Substituted benzaldehydes in the Darzens condensation with alkyl dihaloacetates

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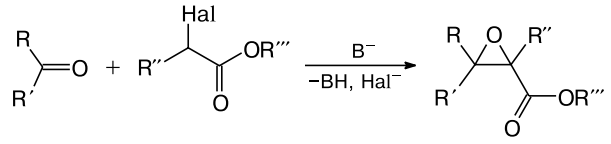
The Darzens reaction of dihaloacetic acid esters with aromatic aldehydes produces either arylhaloglycidic or arylhalopyruvic esters depending on the nature of the substituent in the aromatic ring. Alkyl *p*-methoxyphenylchloropyruvates undergo spontaneous intermolecular cyclocondensation to form pyranone or furanone derivatives depending on the character of the alkyl fragment.

Key words: Darzens reaction, benzaldehydes, dihaloacetic acids, epoxides, glycidic acids, pyruvic acids, pyran-2,3-diones, furan-2-ones, X-ray diffraction study.

The Darzens reaction consists in condensation of aldehydes or ketones with α-halocarboxylic acid esters in the presence of bases to give glycidic esters[1,2] (Scheme 1).

Scheme 1



The classical Darzens reaction has attracted interest because it is widely used in the synthesis of numerous biologically active natural compounds, including vitamin A,[3] highly selective leukotriene receptor antagonists,[4—6] the mosquito pheromone,[7] the active component of the antibiotics Virginiamycin M [8] and Roflamycoin[9], amastatin,[10] *N*-substituted L-homophenylalanine,[11] thiam- (R = OH)[12] and fluorophenicol (R = F),[13] gemcitabine,[14] the C-13 side chain of Taxol,[15] a calcium channel blocker of dilthiazem,[16] *etc.*[17]

The synthesis with the use of esters of α,α-dihalo derivatives instead of α-haloacetic esters would be expected to give reactive haloglycidates, thus substantially extending the scope of this reaction. The reaction can be directed to the formation of not only α,α-dihalohydrins,[18—23] α-haloepoxides,[24—26] and α-haloketones[21,22,24,27] but also products, which are not typical of the Darzens reaction,[28—33] by varying the nature of the substituents in aldehyde, a base, and a halogen, as well as the reaction conditions.

Earlier,[26] the fact that the structure of the products depends on the nature of the substituent in the aromatic ring has been exemplified by the reactions of methyl dichloroacetate with various benzaldehydes. The reactions of unsubstituted benzaldehyde and its 4-chloro and 4-bromo derivatives produce methyl arylchloropyruvates, whereas the reaction with *p*-nitrobenzaldehyde stops at the step of formation of intermediate methyl arylchloroglycidate. These results require a more detailed investigation of the factors influencing the reaction pathway.

In the present study, we examined reactions of a broad range of aromatic aldehydes (**1**) containing electron-withdrawing and electron-donating substituents with dihaloacetic esters (**2a—d**) under different conditions (Scheme 2, Table 1). Compounds **3b—g,n—q,v,w** and **4h—m,r,s** were produced in minor amounts and were not isolated.

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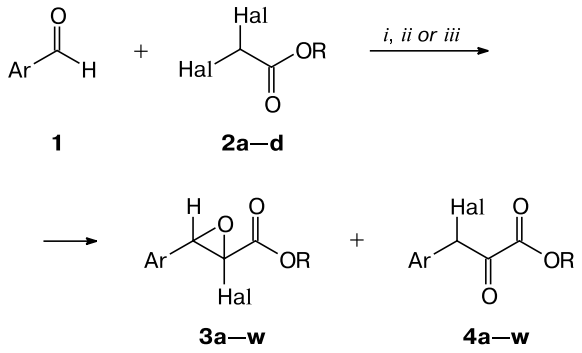
Scheme 2



2	Hal	R	**2**	Hal	R
a	Cl	Me	**c**	Br	Et
b	Cl	Bu^t	**d**	Br	Me

3, **4**	Ar	R	Hal	**3**, **4**	Ar	R	Hal
a	Ph	Me	Cl	**m**	4-$NO_2C_6H_4$	Me	Br
b	Ph	Bu^t	Cl	**n**	2-$MeOC_6H_4$	Bu^t	Cl
c	Ph	Et	Br	**o**	3-$MeOC_6H_4$	Bu^t	Cl
d	2-$C_{10}H_7$	Me	Cl	**p**	4-$MeOC_6H_4$	Bu^t	Cl
e	2-MeC_6H_4	Me	Cl	**q**	4-$MeOC_6H_4$	Me	Cl
f	3-MeC_6H_4	Me	Cl	**r**	2-ClC_6H_4	Me	Cl
g	4-MeC_6H_4	Me	Cl	**s**	3-ClC_6H_4	Me	Cl
h	3-$NO_2C_6H_4$	Me	Cl	**t**	4-ClC_6H_4	Me	Cl
i	3-$NO_2C_6H_4$	Et	Br	**u**	4-BrC_6H_4	Me	Cl
j	4-$NO_2C_6H_4$	Me	Cl	**v**	4-BrC_6H_4	Et	Br
k	4-$NO_2C_6H_4$	Bu^t	Cl	**w**	2,4-$Cl_2C_6H_3$	Et	Br
l	4-$NO_2C_6H_4$	Et	Br				

Reagents and conditions: *i*. NaOMe, THF, −80→20 °C; *ii*. Bu^tOK, THF, −80→20 °C; *iii*. Bu^tOK, toluene, −40→20 °C.

As can be seen from Table 1, the reactions of benzaldehydes **1** containing electron-withdrawing substituents afford the corresponding haloglycidates **3**, whereas intermediate haloglycidates **3** produced in the reactions with benzaldehydes **1** containing electron-donating substituents, unsubstituted benzaldehyde, or naphthyl-2-aldehyde are isomerized to give halopyruvates **4**.

A comparison of the reaction times (see the Experimental section) of thermal isomerization of chloroglycidates **3** (in boiling benzene) giving rise to chloropyruvates **4** shows that stability of these chloroglycidates changes depending on the nature of the substituents in the aromatic ring in the following series: 4-NO_2 > > 3-NO_2 ≫ Cl, Br, H.

The ratio of isomers **3** and **4** depends also on the amount of the base use. As can be seen from Table 2, an increase in the amount of Bu^tOK used in the reaction leads to an increase in the percentage of chloroglycidate **3** in the mixture. This can be associated with the fact that chloride anions, which apparently initiate this isomerization, are more rapidly removed from the reaction medium (Scheme 3).

The influence of chloride anions is evidenced by the fact that the reaction of methyl dichloroacetate **2a** with benzaldehyde in the presence of equimolar amounts of Bu^tOK and $AgNO_3$ (the latter serves as a scavenger for chloride anions) produces exclusively chloroglycidate **3a**.

This is additionally confirmed by the fact that the reaction of chloroglycidate **3k** with an equimolar amount of magnesium bromide produces bromopyruvate **4l** in quantitative yield (Scheme 4). Bromopyruvate **4l** was also prepared by thermal isomerization of bromoglycidate **3l**.

Therefore, the ratio of haloglycidates **3** to halopyruvates **4** can be controlled by varying the reaction

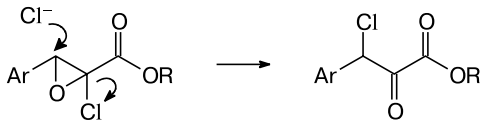
Table 1. Reaction products of aromatic aldehydes **1** with dihaloacetic esters **2a—c**

Product	Ester **2**	Method	Yield (%)
3h	**a**	*ii*	58
3i	**c**	*iii*	86
3j	**a**	*ii*	84
3k	**b**	*ii*	94
3l	**c**	*iii*	58
3m	**d**	*iii*	64
3r	**a**	*ii*	89
3s	**a**	*ii*	87
4a	**a**	*i*	81
		ii	96
4b	**b**	*ii*	77
4c	**c**	*iii*	70
4d	**a**	*ii*	79
4e	**a**	*ii*	89
4f	**a**	*ii*	62
4g	**a**	*ii*	97
4n	**b**	*ii*	84
4o	**b**	*ii*	65
4p	**b**	*ii*	78
4q	**a**	*ii*	88
4t	**a**	*ii*	55
4u	**a**	*ii*	83
4v	**c**	*iii*	72
4w	**c**	*iii*	56

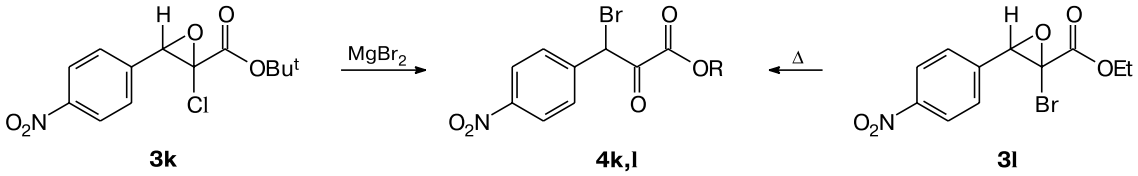
Table 2. Influence of the amount of Bu^tOK used in the reaction on the ratio of chloroglycidate **3a** to chloroketone **4a** (^1H NMR)

Amount of Bu^tOK (equiv.)	**3a** : **4a**	Total yield (%)
1.0	18 : 82	81
2.0	47 : 53	79
3.0	65 : 35	84

Scheme 3



Scheme 4



conditions and controlling primarily the percentage of halide ions in the reaction mixture. The ease of isomerization **3** → **4** is determined by the reactivity of the C(3) atom in glycidate, which decreases in the presence of electron-withdrawing substituents in the aryl moiety and increases in the presence of electron-donating substituents.

It is worthy of note that the formation of haloglycidates **3** is stereoselective and the reaction affords only one of two possible isomers. X-ray diffraction study of compounds **3j**,**l**,**m** (Figs 1—3) showed that haloglycidates adopt a *Z* configuration. It should be noted that the reactions of

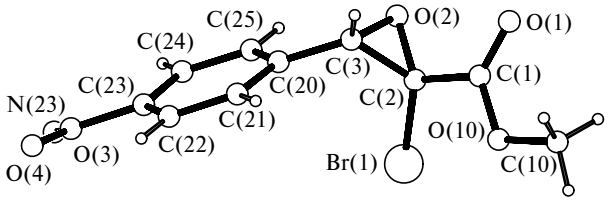


Fig. 1. Molecular structure of bromoepoxide **3m** in crystals.

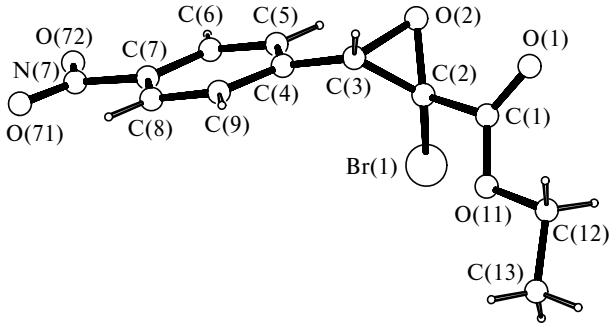


Fig. 2. Molecular structure of bromoepoxide **3l** in crystals.

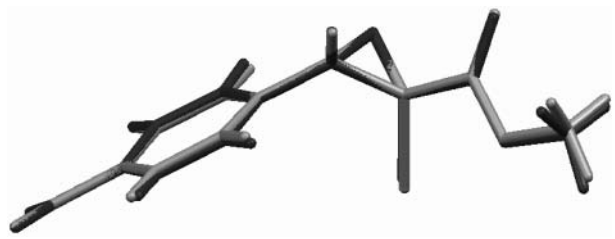


Fig. 3. Arbitrary superposition of the molecules of chloroepoxide **3j** (dark gray) and bromoepoxide **3m** (pale gray).

nitrobenzaldehydes with (+)- and (−)-menthyl dichloroacetates, which we have performed earlier,[34,35] also produced individual *Z* isomers.

Chloroepoxide **3j** (see Ref. 34) and bromoepoxide **3m** form isostructural crystals with similar unit cell parameters and, consequently, these compounds have similar molecular structures (see Fig. 3), crystal packings, and systems of intermolecular contacts. In particular, the dihedral angle between the benzene ring and the plane of the epoxide ring in molecules **3j** and **3m** is 63.4(4) and 62.6(2)°, respectively.

Compounds **3j**,[34] **3l**, and **3m** form monoclinic centrosymmetric crystals containing one molecule per asymmetric unit. In the molecules of all three compounds, the chiral C(2) and C(3) atoms have the same configuration (*R*,*R* or *S*,*S*). In chloroepoxide **3j** and bromoepoxide **3m**, the plane of the nitro group is twisted with respect to the plane of the benzene ring by approximately 16°, whereas this fragment in molecule **3l** is flattened.

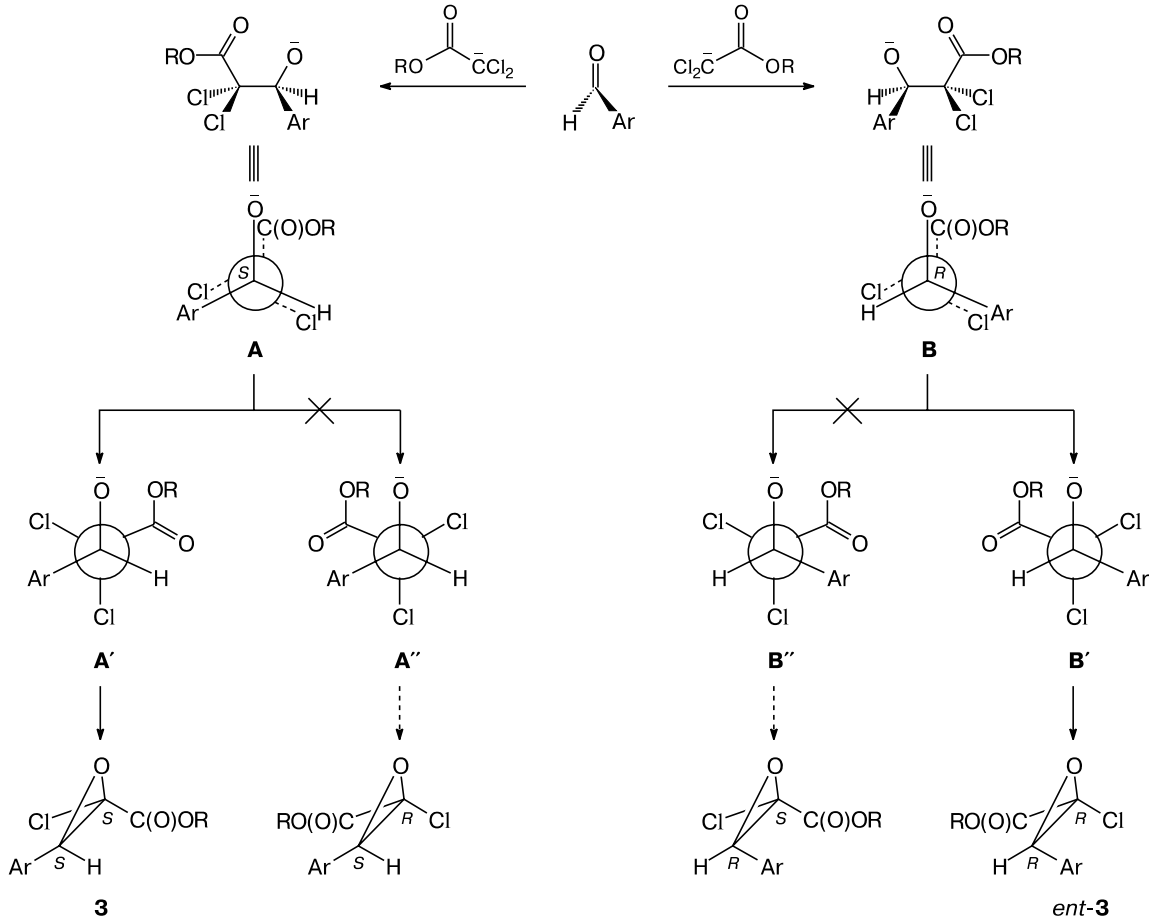
The formation of haloglycidates (**3** and *ent*-**3**) exclusively with the *Z* geometry can be explained with Scheme 5. Intramolecular cyclization of two enantiomeric oxy anions **A** and **B**, which are generated through the attack of the dichloroacetate anion on the *si* and *re* sides of the aldehyde group, respectively, occurs apparently through the sterically more favorable conformers **A′** and **B′** rather than through **A″** and **B″**.

Halopyruvates **4p** and **4q**, unlike other analogs of this series, are unstable. For example, spectrally pure chloropyruvate **4q** undergoes intermolecular cyclocondensation at ~20 °C for 1 day to form pyran-2,3-dione derivative **5**,* whereas on attempted vacuum distillation, chloropyruvate **4p** (brief heating to 100 °C) was converted into furan-2-one **6** (Scheme 6).

The $^{13}C\{^1H\}$ and ^{13}C NMR spectra of compound **5** are characterized by the presence of ten signals of two nonequivalent 4-methoxycarbonyl fragments, two signals of the methoxycarbonyl group, two signals of the carbonyl groups of the pyran ring, one signal for the quaternary

* Upon prolonged storage, pyrandione **5** undergoes partial transformation apparently into isomeric 4-chloro-6-methoxycarbonyl-4,5-di(4-methoxyphenyl)-3,4-dihydro-2*H*-pyran-2,3-dione, which was confirmed by the fact that the ^1H NMR spectrum shows closely positioned signals, whose multiplicities and integrate intensities are analogous to those observed for compound **5**.

Scheme 5



sp^3-hybridized carbon atom, and two signals for the sp^2-hybridized carbon atoms.

The structure of lactone **6** was established by X-ray diffraction (Fig. 4).

The furan ring in molecule **6** is planar within 0.001(1) Å. The dihedral angles between the planes of the furan ring and two benzene rings C(30)—C(35) and C(40)—C(45) are 66.9(1) and 16.9(2)°, respectively. The methoxy groups lie in the planes of the benzene rings (the C(36)—O(33)—C(33)—C(32) and C(46)—O(43)—C(43)—C(42) torsion angles are 179.9(3) and −178.5(2)°, respectively). In the crystals, the molecules are linked to each other only by weak C—H...O, C—H...π, and π...π interactions.

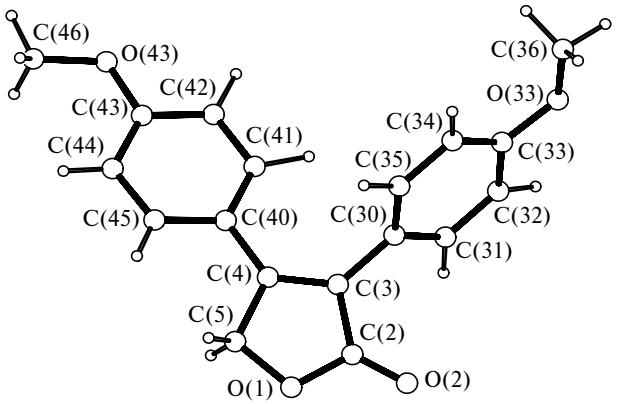
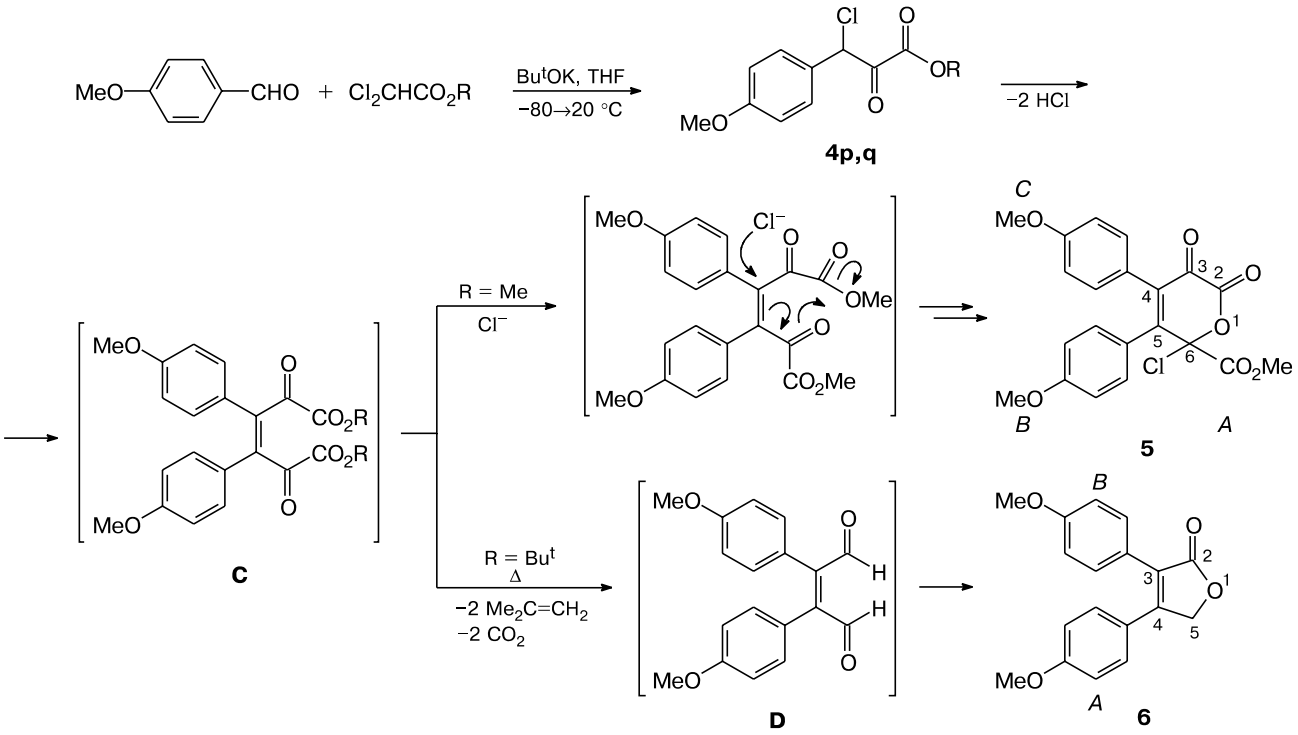


Fig. 4. Molecular structure of lactone **6** in crystals.

The first step of the formation of products **5** and **6** apparently involves dimerizative dehydrohalogenation giving rise to the intermediate compound **C**. The reaction of compound containing R = Me involves the addition of the Cl^- anion followed by cyclization to form pyrandione **5**. In the case of R = Bu^t, the intermediate **C**, like other *tert*-butyl esters,[36,37] is transformed into 1,4-dialdehyde **D** through elimination of isobutylene and decarboxylation, and the Cannizzaro-type redox disproportionation of this 1,4-dialdehyde affords lactone **6**.

To summarize, we demonstrated that the pathway of the Darzens reaction of aromatic aldehydes with dihaloacetic esters depends on the structures of the starting compounds. It should be noted that 4-methoxybenzaldehyde

Scheme 6



exhibits unusual behavior and gives products, which are not typical of the Darzens reaction.

Experimental

The melting points were determined on a Boetius heating stage. The IR spectra were recorded on JASCO FT/IR-5000 or Vector-22 (Bruker) Fourier-transform spectrophotometers in KBr pellets. The ^{1}H NMR spectra were measured on Varian Gemini-200 (200.057 MHz), JEOL AL-300 (300.13 MHz), Bruker MSL-400 ^{1}H (400.13 MHz), and Bruker AVANCE-600 (600.00 MHz) spectrometers. The chemical shifts are given on the δ scale and were experimentally measured relative to the signals of the solvents.

All solvents were dried before use according to known procedures.[38] The reactions were carried out under nitrogen. Column chromatography was performed on silica gel 60N (Merck). Methyl dichloroacetate and methyl dibromoacetate were prepared from chloral[39] and bromal,[40] respectively, according to known procedures. Ethyl dibromoacetate (Acros Organics) and potassium *tert*-butoxide (Lancaster) were used.

***tert*-Butyl dichloroacetate (2b).** Dichloroacetyl chloride (88.4 g, 0.60 mol) was added dropwise to a solution of Bu^{t}OH (44.4 g, 0.60 mol) and pyridine (47.4 g, 0.60 mol) in THF (500 mL) at −20 °C, and the reaction mixture was stirred at this temperature for 8 h. After evaporation of the solvent, the reaction mixture was treated with water and extracted with EtOAc (3×50 mL). The combined organic layers were washed with a 25% aqueous NaCl solution and concentrated. After vacuum distillation, compound **2b** was obtained in a yield of 112 g (85%) as a colorless liquid, b.p. 65—67 °C (15 Torr) (*cf.* lit. data[41]: b.p. 54—55 °C (8 Torr)). Found (%): C, 38.89; H, 5.58. $C_6H_{10}Cl_2O_2$. Calculated (%): C, 38.94; H, 5.45. IR, ν/cm^{-1}: 2986, 1758, 1373, 1307, 1147, 851. ^{1}H NMR ($CDCl_3$), δ: 1.51 (s, 9 H, OCBu^t); 5.80 (s, 1 H, $CHCl_2$).

Darzens condensation of aromatic aldehydes 1 with dihaloacetates 2 (general procedure). Potassium *tert*-butoxide (1.12 g, 10 mmol) was added to a solution of the corresponding dihaloacetate (10 mmol) and arylaldehyde (10 mmol) in a dry solvent (20—25 mL) at −(40—80) °C (for the solvent, see Scheme 2 and Table 1). The reaction mixture was stirred at this temperature for 3 h and then kept at ~20 °C for ~14 h. After removal of the solvent *in vacuo*, the residue was treated with a 25% aqueous NaCl solution and extracted with toluene (3×50 mL). The combined organic extracts were dried with $MgSO_4$. After removal of the solvent, esters of 3-aryl-2-halo-2,3-epoxypropionic acid derivatives **3** or esters of 3-aryl-3-halo-2-oxopropionic acid derivatives **4** were obtained.

Methyl 3-chloro-2-oxo-3-phenylpropionate (4a), a yellow oil. IR, ν/cm^{-1}: 1740, 1458, 1247, 1064, 702. ^{1}H NMR ($CDCl_3$), δ: 3.84 (s, 3 H, OMe); 6.23 (s, 1 H, CH); 7.32—7.38 (m, 5 H, Ph).

***tert*-Butyl 3-chloro-2-oxo-3-phenylpropionate (4b)**, a yellow oil. Found (%): C, 61.33; H, 5.99. $C_{13}H_{15}ClO_3$. Calculated (%): C, 61.30; H, 5.94. IR, ν/cm^{-1}: 2984, 1748, 1725, 1458, 1398, 1373, 1257, 1158, 1060, 932, 837, 696. ^{1}H NMR ($CDCl_3$), δ: 1.42 (s, 9 H, OCBu^t); 6.06 (s, 1 H, CH); 7.39 (m, 5 H, Ar).

Ethyl 3-bromo-2-oxo-3-phenylpropionate (4c), a yellow oil. Found (%): C, 48.70; H, 4.11; Br, 29.63. $C_{11}H_{11}BrO_3$. Calculated (%): C, 48.73; H, 4.09; Br, 29.47. IR, ν/cm^{-1}: 1730, 1590, 1489, 1438, 1247, 1061, 1013, 864, 820, 756. ^{1}H NMR ($CDCl_3$), δ: 1.19 (t, 3 H, $OCH_2C\underline{H}_3$, J = 6.9 Hz); 4.19 (q,

2 H, OC<u>H</u>$_2$CH$_3$, J = 6.9 Hz); 6.17 (s, 1 H, CH); 7.26—7.37 (m, 5 H, Ph).

Methyl 3-chloro-3-(naphth-2-yl)-2-oxopropionate (4d), a yellow oil. Found (%): C, 64.32; H, 4.58. $C_{14}H_{11}ClO_3$. Calculated (%): C, 64.01; H, 4.22. IR, ν/cm^{-1}: 1740, 1458, 1247, 1064, 702. ^{1}H NMR ($CDCl_3$), δ: 3.75 (s, 3 H, OMe); 6.91 (s, 1 H, CH); 7.43—8.13 (m, 7 H, Ar).

Methyl 3-chloro-3-(2-methylphenyl)-2-oxopropionate (4e), a yellow oil. Found (%): C, 58.34; H, 4.76. $C_{11}H_{11}ClO_3$. Calculated (%): C, 58.29; H, 4.89. IR, ν/cm^{-1}: 2960, 1742, 1543, 1419, 1439, 1310, 1249, 913, 861, 698. ^{1}H NMR ($CDCl_3$), δ: 2.49 (s, 3 H, Me); 3.75 (s, 3 H, OMe); 6.91 (s, 1 H, CH); 7.12—7.21 (m, 4 H, Ar).

Methyl 3-chloro-3-(3-methylphenyl)-2-oxopropionate (4f), a yellow oil. Found (%): C, 58.24; H, 4.79. $C_{11}H_{11}ClO_3$. Calculated (%): C, 58.29; H, 4.89. IR, ν/cm^{-1}: 2960, 1823, 1744, 1609, 1491, 1437, 1249, 1160, 859, 706. ^{1}H NMR ($CDCl_3$), δ: 2.38 (s, 3 H, Me); 3.83 (s, 3 H, OMe); 6.13 (s, 1 H, CH); 7.17—7.34 (m, 4 H, Ar).

Methyl 3-chloro-3-(4-methylphenyl)-2-oxopropionate (4g), white crystals, m.p. 56 °C. Found (%): C, 58.25; H, 4.73. $C_{11}H_{11}ClO_3$. Calculated (%): C, 58.29; H, 4.89. IR, ν/cm^{-1}: 2960, 1742, 1613, 1514, 1437, 1249, 1064, 864, 816, 795, 706. ^{1}H NMR ($CDCl_3$), δ: 2.36 (s, 3 H, Me); 3.87 (s, 3 H, OMe); 6.14 (s, 1 H, CH); 7.17 and 7.29 (both d, 2 H each, Ar, J = 8.0 Hz).

***tert*-Butyl 3-chloro-3-(2-methoxyphenyl)-2-oxopropionate (4n)**, a yellow oil. Found (%): C, 58.79; H, 6.01. $C_{14}H_{17}ClO_4$. Calculated (%): C, 59.05; H, 6.02. IR, ν/cm^{-1}: 2982, 1719, 1688, 1489, 1468, 1290, 1249, 1162, 1025, 835, 758. ^{1}H NMR ($CDCl_3$), δ: 1.35 (s, 9 H, OCBu^t); 3.84 (s, 3 H, OMe); 6.27 (s, 1 H, CH); 6.92 (dd, 2 H, Ar, J = 7.70 Hz, J = 8.8 Hz); 6.99 (dd, 1 H, Ar, J = 7.6 Hz, J = 8.8 Hz); 7.30 (d, 1 H, Ar, J = 7.6 Hz); 7.83 (d, 1 H, Ar, J = 7.7 Hz).

***tert*-Butyl 3-chloro-3-(3-methoxyphenyl)-2-oxopropionate (4o)**, a yellow oil. Found (%): C, 58.91; H, 5.97. $C_{14}H_{17}ClO_4$. Calculated (%): C, 59.05; H, 6.02. IR, ν/cm^{-1}: 2982, 1736, 1603, 1493, 1460, 1263, 1156, 1052, 837. ^{1}H NMR ($CDCl_3$), δ: 1.58 (s, 9 H, OCBu^t); 3.82 (s, 3 H, OMe); 6.03 (s, 1 H, CH); 6.90—7.18 and 7.39—7.47 (both m, 2 H each, Ar).

***tert*-Butyl 3-chloro-3-(4-methoxyphenyl)-2-oxopropionate (4p)**, a yellow oil. Found (%): C, 59.06; H, 6.02. $C_{14}H_{17}ClO_4$. Calculated (%): C, 59.05; H, 6.02. IR, ν/cm^{-1}: 2984, 1750, 1609, 1580, 1462, 1259, 1160, 1060, 1033, 835. ^{1}H NMR ($CDCl_3$), δ: 1.43 (s, 9 H, OCBu^t); 3.89 (s, 3 H, OMe); 6.05 (s, 1 H, CH); 6.89 and 7.30 (both d, 2 H each, Ar, J = 8.8 Hz).

Methyl 3-chloro-3-(4-methoxyphenyl)-2-oxopropionate (4q), a yellow oil. Found (%): C, 54.42; H, 4.43. $C_{11}H_{11}ClO_4$. Calculated (%): C, 54.59; H, 4.54. IR, ν/cm^{-1}: 2962, 1742, 1609, 1514, 1441, 1259, 1170, 1033, 696. ^{1}H NMR ($CDCl_3$), δ: 3.81 and 3.84 (both s, 3 H each, OMe); 6.15 (s, 1 H, CH); 6.91 and 7.32 (both d, 2 H each, Ar, J = 9.0 Hz).

Methyl 3-chloro-3-(4-chlorophenyl)-2-oxopropionate (4t), a yellow oil. Found (%): C, 48.29; H, 3.65. $C_{10}H_8Cl_2O_3$. Calculated (%): C, 48.61; H, 3.26. IR, ν/cm^{-1}: 1740, 1591, 1491, 1439, 1247, 1062, 861, 820, 756. ^{1}H NMR ($CDCl_3$), δ: 3.86 (s, 3 H, OMe); 6.13 (s, 1 H, CH); 7.36—7.38 (m, 4 H, Ar).

Methyl 3-(4-bromophenyl)-3-chloro-2-oxopropionate (4u), a yellow oil. Found (%): C, 41.24; H, 2.79. $C_{10}H_8BrClO_3$. Calculated (%): C, 41.20; H, 2.77. IR, ν/cm^{-1}: 1740, 1591, 1491, 1439, 1247, 1062, 1013, 861, 820, 756. ^{1}H NMR ($CDCl_3$), δ: 3.57 (s, 3 H, OMe); 4.29 (s, 1 H, CH); 6.88—6.91 and 8.25—8.32 (both m, 2 H each, Ar).

Ethyl 3-bromo-3-(4-bromophenyl)-2-oxopropionate (4v), a yellow oil. Found (%): C, 37.69; H, 2.92; Br, 46.01. $C_{11}H_{10}Br_2O_3$. Calculated (%): C, 37.75; H, 2.88; Br, 45.66. IR, ν/cm^{-1}: 1740, 1591, 1491, 1439, 1247, 1062, 1013, 861, 820, 756. ^{1}H NMR ($CDCl_3$), δ: 1.25 (t, 3 H, OCH$_2$C<u>H</u>$_3$, J = 7.2 Hz); 4.22 (q, 2 H, OC<u>H</u>$_2$CH$_3$, J = 7.2 Hz); 6.09 (s, 1 H, CH); 7.25 and 7.42 (both d, 2 H each, Ar, J = 8.2 Hz).

Ethyl 3-bromo-3-(2,4-dichlorophenyl)-2-oxopropionate (4w), a yellow oil. Found (%): C, 38.63; H, 2.70; Br, 23.54; Cl, 21.00. $C_{11}H_9BrCl_2O_3$. Calculated (%): C, 38.86; H, 2.67; Br, 23.50; Cl, 20.85. IR, ν/cm^{-1}: 2945, 1752, 1696, 1595, 1477, 1449, 1247, 1072, 940, 853. ^{1}H NMR ($CDCl_3$), δ: 1.35 (t, 3 H, OCH$_2$C<u>H</u>$_3$, J = 4.9 Hz); 4.22 (q, 2 H, OC<u>H</u>$_2$CH$_3$, J = 4.9 Hz); 6.57 (s, 1 H, CH); 7.24 (d, 1 H, Ar, J = 5.6 Hz); 7.35 (s, 1 H, Ar); 7.44 (d, 1 H, Ar, J = 5.6 Hz).

Methyl 2-chloro-3-phenyl-2,3-epoxypropionate (3a) was detected in a mixture with compound **4a**, which was prepared by the reaction of methyl dichloroacetate (**2a**) with benzaldehyde in the presence of Bu^{t}OK (see Table 2). ^{1}H NMR, characteristic signals (δ): 3.93 (s, 3 H); 4.35 (s, 1 H).

Methyl 2-chloro-3-(3-nitrophenyl)-2,3-epoxypropionate (3h), a yellow oil. Found (%): C, 46.47; H, 3.05; N, 5.54. $C_{10}H_8ClNO_5$. Calculated (%): C, 46.62; H, 3.13; N, 5.54. IR, ν/cm^{-1}: 1752, 1606, 1514, 1350, 1282, 1253, 1013, 930, 878, 784, 731. ^{1}H NMR ($CDCl_3$), δ: 3.95 (s, 3 H, OMe); 4.61 (s, 1 H, CH); 7.73 (dd, 1 H, Ar, J = 8.5 Hz, J = 8.5 Hz); 7.81 and 8.25 (both d, 1 H each, Ar, J = 8.5 Hz); 8.72 (s, 1 H, Ar).

Ethyl 2-bromo-3-(3-nitrophenyl)-2,3-epoxypropionate (3i), a yellow oil. Found (%): C, 41.63; H, 3.12; Br, 25.48; N, 4.40. $C_{11}H_{10}BrNO_5$. Calculated (%): C, 41.80; H, 3.19; Br, 25.28; N, 4.43. IR, ν/cm^{-1}: 3116, 3083, 1747, 1707, 1609, 1473, 1320, 1276, 1243, 1198, 1109, 1027, 1016, 948, 882, 865, 835, 778, 695, 525. ^{1}H NMR ($CDCl_3$), δ: 1.27 (t, 3 H, OCH$_2$C<u>H</u>$_3$, J = 4.5 Hz); 4.36 (q, 2 H, OC<u>H</u>$_2$CH$_3$, J = 4.5 Hz); 4.44 (s, 1 H, CH); 7.52 (dd, 1 H, Ar, J = 5.2 Hz, J = 5.6 Hz); 7.75 (d, 1 H, Ar, J = 5.2 Hz); 8.11 (d, 1 H, Ar, J = 5.6 Hz); 8.25 (s, 1 H, Ar).

Methyl 2-chloro-3-(4-nitrophenyl)-2,3-epoxypropionate (3j), yellow crystals, m.p. 102 °C. Found (%): C, 46.51; H, 3.05; N, 5.68. $C_{10}H_8ClNO_5$. Calculated (%): C, 46.62; H, 3.13; N, 5.54. IR, ν/cm^{-1}: 1752, 1607, 1522, 1437, 1350, 1282, 1253, 1013, 930, 784, 731. ^{1}H NMR ($CDCl_3$), δ: 3.57 (s, 3 H, OMe); 4.29 (s, 1 H, CH); 6.88—6.91 and 8.25—8.32 (both m, 2 H each, Ar).

***tert*-Butyl 2-chloro-3-(4-nitrophenyl)-2,3-epoxypropionate (3k)**, yellow crystals, m.p. 60—62 °C. Found (%): C, 52.24; H, 4.75; Cl, 11.88; N, 4.52. $C_{13}H_{14}ClNO_5$. Calculated (%): C, 52.10; H, 4.71; Cl, 11.83; N, 4.67. IR, ν/cm^{-1}: 1740, 1611, 1524, 1460, 1427, 1394, 1377, 1350, 1315, 1251, 1201, 1156, 1100, 1007, 878, 784, 961. ^{1}H NMR ($CDCl_3$), δ: 1.56 (s, 9 H, OCBu^t); 4.53 (s, 1 H, CH); 7.57 and 8.26 (both d, 2 H each, Ar, J = 8.8 Hz). ^{13}C NMR, δ: 27.74, 61.90, 85.47, 123.36, 128.46, 138.41, 148.14, 148.42, 162.67.

Ethyl 2-bromo-3-(4-nitrophenyl)-2,3-epoxypropionate (3l), yellow crystals. Found (%): C, 41.62; H, 3.22; Br, 25.36; N, 4.21. $C_{11}H_{10}BrNO_5$. Calculated (%): C, 41.80; H, 3.19; Br, 25.28; N, 4.43. IR, ν/cm^{-1}: 3116, 3083, 1747, 1707, 1609, 1473, 1320, 1276, 1243, 1198, 1109, 1027, 1016, 948, 882, 865, 835, 778, 695, 525. ^{1}H NMR ($CDCl_3$), δ: 1.38 (t, 3 H, OCH$_2$C<u>H</u>$_3$, J =

7.2 Hz); 4.37 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.48 (s, 1 H, CH); 7.56 and 8.27 (both d, 2 H each, Ar, J = 8.6 Hz).

Methyl 2-bromo-3-(4-nitrophenyl)-2,3-epoxypropionate (3m), yellow crystals. Found (%): C, 39.60; H, 2.62; Br, 26.56; N, 4.68. $C_{10}H_8BrNO_5$. Calculated (%): C, 39.73; H, 2.64; Br, 26.49; N, 4.63. IR, ν/cm^{-1}: 1748, 1608, 1525, 1446, 1342, 1280, 1249, 1185, 1011, 942, 866, 780, 730, 691. ^{1}H NMF ($CDCl_3$), δ: 3.59 (s, 3 H, OMe); 4.35 (s, 1 H, CH); 6.96 and 8.31 (both d, 2 H each, Ar, J = 8.6 Hz).

Methyl 2-chloro-3-(2-chlorophenyl)-2,3-epoxypropionate (3r), a yellow oil. Found (%): C, 48.59; H, 3.69. $C_{10}H_8Cl_2O_3$. Calculated (%): C, 48.61; H, 3.26. IR, ν/cm^{-1}: 2960, 1742, 1698, 1595, 1477, 1439, 1247, 1068, 940, 864. ^{1}H NMR ($CDCl_3$), δ: 3.94 (s, 3 H, OMe); 4.69 (s, 1 H, CH); 7.29—7.58 (m, 3 H, Ar); 7.93 (d, 1 H, Ar, J = 7.6 Hz).

Methyl 2-chloro-3-(3-chlorophenyl)-2,3-epoxypropionate (3s), a yellow oil. Found (%): C, 48.23; H, 3.64. $C_{10}H_8Cl_2O_3$. Calculated (%): C, 48.61; H, 3.26. IR, ν/cm^{-1}: 2960, 1744, 1699, 1595, 1477, 1439, 1247, 1065, 940, 864, 685. ^{1}H NMR ($CDCl_3$), δ: 3.92 (s, 3 H, OMe); 4.48 (s, 1 H, CH); 7.25—7.42 (m, 4 H, Ar).

***tert*-Butyl 3-bromo-3-(4-nitrophenyl)-2-oxopropionate (4k).** A solution of $MgBr_2 \cdot Et_2O$ (3.66 g, 14 mmol) in diethyl ether (15 mL) cooled to 5 °C was added to an ethereal solution of chloroglycidate **3k** (4.25 g, 14 mmol) at 5—8 °C. After stirring for 1 min, the reaction mixture was poured onto crushed ice and extracted with diethyl ether (2×50 mL). The ethereal solution was dried with $MgSO_4$. After removal of the solvent, the crude product was chromatographed on a column with the use of an AcOEt—hexane mixture as the eluent (1 : 1 → 1 : 0). Compound **4k** was obtained in a yield of 4.79 g (98%) as an yellow oil. Found (%): C, 45.26; H, 4.14; Br, 23.56; N, 3.95. $C_{13}H_{14}BrNO_5$. Calculated (%): C, 45.37; H, 4.10; Br, 23.22; N, 4.07. IR, ν/cm^{-1}: 1752, 1607, 1522, 1437, 1350, 1282, 1253, 1013, 930, 784, 731. ^{1}H NMR ($CDCl_3$), δ: 1.55 (s, 9 H, $OCBu^t$); 6.18 (s, 1 H, CH); 7.64 and 8.24 (both d, 2 H each, Ar, J = 8.8 Hz).

Ethyl 3-bromo-3-(4-nitrophenyl)-2-oxopropionate (4l). Upon refluxing of bromoglycidate **3l** in benzene over a short period of time (1—2 min), this compound was quantitatively transformed into bromopyruvate **4l**. The yield was ~100%, a yellow oil. Found (%): C, 41.68; H, 3.22; Br, 25.52; N, 4.39. $C_{11}H_{10}BrNO_5$. Calculated (%): C, 41.80; H, 3.19; Br, 25.28; N, 4.43. IR, ν/cm^{-1}: 3116, 3083, 1747, 1707, 1609, 1473, 1320, 1276, 1243, 1198, 1109, 1027, 1016, 948, 882, 865, 835, 778, 695, 525. ^{1}H NMR ($CDCl_3$), δ: 1.38 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 4.37 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 6.24 (s, 1 H, CH); 7.56 and 8.27 (both d, 2 H each, Ar, J = 8.6 Hz).

3,6-Di(4-methoxyphenyl)-2,5-dihydrofuran-2-one (6). Upon heating of liquid chloropyruvate **4p** over a short period of time (5—8 min) at ~100 °C (0.1 Torr), a crystalline product was obtained. Recrystallization of this product from Pr^iOH afforded compound **6**. The yield was 91%, m.p. 178—180 °C. Found (%): C, 68.02; H, 4.38. $C_{18}H_{16}O_4$. Calculated (%): C, 72.96; H, 5.44. IR, ν/cm^{-1}: 1734, 1642, 1605, 1574, 1510, 1458, 1340, 1307, 1257, 1183, 1164, 1122, 1067, 1019, 963, 843, 826, 717, 580, 524. ^{1}H NMR ($CDCl_3$), δ: 3.82 and 3.83 (both s, 3 H each, MeO); 5.13 (s, 1 H, CH); 6.84, 6.92, 7.25, and 7.37 (all d, 2 H each, Ar, J = 9.0 Hz). ^{13}C NMR, δ: 55.24 (MeO-*B*); 55.33 (MeO-*A*); 70.35 (C(5)); 114.17 (C_o-*A*); 114.33 (C_o-*B*); 122.74 (C(3)); 123.32 (C_p-*A*); 123.80 (C_p-*B*); 128.98 (C_m-*B*); 130.59 (C_m-*A*); 154.52 (C(4)); 159.77 (C_i-*B*); 161.25 (C_i-*A*); 174.06 (C=O).

6-Chloro-6-methoxycarbonyl-4,5-di(4-methoxyphenyl)-3,6-dihydro-2*H*-pyran-2,3-dione (5). Liquid chloroketone **4q** was transformed into a crystalline product at ~20 °C on standing for 1 day. Recrystallization of this product from a 1 : 1 diethyl ether—hexane mixture afforded compound **5** in ~100% yield, m.p. 175—175.5 °C. Found (%): C, 60.54; H, 4.13; Cl, 8.57. $C_{21}H_{17}ClO_7$. Calculated (%): C, 60.51; H, 4.11; Cl, 8.51. IR, ν/cm^{-1}: 1746, 1725, 1647, 1605, 1516, 1437, 1303, 1257, 1230, 1170, 1152, 1100, 1021, 917, 886, 797, 764, 745, 704. ^{1}H NMR (200 MHz, $CDCl_3$), δ: 3.76, 3.85, and 3.88 (all s, 3 H each, OMe); 6.92 and 6.98 (both d, 2 H each, Ar, J = 9.0 Hz); 7.42 (d, 2 H, Ar, J = 8.8 Hz); 7.65 (d, 2 H, Ar, J = 9.0 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$), δ: 52.29 (MeOC(O)-*A*); 55.34 (MeOAr-*C*); 55.38 (MeOAr-*B*); 113.52 (C_o-*B*); 113.60 (C_o-*C*); 120.87 (C_p-*B*); 123.64 (C—Cl); 126.48 (C_p-*C*); 131.00 (C_m-*C*); 131.78 (C_m-*B*); 132.46 (C_i-*C*); 132.53 (C_i-*B*); 148.39 (C(5)); 153.77 (C(6)); 160.87 (C(2)); 161.14 (MeOC(O)); 162.00 (C(3)). ^{1}H NMR (600.13 MHz, DMSO-d_6), δ: 3.67, 3.84, and 3.87 (all s, 3 H each, OMe); 6.99, 7.07, 7.49, and 7.61 (all d, 2 H each, Ar, J = 8.9 Hz). ^{13}C NMR (DMSO-d_6), δ: 52.66 (q, MeO—C(O), $^1J_{C,H}$ = 148.0 Hz); 56.10 (q, MeOAr, $^1J_{C,H}$ = 144.8 Hz); 56.16 (q, MeOAr, $^1J_{C,H}$ = 145.0 Hz); 114.29 (dd, $^1J_{C,H}$ = 161.2 Hz, $^3J_{C,H}$ = 4.9 Hz); 114.34 (dd, $^1J_{C,H}$ = 161.2 Hz, $^3J_{C,H}$ = 4.9 Hz); 122.09 (dd, $^3J_{Cp,Ho}$ = 8.1 Hz, $^3J_{Cp,Ho}$ = 8.1 Hz); 124.29 (s); 127.57 (dd, $^3J_{Cp,Ho}$ = 8.1 Hz, $^3J_{Cp,Ho}$ = 8.1 Hz); 129.83, 131.86 (dd, $^1J_{C,H}$ = 162.2 Hz, $^3J_{C,H}$ = 6.6 Hz); 132.14 (dd, $^1J_{C,H}$ = 162.2 Hz, $^3J_{C,H}$ = 7.2 Hz); 133.79 (s); 147.35 (dd, $^3J_{C,H}$ = 4.2 Hz, $^3J_{C,H}$ = 4.2 Hz); 153.89 (s); 161.08 (s, C(2)); 161.34 (s, MeOC(O)); 162.13 (s, C(3)). Upon prolonged storage of compound **5**, additional signals appeared in the ^{1}H NMR spectrum (600.13 MHz, DMSO-d_6), δ: 3.65, 3.81, and 3.85 (all s, 3 H each, OMe); 6.92, 7.05, 7.27, and 7.65 (all d, 2 H each, Ar, J = 8.9 Hz).

A mixture of methyl 3-(4-bromophenyl)-2-chloro-2,3-epoxypropionate (3u) and 3-(4-bromophenyl)-3-chloro-2-oxopropionate (4u). Powdered Bu^tOK (1.12 g, 10 mmol) was added with stirring to a solution of methyl dichloroacetate (1.43 g, 10 mmol) and 4-bromobenzaldehyde (1.84 g, 10 mmol) in THF (25 mL) at −80 °C. The reaction mixture was stirred at this temperature for 3 h and then the temperature was gradually raised to ~20 °C for 3 h. The reaction solution was concentrated to one-half of the initial volume *in vacuo* using a water-aspirator pump, treated with a 25% aqueous NaCl solution, and extracted with AcOEt (3×30 mL). The combined organic extracts were dried with $MgSO_4$, the solvent was removed *in vacuo*, and a mixture of chloroglycidate **3u** and chloropyruvate **4u** was obtained (physicochemical characteristics are identical to those reported above). After silica gel column chromatography (AcOEt—hexane, 20 : 1→8 : 1, as the eluent) of the crude product, chloropyruvate **4u** and compound **3u** were obtained in yields of 1.16 g (40%) and 1.25 g (43%), respectively.

Compound **3u** is a yellow oil. Found (%): C, 41.33; H, 2.63. $C_{10}H_8BrClO_3$. Calculated (%): C, 41.20; H, 2.77. IR, ν/cm^{-1}: 1746, 1695, 1597, 1472, 1439, 934, 864, 702. ^{1}H NMR ($CDCl_3$), δ: 3.92 (s, 3 H, OMe); 4.46 (s, 1 H, CH); 7.25 and 7.54 (both d, 2 H each, Ar, J = 8.44 Hz).

Thermal isomerization of 2-halo-2,3-epoxypropionic ester 3h,j,s,u into 3-halo-2-oxopropionic esters 4h,j,s,u (general procedure). A solution of 2-halo-2,3-epoxypropionic ester **3** (10 mmol) in benzene (15 mL) was refluxed until the haloepoxide

was completely transformed into the corresponding haloketone. The completion of isomerization was monitored by TLC, which demonstrated that isomerization of **3h** (R_f = 0.30) into **4h** (R_f = 0.10), of **3j** (R_f = 0.20) into **4j** (R_f = 0.11), of **3s** (R_f = 0.30) into **4s** (R_f = 0.15), and of **3u** (R_f = 0.35) into **4u** (R_f = 0.12) was completed within ~15, ~25, ~1, and ~5 min, respectively (EtOAc—hexane, 1 : 4, as the eluent). Under standard conditions of Darzens condensation, the expected chloroepoxide **3a** from the reaction of benzaldehyde with methyl dichloroacetate was not detected by both TLC and NMR spectroscopy of the crude product.

X-ray diffraction study of compounds **3l,m,j** and **6** was performed on automated four-circle Enraf—Nonius CAD-4 diffractometers (Mo-Kα (**3m,j**) and Cu-Kα (**3l** and **6**) radiation) at 20 °C using the ω/2θ scanning technique; the θ scan rate was variable, 1—16.4 deg min^{-1}. The intensities of check reflections showed no decrease in the course of X-ray data collection. For the crystals of **3l,j**, the absorption correction was applied (for the crystals of **3m** and **6**, no absorption corrections were applied because intense reflections suitable for measurements of ψ curves were absent). The structures were solved by direct methods using the SIR program[42] and refined first isotropically and then anisotropically. All hydrogen atoms were revealed in difference electron density maps. The hydrogen atoms in the structures of **3j** and **6** were refined isotropically. In the structure of **3l**, the contributions of the hydrogen atoms to the structure amplitudes were taken into account with fixed positional and isotropic thermal displacement parameters. In the structure of **3m**, the coordinates of the hydrogen atoms were calculated based on stereochemical criteria and refined using a riding model. All calculations were carried out with the use of the MolEN program package[43] (**3l,j** and **6**) on an AlfaStation 200 computer and using the WINGX program package[44] (**3m**). Intermolecular contacts, including hydrogen bonds in the crystals, were analyzed using the PLATON program.[45] The unit cell parameters, details of X-ray diffraction study, and results of structure refinement are given in Table 3. Crystallographic data for compounds **3l**, **3m**, **3j**, and **6** were deposited with the Cambridge Structural

Table 3. Crystallographic parameters of compounds **3l,m,j** and **6** and details of X-ray diffraction study

Parameter	**3l**	**3m**	**3j**	**6**
Color, crystal shape	Colorless, prismatic	Yellow, rhombohedral		Pale brown, prismatic
Molecular formula	$C_{11}H_{10}BrN_1O_5$	$C_{10}H_8BrN_1O_5$	$C_{10}H_8ClN_1O_5$	$C_{18}H_{16}O_4$
Molecular weight	316.12	302.08	257.63	296.33
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/n$	$P2_1/c$
Unit cell parameters[3]				
a/Å	10.405(9)	12.058(6)	11.878(4)	5.61(1)
b/Å	7.743(5)	7.968(2)	7.929(2)	29.02(2)
c/Å	16.14(1)	12.058(6)	11.916(4)	9.37(1)
β/deg	104.99(7)	102.93(2)	102.34(2)	99.1(1)
Volume/Å^3	1256(2)	1129.1(8)	1096.3(2)	1507(2)
Z	4	4	4	4
ρ_{calc}/g cm^{-3}	1.67	1.78	1.56	1.31
Absorption coefficient/cm^{-1}	46.14	36.5	3.53	7.16
F(000)	632	600	528	624
Radiation (λ/Å)	Cu-Kα (1.53184)	Mo-Kα (0.71073)	Mo-Kα (0.71073)	Cu-Kα (1.53184)
θ Angle range/deg	$5.46 \le \theta \le 57.2$	$2.71 \le \theta \le 26.3$	$2.71 \le \theta \le 26.3$	$5.46 \le \theta \le 57.2$
Standard reflections	Two check reflections distributed in orientation and three check reflections distributed in intensity after each 200 reflections			
Ranges of measured indices	$0 \le h \le 10$, $0 \le k \le 7$, $-15 \le l \le 15$	$-9 \le h \le 15$, $0 \le k \le 9$, $-15 \le l \le 9$	$-14 \le h \le 14$, $-9 \le k \le 0$, $-14 \le l \le 0$	$0 \le h \le 6$, $-31 \le k \le 0$, $-10 \le l \le 10$
Number of measured reflections	2325	2297	2493	2346
Number of observed independent reflections	1758 ($I > 3\sigma(I)$)	1505 ($I > 2\sigma(I)$)	1964 ($I > 3\sigma(I)$)	1960 ($I > 3\sigma(I)$)
Absorption correction	Empirical	Ignored	Empirical	Ignored
Method of refinement, least-squares	Against $\|F\|$ (MolEN)	Against $\|F\|^2$ (SHELX)	Against $\|F\|$ (MolEN)	Against $\|F\|$ (MolEN)
Final R factors				
R	0.049	0.049	0.040	0.050
R_w	0.070	0.122	0.064	0.067
GOOF	3.074	0.965	2.524	2.388
Δ/σ	0.002	0.000	0.000	0.008
Number of parameters in refinement	163	159	186	263

Database (CCDC 279411, 279413, 279412, and 279410, respectively).

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