); IR ($CHCl_3$) ν_{max} 3500–2700 (COOH), 1720–1680 (C=O), 1620 cm^{-1}; ($CDCl_3$) δ 3.86 (3 H, s, COOMe), 7.58, 8.21 (4 H, AB q, $J = 9$ Hz, Ar); MS (EI), m/z (relative intensity) 222 (100, M – Cl – CO), 206 (22, M – Cl – CO_2), 177 (16, M – Cl – CO_2 – NO_2); MS (CI), m/z (relative intensity) 256, 254 (2, 6, M + 1 – MeOH), 226, 224

(30, 100, M + 1 – NO – MeOH), 208, 206 (6, 16, M + 1 – NO – MeOH – H_2O), 194 (12, 32, M – NO_2 – COOMe). Anal. Calcd for $C_{11}H_8ClNO_6$: C, 46.24; H, 2.80; N, 4.90; Cl, 12.42. Found: C, 49.37; H, 3.14; N, 5.96; Cl, 7.62.

The first crystallization from CH_2Cl_2 gave a 60:40 Z/E mixture from which the following NMR data were obtained for the E isomer: ($CDCl_3$) δ 3.60 (3 H, s, COOMe), 7.58, 8.27 (4 H, AB q, J = 9 Hz, Ar). The retention time in HPLC was 2.2 min and R_f (85:15 CH_2Cl_2–MeOH) = 0.5.

The reaction was repeated by adding methyl(*p*-nitrobenzoyl)acetate (**7**) (23 g, 103.5 mmol) to a Vilsmeier reagent prepared from $POCl_3$ (24.5 g, 150 mmol) and DMF (14.6 g, 199 mmol) in trichloroethylene (160 mL). Heating with stirring for 20 h followed by workup as above gave a viscous oil (16 g). Crystallization of the crude oil from benzene gave 97% pure (*E*)-**6** (1.2 g, 4%). Chromatography of the remainder gave unreacted methyl benzoylacetate (2.6 g, 11.2%) and 10 g of an oil, which (by NMR) consists of 80% of 4:6 (*E*)-**6**/(*Z*)-**6** mixture and 20% of (*E*)-**8** and (*Z*)-**8** together with the starting material. No β-chloro-α-(methoxycarbonyl)-*p*-nitrocinnamic acid was formed.

Reaction of (*E*)-6 with Nucleophiles. (a) With *p*-Toluenethiolate Ion. To a solution of (*E*)-**6** (1.05 g, 3.7 mmol) in DMF (10 mL) was added sodium *p*-toluenethiolate (0.74 g, 5 mmol). A brown-yellow color was developed immediately. After being stirred for 2.5 h at room temperature the mixture was poured into 1 N HCl (50 mL), extracted with $CHCl_3$ (2 × 50 mL), and dried, and the solvent was evaporated, giving a yellowish oily solid, which according to the NMR was a 55:45 mixture of (*E*)- and (*Z*)-α-(methoxycarbonyl)-*p*-nitro-β-(tolylthio)cinnamaldehydes [(*E*)-**11** and (*Z*)-**11**]. Chromatography on silica column gave (*E*)-**6** (0.2 g, 19%) and a yellow oily solid (0.45 g, 45% taking into account the recovered (*E*)-**6**), with fractions changing from 80:20 to 25:75 (*E*)-**11**/(*Z*)-**11**. An attempt to separate the (*Z*)-**11**-rich fraction on a preparative TLC plate (four times, by using 70% CH_2Cl_2–30% hexane) gave only a 65:35 (*Z*)-**11**/(*E*)-**11** mixture. The NMR and the analysis are for this mixture.

(*E*)-**11**: ^1H NMR ($CDCl_3$) δ 2.19 (3 H, s, Me), 3.53 (3 H, s, COOMe), 6.93, 7.08 (4 H, AB q, J = 8.2 Hz, ArS), 7.26, 8.04 (4 H, AB q, J = 8.4 Hz, $O_2NC_6H_4$), 10.21 (1 H, s, CHO).

(*Z*)-**11**: ^1H NMR ($CDCl_3$) δ 2.22 (3 H, s, Me), 3.94 (3 H, s, COOMe), 6.92, 7.04 (4 H, AB q, J = 8.2 Hz, ArS), 7.17, 7.98 (4 H, AB q, J = 8.4 Hz, $O_2NC_6H_4$), 9.30 (1 H, s, CHO).

Anal. Calcd for $C_{18}H_{15}NO_5S$: C, 60.50; H, 4.20; N, 3.92; S, 8.96. Found: C, 60.40; H, 4.08; N, 4.02; S, 9.09.

(b) With *p*-Methylphenolate Ion. To a solution of (*E*)-**6** (1.1 g, 4 mmol) in DMF (20 mL) was added sodium *p*-methylphenolate (0.65 g, 5 mmol). A red color was immediately developed. The mixture was stirred for 30 h at room temperature, poured into 1 N HCl (50 mL), extracted with $CHCl_3$ (2 × 50 mL), and dried, and the solvent was evaporated, leaving a yellow oily solid. The ^1H NMR showed mainly a 45:55 mixture of (*E*)- and (*Z*)-α-(methoxycarbonyl)-*p*-nitro-β-(tolyloxy)cinnamaldehydes [(*E*)-**12** and (*Z*)-**12**] and a few unidentified small signals. An identical product distribution was obtained when small samples were withdrawn from the reaction mixture after 3, 6, and 24 h and worked up as above. The R_f's of the two isomers (0.3 and 0.25 on silica with CH_2Cl_2) are nearly identical in TLC. Chromatography on silica gave an oily solid (0.45 g, 32%) without further separation of the 45:55 mixture. Attempted crystallization or separation on HPLC columns were unsuccessful. NMR spectra and elemental analysis were conducted on the mixture.

(*E*)-**12**: ^1H NMR ($CDCl_3$) δ 2.25 (3 H, s, Me), 3.67 (3 H, s, COOMe), 6.76, 7.05 (4 H, AB q, J = 8.2 Hz, Tol), 7.65, 8.28 (4 H, AB q, J = 8.4 Hz, *p*-$O_2NC_6H_4$), 10.17 (1 H, s, CHO).

(*Z*)-**12**: ^1H NMR ($CDCl_3$) δ 2.22 (3 H, s, Me), 3.80 (3 H, s, COOMe), 6.86, 7.05 (4 H, AB q, J = 8.2 Hz, Tol), 7.68, 8.22 (4 H, AB q, J = 8.4 Hz, $O_2NC_6H_4$), 9.40 (1 H, s, CHO).

Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.63; H, 4.40; N, 4.10. Found: C, 63.48; H, 4.64; N, 4.15.

The (*E*)-**12**/(*Z*)-**12** mixture is unstable on the silica column, and in a similar reaction the relative intensity of the CHO signal after chromatography was appreciably reduced compared with the expected value.

(b) When a mixture of (*E*)-**6** (10 mg, 0.037 mmol) and sodium *p*-methylphenolate (5.16 mg, 0.04 mmol) ([ArO^-]/[(*E*)-**6**] = 1.1) was dissolved in Me_2SO-d_6 (0.5 mL, 0.074 mmol) in an NMR tube a red color was developed. Me_4Si was not used, and the assignments of the signals were based on δ (Me_2SO) = 2.5. Those used for analysis were as follows: (*E*)-**6**, 3.60 (COOMe), 10.08 (CHO); (*E*)-**12**, 3.65 (COOMe), 10.08 (CHO); (*Z*)-**12**, 3.71 (COOMe), 9.29 (CHO). The development of the vinyl ethers signals was followed in the NMR probe as a function of time. The percentage reaction and the (*E*)-**12**/(*Z*)-**12** ratios were calculated from the relative intensities of the COOMe signals, and the ratio at the end of the reaction was corroborated from the relative intensities of the CHO signals. The following results were obtained [time (min), % reaction, (*E*)-**12**/(*Z*)-**12** ratio]: 2.0, 91:9; 4.3, 45, 89:11; 6.6, 45, 90:10; 8.9, 48, 85:15; 11.2, 53, 81:19; 30.0, 55, 82:18. The extrapolated product distribution to zero reaction time is 92:8 (*E*)-**12**/(*Z*)-**12**.

The spectral evidence shows that (*Z*)-**6** is not formed during the reaction. However, new signals at δ 3.55 (COOMe) and 8.0 (aromatic multiplet) which were ca. 20% of the total product were observed but not identified.

When an identical reaction was conducted with [ArO^-]/[(*E*)-**6**] ratio of 1.6, the (*E*)-**12** ⇌ (*Z*)-**12** isomerization was much faster. After 5 min (60% reaction) the (*E*)-**12**/(*Z*)-**12** ratio was 66:33, and after 37 min (100% reaction) it was 45:55.

(c) With Methoxide Ion. A solution of (*E*)-**6** (0.54 g, 2 mmol) in MeOH (30 mL), to which sodium methoxide (110 mg, 2 mmol) was added turned light red immediately. After being stirred for 90 min at 20 °C the reaction mixture was worked up as above, giving a viscous yellow oil. TLC showed the presence of (*E*)-**6** and of a new material. Crystallization from benzene–cyclohexane gave unreacted (*E*)-**6** (70 mg, 12.3%). Trituration with ethanol or cyclohexane gave an oily solid, which by NMR consisted of a 35:65 mixture of (*E*)- and (*Z*)-α-methoxy-β-(methoxycarbonyl)-*p*-nitrocinnamaldehydes [(*E*)-**13** and (*Z*)-**13**]. Chromatography over silica gave an oily solid (0.3 g, 56%) in which the ratio changed to 40:60, but the compounds are apparently unstable since new signals also appeared. The NMR spectra were taken on the mixture since separation was not achieved.

(*Z*)-**13**: ^1H NMR ($CDCl_3$) δ 3.53 (3 H, s, MeO), 3.96 (3 H, s, COOMe), 7.7–8.3 (4 H, m, Ar), 9.38 (1 H, s, CHO); (Me_2SO) δ 3.26 (3 H, s, MeO), 3.86 (3 H, s, COOMe), 8.0–8.3 (4 H, m, Ar), 9.31 (1 H, s, CHO). (*E*)-**13**: ($CDCl_3$) δ 3.40 (3 H, s, MeO), 3.74 (3 H, s, COOMe), 7.7–8.3 (4 H, m, Ar), 10.19 (1 H, s, CHO); (Me_2SO) δ 3.40 (3 H, s, MeO), 3.62 (3 H, s, COOMe), 8.0–8.3 (4 H, m, Ar), 10.08 (1 H, s, CHO).

(d) With Chloride Ion. (*E*)-**6** (6.4 mg, 0.024 mmol) and tetrabutylammonium chloride (11 mg, 0.040 mmol, dried in vacuo for 24 h before use) were dissolved in $CDCl_3$ (0.4 mL) in an NMR tube. The (*E*)-**6**/(*Z*)-**6** ratios were analyzed after 1, 3, 56, 76, 122 and 170 h at room temperature by monitoring the relative intensities of the COOMe and CHO signals and found to be 94:6, 90:10, 74:24, 62:38, 52:48, and 52:48, respectively.

Control experiments showed that in the absence of added chloride ion, (*E*)-**6** did not isomerize (within the detection limits of the NMR) on standing for 40 h in DMF or for 60 h in $CDCl_3$ at room temperature.

Methyl Benzoylacetate (14). A mixture of ethyl benzoylacetate (Aldrich, 25 g, 0.14 mol) and concentrated H_2SO_4 (1 mL) in MeOH (300 mL) was refluxed for 20 h. The solvent was evaporated, water (50 mL) and $CHCl_3$ (20 mL) were added, and the organic phase was separated, dried, and evaporated leaving 19 g of (82%) of an oil, with a positive (violet-red) $FeCl_3$ test: R_f (8:2 CH_2Cl_2–hexane) 0.6; UV (EtOH) λ_{max} 243 nm (ϵ 21 600), 284 (7800); IR (neat) ν_{max} 1740 (CO_2R), 1685 (C=O) cm^{-1}; ^1H NMR [shows a 24:76 enol/ketone ratio] ($CDCl_3$) δ [keto form] 3.75 (3 H, s, CO_2Me), 4.01 (2 H, s, CH_2), 7.44–7.96 (5 H, m, Ph); [enol form] 3.80 (3 H, s, CO_2Me), 5.68 (1 H, s, CH=), 7.44–7.96 (5 H, m, Ar, overlap the ketone signals). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.62. Found: C, 67.13; H, 5.75.

β-Chloro-α-(methoxycarbonyl)cinnamaldehydes [(*E*)-15/(*Z*)-15]. Methyl benzoylacetate (18 g, 0.1 mol) was added to Vilsmeier reagent prepared from $POCl_3$ (20.6 g, 160 mmol) and DMF (19 g, 260 mmol) in trichloroethylene (150 mL). The mixture was heated at 105 °C for 20 h, poured into water containing NaOAc (40 g), and extracted with $CHCl_3$ (50 mL), and the solvent was dried and evaporated. Chromatography on a silica column gave two fragments in overall 25% yield: (a) 4.5 g of a 40% 6:4 (*E*)-**15**/(*Z*)-**15** mixture to 60% of (*E*)- and (*Z*)-β-chlorocinnamaldehydes [($CDCl_3$) δ [*Z* isomer] 6.67 (1 H, s, CH=), 10.23 (1 H,

s, CHO); [*E* isomer] 6.69 (1 H, s, CH=), 10.21 (1 H, s, CHO)], which was not purified further; this fraction becomes a black oil after a few weeks; (b) yellow viscous oil (3.4 g, 15%), consisting of a 35:65 (*E*)-**15**/(*Z*)-**15** mixture; R_f (8:2 CH_2Cl_2–hexane) 0.6; UV (EtOH λ_{max} 279 nm (ϵ 9200); IR (neat) ν_{max} 1730 (CO_2Me), 1670 (C=O), 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ [(*E*)-**15**] 3.64 (3 H, s, CO_2Me), 7.50 (5 H, m, Ph), 10.16 (1 H, s, CHO); [(*Z*)-**15**] 3.93 (3 H, s, CO_2Me), 7.50 (5 H, m, Ar), 9.37 (1 H, s, CHO). Anal. Calcd for $C_{11}H_9ClO_3$: C, 58.80; H, 4.00; Cl, 15.81. Found: C, 58.76; H, 4.23; Cl, 13.27.

β-Chloro-α-(ethoxycarbonyl)cinnamaldehydes [(*E*)-16 and (*Z*)-16].[12] (a) To a solution of $POCl_3$ (22.6 g, 0.16 mol) in DMF (20 mL)–trichloroethylene (150 mL) was added ethyl benzoylacetate (19.2 g, 0.1 mol), and the mixture was kept for 20 h at 95 °C. NaOAc (40 g, 0.49 mol) in water (100 mL) was added, the solution was stirred at room temperature for 30 min and separated, and the organic phase was washed with 0.1 N HCl (2 × 100 mL) and water, separated, dried, and evaporated. A black oil, which by NMR contains a 1:1 ratio of (*E*)- and (*Z*)-β-chloro-α-(ethoxycarbonyl)cinnamaldehydes [(*E*)-**16**) and (*Z*)-**16**] (lit.[12] 48:52 *E*/*Z*) was obtained. Chromatography on silica gel using 35% $CHCl_3$ in hexane gave a 40:60 (*E*)-**16**/(*Z*)-**16** ratio as a light yellow oil (10.7 g, 45%). On HPLC silica column (F = 1.0, UV = 254, CH_2Cl_2) both isomers gave R_f = 9.3 min: UV (EtOH) λ_{max} (4:1 *Z*/*E*) 258 nm (ϵ 5500); IR (neat) ν_{max} 1720, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ [(*E*)-**16**] 1.03 (3 H, t, Me), 4.09 (2 H, q, CH_2), 7.3–7.7 (5 H, m, Ph), 10.19 (1 H, s, CHO); [(*Z*)-**16**] 1.38 (3 H, t, Me), 4.41 (2 H, q, CH_2), 7.3–7.7 (5 H, m, Ph), 9.38 (1 H, s, CHO). Anal. Calcd for $C_{12}H_{11}ClO_4$: C, 56.58; H, 4.32; Cl, 13.95. Found: C, 56.85; H, 4.53; Cl, 14.02.

Substitution of (*E*)-15 by Sodium *p*-Methylphenolate. To a 20:80 (*E*)-**15**/(*Z*)-**15** mixture (1.1 g, 4.9 mmol) in DMF (10 mL) was added sodium *p*-methylphenolate (0.85 g, 6.5 mmol). A red color was developed, and a solid was precipitated. After 70 h of being stirred at room temperature the mixture was poured into 1 N HCl (50 mL), extracted with $CHCl_3$ (2 × 50 mL), dried, and evaporated. The NMR of the remainder showed the presence of traces of (*E*)-**15** and a 67:33 mixture of (*E*)- and (*Z*)-β-(tolyloxy)-α-carbomethoxycinnamaldehyde [(*E*)-**17** and (*Z*)-**17**]. Chromatography over silica gave an oil (0.6 g, 41%) with the same composition, which could not be induced to crystallize from several solvents: UV (EtOH) λ_{max} 243 nm (ϵ 27 100), 279 (4900); IR (neat) ν_{max} 1740 (CO_2R), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ [(*E*)-**17**] 2.26 (3 H, s, Ar*Me*), 3.66 (3 H, s, COOMe), 6.76, 6.89, (4 H, AB q, *J* = 8.2 Hz, Ar), 7.5 (5 H, m, Ph), 10.10 (1 H, s, CHO); [(*Z*)-**17**] 2.22 (3 H, s, Ar*Me*), 3.77 (3 H, s, COOMe), 6.85, 6.88 (4 H, AB q, *J* = 8.2 Hz, Ar), 7.5 (5 H, m, Ph), 9.39 (1 H, s, CHO). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.97; H, 5.40. Found: C, 73.12; H, 5.55.

Substitution of 16 by Sodium *p*-Methylphenolate. To a 40:60 mixture of (*E*)-**16** and (*Z*)-**16** (2.5 g, 10 mmol) in DMF (20 mL) was added sodium *p*-methylphenolate (1.6 g, 12.3 mmol). A red color was developed immediately. After 60 h at room temperature, the solution was worked up as above, giving a yellow oil whose NMR showed only a 1:1 mixture of (*E*)- and (*Z*)-β-(tolyloxy)-α-(ethoxycarbonyl)cinnamaldehydes [(*E*)-**18** and (*Z*)-**18**]. Chromatography on silica changed the *E*/*Z* ratio to 40:60 (*Z*)-**18**/(*E*)-**18**, but complete separation was not achieved. The viscous oil (1.6 g, 49%) could not be induced to crystallize from several solvents: R_f (CH_2Cl_2) 0.5; UV (EtOH λ_{max} 244 nm (ϵ 23 300), 278 sh (16 000); IR (neat) ν_{max} 1740 (CO_2R), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ [(*E*)-**18**] 1.02 (3 H, t, *J* = 7.0 Hz, CH_2Me), 2.20 (3 H, s, Ar*Me*), 4.12 (2 H, q, *J* = 7.0 Hz, CH_2), 6.85, 6.97 (4 H, AB q, *J* = 8.2 Hz, Ar), 7.43 (5 H, m, Ph), 10.10 (1 H, s, CHO); [(*Z*)-**18**] 1.26 (3 H, t, *J* = 7.0 Hz, CH_2Me), 2.25 (3 H, s, Me), 4.26 (2 H, q, *J* = 7.0 Hz, CH_2), 6.74, 6.99 (4 H, AB q, *J* = 8.2 Hz, Ar), 7.43 (5 H, m, Ph), 9.39 (1 H, s, CHO). Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.55; H, 5.81. Found: C, 73.67; H, 5.97.

(*E*)- and (*Z*)-*tert*-Butyl Methyl β-Bromo(*p*-methylbenzylidene)malonates [(*E*)-21 and (*Z*)-21]. (A) *tert*-Butyl Methyl (*p*-Methylbenzylidene)malonate (19). (i) A mixture of *p*-tolualdehyde (6 g, 50 mmol), *tert*-butyl methyl malonate (10.6 g, 60 mmol), piperidine (1 mL), and AcOH (1.3 mL) in benzene (100 mL) was refluxed for 24 h in a Dean–Stark apparatus. Water was added, the layers were separated, and the aqueous phase was extracted with benzene (100 mL) and ether (100 mL). The combined organic phase was washed with water and then with dilute HCl solution, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel gave a colorless viscous oil (12 g, 87%), which showed two spots for the cis and trans vinyl esters with R_f = 0.25 and 0.35 on TLC column, with 60% CH_2Cl_2–40% hexane. The ^1H NMR shows a single peak for each of the vinylic, aromatic methyl, and ester groups and closely overlapping two aromatic quartets. A part (1.3 g) of the mixture was carefully chromatographed on dry silica gel, by using 20% CH_2Cl_2–80% hexane as eluant. The middle fractions (0.35 g) gave a colorless viscous oil, which gave a spot with R_f = 0.3 in TLC. Following fractions are an oil (0.75 g), which solidified on standing to white crystals, mp 45 °C. The IR and the 60-MHz ^1H NMR spectra are almost identical for both isomers (vide infra).

(ii) A mixture of *p*-tolualdehyde (6 g, 50 mmol), *tert*-butyl methyl malonate (10.6 g, 60 mmol), piperidine (1 mL), and AcOH (1.3 mL) in benzene (100 mL) was refluxed for 24 h and worked up as described above. After extraction with CH_2Cl_2 an oil was obtained. Seeding with the solid isomer obtained above and cooling overnight to 0 °C gave white crystals (5 g, 36%) of 97% pure (*Z*)-*tert*-butyl methyl (*p*-methylbenzylidene)malonate [(*Z*)-**19**], mp 63 °C.

The composition of the crude oil was 55:45 (*Z*)-**19**/(*E*)-**19**. After evaporation of the mother liquor an oil, a 67:33 *E*/*Z* mixture (5.75 g, 41%), was obtained: IR (neat or $CHCl_3$) ν_{max} 1720 cm^{-1} for both isomers.

(*Z*)-**19**: (ArC_1), (EtOH) λ_{max} 223 nm (ϵ 13 600), 227 sh (11 200), 288 (24 400); ^1H NMR ($CDCl_3$) δ 1.54 (9 H, s, *t*-Bu), 2.37 (3 H, s, Ar*Me*), 3.83 (3 H, s, COOMe), 7.18, 7.42 (4 H, AB q, 2 centers of d, *J* = 8 Hz, Ar), 7.62 (1 H, s, =CH); (C_6D_6) δ 1.46 (9 H, s, *t*-Bu), 1.96 (3 H, s, Me), 3.39 (3 H, s, COOMe), 6.83, 7.36 (4 H, AB q, Ar), 7.74 (1 H, s, =CH); ^{13}C NMR ($CDCl_3$) δ 21.34 (Ar*Me*), 27.8 (CMe_3), 52.8 (COO*Me*), 82.5 (CMe_3), 126.8 (C_α), 129.3 (Ar C_2), 129.6 (Ar C_3), 130.4 (Ar C_1), 140.8 (Ar C_4), 140.9 (C_β), 165.1, 165.8 (COOR); MS, *m*/*z* (relative intensity) 276 (15, M), 221 (12, M – *t*-Bu), 205 (22, M – OBu-*t*), 203 (15), 175 (23, M – CO_2Bu-*t*), 174 (8, M – HCO_2Bu-*t*), 160 (15, M – Me – CO_2Bu-*t*), 144 (22, M – OMe – CO_2Bu-*t*), 119 (32), 91 (13).

(*E*)-**19**: ^1H NMR ($CDCl_3$) δ 1.53 (9 H, s, COOBu-*t*), 2.36 (3 H, s, Me), 3.83 (3 H, s, COOMe), 7.17, 7.41 (4 H, AB q, center of 2 d, Ar), 7.61 (1 H, s, =CH); (C_6D_6) δ 1.38 (9 H, s, *t*-Bu), 1.94 (3 H, s, Me), 3.51 (3 H, s, COOMe), 6.79, 7.23 (4 H, AB q, Ar), 7.81 (1 H, s, =CH); ^{13}C NMR ($CDCl_3$) δ 21.34 (Ar*Me*), 27.7 (CMe_3), 42.46 (COO*Me*), 81.9 (CMe_3), 126.5 (C_α), 126.6 (Ar C_3), 129.3 (Ar C_2), 130.2 (Ar C_1), 141.2 (C_β, Ar C_4), 165.0, 167.5 (COOR).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.56; H, 7.24. Found for (*Z*)-**19**: C, 69.70; H, 7.02. Found for *E*/*Z* mixture: 69.37; H, 7.39.

Isomerization of (*Z*)-19. (a) A mixture of (*Z*)-**19** (70 mg, 0.25 mmol) and DBN (80 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was kept for 16 h at 20 °C. Water (10 mL) was added, the layers were separated, and the organic phase was washed with water, dried ($MgSO_4$), and evaporated. TLC shows the formation of an *E*/*Z* mixture and an additional spot. ^1H NMR (300 MHz) showed formation of a 58:42 (*Z*)-**19**/(*E*)-**19** mixture. The new compound consists (by NMR) 30% of the product with the following signals and intensities: (C_6D_6) δ 1.32, 1.33 (*t*-Bu, 9, 0.3), 3.03 (Me, 1), 3.33, 3.34, 3.35 (CH_2, 1), 6.40 (1).

(b) A solution of (*Z*)-**19** (40 mg), piperidine (0.05 mL), and AcOH (0.06 mL) in dry benzene (10 mL) was refluxed for 3 h and then poured into 0.1 N HCl (30 mL), and the organic phase was separated, dried, and evaporated. The oil obtained consists only of (*Z*)-**19** and (*E*)-**19** (by TLC) and by NMR is a 54:46 (*Z*)-**19**/(*E*)-**19** mixture.

(c) A solution of (*Z*)-**19** (30 mg, 7 mmol) in CH_2Cl_2 (5 mol), to which 5 drops of concentrated HCl solution was added, was stirred for 3 h at room temperature. After the usual workup only a 60:40 ratio of (*Z*)-**19**/(*E*)-**19** was detected by NMR.

(B) *tert*-Butyl Methyl (*p*-Methylbenzylidene)malonate Dibromides (20). (a) Bromine (3.3 g, 20 mmol) was added to a solution of (*E*)-**19**/(*Z*)-**19** (4 g, 14 mmol) in CCl_4 (30 mL), and the solution stood for 72 h at room temperature until complete decoloration of the bromine color. Water was added, the layers were separated, and the organic phase was extracted with CCl_4, washed with water and $Na_2S_2O_3$ solution, dried ($MgSO_4$), and evaporated. The remaining colorless oil showed two spots on a TLC plate, R_f 0.5 and 0.6 (6:4 CH_2Cl_2–hexane). Chromatography on silica gel, using 15% CH_2Cl_2 in hexane, gave two compounds:

(a) colorless oil; R_f 0.6 (0.3 g); ^{1}H NMR ($CDCl_3$) δ 1.16–1.5 (7–8 H, m), 2.33 (3 H, s, Me), 3.83 (3 H, s, CO_2Me), 7.03 and 7.06 (two halves of an AB q, J = 8 Hz, Ar), 8.03 (1 H, s, =CH), which was not investigated further; (b) A colorless oil (1.7 g, 27%); R_f 0.5, which by NMR is a 1:1 mixture of the 1*R*,2*R*/1*S*,2*S* (**20a**) and 1*R*,2*S*/1*S*,2*R* (**20b**) dibromides **20** (see below).

(b) (*Z*)-**19** and (*E*)-**19** were brominated separately as described above. The NMR's showed the formation of 66:34 and 45:55 mixtures of **20a** to **20b**, starting from pure (*Z*)-**19** and (*E*)-**19**, respectively.

(c) (*Z*)-**19** (2.5 g, 9 mmol) in CCl_4 (50 mL) was brominated with bromine (0.7 mL, 13.5 mmol) for 16 h at room temperature, and the reaction was worked up as in a above. Chromatography of the viscous oil on silica gave a solid dibromide and a fraction richer in the oily dibromide. Crystallization of the solid from hexane gave *d,l*-(1*R*,2*R*/1*S*,2*S*)-*tert*-butyl methyl (*p*-methylbenzylidene)malonate dibromide (**20a**), 97% diastereomerically pure, mp 96 °C (0.9 g, 23%). Two additional crystallizations from hexane gave needles of the pure compound, mp 100 °C, whose structure was determined by X-ray diffraction as that of **20a**. Evaporation of the remaining solution left a 2:1 mixture of **20b** and **20a**.

20a: ^{1}H NMR ($CDCl_3$) δ 1.53 (9 H, s, *t*-Bu), 2.33 (3 H, s, Me), 3.72 (3 H, s, COOMe), 5.71 (1 H, s, CHBr), 7.12, 7.48 (4 H, AB q, centers of d, J = 8.2 Hz, Ar); MS, *m*/*z* (relative intensity) 438, 436, 434 (1.3, 2.9, 1.3, M), 357, 355 (8, 9, M – Br), 301, 299 (3, 3, M – Br – C_4H_8), 257, 255 (95, 100, MH – Br – CO_2Bu-*t*), 225, 223 (47, 50, M – Br – CO_2Bu-*t* – MeO), 220 (23), 205 (23), 185, 183 (31, 31, TolCHBr), 175 (60, TolC$^+$=CHCOOMe), 143 (38, TolC≡CCO$^+$), 115 (15, $TolC_2$), 91 (91, tropylium). Anal. Calcd for $C_{16}H_{20}Br_2O_4$: C, 44.05; H, 4.59; Br, 36.67. Found: C, 44.08; H, 4.35; Br, 36.34.

20b: ^{1}H NMR ($CDCl_3$) δ 1.38 (9 H, s, *t*-Bu), 2.33 (3 H, s, Me), 3.87 (3 H, s, COOMe), 5.71 (1 H, s, CHBr), 7.12, 7.46 (4 H, AB q, centers of d, J = 8.2 Hz, Ar).

(C) *tert*-Butyl Methyl β-Bromo(*p*-methylbenzylidene)malonates [(*E*)-21 and (*Z*)-21]. (a) A 1:1 mixture of **20a** and **20b** (1.6 g, 3.6 mmol) and DBN (0.65 g, 5.3 mmol) in CH_2Cl_2 (40 mL) was kept for 24 h at room temperature. Water was added, the layers were separated, the aqueous phase was extracted with CH_2Cl_2, and the organic layer was washed with dilute HCl, dried ($MgSO_4$), and evaporated. Chromatography on silica gave unreacted **20a**/**20b** (0.5 g, 31%) and a 1:2:2 mixture of (*E*)-**19**/(*Z*)-**19**–(*E*)-**21**–(*Z*)-**21**.

(b) A mixture of 9:1 **20a** to **20b** (2.7 g, 6.2 mmol) and DBN (1.1 g, 9 mmol) in CH_2Cl_2 (40 mL) was kept for 5 h at room temperature. TLC and NMR were similar after 2, 5, and 22 h. Workup as above gave a mixture consisting of (by NMR) 7% (*E*)-**21**, 60% (*Z*)-**21**, 10% (*E*)-**19**, and 23% (*Z*)-**19**. Chromatography gave 99% pure crystalline (*Z*)-**21**, mp 78 °C (0.71 g, 32%), whereas pure (*E*)-**21** could not be separated by chromatography from the other components of the mixture.

(*Z*)-**21**: IR ($CHCl_3$) ν_{max} 1725 (COOMe), 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (9 H, s, *t*-Bu), 2.37 (3 H, s, Me), 3.60 (3 H, s, COOMe), 7.17, 7.28 (4 H, AB q, centers of 2 d, J = 8 Hz, Ar); (C_6D_6) δ 1.50 (9 H, s, *t*-Bu), 1.91 (3 H, s, Me), 3.12 (3 H, s, COOMe), 6.7, 7.1 (4 H, AB q, Ar); MS, *m*/*z* (relative intensity) 356, 354 (0.6, 0.5, M), 300, 298 (21, 21, M – C_4H_8), 285 (4.5), 283 (16), 268, 266 (12, 12, M – *t*-BuOO), 253, 251 (4, 4, M – *t*-BuO-MeOO), 175 (100, M – Br – CO_2 – C_4H_8), 143 (83, M – Br – MeO – CO_2Bu-*t*). In spite of repeated attempts good crystals for X-ray diffraction were not obtained. Anal. Calcd for $C_{16}H_{19}BrO_4$: C, 54.10; H, 5.35; Br, 22.54. Found: C, 54.26; H, 5.57; Br, 22.45.

(c) A 20:80 **20a**/**20b** mixture (4.7 g, 10.8 mmol) and DBN (1.7 g, 13.7 mmol) in CH_2Cl_2 (100 mL) was stirred for 5 h at room temperature. After the usual workup the mixture was chromatographed on silica, giving unreacted **20a**/**20b** (1 g, 21%) and 0.9 g of a mixture which by NMR and HPLC consists of a 35:25:32:8 of (*E*)-**19**/(*Z*)-**19**/(*E*)-**21**/(*Z*)-**21**. The HPLC conditions were silica gel 60, F = 1.0, UV = 254 nm, and solvent CH_2Cl_2, and the retention times in minutes were as follows: **20a**, 3.9; **20b**, 4.3; (*Z*)-**21**, 5.8; (*E*)-**21**, 6.5; (*Z*)-**19**, 7.5; (*E*)-**19**, 10.6. Conditions for an efficient large scale separation of (*E*)-**21** were not found.

(d) To a 9:1 mixture of **20b** and **20a** (8 g, 18 mmol) in CH_2Cl_2 (150 mL) were added DBN (3.4 g, 27 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (0.3 g, 1.3 mmol) under argon, and the mixture was stirred for 2.5 h at room temperature. After the mixture was poured into 0.1 N HCl solution (100 mL) and extraction with $CHCl_3$ and evaporation of the solvent, ca. 9:1 (*E*)-**21** and (*Z*)-**21** was observed by ^{1}H NMR. Two chromatographies on silica gel and crystallization from hexane gave the pure (*E*)-**21** as a white solid, mp 84 °C (0.17 g, 3%): IR ($CHCl_3$) ν_{max} 1725, 1695 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (9 H, s, Bu-*t*), 2.38 (3 H, s, Me), 3.88 (3 H, s, CO_2Me), 7.18, 7.28 (4 H, AB q, J = 8 Hz, Ar); (C_6D_6) δ 1.10 (9 H, s, *t*-Bu), 1.92 (3 H, s, Me), 3.51 (3 H, s, COOMe); MS, *m*/*z* (relative intensity) 356, 354 (1.5, 1.5, M), 300, 298 (27, 27, M – Me_2C=CH_2), 285, 283 (8, 21, M – Me_2C=CH_2 – Me), 268, 266 (17, 16, M – Me_2C=CH_2 – MeOH), 253, 251 (6, 8, M – OBu – OMe), 213 (7), 175 (100, M – Br – CO_2 – Me_2C=CH_2), 143 (89, TolC≡CCO$^+$), 119 (8, TolCO$^+$), 115 (26, TolC≡C$^+$). Anal. Calcd for $C_{16}H_{19}BrO_4$: C, 54.10; H, 5.35. Found: C, 54.23; H, 5.35. For X-ray data see Table I.

Isomerization of (*Z*)-21 by Tetrabutylammonium Bromide. (a) (*Z*)-**21** (35 mg, 0.1 mmol) and Bu_4NBr (40 mg, 0.12 mmol) in DMF (0.5 mL) were stirred for 20 h at room temperature. The usual workup gave a 9:1 (*Z*)-**21**/(*E*)-**21** mixture (by NMR).

This solid mixture was dissolved in DMF (1 mL) to which Bu_4NBr (87 mg, 0.27 mmol) was added, and the solution was stirred for 240 h at room temperature. After workup NMR analysis showed a 80:20 (*Z*)-**21**/(*E*)-**21** mixture.

(b) When a mixture of (*Z*)-**21** (32 mg, 0.1 mmol) and Bu_4NBr (34 mg, 0.1 mmol) in MeCN (10 mL) was refluxed for 4 h, (*Z*)-**21** was recovered after workup.

(c) When a mixture of (*E*)-**21** or (*Z*)-**21** (40-60 mmol) with 4.2–5.0 mol equiv of Bu_4NBr in $CDCl_3$ was kept for 126 h in the absence of light no isomerization was detected.

Reaction of (*Z*)-21 with Sodium *p*-Toluenethiolate. (a) A heterogeneous mixture of (*Z*)-**21** (70 mg, 0.2 mmol) and sodium *p*-toluenethiolate (40 mg, 0.27 mmol) in DMF (1 mL) was stirred for 20 h at room temperature. The initially formed red color gradually turned yellow, and the mixture became nearly homogeneous after 4 h. It was then poured into 0.1 N HCl (10 mL) and extracted with CH_2Cl_2 (5 mL), and the organic phase was dried and evaporated. NMR of the remainder showed the presence of a 45:55 mixture of (*E*)- and (*Z*)-*tert*-butyl methyl β-(tolylthio)-(*p*-methylbenzylidene)malonates [(*E*)-**22** and (*Z*)-**22**]. Crystallization from hexane gave a white solid, mp 115 °C (40 mg, 50%), which by NMR consists of a 10:90 mixture of (*Z*)-**22** and (*E*)-**22**. The NMR of the mother liquor shows a 45:55 (*Z*)-**22**/(*E*)-**22** ratio: R_f (7:3 CH_2Cl_2–hexane) (*E*)-**22** 0.25, (*Z*)-**22**, 0.3.

The following spectra were measured on the 10:90 (*Z*)-**22**/(*E*)-**22** mixture: UV (EtOH) λ_{max} 262 nm (ε 4800), 293 (6600); IR ($CHCl_3$) ν_{max} 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ [(*E*)-**22**] 1.19 (9 H, s, *t*-Bu), 2.18, 2.19 (6 H, 2 s, 2 Me), 3.82 (3 H, s, COOMe), 6.88 (4 H, narrow AB q, STol), 6.83, 7.04 (4 H, AB q, J = 8.2 Hz, Tol); [(*Z*)-**22**] 1.55 (9 H, s, *t*-Bu), 2.18, 2.19 (6 H, 2 s, 2 Me), 3.45 (3 H, s, COOMe) [the aromatic region overlaps that for (*E*)-**22**]; MS, *m*/*z* (relative intensity) 398 (19, M), 325 (14, M-OBu-*t*), 297 (29, M – COOBu-*t*), 294 (21, M – OBu-*t* – OMe), 265 (100, M – HCOOBu-*t* – OMe), 238 (34, M – COOMe – COOBu-*t*), 206 (65, M – Tol – COOBu-*t*), 202 (28, M – STol – OBu-*t*), 175 (45, M – Tol – MeO – COOBu-*t*), 144 (78). Anal. Calcd for $C_{23}H_{26}O_4S$: C, 69.34; H, 6.53; S, 8.04. Found: C, 69.52; H, 6.70; S, 8.41.

(b) When (*Z*)-**21** (470 mg, 1.3 mmol) and sodium *p*-toluenethiolate (220 mg, 1.5 mmol) in MeCN (10 mL) were refluxed for 16 h, the NMR showed that the main compound obtained after workup was the unreacted (*Z*)-**21**.

(c) When (*Z*)-**21** in Me_2SO-d_6 or 1:1 Me_2SO-d_6–$CDCl_3$ was reacted with a slight molar excess of sodium *p*-toluenethiolate in an NMR tube for 2 or 5 min, the only product observed was (*Z*)-**22**. Details are given in Table V.

Reaction of (*E*)-21 with Sodium *p*-Toluenethiolate. (a) To a mixture of (*E*)-**19**/(*Z*)-**19** (42%)–(*E*)-**21** (43%)–(*Z*)-**21** (15%) (120 mg) in DMF (1 mL) was added sodium *p*-toluenethiolate (80 mg, 0.55 mmol), and the solution was stirred for 20 h at room temperature. After workup as above the NMR showed the presence of (*E*)-**19** and (*Z*)-**19**, a few unidentified signals and a 68:32 ratio of (*E*)-**22**/(*Z*)-**22**. On standing, crystals started to separate and on trituration with hexane 30 mg (38%) of a 60:40 (*E*)-**22**/(*Z*)-**22** mixture was obtained.

(b) When (*E*)-**21** in Me_2SO-d_6 or in 1:1 Me_2SO-d_6–$CDCl_3$ was reacted with a slight molar excess of sodium *p*-toluenethiolate for 2 min, the only product observed was (*E*)-**22**. Details are given in Table V.

Reaction of (*Z*)-21 with Sodium *p*-Methylphenolate. To a solution of (*Z*)-**21** (250 mg, 0.7 mmol) in Me_2SO (10 mL) was added sodium *p*-methylphenolate (130 mg, 1 mmol). After 23 h of stirring at room temperature, the green mixture was worked up as usual. The NMR of the crude $CHCl_3$ extract showed 82% of the 1:1 *E*/*Z* substitution product and 18% of (*Z*)-**21**. On crystallization from EtOH or hexane an oil was obtained. Chromatography on silica gel with 1:1 hexane–$CHCl_3$ as eluant gave white crystals of a 1:1 *E*/*Z* mixture of *tert*-butyl methyl [α-(*p*-methylphenoxy)-*p*-methylbenzylidene]malonate [(*E*)-**23** and (*Z*)-**23**] (80 mg, 30%), R_f (1:1 hexane–$CHCl_3$) 0.2. Slow crystallization from hexane gave white crystals of an 85:15 (*E*)-**23**/(*Z*)-**23** mixture, mp 100 °C (40 mg, 15%): UV (EtOH) λ_{max} 278 nm (15 400); IR ($CHCl_3$) ν_{max} 1720 (CO_2Me), 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ [(*E*)-**23**] 1.33 (9 H, s, *t*-Bu), 2.19 (3 H, s, TolO), 2.28 (3 H, s, Tol), 3.75 (3 H, s, COOMe), 6.83, 6.96 (4 H, AB q, *J* = 8.6 Hz, TolO), 7.06, 7.32 (4 H, AB q, *J* = 8.0 Hz, Tol); [(*Z*)-**23**] 1.41 (9 H, s, *t*-Bu), 3.66 (3 H, s, COOMe) [the other signals overlap the analogous signals for (*E*)-**23**]; MS, *m*/*z* (relative intensity) 382 (2, M), 326 (6, M – $Me_2C{=}CH_2$), 281 (42, M – COOBu-*t*), 250 (44, M – COOBu-*t* – MeO), 219 (73), 190 (37, M – COOBu-*t* – Tol), 143 (52, $TolC{\equiv}CCO^+$), 119 (100, $TolCO^+$). Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.25; H, 6.80. Found: C, 72.16; H, 6.85%.

(*E*)- and (*Z*)-*tert*-Butyl Methyl β-Bromo(*p*-nitrobenzylidene)malonate [(*E*)-26 and (*Z*)-26]. (A) *tert*-Butyl Methyl (*p*-Nitrobenzylidene)malonate [(*E*)-24 and (*Z*)-24]. To a solution of *p*-nitrobenzaldehyde (27 g, 0.18 mol) and *tert*-butyl methyl malonate (45 g, 0.26 mol) in dry benzene (150 mL) were added piperidine (2 mL) and AcOH (3 mL), and the mixture was refluxed in a Dean–Stark azeotropic apparatus for 100 h. It was then poured into water (300 mL) and separated, and the organic layer was washed successively with dilute HCl and water, dried ($MgSO_4$), and evaporated. Distillation at 76 °C (5 torr) gave unreacted *tert*-butyl methyl malonate (21 g). Chromatography of the residue on silica gel gave 25 g, of which 20 g were products (45%) together with 5 g of *p*-nitrobenzaldehyde. ^1H NMR shows formation of a 1:1 *E*/*Z* mixture of the olefins. Separation from the aldehyde either by chromatography or by crystallization was difficult and further reactions were conducted with the mixture. Repeated crystallization of a sample from benzene–hexane and ethanol gave pure (*Z*)-*tert*-butyl methyl (*p*-nitrobenzylidene)-malonate (*Z*)-**24** (0.3 g) as a white solid, mp 95 °C: UV (EtOH) λ_{max} 296 nm (18 800); IR ($CHCl_3$) ν_{max} 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ [(*Z*)-**24**] 1.52 (9 H, s, *t*-Bu), 3.88 (3 H, s, COOMe), 7.68 (1 H, s, =CH), 7.67, 8.24 (4 H, AB q, *J* = 8.8 Hz, Ar); MS, *m*/*z* (relative intensity) 251 (68, M – $Me_2C{=}CH_2$), 234 (100, M – OBu-*t*), 220 (20, M – OMe – $CH_2{=}CMe_2$), 219 (42, M – MeOH – $CH_2{=}CMe_2$), 205 (20, M – HCOOBu-*t*), 202 (14, M – MeOH – OBu-*t*), 166 (18%). (*E*)-**24** (admixed with (*Z*)-**24**): ^1H NMR ($CDCl_3$) δ 1.55 (9 H, s, *t*-Bu), 3.84 (3 H, s, COOMe), 7.66 (1 H, s, =CH), 7.58, 8.22 (4 H, AB q, *J* = 8.8 Hz, Ar). Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63, H, 5.54. Found: C, 58.80; H, 5.70.

(B) *tert*-Butyl Methyl (*p*-Nitrobenzylidene)malonate Dibromides (25). To an *E*/*Z* mixture of **24** (25 g, 65 mmol, containing 20% of *p*-nitrobenzaldehyde) in CCl_4 (200 mL) – CH_2Cl_2 (50 mL) was added bromine (6 mL, 0.12 mol). After 2.5 h at room temperature the solution was poured onto water (500 mL), and the organic phase was washed successively with $Na_2S_2O_3$ solution and with water, dried, and evaporated, giving an oil (38 g). ^1H NMR shows the presence of a 1:1 mixture of the *RR* and *RS* dibromides **25**: ^1H NMR ($CDCl_3$) δ 1.40, 1.55, (9 H, s, *t*-Bu), 3.76, 3.91 (3 H, s, COOMe), 5.79, 5.80 (1 H, s, CHBr), 7.80, 7.82, 8.20, 8.22 (4 H, 2 overlapping AB q, Ar). No separation or crystallization was attempted.

(C) *tert*-Butyl Methyl β-Bromo(*p*-nitrobenzylidene)-malonates [(*E*)-26 and (*Z*)-26]. (a) To a solution of the oily dibromide **25** obtained in the reaction above (38 g, ca. 70 mmol) in CH_2Cl_2 (150 mL) were added 2,6-di-*tert*-butyl-4-methylphenol (1 g) and DBN (14 g, 110 mmol) under argon. An exothermic reaction took place, and the solution turned black. After 4.5 h at room temperature the reaction was worked up as described above, and the oil obtained was chromatographed on silica gel using 3:1 hexane–$CHCl_3$ as the eluant. The main fraction (15 g) consisted of a 1:1 (*E*)-**26**/(*Z*)-**26** (admixed with traces of (*E*/*Z*)-**24** and *p*-nitrobenzaldehyde). The second fraction (2 g) contained 65% of a 4:6 (*E*)-**26**/(*Z*)-**26** mixture, and 35% of (*E*/*Z*)-**24**. Crystallization of the first fraction from EtOH gave white crystals (8 g, 35%) of a 1:1 (*E*)-**26**/(*Z*)-**26** mixture.

(b) In a reaction similar to a above, starting with 3.8 g of **25**, without adding 2,6-di-*tert*-butyl-4-methylphenol, a 1:4 mixture of (*E*/*Z*)-**24** and (*E*/*Z*)-**26** (1:1) was obtained. Chromatography on silica gel followed by crystallizations from benzene–hexane gave (*E*)-**26** (0.16 g, 96% isomeric pure), mp 128 °C: UV (EtOH) λ_{max} 277 nm (ε 15 100); IR ($CHCl_3$) ν_{max} 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (9 H, s, *t*-Bu), 3.92 (3 H, s, COOMe), 7.56, 8.26 (4 H, AB q, *J* = 8.6 Hz, Ar); MS, *m*/*z* (relative intensity) 331, 329 (49, 43, M – $CH_2{=}CMe_2$), 315, 313 (46, 46, M – OBu-*t*), 300, 298 (33, 33, M – Me – OBu-*t*), 205 (100, M – Br – CO_2 – $Me_2C{=}CH_2$), 174 (92, M – Br – OMe – COOBu-*t*), 128 (99, M – Br – COOBu-*t* – OMe – NO_2). Anal. Calcd for $C_{15}H_{16}BrNO_6$: C, 46.63; H, 4.14. Found: C, 46.51; H, 4.19.

(c) A 1:1 (*E*)-**26**/(*Z*)-**26** mixture, obtained by method a above (0.6 g) was crystallized from cyclohexane (5 mL). On slow evaporation of the solvent at room temperature, three fractions were obtained: (i) (*E*)-**26** (90% isomerically pure, 0.22 g); (ii) (*Z*)-**26** (91%, admixed with 9% of (*E*)-**26**, 0.1 g), mp 85 °C; (iii) 33:67 (*E*)-**26**/(*Z*)-**26** mixture (0.15 g, obtained by evaporation of the solvent). 91:9 (*Z*)-**26**/(*E*)-**26** mixture: UV (EtOH) λ_{max} 278 nm (ε 13 100); ^1H NMR ($CDCl_3$) δ 1.59 (9 H, s, *t*-Bu), 3.63 (3 H, s, COOMe), 7.54, 8.25 (4 H, AB q, *J* = 8.6 Hz, Ar).

Reaction of 26 with Nucleophiles. (a) With *p*-Toluenethiolate Ion. To a solution of 1:1 (*E*)-**26**/(*Z*)-**26** mixture (0.5 g, 1.3 mmol) in MeCN (20 mL) was added sodium *p*-toluenethiolate (0.25 g, 1.7 mmol). The light yellow solution was heterogeneous, and Me_2SO (10 mL) was added until an orange homogeneous solution was obtained. After the mixture was stirred for 16 h at room temperature and after the usual workup, an oil (0.5 g), which by ^1H NMR consisted of a 6:4 (*E*)-**27**/(*Z*)-**27** mixture, was obtained. Crystallization from EtOH gave a light yellow solid (0.15 g, 27%), mp 137 °C, which by ^1H NMR was 96% (*E*)-*tert*-butyl methyl β-(*p*-tolylthio)-(*p*-nitrobenzylidene)malonate (*E*)-**27** (admixed with 4% (*Z*)-**27**): UV (EtOH) λ_{max} 255 sh nm (ε 16 300), 276 (20 900); IR ($CHCl_3$) ν_{max} 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (9 H, s, COOBu-*t*), 2.19 (3 H, s, Me), 3.88 (3 H, s, COOMe), 6.87, 7.05 (4 H, AB q, *J* = 8.0 Hz, STol), 7.20, 7.95 (4 H, AB q, *J* = 8.6 Hz, *p*-$O_2NC_6H_4$); MS, *m*/*e* (relative intensity) 429 (45, M), 373 (42, M – $Me_2C{=}CH_2$), 329 (80, M – $Me_2C{=}CH_2$ – CO_2), 297 (100, M – COOBu-*t* – OMe), 270 (92, M – $Me_2C{=}CH_2$ – CO_2Me), 224 (31, M – $Me_2C{=}CH_2$ – CO_2 – COOMe – NO_2), 174 (30, M – COOBu-*t* – OMe – STol), 166 (64), 128 (25, M – COOBu-*t* – OMe – STol – NO_2). Anal. Calcd for $C_{22}H_{23}NO_6S$: C, 61.54; H, 5.36. Found: C, 61.70; H, 5.47. (*Z*)-**26** was not obtained in pure form and its ^1H NMR is based on that of a 1:1 (*E*)-**26**/(*Z*)-**26** mixture from which the signals for (*E*)-**26** were subtracted: ($CDCl_3$) δ 1.58 (9 H, s, COOBu-*t*), 2.19 (3 H, s, Me), 3.48 (3 H, s, COOMe), 6.87, 7.05 (4 H, AB q, *J* = 8.0 Hz, STol), 7.19, 7.94 (4 H, AB q, *J* = 8.6 Hz, *p*-$O_2NC_6H_4$).

(b) With *p*-Methylphenolate Ion. To a solution of 1:1 (*E*)-**26**/(*Z*)-**26** mixture (1.1 g, 2.85 mmol) in MeCN (50 mL) was added sodium *p*-methylphenolate (0.59, 3.8 mmol). Addition of Me_2SO (10 mL) to the heterogeneous mixture resulted in the formation of a red homogeneous solution. After the mixture was stirred 16 h at room temperature, followed by the usual workup, an oil (1 g), which was 53:47 (*E*)-**28**/(*Z*)-**28** mixture by ^1H NMR, was formed. Crystallization from EtOH gave (*E*)-*tert*-butyl methyl [α-(*p*-methylphenoxy)-*p*-nitrobenzylidene]malonate [(*E*)-**28**] (96% isomeric pure), mp 127 °C, as a white solid (0.2 g, 17%): UV (EtOH) λ_{max} 235 sh nm (ε 8100), 285 (7800); IR ($CHCl_3$) ν_{max} 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (3 H, s, COOBu-*t*), 2.21 (3 H, s, Me), 3.81 (3 H, s, COOMe), 6.82, 6.97 (4 H, AB q, *J* = 8.8 Hz, OTol), 7.59, 8.14 (4 H, AB q, *J* = 8.8 Hz, *p*-$O_2NC_6H_4$); MS, *m*/*e* (relative intensity) 413 (12, M), 357 (21, M – $Me_2C{=}CH_2$), 340 (37, M – OBu-*t*), 327 (13, M – $Me_2C{=}CH_2$ – NO), 308 (69, M – COOMe – NO_2), 296 (17), 281 (20), 262 (10), 250 (49, M – $Me_2C{=}CH_2$ – OTol), 206 (10, M – $Me_2C{=}CH_2$ – Tol – CO_2), 190 (27, M – COOBu-*t* – OMe – Tol), 174 (49, M – CO_2Bu-*t* – OMe – OTol), 150 (100, *p*-$O_2NC_6H_4CO^+$), 128 (41, M – COOBu-*t* – OMe – OTol – NO_2). Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.57.

Found: C, 63.70; H, 5.49. (*Z*)-**28** was not obtained in a pure form and its ^{1}H NMR spectrum was extracted from that of a 1:1 (*E*)-**28**/(*Z*)-**28** mixture: ($CDCl_3$) δ 1.46 (9 H, s, COOBu-*t*), 2.21 (3 H, s, Me), 3.68 (3 H, s, COOMe), 6.82, 6.97 (4 H, AB q, J = 8.8 Hz, OTol), 7.58, 8.14 (4 H, AB q, J = 8.8 Hz, *p*-$O_2NC_6H_4$).

Acknowledgment. We are indebted to Dr. S. Cohen for the X-ray diffractions, and to the Israel Commission for Basic Research, The Israel Academy for Sciences and Humanities, who supported this work.

Supplementary Material Available: Tables S1–S16 giving the crystallographic data (bond lengths and angles, positional and thermal parameters) for (*E*)-**6**, (*Z*)-**19**, (*RR*)-**20**, and (*E*)-**21** and Figures S1–S4 giving their stereoscopic views (20 pages). Ordering information is given on current masthead page.

A New Synthesis of Indoles by Electrocyclic Ring Closure of Dialkenylpyrroles. Synthesis of Alkenylpyrroles from 1-Tosylalkenyl Isocyanides and Michael Acceptors[1]

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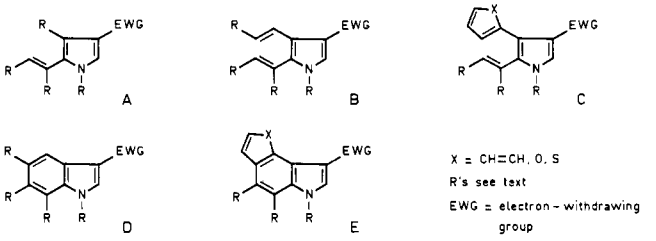
Received April 21, 1986

Addition of allylic anions derived from 1-tosylalk-1-enyl isocyanides **1** to Michael acceptors, in combination with ring closure to the isocyano carbon, provides a highly efficient synthesis of 2-alk-1′-enylpyrroles (types A–C). A proper selection of Michael acceptors permits the introduction of additional alkenyl or aryl substituents at C-3 and/or C-4 of the pyrrole ring (types B and C). Thermal or photochemical electrocyclization of 2,3-dialk-1′-enylpyrroles B, followed by dehydrogenation (DDQ), gives indoles D in excellent yields. Photochemical electrocyclization of 2-alk-1′-enyl-3-arylpyrroles C, together with dehydrogenation, provides an important extension of this synthesis to fused indole derivatives E.

The indole ring system constitutes the characteristic core of a great number of natural products, among which are the well-known indole alkaloids.[2] Thus, a new method to construct the indole ring may well be of advantage to the art of natural product synthesis. It is the purpose of this paper to describe an attractive new indole synthesis that is the result of two achievements: (1) a highly efficient new synthesis of monoalk-1′-enyl- and dialk-1′-enylpyrroles (types A–C; eq 1, Table I) and (2) an equally efficient electrocyclic ring closure of 2,3-dialk-1′-enylpyrroles (types B and C), followed by aromatization to the desired indoles (D and E; eqs 2 and 3, Tables II and III, respectively).

Indoles have been synthesized almost exclusively by constructing the pyrrole ring on to a benzene nucleus. Several classical methods are available to serve this purpose (Fischer, Madelung, and Reissert indole syntheses and the like).[3] The alternative of building a benzene ring on to a pyrrole has hardly been employed.[4] An obvious and potentially simple indole synthesis of this type would consist in the electrocyclization of pyrrole derivatives of type B and C, followed by dehydrogenation. This approach to indoles, however, has never been realized. The reason for this, evidently, is the lack of a good synthesis of the precursor pyrroles B and C.

Pyrroles with alk-1-enyl substitutents at the pyrrole ring carbons are uncommon among the large variety of known pyrrole derivatives.[5] Such alkenylpyrroles have been obtained from pyrrolecarboxaldehydes by Knoevenagel-type condensations.[6] Occasionally, other methods have been used, such as Wittig reactions[4a,b,7] or catalytic dehydrogenation of alkylpyrroles.[8] However, these methods are of limited scope, partly because the starting materials are not always easy to obtain. Anyhow, pyrroles of type B and C with two unsaturated substituents (at C-2 and C-3) have not been reported previously.



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