Fluorination with Xenon Difluoride. 20. Fluorination of Halo-Substituted Alkenes[1]

Ana Gregorčič and Marko Zupan*

Department of Chemistry and "Jožef Stefan" Institute, University of Ljubljana, Ljubljana, Yugoslavia

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Acid-catalyzed liquid phase fluorine addition with xenon difluoride to 1,1-diphenyl-2-haloethylenes resulted in the formation of vicinal difluorides. *trans*-α-Fluorostilbene and α,β-difluorostilbene easily reacted with xenon difluoride, thus forming the corresponding trifluoro or tetrafluoro products. *cis*- and *trans*-α-chloro- or -bromostilbene were converted with XeF_2 to vicinal difluorides. The predominance of syn addition of fluorine over anti addition was observed. In the case of *cis*- and *trans*-α-bromostilbene, in addition to vicinal products, the rearranged product 1,1-difluoro-2-bromo-1,2-diphenylethane was formed as well.

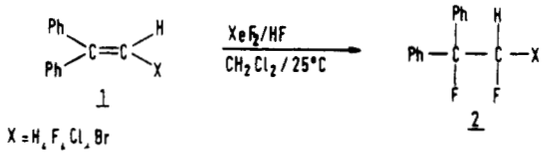
It has been demonstrated that xenon difluoride represents an easy handling mild reagent for fluorination of alkenes,[2-9] acetylenes,[10] aromatic molecules,[11-19] heteroaromatic molecules,[20,21] and some organic molecules containing heteroatoms.[22-26] The above mentioned reactions are usually catalyzed by HF or CF_3COOH and the present experimental evidence suggests that the use of XeF_2 is limited to fluorination of substrates reactive enough. It is known that haloalkenes are much less reactive than the corresponding unsubstituted alkenes.[27] We now report studies of HF-catalyzed fluorine addition to fluoro-, chloro-, and bromo-substituted 1,1-diphenylethylenes and *cis*- and *trans*-α-halostilbenes.

Results and Discussion

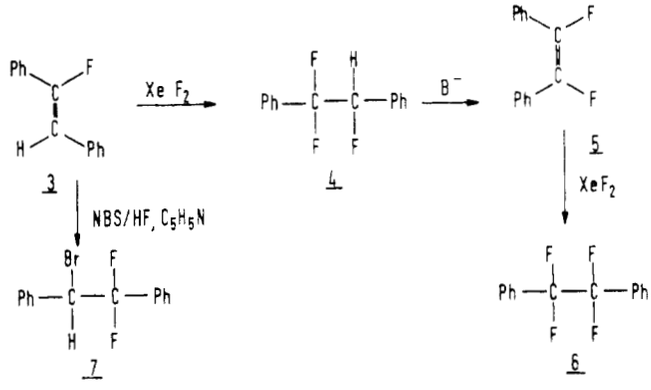
We have already demonstrated that HF-catalyzed fluorination of 1,1-diphenylethylene[2,4] with XeF_2 gave vicinal difluorides in high yield. Fluorination of 1,1-diphenyl-2-chloroethylene (**1**, Scheme I) with xenon difluoride in the presence of HF as catalyst proved to be much slower and needed 25 h for completion. The crude product showed only two signals in its ^{19}F NMR spectrum at δ 161 ppm (dd) and δ 168 ppm (dd). On the basis of NMR, mass, and IR spectra we concluded that only 1,1-diphenyl-1,2-difluoro-2-chloroethane was formed (**2**). The same result was obtained when 1,1-diphenyl-2-bromoethylene was fluorinated. We have found no evidence for elimination reactions, which predominate in fluorination of 1,1-diphenylethylene with fluorine at low temperature,[28] nor any rearranged products, observed when 1,1-diphenylethylene was fluorinated with difluoroiodobenzene;[29] neither have we found any hydrogen fluoride adducts which were found on fluorination of alkenes with xenon difluoride in the gas phase.[30]

We have already established that phenyl-substituted acetylenes[10] react with XeF_2, but in no case have primarily formed difluoroalkenes been isolated. The possibility is that there is either no formation of difluoroalkenes or, in this case, a higher reactivity of difluoroalkenes compared to acetylenes, which is rather surprising for they are known to be much less reactive for electrophilic addition.[27,31,32] The HF-catalyzed room-temperature fluorination of *trans*-fluorostilbene (**3**, Scheme II) with XeF_2 gave only one product, which shows two signals in ^{19}F NMR. The signal at lower field proved to be an ABMX type of spectrum, with the chemical shift at 109.53 and at 113.75 ppm, with the following coupling constants: $^2J_{FF}$ =

Scheme I



Scheme II



276 Hz, $^3J_{FF}$ = 16.5 and 15 Hz, and $^3J_{FH}$ = 9 Hz. The higher field signal appeared as ddd at 198 ppm with the following coupling constants: $^2J_{FH}$ = 49.5 Hz and $^3J_{FF}$ = 16.5 and 15 Hz. On the basis of NMR, mass, and IR data we established that 1,1,2-trifluoro-1,2-diphenylethane (**4**) was formed. A 7-h reaction under basic conditions (KO-*t*-Bu), convenient for anti elimination, resulted in only one product (**5**), which shows a singlet signal in ^{19}F NMR at δ 133 ppm. The liquid product **5** was converted under photochemical conditions[33] to a solid product, which shows a singlet signal in ^{19}F NMR at 157 ppm. On the basis of this transformation, we established that 1,1,2-trifluoro-1,2-diphenylethane converted under basic conditions only to *cis*-1,2-difluoro-1,2-diphenylethylene (**5**), which readily further reacted with XeF_2 to form 1,1,2,2-tetrafluoro-1,2-diphenylethane (**6**).

Recently, we have demonstrated that product distribution in fluorine addition with XeF_2 to a series of *cis*- and *trans*-1-phenyl-2-substituted ethylenes is little influenced by the starting alkenes (cis or trans), or by the magnitude of the substituent, and the formation of a β-fluorocarbonium ion was suggested.[5] Accordingly, we studied the influence of the halogen bonded to the double bond on the stereochemistry of fluorine addition. The fluorination of *trans*-α-chlorostilbene (**8**, Scheme III) afforded two isomeric addition products, **10** and **11**, in relative yields of 30 and 70%, respectively (Table II). NMR data for both isomers are collected in Table I. Since the isomers could not be separated, the mixture (**11**–**10** 2.36:1) was treated with KO-*t*-Bu to afford *cis*- (**5**) and *trans*- (**12**) difluorostilbene in a ratio of 2.4:1. Besides elimination of hydrogen chloride, leading to **5** and **12**, a small amount of α-fluoro-β-chlorostilbene was also formed. *cis*-α-Chlorostilbene (**9**), after the fluorination with XeF_2, gave 31% of **10** and 69% of **11**. On the basis of the above mentioned data, it is evident that the structure of the starting olefin (cis or trans) has no effect on the product distribution, but it is clear that the chlorine atom changes the course of fluorine addition, where

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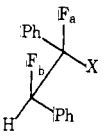
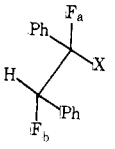
Table I. NMR Data for 1,2-Difluoro-1-halo-1,2-diphenylethanes





X	Br	Cl	H	Br	Cl	H	F
δ_{F_a}	125.8	123.5	203.3	126.2	122.5	206.3	109.53, 113.97
δ_{F_b}	179.5	182.3	(AA'XX')	180.5	183.7	(AA'XX')	198
δ_H	6.01	5.62	5.37	5.98	5.60	5.46	5.8
J_{F_bH}	48	49.5		48	48		48
J_{F_aH}	14	12		18	12		9
$J_{F_aF_b}$	25.5	21		22.5	19.5		16.5
							15.0

Scheme III

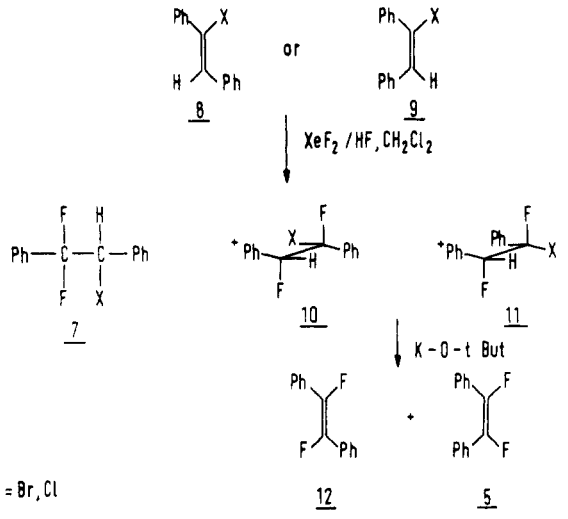
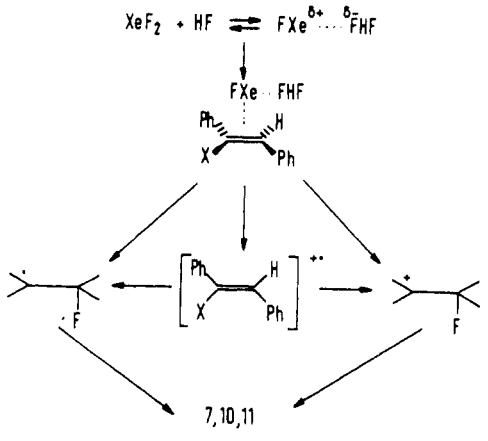


Table II. Product Distribution in Fluorination of Substituted Halostilbenes (8 and 9) with Xenon Difluoride in Methylene Chloride at 25 °C

olefine	X	relative yields[a] 10	11	7
trans	H[b]	62[h]	38[k]	ref 5
	Cl[c]	30[i]	70[l]	trace
	Br[d]	27[j]	58[m]	15[n]
cis	H[e]	53	47	ref 5
	Cl[f]	31	69	trace
	Br[g]	20	60	20

[a] Determined by ^{19}F NMR spectroscopy. [b-n] Registry no.: [b] 103-30-0. [c] 948-98-1. [d] 14447-41-7. [e] 645-49-8. [f] 948-99-2. [g] 15022-93-2. [h] 14090-31-4. [i] 68936-72-1. [j] 68936-73-2. [k] 52795-54-7. [l] 68936-74-3. [m] 68936-75-4. [n] 724-66-3.

Scheme IV

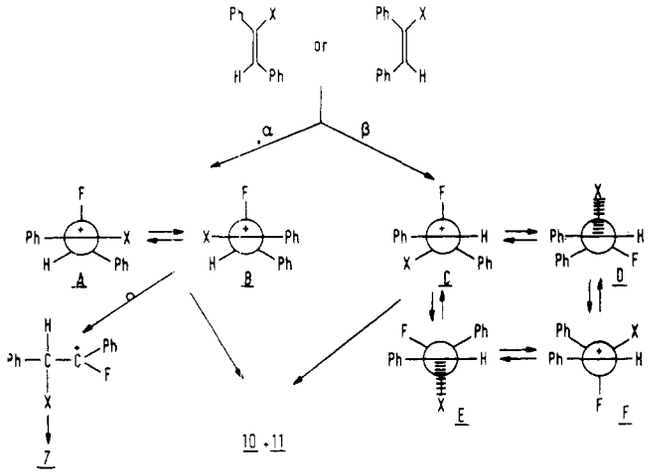


syn addition predominates over anti addition in the case of *trans*-α-chlorostilbene, while in the case of *trans*-stilbene, trans addition was slightly predominant.[5]

The fluorination of *trans*-α-bromostilbene gave two isomeric vicinal difluorides, whose structures were also determined on the basis of the chemical transformation (mixture **11**–**10** 2.2:1) to *cis*- and *trans*-difluorostilbene (**5**–**12** 2.18:1). Besides vicinal difluorides, the rearranged product **7** was formed as well in a relative yield of 15%. The product 1,1-difluoro-2-bromo-1,2-diphenylethane (**7**) was isolated by preparative GLC and identified on the basis of its IR, NMR, and mass spectral data, and by comparison to the products formed by bromofluorination of *trans*-fluorostilbene (**3**), (Scheme II) with a mixture of *N*-bromosuccinimide–HF–pyridine.[34] The fluorination of *cis*-α-bromostilbene (**9**) afforded 20% of rearranged product (**7**) and two vicinal difluorides (**10** and **11**, Table II). As in the case of the chlorine substituent in chloro-substituted stilbenes, the bromine substituent has a significant effect on the course of fluorine addition.

On the basis of earlier observations of the addition of fluorine, and observations already made in this paper, the following reaction mechanism (Scheme IV) could be suggested. It might be expected that in the presence of hydrogen fluoride xenon difluoride behaves as an electrophile. In the next step, a π complex is probably formed between this electrophilic species and the olefin, which could be transformed by a heterolytic Xe–F bond cleavage into a fluorocarbonium intermediate or by homolytic Xe–F bond cleavage to a fluoroalkyl radical intermediate, which can then react further and thus form products **7**, **10**, and **11**. Furthermore, another possibility is the formation of an ion radical, which has already been observed in the fluorination of benzene and its derivatives,[11] transforming in the next step by ·Xe–F or XeF_2 into a free radical or carbonium ion intermediate. The fluorocarbonium ions could be formed in two ways (Scheme V), i.e., α and β. The α path must be taken into account for the explanation of the formation of rearranged products (**7**). The formation of carbonium ions via the β path can give a better explanation of the differences in the stereochemistry of fluorine addition in comparison to unsubstituted stilbene. The primary formed ions C, formed by fluorination of *trans*-α-halostilbene (Scheme V), could be stabilized by the formation of cyclic ion E (it is known that chlorine and bromine substituents form partly or completely bridged cyclic halonium ions in the addition reactions of chlorine and bromine, depending on the structure of the alkene, solvent polarity, temperature,

Scheme V



etc.[27,35]), which could be further attacked from the other side by a fluorine anion, thus forming predominanting isomer **11**. In the case of *cis*-α-halostilbene, the primary formed ion formed via path β probably has structure F, which can then be stabilized by neighboring group participation, thus forming the bridged ions D or E, the latter being more stable than the former. Further attack of a fluoride ion on ion E again favors the formation of isomer **11**.

Experimental Section

IR spectra were recorded using a Perkin-Elmer 257 spectrometer and ^1H and ^{19}F NMR spectra by a Jeol-JNM-PS-100 from CCl_4 solution with Me_3Si or CCl_3F as internal reference. Mass spectra and high-resolution measurements were taken on a CEC-21-110 spectrometer. Gas–liquid partition chromatography was carried out on a Varian Aerograph Model 1800 and TLC on Merck PSC-Fertigplatten silica gel F 254 (activated for 3 h at T = 120 °C before use).

Materials. Pure samples of olefins were prepared by known methods: 1,1-diphenyl-2-chloroethylene,[36] 1,1-diphenyl-2-bromoethylene,[37] *cis*- and *trans*-fluorostilbene,[5] *cis*- and *trans*-chlorostilbene,[38] and *cis*- and *trans*-bromostilbene.[39] Hydrogen fluoride of Fluka Purum quality was used without further purification. Methylene chloride was purified[40] and stored over molecular sieves. Xenon difluoride was prepared by a photosynthetic method[41] and its purity was better than 99.5%.

Addition and Isolation Procedures. To a solution of 1 mmol of olefin in methylene chloride (2 mL) in a Kel-F vessel, 1 mmol of xenon difloride was added at T = 25 °C and under stirring anhydrous hydrogen fluoride was introduced into the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was evolved. After 3–24 h (depending on the substrate) xenon gas evolution ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 mL), washed with 10 mL of 5% $NaHCO_3$ and water, and dried over anhydrous sodium sulfate. The crude reaction mixture was separated by preparative GLC or TLC.

1,1-Diphenyl-1,2-difluoro-2-bromoethane (2):[34] an oily product (50%) (decomposition on heating); NMR δ_F −156 (dd), −161.5 (dd), δ_H 6.9 (dd) ($^2J_{F,H}$ = 48 Hz, $^3J_{F,F}$ = 27 Hz, $^3J_{F,H}$ = 10.5 Hz); mass spectrum calcd for $C_{14}H_{11}BrF_2$ *m/e* 296.0012, found 296.0018, *m/e* 296 (M^+, 1%), 216 (37), 199 (72), 198 (100), 197 (89), 196 (84), 183 (67), 178 (57), 165 (79), 98 (61), 51 (54).

1,1-Diphenyl-1,2-difluoro-2-chloroethane (2):[34] an oily product (50%) (decomposition on heating); NMR δ_F −161 (dd), −168.5 (dd), δ_H 6.6 (dd) ($^2J_{F,H}$ = 49.5 Hz, $^3J_{F,F}$ = 21 Hz, $^3J_{F,H}$ = 9 Hz); mass spectrum calcd for $C_{14}H_{11}ClF_2$ *m/e* 252.0516, found 252.0513, *m/e* 254 (M^+ + 2, 5%), 252 (M^+, 17), 198 (58), 185 (100), 165 (63).

1,1,2-Trifluoro-1,2-diphenylethane (4): solid product (50%); mp 80–83 °C; NMR δ_F 109.53, −113.75 (ABMX), −198 (ddd) ($^2J_{F,F}$ = 276 Hz, $^3J_{F,F}$ = 16.5, and 15 Hz, $^3J_{F,H}$ = 9 Hz, $^2J_{F,H}$ = 49.5 Hz), δ_H 5.64 (dt); mass spectrum calcd for $C_{14}H_{11}F_3$ *m/e* 236.0812, found 236.0818, *m/e* 236 (M^+, 28%), 127 (100), 109 (73), 77 (20).

1,1,2,2-Tetrafluoro-1,2-diphenylethane (6): solid product (80%); mp 122–123 °C; NMR δ_F −116 (s); mass spectrum calcd for $C_{14}H_{10}F_4$ *m/e* 254.0718, found 254.0721, *m/e* 254 (M^+, 33%), 127 (100), 77 (24), 51 (10).

1,2-Difluoro-1-chloro-1,2-diphenylethane (10 and 11): 70% of oily mixture of isomers; NMR data are collected in Table I; mass spectrum calcd for $C_{14}H_{11}ClF_2$ *m/e* 252.0517, found 252.0517, *m/e* 254 (M^+ + 2, 10%), 252 (M^+, 33), 216 (50), 143 (80), 127 (100), 109 (88). The structures of the isomers were determined on the basis of the chemical transformation to *cis*- and *trans*-difluorostilbene.

1,2-Difluoro-1-bromo-1,2-diphenylethane (10 and 11): 60% of oily mixture of diastereoisomers; NMR data are collected in Table I; mass spectrum calcd for $C_{14}H_{11}BrF_2$ 296.0012, found 296.0019, *m/e* 298 (M^+ + 2, 5%), 296 (M^+, 5%), 217 (100), 197 (62), 189 (67), 187 (67), 127 (87), 109 (89). The structures of the isomers were determined on the basis of the chemical transformation to *cis*- and *trans*-difluorostilbene.

1,1-Difluoro-2-bromo-1,2-diphenylethane (7): in a mixture of 70% hydrogen fluoride (2 mL) and ether (2 mL), NBS (250 mg, 1.4 mmol) was dissolved with stirring at 0 °C, and 1 mmol (198 mg) of *trans*-fluorostilbene (**3**) was added. The mixture was stirred for 24 h at 15 °C, then poured into ice–water and extracted with ether. The ether layer was washed with water, aqueous sodium hydrogen carbonate, then water again, dried (Na_2SO_4), and evaporated, and 88% of oily product was isolated. Purification by GLC gave 45% of solid product, mp 44–47 °C (mp[42] 44–45 °C), NMR δ_F −97.5 (dd), −104.5 (dd), δ_H 5.1 (dd) ($^2J_{F,F}$ = 258 Hz, $^3J_{F,H}$ = 16.5 and 9 Hz).

Treatment of 1,2-Difluoro-1-halo-1,2-diphenylethane (10 and 11) under Basic Conditions: A 2.36:1 mixture (0.5 mmol) of 1,2-difluoro-1-chloro-1,2-diphenylethane **11–10**, in 1 M potassium *tert*-butoxide in *tert*-butyl alcohol, was stirred at 50 °C for 7 h, then cooled, mixed with water (15 mL), and extracted with methylene chloride. The extract was washed with dilute acid and water, dried (Na_2SO_4), filtered, and evaporated, and the residue was analyzed by GLC and NMR spectroscopy. The product was a 2.4:1 mixture of *cis*- (**5**) and *trans*-difluorostilbene (**12**). The two components were separated by GLC on 10% Carbowax 20M on Varaport 30 at 210 °C: 40% of oily *cis*-difluorostilbene (NMR δ_F −133 (s), mass spectrum calcd for $C_{14}H_{10}F_2$ *m/e* 216.0750, found 216.0746, *m/e* 216 (M^+, 100%), 165 (30), 127 (34), 109 (13)) and 20% of solid *trans*-difluorostilbene (mp 66–70 °C (lit.[33] mp 74–75 °C); NMR δ_F −157.5 (s); mass spectrum calcd for $C_{14}H_{10}F_2$ *m/e* 216.0750, found 216.0750, *m/e* 216 (M^+, 100%), 165 (28)) were isolated.

A 2.2:1 mixture (0.5 mmol) of 1,2-difluoro-1-bromo-1,2-diphenylethane **11–10** gave, under the conditions mentioned above, a 2.18:1 mixture of *cis*- (**5**) and *trans*-difluorostilbene (**12**).

Fluorination of *cis*- and *trans*-halostilbene (**8** and **9**) with XeF_2 was repeated three times, and ^{19}F NMR spectra were recorded for the crude reaction mixtures.

To test the stability of the difluorides in the reaction mixture, a sample (0.2 g) of the mixture of **10** and **11** was dissolved in 2 mL of methylene chloride, 20 mg of XeF_2, and a catalytic amount of HF and was stirred at 25 °C for 3 h. After workup, the NMR spectra showed no significant differences.

Acknowledgments. We thank Professor J. Slivnik for the xenon difluoride. The financial assistance of the Boris Kidrič Foundation is acknowledged.

Registry No.—**1** (X = Cl), 4541-89-3; **1** (X = Br), 13249-58-6; **2** (X = Br), 59974-24-2; **2** (X = Cl), 68936-76-5; **3**, 671-19-2; **4**, 68936-77-6; **5**, 20488-55-5; **6**, 425-32-1; **12**, 20488-54-4; xenon difluoride, 13709-36-9.

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Ring-Closure Reactions. 12.[1] *gem*-Dimethyl Effect in Some Medium and Large Rings[2]

Carlo Galli,* Giuseppe Giovannelli, Gabriello Illuminati,* and Luigi Mandolini*

Centro C.N.R. di Studio sui Meccanismi di Reazione, Istituto di Chimica Organica, Università di Roma, 00185, Rome, Italy

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A quantitative determination of the *gem*-dimethyl effect on the rate of lactonization of ω-bromoalkanoate ions in 99% aqueous Me_2SO is reported for five representative ring sizes in the common-, medium-, and large-ring regions. The experimental results are tentatively discussed by extension to the many-membered rings of the Allinger and Zalkow approach to the *gem*-dimethyl effect on common ring formation. More pictorial interpretations as based on preferential conformations to cyclization are critically compared.

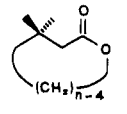
Our studies[1,3] on the energetics of the intramolecular reactions of bifunctional chains have shown that structural effects are quite marked up to chain lengths leading to the formation of common and medium rings and become less and less important as the chain length increases. As a consequence, the effective molarity (EM) of the reaction tends to level off toward the formation of large rings and to approach an average value of about −1.6 log EM units.[4]

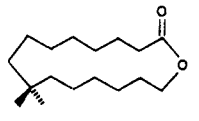
There is evidence that such a behavior also applies to structural modifications within the chain of a given series, as illustrated by the oxygen atom effect and by the rigid group effect for the formation of benzocyclo ethers.[3a,4] A structural modification of special interest is the geminal substitution of methyl groups at a methylene carbon of the chain to give rise to rate enhancements of varying intensity.[5] The *gem*-dimethyl effect has been interpreted by Allinger and Zalkow[6] in thermodynamic terms and by other authors[7,8] in terms of profitable rotamers or stereopopulation control.

Quantitative data for the *gem*-dimethyl effect can be found for three- to six-membered rings.[5] However, little is known for medium- and large-ring formation. Preparative work[9,10] has yielded some evidence of this effect for 8-, 9-, and 16-membered rings.

It seemed of interest to carry out a kinetic study of the *gem*-dimethyl effect as a function of chain length to cover a broad spectrum of ring sizes (n). Although a systematic investigation of this kind would require a considerable and supposedly tedious effort[11] to test bifunctional substrates of varying lengths and positions of geminal methyl substitution along the chain of any member in a series, the study of a selected group of the more accessible substrates was still expected to provide significant information on the general features of the effect in medium and large rings.

In this paper we wish to report on the kinetics of cyclization





1 n=6 ; 2 n=9
3 n=10 ; 4 n=11
5 n=16

of the ω-bromo derivatives of the 3,3-dimethylalkanoate (C_5, C_8, C_9, C_{10}) ions and of the 9,9-dimethylpentadecanoate (C_{15}) ion leading to 6-, 9-, 10-, 11-, 16-membered macrolides **1–5**, respectively, and to compare their reactivity with that of the related unsubstituted ω-bromoalkanoates.[1,3b]

Results and Discussion

The synthesis of ω-bromo acids generally involves long reaction sequences and low to moderate overall yields.[11] Mixed anodic coupling in MeOH of ω-bromo acids and half esters of bicarboxylic acids offers a simple one-step route to long-chain ω-bromo esters.[12] This method was studied in some detail by Woolford,[13] who found that, besides the expected symmetrical and unsymmetrical products, significant amounts of the methyl esters of starting materials were also formed. The presence of these unexpected products lowered the yields, increased the difficulties of purification, and seemed to hamper the general validity of the method.[13c] Although the conditions used in the present work (see, also, Experimental Section) differ from Woolford's but slightly, we obtained better results for all tested compounds. We used electrodes placed 5 mm apart and no more than 80–110 V (1.2–1.4 A). The internal temperature was always kept at 45 °C or less (35 °C for the coupling with 5-bromopentanoic acid, that failed to react under Woolford's conditions[13a]). The total molar concentration was in the range 0.2–0.4 M. Lower concentrations generally led to poor yields of product. In order to in-

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