Different Reversibility of Bromonium vs β-Bromocarbonium Ions Formed during the Electrophilic Bromination of Substituted Stilbenes. Evidence for Rate Determination during the Product-Forming Step

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Abstract: In order to check the relative reversibility of brominium and β-bromocarbonium ion formation, the product distributions of the reactions of Br_2 with *cis*- and *trans*-stilbene (**1b** and **2b**) and with their *p*-methyl (**1a** and **2a**), *p*-(trifluoromethyl) (**1c** and **2c**), and *p,p'*-bis(trifluoromethyl) derivatives (**1d** and **2d**) in 1,2-dichloroethane have been determined in the 10^{-1}–10^{-4} M concentration range. The rate constants (k_3) for the bromination of these stilbenes at 25 °C spanned 7 orders of magnitude. The observed dibromide ratios showed that an open β-bromocarbonium ion was the intermediate of the bromination of **1a** and **2a**, whereas bridged or partially bridged ions were involved with all other olefins. In these cases, the extent of bridging increased, and equilibration to the more stable trans bromonium ion occurred at the lowest reagent concentrations to give the erythro (or meso) dibromide **3** as the main product. The increase in **3** was always accompanied by an increase in cis–trans olefin isomerization during the bromination of the cis olefin. This is attributed to a return of the trans bromonium ion to the corresponding olefin. This process was maximum with **1d**, and minimum with **1a**. It is concluded that, whereas the formation of the β-bromocarbonium ion intermediate is completely rate-determining in the case of **2a**, both the formation of the trans bromonium ion and the following dibromide formation are partially rate-determining in the case of **2d**.

Introduction

The electrophilic bromination of olefins by free Br_2 is a multistep reaction (Scheme I) in which the rate is generally considered to be determined by a single step,[1] consisting of the ionization of an olefin–Br_2 charge-transfer complex in rapid equilibrium with the reactants.[2] It has been shown that in protic media this ionization is assisted by solvent hydrogen bonding to the developing bromide ion,[3,4] whereas in aprotic media the assistance is provided by a second Br_2 molecule, stabilizing the anion as tribromide ion.[2,5,6] Furthermore, in aprotic low-polarity solvents at relatively high Br_2 concentrations, the anion can also be in the form of a pentabromide ion.[7] Depending upon the olefin structure, the cationic moiety of the intermediates can consist of symmetrically or asymmetrically bridged bromonium or open β-bromocarbonium ions.[8] The two counterions can be present as tight or solvent-separated ion pairs, depending upon the solvent polarity and reagent concentrations.[9] In nonnucleophilic solvents, these ion pairs usually collapse directly to dibromide products, whereas nucleophilic solvents can trap the cations and generate solvent-incorporated products.[10-12] In all kinetic treatments presented until a few years ago, the formation of the ionic intermediates has generally been considered to be irreversible and their collapse to products to be fast.[1,8] However, evidence for the reversibility of the ionization step has been recently accumulated.[13-19] Reversibility appears most easily demonstrable in solvents of low polarity and with special olefins in which (1) steric bulk impedes the product-forming step or (2) a less stable cis olefin can revert to a more stable trans isomer. This would imply that the product-determining step can also be partially rate-determining.[17] For *cis*-stilbene this reversibility was shown[14] by the occurrence of a cis–trans isomerization accompanying the bromination of the olefin. This isomerization was rationalized[14] by a release of molecular Br_2 from the trans-bromonium–tribromide ion pair resulting from the rearrangement of the first-formed, strained cis-bromonium species through an open β-bromocarbonium ion.

Herein we describe the dependence of the reversibility of ion pair formation on para substituents in the phenyl rings of *cis*-stilbene and on the initial concentration of reagents in 1,2-dichloroethane. It is shown that the extent of reversibility depends mainly on the amount of bridging in the cation, which is highest

Table I. Third-Order Rate Constants for the Bromination of Stilbenes **1a–d** and **2a–d** in 1,2-Dichloroethane at 25 °C

	k_3 (M^{-2} s^{-1})
1a	$(1.58 \times 10^4) \pm (5.0 \times 10^2)$
2a	$(3.60 \times 10^3) \pm 50$
1b	$(2.80 \times 10^2) \pm 10$
2b	50 ± 2
1c	5.26 ± 0.2
2c	0.96 ± 0.1
1d	$(9.40 \times 10^{-3}) \pm (1.5 \times 10^{-4})$
2d	$(2.60 \times 10^{-3}) \pm (2.7 \times 10^{-5})$

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Scheme I

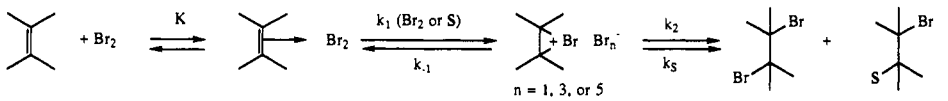


Table II. Product Distribution in the Bromination of Stilbenes in 1,2-Dichloroethane at 25 °C[a]

olefin (M)	a		b		c		d	
	2/(3 + 4)	3/4	2/(3 + 4)	3/4	2/(3 + 4)	3/4	2/(3 + 4)	3/4
1								
2×10^{-1}	0.025	68:32	0.07	52:48	0.10	72:28		
1×10^{-1}							0.25	45:55
2×10^{-2}	0.055	68:32	0.10	53:47	0.15	73:27	1.20	64:36
1×10^{-2}							1.60	82:18
5×10^{-3}							2.10	>95:5
2×10^{-3}	0.060	68:32	0.17	55:45	0.30	76:24		
2×10^{-4}	0.070	68:32	1.20	82:18[b]	1.25	95:5		
2								
2×10^{-1}		70:30		68:32		82:18		>98:2
2×10^{-3}		70:30		72:28		85:15		>98:2
2×10^{-4}		71:29		84:16[b]		95:5		>98:2

[a] In all reactions the Br_2 concentration was one-half of the olefin concentration. All of the reported ratios were independent of the progress of the reaction. [b] At lower initial reagent concentrations this ratio increased up to >95:5.

for symmetrically bridged bromonium ions and lowest for open β-bromocarbocations. It is also demonstrated that, in the former case, the product-forming step can be, at least partially, rate-limiting.

Results

The cis olefins **1a**, **1c**, and **1d** were obtained by photochemical isomerization of the respective trans isomers **2a** and **2c**, prepared by conventional Grignard methods followed by dehydration of the resulting alcohols. McMurry coupling[20] of *p*-(trifluoromethyl)-benzaldehyde gave **2d**.

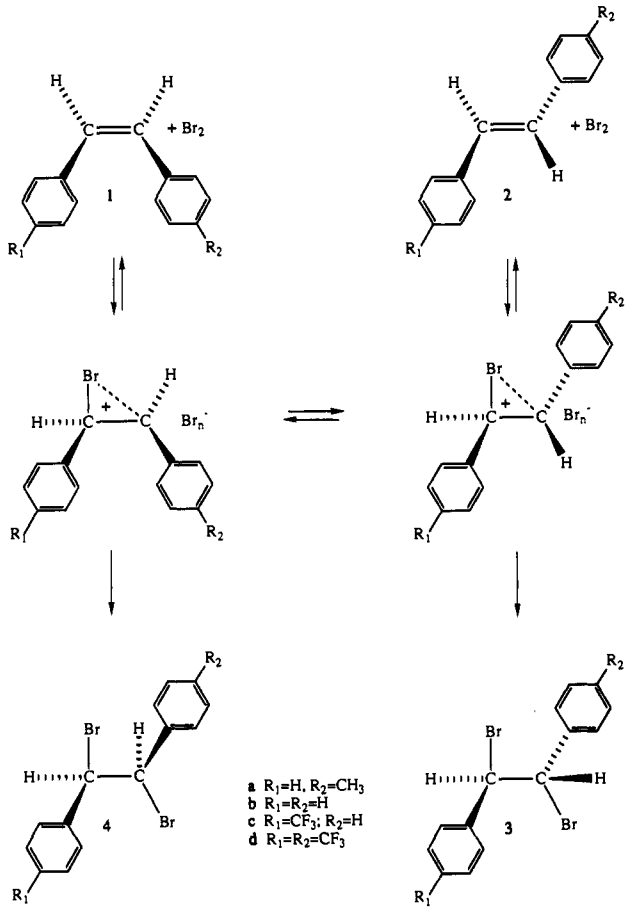
These olefins were subjected to bromination with $Bu_4N^+Br_3^-$ in 1,2-dichloroethane in the presence of an excess of $Bu_4N^+Br^-$, a reaction that is known to give only anti addition products.[21-23] The pure erythro dibromides **3a** and **3c** and the meso dibromides **3b** and **3d** were thus obtained from the trans olefins **2a**, **2c**, and **2d**, whereas the corresponding cis olefins gave the pure threo isomers **4a** and **4c** and the *d,l* isomers **4b** and **4d**.

The rates of bromination of all olefins **1** and **2** by free Br_2 were measured spectrophotometrically in 1,2-dichloroethane at 25 °C by monitoring the disappearance of Br_2. All reactions obeyed the third-order rate law of eq 1, with k_3 values spanning 7 powers of ten (Table I). For each cis–trans couple, the cis olefin was brominated 3.5 to 5.5 times faster than the trans isomer.

$$-d[Br_2]/dt = k_3\,[\text{olefin}][Br_2]^2 \qquad (1)$$

The ratios between the syn and anti dibromo adducts **3** and **4** obtained for reactions of free Br_2 with all olefins **1** and **2** in 1,2-dichloroethane at 25 °C and the ratios between the trans olefin **2** and the total dibromides (**3** + **4**) found in the reactions of cis olefins are given in Table II. All reactions were performed at an initial Br_2 to olefin molar ratio of 1:2. The use of such an excess of the cis olefin and its faster rate of bromination with respect to the trans isomer that was formed during the course of the reaction assured that, in all cases the dibromides were produced only from the former olefin, while the latter was accumulated in the reaction medium. All brominations were also carried out in the presence of *trans*-1,2-dichloroethylene, which would have been produced in the presence of free radicals,[24] was ever observed. To further exclude the formation of radicals, **1d** (5×10^{-3} M) was reacted with Br_2 (2.5×10^{-3} M) in 1,2-dichloroethane under conditions that would produce maximum olefin isomerization (e.g., where the product composition of **2d**/(**3d** + **4d**) = 2.1). No EPR signal was observed during the course of the reaction, thereby excluding the presence of radicals at the limits of detectability (estimated at $\approx 10^{-12}$ M).

Scheme II



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The possibility that the cis–trans isomerization occurring during the bromination of the cis olefins **1** was due to a competing free radical bromination process can thus be safely rejected. This leaves the ionic bromination as the only process responsible for the observed olefin isomerization. All of the product ratios reported in Table II were found to be independent of the progress of the reactions. Furthermore, dibromides **3** and **4** were quantitatively recovered after exposure to Br_2 under conditions identical with those employed in all of the bromination runs of Table II. This excluded any Br_2-promoted dibromide interconversion during the brominations and assured that the measured **3**/**4** ratios were actually obtained under kinetic control.

Discussion

All of the results of the product study summarized in Table II can be rationalized on the basis of the reaction sequence shown in Scheme II. Whether the involved intermediate ions are symmetrically or asymmetrically bridged or are open β-bromocarbocations depends upon the ability of the remote substituents to stabilize a positively charged benzylic carbon. Bridging, or partial bridging, is required to explain the product stereochemistry and differences in the amount of cis–trans isomerization, as discussed below. The partially bridged ions shown in Scheme II are viewed as members of a continuum connecting the extremes of open and fully closed ions, with the ions formed from the bromination of **1a** and **2a** lying toward the former, and those from bromination of **1d** and **2d** lying toward the latter extreme.

Only the bromination of **2d** was anti stereospecific at all examined reagent concentrations, confirming that the reaction was occurring exclusively through an apparently symmetric trans bromonium intermediate. On the other hand, the reactions of **1a** and **2a** were always stereoconvergent to give an approximately 7:3 mixture of **3** and **4**. This showed that the same open β-bromocarbonium ion was essentially involved in both cases. Both dibromides **3** and **4** were instead formed in different ratios from couple **1b–2b** as well as from couple **1c–2c**, pointing to the involvement of partially bridged intermediates.[25] Furthermore, the 3:4 ratio increased with decreasing initial reagent concentrations, and the reactions tended to become stereoconvergent and anti stereospecific at [olefin] $< 2 \times 10^{-4}$ and $[Br_2] < 1 \times 10^{-4}$ M. This behavior, which had been observed previously for the bromination of unsubstituted stilbenes,[9] points to equilibration of the reaction intermediates formed from either isomer of the cis–trans couple to a symmetrically bridged trans bromonium ion, which, at low concentrations, appears to be the more stable form of the intermediate and can be opened only in a trans fashion to give the erythro or meso dibromide **3**. The higher stability of symmetrically bridged forms, when produced under high-dilution conditions, is likely related to the tendency of the intermediates to dissociate from ion pairs to separated ions when the concentration of the reagents, and hence of the intermediate itself, is lowered enough. More bridging is probably required to stabilize the separated carbocation than a tight ion pair, because the positive charge on the benzylic carbon is no longer stabilized electrostatically by the close counteranion.[9] On the other hand, in nonnucleophilic solvents, the lifetimes of the intermediates are expected to be longer for separated species than for tight ion pairs, so that the former have more opportunity to equilibrate to the more stable trans bromonium ion form, free of steric strain, before reacting. While this rationalization, invoking dissociation and consequent equilibration of the ion pair intermediates with increasing dilution, cannot presently be supported by more direct evidence, we consider it to be the most reasonable hypothesis that is consistent with the results. The concentration-dependent equilibration of the intermediates is most clearly shown by the large change in the **3**/**4** ratio obtained from *cis-p,p'*-bis(trifluoromethyl)stilbene (**1d**),

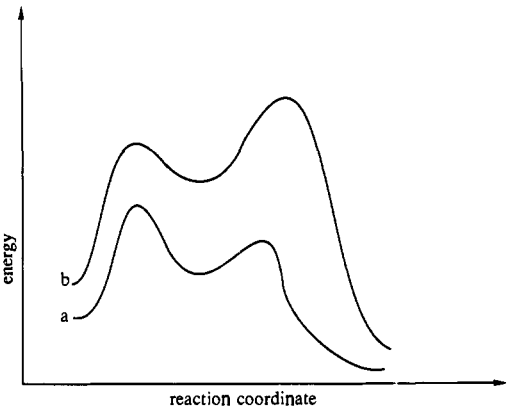

Figure 1. Reaction coordinate diagram for the bromination of *trans-p*-methylstilbene (**2a**) (a), and *trans-p,p'*-bis(trifluoromethyl)stilbene (**2d**) (b).

where symmetrically bridged bromonium ions are highly favored owing to the electron-withdrawing effect of the two para substituents. Evidently, the steric strain present in the cis bromonium ion is so high that isomerization to the trans ion does occur in spite of the destabilization of the necessarily involved open β-bromocarbonium ion. However, the latter is likely very short-lived and is only responsible for the cis–trans isomerization and not for the product formation.

The data of Table II also show that the **2**/(**3** + **4**) ratio was concentration-dependent. It was lowest for the bromination of **1a**, where the electron-releasing *p*-CH_3 allows the formation of a benzylic β-bromocarbonium ion, and highest for that of **1d**, where the two electron-withdrawing *p*-CF_3 groups interfere with the development of a carbonium ion center at either benzylic carbon and favor the formation of symmetrically bridged ions. The reactions of **1b** and **1c**, where the extent of bridging appears to depend upon the concentration, are intermediate cases. Furthermore, with olefins **1b–d** the increase in the **2**/(**3** + **4**) ratio found by decreasing the reagent concentrations below a given threshold is accompanied by the above discussed increase in the **3**/**4** ratio, indicating that both effects are related to an increased involvement of the trans bromonium ion in the subsequent step. In fact, attack of the anion at the benzylic carbon of this ion will give the erythro or meso dibromide **3**, whereas attack at the bromonium Br^+ will lead to the isomerized olefin **2** and free Br_2. At the lowest concentrations, where the reactions of **1b–d** are nearly stereospecific because of the dominant contribution of symmetrically bridged trans bromonium ions, the **2**/(**3** + **4**) ratio gives a measure of the relative rates of the return of these ions to olefins **2b–d** and of their collapse to dibromide. The results in Table II provide experimental confirmation of the speculation[18] that open or weakly bridged ions should be attacked more preferentially at carbon than should a fully bridged bromonium ion. This provides valuable, although indirect, information about the nature of the rate-determining step of the bromination of trans olefins of type **2**. Reaction coordinate diagrams for the two extreme cases of the brominations of **2a** and **2d** can be inferred to be of the type shown in Figure 1. Clearly, while the formation of the β-bromocarbonium ion intermediate from **2a** is completely rate-determining, both the formation of the trans bromonium ion intermediate and the following dibromide formation are partially rate-determining in the case of **2d**. Thus, a part of the very large difference in the k_3's found for the brominations of the *p*-methyl- and *p,p'*-bis(trifluoromethyl)stilbenes appears to be due to the high extent of reversibility and to partial rate determination during the product-forming step in the bromination of the latter.

It can also be observed that for olefins **1a–c** the **2**/(**3** + **4**) ratio increases slightly also in a concentration range (2×10^{-1} to 2×10^{-3} M) in which no change in the dibromide ratio is observed. This increase cannot be due to a change in the cationic moiety of the intermediate but may be related to a progressive transformation of the anionic moiety from a Br_3^- to a Br_5^- ion with increasing initial Br_2 concentration.[7] How this can affect the

(25) The simultaneous involvement of bridged and open cations according to the Ruasse-Dubois multipathway mechanism (ref 8) could rationalize these results as well (see ref 9). In the present paper we adopt the formulation of a unique intermediate with a variable extent of bridging on account of the final considerations discussed in ref 8, but in our opinion a choice between the two alternatives can only be a matter of speculation.

competition between product formation and reversal to olefin and Br_2 is not clear at present. However, we want to underline that this effect is much smaller than the above discussed dilution effect.

Finally it must be mentioned that reversibility of bromonium ions has recently also been recognized in protic solvents, but only for highly congested bromonium ions where the product-forming step is made energetically difficult by steric hindrance.[17-19] It has been speculated[19] that the occurrence of return for uncrowded bromonium ions in halogenated solvents is due to the low nucleophilicity of the Br_3^- counterion that must dissociate at least partially to Br^- in order to effect attack at the bromonium carbons. However, it is difficult to envisage reasons why any retarded attack of Br_3^- would selectively change the nucleophilicity toward carbon and bromine. Furthermore, reversibility in the stilbene system was first demonstrated[14] for bromonium ions generated in chlorinated hydrocarbons by reacting bromohydrins with HBr where the counterion is certainly Br^-. In addition, reversibility was demonstrated for the cyclohexene and cyclopentene systems for bromonium ions produced solvolytically in acetic acid in the presence of added Br^-.[13] Thus, the nature of Br_3^- anion in brominations carried out in low-polarity aprotic solvents seems unlikely to be responsible for the apparently increased return with respect to polar solvents. In the light of the present results, different distribution of positive charge between bromine and carbon may be a more important factor.

Conclusion

The results of the present investigation unambiguously show the following. (1) The extent of reversibility during the bromination of stilbenes appears to be affected by remote substituents that can modify the extent of bridging and the charge distribution between the bromine and carbons of the intermediate. Open β-bromocarbocations do not significantly revert to the olefin. Symmetrically bridged bromonium ions are the most prone to reversal. This is consistent with the conclusions recently inferred from an investigation of the bromination of 5*H*-dibenzo[*a*,*d*]-cycloheptene.[26] (2) The partitioning of stilbene trans bromonium ions between reversal and product formation can be quantitatively assessed by measuring the amount of trans olefin produced during the bromination of the cis olefins under conditions leading to the stereospecific formation of erythro or meso dibromides. A spectrum of situations ranging from essentially irreversible ion formation to prevalent ion reversal has been brought to light in this way. This corresponds to a gradual mechanistic shift of rate determination from the ionization step to the product-forming step, which can give a relevant contribution to differences in the bromination rates observed for differently substituted members of a same olefin family. (3) The use of LFERs in multistep reactions like olefin bromination has been subjected to criticism.[26,27] The conclusions of the present study impose a further, more severe caveat to a generalized application of such relationships, particularly when mechanistic changes of the type discussed in this work can be expected.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. ^1H NMR spectra were registered in $CDCl_3$ with a Bruker AC 200 instrument and TMS as the internal reference. Mass spectra were measured on an AEI MS 50 high-resolution mass spectrometer. HPLC analyses were measured on a Waters 600E apparatus equipped with a diode array detector. Kinetic experiments were performed with a Durrum Model D-110 stopped flow apparatus equipped with a 2-cm observation cell for **1a** and **2a** and with a Cary 2200 spectrophotometer for all other olefins.

1,2-Dichloroethane (C. Erba RPE) was treated as previously reported.[28] Bromine (1-mL sealed ampules (C. Erba ≥ 99.5%)) was used as supplied.

Olefins 1–2. Commercial *trans*-stilbene (**2b**) (Schuchard, >99%) was crystallized from ethanol, mp 124–125 °C. Commercial *cis*-stilbene (**1b**) (Aldrich, >97%) was fractionally distilled, collecting a fraction with bp 93 °C (5 mmHg).

Olefins **2a** and **2c** were prepared by reaction of benzylmagnesium chloride with *p*-methyl- and *p*-(trifluoromethyl)benzaldehyde, respectively, followed by dehydration with *p*-toluenesulfonic acid in refluxing benzene. Olefin **2d** was obtained via McMurry coupling[20] of *p*-(trifluoromethyl)benzaldehyde as follows. To a 50-mL THF solution containing 17.7 g (115 mmol) of $TiCl_3$ was added 2.17 g (57.5 mmol) of $LiAlH_4$. To the resultant black mixture was added 10 g (57.5 mmol) of *p*-(trifluoromethyl)benzaldehyde, and the mixture was heated at reflux for 4 h. Standard extraction workup followed by recrystallization from ethanol gave 4.0 g (22% based on aldehyde) of **2d**.

All *trans*-stilbenes were isomerized to their cis isomers by irradiation of hexane solutions with a 70-W Hg high-pressure immersion lamp (Hanau Model TQ 81) for 24–48 h. The separation of the resulting cis–trans mixtures was performed by column chromatography over alumina (Aluminum Oxide S, 100–290 mesh ASTM), eluting with hexane. The cis isomers were always eluted first. All olefins were finally checked by HPLC and were found to be >99% pure.

1a: bp 110 °C (2 mmHg) (lit.[29] 110–112 °C (2 mmHg)); ^1H NMR δ 2.30 (s, 3 H, CH_3), 6.55 (s, 2 H, CH=), 7.0–7.35 (9 aromatic H). **1c**: bp 63–64 °C (0.1 mmHg) (lit.[30] bp 63–64 °C (0.1 mmHg)); ^1H NMR, δ 6.57 (d, *J* 12.3 Hz, 1 H, CH=), 6.71 (d, *J* 12.3 Hz, 1 H, CH=), 7.22–7.50 (9 aromatic H). **1d**: mp 56–57 °C (lit.[30] mp 58–59 °C); ^1H NMR δ 6.72 (s, 2 H, CH=), 7.30–7.50 (AA'BB' system, 8 aromatic H). **2a**: mp 118–119 °C (lit.[29] mp 119–120 °C); ^1H NMR δ 2.35 (s, 3 H, CH_3), 7.05 (s, 2 H, CH=), 7.10–7.50 (9 aromatic H). **2c**: mp 132–134 °C (lit.[30] mp 134–135 °C); ^1H NMR δ 7.09 (d, *J* 16.5 Hz, 1 H, CH=), 7.22 (d, *J* 16.5 Hz, 1 H, CH=), 7.25–7.60 (9 aromatic H). **2d**: mp 133–135 °C (lit.[30] mp 134–135 °C); ^1H NMR δ 7.20 (s, 2 H, CH=), 7.60–7.80 (8 aromatic H).

Dibromides 3–4. All stilbenes **1–2** were brominated with $Bu_4N^+Br_3^-$ as follows. 1,2-Dichloroethane solutions containing 10^{-2} M **1a–c** or **2a–c**, 2×10^{-2} M $Bu_4N^+Br_3^-$, and 2×10^{-2} M $Bu_4N^+Br^-$ were left at room temperature until the olefin was completely consumed (HPLC checks). The corresponding reactions of **1d** and **2d** were much slower and were therefore carried out at 5-fold higher concentrations of all reagents. The reaction mixtures were then washed with saturated aqueous $NaHSO_3$ and water, dried, and evaporated. The residues were crystallized from chloroform to give the pure dibromides **3–4**.

3a: mp 203–205 °C; ^1H NMR δ 2.40 (s, 3 H, CH_3), 5.45 (s, 2 H, CHBr), 7.20–7.60 (9 aromatic H); HRMS calcd for $C_{15}H_{14}Br_2$ 355.9421, found 355.9432. Anal. Calcd for $C_{15}H_{14}Br_2$: C, 50.88; H, 3.98. Found: C, 51.05; H, 3.85. **3c**: mp 205–207 °C; ^1H NMR δ 5.42 (d, *J* 11.6 Hz, 1 H, CHBr), 5.50 (d, *J* 11.6 Hz, 1 H, CHBr), 7.30–7.70 (9 aromatic H); HRMS calcd for $C_{15}H_{11}F_3Br_2$ 409.9139, found 409.9153. Anal. Calcd for $C_{15}H_{11}Br_2F_3$: C, 44.15; H, 2.72. Found: C, 44.25; H, 2.57. **3d**: mp 237–238 °C; ^1H NMR δ 5.44 (s, 2 H, CHBr), 7.60–7.70 (AA'BB' system, 8 aromatic H); HRMS calcd for $C_{16}H_{10}Br_2F_6$ 477.9013, found 477.9021. Anal. Calcd for $C_{16}H_{10}Br_2F_6$: C, 40.36; H, 2.18. Found: C, 40.64; H, 2.12. **4a**: mp 113–115 °C; ^1H NMR δ 2.25 (s, 2 H, CH_3), 5.45 (s, 2 H, CHBr), 7.0–7.35 (9 aromatic H); HRMS calcd for $C_{15}H_{14}Br_2$ 355.9421, found 355.9426. Anal. Calcd for $C_{15}H_{14}Br_2$: C, 50.88; H, 3.98. Found: C, 50.67; H, 4.02. **4c**: mp 52–53 °C; ^1H NMR δ 5.45 (d, *J* 8.1 Hz, CHBr), 5.51 (d, *J* 8.1 Hz, 1 H, CHBr), 7.20–7.60 (9 aromatic H); HRMS calcd for $C_{15}H_{11}Br_2F_3$ 409.9139, found 409.9140. Anal. Calcd for $C_{15}H_{11}Br_2F_3$: C, 44.15; H, 2.72. Found: C, 44.66; H, 2.85. **4d**: mp 210–211 °C; ^1H NMR δ 5.50 (s, 2 H, CHBr), 7.30–7.50 (AA'BB' system, 8 aromatic H); HRMS calcd for $C_{16}H_{10}Br_2F_5$ ($M^+ - F$) 458.9029, found 458.9029. Anal. Calcd for $C_{16}H_{10}Br_2F_6$: C, 40.36; H, 2.18. Found: C, 40.33; H, 2.03.

Bromination Procedure and Product Analysis. 1,2-Dichloroethane solutions of stilbenes **1** or **2** of concentrations ranging between 4×10^{-1} and 4×10^{-4} M were mixed with equal volumes of 2×10^{-1} to 2×10^{-4} M in the same solvent, and the reaction mixtures were stored in the dark at 25 °C. The reactions were stopped by addition of cyclohexene, rapidly consuming the unreacted Br_2. The solutions were directly analyzed by HPLC after the addition of *erythro*-1,2-dibromo-1-phenylpropane as a standard for the quantification of the formed dibromides and unreacted olefins, with use of a 25-cm Hypersil 10 C18 column (HPLC technology) with methanol–water (70:30 v/v) as the eluent at a flow rate of 1.5 mL/min. Under these conditions all *cis*- and *trans*-stilbenes **1** and **2** were well-separated, but only the peaks of dibromides **3b** and **4b** were well-resolved. The **3a**/**4a** and **3d**/**4d** ratios were therefore measured by NMR on the basis of the methyl and benzyl proton signals, respectively, after stopping the reaction by washing with saturated aqueous $NaHSO_3$ and

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evaporating. The **3c/4c** ratio was instead determined by HPLC with use of a 25-cm Hypersil 10 silica column (HPLC technology) with hexane–ethyl acetate (99:1 v/v) as the eluent at a flow rate of 2 mL/min. All reactions were carried out in triplicate. The **3/4** ratios reported in Table II were reproducible to ±1%, whereas the **2/(3 + 4)** ratios were reproducible to ±10% of the quoted figures. All product ratios were independent of the percent conversion. The reactions performed at the lowest concentrations were slow and were analyzed only at incomplete conversion. However, reactions stopped at several different conversions gave similar **3/4** and **2/(3 + 4)** ratios. For each olefin **1**, reactions were also carried out in the presence of *trans*-1,2-dichloroethylene at a concentration equal to that of **1**. No isomerization to *cis*-1,2-dichloroethylene was ever observed by HPLC analysis.

The stability of dibromides **3** and **4** in the presence of the halogen was checked by exposing all dibromides to Br_2 under conditions identical with those employed in the bromination reactions, followed by HPLC analysis (for **3b,4b** and **3c,4c**) or NMR analysis (for **3a,4a** and **3d,4d**).

Kinetic Measurements. 1,2-Dichloroethane Br_2 solutions, prepared shortly before use, were protected from the daylight and adjusted to twice the desired initial concentrations in the kinetic runs. Aliquots of these solutions, prethermostated at 25 ± 0.05 °C, were mixed with equal volumes of prethermostated solutions of olefins **1** and **2** of suitable concentrations. The reactions of **1a** and **2a** were carried out with the stopped-flow apparatus, those of **1b** and **2b**, **1c** and **2c**, and **1d** and **2d** with the conventional spectrophotometer. The following olefin and Br_2 concentrations (molar), pathlength (centimeters), and monitored wavelengths (nanometers) were used. **1a**: 1 and 2×10^{-1}, 2 and 4×10^{-3}, 2, 410 and 480. **2a**: 1×10^{-3}, 1×10^{-3}, 2, 410. **1b**: 5×10^{-3}, 5×10^{-3}, 1, 410. **2b**: 3×10^{-3}, 3×10^{-3}, 1, 410. **1c**: 4×10^{-2}, 4×10^{-3}, 1, 410. **2c**: 5×10^{-2}, 5×10^{-2}, 0.1, 410. **1d**: 5×10^{-2}, 5×10^{-2}, 0.1 and 0.2, 410 and 480. **2d**: 1×10^{-1}, 1×10^{-1}, 0.1 and 0.2, 410 and 500. The absorbance/time data were fitted to the appropriate third-order or pseudo-second-order rate equation. All reactions were carried out at least in triplicate. The k_3 values are reported in Table I.

Acknowledgment. The authors gratefully acknowledge the financial support of the CNR and MURST of Italy, the NSERC of Canada, and NATO for a travel grant to R.S.B and G.B. in support of collaborative research.

Registry No. 1a, 1657-45-0; **1b**, 645-49-8; **1c**, 124562-04-5; **1d**, 42134-70-3; **2a**, 1860-17-9; **2b**, 103-30-0; **2c**, 1149-56-0; **2d**, 42134-74-7; (±)-**3a**, 135733-73-2; **3c**, 135733-74-3; (±)-**3d**, 135733-72-1; (±)-**4a**, 135733-75-4; (±)-**4c**, 135733-76-5; (±)-**4d**, 135733-77-6; Br_2, 7726-95-6.

The Total Synthesis of Cystodytins

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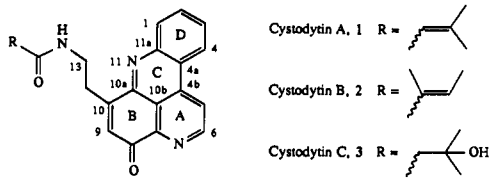
Abstract: The first chemical preparation of the cystodytins has been accomplished. A modified Knoevenagel–Stobbe pyridine formation and a photochemical nitrene insertion into a C–H bond constitute the key phases of this efficient total synthesis.

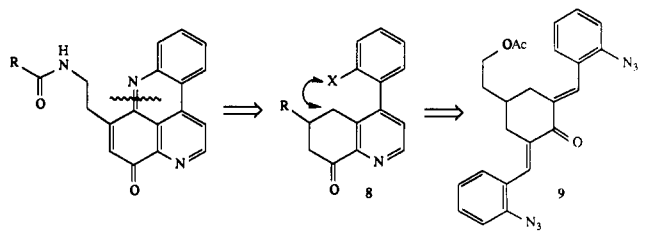
Introduction

The cystodytins are antineoplastic alkaloids isolated from the Okinawan tunicate, *Cystodytes dellechiajei* (Della Valle).[2] An inseparable 3.5:1 mixture of cystodytins A, **1**, and B, **2**, exhibited strong cytotoxicity (ID50 toward L1210 murine leukemia: 240 ng/mL = 6.7×10^{-7} M) and Ca^{2+} releasing activity from sarcoplasmic reticulum equal to 36 times that of caffeine. A third substance, cystodytin C, **3**, was obtained in pure form, but it was found to be almost devoid of biological activity.[2] The biological



effects induced by **1** and **2**[3] and their novel ring system render them particularly appealing both as targets for total synthesis and as candidates for pharmacological evaluation. Interest in cystodytins is reinforced by the recent discovery that many quinones, particularly heterocyclic ones, inhibit reverse transcriptase;[4] questions concerning the possible antiretroviral activity of **1–3** therefore emerge. Bioassay and analogue work would require

Scheme I



significant quantities of cystodytins, but given the scarcity of the compounds in their natural sources, totally synthetic materials are clearly needed.

Cystodytins share architectural similarities with other recently discovered marine natural products incorporating highly condensed polycyclic heteroaromatic skeleta, some of which attain a considerable degree of complexity.[5] It is remarkable that, in contemplating possible routes to such structures, a number of deficiencies of contemporary methodology become evident. In particular, lengthy sequences and low-yielding steps may be anticipated to adversely affect plans based on existing reactions. The difficulties associated with the construction of the framework of

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