6214 J. Org. Chem. 1995, 60, 6214−6217

Facial Stereoselectivity of Two-Step Additions Initiated by Electrophilic Halogens to Methylenecyclohexanes. A Comparison with Epoxidation

Giuseppe Bellucci, Cinzia Chiappe,* and
Giacomo Lo Moro

*Dipartimento di Chimica Bioorganica, via Bonanno 33,
56126 Pisa, Italy*

Giovanni Ingrosso

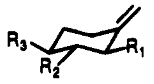
Dipartimento di Biologia, via Monteroni, 73100 Lecce, Italy

Received March 13, 1995

Our research has been aimed at the stereoselective synthesis of epoxides of methylenecyclohexane derivatives for use as substrates for the stereochemical study of hydrolysis by epoxide hydrolases. We undertook an investigation of the stereo- and regiochemistry of additions initiated by electrophilic halogen to these methylene cyclohexanes, for comparison with the stereochemistry of peroxyacid epoxidation. This turned us to the debated question of the π-facial stereoselectivity of additions to this class of compounds,[1−6] which had not been previously examined for two-step additions of the above mentioned type.

Results and Discussion

The olefins, obtained by Corey's procedure,[7] were the 2-methyl, 3-methyl, and 4-*tert*-butyl substituted derivatives **1a−c**, the last having been chosen as a model for a conformationally homogeneous methylenecyclohexane structure.

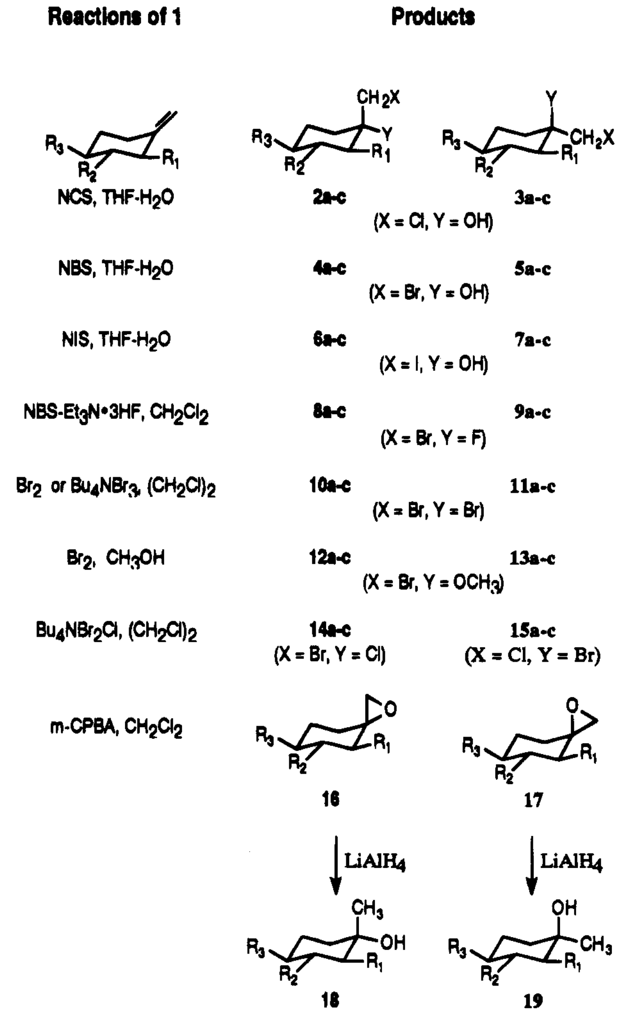


1

a: R_1=CH_3, R_2=R_3=H;
b: R_1= R_3=H, R_2=CH_3;
c: R_1=R_2=H R_3=$C(CH_3)_3$

The investigated reactions are sketched in Scheme 1. They were designed to lead to products whose regio- and stereochemistry could be determined by chemical correlation with known compounds, or by NMR analysis. Epoxides **16** and **17**, obtained either by peroxyacid epoxidation of the olefins **1**, or by base promoted dehydrohalogenation of halohydrins **2−7**, were correlated to the known methyl carbinols **18** and **19**[8] by $LiAlH_4$ reduction. Halohydrins **2−7**, obtained by *N*-chloro- (NCS), *N*-bromo- (NBS), and *N*-iodosuccinimide (NIS)−water addition, were identified by ^{13}C NMR, based on the fact that the diastereoisomer with an axial hydroxyl group rather than an equatorial hydroxyl group, exhibits a lower chemical shift for the quaternary carbinol carbon.[8] The ^{13}C spectra revealed that, for all halohydrins, the CH_2X (X = Cl, Br, I) was more deshielded when located in an equatorial rather than an axial position. These assignments were confirmed by ring closure to epoxides **16** and **17**.

Scheme 1



a: R_1=CH_3, R_2=R_3=H; **b**: R_1=R_3=H, R_2=CH_3; **c**: R_1=R_2=H R_3=$C(CH_3)_3$

The regiochemistry of the *N*-haloamide−water reactions, easily anticipated on the basis of the known Markovnikov attack of the nucleophile at the intermediate cation, was confirmed for NBS−$Et_3N{\cdot}3HF$ addition by the presence of a vicinal F−H coupling of 23 and 18 Hz for the CH_2Br group in the ^1H NMR spectra of compounds **8** and **9**, respectively. The axial and equatorial orientation of the fluorine atom in these compounds was inferred from the ^{13}C chemical shifts,[9] the carbons α, β, and γ to equatorial fluorine being more deshielded than those in the axial form. Further evidence was gleaned from the $^{13}C-^{19}F$ coupling constants,[9] those to the α and γ carbons being higher and that to the β carbon being lower, in the form with equatorial fluorine.

---

(1) Klein, J.; Lichtenberg, D. *J. Org. Chem.* **1970**, *35*, 2654. Klein, J. *Tetrahedron Lett.* **1973**, *44*, 4307.

(2) Sevin, A. Cense, J.-M. *Bull. Soc. Chim. Fr.* **1974**, *5−6*, 963.

(3) Carlson, R. G.; Behn, N. S. *J. Org. Chem.* **1967**, *32*, 1363.

(4) Sende, Y.; Kamiyame, S.; Imaizumi, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 531.

(5) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874. Lin, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 997.

(6) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875.

(7) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

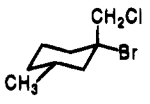
(8) Sende, Y.; Ishiyama, J.; Imaizumi, S. *Tetrahedron* **1975**, *31*, 1601.

(9) Subbotin, O. A.; Sergeyev, N. M. *J. Am. Chem. Soc.* **1975**, *97*, 1080.

0022-3263/95/1960-6214$09.00/0

The dibromides **10** and **11** were likewise identified on the basis of the higher chemical shift reported for the carbon bearing axial bromine,[9] and of the more deshielded equatorial CH_2Br, relative to the CH_2Br of bromohydrins **4/5** and bromo fluorides **8/9**. The assignments of methoxy bromides **12** and **13** were similarly based on the lower ^{13}C chemical shift of the axial with respect to the equatorial CH_2Br group and on the lesser deshielding of the carbon bearing axial oxygen, in analogy to the carbinol carbon of halohydrin couples **2/3**, **4/5**, **6/7**, and alcohols **18/19**.

Bromo chlorides **14** and **15** were obtained by reacting olefins **1** with Br_2 in the presence of a large excess of tetrabutylammonium chloride. The actual reactant was presumably the Br_2Cl^- anion, which is immediately formed from the interaction of Br_2 and Cl^-, as shown by the disappearance of the Br_2 absorption maximum at 410 nm and the appearance of a new intense band centered at 242 nm in the electronic spectrum. This anion is expected to react with olefins by a mechanism similar to that established for the Br_3^- reactions.[10] The regiochemistry of these bromo chloro adducts was determined from the ^{13}C chemical shift of the CH_2X group, which is definitely greater for X = Cl than for X = Br. The stereochemistry was rigorously deduced only for bromo chloride **15b**, whose formation from **1b** was accompanied by that of the minor stereoisomer **20b**. The stereoisomer having the higher ^{13}C chemical shifts for both the CH_2Cl group and the quaternary carbon bearing bromine was assigned the configuration **15b**, by analogy with the CH_2Cl group of the diastereoisomeric couples of chlorohydrins **2/3** and the quaternary carbon of dibromides **10/11**. The same stereochemistry was attributed, by extension, to the main products **15** of the Bu_4NBr_2Cl reaction of olefins **1a** and **1c**. The stereochemistry of the minor products **14** was assumed on the basis of mechanistic considerations discussed below.



20b

The product distributions of all investigated additions were determined from the CH_2X ^1H NMR signals of the reaction mixtures, which were different for each diastereoisomeric couple. They appeared as singlets for compounds of type **b** and **c**, and as AB quartets for most compounds **a**, where the proximity of the methyl substituted chiral center made the CH_2X protons diastereotopic. In the case of methoxy bromides **12** and **13**, the diastereoisomer ratio was evaluated using the methoxyl singlets. Halohydrins **2**–**7** were also cyclized to epoxides **16** and **17**, which were quantitated by GLC. The ratios obtained with the two techniques were in satisfactory agreement. All reactions of *N*-haloamides and those of Br_2 in methanol were completely regiospecific with the nucleophilic attack occurring at the quaternary carbon. Those of Bu_4NBr_2Cl gave instead various regioisomers.

The ratios of products of type **a**, **b**, and **c** having the same regiochemistry and the CH_2X group in the axial and equatorial positions are reported in Table 1.

Table 1. Diastereoisomer Ratios Obtained in Additions to Olefins 1a–c

	products[a]		
reagent	**a**: CH_2X_{ax}/ CH_2X_{eq}	**b**: CH_2X_{ax}/ CH_2X_{eq}	**c**: CH_2X_{ax}/ CH_2X_{eq}
m-CPBA	45:55	25:75	28:72
NCS–H_2O	95:5	96:4	90:10
NBS–H_2O	85:15	85:15	82:18
NIS–H_2O	55:45	60:40	55:45
NBS–$Et_3N{\cdot}3HF$	85:15	80:20	82:18
$Br_2/(CH_2Cl)_2$	b	70:30	70:30
Br_2/MeOH	90:10	95: 5	90:10
Bu_4NBr_3	30:70	20:80	15:85

[a] **a**: $R_1 = CH_3$, $R_2 = R_3 = H$; **b**: $R_1 = R_3 = H$, $R_2 = CH_3$; **c**: $R_1 = R_2 = H$ $R_3 = C(CH_3)_3$. [b] A complex products mixture was obtained, due to rearrangements involving the tertiary carbon adjacent to the double bond.

The peroxyacid epoxidation[11] is a typical one-step, irreversible electrophilic addition and can serve as a model for the electrophilic step of two-step additions initiated by electrophilic halogens, that lead to halonium ion intermediates. Epoxidation has previously been examined for the 2-methyl and the 4-*tert*-butyl derivatives **1a** and **1c**.[2,3] Our results are in good agreement with the previously reported 69% preference for axial attack on **1c** by mCPBA in dichloromethane[3] and with the substantial lack of stereoselectivity (54% axial attack) reported for **1a**.[2] A greater preference (75%) for axial approach has been found in this current study for the epoxidation of the 3-methyl derivative **1b** with respect to the 3,6-dimethyl substituted (64%) and the 3-*tert*-butyl substituted (60%) methylenecyclohexane derivatives.[2]

Several rationalizations have been put forth[2,3,5,6] for the preference for axial attack in the epoxidation of unhindered exocyclic olefins, the most convincing being the Cieplak proposal[6] involving hyperconjugative σ assistance, which is claimed to be valid for any addition reaction to a trigonal carbon, provided that the transition state is electron deficient. According to this model, whereas steric hindrance promotes equatorial attack, electron donation from the cyclohexane σ C(2)–C(3) and C(5)–C(6) bonds and σ C(2)–H and C(6)–H axial bonds into the developing σ^* orbital in the transition state promotes axial approach, since the C–H bonds are better donors than the C–C bonds.[12] In unhindered compounds, the hyperconjugative σ assistance overcomes the steric effect, causing the observed preference for axial attack and leading to the epoxide with equatorial CH_2 as the main product. If this rationale is correct, in 2-substituted derivatives the two effects may counterbalance, and this can explain the substantial loss of stereoselectivity observed in the epoxidation of **1a**.

The Cieplak model can likewise explain the preference for axial approach of the halogen observed in all additions of NCS and NBS and in those of Br_2, if bonding of the electrophilic halogen to both olefinic carbons occurs in the transition state, as expected for the formation of halonium ion intermediates. The subsequent nucleophilic attack on these intermediates occurs with inversion at the tertiary carbon, leading regiospecifically to compounds with axial CH_2X groups as the main products (Scheme 2). If the intermediates of these additions were tertiary open halocarbonium ions, their capture by nu-

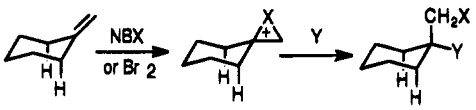
---

(10) Bellucci, G.; Bianchini, R.; Ambrosetti, R.; Ingrosso, G. *J. Org. Chem.* **1985**, *50*, 3313. Bellucci, G.; Bianchini, R.; Vecchiani, S. *J. Org. Chem.* **1987**, *55*, 3355.

(11) Lang, T. J.; Wolber, G. J.; Bach, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 3275.

(12) See footnote 20 of ref 6.

Scheme 2



cleophiles should preferentially occur[5] by an axial attack with hyperconjugative σ assistance, leading to products with equatorial CH_2X, in contrast with the experimental results. This is evidence for the product-determining formation of bridged intermediates.

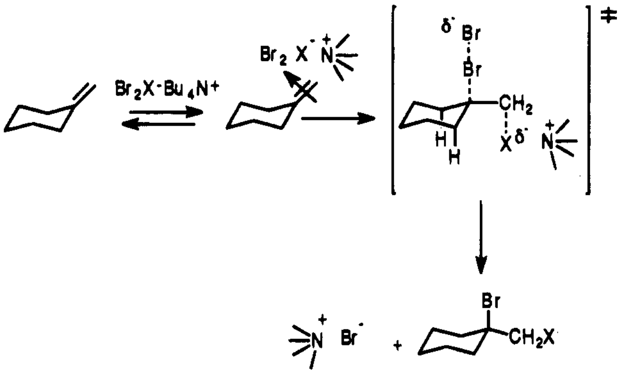
It must be emphasized that, with the exception of the addition of Br_2 in 1,2-dichloroethane, all other above mentioned reactions exhibit a greater preference for axial approach of the electrophile than that found in the peroxyacid epoxidation. This suggests that NCS and NBS (but expecially the former) and molecular Br_2 have lesser steric requirements than the peroxyacid in their respective transition states.[13] These requirements appear to be so small that no steric interaction with the 2-methyl group of **1a**, which would hinder an axial approach in the epoxidation of this olefin, seems to occur. From the synthetic point of view, it is noted that NCS–water additions followed by dehydrochlorination provide a simple and efficient access to the minor product of epoxidation of methylenecyclohexane derivatives in a nearly stereoisomerically pure (≥90%) form.

At variance with the NCS and NBS reactions, the NIS–water additions are essentially nonstereospecific. In the framework of the Cieplak model, this could be ascribed to the increased steric requirements of iodine with respect to bromine and chlorine. In this case, however, a larger effect would be expected in the 2-methyl substituted than in the 3- and 4-substituted compounds. The similar diastereoisomer ratios obtained for the 2-methyl, 3-methyl, and 4-*tert*-butyl derivatives speak against this explanation. An alternative rationalization can be found in the fact that additions initiated by electrophilic iodine are considered to involve the reversible formation of iodonium ions.[14,15] Under these conditions, if the rate of interconversion of the iodonium intermediates is comparable with the rate of their nucleophilic opening, the overall regio- and stereochemistry of the addition will be determined partially in both the electrophilic and the nucleophilic step. A balance of opposing effects in the two steps (i.e. σ hyperconjugative stabilization of axial approach of the electrophile and stabilization of the axial approach of the nucleophile at the tertiary carbon of the iodonium intermediate) may be responsible for the loss of stereoselectivity observed in these reactions.

A similar rationalization can perhaps explain the decreased formation of the product with axial CH_2Br in the reactions of **1b** and **1c** with Br_2 in 1,2-dichloroethane with respect to those with NBS–water and with Br_2 in methanol, where the bromonium intermediates are immediately captured by the nucleophilic solvent.

The use of Bu_4NBr_3 as brominating reagent was examined in order to obtain information about the stereochemistry of additions in which product formation is completely controlled during the nucleophilic step. It has been shown that the reaction mechanism of tribromides with olefins consists of a rate and product-determining nucleophilic attack of Br^- on equilibrating olefin–Br_2 charge transfer complexes formed at the two faces of the double bond.[10] A diastereoisomer ratio in favor of the products with an equatorial CH_2Br group was found with this reagent. However, on account of its different mechanism, the same regiochemistry seen in the molecular Br_2 reactions could not be safely assumed for the Br_3^- additions.

Scheme 3



The reaction of **1c** with Bu_4NBr_2Cl, in which the nucleophilic attack is made by the Cl^- anion, gave products **14c** and **15c**, arising, respectively, by attack of this anion at the tertiary and the primary carbon of the axially formed olefin–Br_2 charge transfer complex, in a ratio of 15:85. In the analogous reactions of **1a** and **1b**, adducts of type **15** were again the main products. In the case of **1b**, minor amounts of products **14b** and **20b** were also detected and quantified by ^1H NMR spectroscopy. The **14b**:**15b**:**20b** ratio was 17:73:10. Minor amounts of products of type **14** and **20** were found in the reaction of **1a**, too. However, their quantification by ^1H NMR was made difficult by the diastereotopic nature of the CH_2X protons, leading to AB quartets instead of singlets.

When compared with the stereochemistry of the molecular Br_2 and NBS additions, the course of the Bu_4NBr_3 and Bu_4NBr_2Cl reactions seems at first sight to diverge from the Cieplak model. The inconsistency is, however, removed if one considers that, at variance with the Br_2 and NBS reactions, the Br_3^- and Br_2Cl^- reactions do not involve the intermediate formation of bromonium ions, but occur through a rate and product determining transition state in which the formation of the bond of the nucleophile to the primary exocyclic carbon is sychronous with bond formation between bromine and the tertiary carbon (Scheme 3).[10] The formation of this bond from the axial side can again be promoted by hyperconjugative σ assistance by the C(2)–H and C(6)–H axial bonds, dictating a preferential nucleophilic attack on the axially formed olefin–Br_2 charge transfer complex, which leads to the product with equatorial CH_2X.

Thus, all examined electrophilic additions initiated by electrophilic halogens appear to be consistent with the Cieplak model irrespective of whether the stereochemical outcome is determined during the electrophilic step or the nucleophilic step.

Experimental Section

^1H and ^{13}C NMR spectra were registered at 200 MHz in $CDCl_3$. GLC analyses were carried out using a G-TA column (10 m, 75 °C, helium flow 1.5 mL/min).

---

[13] According to the Bartlett mechanism (Bartlett, P. D. *Record. Chem. Prog.* **1957**, *18*, 111) the transition state of the peroxyacid epoxidation of olefins involves a fairly rigid and sterically demanding arrangement of the reagents, with the peroxyacid forming an intramolecular hydrogen bond and the two C–O bonds being formed simultaneously.

[14] Bowers, A.; Denot, E.; Becerra, R. *J. Am. Chem. Soc.* **1960**, *82*, 4007.

[15] Freppel, C.; Richer, J.-C. *Tetrahedron Lett.* **1972**, *23*, 2321.

All solvents were reagent grade. Commercial 2-methylcyclohexanone (99%), 3-methylcyclohexanone (97%), 4-*tert*-butylcyclohexanone (99%), *m*-chloroperoxybenzoic acid (70%), *N*-chlorosuccinimide (98%), *N*-bromosuccinimide (99%), *N*-iodosuccinimide (95%), tetrabutylammonium tribromide (98%), tetrabutylammonium chloride (dry, 99%), and bromine (1 mL sealed ampules, > 99.5%) were used as supplied. Olefins **1a–c** were prepared from the corresponding cyclohexanones following the Corey procedure.[7]

Epoxidations with *m*-Chloroperoxybenzoic Acid. To 1 mmol of the appropriate olefin **1** in 10 mL of dichloromethane at 0 °C a 20% excess of *m*-chloroperoxybenzoic acid was added. The reaction mixture was stirred for 4 h and then washed with 10% aqueous $NaHSO_3$ and saturated aqueous Na_2CO_3. The organic phase was dried ($MgSO_4$) and evaporated. The crude epoxide mixtures were analyzed by ^1H and ^{13}C NMR and by GLC. The product ratios are reported in Table 1.

Reactions with *N*-Halosuccinimide–Water. *N*-Chloro, *N*-bromo, or *N*-iodosuccinimide (1.1 mmol) was added at room temperature to 1 mmol of the appropriate olefin **1** dissolved in 10 mL of THF–H_2O (4:1). The reaction mixtures were stirred at room temperature for 2–3 h and then washed with a 10% aqueous $NaHSO_3$, dried, and evaporated. The crude residues were analyzed by ^1H and ^{13}C NMR. The halohydrin mixtures were then transformed into the corresponding epoxides by titration of 2-propanol–water (3:2) solutions with NaOH (0.1 N), using phenolphthalein as indicator, followed by dilution with water and extraction with dichloromethane. The resulting epoxide mixtures were analyzed by GLC. The product ratios are reported in Table 1.

Additions of *N*-Bromosuccinimide–$Et_3N{\cdot}3HF$. *N*-Bromosuccinimide (2 mmol) and $Et_3N{\cdot}3HF$ (3.6 mmol) were added to 2 mmol of olefins **1** dissolved in 2 mL of dichloromethane. The mixtures were stirred at room temperature for 8 h and then washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The crude residues were analyzed by ^1H and ^{13}C NMR. The product ratios are reported in Table 1.

Additions of Bromine and Bu_4NBr_3. (a) In Aprotic Solvent. 1,2-Dichloroethane solutions of Br_2 or Bu_4NBr_3 (5 mL, *ca.* 0.2 M) were rapidly mixed with 5 mL of 0.2 M solutions of olefins **1** in the same solvent. When the color disappeared, the reaction mixtures were evaporated (after washing with water for the Bu_4NBr_3 reactions), and the residues were analyzed by ^1H and ^{13}C NMR. The product ratios are shown in Table 1.

(b) In Protic Solvent. The same procedure used for the reactions of Br_2 in 1,2-dichloroethane was applied to the brominations in methanol, except that lower reagent concentrations (2×10^{-3} M) were employed in order to avoid the formation of dibromides.[16] At the end of the reactions the mixtures were diluted with water, and the products were extracted with dichloromethane and analyzed by ^1H and ^{13}C NMR. The product ratios are reported in Table 1.

Additions of Bu_4NBr_2Cl. Dry tetrabutylammonium chloride (20 mmol) was added to 50 mL of a 4×10^{-2} M solution of Br_2 in 1,2-dichloroethane. The solution immediately turned to yellow, while the Br_2 absorption band centered at 410 nm disappeared and a new intense UV band appeared, whose $\lambda_{max} = 242$ nm was determined under more diluted conditions. This solution was rapidly mixed with 50 mL of a 4×10^{-2} M solution of the appropriate olefin **1** in the same solvent. The mixtures were stored in the dark at room temperature for *ca.* 1 h and then repeatedly washed with water, dried, and evaporated. The residue was analyzed by ^1H and ^{13}C NMR.

Reduction of Epoxides 16 and 17 with $LiAlH_4$. To a solution (5 mL) of epoxide **16** or **17** (1 mmol) in anhydrous ethyl ether was added $LiAlH_4$ (2 mmol), and the mixture was stirred at room temperature for 1 h and then diluted with ice–water. The organic phase was dried ($MgSO_4$) and evaporated to give alcohols **18** or **19**, which were identified by ^1H and ^{13}C NMR.[8]

Complete listings of ^1H and ^{13}C NMR data of all obtained compounds are given in the supporting information.

Acknowledgment. This work was supported in part by grants from Consiglio Nazionale delle Ricerche (CNR, Roma) and Ministero dell'Universita' e della Ricerca Scientifica e Tecnologica (MURST, Roma).

Supporting Information Available: Spectral data of all mentioned compounds (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9504833

---

(16) It has been shown that the chemoselectivity of olefin bromination in methanol depends on the reagent concentrations, exclusive solvent incorporation into the products being observed at low concentrations (unpublished results). A similar effect was found in acetonitrile. (see: Bellucci, G.; Bianchini, R.; Chiappe, C. *J. Org. Chem.* **1991**, *56*, 3067).