ride was added 40.0 g (0.26 mol) of (−)-citronellol, $[\alpha]^{23}D$ −4.1° (neat).[12] The slurry was stirred at 25° for 36 hr.[13] The mixture was filtered through Celite and the solids were washed thoroughly with methylene chloride. The solution was evaporated to ca. 500 ml and washed with 10% hydrochloric acid, 10% sodium bicarbonate, and water. The methylene chloride solution was evaporated to give a mobile oil (43 g). The oil was taken up in 300 ml of ethanol and treated with 600 mg (15 mmol) of sodium hydroxide. The solution was heated for 1 hr, then the ethanol was evaporated under reduced pressure and the residue was partitioned between 200 ml of ether and 100 ml of water. The ether was washed with 10% hydrochloric acid and then brine. Evaporation of the solvent and distillation of the residue gave 28 g (0.184 mol, 71%) of (−)-pulegone, bp 104–106° (18 mm), $[\alpha]^{22}D$ −20° (neat), homogeneous by gas chromatographic analysis.

Preparation of (*S*)-(−)-Pulegone Semicarbazone. To a solution of 35 g (230 mmol) of (−)-pulegone, $[\alpha]^{22}D$ −20° (neat), in 400 ml of ethanol and 200 ml of water cooled to 0° was added 55 g (404 mmol) of sodium acetate trihydrate and 40 g (359 mmol) of semicarbazide hydrochloride. The solution was stirred at 0° for 2 hr and then at 20° for 36 hr. The precipitated solid (53 g) was separated by filtration and was extracted three times with 200 ml of chloroform. Evaporation of the chloroform and recrystallization of the residue from ethanol gave 47 g (225 mmol, 98%) of the semicarbazone, mp 169–171°. This material was recrystallized twice from ethanol to afford 40.2 g (192 mmol, 83%), of pure semicarbazone: mp 170–171°; $[\alpha]^{23}D$ −65.2° (*c* 2.2, $CHCl_3$);[9] ir (CCl_4) 3522, 3489, 3419, 3200 (NH), 1689 (C=O), 1510 cm^{-1} (C=N); NMR ($CDCl_3$) δ 8.73 (1 H, s, NNH), 5.88 (2 H, bs, NH_2), 2.83–0.88 (16 H, m), 1.87 (3 H, s, allylic CH_3), 1.74 (3 H, s, allylic CH_3), 1.00 (3 H, d, J = 5.5 Hz, CH_3).

Regeneration of Optically Pure (−)-Pulegone (2). To 40 g (191 mmol) of (−)-pulegone semicarbazone dissolved in 100 ml of hot glacial acetic acid was slowly added (ca. 30 min) 35 g (398 mmol) of freshly distilled pyruvic acid. The solution was heated on a steam bath for 2 hr. The volume was reduced to ca. 50 ml under reduced pressure and the residue was partitioned between 200 ml of water and 400 ml of ether. The ether layer was washed with 200 ml of water, 200 ml of saturated sodium bicarbonate, and 50 ml of brine. The ether solution was dried ($MgSO_4$), evaporated, and distilled to give 25 g (164 mmol, 86%) of (−)-pulegone, bp 104–108° (22 mm), $[\alpha]^{23}D$ −22.5° (neat).[11,14]

Registry No.—**2**, 3391-90-0; **2** semicarbazone, 57237-90-8; (−)-citronellol, 7540-51-4; semicarbazide hydrochloride, 18396-65-1.

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(9) For lit. mp 171–172° and $[\alpha]^{20}D$ +61.7° (*c* 4.0, $CHCl_3$) for the semicarbazone of (+)-pulegone, see ref 3c; we observed mp 170–171° and $[\alpha]^{23}D$ +66° (*c* 2.05, $CHCl_3$).
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(13) The reaction can easily be followed by TLC (silica gel, methylene chloride). R_f values: citronellol, 0.17; citronellal, 0.65; isopulegols, 0.27 and 0.35; isopulegone, 0.41; pulegone, 0.36.
(14) This work was supported in part by a grant from the National Science Foundation.

Reactions of Cholesteryl Substrates with Chloride Ion in Aprotic Solvents. Synthesis of Epicholesteryl Chloride

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Shoppee,[2] after a review of the literature, concluded that, owing to homoallylic participation by the 5,6 π bond,[2,3] the hydroxyl group of cholesterol invariably undergoes replacement by chlorine with retention of configuration. Epicholesteryl chloride (3-α-chlorocholest-5-ene, **1**) was subsequently prepared by a variety of methods,[4,5] all of which involved replacement, with inversion, of a 3-α-hydroxyl group by chlorine prior to introduction of the 5,6 π bond by dehydration of a 5- or 6-ol. Column and thin layer chromatography were used to separate it from cholesta-3,5-diene (**2**). Recently, it has been shown that reaction of cholesterol with triphenylphosphine–carbon tetrachloride reagent does give rise to a small (~8%) amount of **1** within the product mixture.[6]

Since dipolar aprotic solvents are excellent media for SN2 reactions,[7] it might be possible to utilize them to prepare **1** by direct attack of chloride ion upon a suitable cholesteryl substrate. Several bimolecular inversions at C-3 of cholesteryl derivatives have been documented.[8] Plausible products from chloride-ion attack are indicated in Scheme I.

Reaction of cholesteryl *p*-toluenesulfonate (**3a**) with lithium chloride in refluxing acetone[9] was found to lead to a crude product, mp 91–92°, which after recrystallization gave pure cholesteryl chloride (3-β-chlorocholest-5-ene, **3b**), mp 95°. Unfortunately, neither crude nor purified yields are given but, from the small increase in melting point after recrystallization, it would appear that the reaction gave almost entirely substitution products, formed with retention of configuration. However, when the same reaction was carried out in refluxing acetonitrile,[6] a crude product was obtained which on chromatographic analysis yielded 8% **1**, 71% **3b**, and 18% **2**.

Scheme I

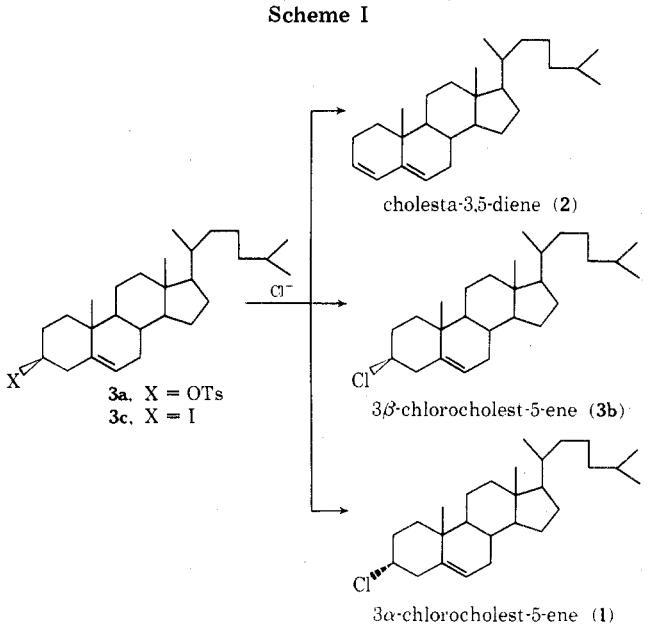


Table I
Product Studies for Reactions of Cholesteryl Substrates with Chloride Ion[a]

Entry	Reaction	% 2[b] Uv	% 2[b] ^{1}H NMR	% 1 ^{1}H NMR	% 3b ^{1}H MNR
1	3a, LiCl, CH_3CN, reflux	2	6	0	94
2	3a, LiCl, CH_3CN, reflux, TMU[c] (2 equiv)	2	6	0	94
3	3c, n-Bu_4NCl, acetone	46	39	37	24
4	3c, n-Bu_4NCl, acetone, TMU[c] (1 equiv)	56	59	41	0
5	3c, n-Bu_4NCl, acetone, TMU[c] (2 equiv)	64	58	42	0
6	3b, n-Bu_4NCl, acetone	1	1	0	99
7	3b, n-Bu_4NCl, acetone, TMU[c] (1 equiv)	0	3	0	97
8	3b, n-Bu_4NCl, HCl, acetone	0	0	0	100
9	1, n-Bu_4NCl, HCl, acetone	5	9	91	0

[a] Reaction at 50.0° unless otherwise noted and percentages are those within crude isolated product mixture (usually >90% recovery). [b] Especially for low percentages of conjugated diene, 2, the uv determination would be expected to give the more accurate value. [c] TMU = tetramethylurea.

The apparent contribution of a small SN2 component to the reaction in acetonitrile led us to consider the possibility of further modification of the conditions so as to substantially increase the fraction of inversion product; the procedure would then be preferable to the several-steps schemes for the synthesis of 1 devised by Shoppee and co-workers.[4,5]

The reaction of **3a** to give a small (8%) yield of 1 was, unfortunately, reported only in preliminary form[6] and, in particular, the concentration of lithium chloride within the refluxing acetonitrile was not specified. If it is assumed that 1 is formed by SN2 reaction and **3b** by SN1 reaction, then the product ratio would be directly related to the concentration of chloride ion. The reaction has been repeated with a substantial (0.236 M) concentration of lithium chloride. The ^{1}H NMR spectrum of the crude product did not show any signal at δ 4.50 for the 3-β hydrogen of 1 (Table I, entry 1); spectra of standard mixtures indicated that amounts in excess of 2% would have been detected. To see whether any **3b** was formed from 2 via an elimination–addition reaction,[10] the experiment was repeated in the presence of 2 equiv of tetramethylurea, a strong base which does not readily participate directly in substitution or elimination reactions.[11,12] Within experimental error, identical results were obtained (Table I, entry 2). The percentage of conjugated diene (~2%) and the absence of 1 are consistent with the claim by Madaeva[9] that reaction of **3a** with chloride ion in refluxing acetone led to the isolation of only **3b**. The present data are not necessarily inconsistent with the previous report,[6] provided that the unspecified concentration of lithium chloride used by the earlier workers was extremely large.

Table II
Second-Order Rate Coefficients, k_2 (M^{-1} sec^{-1}), and Fraction of Reaction Proceeding with Elimination, F_E, in Reaction of Cholesteryl Iodide (3c) with Tetra-n-butylammonium Chloride in Acetone at 50.0°

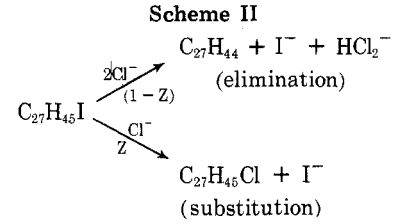
[3c]	[n-Bu_4NCl]	% reaction followed[a]	$10^4 k_2$[b]	F_E[c]
0.0400	0.0447	42	1.61	0.64
0.0400	0.0596	69	1.59	0.62
0.0200	0.0876	72	1.78	0.53
0.0400	0.0992	80	1.71	0.56
0.0400	0.117	80	1.74	0.58

[a] Of 3c. [b] Second-order rate coefficient for iodide ion formation. [c] Average value, as indicated by titration.

Since SN1 reaction leading to **3b** dominated the interaction of lithium chloride with **3a**, we attempted to obtain increased fractions of 1 within the product by introduction of a nucleofugic group which is somewhat better than tosylate in bimolecular reaction but much poorer in unimolecular reaction, namely iodide.[13] Cholesteryl iodide (**3c**) can be conveniently synthesized[14] from the commercially available chloroformate. Also, lithium chloride is only partially dissociated in dipolar aprotic solvents, with paired chloride ion of considerably less nucleophilic reactivity than free chloride ion, and the tendency to SN2 reaction can be considerably increased by substitution of tetra-n-butylammonium chloride.[15]

Under nonsolvolytic conditions, molecularity is frequently simply related to kinetics and we undertook a kinetic study of the reaction of cholesteryl iodide with tetra-n-butylammonium chloride in acetone at 50°. After due allowance for two chloride ions being consumed in elimination reaction but only one in substitution reaction (Scheme II), good second-order kinetics were observed, indicative of

Scheme II



a bimolecular process. Titration of acid developed relative to iodide developed indicated that, over an appreciable extent of reaction, ~60% of reaction was with elimination and ~40% was with substitution (Table II).

A product study, carried out using concentrations of reactants similar to those used in the kinetic study, led to a product which consisted of 37% 1, 24% **3b**, and only 39% 2 (Table I, entry 3). The discrepancy between the 39% of diene in the product study and the ~60% in the kinetic study was found to be due to an elimination–addition reaction[10] providing a route from **3c** to **3b** via 2. This reaction could be suppressed by the addition of excess tetramethylurea[11,12] and the product study then gave ratios consistent with those indicated by the kinetic study (Table I, entries 4 and 5).

While addition of tetramethylurea did not raise the fraction of 1, it did simplify its isolation insofar as that it only had to be separated from 2, rather than from a mixture of 2 and **3b**. Isolation of 1 was therefore from reactions carried out in the presence of excess tetramethylurea. Column chromatography on Florisil–Celite[16a] using pentane as eluent gave reasonably good separation but thin layer chro-

matography indicated that a small amount of diene remained within the epicholesteryl chloride fraction; to obtain analytically pure **1**, this fraction had to be submitted to preparative thin layer chromatography. These difficulties paralleled those of Shoppee, Holley, and Newsoroff,[5] who also obtained, from column chromatography, samples of **1** contaminated with **2**. Our scheme for synthesis of epicholesteryl chloride is considerably simpler than those previously available in the literature but it does share with the earlier schemes the need for thin layer chromatography for complete separation from simultaneously formed cholesta-3,5-diene.

Experimental Section[16b]

Materials. Cholesteryl iodide (**3c**) was prepared from cholesteryl chloroformate (Eastman) as described previously.[14] Cholesteryl *p*-toluenesulfonate (**3a**) was either the Eastman product or synthesized by the procedure of Wallis, Fernholtz, and Gephart.[17] A reference sample of epicholesteryl chloride (**1**) was prepared[4,5] by treatment of 6-ketocholestanol (Sigma) with phosphorus pentachloride to introduce the 3-α chlorine, followed by reduction of the keto group with lithium aluminum hydride and dehydration with phosphorus oxychloride–pyridine reagent. Tetra-*n*-butylammonium chloride and iodide (K and K) were recrystallized from acetone and dried under vacuum at 50°. Tetramethylurea was purified by distillation and used immediately. Acetonitrile[18] and acetone[19] were purified as described previously. A solution of dry hydrogen chloride in acetone was standardized against aqueous sodium hydroxide.

Analysis of Product Mixtures. The three predicted products from reaction of cholesteryl derivatives with chloride ion in aprotic solvents, **1**, **2**, and **3b**, did not, in our hands, separate completely by column chromatography. However, quite accurate analyses could be obtained from the integration of the ^{1}H NMR spectrum within the δ 3.5–6.5 range. Available spectra[20] reported, for **3b**, signals for the 3-α hydrogen at δ 3.76 and for the C-6 vinylic hydrogen at δ 5.36 and, for **2**, signals for the three vinylic protons at δ 5.41, 5.69, and 5.99. The authentic sample of **1** was found to exhibit signals at δ 4.50 for the 3-β hydrogen and at δ 5.38 for the C-6 vinylic hydrogen. Accordingly, the integrations at δ 3.76 and 4.50 are proportional to the concentrations of **3b** and **1** and, within the region of vinylic proton signals (δ 5.2–6.2), subtraction of the integrations at δ 3.76 and 4.50 (equal to those for the identical components at δ 5.36 and 5.38) leads to the integration for the three vinylic protons of the diene; one-third of this value can then be utilized together with the integrations at δ 3.76 and 4.50 to give the relative concentrations.

The percentage of conjugated diene, **2**, within the product mixture can also be determined from the ultraviolet spectrum, where its absorption swamps out those from the products with an isolated double bond. In cyclohexane, **2** has been shown[21] to exhibit absorption maxima with log ϵ 4.23 at 228 nm, log ϵ 4.27 at 235 nm, and log ϵ 4.07 at 244 nm. An average of the observed absorptions at each of these three wavelengths can be used to calculate the weight percentage, and hence the molar percentage, of a mixture with **1** and **3b**. For low concentrations of diene, this determination is preferable to the ^{1}H NMR determination, which has to be determined from a small difference between two relatively large numbers.

The above techniques have been used to determine the compositions of the product mixtures obtained in each of the following experiments (Table I).

Reaction of Cholesteryl *p*-Toluenesulfonate (3a) with Lithium Chloride. The **3a** (0.0185 *M*) was refluxed in acetonitrile with dry lithium chloride (0.236 *M*) for 16 hr. The solution was partitioned between ether and water. The ether layer was washed with a little water and dried over anhydrous $MgSO_4$, and the product mixture isolated by flask evaporation of solvent (Table I, entry 1). The experiment was also performed in the presence of 0.0370 *M* tetramethylurea (Table I, entry 2).

Reaction of Cholesteryl Iodide (3c) with Tetra-*n*-butylammonium Chloride. The **3c** (0.0400 *M*) and *n*-Bu_4NCl (0.200 *M*) were allowed to react in acetone for 72 hr at 50.0°. The solution was partitioned between ether and ice–water. The ether layer was dried over anhydrous $MgSO_4$ and the product mixture remained after flash evaporation (Table I, entry 3). The experiment was repeated in the presence of 0.040 and 0.080 *M* tetramethylurea (Table I, entries 4 and 5).

Control Experiments. Cholesteryl chloride (**3b**, 0.0400 *M*) was allowed to stand in acetone for 72 hr at 50.0° in the presence of *n*-Bu_4NCl (0.200 *M*). After partitioning between ether and water, a 90% recovery of cholesteryl chloride was made (Table I, entry 6). The experiment was repeated in the presence of 0.040 *M* tetramethylurea and a 97% recovery was made (Table I, entry 7).

An acetone solution of **3b** (0.0160 *M*) was allowed to stand for 72 hr in the presence of *n*-Bu_4NCl (0.200 *M*) and hydrogen chloride (0.0240 *M*). The solution was then partitioned between ether and water, and the ether layer was washed with a little water, dried over anhydrous $MgSO_4$, and flash evaporated to dryness (Table I, entry 8). The experiment was repeated with **1** substituted for **3b** (Table I, entry 9).

Column Chromatography. A 250-mg portion of the product from reaction of **3c** with *n*-Bu_4NCl in the presence of tetramethylurea (Table I, entries 4 and 5) was chromatographed, using pentane as eluent, on a 14 × 0.75 in. column packed with 45 g of a 4:1 Florisil–Celite[16a] mixture. Three fractions were collected, consisting of **2**, mp 80–81.5° (lit.[5] mp 79–80°), a mixture of **2** with **1**, and, finally, relatively pure **1**, mp 112–115° (lit. mp 105–107° [4], 114–117° [5]). Thin layer chromatography on silica with pentane as solvent showed for the first fraction one large spot (R_f 0.89), for the second fraction two spots (R_f 0.89 and 0.94), and for the third fraction a large spot (R_f 0.94), mp 115–117°, together with a small spot (R_f 0.89).

Kinetic Measurements. Solutions were made up by appropriate dilution of acetone solutions of **3c** and tetrabutylammonium chloride with acetone at 50.0°. After a few minutes for temperature equilibration, two 5-ml aliquots were withdrawn, followed by others at appropriate time intervals. One series of aliquots was added to 20 ml of acetone maintained at −78° (solid CO_2–acetone slush) and the acid developed, corresponding to elimination reaction, was titrated to Lacmoid (resorcinol blue) end point against a standard solution of sodium methoxide in methanol. The second series of aliquots was used to determine the iodide formation, corresponding to total reaction; the aliquot was introduced into 20 ml of concentrated HCl and 20 g of ice and titrated against a standard aqueous solution of potassium iodate. Starch was found to give an unsatisfactory end point, possibly owing to the presence of acetone, and the end point was determined by adding 5 ml of CCl_4 and titrating, with shaking after each drop near the end point, until the purple color of iodine within the organic layer changed to pale yellow.[22]

In analyzing the data in terms of second-order rate coefficients, it is necessary to take into account the consumption of one chloride ion in each act of substitution and two chloride ions in each act of elimination. The appropriate kinetic equation is

$$\frac{dx}{dt} = zk_2(a - x)(b - x) + (1 - z)k_2(a - 2x)(b - x)$$

where x is the concentration of iodide produced, a is the initial concentration of chloride ion, b is the initial concentration of **3c**, k_2 is the second-order rate coefficient for iodide production, and z is the fraction of reaction proceeding with substitution. Integrating:

$$k_2 = \frac{1}{[a + (z - 2)b]t} \ln \frac{b}{a}\left[\frac{a + (z - 2)x}{(b - x)}\right]$$

The second-order rate coefficients and fractions of reaction proceeding with elimination are listed in Table II.

An acetone solution 0.0387 *M* in **3c** and 0.0400 *M* in tetra-*n*-butylammonium iodide showed no acid formation after 24 hr at 50.0°.

Registry No.—**1**, 2863-79-8; **2**, 747-90-0; **3a**, 1182-65-6; **3b**, 910-31-6; **3c**, 2930-80-5; lithium chloride, 7447-41-8; *n*-Bu_4NCl, 1112-67-0; *n*-Bu_4NI, 311-28-4.

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Ring Enlargement of Geminal Dibromocyclopropanes with Silver Tosylate. An Approach to Medium Sized Rings

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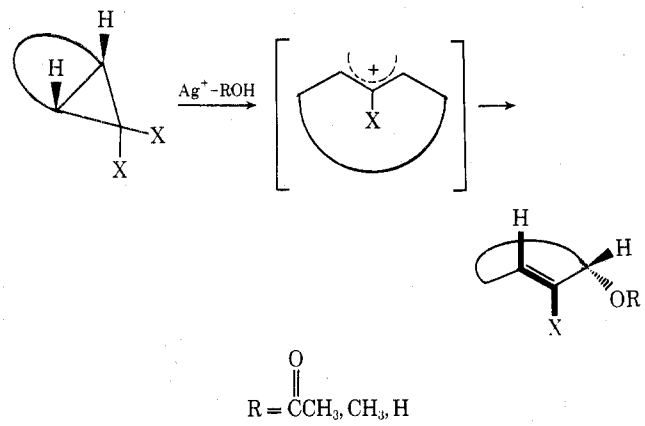
The reaction of geminal dihalocyclopropanes with silver perchlorate under solvolytic conditions has recently attracted attention as a synthetically useful approach for ring enlargement.[1-4] These reactions obey the Woodward–Hoffmann rules of conservation of orbital symmetry and proceed in a disrotatory manner.[5,6] The allylic system formed has been postulated to have the trans conformation, obtained by release of the exo halogen atom.

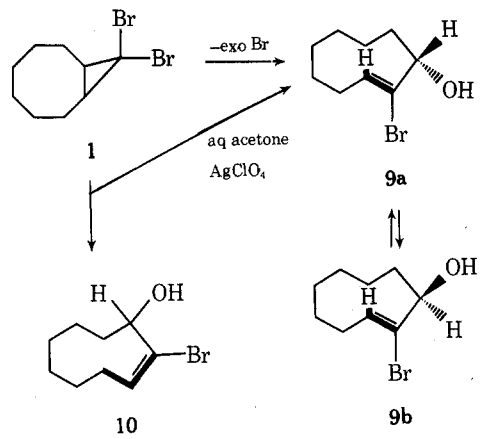


The nucleophile attacks at the same site of the incipient allylic system where the halogen atom is departing and thus leads to the formation of one single diastereoisomer in most cases.

In the absence of silver salts severing of the exo halogen atom is preferred on steric considerations, unless the expanded ring would become too small to accommodate a trans double bond. In the latter case the endo halogen is lost, leading to a cis allylic system.[7a,b]

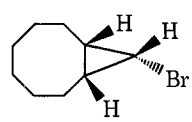
We now wish to present a highly stereospecific method to generate tosylated medium sized rings by ring opening of dibromocyclopropanes in one step and with excellent yields. Reaction of the bicyclic systems **1–4** for 2 hr with a slight excess of silver tosylate in refluxing acetonitrile led in a smooth reaction to the tosylates **5–8** (Table I). Examination of the reaction products (TLC, ^{1}H NMR) revealed that in all four cases one single diastereoisomer had been formed. The ring opening of **3** and **4** proceeds mechanistically in a similar fashion as the above-mentioned reactions. This could easily be demonstrated by synthesizing compounds **7** and **8** by tosylation of the corresponding alcohols with known stereochemistry.[1] Therefore, the tosylates **7** and **8** have the configuration as assigned in Table I.

The formation of tosylates **5** and **6** deserves some comment. Earlier literature concerning the silver perchlorate catalyzed solvolysis of **1** showed that two diastereoisomeric trans alcohols were formed, which were rapidly equilibrating at room temperature.[2] However, in our hands, besides the trans alcohols **9a,b**, also considerable and reproducible amounts of the cis alcohol **10** could be isolated (ca. 30%).[8]



Tosylation of the cis alcohol **10** gave the tosylate **4**, whereas the product obtained by reaction of the mixture of diastereoisomers **9a** and **9b** with tosyl chloride proved to be quite different (NMR spectrum displayed multiplet structures at δ 4.87 and 6.05 for the allylic part of the spectrum). A possibility of initial formation of a trans tosylate followed by an Ag^+-assisted isomerization to the cis conformer could be ruled out easily by refluxing the trans tosylate of **9a,b** with excess silver tosylate in acetonitrile; no traces of **5** could be detected.

Disrotatory ring opening of **1** with release of the sterically less accessible endo bromine atom leading to a cis-allylic system seems very improbable. Upon treating *endo*-9-bromobicyclo[6.1.0]nonane (**11**) with silver tosylate in refluxing acetonitrile no noticeable reaction was observed. A similar observation was made in the expansion of the nine-membered compound **2**.



11

In this case we found that besides the expected 2-bromo-3-hydroxy-*trans*-cyclodec-1-ene (**12**)[11] also the 2-bromo-3-hydroxy-*cis*-cyclodec-1-ene (**13**) could be isolated in 30% yield by ring expansion with silver perchlorate in 5% aqueous acetone.

The tosylate derived from **13** proved to be identical with **6**, whereas the trans alcohol **12** gave a tosylate displaying