REACTION SEQUENCE ARYLSULFENYL CHLORIDE + ALKOXYALKENE-I + ALKOXYALKENE-II + ALLYLMAGNESIUM OR BORON DERIVATIVES AS A NEW METHOD FOR THE CONTROLLED SYNTHESIS OF POLYFUNCTIONAL DERIVATIVES

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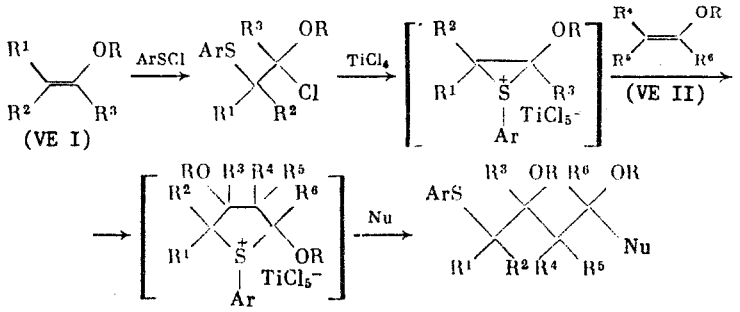
A new method is proposed for the controlled synthesis of polyfunctional compounds with formation of two new carbon–carbon bonds; the method is based on the following reaction sequence, which can be carried out in a single flask: addition of ArSCl to vinyl ether I, reaction of the resultant adduct with vinyl ether II in the presence of Lewis acid to form a cationic complex, and treatment of the latter with allyl derivatives of boron or magnesium.

Earlier it was shown that β-arylthio-α-alkoxyalkyl chlorides (adducts of vinyl ethers with ArSCl) in the presence of Lewis acids readily react with various π-donor nucleophiles to give β-arylthio-α-alkoxyalkylation products [1-3]. With the use of vinyl ethers as π-donor substrates, a characteristic of this reaction is the formation of a cationic intermediate, for which a thiophan salt (TPS) structure has been proposed [1]. Such intermediates react with O- or N-nucleophiles (H_2O, MeOH, Bu_4NBH_4) to form vinyl ether coupling products (VE I and VE II) that include an electrophile (ArS^+) and a nucleophile (HO^-, MeO^-, H^-) at the ends of the four-carbon fragment [1]. It should be noted that the three-reaction sequence shown in Scheme 1 is carried out in one flask.

Scheme 1



Further development of this synthetic methodology required elucidation of the possibility of using C-nucleophiles at the TPS "quenching" stage, since the result of this process would be the formation of two new carbon–carbon bonds. In this endeavor the most promising reagents were Mg and B organic compounds. In the present work we investigated their use as nucleophiles in the reaction sequence shown in Scheme 1.

Treatment of cationic intermediate (IVa) – obtained from the reaction of 1-methoxy-2-(p-tolylthio)ethyl chloride (IIa) [an adduct of methyl vinyl ether (I) with TolSCl] with 2-methyl-1-methoxypropene-1 (III) in the presence of $TlCl_4$ – with allylmagnesium chloride at −78°C afforded the allylation product 5,5-dimethyl-4,6-dimethoxy-7-(p-tolylthio)heptene-1 (Va).

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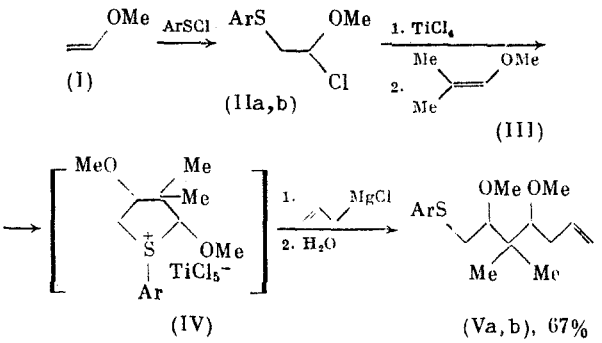
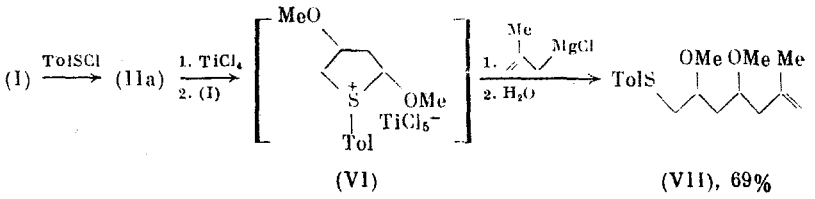
Scheme 2



Ar = *p*-Tol (a), *p*-ClC_6H_4 (b).

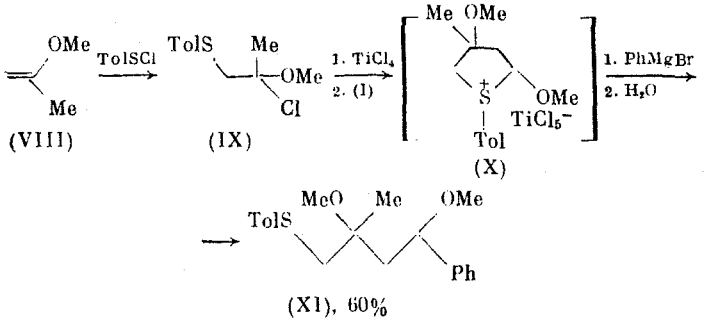
Similarly, reaction of cationic intermediate (VI) – prepared from the addition of adduct (IIa) to ether (I) – with methallylmagnesium chloride afforded 2-methyl-4,6-dimethoxy-7-(p-tolylthio)heptene-1 (VII) in a yield of 69%.

Scheme 3



Phenylmagnesium chloride can also be used as a nucleophile. Thus, reaction of the latter with TPS (X) – obtained from ether (I) and adduct (IX) [the reaction product of 2-methoxypropene (VIII) with ArSCl] – afforded 2-methyl-4-phenyl-2,4-dimethoxy-7-(p-tolylthio)pentane (XI).

Scheme 4



Our attempts to use methylmagnesium halide and vinylmagnesium bromide as nucleophiles were not successful. TPS "quenching" was not observed at −78°C, whereas a complex product mixture was obtained at higher temperatures.

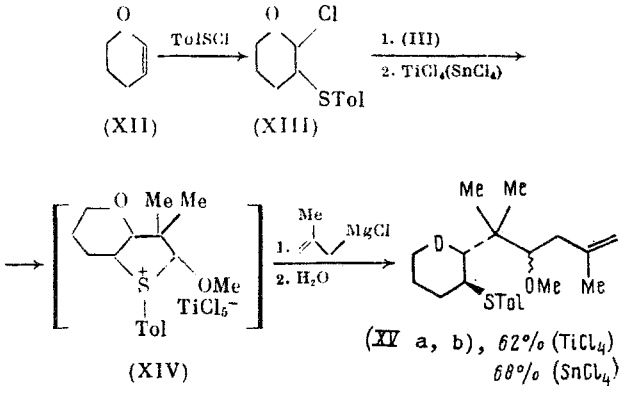
Compounds (V), (VII), and (XI) were isolated as diastereomeric mixtures in a ratio of 3:2 [for (V)] and 5:2 [for (VII) and (XI)] (PMR spectral data). The stereochemistry of the reaction is controlled to a large extent by the use of cyclic alkoxyalkenes. Thus, 2-(1', 1',4'-trimethyl-2'-methoxypenten-4'-yl)-3-(p-tolylthio)oxane (XVa) was synthesized by the reaction of adduct (XIII), obtained from dihydropyran (XII) and TolSCl, with ether (III) in the presence of $TiCl_4$ followed by treatment of the reaction complex with methallylmagnesium chloride. Although this compound can exist in the form of four diastereomers, PMR data showed that the isolated product was stereochemically individual (purity ≥95%). When the same reaction was crried out in the presence of another Lewis acid ($SnCl_4$), the same product was obtained in the form of two diastereomers, (XVa):(XVb) = 1:1, which were separated by preparative liquid chromatography.

TABLE 1. Nuclear Overhauser Effects Observed during Irradiation of gem-Dimethyl Group Protons of Compounds (XVa) and (XVb)

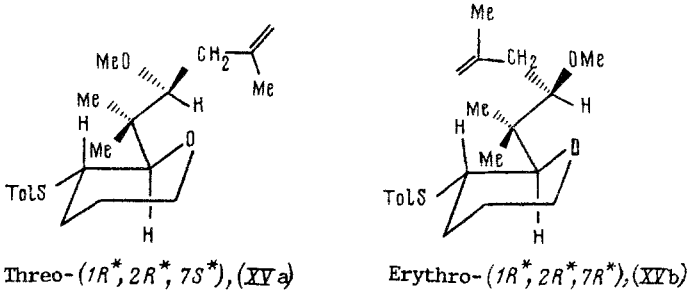
Irradiated proton	NOE values, %*						
	H^1	H^2	H^7	OCH_3	H^8	o-Ph	$H_2C=$
CH_3 at 1,11 ppm (XVa)	2,5	1,0	1,0	–	3,0	1,0	–
CH_3 at 1,15 ppm (XVa)	0,5	2,5	3,0	0,5	0	0	–
CH_3 at 0,94 ppm (XVb)	0,6	3,3	1,9	–	3,3	0,4	0,5
CH_3 at 1,095 ppm (XVb)	1,5	2,1	–	1,0	4,1	0,9	0

*All positive; signal of irradiated protons in differential spectrum.

Scheme 5



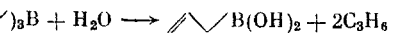
One of these diastereomers was identical to the isomer obtained using $TiCl_4$ (^{13}C NMR data). PMR spectral analysis showed that both diastereomers have a trans configuration of ring substituents. Nuclear Overhauser effect (NOE) studies of both diastereomers (Table 1) indicate that isomer (XVa), synthesized using $TiCl_4$, is a threo-diastereomer (1R*, 2R*, 7S*) and that the second isomer (XVb) is an erythro-compound (1R*, 2R*, 7R*).



It should be noted that the difference in the chemical shifts (CS) of the gem-dimethyl group in the threo-isomer is smaller than in the erythro-product. These data are in agreement with the rule for determining threo- and erythro-configurations of substituents for $R^*CH_2R^*$-type systems, where R is a substituent with a chiral carbon atom: $\Delta\delta_{threo}^{CH_2} < \Delta\delta_{erythro}^{CH_2}$ [4].

Next we attempted using trialkylboranes – tripropyl- and triallylboranes – as nucleophiles for quenching complex (IVb) and other cationic intermediates of this type. Unlike trialkylboranes, triallylborane, like Grignard reagents, is readily added to carbonyl compounds and can be cleaved by water and alcohols to form two moles of propylene and allylboric acid or its esters [5, 6].

Scheme 6

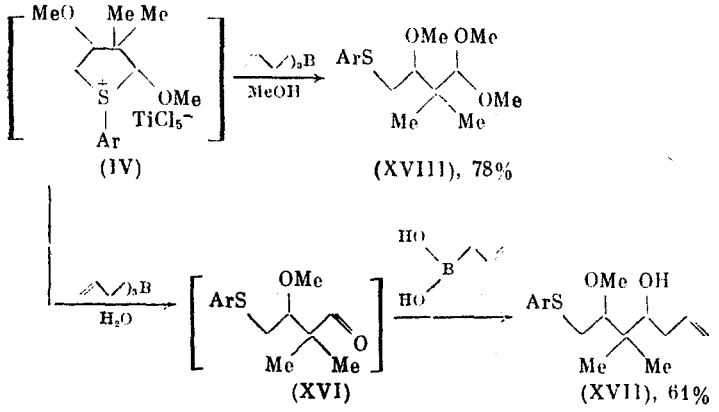


Thiophan salts (IVb), (XIV), and (XXI) were inert toward tripropyl- and triallylborane. Nevertheless, we were able to find conditions under which thiophan salts reacted fairly readily with allylboranes to yield homoallyl alcohols.

Thus, sequential treatment of salt (IVb) with triallylborane and water afforded 4,4-dimethyl-6-methoxy-7-(p-chlorophenylthio)hepten-1-ol-4 (XVII) (Ar = p-ClC_6H_4) in a yield of 61% (a 5:4 diastereomeric mixture).

When water was replaced by methanol, acetal (XVIII) was obtained in a yield of 78%, and allylation product (XVII) was not formed at all.

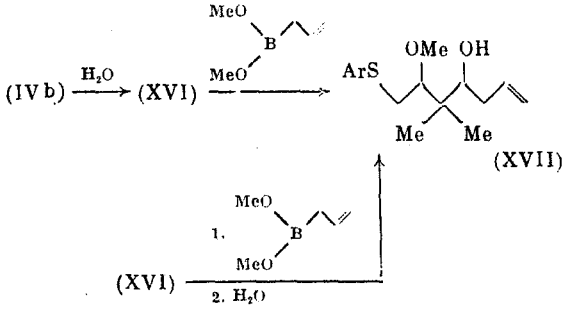
Scheme 7



This reaction course may be explained as follows. In the presence of water TPS (IVb) is converted to aldehyde (XVI), which immediately reacts with triallylborane or allylboric acid that is formed under these conditions. The boric ester formed in this manner is hydrolyzed, affording homoallyl alcohol. (Allylborylation of carbonyl compounds in aqueous media is described in [7].) If the reaction mixture obtained by adding triallylborane to TPS (IVb) is treated with methanol, acetal (XVIII) is obtained, and acetals do not react with allylboranes [5].

To confirm the scheme presented above, the following reactions were carried out: reaction of allylboric acid methyl ester 1) directly with aldehyde (XVI) and 2) with TPS (IVb) followed by treatment with water.

Scheme 8

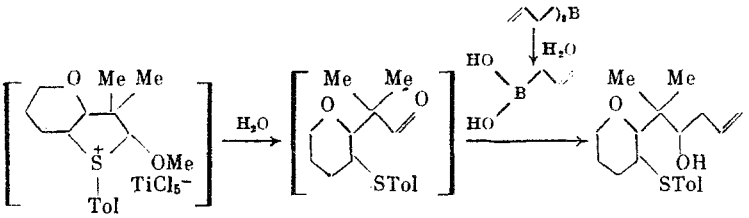


In both cases homoallyl alcohol (XVII) was obtained as a mixture of two diastereomers in the ratio 5:4. The absence of dimethoxy product (Vb) and the identical results obtained for the latter two reactions indicate that allylboric acid methyl ester does not react with TPS (IVb) but, rather, with aldehyde (XVI), formed in situ during the hydrolysis of salt (IVb).

When tripropylborane and water reacted with salt (IVb), aldehyde (XVIII) was obtained. This reaction course is explained by the fact that trialkylboranes are inert toward aliphatic aldehydes at 20-60°C [5].

Allylborylation of complex (XIV) under conditions described for (IVb) (see above) afforded 2-(1',1'-dimethyl-2'-hydroxypenten-4'-yl)-3-(p-tolylthio)oxane (XIX) in a yield of 66% and a diastereomer ratio of 5:2.

Scheme 9

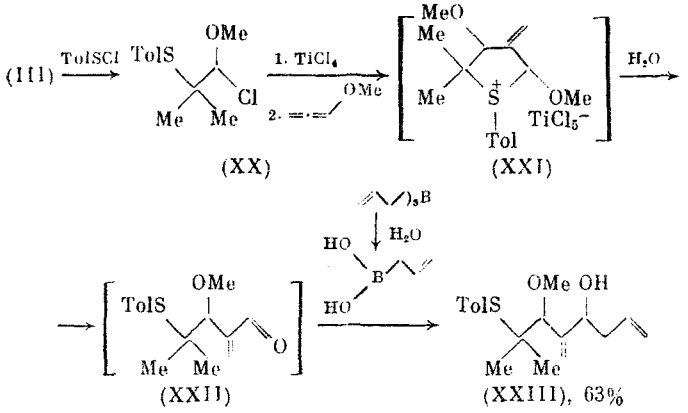


(XIV) (XVIII) (XIX), 66%

Similarly, 7-methyl-5-methylene-4-hydroxy-6-methoxy-7-(p-tolylthio)octene-1 (XXIII) (yield, 63%; diastereomer ratio, 1:1) was synthesized from TolSCl, 2-methyl-1-methoxypropene-1 (VE I), methoxyallene (VE II), and triallylborane.

The stereoisomeric composition of the homoallyl alcohols was established by means of PMR spectral data.

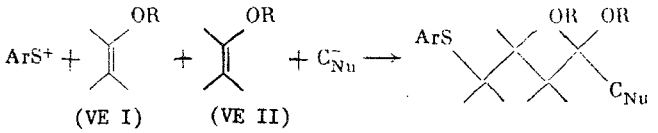
Scheme 10



(XX) (XXI) (XXII) (XXIII), 63%

The results presented in this work show that coupling reactions of vinyl ethers in the presence of arylsulfenyl chlorides can be used to carry out short syntheses of polyfunctional compounds from simple precursors in accordance with Scheme 11.

Scheme 11



(VE I) (VE II)

This entire sequence of operations is carried out in a single reaction vessel.

The use of ArSCl as an electrophile in the first step plays a decisive role in the outcome of the reaction sequence. Indeed, the presence of the arylthio group not only ensures stabilization of the episulfonium intermediate (ESI, Scheme 1) formed from VE I, but also leads to the formation of thiophan salt as a result of subsequent reaction with VE II; this eliminates the usual complications caused by oligomerization of vinyl ethers.

The synthetic method developed by us contains the following important advantages: 1) the possibility of broad and independent variation of VE I and VE II (see data in [1-3]); 2)

the possibility of varying the C-nucleophile (allyl- or arylmagnesium derivatives, various allylboron derivatives); 3) the possibility of changing the stereochemistry by varying the reagents (see data for Mg and B derivatives) and the reaction conditions (see stereochemistry of products in reactions with $TiCl_4$ and $SnCl_4$). It should also be noted that the reactions described in this paper result in the formation of two new carbon–carbon bonds – an important synthetic result that is rarely achieved in electrophilic addition reactions.

EXPERIMENTAL

NMR spectra were recorded on a Bruker WM-250 instrument (250 MHz for ^1H and 62.5 MHz for ^{13}C); solvent, $CDCl_3$; internal standard, TMS; chemical shifts (δ) shown in ppm; SSICs given in Hz. Mass spectrometric studies were performed on a Varian MAT-CH-6 instrument.

All procedures were carried out in a dry argon atmosphere. p-Tolyl- and p-chlorophenylsulfenyl chlorides were synthesized by chlorination of the appropriate thiophenols with SO_2-Cl_2 in CCl_4 at −10°C. Methyl vinyl ether was obtained by reetherification of butyl vinyl ether in the presence of $Hg(OAc)_2$ [8]. The synthesis of 2-methyl-1-methoxypropene-1 was carried out by pyrolysis of isobutyric acid methyl acetal in the presence of $NH_4H_2PO_4$. Methoxyallene was obtained by isomerization of methyl propargyl ether in the presence of t-BuOK [9].

5,5-Dimethyl-4,6-dimethoxy-7-(p-tolylthio)heptene-1 (V). A 58-mg (1-mmole) solution of methyl vinyl ether in 2 ml CH_2Cl_2 was added dropwise to 159 mg (1 mmole) p-TolSCl in 15 ml CH_2Cl_2 (−78°C) until the reaction mixture was decolorized. Then 0.12 ml (1.1 mmoles) $TiCl_4$ and 95 mg (1.1 moles) 2-methyl-1-methoxypropene were added consecutively and, after 5 min, 4 mmoles of allylmagnesium chloride in ether. After 30 min, the reaction mixture was decanted into saturated $NaHCO_3$, extracted with ether, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed twice on SiO_2 (eluant, ether–hexane, 1:4). A 205-mg (67%) yield of compound (V) was isolated as a mixture of two diastereomers with a ratio of 2:3; R_f 0.81 (Silufol, ether–hexane, 1:1), n_D^{20} 1.5257, M^+ 308. IR spectrum: $\nu C{=}C$ 1640 cm^{-1} (film). PMR spectrum: 0.86 and 0.97 two s (6H, $C(CH_3)_2$), 2.18 m (2H, CH_2), 2.32 s (3H, CH_3), 2.9-3.4 m (4H, SCH_2, and two $CHOCH_3$ groups), 5.06 and 5.92 m (3H, $CH{=}CH_2$), 7.21 m (4H, H_{arom}). Found, %: C 70.08; H 9.04; S 10.36. $C_{18}H_{28}O_2S$. Calculated, %: C 70.08, H 9.15; S 10.37.

2-Methyl-4,6-dimethoxy-7-(p-tolylthio)heptene-1 (VII) was synthesized in a manner similar to (V) with a yield of 69%; R_f 0.60 (Silufol, ether–hexane, 1:1). PMR spectrum: 1.76 s (3H, CH_3), 1.82 t (2H, $CHCH_2CH$, J = 6), 2.13 m (2H, $CH_2C{=}$), 2.33 s (3H, CH_3), 3.08 AB part of ABX spectrum (2H, SCH_2, J_{AB} = 13, $J_{AX} = J_{BX} = 6$), 3.12 and 3.14 two s (6H, two OCH groups), 3.48 m (2H, two CHOCH groups), 4.73 and 4.81 two s (2H, $=CH_2$), 7.20 m (4H, H_{arom}). Contains about 30% of the second diastereomer: 1.67 t ($CHCH_2CH$), 3.15 and 3.18 two s (two OCH_3 groups). High-resolution mass spectrum: 294, 1673. $C_{17}H_{26}O_2S$. Calculated: 294, 4512.

2-Methyl-4-phenyl-2,4-dimethoxy-1-(p-tolylthio)pentane (XI) was obtained in a manner similar to (V) with a yield of 60%; R_f 0.50 (Silufol, ether–hexane, 1:2), M^+ 330. PMR spectrum: 1.42 and 1.28 two s (3H, CH_3), 1.93 AB part of ABX spectrum (2H, CH_2, J_{AB} = 15, J_{AX} = 2.5, J_{BX} = 2.75), 2.31 s (3H, CH_3), 3.15-3.25 six s (8H, two OCH_3 and SCH_2 groups), 4.32 X part of ABX spectrum (1H, CHPh), 7.2 m (9H, H_{arom}). Contains up to 30% of a second isomer according to CH_3 and OCH_3 group signals. Found, %: C 72.78; H 8.12. $C_{20}H_{26}O_2S$. Calculated, %: C 72.69; H 7.93.

2-(1',1',4'-Trimethyl-2'-methoxypenten-4'-yl)-3-(p-tolylthio)oxane (XV) was synthesized in a manner similar to (V) with yields of 62% ($TiCl_4$) and 68% ($SnCl_4$); R_f 0.74 (Silufol, ether–hexane, 1:2), M^+ 348. Found, %: C 72.55; H 9.25; S 9.30. $C_{21}H_{32}O_2S$. Calculated, %: C 72.37; H 9.25; S 9.20. NMR spectra of the threo-isomer: PMR spectrum: 1.11 and 1.16 two s (6H, $C(CH_3)_2$), 1.60 and 1.97 two m (4H, CH_2CH_2), 2.14 m (2H, $CH_2C{=}$), 2.34 s (3H, CH_3), 3.12 d (2H, SCHCHO, J = 8.6), 3.21 t.d (1H, SCH, J_T = 8.6, J_D = 4*), 3.33 t.d (1H, $CH_{ax}O$, J_T = 11, J_D = 5.25), 3.41 s (3H, OCH_3), 3.53 X part of ABX spectrum (1H, $CHOCH_3$, J_{AX} = 8.4, J_{BX} = 2.75) 3.93 m (1H, $CH_{eq}O$), 4.79 and 4.87 two s (2H, $=CH_2$), 7.21 m (4H, H_{arom}). ^{13}C NMR spectrum: 19.23, 19.58, 21.13, and 22.65 (four CH_3 groups), 24.91 and 30.77 (CH_2CH_2), 39.34 ($CH_2C{=}$), 43.63 ($C(CH_3)_2$), 46.72 (CHS), 60.93 (OCH_3), 67.24 (OCH_2), 84.23 and 85.35 (two OCH

*J values are taken from the spectrum in C_6D_6.

groups), 112.32 (=CH_2), 129.74, 130.68, 133.23, 137.34, and 144.56 (C_{arom} and =$\underline{C}CH_3$). NMR spectra of erythro-isomer: PMR spectrum: 0.94 and 1.10 two s (6H, $C(CH_3)_2$), 1.55-2.0 m (4H, CH_2CH_2), 1.85 s (3H, CH_3), 2.18 d (2H, $\underline{CH_2}C$=, J = 6.2), 2.34 s (3H, CH_3(Tol)), 3.25 m (1H, SCH), 3.33 d (1H, OC$\underline{H}$CHS, J = 7.6), 3.45 m (1H, $CH_{ax}O$), 3.41 s (3H, OCH_3), 3.65 X part of ABX spectrum (1H, $\underline{CH}OCH_3$, J_{AX} = 5, J_{BX} = 7.2), 3.95 m (1H, $CH_{eq}O$), 4.81 and 4.88 two s (2H, =CH_2), 7.22 m (4H, H_{arom}). ^{13}C NMR spectrum: 18.68, 18.75, 21.15, 22.99 (four CH_3 groups), 23.08 and 28.59 (CH_2CH_2), 39.60 ($\underline{CH_2}C$=), 43.58 ($C(CH_3)_2$), 46.32 (CHS), 60.30 (OCH_3), 66.14 (OCH_2), 83.23 and 83.38 (OCH, $CH_3O\underline{C}H$), 112.65 (=CH_2), 129.79, 131.25, 133.06, 137.30, and 144.51 (C_{arom} and =$\underline{C}CH_3$).

5,5-Dimethyl-4-hydroxy-6-methoxy-7-(p-chlorophenylthio)heptene-1 (XVII). A 58-mg (1-mmole solution of methyl vinyl ether in 2 ml CH_2Cl_2 was added dropwise to 179 mg (1 mmole) p-ClC_6H_4SCl in 15 ml CH_2Cl_2 (−78°C). Then 0.12 ml (1.1 mmoles) $TiCl_4$ and 95 mg (1.1 mmoles) 2-methyl-1-methoxypropene-1 were added consecutively and, after 5 min, 0.29 ml (1.5 mmoles) triallylborane. The reaction mixture was decanted into aqueous $NaHCO_3$, extracted with ether, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on an SiO_2 (eluant, ether–hexane, 1:2). A 190-mg (61%) yield of compound (XVII) was isolated; R_f 0.57 (Silufol, ether–hexane, 1:1), n_D^{20} 1.5455, M^+ 314.316. IR spectrum: νOH 3480, νC=C 1640 cm^{-1} (film). PMR spectrum: 0.85 and 0.97 two s (6H, $C(CH_3)_2$), 1.95-2.45 m (3H, CH_2, OH), 2.9-3.7 m (6H, SCH_2, two CH groups), 3.48 and 3.53 two s (5:4 ratio, 3H, OCH_3), 5.12 and 5.87 m (3H, $CH=CH_2$), 7.27 m (4H, H_{arom}). Found, %: C 61.51; H 7.43. $C_{16}H_{23}O_2SCl$. Calculated, %: C 63.03; H 7.36.

2-(1',1'-Dimethyl-3'-hydroxypenten-4'-yl)-3-(p-tolylthio)oxane (XIX) was obtained in a manner similar to (XVII) with a yield of 66%. PMR data show that (XIX) is a mixture of two diastereomers with a ratio of 5:2; R_f 0.46 (Silufol, ether–hexane, 1:1), n_D^{20} 1.5470, M^+ 320. IR spectrum (film): νOH 3480, νC=C 1640 cm^{-1}. PMR spectrum: 1.01 and 1.07 two s, 1.10 and 1.16 two s (6H, $C(CH_3)_2$), 2.5-2.3 m (6H, CH_2, CH_2–CH_2), 2.28 s (3H, CH_3), 3.1-3.5 m (4H, $\underline{CH}OH$, SCH, HCO), 3.74 d.d (1H, HCO, J_1 = 10, J_2 = 2.5), 3.90 m (1H, HCO), 5.07 and 5.90 two m (3H, $CH=CH_2$), 7.18 m (4H, H_{arom}).

7-Methyl-5-methylene-4-hydroxy-6-methoxy-7-(p-tolylthio)octene-1 (XXIII) was synthesized in a manner similar to (XVII) with a yield of 63%; R_f 0.44 (Silufol, ether–hexane, 1:1), n_D^{20} 1.5470, M^+ 306. IR spectrum (film): νOH 3440, νC=C 1640 cm^{-1}. Found, %: C 70.53; H 8.47; S 10.44. $C_{18}H_{26}O_2S$. Calculated, %: C 70.55; H 8.55; S 10.46. The data presented above are for a mixture of diastereomers with the ratio 1:1 (PMR data). This mixture was separated into individual isomers by means of TLC on Silpearl. The PMR spectrum of the isomer with the higher R_f value is as follows: 1.18 and 1.27 two s (6H, $C(CH_3)_2$), 2.32 m (2H, CH_2), 2.37 s (3H, CH_3), 3.30 s (3H, OCH_3), 3.53 s (1H, CH), 4.21 two d (1H, CH, $J_1 = J_2$ = 2.5), 5.17 and 5.88 two m (3H, $CH=CH_2$), 5.28 and 5.56 two s (2H, =CH_2), 7.27 m (4H, H_{arom}). PMR spectrum of the isomer with the lower R_f value: 1.23 and 1.26 two s (6H, $C(CH_3)_2$), 2.37 s (3H, CH_3), 2.40 m (2H, CH_2), 3.30 s (3H, OCH_3), 3.70 s (1H, CH), 4.34 m (1H, CH), 5.24 and 5.52 two s (2H, =CH_2), 5.15 and 5.9 two m (3H, $CH=CH_2$), 7.28 m (4H, H_{arom}).

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