Ring-opening reactions of functionalized bicyclo[2.2.0]hexanes

M. Liliana Graziano,* M. Rosaria Iesce, Flavio Cermola and Giuseppina Ialongo

Dipartimento di Chimica Organica e Biologica dell'Università di Napoli Federico II, via Mezzocannone 16, I-80134 Napoli, Italy

On hydrolysis, the bicyclohexanes 1a,b give the cyclobutanes 2a,b and/or the cyclobutenes 3a,b. On bromination they lead to the bromocyclobutanes 5a,b and the dibromocyclobutane 6a or the bromocyclobutene 7b, respectively. The ease of the electrophilic ring-opening of compounds 1a,b can be explained by assuming that the presence of the methoxycarbonyl and *gem*-dimethoxy groups at C-1 and C-2 favours the formation of well-stabilized ionic intermediates or polar transition states. However, the brominations may involve radical pathways, even to a minor extent, and these would lead to the same products.

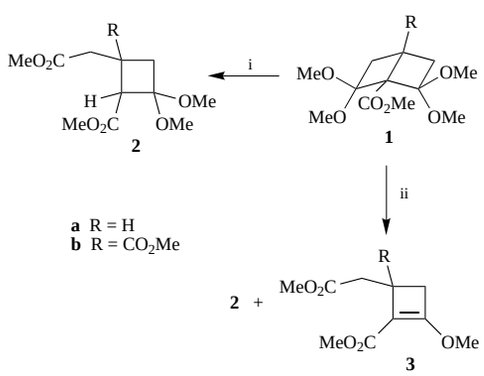
The chemical behaviour of strained bicycloalkyl structures is closely related to their rigid molecular framework since the presence of a large amount of strain energy makes C–C bond scission a common process.[1] Thus, bicyclo[2.2.0]hexanes undergo ring-opening reactions involving the cleavage of the inter-ring bond. Apart from the reaction of *N*,*N*-dimethylbicyclo-[2.2.0]hexan-1-amine with water, which leads to cyclohexanone at high temperature,[2] the only reported ring-opening reactions of bicyclo[2.2.0]hexane and its halogen and alkyl derivatives occur through radical or radical cation intermediates (thermolysis,[3] photobromination,[4] photoinduced electron-transfer[5]). In particular, bicyclo[2.2.0]hexane undergoes bimolecular homolytic substitution at the bridgehead carbon atoms with bromine atoms,[4] in contrast to cyclobutane and its derivatives for which bromination occurs by straightforward hydrogen abstraction.[6] However, bicyclo[2.2.0]hexane, as well as cyclobutane, is almost inert toward electrophiles, even if these reactions can occur on the basis of theoretical calculations.[7] In order to verify the effect of substituents other than halogens or alkyls on the chemical behaviour of the bicyclo-[2.2.0]hexane system, we investigated the ring-opening reactions of methyl 2,2,6,6-tetramethoxybicyclo[2.2.0]hexane-1-carboxylates **1a**,**b**, which we recently synthesized.[8] The first results, reported in a preliminary paper, showed that by using ruthenium tetraoxide compounds **1a**,**b** undergo regioselective oxidative scission of the C(1)–C(2) and C(1)–C(6) bonds with the formation of dimethyl 3-substituted 2-oxopentane-1,5-dioates.[9] Here we describe the hydrolysis and bromination of products **1a**,**b**.

Results and discussion

Hydrolysis of the bicyclohexanes 1

When a solution of **1** in acetone–water (4:1, v/v) was refluxed (8 h for **1a**, 48 h for **1b**), the cyclobutanes **2** were almost quantitatively obtained as *ca*. 4:5 mixtures of diastereoisomers (Scheme 1). Compounds **2** were purified by silica gel chromatography and their structures assigned on the basis of analytical and spectral data. Each stereoisomer of the cyclobutanes **2** was separated but its stereochemistry was not assigned. Indeed, as expected,[10] similar values of *cis* and *trans* couplings of the vicinal protons were found and NOE experiments carried out on the four products proved insignificant. Moreover, the stereochemical assignment made by comparing the deshielding effect[10] exerted by the methoxycarbonyl groups at C-2 or/and C-1 on neighbouring *cis* protons or chain methylenes with that observed for similarly substituted cyclobutanes[11] was unsuccessful.

When the bicyclohexanes **1** were treated with dilute hydrochloric acid at room temperature (30 min for **1a**, 12 h for **1b**), they afforded the cyclobutenes **3**, in addition to the stereoisomers of the cyclobutanes **2** (Scheme 1). Products **2** and **3** were



Scheme 1 *Reagents:* i, acetone–H_2O (4:1 v/v), reflux; ii, acetone–1 mol dm^{-3} aq. HCl (4:1 v/v), RT

inseparable by normal chromatographic methods, so the yields (30% and 30% yields for **2a** and **3a;** 25% and 50% yields for **2b** and **3b**) were evaluated on the basis of the ^{1}H NMR spectrum of the reaction mixture after filtration through silica gel. The cyclobutenes **3** were identified by comparing the IR and NMR spectra of these mixtures with those of authentic samples.†

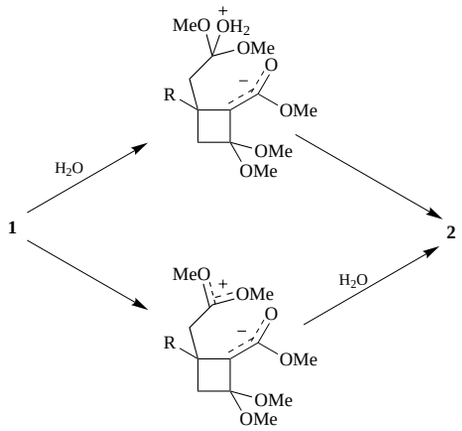
Control experiments showed that the cyclobutanes **2** and the cyclobutenes **3** do not interconvert under the conditions used for uncatalysed and catalysed hydrolysis of the bicyclohexanes **1**. In fact, when heated in acetone–water under reflux or by treatment with dilute hydrochloric acid: (i) the cyclobutanes **2** were almost quantitatively recovered while the cyclobutenes **3** were partially changed (*ca*. 20–30%) to unidentified products; (ii) the cyclobutenes **3** did not afford the cyclobutanes **2** in the presence of methanol.‡

The results show that the bicyclohexanes **1** undergo scission of their C(1)–C(2) or C(1)–C(6) bonds both in water and in acidic media. However, under neutral conditions the cyclobutanes **2** are formed while in acidic media, in addition to **2,** the

† Compounds **3** were obtained almost quantitatively by treating **1** with tetracyanoethene (TCNE). Detailed investigation of this reaction is in progress.

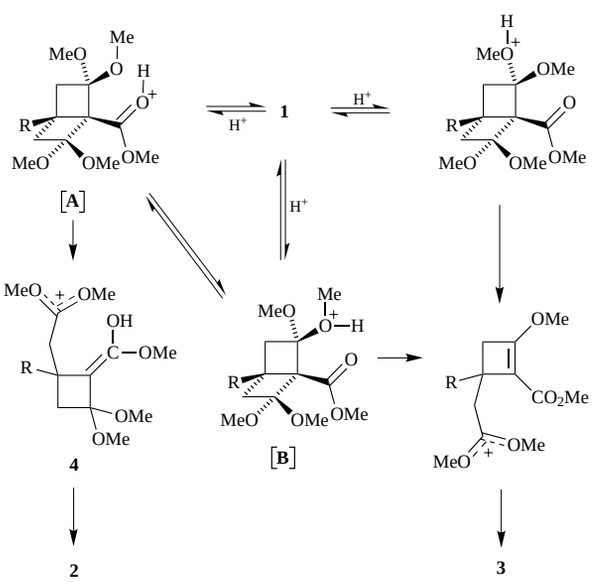
‡ For longer times than used for **1**, both the cyclobutanes **2** and the cyclobutenes **3** led in dilute hydrochloric acid, although at different rates, to acyclic carbonyl compounds as reported for hydrolysis of ketals and enol ethers.[12]

cyclobutenes **3** are also obtained. It is likely that under neutral conditions a nucleophilic substitution by water takes place at C-2 and cleavage of the C(1)–C(2) bond (Scheme 2) is favoured in



Scheme 2

that the emerging negative charge at C-1 is stabilized by delocalization on the methoxycarbonyl group and by the inductive electron-withdrawing effect of the *gem*-dimethoxy group linked to the adjacent carbon.[8b] Moreover, the process is aided by the protic solvent and by relief of ring strain.[13] However, it cannot be excluded that, as reported in other cases,[14] both the polar medium and ring strain promote the cleavage of the C(1)–C(2) bond before attack by water since a well-stabilized zwitterion is formed (Scheme 2). In acidic media, protonation of the methoxycarbonyl group facilitates formation of the cyclobutanes **2** which occurs *via* the enols **4**. However, under these conditions protonation of the methoxy acetal groups can also occur and this**,** followed by β-elimination,§ should afford the cyclobutenes **3**.¶ As shown in Scheme 3, cleavage of the C(1)–C(2) or



Scheme 3

C(1)–C(6) bonds should be promoted by the stabilization of the developing positive charge on a dimethoxy substituted carbon.‖

§ Since only the *exo* C(2)–OMe bond is well aligned stereoelectronically with the C(1)–C(6) bond, it is likely that for *endo*-protonation β-elimination occurs through a stepwise route.

¶ It should be noted that owing to the closeness of the methoxycarbonyl and *exo*-methoxy groups [**A**] and [**B**] could partly interconvert by proton transfer *via* a hydrogen-bonded ion.

‖ The acid-catalysed reaction which leads to the cyclobutanes **2** is reminiscent of the acid-catalysed nucleophilic ring-opening of cyclopropyl ketones where the ring-opening in related cyclopropyl carbocations occurs toward the carbon atom which bears those substituents best able to stabilize a positive charge.[15]

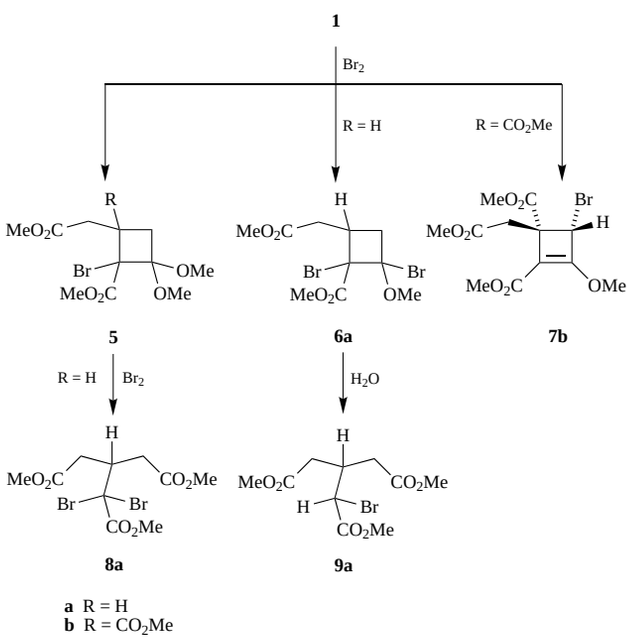
Table 1 Bromination of the bicyclohexanes **1**

		Product distribution[b]			
Entry	Conditions[a]	**5**	**6**[c]	**7**	**8**
1a	Br_2	50 (3:1)	15	—	5
1a	Br_2–TTBP[d]	48 (3:1)	18	—	4
1a	HBr-free Br_2[e]	70 (2:1)	—	—	3
1b	Br_2	62 (2.5:1)	—	18	—
1b	Br_2–TTBP[d]	30 (3:1)	—	30	—
1b	HBr-free Br_2[e]	50 (3:2)	—	10	—

[a] Equimolecular amounts of **1** and bromine. Solution of **1** in CCl_4 (0.15 mol dm^{-3}). [b] Yields and isomeric ratios were evaluated on the basis of the ^1H NMR spectrum of the bromination mixture and confirmed by silica gel chromatography. [c] Yields based on the bromo ester **9a** obtained by silica gel chromatography of the reaction mixture. [d] **1**:TTBP = 3:1 molar ratio. [e] Solution of bromine in trimethyl phosphate (1 mol dm^{-3}).

Bromination of the bicyclohexanes 1

Bromination of **1a** and **1b** was carried out at room temperature using an equimolecular ratio of bromine in a CCl_4 solution and was complete within a few minutes (with the disappearance of the bromine colour) (Scheme 4, Table 1). The bicyclohexanes **1a**



Scheme 4

and **1b** gave the bromocyclobutanes **5a** and **5b** as diastereoisomeric mixtures in addition to the dibromocyclobutane **6a** and the bromocyclobutene **7b,** respectively, as by-products (Scheme 4). In the bromination of **1a** a small amount of the dibromo ester **8a**, resulting from bromination of **5a** as shown by control experiments, was also formed. The yields of the products **5**–**8** as well as the stereoisomeric ratio of **5** were evaluated on the basis of the ^1H NMR spectrum of a sample of the CCl_4 solution recorded in $CDCl_3$ and confirmed by silica gel chromatography (Table 1).** The dibromocyclobutane **6a** was not isolated since it is converted quantitatively into the bromo ester **9a (**slowly in the reaction mixture and rapidly on contact with chromatographic adsorbents).†† Therefore the yield of **6a**, reported in Table 1, was based on the bromo ester **9a** which was recovered by silica gel chromatography of the bromination mixture.

The structures of the products **5**, **7b** and **9a** were assigned on the basis of their analytical and spectral data. Although each of

** In the mixtures MeOH and MeBr were also present in amounts which could not be quantified owing to their volatility.

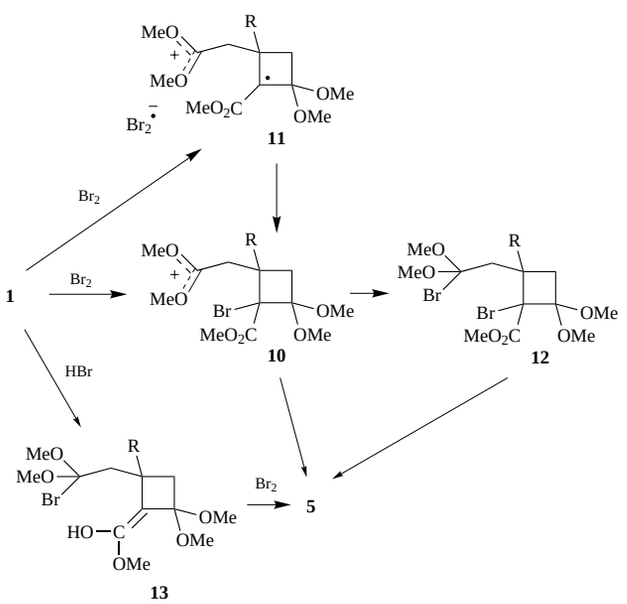
†† Bromocyclobutane **5a** under these conditions is completely stable.

the isomers of **5** was isolated their stereochemistry was not assigned. The stereochemistry of the bromocyclobutene **7b** was established on the basis of differential ^{1}H NMR NOE experiments. Irradiation at the resonance frequency of the CH signal (δ 5.46) caused enhancement of the signals for the proton of the chain methylene resonating at δ 3.60 and for the 2-OMe at δ 4.20. The structure of the dibromocyclobutane **6a**‡‡ was assigned on the basis of its quantitative conversion into the bromo ester **9a** and confirmed by the fact that it was obtained by the bromination of the cyclobutene **3a** (see below). The structure of the dibromo ester **8a** was assigned by comparison with a sample obtained by bromination of the bromocyclobutane **5a**.

In order to test the occurrence of a radical or an acid-catalysed pathway§§ we carried out reactions in the presence of a free-radical inhibitor such as 2,4,6-tri-*tert*-butylphenol (TTBP),[16] or using bromine in trimethyl phosphate[17] as HBr-free bromine. In the presence of TTBP the reaction times were the same for both bicyclohexanes **1a** and **1b**, whereas the ratio of the products was almost unchanged for **1a**, and for **1b** a different ratio between **5b** and **7b** was observed (Table 1). When HBr-free bromine was used, the bicyclohexane **1a** gave almost exclusively the bromocyclobutane **5a**, while the bicyclohexane **1b** yielded both **5b** and **7b** in a *ca*. 5:1 molar ratio (Table 1).

Control experiments showed that: (i) the bicyclohexanes **1** with HBr in the time required for bromination partly afforded the cyclobutenes **3** and the cyclobutanes **2** in addition to MeBr; (ii) bromination of the cyclobutenes **3a** and **3b** led to the dibromocyclobutane **6a** and to the bromocyclobutene **7b**, respectively, in addition to polymeric material; (iii) bromination of the cyclobutanes **2** was slow and, in addition to the bromocyclobutanes **5**, led to other bromination products.[18]

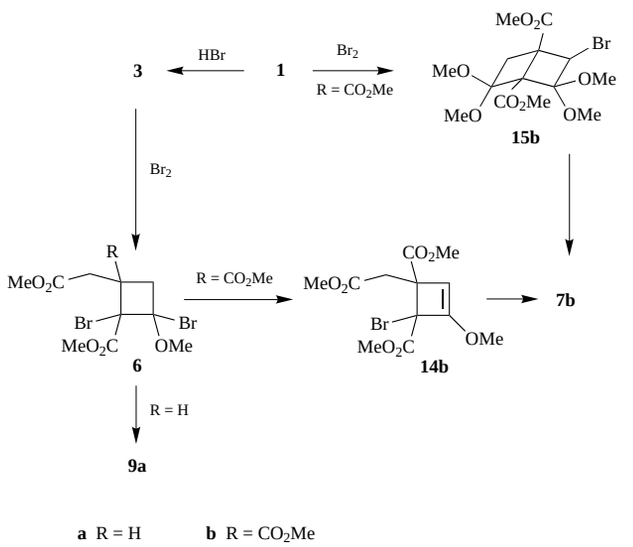
All of the results can be interpreted assuming different pathways for the observed bromination products. As regards formation of the bromocyclobutanes **5**, the minimal effect of TTBP suggests that a radical chain mechanism, as reported for the photobromination of arylcyclopropanes[19] and bicyclo[2.2.0]hexane,[4] is negligible especially for **1a**. Therefore, according to Scheme 5, it is likely that electrophilic addition of bromine to the C(1)–C(2) or C(1)–C(6) bond in **1** occurs with formation of the dimethoxy carbocation **10**, as observed for polar bromination of alkenes[20] and cyclopropanes[21] bearing substituents able to stabilize the developing positive charge. However, since the direct attack of bromine seems subject to steric hindrance, the first step of the reaction could be an electron-transfer from the substrate to bromine with cleavage of the C(1)–C(2) or C(1)–C(6) bond and formation of the radical ion-pair **11**, as observed in bromination of some bicyclobutane derivatives.¶¶[22] The carbocation intermediate **10**, for reaction with bromide, could lead to MeBr and the bromocyclobutane **5** by way of an S_N2 type of displacement or *via* formation of the unstable dibromide **12**.[24]



Scheme 5

On the other hand, the formation of **5** can occur, even if to a small extent, by bromine addition to the enols **13**, which can derive from the HBr-catalysed ring-opening of the bicyclohexanes **1** (Scheme 5). The enols **13** should add bromine very rapidly leading to the bromocyclobutanes **5** before they tautomerize to the cyclobutanes **2**,|||| as occurs in the case of the well-known α-bromination of ketones.[25]

As regards the formation of the secondary products **6a** and **7b**, we assume that the HBr-catalysed ring-opening of **1** affords **3** which undergoes electrophilic addition of bromine leading to the dibromocyclobutanes **6a,b** (Scheme 6). While **6a** is hydrolysed to the bromo ester **9a**, **6b** loses HBr*** and affords the unstable bromocyclobutene **14b** which, by an allylic rearrangement,[26] leads to **7b**. On the other hand, the recovery of **7b** in the reaction with HBr-free bromine indicates that this product can also be formed by a radical pathway. It is likely that the bicyclohexane **1b** partly undergoes radical substitution at the ring methylene with the formation of unstable 3- or 5-bromobicyclohexane **15b**††† which decomposes to the bromocyclo-



Scheme 6

‡‡ The ^{1}H NMR signals of **6a** overlap with those of the products present in the bromination mixture of **1a**, apart from three methoxy signals at δ 3.58, 3.69 and 3.84.

§§ Trace amounts of HBr present in the reaction mixtures could induce acid-catalysed ring-opening of the bicyclohexanes **1** to give the cyclobutanes **2** and the cyclobutenes **3**, which could undergo bromination providing the observed products.

¶¶ In the bromination of alkenes donor–acceptor charge-transfer complexes are formed.[23] On the other hand, alkyl derivatives of bicyclo[2.2.0]hexane undergo photoinduced electron-transfer;[5] therefore, it is likely that in **1** the presence of the methoxy acetal groups promotes the electron-transfer to bromine which is an electrophile with sufficiently low LUMO.

|||| This is proved by the absence of the cyclobutanes **2** and their other bromination products in the reaction mixtures.

*** The different behaviour of the dibromocyclobutane **6b** with respect to that of **6a** is presumably due to the electron-withdrawing inductive effect of the 4-CO_2Me group.

††† It is to be noted that all attempts to obtain bicyclohexanes **1** 3- or 5-substituted were unsuccessful.[8b]

butene **7b**.‡‡‡ The isolation of the stereoisomer **7b** (the only one present) shows that the substitution of H_{exo} is selective as was found for the bromination of norbornane.[27]

Conclusion

The behaviour of the bicyclohexanes **1** is different from that of the parent and its halogeno and alkyl derivatives, in that they easily undergo electrophilic ring-opening reactions with selective cleavage of the C(1)–C(2) or C(1)–C(6) bond. Evidently, the combination of methoxycarbonyl and *gem*-dimethoxy groups at C-1 and C-2 favours the formation of well-stabilized ionic intermediates or polar transition states. However, in bromination radical pathways can be involved, even if to a much lesser extent, and can lead to the same products.

Experimental

IR spectra were recorded on a Perkin-Elmer 1760/X-FT spectrophotometer using $CHCl_3$ as solvent unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-270 spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard; *J* values are given in Hz. DEPT techniques were employed to determine the multiplicity in the ^{13}C NMR spectra and gated decoupling methods to obtain quantitative noise-decoupled spectra. HPLC was performed on a Shimadzu LC-9A instrument equipped with a Beckman UV detector using a Merck Lichrosorb Si-60 (10 μm) column and *tert*-butyl methyl ether–hexane (1:3) as eluent with a 3 cm^3 min^{-1} flow rate of elution. CCl_4 used in the reactions was anhydrous. Silica gel [0.063–0.20 mm (Macherey-Nagel)] and light petroleum (bp 40–60 °C) were used for column chromatography. Bromine, 2,4,6-tri-*tert*-butylphenol (TTBP), bromine in trimethyl phosphate (1.0 mol dm^{-3}), anhydrous hydrogen bromide and tetracyanoethene (TCNE) were purchased from commercial supplies.

Hydrolysis of the bicyclo[2.2.0]hexanes 1

A solution of the bicyclohexane **1** (0.5 mmol) in acetone–water (4:1; 7 cm^3) was refluxed until disappearance of **1** (^1H NMR). After termination of the reaction (6 h for **1a**, 48 h for **1b**), the mixture was evaporated under reduced pressure and the residue was slowly chromatographed on silica gel with light petroleum–diethyl ether (4:1) as eluent: the reaction with **1a** gave the major isomer of **2a** (50%) and its minor isomer (40%), successively, and that of **1b** afforded the minor isomer of 2**b** (40%) and its major isomer (50%), successively.

Methyl 2,2-dimethoxy-1-methoxycarbonylcyclobutan-4-yl-acetate 2a. Major isomer as an oil; ν_{max}/cm^{-1} 1735; δ_H 2.15 (1 H, dd, *J* 12.0, 7.8, 3-H), 2.33 (1 H, ddd, *J* 12.0, 8.0, 2.8, 3-H), 2.68 (2 H, m, 4-H + *H*-$CHCO_2Me$), 2.94 (1 H, dd, *J* 16.1, 7.0, *H*-$CHCO_2Me$), 3.15 and 3.26 (6 H, 2 × s, 2 × OMe), 3.45 (1 H, dd, *J* 8.0, 2.8, 1-H) and 3.66 and 3.69 (6 H, 2 × s, 2 × CO_2Me); δ_C 24.9 (d), 34.9 (t), 36.9 (t), 48.7 (q), 49.2 (q), 50.6 (d), 51.3 (q), 51.4 (q), 100.9 (s), 170.4 (s) and 173.2 (s) (Found: C, 53.2; H, 7.5. $C_{11}H_{18}O_6$ requires C, 53.65; H,7.37%). Minor isomer as an oil; ν_{max}/cm^{-1} 1734 ; δ_H 1.70 (1 H, dd, *J* 12.0, 8.0, 3-H_a), 2.51 (3 H, m, CH_2CO_2Me + 3-H_b), 2.82 (1 H, m, 4-H), 3.10 (1 H, d, *J* 7.8, 1-H), 3.15 and 3.28 (6 H, 2 × s, 2 × OMe) and 3.65 and 3.72 (6 H, 2 × s, 2 × CO_2Me); δ_C 24.5 (d), 35.4 (t), 39.1 (t), 48.7 (q), 49.3 (q), 51.5 (q), 51.7 (q), 54.3 (d), 100.8 (s), 170.2 (s) and 172.2 (s) (Found: C, 53.2; H, 7.5. $C_{11}H_{18}O_6$ requires C, 53.65; H,7.37%).

Methyl 2,2-dimethoxy-1,4-bis(methoxycarbonyl)cyclobutan-4-ylacetate 2b. Major isomer as an oil; ν_{max}/cm^{-1} 1739; δ_H 2.16 (1 H, dd, *J* 12.5, 3.1, 3-H), 2.78 and 3.03 (2 H, 2 × d, *J* 15.6, CH_2CO_2Me), 3.16 (d, *J* 12.5, 3-H) and 3.15 (s, OMe) (together 4 H), 3.24 (3 H, s, OMe), 3.37 (1 H, d, *J* 3.1, 1-H) and 3.64, 3.67 and 3.74 (9 H, 3 × s, 3 × CO_2Me); δ_C 38.5 (t), 39.1(s), 42.4 (t), 48.8 (q), 49.0 (q), 51.7 (q), 51.9 (q), 52.3 (q), 57.2 (d), 98.7 (s), 168.5 (s), 170.7 (s) and 173.3 (s) (Found: C, 51.1; H, 6.4. $C_{13}H_{20}O_8$ requires C, 51.31; H, 6.63%). Minor isomer as an oil; ν_{max}/cm^{-1} 1738; δ_H 2.37 and 2.47 (2 H, 2 × d, *J* 12.5, 3-H_2), 2.98 and 3.42 (2 H, 2 × d, *J* 17.1, CH_2CO_2Me), 3.17 and 3.30 (6 H, 2 × s, 2 × OMe), 3.64, 3.67 and 3.73 (9 H, 3 × s, 3 × CO_2Me) and 3.90 (1 H, s, 1-H); δ_C 37.5 (t), 39.2 (s), 40.1 (t), 48.7 (q), 49.7 (q), 51.6 (two overlapping q), 52.4 (d), 52.6 (q), 99.7 (s), 168.4 (s), 172.0 (s) and 174.5 (s) (Found: C, 51.1; H, 6.4. $C_{13}H_{20}O_8$ requires C, 51.31; H, 6.63%).

Cyclobutanes **2** (0.5 mmol) were almost quantitatively recovered by silica gel chromatography, after refluxing in acetone–water (4:1; 7 cm^3) for the time reported for the corresponding bicyclohexanes **1**.

Acid-catalysed hydrolysis of the bicyclohexanes 1

A solution of **1a** (130 mg, 0.5 mmol) in 1 mol dm^{-3} aq. HCl–acetone (1:4; 3.2 cm^3) was kept at room temperature. After 30 min work-up gave a mixture which was filtered through silica gel with light petroleum–diethyl ether (4:1) as eluent. The fraction collected (70 mg) was composed of **2a** and **3a** in a *ca*. 1:1 molar ratio with a stereoisomeric ratio for **2a** of *ca*. 1:1 (^1H NMR). Quantification was based on the relative areas of the signals at δ 3.26 (OMe of the major isomer of **2a**), 3.28 (OMe of the minor isomer of **2a**) and 3.88 (OMe of **3a**). Since all attempts to separate **2a** and **3a** failed, the yields (30% for **2a** and 30% for **3a**) were calculated by ^1H NMR of this fraction and the products were identified by comparison (^1H NMR and IR spectra) with authentic samples.

A solution of **1b** (160 mg, 0.5 mmol) in 1 mol dm^{-3} aq. HCl–acetone (1:4; 4 cm^3) was kept at room temperature. After 12 h work-up gave a mixture which was filtered through silica gel, with light petroleum–diethyl ether (4:1) as eluent. The resulting fraction (100 mg) was composed of **2b** and **3b** in a *ca.* 1:2 molar ratio [by ^1H NMR, on the basis of the relative areas of the signals at δ 4.06 (OMe of **3b**) and 3.64 (OMe of **2b**)] with a stereoisomeric ratio for **2b** of *ca*. 1:1 (by ^1H NMR, on the basis of the relative areas of the signals at δ 2.16 and 3.90). Thus, the yields calculated as for **1a** were 25% for **2b** and 50% for **3b.** The products were identified by comparison (^1H NMR and IR spectra) of this fraction with authentic samples.

A solution of the cyclobutane **2a** (123 mg, 0.5 mmol) in 1 mol dm^{-3} aq. HCl–acetone (1:4; 3.2 cm^3) was kept at room temperature for 30 min. Work-up of an aliquot of the mixture (2 cm^3) allowed the almost quantitative recovery of **2a**. The remainder of the solution was periodically sampled and the samples analysed by ^1H NMR spectroscopy. It was observed that over time the signals of the cyclobutane **2a** decreased while those of unidentified products increased. After 24 h only the latter were present. In no spectrum were the signals of the cyclobutene **3a** present. A solution of the cyclobutane **2b** (152 mg, 0.5 mmol) was treated in a similar manner to that described for **2a**; after 12 h an aliquot (2 cm^3) showed the presence of **2b** in almost quantitative amount whilst analysis of the ^1H NMR of a sample after 10 days showed that the cyclobutane **2b** was still present (*ca*. 70%) together with unidentified products.§§§ In no spectrum were the signals of the cyclobutene **3b** present.

Preparation of the cyclobutenes 3

An equimolecular amount of TCNE was added to a 0.5 mol dm^{-3} solution of the bicyclohexanes **1** (4 cm^3) in dry CH_3CN and the resulting mixture was kept at room temperature. After 2 h the mixture was evaporated and the residue suspended in

‡‡‡ The H-extraction is competitive only for **1b** since presumably the 4-CO_2Me group slows down bromine addition owing to steric hindrance.

§§§ On the basis of that reported for the hydrolysis of ethyl 2,2-diethoxycyclobutane-1-carboxylate,[12b] it is likely that these products are derivatives of dimethyl pentane-1,5-dioate.

dry CCl_4 and TCNE, filtered and evaporated. The crude product **3** was purified by filtration through silica gel (light petroleum–diethyl ether, 4:1) and obtained in 90% yields.

Methyl 2-methoxy-1-methoxycarbonylcyclobut-1-en-4-ylacetate 3a. An oil; ν_{max}/cm^{-1} (CCl_4) 1741, 1709 and 1636; δ_H 2.04–2.23 (2 H, m) and 2.65–2.92 (3 H, m) (CH_2CHCH_2), 3.59 (6 H, s, 2 × CO_2Me) and 3.88 (3 H, s OMe); δ_C 28.9 (d), 35.3 (t), 37.8 (t), 50.5 (q), 51.2 (q), 58.5 (q), 104.3 (s), 161.5 (s), 161.6 (s) and 172.7 (s) (Found: C, 56.2; H, 6.5. $C_{10}H_{14}O_5$ requires C, 56.07; H, 6.59%).

Methyl 2-methoxy-1,4-bis(methoxycarbonyl)cyclobut-1-en-4-ylacetate 3b. An oil; ν_{max}/cm^{-1} (CCl_4) 1740, 1714 and 1641; δ_H 2.43 and 3.43 (2 H, 2 × d, *J* 17.1, C*H*$_2$$CO_2Me$), 2.70 and 3.20 (2 H, 2 × d, *J* 15.3, 3-H_2), 3.67, 3.69 and 3.70 (9 H, 3 × s, 3 × CO_2Me) and 4.06 (3 H, s, OMe); δ_C 38.3 (t), 39.9 (t), 42.7 (s), 51.0 (q), 51.6 (q), 52.3 (q), 59.4 (q), 105.5 (s), 160.7 (s), 163.7 (s), 172.1 (s) and 173.7 (s) (Found: C, 52.8; H, 5.9. $C_{12}H_{16}O_7$ requires C, 52.94; H, 5.92%).

A solution of the cyclobutene **3a** (107 mg, 0.5 mmol) in acetone–water (4:1; 7 cm^3) was refluxed for 6 h after which work-up and silica gel chromatography afforded **3a** (70%) and unidentified products. A solution of cyclobutene **3b** (136 mg, 0.5 mmol) in acetone–water (4:1; 7 cm^3) was refluxed for 48 h after which silica gel chromatography afforded **3a** (70%) and unidentified products. The cyclobutenes **3** (0.5 mmol) when treated as reported above in acetone–water–methanol (3.5:1:0.5; 4 cm^3) gave similar results.

A solution of the cyclobutene **3a** (107 mg, 0.5 mmol) in 1 mol dm^{-3} aq. HCl–acetone (1:4; 3.2 cm^3) was kept at room temperature for 30 min after which work-up of an aliquot of the mixture (2 cm^3) gave **3a** (70%) and unidentified products. The remaining solution was periodically sampled and the samples analysed by ^{1}H NMR spectroscopy. It was observed that over time signals for the cyclobutene **3a** decreased while those of unidentified products increased until after 12 h only the latter were present. In no spectrum were signals of the cyclobutane **2a** present. When the cyclobutene **3b** (136 mg, 0.5 mmol) was treated in a similar manner to that described for **3a**, work-up after 12 h afforded **3b** (80%) and unidentified products; analysis of the ^{1}H NMR spectrum of a sample of the solution after 36 h showed that only the latter were present. In no spectrum were signals of the cyclobutane **2b** present. When the cyclobutenes **3** (0.5 mmol) were treated as reported above in 1 mol dm^{-3} aq. HCl–acetone–methanol (1:3.5:0.5; 4 cm^3), the same results were obtained.¶¶¶ In no spectrum were signals for the cyclobutanes **2** present.

General procedure for bromination

To a 0.15 mol dm^{-3} solution of the substrate in CCl_4 was added an equimolecular amount of bromine and the resulting mixture was kept at room temperature until the disappearance of bromine colour. An aliquot of the solution (0.1 cm^3) was dissolved in $CDCl_3$ (0.4 cm^3) and the resulting mixture was monitored by ^{1}H NMR. The remaining solution, after removal of the solvent under reduced pressure, was chromatographed on silica gel.

Bromination of the bicyclohexanes 1

The reaction of **1a** (130 mg, 0.5 mmol) was complete in 15 min and the ^{1}H NMR spectrum in CCl_4–$CDCl_3$ showed the presence of the major isomer of the bromocyclobutane **5a**, of its minor isomer, and of the dibromocyclobutane **6a** (*ca.* 3:1:1 molar ratio) in addition to MeBr, MeOH and small amounts of the dibromo ester **8a**. Quantification was based on the relative areas of the signals at δ 2.11 (H of the major isomer of **5a**), 1.89 (H of the minor isomer of **5a**), 3.84 (OMe of **6a**). MeBr and MeOH were identified by comparison with authentic samples. Chromatography of the mixture on a short column of silica gel [light petroleum–diethyl ether (4:1) as eluent] followed by HPLC afforded **5a** (major isomer: 62 mg, 38%; minor isomer: 20 mg, 12%), **8a** (9 mg, 5%) and **9a** (23 mg, 15%). Compound **8a** was identified by comparison with authentic sample (see below).

Methyl 1-bromo-2,2-dimethoxy-1-methoxycarbonylcyclobutan-4-ylacetate 5a. Major isomer as an oil; t_R = 10.2 min; ν_{max}/cm^{-1} 1734; δ_H 2.11 (1 H, dd, *J* 12.2, 7.3), 2.55–2.70 (2 H, m) and 2.90–3.03 (2 H, m) (CH_2CHCH_2) and 3.25, 3.41, 3.68 and 3.78 (12 H, 4 × s, 4 × OMe); δ_C 34.3 (t), 34.5 (t), 39.2 (d), 49.9 (q), 50.2 (q), 51.6 (q), 52.8 (q), 64.3 (s), 101.8 (s), 167.8 (s) and 172.1 (s) (Found: C, 40.8; H, 5.1. $C_{11}H_{17}BrO_6$ requires C, 40.63; H, 5.27%). Minor isomer as an oil; t_R = 10.7 min; ν_{max}/cm^{-1} 1734; δ_H 1.89 (1 H, dd, *J* 11.2, 7.3), 2.50–2.77 (3 H, m) and 3.05 (1 H, m) (CH_2CHCH_2) and 3.25, 3.41, 3.67 and 3.79 (12 H, 4 × OMe); δ_C 31.4 (d), 33.5 (t), 37.3 (t), 50.3 (q), 50.6 (q), 51.6 (q), 52.9 (q), 69.3 (s), 102.4 (s), 168.5 (s) and 172.1 (s) (Found: C, 40.7; H, 5.1. $C_{11}H_{17}BrO_6$ requires C, 40.63; H, 5.27%).

Dimethyl 2-bromo-3-methoxycarbonylmethylpentane-1,5-dioate 9a. An oil; t_R = 14.3 min; ν_{max}/cm^{-1} 1738; δ_H 2.50 (dd, *J* 16.4, 7.7), 2.58 (d, *J* 6.3) and 2.75 (dd, *J* 16.4, 4.4) (together 4 H, 2 × CH_2), 2.95 (1 H, m, CH), 3.68 (6 H, s, 2 × OMe), 3.78 (3 H, s, OMe) and 4.72 (1 H, d, *J* 5.5, CHBr); δ_C 35.0 (d), 35.3 (t), 35.7 (t), 49.6 (d), 51.6 (two overlapping q), 53.1 (q), 169.0 (s), 171.7 (s) and 171.9 (s) (Found: C, 38.7; H, 4.8. $C_{10}H_{15}BrO_6$ requires C, 38.60; H, 4.86%).

Bromination of the bicyclohexane **1b** (160 mg, 0.5 mmol) was terminated within 15 min and the ^{1}H NMR spectrum in CCl_4–$CDCl_3$ showed, in addition to MeBr and MeOH, the presence of the major isomer of the bromocyclobutanes **5b,** of its minor isomer and of the bromocyclobutene **7b** (*ca.* 2.5:1:1 molar ratio). Quantification was based on the relative areas of the signals at δ 3.40 (OMe of the major isomer of **5b**), 3.43 (OMe of its minor isomer) and 4.20 (OMe of **7b**). Silica gel chromatography (light petroleum–diethyl ether, 4:1) followed by HPLC afforded the minor isomer of **5b** (34 mg, 18%), the major isomer of **5b** (85 mg, 44%) and **7b** (32 mg, 18%).

Methyl 1-bromo-2,2-dimethoxy-1,4-bis(methoxycarbonyl)-cyclobutan-4-ylacetate 5b. Major isomer as an oil; t_R = 24.1 min; ν_{max}/cm^{-1} 1737; δ_H 2.64 and 2.97 (2 × d, *J* 13.0) and 2.89 and 3.01 (2 × d, *J* 14.2) (together 4 H, 2 × CH_2), 3.26 and 3.40 (6 H, 2 × s, 2 × OMe) and 3.66, 3.72 and 3.80 (9 H, 3 × s, 3 × CO_2Me); δ_C 35.9 (t), 42.7 (t), 45.9 (s), 50.2 (q), 50.6 (q), 51.9 (q), 52.3 (q), 53.6 (q), 71.2 (s), 98.8 (s), 167.5 (s), 170.6 (s) and 172.2 (s) (Found: C, 40.6; H, 4.9. $C_{13}H_{19}BrO_8$ requires C, 40.74; H, 5.00%). Minor isomer as an oil: t_R = 20.1 min; ν_{max}/cm^{-1} 1741; δ_H 2.25 (1 H, d, *J* 12.8, 3-H), 2.92 (d, *J* 16.4, *H*-$CHCO_2$) and 3.01 (d, *J* 12.8, 3-H) (together 2 H), 3.27 and 3.43 (6 H, 2 × s, 2 × OMe), 3.65 (3 H, s, CO_2Me), 3.79 and 3.80 (2 × s, 2 × CO_2Me) and 3.80 (d, *J* 16.4, *H*-$CHCO_2$) (together 7 H); δ_C 34.1 (t), 38.7 (t), 48.5 (q), 49.3 (s), 50.1 (q), 50.6 (q), 51.8 (q), 52.4 (q), 52.8 (q), 64.9 (s),101.2 (s), 166.6 (s), 170.6 (s) and 171.1 (s) (Found: C, 40.5; H, 4.8. $C_{13}H_{19}BrO_8$ requires C, 40.74; H, 5.00%).

Methyl 3-bromo-2-methoxy-1,4-bis(methoxycarbonyl)cyclobut-1-en-4-ylacetate 7b. An oil; t_R = 22.2 min; ν_{max}/cm^{-1} 1738 and 1651; δ_H 2.73 and 3.60 (2 H, 2 × d, *J* 17.5, CH_2), 3.70 (6 H, s) and 3.75 (3 H, s) (3 × CO_2Me), 4.20 (3 H, s, OMe) and 5.46 (1 H, s, CH); δ_C 37.2 (t), 48.9 (d), 49.4 (s), 52.0 (q), 52.3 (q), 53.2 (q), 60.9 (q), 106.2 (s), 161.0 (s), 161.3 (s), 171.8 (s) and 172.4 (s) (Found: C, 40.9; H, 4.3. $C_{12}H_{15}BrO_7$ requires C, 41.04; H, 4.31%).

Bromination of the bromocyclobutane 5a

Reaction of the isomeric mixture of compounds **5a** (65 mg, 0.2 mmol) was complete in 30 min and work-up followed by silica gel chromatography with light petroleum–diethyl ether (4:1) as eluent gave dimethyl 2,2-dibromo-3-(methoxy-

¶¶¶ On the basis of that reported for hydrolysis of the enol ethers,[12a] it is likely that these products are derivatives of dimethyl pentane-1,5-dioate.

carbonyl)methylpentane-1,5-dioate **8a** (62 mg, 80%) as an oil, t_R = 15.9 min; ν_{max}/cm^{-1} 1750; δ_H 2.57 (dd, *J* 16.1, 8.2) and 2.81 (dd, *J* 16.1, 3.5) (together 4 H, 2 × CH_2), 3.58 (1 H, m, *J* 8.2, 3.5, CH), 3.70 (6 H, two overlapping s, 2 × OMe) and 3.91 (3 H, s, OMe); δ_C 38.1 (two overlapping t), 44.8 (d), 52.0 (two overlapping q), 54.8 (q), 65.6 (s), 165.8 (s) and 171.1 (two overlapping s) (Found: C, 30.9; H, 3.6. $C_{10}H_{14}Br_2O_6$ requires C, 30.79; H, 3.62%).

Bromination of the cyclobutenes 3

Bromination of the cyclobutene **3a** (107 mg, 0.5 mmol) was complete within 15 min and an ^{1}H NMR spectrum of the reaction mixture showed the presence of the dibromocyclobutane **6a** in addition to unidentified material. Silica gel chromatography (light petroleum–diethyl ether, 4:1) followed by HPLC gave the bromo ester **9a** (54 mg, 35%), resulting from hydrolysis of **6a** on contact with the adsorbent.

Bromination of the cyclobutene **3b** (136 mg, 0.5 mmol) was complete within 15 min and an ^{1}H NMR spectrum of the reaction mixture showed, in addition of unidentified material, the presence of **7b**. Work-up followed by silica gel chromatography (light petroleum–diethyl ether, 4:1) and HPLC gave **7b** (70 mg, 40%).

Bromination of the bicyclohexanes 1 in the presence of TTBP

Bromination of **1a** (130 mg, 0.5 mmol) in the presence of TTBP (0.3 equiv.) was complete within 15 min (^{1}H NMR) after which the mixture was evaporated and the residue chromatographed on silica gel. Elution with light petroleum–diethyl ether (9:1 and 4:1) gave TTBP and, successively, a mixture (70 mg) composed of the isomeric bromocyclobutanes **5a,** the bromo ester **9a** and the dibromo ester **8a.** HPLC of the last-mentioned fraction, performed as described above, allowed the separation of **5a** (20 mg, 12% for the minor isomer and 58 mg, 36% for the major isomer), **9a** (28 mg, 18%) and **8a** (8 mg, 4%).

Bromination of **1b** (160 mg, 0.5 mmol) was carried out as reported above. After completion of the reaction (15 min, ^{1}H NMR) the mixture was worked up as for **1a** to give the bromocyclobutene **7b** (53 mg, 30%) and the bromocyclobutanes **5b** (15 mg, 8% for minor isomer and 43 mg, 22% for major isomer).

Bromination of the bicyclohexanes 1 with HBr-free Br_2

Bromine in trimethyl phosphate (0.42 cm^3) was added to the bicyclohexane **1a** (130 mg, 0.5 mmol) in CCl_4 (1.7 cm^3) and the mixture was kept at room temperature until the colour noticeably lightened (30 min). After evaporation of CCl_4 from the mixture, rapid silica gel chromatography of the residue [light petroleum–diethyl ether (4:1) as eluent] followed by HPLC gave the major isomer of the bromocyclobutane **5a** (75 mg, 46%), its minor isomer (38 mg, 24%) and the dibromo ester **8a** (6 mg, 3%).

The reaction of **1b** (160 mg, 0.5 mmol) was performed and worked up as described for **1a**. After 30 min silica gel chromatography of the reaction mixture afforded the major isomer of the bromocyclobutane **5b** (57 mg, 30%), its minor isomer (38 mg, 20%) and the bromocyclobutene **7b** (17 mg, 10%).

Reaction of the bicyclohexanes 1 with HBr

HBr was bubbled at room temperature through a 0.15 mol dm^{-3} solution of **1a** (0.5 mmol) in CCl_4. After 15 min an aliquot (0.1 cm^3) of the solution was dissolved in $CDCl_3$ (0.4 cm^3) and the resulting mixture was monitored by ^{1}H NMR spectroscopy. The spectrum showed, in addition to the presence of MeBr and MeOH, the products **1a**, **3a**, **2a** (*ca*. 3:1:1 molar ratio). When **1b** was treated in the same manner, a ^{1}H NMR in $CDCl_3$–CCl_4 of the mixture after 15 min showed the products **1b**, **3b** and **2b** (*ca*. 6:2:1 molar ratio).

Acknowledgements

This work was financially supported by CNR (Roma) and MURST (Roma). The NMR spectra were run at the Centro di Metodologie Chimico Fisiche, Università di Napoli Federico II.

References

1 U. Ingold and J. C. Walton, *Acc. Chem. Res*., 1986, **19**, 72.
2 W. Kirmse and P. Sandkuhler, *Liebigs Ann. Chem*., 1981, 1394.
3 K. B. Wiberg, J. J. Caringi and M. G. Matturro, *J. Am. Chem. Soc.*, 1990, **112**, 5854; D. Kaufmann and A. de Meijere, *Tetrahedron Lett*., 1979, 787; A. Sinnema, F. Van Rantwijk, A. J. De Koning, A. M. Van Wijk and H. Van Bekkum, *Tetrahedron*, 1976, **32**, 2269; E. N. Cain, *Tetrahedron Lett*., 1971, 1865.
4 J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1371.
5 T. Tsuji, T. Miura, K. Sugiura, Y. Matsumoto and S. Nishida, *J. Am. Chem. Soc.*, 1993, **115**, 482.
6 J. C. Walton, *J. Chem. Soc., Chem. Commun*., 1987, 1252 and references therein.
7 K. B. Wiberg and S. R. Kass, *J. Am. Chem. Soc.*, 1985, **107**, 988.
8 (*a*) F. Giordano, M. R. Iesce and M. L. Graziano, *Gazz. Chim. Ital*., 1994, **124**, 209; (*b*) M. L. Graziano, M. R. Iesce, F. Cermola, F. Giordano and G. Ialongo, *J. Chem. Res.*, 1995, (*S*) 176; (*M*) 1171.
9 M. L. Graziano, M. Lasalvia, V. Piccialli and D. Sica, *Tetrahedron Lett*., 1996, **37**, 527.
10 A. Gaudemer in *Stereochemistry, Fundamentals and Methods,* ed. H. B. Kagan, George Thieme, Stuttgart, 1977, vol. 1, p. 83.
11 G. S. Bisacchi, A. Braitman, C. W. Cianci, J. M. Clark, A. Kirk Field, M. E. Hagen, D. R. Hockstein, M. F. Malley, T. Mitt, W. A. Slusarchyk, J. E. Sundeen, B. J. Terry, A. V. Tuomari, E. R. Weaver, M. G. Young and R. Zahler, *J. Med. Chem*., 1991, **34**, 1415.
12 (*a*) J. March in *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th edn., John Wiley & Sons, New York, 1992, p. 373–376 and references therein; (*b*) Ph. Amice and J. M. Conia, *Bull. Soc. Chim. Fr*., 1974, 1015.
13 Ref. 12*a*, p. 352–362.
14 P. G. Wiering and H. Steinberg, *J. Org. Chem*., 1981, **46**, 1663.
15 W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1029 and references therein.
16 A. Dastan, U. Demir and M. Balci, *J. Org. Chem*., 1994, **59**, 6534.
17 D. E. Pearson, M. G. Frazer, V. S. Frazer and L. C. Washburn, *Synthesis*, 1976, 621.
18 M. L. Graziano, M. R. Iesce, F. Cermola and A. Guitto, unpublished work.
19 J. M. Tanko, R. H. Mas and N. K. Suleman, *J. Am. Chem. Soc.*, 1990, **112**, 5557.
20 M. F. Ruasse, *Acc. Chem. Res*., 1990, **23**, 87.
21 J. B. Lambert, E. C. Chelius, W. J. Schulz, Jr. and N. E. Carpenter, *J. Am. Chem. Soc*., 1990, **112**, 3156 and references therein.
22 S. Hoz, M. Livneh and D. Cohen, *J. Am. Chem. Soc*., 1987, **109**, 5149.
23 S. Fukuzumi and J. K. Kochi, *J. Am. Chem. Soc*., 1982, **104**, 7599.
24 E. Schmitz and I. Eichhorn in *The Chemistry of the Ether Linkage*, ed. S. Patai, Interscience, London, 1967, p. 342.
25 J. Toullec in *Advances in Physical Organic Chemistry,* eds. V. Gold and D. Bethell, Academic Press, London, 1982, vol. **18**, p. 1.
26 R. Huisgen and W. E. Konz, *J. Am. Chem. Soc.*, 1970, **92**, 4102; C. Rappe in *The Chemistry of the Carbon-Halogen Bond*, ed. S. Patai, Wiley, London, 1973, part 2, ch. 17, p. 1071.
27 W. A. Thaler in *Methods in Free-Radical Chemistry*, ed. E. S. Huiser, Marcel Dekker, New York, 1969, vol. 2, p. 121.

Paper 6/07507J
Received 4*th November* 1996
Accepted 8*th April* 1997