Solvolysis of allylic prostaglandin mesylates: moderate 1,3-*syn*-stereoselectivity

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The stereochemistry of S_N2 and S_N2' substitutions of the allylic mesyloxy group in mesylates of prostaglandin allylic epimeric 13- and 15-alcohols under the action of various nucleophiles (H_2O, MeOH, AcOH, LiBr) was studied. The substitution accompanied by rearrangement occurs with moderate (1.4—1.6 : 1) *syn*-stereoselectivity with respect to the configuration of the mesyloxy group, which increases with decreasing temperature and depends only slightly on the nature of the nucleophile.

Key words: allylic mesylates, allylic rearrangement, 11-deoxyprostaglandins, oxylipins, prostaglandins, *syn*-stereoselectivity, solvolysis.

Recently, a new lipoxygenase metabolic pathway of arachidonic acid (and other polyunsaturated fatty acids) has been found in marine algae giving rise to new "marine" oxylipins, whose structures are characterized by the presence of the cyclopropane and lactone rings.[1] The mechanism postulated for biogenesis of these "marine" oxylipins is exemplified in Scheme 1 for the typical (for 12-lipoxygenation) constanolactone family.[2] According to this mechanism, allylic carbocation **B** generated from hydroperoxide **A** undergoes the allylic rearrangement* to form homoallylic carbocation **C**, which is rearranged to cyclopropylcarbinyl cation **D**. The latter is stabilized by a nucleophilic attack of the carboxy group to form cyclopropyllactone **E**, which is a close precursor of constanolactones. All these rearrangements involved in biosynthesis occur with strict stereoselectivity, resulting in the configurations of the newly formed asymmetric centers at the C(5), C(6), and C(8) atoms shown in the scheme.

Since cyclopropane "marine" oxylipins (CMO) are of interest because of their expected biological activity, their total syntheses have attracted considerable attention.[4,5] An attractive possibility is to use the biomimetic rearrangement of the carbocations presented in Scheme 1 in the chemical synthesis, which would enable one to perform a short synthesis.[6] In addition to the very possibility of performing this rearrangement, an equally important problem is the stereoselectivity of the reaction center transfer.

Earlier,[7] in a biomimetic synthesis of hepoxilins HxA_3, we have used hydrolysis of allylic mesylates of hepoxilins HxB_3 epimeric at the hydroxyl group, which are considered as potential sources of the carbocations **B** (R = *Z*-$CH_2CH{=}CHC_5H_{11}$-*n*). This hydrolysis was accompanied by the allylic rearrangement to give mixtures of epimeric HxA_3 with moderate (1.6—1.7 : 1) 1,3-*syn*-stereoselectivity* regarding the transfer of the configuration of the hydroxyl group in the starting epimer of HxB_3 (the S_N2' mechanism). It was of interest to use this reaction for the synthesis of CMO. However, in this case the rearranged (homo)allylic carbocation of type **C** should be attacked (see Scheme 1) not by a water molecule (as in hydrolysis) but by a nucleophile of a different type, *viz.*, a double bond of the molecule. To our knowledge, only the above-mentioned hydrolysis, the replacement of the mesyloxy group by the chloride ion with allylic rearrangement,[8] and the replacement of 15-mesylates of prostaglandins by the superoxide anion, which proceeded strictly by an S_N2 mechanism with complete inversion of the configuration[9] were documented for poorly studied substitution reactions of secondary aliphatic allylic mesylates (SAAM). Hence, in continuation of studies aimed at developing the biomimetic synthesis of CMO, in the present study we focused on a more thorough consideration of the

* In reality, the carbocations **B**, **C**, and **D** are either the limiting forms of the same mesomeric cation with the charge distribution among the C(5)—C(10) atoms or very tight ion pairs ("ion pairs more intimate than intimate"[3]). The term "the rearrangement of carbocations" is used only for convenience of discussion and implies the reaction center transfer.

* In the present study, as in Ref. 7, the term "*syn*" (or "*anti*") implies the attack by a nucleophile on the double bond from the same (or opposite) side where the leaving allylic substituent is located in the most stable "extended" conformation of the carbon chain.

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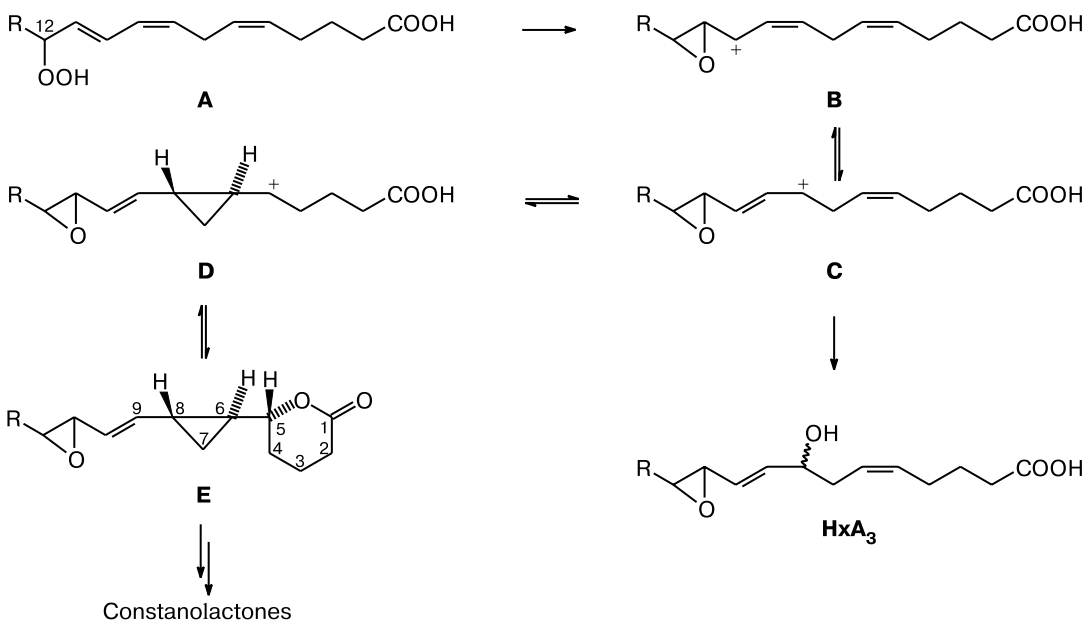
Scheme 1



stereochemistry of solvolytic substitution of SAAM using model substrates.

Results and Discussion

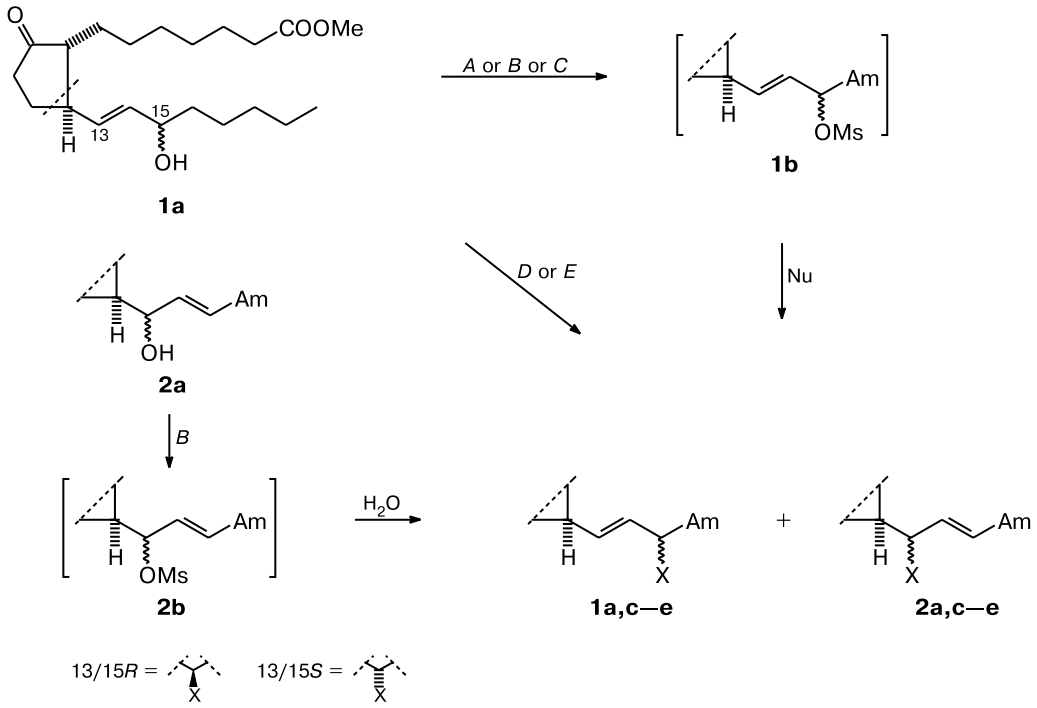
We used prostaglandins accessible by total synthesis, *viz.*, methyl esters of 15-epimers of 11-deoxyprostaglandins E_1 (*R*-**1a** and *S*-**1a***)[10] and the corresponding regioisomeric pair of epimers (*R*-**2a** and *S*-**2a**),[11] as substrates (Scheme 2). These substrates allow one to rather easily analyze mixtures of regio- and stereoisomeric substitution products and, in addition, to estimate the influence of remote asymmetric centers of the molecule on the stereochemistry of the process. The single allylic hydroxy group in the substrates was mesylated with Ms_2O in the presence of Et_3N at 0 °C (method A, see Experimental) or at room temperature (method C) or, alternatively, with MsCl at −78 °C (method B). The resulting SAAM **1b** and **2b** are too reactive to be isolated. Earlier, it has been reported[12] that one of the simplest SAAM cannot be obtained because of thermal instability. In our case, the completeness of the formation of mesylates **1b** and **2b** was confirmed by virtually quantitative yields of their solvolysis products. Solvolysis (or substitution) of the mesylates was performed by adding water, methanol, acetic acid, or LiBr to the reaction mixtures obtained after completion of mesylation. As a result, mesylates **1b** were always transformed into mixtures of the four corresponding products, *viz.*, pairs of epimers **1a,c—e** (without the allylic rearrangement, 1,1-products) and **2a,c—e** (with the allylic rearrangement, 1,3-products). Hydrolysis of mesylates **2b** afforded alcohols **1a** and **2a** as the 1,3- and 1,1-products, respectively.

Since the starting allylic alcohols **1a** and **2a** are chiral, their asymmetric centers can affect the stereochemistry of substitution at C(13) and C(15) (intramolecular stereochemical induction). To estimate this induction under conditions of thermodynamic control, we studied also acid-catalyzed isomerization and methanolysis of alcohols **1a** (methods D and E).

Mixtures of solvolysis products were analyzed without separation. Mixtures of alcohols **1a**+**2a** were analyzed by HPLC or transformed into mixtures of 13/15-*O*-methyl ethers **1c**+**2c**. The latter mixtures, which were prepared also by methanolysis of mesylates and according to the method E, were analyzed by ^{1}H NMR spectroscopy using singlets of the 13/15-OMe groups as reporter signals (Table 1). Mixtures of acetates **1d**+**2d** were analyzed analogously based on the signals of the 13/15-OAc groups. In a more complex case of mixtures of bromides **1e**+**2e**, several reporter signals were simultaneously used for complete analysis. The signals of individual isomers **1a,c—d** and **2a,c—d** in the NMR spectra were assigned by direct comparison with the signals in the spectra of authentic samples. The assignment of epimers in pairs of bromides **1e** and **2e** was based on the assumption that the stereo-

* All starting compounds, as well as their products, are racemic compounds, *i.e.*, pairs of enantiomers. The stereochemical notations *R* and *S* correspond to the enantiomers with "natural" configurations of the asymmetric centers at C(8) and C(12) (the racemate index ∗ is omitted) presented in the schemes. For positions 13 and 15 in compounds **2** and **1**, the notations *R* and *S* are equivalent to β and α, respectively, according to the nomenclature used earlier for prostaglandins.

Scheme 2



X = OH (**a**), OMs (**b**), OMe (**c**), OAc (**d**), Br (**e**); Am = C_5H_{11}-*n*

Methods, reagent, and conditions: *A*. 1) Ms_2O, Et_3N, Py, THF, 0 °C, 30 min, 2) nucleophile (H_2O, MeOH, AcOH or LiBr); *B*. 1) MsCl, Et_3N, CH_2Cl_2, −78 °C, 15—30 min, 2) H_2O or MeOH; *C*. Ms_2O, LiBr, Et_3N, Py, THF, 20 °C, 15 min; *D*. MsOH (2 vol.%) in Me_2CO, 20 °C, 1 h; *E*. $HClO_4$ (2 vol.%) in MeOH, 20 °C, 48 h.

Table 1. Reporter signals in the ^{1}H NMR spectra (500 MHz, C_6D_6) used for the analysis of mixtures of stereo- and regioisomers

Proton type	δ			
OMe	3.220 (*R*-**1c**)	3.210 (*S*-**1c**)	3.122 (*R*-**2c**)	3.129 (*S*-**2c**)
OAc	1.774 (*R*-**1d**)	1.746 (*S*-**1d**)	1.716 (*R*-**2d**)	1.704 (*S*-**2d**)
	R-**1e**	*S*-**1e**	*R*-**2e**	*S*-**2e**
HCBr	4.387[a]	4.387[a]	4.520[b]	4.497[c]
C=CHCBr	5.620[d]	5.600[d]	5.450[e]	5.450[e]
CH=CCBr	5.227[f]	5.260[f]	5.450[e]	5.450[e]

[a] td, J = 7.1 and 9.4 Hz; [b] dd, J = 5.6 and 9.4 Hz; [c] dd, J = 5.2 and 9.4 Hz; [d] dd, J = 9.4 and 15.1 Hz; [e] m; [f] dd, J = 8.4 and 15.1 Hz.

Table 2. Solvolysis of allylic alcohols **1a**

Entry	Starting alcohol	Method (T /°C)	Nucleophile (solvent)	Ratios of products		
				2a/**1a**	*R*-**1a**/*S*-**1a**	*R*-**2a**/*S*-**2a**
1r	*R*-**1a**	D (20)	H_2O	0.22	0.95	1.00
1s	*S*-**1a**	*Ditto*	*Ditto*	0.19	0.95	1.00
				2c/**1c**	*R*-**1c**/*S*-**1c**	*R*-**2c**/*S*-**2c**
2r	*R*-**1a**	E (20)	MeOH	0.24	0.95	0.67
2s	*S*-**1a**	*Ditto*	*Ditto*	0.24	0.91	0.52

Note. Pairs of parallel experiments with *R*- and *S*-epimeric alcohols are identically numbered and have the indices *r* and *s*, respectively.

chemistry of substitution of mesylates with bromide ions is identical to that of methanolysis and acetolysis at the same temperature.

The results of solvolysis of allylic mesylates (the ratios of the products with and without the allylic rearrangement and the ratios of epimers at the same asymmetric center) are given in Tables 2 and 3. The ratios of the products with retention (*syn*) and inversion (*anti*) of the configuration of the asymmetric center involved in the reaction are presented in Fig. 1.

Since mesylates **1b** are highly reactive, the question arises about the configuration and isomer stability under the conditions of the synthesis, particularly at 0 °C. Certain experimental results provide evidence for their rather high stability. Among these are: (1) the reliably different

Table 3. Solvolysis of allylic mesylates **1b** and **2b**

Entry	Starting alcohol	Method of mesylation (T/°C)	Nucleophile (T/°C)	Ratios of products		
				2a/**1a**	*R*-**1a**/*S*-**1a**	*R*-**2a**/*S*-**2a**
3r	*R*-**1a**	A (0)	H_2O (0)	0.31±0.01	0.83±0.02	0.69±0.03
3s	*S*-**1a**	*Ditto*	*Ditto*	0.52±0.22	1.03±0.20	0.46±0.09
4r	*R*-**1a**	B (−78)	H_2O (−20)	0.39	1.18	1.00
4s	*S*-**1a**	*Ditto*	*Ditto*	0.30	0.71	0.28
5r	*R*-**1a**	B (−78)	H_2O (−78)	0.22	1.34	1.00
5s	*S*-**1a**	*Ditto*	*Ditto*	0.23	0.65	0.27
6r	*R*-**2a**	B (−78)	H_2O (−78)	0.50±0.05	1.38±0.16	1.48±0.03
6s	*S*-**2a**	*Ditto*	*Ditto*	0.68±0.02	0.63±0.01	0.11±0.01
				2c/**1c**	*R*-**1c**/*S*-**1c**	*R*-**2c**/*S*-**2c**
7r	*R*-**1a**	A (0)	MeOH (0)	0.28±0.01	0.73±0.01	0.66±0.01
7s	*S*-**1a**	*Ditto*	*Ditto*	0.28±0.01	1.37±0.18	0.53±0.13
8r	*R*-**1a**	A[a] (0)	MeOH (0)	0.28	0.88	0.68
9r	*R*-**1a**	A[b] (0)	MeOH (0)	0.30±0.01	0.83±0.02	0.61±0.01
10r	*R*-**1a**	B (−78)	MeOH (−20)	0.20	0.98	1.00
10s	*S*-**1a**	*Ditto*	*Ditto*	0.19	0.95	0.25
11r	*R*-**1a**	B (−78)	MeOH (−78)	0.42±0.12	1.06±0.16	0.79±0.17
11s	*S*-**1a**	*Ditto*	*Ditto*	0.32±0.02	0.70±0.15	0.29±0.02
				2d/**1d**	*R*-**1d**/*S*-**1d**	*R*-**2d**/*S*-**2d**
12r	*R*-**1a**	A (0)	AcOH (0)	0.25±0.01	1.03±0.01	0.52±0.02
12s	*S*-**1a**	*Ditto*	*Ditto*	0.30±0.04	0.99±0.10	0.81±0.11
				2e/**1e**	*R*-**1e**/*S*-**1e**	*R*-**2e**/*S*-**2e**
13r	*R*-**1a**	C (20)	LiBr (20)[c]	0.30±0.03	0.53±0.06	0.61
13s	*S*-**1a**	*Ditto*	*Ditto*[c]	0.40±0.04	0.41±0.05	0.68±0.14
14s	*S*-**1a**	A (0)	LiBr (0)	0.37±0.06	0.47±0.04	0.59

Note. The data presented with standard errors are the average results of two—four independent experiments.
[a] Additional storage of mesylate **1b** for 5 h before the reaction with the nucleophile.
[b] In CH_2Cl_2.
[c] In these experiments, the nucleophile was included in the reagent for activation of the hydroxy group.

ratios of some reaction products (at 0 °C) from the 15*R*- and 15*S*-epimers of alcohols **1a** (see Table 3, entries *7r* and *7s*); (2) the fact that the results of methanolysis of mesylate *R*-**1b** kept under conditions of mesylation for 5 h remain virtually the same (*cf*. entries *8r* and *7r*); (3) the fact that the results of the reaction of mesylate *S*-**1b** with LiBr added before mesylation (method C, entry *13s*) or after completion of mesylation (entry *14s*) are virtually the same. A change of the solvent from THF to CH_2Cl_2 has also no effect on the results of mesylation and methanolysis (entry *9r*). According to the published data,[9] 15-*O*-mesylates of other prostaglandins are also configurationally stable in the absence of nucleophiles.

To determine the distribution of the products under the conditions of thermodynamic control (the S_N1 mechanism), experiments on acid solvolysis of allylic alcohols were performed for comparison. The results of these experiments were close to those expected for such processes (see Table 2). Both epimers of **1a** gave solvolysis products in virtually the same ratio. Both methanolysis and "hydrolysis" gave products with the allylic transfer (**2a** and **2c**) in 19—22% yields, which are close to the equilibrium fraction of 13-acetates **2d** prepared by palladium-catalyzed isomerization of 15-acetates **1d**[11] and indicate that the C(13) center in prostaglandin molecules is more sterically hindered. The ratios of the epimers at the little hindered C(15) center are close to 1 : 1. The same ratio of epimers at the more hindered C(13) center is observed upon substitution by the small in size hydroxyl group (*R*-**2a** : *S*-**2a** ratio). Only in the substitution at C(13) with the bulkier methoxy group, did the chirality of the remaining part of the molecule manifests itself so that epimers are formed in the ratio *R*-**2c** : *S*-**2c** = 1 : (1.5—1.9). Indeed, calculations of the conformations of epimers of **2c** by molecular mechanics demonstrated that two most populated conformers* of the *S* epimer are more stable (by

* Due to flexibility, prostanoids **2c** (like **1b**, see below) adopt several tens of stable conformations with free energies varying within a range of 2 kcal mol^{-1}; however, from two to four energetically similar conformers of similar shape are energetically more stable (by 0.4—0.8 kcal mol^{-1}) and account for 60—80% of the population, which allows one to judge the relative stabilities of isomers.

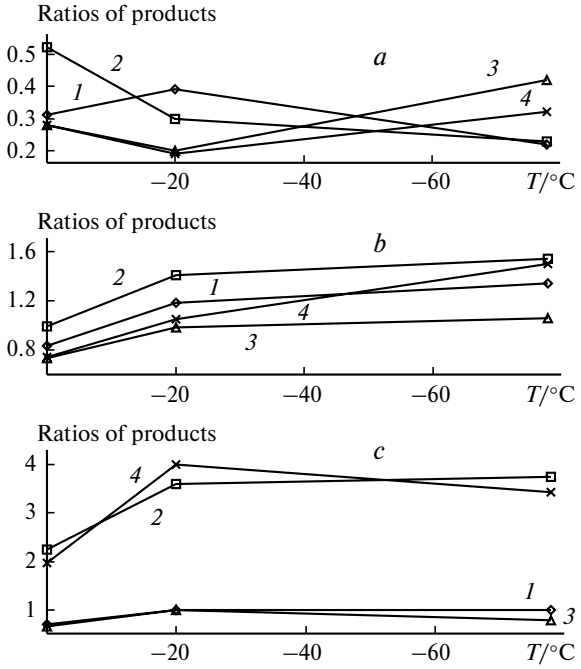


Fig. 1. Temperature dependences of the ratio of the solvolysis products of mesylates **1b**: (*a*) total of the products with and without the allylic rearrangement; (*b*) stereoisomers of the products without the allylic rearrangement with retention and inversion of the configuration of the leaving group; (*c*) analogous stereoisomers of the products in the allylic rearrangement; *1*, hydrolysis products of mesylate *R*-**1b**; *2*, hydrolysis products of *S*-**1b**; *3*, methanolysis products of *R*-**1b**; *4*, methanolysis products of *S*-**1b**.

0.4—0.7 kcal mol^{-1}) than the most stable conformer of the *R* epimer.

Hydrolysis and methanolysis of mesylates **1b** at 0 °C (see Table 3, entries *3r*, *3s*, *7r*, *7s*, *8r*, and *9r*) afforded products, whose ratios differ substantially (for example, **2a** : **1a**, *R*-**1c** : *S*-**1c**, and *R*-**2a** : *S*-**2a** ratios) from the ratios observed upon solvolysis of alcohols **1a** by an S_N1 mechanism (see Table 2), which suggests that this mechanism is of little significance, if at all, even at relatively high temperatures.

At 0 °C, both epimers of mesylate **1b** gave products **2a** and **2c** with the same *S* epimer predominating, which depends to some extent on the configuration of the starting epimer of mesylate **1b** (see Table 3, entries *3r* and *3s*). This result is somewhat unexpected in the light of the earlier data on hydrolysis of mesylates of hepoxilins HxB_3.[7] The dependence of the ratio of epimers of the allylic rearrangement products on the configuration of mesylates **1b** is more pronounced where hydrolysis and methanolysis are performed at low temperatures (entries *4r—5s* and *10r—11s*). In this case, each mesylate **1b** yielded a mixture containing a larger percentage of those epimers of products **2**, whose C(13)-configuration is identical to the C(15)-configuration of the starting mesylate (1,3-*syn* substitution). It should be noted that all the above-mentioned data on hydrolysis of hepoxilin mesylates[7] were obtained at −78 °C. Hence, hydrolysis of SAAM (of both prostaglandins and hepoxilins) at the same temperature is characterized by similar stereochemistry.

The same stereochemical features are observed also in hydrolysis of mesylates of epimeric alcohols **2a**. At −78 °C, each epimer of **2a** gave a mixture of allylic rearrangement products **(*R*+*S*)-1a**, in which epimers with the resulting *syn*-transfer of the hydroxy group are even predominating (entries *6r* and *6s*).

At 20 °C, mesylates **1b** rapidly (during mixing) react also with some other nucleophiles (ethanol, propan-2-ol, *p*-methoxybenzyl alcohol, acetic acid, chloride and bromide ions), but are moderately resistant to such compounds as *tert*-butyl alcohol, acetonitrile, ethyl and *p*-methoxybenzyl acetates, which only induce gradual elimination. To examine the possibility of controlling the stereoselectivity of the replacement of the mesyloxy group by varying the nature of the nucleophile, we studied the reactions with two more reagents, *viz.*, acetic acid and bromide ions. In both cases (at 0—20 °C), the results (entries *12r—14s*) were analogous, in principle, to the results of hydrolysis or methanolysis at the same temperature.

To more clearly show the dependences observed for hydrolysis and methanolysis of mesylates, the results of the experiments with alcohols **1a** are presented as ratios of the *syn* to *anti* products, *i.e.*, those with retention and inversion of the configuration of the hydroxy group, respectively (see Fig. 1). It can be seen that at temperatures from −20 to −78 °C, hydrolysis and methanolysis of mesylates from the *S* alcohols afforded mixtures in which the 1,3-*syn* products substantially predominated. At 0 °C, solvolysis of mesylates from *R* alcohols gave mixtures in which the 1,3-*syn* products did not prevail, but a decrease in the temperature led to a slight, although reliable, increase in their content (see Fig. 1, *c*). An analogous less pronounced dependence is also observed for the 1,1-*syn* products, whereas no regularities are observed for the proportion of the allylic transfer products (ratios of the 1,3 to 1,1 products) (see Fig. 1, *a*,*b*). For alcohols **2a**, the ratio of the 1,3-*syn* to 1,3-*anti* products (1.38—1.59* at −78 °C, see Table 3, entries *6r* and *6s*) is virtually independent of the configuration of the starting alcohol.

The opposite temperature dependence of the stereoselectivity of the substitution observed for 15-epimers of mesylates **1b**, which is expressed as the ratio of the *R*/*S* products (see Table 3), is of most importance for the interpretation of the stereochemical results of 1,3-substitution of the mesyloxy group. For epimer *S*-**1b**, the

* The value of 1.59 is inverse to 0.63 given in Table 3 for the *R*-**1a**/*S*-**1a** ratio, which is the ratio of 1,3-*anti* to 1,3-*syn* products for the starting *S*-**2a**.

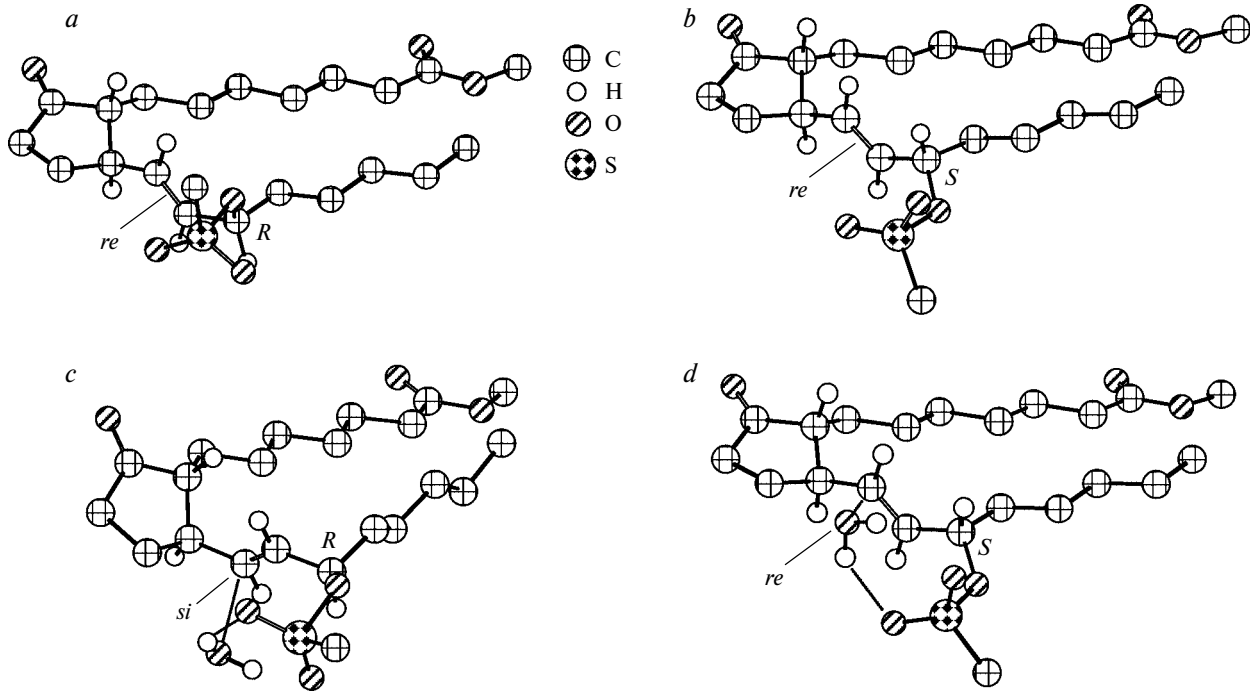


Fig. 2. The most stable conformations calculated by the MM+ method: (*a*) mesylate *R*-**1b**, $E = 20.83$ kcal mol^{-1}; (*b*) mesylate *S*-**1b**, $E = 20.82$ kcal mol^{-1}; *c* and *d*, mesylates *R*-**1b** (*c*) and *S*-**1b** (*d*) in the *syn*-attack of the water molecule on the allylic position C(13), $E = 28.87$ (*R*-**1b**) and 26.52 kcal mol^{-1} (*S*-**1b**). (The H atoms at the non-asymmetric C centers are omitted.)

stereoselectivity increases with a decrease in solvolysis temperature (entries *3s*—*5s*, or *7s*, *11s*, and *12s*), whereas an opposite dependence is observed for *R*-**1b** (entries *3r*—*5r*, or *7r*, *11r*, and *12r*). This suggests a competition between two types of control of the stereoselectivity of the process.

One of them is conformer control, which is related to the accessibility of a particular side of the double bond to the attack. This difference in the accessibility of two sides of the double bond in mesylates **1b** is determined by the presence of two more asymmetric centers (in addition to C(15)) and the second side chain. Conformational analysis showed that two or three most stable conformations* of the molecules of each epimer of mesylate **1b** have a common hairpin conformation typical of prostaglandins (where side chains come close to each other and are nearly parallel), in which the *si* side of the double bond of the "methyl" chain is shielded by the "carboxyl" chain. This is clearly exemplified by the most stable conformers of mesylates **1b** (Fig. 2, *a*,*b*). The attachment of nucleophiles to C(13) from the more accessible *re* side of the double bond in both epimers of mesylate **1b** will afford 13*S*-epimers of **2**. The efficiency of this type of stereochemical control cannot depend substantially on the temperature, because the conformers responsible for this control are most populated at 0 °C.

The second type of stereochemical control of the substitution is related to the configuration of a leaving group (substituent control), if a nucleophile interacts, in one or another way, with this group during the attack.[13] This control is responsible for the formation of different C(13)-epimers of **2** from different epimers of mesylate **1b**. Since the substituent control assumes the highly organized transition state, the efficiency of this control should depend substantially on the temperature. For both epimers of mesylate **1b**, the relative fraction of the epimer resulting from the *syn*-attack of a nucleophile increases in an epimeric mixture of products **2** with a decrease in temperature, which suggests that solvolysis of SAAM occurs predominantly according to a *syn*-S_N2' mechanism.

Evidently, two types of stereochemical control can act in the same or opposite directions. In the former case, the stereoselectivity is high and increases as the reaction temperature decreases (mesylate *S*-**1b**), whereas the opposite situation occurs in the latter case (mesylate *R*-**1b**). This situation was observed in solvolysis reactions. A hypothetical mechanism of the 1,3-*syn* attack of a water molecule on epimers of mesylate **1b** is presented in Fig. 2, *c*,*d*. The attack of molecule *S*-**1b** (see Fig. 1, *d*) from the *re* side of the double bond does not require any substantial change in the geometry of a stable conformation of the molecule (see Fig. 1, *b*) and, hence, it is more energetically favorable than the attack of molecule *R*-**1b** (see Fig. 1, *c*). In the latter case, the attack should occur from

* *Cf.* footnote in p. 2620.

the previously unexposed *si* side of the double bond, which requires additional energy consumption.*

In the case of mesylates **2b**, the efficiency of the conformer control of the configuration of the newly formed asymmetric center at C(15) is close to zero because of the remoteness of the C(15) atom from other asymmetric centers of the molecule. This fact is well known in prostaglandin chemistry. For example, various methods of reduction of the carbonyl group at C(15) in prostanoids proceeds with stereoselectivity of no higher than 1.1 : 1.[14] Due to the fact that the stereochemical control of hydrolysis of mesylates **2b** involves only the influence of the configuration of the leaving substituent, mixtures of the 1,3-products obtained from each starting epimer contain predominantly the corresponding *syn* epimer (see above). The efficiency of this control is low even at −78 °C and is equal to (1.38—1.59) : 1. The virtually identical in value 1,3-*syn*-stereochemical control was observed in hydrolysis of hepoxilin mesylates.[7]

The above-mentioned hypothesis about the existence of two types of stereochemical control in solvolysis of allylic mesylates **1b** and **2b** is equally applicable for the explanation of the observed ratios of epimers of the 1,1-products, which is evidence in support of this hypothesis.

On the whole, the results and their interpretation allow the conclusion that the 1,3-*syn*-stereoselectivity of solvolysis of SAAM with oxygen-containing nucleophiles observed earlier in a single example[7] has a more general character. This stereoselectivity is analogous to the known *syn*-stereoselectivity of the S_N2' substitution of aliphatic secondary allylic compounds with amines (but not with organometallic reagents; see the review[15]), which has been theoretically substantiated.[13] In spite of low stereochemical preference in processes involving SAAM and nucleophiles under consideration, which depends only slightly on their structures, this phenomenon can be used for establishing the configurations of solvolysis products (see Ref. 7). For synthetic purposes, this stereoselectivity can be used only in combination with any other stereochemical control in the substrate molecule acting in the same direction. As applied to the biomimetic synthesis of CMO, the involvement of the terminal carboxyl group as an intramolecular nucleophile can provide such an additional control (an analogous example has been documented[16]).

Experimental

The NMR spectra were recorded on Bruker WM-250 (250.13 MHz), Bruker AM-300 (300.13 MHz), and Bruker DRX500 (500.13 MHz) spectrometers; the chemical shifts are given relative to Me_4Si as the internal standard (δ = 0.00). In the NMR spectra of prostaglandin derivatives, the signals for the protons at C(3)—C(6), C(9)—C(12), and C(16)—C(19), which form an uninterpretable "methylene elevation" at δ 1.0—2.0, are omitted. Conformational analysis was carried out with the use of the HyperChem program (Pro 6.03 version) by the MM+ method with an automatic search of conformations until each of 10—20 most stable conformations was repeated three—six times. The HPLC analysis was carried out on a Milikhrom 1A chromatograph equipped with a 2×64-mm column with Silasorb 600 (8 μm) (the elution rate was 100 μL min^{-1}) and an UV detector. The TLC analysis was performed on Silufol plates; visualization was carried out by spraying with an ethanolic solution of phosphomolybdic acid followed by heating.

Racemic prostaglandins *rac*-(15*R*)- and -(15*S*)-11-deoxy-PGE_1 (m.p. 49—55 °C and 84—86 °C, respectively) from the Pilot-production plant of the Institute of Organic Synthesis (Riga, Latvia) were transformed into the corresponding methyl esters (*R*-**1a** and *S*-**1a**) by esterification of the carboxyl groups with an ethereal CH_2N_2 solution, R_f 0.09 and 0.05 (EtOAc—hexane, 1 : 4, double development). The reagents Ms_2O, MsCl, and MsOH (Fluka) were used without additional purification; THF was dried by distillation from sodium benzophenone ketyl; Et_3N was dried and distilled over KOH.

The extracts were dried with anhydrous $MgSO_4$ and concentrated to dryness first on a rotary evaporator at 30 °C *in vacuo* using a water-jet pump and then by keeping *in vacuo* at 20 °C and 5—7 Torr to a constant weight.

Acetates of methyl esters of 11-deoxy-(15*R*)- and 11-deoxy-(15*S*)-PGE_1 (*R*-1d and *S*-1d) were prepared in nearly quantitative yields by treatment of *R*-**1a** or *S*-**1a** (100 mg) with a mixture of Ac_2O (2 mL) and Py (2 mL) at 20 °C for 30 h. Then the mixtures were concentrated to dryness and viscous yellow oils were obtained, R_f 0.24 and 0.26 (EtOAc—hexane, 1 : 4, double development) for *S*-**1d** and *R*-**1d**, respectively. ^{1}H NMR (250 MHz, C_6D_6), δ of *R*-**1d**: 0.88 (t, 3 H, C(20)H_3, J = 6.6 Hz), 1.77 (s, 3 H, OAc), 2.12 (t, 2 H, C(2)H_2, J = 7.4 Hz), 3.36 (s, 3 H, OMe), 5.39 (m, 2 H, H(14) + H(15)), 5.50 (dd, 1 H, H(13), J = 7.9 and 14.8 Hz); *S*-**1d**: 0.88 (t, 3 H, C(20)H_3, J = 7.0 Hz), 1.75 (s, 3 H, OAc), 2.12 (t, 2 H, C(2)H_2, J = 7.4 Hz), 3.36 (s, 3 H, OMe), 5.42 (m, 3 H, H(13)—H(15)).

Methyl (13*S*,14*E*)-13-hydroxy-9-oxoprost-14-enoate (*S*-2a) (for the method of the synthesis and the spectrum, see Refs 11 and 17). A solution of acetate *S*-**1d** (50 mg, 0.13 mmol) and $PdCl_2 \cdot (MeCN)_2$ (1.3 mg, 5.2 μmol) in anhydrous THF (1 mL) was stirred at 20 °C, isomerization being monitored by TLC (R_f 0.31 and 0.38 for *S*-**1d** and *S*-**2d**, respectively; EtOAc—hexane, 1 : 4; fourfold development) until the ratio of the starting reagent to the products ceased to change (4 h, *S*-**1d** : *S*-**2d** = ~85 : 15). The solution was diluted with EtOAc, filtered through Al_2O_3 (500 mg), and concentrated to dryness. A mixture of isomeric acetates was obtained in a yield of 50 mg (100%). In the ^{1}H NMR spectrum of the mixture, a characteristic signal of acetate *S*-**2d** was identified (see Table 1). Water (5 mL) and a 1 *M* KOH solution (10 mL) were added to this mixture in MeOH (20 mL). The reaction mixture was stirred at 20 °C for 1.5 h, acidified with 10% HCl (20 mL), and extracted with EtOAc. The extract was dried, an ethereal solution of CH_2N_2 was added until the solution turned yellow, and the mixture was concentrated to dryness. Silica gel column chroma-

* The estimates of the energies given in Fig. 2, *c*,*d* are only qualitative because the molecular mechanics method MM+ does not take into account fine interactions of electron orbitals responsible for *syn*-stereoselectivity of the 1,3-substitution in allylic systems.[13]

tography (gradient elution, 20→50% EtOAc in hexane) of the residue afforded alcohol *S*-**2a** in a yield of 7.0 mg (14%) and alcohol *S*-**1a** in a yield of 38 mg (76%), R_f 0.49 and 0.29 (EtOAc—hexane, 1 : 2, threefold development), respectively.

Methyl (13*R*,14*E*)-13-hydroxy-9-oxoprost-14-enoate (*R*-2a) was prepared from *R*-**1d** as described above *via* *R*-**2d** (R_f 0.36 and 0.38 for *R*-**1d** and *R*-**2d**, respectively). The yields were 13.5% (*R*-**2a**) and 74% (*R*-**1a**), R_f 0.49 and 0.40.

Synthesis and solvolysis of mesylates (general procedures). ***Method A.*** Triethylamine (98 mg, 0.97 mmol), Py (1 μL, 0.01 mmol) (pyridine substantially accelerates mesylation), and a solution of Ms_2O (129 mg, 0.74 mmol) in anhydrous THF (1 mL) were successively added to a solution of alcohol *R*-**1a** or *S*-**1a** (52.4 mg, 0.15 mmol) in anhydrous THF (1 mL). The reaction mixture was stirred at 0 °C until the starting alcohol was completely transformed (generally, for 30 min); the completeness of mesylation was monitored by treatment of an aliquot of the reaction mixture with anhydrous MeOH and TLC analysis: R_f of the starting alcohols were 0.37 (or 0.33), R_f of methyl ethers **1c**+**2c** was 0.65 (EtOAc—hexane, 3 : 2, double development).* The nucleophile was immediately (except for entry *8r*, see Table 3) added to the resulting solution of mesylate *R*-**1b** or *S*-**1b** (modifications *a*—*d* of the method).

(*a*) Water (3 mL) was added. The solution was acidified with 10% HCl to pH 2 and extracted with EtOAc. The extract was washed with water to pH 7, dried, and concentrated to dryness. A crude mixture of alcohols **1a**+**2a** was obtained as a yellow oil in a yield of 55 mg (105%). The mixture was transformed with MeI in the presence of Ag_2O (see below) into a mixture of methyl ethers **1c**+**2c** and analyzed by ^{1}H NMR spectroscopy.

(*b*) Anhydrous MeOH (2 mL) was added. The reaction mixture was stirred for 2 min, diluted with water (3 mL), and worked up as in (*a*). A mixture of ethers **1c**+**2c** was obtained as a pale-yellow oil in a yield of 60 mg (100%) and analyzed by ^{1}H NMR spectroscopy.

(*c*) Anhydrous AcOH (2 mL) was added. The reaction mixture was stirred at 20 °C for 2 h and then diluted with water (2 mL). The solution was extracted with diethyl ether. The extracts were washed first with a saturated aqueous $NaHCO_3$ solution to pH 8 and then with water to pH 7, dried, and concentrated to dryness. A mixture of acetates **1d**+**2d** was obtained as a pale-yellow oil in a yield of 61 mg (100%) and analyzed by ^{1}H NMR spectroscopy.

(*d*) A solution of LiBr (70 mg, 0.8 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred for 15 min, acidified with 10% HCl to pH 2, and extracted with EtOAc. The extracts were washed with water to pH 7, dried, and concentrated to dryness. A mixture of bromides **1e**+**2e** was isolated in a yield of 60 mg (94%), R_f 0.69 (*R*-**1e** + *S*-**1e**) and 0.79 (*R*-**2e** + *S*-**2e**) (DC-Alufolien Merck Kieselgel 60, hexane—EtOAc, 7 : 3, double development). To identify the structures of regioisomers, the epimeric pairs *R*-**1e** + *S*-**1e** and *R*-**2e** + *S*-**2e** were isolated by silica gel column chromatography (hexane—EtOAc, 9 : 1 → 7 : 3). The ^{1}H NMR spectra of the epimeric pairs show characteristic signals of the individual isomers (see Table 1). Unseparated four-component mixtures were analyzed by ^{1}H NMR spectroscopy.

Method B. Triethylamine (77.2 mg, 0.76 mmol) and a solution of MsCl (67.4 mg, 0.59 mmol) in anhydrous CH_2Cl_2 (1 mL) were successively added to a solution of individual alcohol *R*-**1a**, *S*-**1a**, *R*-**2a**, or *S*-**2a** (41.4 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (1 mL) at −78 °C. The reaction mixture was kept at this temperature for 15 min and then the nucleophile was added.

(*a*) At −78 °C or after warming to −20 °C, a saturated aqueous $NaHCO_3$ solution (0.4 mL) was added. The reaction mixture was warmed to room temperature and worked up as in (*a*), method *A*. A mixture of alcohols **1a**+**2a**, which was prepared in nearly quantitative yield, was analyzed by HPLC. The retention times were 7.0, 7.4, 9.6, and 14.7 min for *R*-**2a**, *S*-**2a**, *R*-**1a**, and *S*-**1a**, respectively (a EtOAc—hexane—Pr^{i}OH system, 13 : 27 : 0.15, the detection at 202 nm).

(*b*) Methanol (2 mL) was added. The mixture was kept at −78 °C for 5 min and worked up as described above. A mixture of ethers **1c**+**2c**, which was prepared in virtually quantitative yield, was analyzed by ^{1}H NMR spectroscopy.

Method C. Precalcined (240 °C, 40 min) LiBr (191 mg, 2.2 mmol) was placed in a flask, molten *in vacuo*, cooled, and dissolved in anhydrous THF (1.5 mL). Then a solution of alcohol *R*-**1a** or *S*-**1a** (40 mg, 0.11 mmol) in anhydrous THF (1 mL), Et_3N (145 mg, 1.4 mmol), Py (1 μL, 0.01 mmol), and a solution of Ms_2O (145 mg, 1.1 mmol) in anhydrous THF (1 mL) were successively added. The reaction mixture was stirred at 20 °C for 15 min, diluted with water (2 mL), and worked up as described in the method *A*. A mixture of bromides **1e**+**2e** was obtained in a yield of 44 mg (94%) and analyzed as in (*d*), method *A*.

Solvolysis of allylic alcohols (general procedures). ***Method D.*** A solution of alcohol *R*-**1a** or *S*-**1a** (2.0 mg) in a freshly prepared 2% solution of methanesulfonic acid in acetone (1 mL) was kept at 20 °C for 1 h. The colorless solution was diluted with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with diethyl ether and benzene. The combined extracts were washed with water, dried, and concentrated to dryness. The residue was analyzed by HPLC, which revealed up to 20% of dehydration products (diene chromophore) along with alcohols **1a** and **2a**.

Method E. Perchloric acid (65%) (100 μL) was added to a solution of alcohol *R*-**1a** or *S*-**1a** (55.6 mg) in MeOH (1 mL). The reaction mixture was kept at 20 °C for 5 h, the same amount of $HClO_4$ was added, and the mixture was kept at 20 °C for 20 h. According to TLC, the conversion of the starting alcohol was ~70%. The solution was diluted with water (3 mL), carefully (foaming!) neutralized with a saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The extract was washed with water, dried, and concentrated to dryness. Column chromatography of the residue on silica gel (2.5 g; 5—40 μm, elution with hexane—EtOAc, 9 : 1 → 8 : 2) afforded a mixture of ethers **1c**+**2c** (pale-yellow oil) in a yield of 37 mg (67%). The mixture was analyzed by ^{1}H NMR spectroscopy.

***O*-Methylation of allylic alcohols 1a and 2a and their mixtures (general procedure).** A mixture of Ag_2O (586 mg, 2.52 mmol) and a solution of alcohol **1a** or **2a** (31.5 mg, 0.089 mmol) in MeI (2 mL) was refluxed with stirring for 3 h. The insoluble material was filtered off and washed with EtOAc. The filtrate was concentrated and filtered through silica gel (~200 mg) with additional elution with EtOAc. The eluate was

* It is impossible to perform direct TLC analysis of the reaction mixture, because this contains, in addition to the starting alcohol, unidentified products with R_f 0.49, 0.57, and 0.83, none of which is mesylate.

concentrated to dryness and the corresponding methyl ether was isolated as a pale-yellow oil, yield 33 mg (100%).

Methyl ester of 15-*O*-methyl-11-deoxy-(15*R*)-PGE$_1$ (*R*-1c). ^{1}H NMR (300 MHz, C_6D_6), δ: 0.91 (dist.t*, 3 H, C(20)H_3, J = 6.6 Hz); 2.11 (t, 2 H, C(2)H_2, J = 7.4 Hz); 3.22 (s, 3 H, C(15)OMe); 3.36 (s, 3 H, COOMe); 3.44 (m, 1 H, C(15)H); 5.28—5.32 (m, 2 H, CH=CH).

Methyl ester of 15-*O*-methyl-11-deoxy-(15*S*)-PGE$_1$ (*S*-1c). The ^{1}H NMR spectrum (300 MHz, C_6D_6) is identical to the above-given spectrum of epimeric *R*-**1c**, except for the signal of C(15)OMe (δ 3.21).

Methyl (13*R*,14*E*)-13-methoxy-9-oxoprost-14-enoate (*R*-2c) (in a mixture with *R*-1c). A mixture of finely ground precalcined K_2CO_3 (100 mg, 0.72 mmol) and a solution of the above-described mixture of acetates *R*-**1d**+*R*-**2d** (85 : 15) (100 mg, 0.25 mmol) in anhydrous MeOH (2 mL) was stirred at 20 °C for 2 h. Then the mixture was diluted with benzene (2 mL) and filtered, and the filtrate was concentrated to dryness. The residue was dissolved in EtOAc and filtered through Al_2O_3 (500 mg). The filtrate was concentrated to dryness and the resulting mixture of alcohols *R*-**1a**+*R*-**2a** was *O*-methylated according to the general procedure. A mixture of ethers *R*-**1c**+*R*-**2c** (~85 : 15) was obtained in quantitative yield. In the ^{1}H NMR spectrum of the mixture, a characteristic signal of ether *R*-**2c** was identified (see Table 1). The signal of isomeric *S*-**2c** given in Table 1 was identified in the spectrum of a four-component mixture of regio- and stereoisomers.

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* A distorted triplet.

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