instrument facility essential to this project. The principal investigator thanks the Alexander von Humboldt Foundation for a U.S. Senior Scientist Award during whose tenure this paper was drafted at Universität Freiburg, FRG, a very gracious host institution.

Registry No. 1, 106711-49-3; $PhCO_2Pr$-i, 939-48-0; PhCN, 100-47-0; ClPh, 108-90-7; o-$BrC_6H_4CO_2Pr$-*i*, 59247-52-8; 2,6-$Br_2C_6H_3CO_2Pr$-*i*, 113586-25-7; 2,6-$Br_2C_6H_3CN$, 6575-12-8; 2-bromo-*N*,*N*-diethylbenzamide, 76041-86-6; *N*,*N*-diethylbenzamide, 1696-17-9; 2,6-dibromo-*N*,*N*-diethylbenzamide, 85370-72-5; 2,6-diiodo-*N*,*N*-diethylbenzamide, 97567-50-5; 2,6-dimethyl-*N*,*N*-diethylbenzamide, 57806-77-6; 2-methyl-*N*,*N*-diethylbenzamide, 2728-04-3; 2,6-dibromochlorobenzene, 19230-27-4.

Synthesis of a Model Hapten with Cyclohexanediol and α-Methylene-γ-butyrolactone Groups, a Synthetic Analogue of Poison Ivy and Tulipalin Allergens Connected with a Carbon Chain

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Potential skin sensitizers 1 and 1* with two different haptenic ends, (a) a cyclohexanediol group (saturated poison ivy analogue) and (b) an α-methylene-γ-butyrolactone moiety (tulipalin A), separated by a nine carbon atoms chain containing a double bond have been prepared. The trans,trans relationship in the substituted cyclohexanediol was secured by a tandem Michael addition–hydroboration reaction. Contrary to an earlier example of a double-headed hapten containing pyrocatechol and α-methylene-γ-butyrolactone ends, the cyclohexanediol–α-methylene-γ-butyrolactone does not show any tolerance induction to the α-methylene-γ-butyrolactone end. It therefore seems that induction of tolerance as well as sensitization requires the formation of covalent bond with a protein carrier.

Structure–activity relationship studies in allergic contact dermatitis (ACD) have shown that the induction of sensitization is controlled by the binding of the sensitizer (or hapten, i.e., an allergy-producing compound) with "immunocompetent structures" such as cells (in particular white cells or T-cells) or protein carriers.[1,2] Most of the skin haptens (i.e., incomplete allergen) are electrophilic[2] or "proelectrophilic"; i.e., they can be transformed in vivo into true electrophiles[2] and therefore show the capacity to form covalent bonds with epidermal proteins. However apparently nonelectrophilic skin sensitizers do exist[3,4] and are capable of forming strong hydrophobic bonds in particular with cell membranes. This is the case in particular of urushiols, a mixture of penta- and heptadecylcatechols containing 0, 1, 2, or 3 double bonds and present in the famous poison ivy (*Rhus radicans L.*) and poison oak (*Rhus diversiloba L.*). It is believed that these compounds insert into cell membranes through their hydrocarbon chains.[3]

Structural modifications to transform an allergen into a tolerogen (tolerance-producing substance) have attacted much interest.[5] By linking two well-known haptens, i.e., a catechol (poison ivy like) and a methylene lactone (present in particular in sesquiterpene lactones from Compositae) by a straight hydrocarbon chain, we recently observed a "tolerance" (immunological nonresponse to an allergen) directed toward the methylene lactone moiety.[6] In order words, animals treated with this "double-headed" hapten prior to sensitization could not be sensitized (i.e., made allergic) to a hapten only containing the methylene lactone moiety. Treatment with this "double-headed" hapten protected these animals against one end, the γ-lactone moiety. We interpreted this as resulting from the "burial" of the methylene lactone end inside the membrane, while the hydrophilic part of the molecule (catechol) was projected outwards. Thus only the emerging part of the molecule could be recognized by the T-cell receptors[7] leading to sensitization to the catechol part alone.

The question raised by this interpretation was as follows: was the observed tolerance to the lactone moiety a result of its "burial" into a cell membrane and/or was a preliminary recognition of the catechol moiety a necessary step? As the pyrocatechol is capable of transformation into an electrophile, an *o*-quinone, through oxidation, it is quite possible that nucleophilic proteins, for instance transmembrane proteins, could covalently bind to the hapten, transforming it into a complete antigen. The question therefore was as follows: what would happen if the catechol, a proelectrophilic moiety, is replaced by a hydrophilic group showing no or little electrophilic or proelectrophilic properties?

The aim of this work was to answer this question. We describe in this paper the syntheses and some biological results of the two new bihaptens 1 and 1* containing cyclohexanediol and methylene lactone ends. The cyclo-

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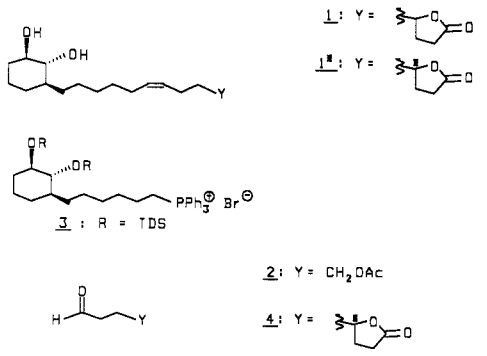
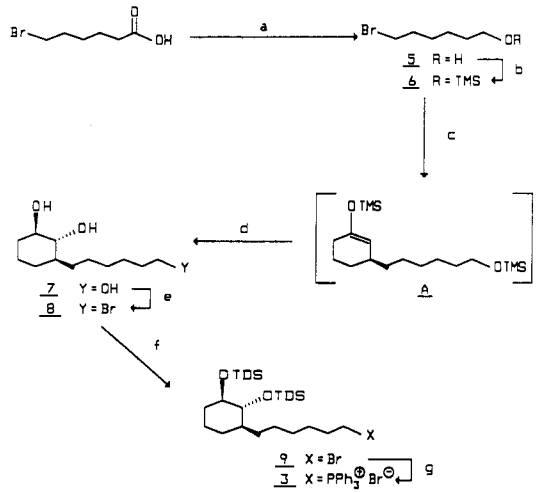


Figure 1.

Scheme I[a]



[a] (a) $BH_3 \cdot Me_2S$, 99% yield; (b) TMSCl, HMDSA, Et_3N, 95% yield; (c) Mg, CuI, then cyclohexenone, TMSCl; (d) $BH_3 \cdot Me_2S$, then H_2O_2, NaOH, 63% yield from cyclohexenone; (e) CBr_4, PPh_3, 84% yield; (f) TDSOTf, lutidine, 95% yield; (g) PPh_3, 85% yield.

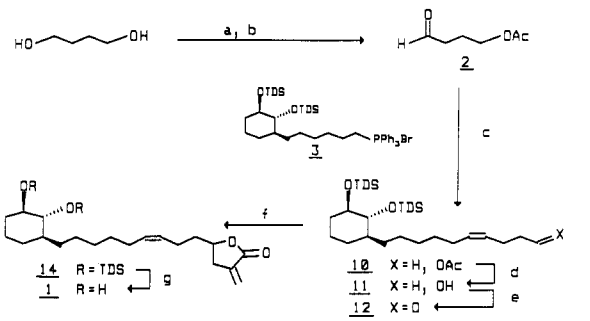
hexanediol was chosen as a nonelectrophilic analogue of the catechol; a double bond was introduced into the link in order to favor the insertion of the hydrophobic part, the methylene lactone moiety, into cell membranes. We[8] and others[9] have shown that allergic contact dermatitis (ACD) is enantiospecific. Bearing this in mind, we also prepared diastereomeric bihapten 1* possessing an enantiomerically pure α-methylene-γ-butyrolactone moiety, in order to determine whether induction of tolerance was also an enantiospecific phenomenon.

Syntheses

The target molecule chosen was compound 1 (Figure 1). An appropriate intermediate for its synthesis seemed to be aldehyde 2, which could be reacted with phosphonium salt 3. Alternately in case this synthetic scheme did not succeed, we envisaged another pathway involving the reaction of aldehyde 4 with compound 3. In this second approach, aldehyde 4 precursors available from glutamic acid, were optically pure. In this plan the target would be 1*.

Synthesis of Phosphonium Salt 3 (Scheme I). Reduction of 6-bromohexanoic acid with borane–dimethyl sulfide ($BH_3 \cdot Me_2S$, 99% yield) followed by silylation of the alcohol 5 with trimethylsilyl chloride and bis(trimethylsilyl)amine ($HN(TMS)_2$, 95% yield) led to bromide 6. Copper-catalyzed Michael addition of this bromide to cyclohexenone was effected by successively adding magnesium and a catalytic amount of CuI and cyclohexenone and subsequent trapping of the enolate with trimethylsilyl chloride, leading to the intermediate tris(trimethylsilyl) ether A. The crude intermediate was hydroborated with borane–dimethyl sulfide, followed by hydrogen peroxide and sodium hydroxide, affording the triol 7 in 63% overall yield from cyclohexenone.[10] The relative configuration was deduced from the coupling constants observed between the three contiguous axial protons. The triol was then selectively brominated with CBr_4 and PPh_3 (84% yield) and the resulting bromide 8 treated successively with thexyldimethylsilyl trifluoromethanesulfonate (TDSOTf) and 2,6-lutidine to yield the bis(silyl) ether 9 (95% yield); PPh_3 afforded then the phosphonium salt 3 (85% yield) needed for the Wittig reaction.

Scheme II[a]



[a] (a) AcCl, pyridine, 74% yield; (b) CrO_3, pyridine; (c) 3, $NaN(TMS)_2$, then 2, 75% yield; (d) K_2CO_3, MeOH, 99% yield; (e) Swern reagent; (f) $CrCl_2$, $CH_2{=}C(COOC_2H_5)CH_2Br$ (13), 83% yield; (g) HCl concentrated 2% in THF, 82% yield.

Synthesis of Bihapten 1 (Scheme II). Aldehyde 2, was prepared by reacting 1,4-butanediol with acetyl chloride (74% yield with respect to AcCl) followed by oxidation of the alcohol with chromium oxide–pyridine complex in dichloromethane. Reaction of this aldehyde with phosphonium salt 3 under reflux with butene oxide[11] afforded alkene 10 in 72% yield. The reaction worked well only on less than 200 mg of 3. Alternatively, phosphonium salt 3 was deprotonated using $NaN(TMS)_2$ in THF[12] and condensed with aldehyde 2 to yield alkene 10 (75% yield). Both experiments afforded exclusively 10 with a cis double bond. No trans double bond could be detected by 200- or 400-MHz ^1H NMR spectroscopy. Treatment of 10 with K_2CO_3 in MeOH afforded alcohol 11 (99% yield), which was oxidized by the Swern reagent [$(COCl)_2$, DMSO, Et_3N][13] to give aldehyde 12. The pseudo-Reformatsky reaction of this aldehyde with ethyl 2-(bromomethyl)-acrylate (13)[6] under previously reported conditions[14] led to partial deprotection of the silyl ethers and destruction of the material. We thus used crude material 12 and condensed it with the organochromium reagent obtained from ethyl 2-(bromomethyl)acrylate (13) and $CrCl_2$ to yield lactone 14 in 83% yield.[15] Lactone 14 was then deprotected with 2% concentrated HCl in THF to afford bi-

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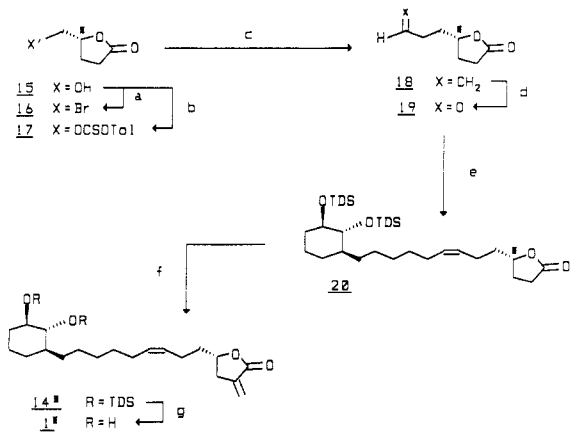
Table I. Results of Open Epicutaneous Tests at Equimolar Doses

sensitizer[a]	tested to[b]	reactn intensity[c] 3	2	1	0.5	0	avg reactn intensity[d]	no. of positive animals
bihapten 1	bihapten 1	0	3	3	1	1	1.2	7/8
	diol 21	0	0	0	0	8	0	0/8
	lactone 22	0	0	3	5	0	0.7	8/8
diol 21	bihapten 1	0	0	0	0	8	0	0/8
	diol 21	0	0	2	2	4	0.4	4/8
lactone 22	bihapten 1	0	0	0	1	7	0.1	1/8
	lactone 22	0	0	4	3	1	0.7	7/8

[a] Sensitized by the FCAT method, using three injections (each other day) of a 1:1 FCA/saline emulsion of the hapten (2% w/v). [b] Open epicutaneous test using a 4:1 acetone/olive oil solution of the hapten at equimolar concentrations: 0.049 M. [c] The scale used is the following: 0 = no reaction; 0.5 = slight erythema not covering the whole test area; 1 = definite erythema covering the whole test area; 2 = erythema plus swelling of the test area; 3 = erythema plus swelling going well beyond the test area. The figures represent the number of animals responding with a 0, 0.5, 1, 2, or 3 skin intensity test. [d] The average skin intensity is obtained by adding all the test scores and dividing by the number of animals tested.

Scheme III[a]



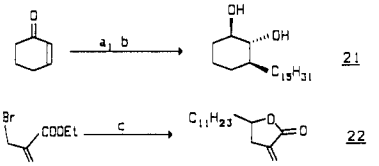
[a] CBr_4, PPh_3, 84% yield; (b) ClCSOTol, Et_3N, 87% yield; (c) allyltributyltin, AIBN, 70% yield; (d) O_3, $MeOH/CH_2Cl_2$, then Me_2S; (e) **3**, butene oxide, reflux, 57% yield; (f) (1) LiICA, $H_2C{=}NMe_2$, (2) MeI, (3) $NaHCO_3$, 70% yield; (g) HCl concentrated 2% in THF, 82% yield.

hapten 1 (82% yield). The reaction was sluggish. Several other reagents[16] gave either unidentified products or unreacted starting material.

Synthesis of Bihapten 1* (Scheme III). Alcohol **15**, available from glutamic acid,[17] was brominated with CBr_4 and PPh_3 (84% yield). The resulting bromide **16** was condensed with allyltributyl tin in the presence of azobisisobutyronitrile[18] to yield lactone **18** (70% yield). Ozonolysis of **18** at −78 °C (O_3, CH_2Cl_2/MeOH and then Me_2S) and the condensation of the resulting aldehyde **19** with phosphonium salt **3** in refluxing butene oxide gave alkene **20** in 57% yield. The exo-methylene group was classically introduced by the reaction of Eschenmoser's salt ($H_2C{=}NMe_2I$)[20] with the enolate (LiICA, THF) of lactone **20** and subsequent Hoffmann degradation [(1) MeI, MeOH; (2) $NaHCO_3$] to afford lactone **14*** in 70% yield. This material was transformed into **1*** by the route indicated above from **14**.

Synthesis of Cyclohexanediol 21 and Lactone 22 (Scheme IV). Cyclohexanediol **21** was obtained by a tandem Michael addition–hydroboration reaction from pentadecyl bromide and cyclohexenone,[4] and lactone **22**[21]

Scheme IV[a]



[a] (a) $C_{15}H_{31}MgBr$, CuI, then TMSCl; (b) $BH_3{\cdot}Me_2S$, then H_2O_2, NaOH, 65% yield from cyclohexenone; (c) $CrCl_2$, $C_{11}H_{23}CHO$, 85% yield.

was synthesized from dodecanal by condensation with the chromium reagent derived from ethyl 2-(bromomethyl)-acrylate in 85% yield.

Biological Results and Discussion

Guinea pigs provide an excellent model of skin sensitization in man. They have been sensitized by using the FCAT method.[21] Results are collected in Table I.

Clearly bihapten 1 as well as lactone **22** are haptens (=ACD-inducing agents or haptens). The reactions are not very strong. The most striking result is that bihapten 1 sensitized animals reacted to lactone **22**, thus "recognizing" the lactone end, but not to the cyclohexanediol moiety (no reaction to compound **21**). Therefore *bihapten 1 was incapable of inducing tolerance to its lactone part.* This result is opposite to the observed nonreaction and tolerance induction to the lactone part of a bihapten-containing pyrocatechol instead of cyclohexanediol.[6] It seems therefore that preliminary recognition with covalent binding of the hydrophilic part (catechol probably transformed in vivo into an *o*-quinone) is a prerequisite for tolerance induction to the other "end" of the bihapten.

Lack of tolerance induction to the α-methylene-γ-butyrolactone moiety did not encourage us to test diastereomeric bihapten 1*, since this compound was synthesized to assess enantiospecific aspects of tolerance.

Conclusion

The concept of bihaptens with a hydrophilic end (pyrocatechol) and a hydrophobic end (α-methylene-γ-butyrolactone) has led to interesting properties, in particular tolerance (=immunological nonreaction) to α′-methylene-γ-butyrolactone.[6] The replacement of catechol by a 1,2-cyclohexanediol group (a hydrophilic nonsensitizing or weakly sensitizing moiety) could not induce tolerance to the lactone end. More work to define structure–activity relationships in order to design bihaptenic

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molecules able to induce tolerance is in progress.

Experimental Section

General Methods. Proton NMR spectra of samples in $CDCl_3$ were recorded on a Perkin-Elmer 60-MHz and on a 200- or 400-MHz Brucker spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with respect to TMS as internal standard. Infrared spectra were obtained on a Beckman Acculab spectrometer using $CHCl_3$ solutions. Melting points were determined on a Buchi Tottoli 510 apparatus and are uncorrected.

Dry solvents were freshly distilled before use. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone. Dichloromethane and acetonitrile were distilled from P_2O_5. Toluene was distilled over LAH. HMPT was distilled over 4A molecular sieves. All air- or moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of dry argon. The chromatographic purifications were conducted according to the flash chromatography technique on silica gel columns.

6-Bromohexan-1-ol (5). To a solution of borane–dimethyl sulfide in THF (300 mL; 600 mmol), was added at 0 °C a solution of 6-bromohexanoic acid (100 g; 512 mmol) in THF (150 mL). After being stirred over one night, the mixture was quenched with EtOH and then water (200 mL) added. After extraction with CH_2Cl_2 (3 × 100 mL), drying with magnesium sulfate, and evaporation of the solvent, the remaining oil was distilled to yield 89.8 g (98%) of alcohol **5**: bp 64 °C (0.15 mmHg). IR: 3660–3640 cm^{-1}. ^1H NMR: δ 4.0–3.2 (4 H, m, CH_2O + CH_2Br); 3.0 (1 H, s, O*H*); 2.0–1.2 (8 H, m, CH_2).

1-Bromo-6-[(trimethylsilyl)oxy]hexane (6). To a solution of alcohol **5** (39 g; 217 mmol) in THF (200 mL) were added bis(trimethylsilyl)amine ($HN(TMS)_2$) (35 g; 217 mmol), trimethylsilyl chloride (TMSCl) (26.2 mL; 217 mmol), and and Et_3N (30.3 mL; 217 mmol) at room temperature. The liquid mixture was stirred overnight and concentrated. the residue was extracted with hexane (3 × 100 mL) and the organic layer dried with magnesium sulfate and evaporated to yield the crude silyl ether, which was purified by distillation [57 °C (5.5 mmHg)] (54.95 g; yield: 95%). IR: 1250 cm^{-1}. ^1H NMR: δ 4.0–3.2 (4 H, m, CH_2O + CH_2Br); 2.0–1.2 (8 H, m, CH_2); 0.15 (9 H, s, $SiMe_3$).

3-[6′-(Trimethylsilyloxy)hexyl]-1-[(trimethylsilyl)oxy]-cyclohexene (A). To a suspension of Mg (972 mg; 40 mmol) in THF (40 mL) under sonication was added bromide **6** (10.12 g; 40 mmol). After 4 h at room temperature CuI (760 mg; 4.0 mmol) was added, and the mixture was stirred and cooled to −40 °C. After 5 min, cyclohexenone (2.4 mL; 25 mmol) was added dropwise. The mixture was stirred at −40 °C for 2 h and cooled to −60 °C. The enolate was then trapped by adding hexamethylphosphorotriamide (HMPA) (4.3 mL; 25 mmole, Et_3N (6.9 mL; 50 mmol), and trimethylsilyl chloride (3.5 mL; 25 mmol). After 1 h at −60 °C followed by 1 h at room temperature the enol ether was extracted with hexane (3 × 100 mL), dried over K_2CO_3, and used without purification for the next step (7.7 g; yield: 90%). IR: 1660–1245 cm^{-1}. ^1H NMR (200 MHz): δ 4.80 (1 H, m, C=C*H*); 3.56 (2 H, t, J = 6.6 Hz, CH_2O); 2.00 (2 H, m, CH_2C=C); 1.52–1.57 (4 H, m); 1.29 (10 H, m); 1.09 (1 H, m); 0.17 (9 H, s, $SiMe_3$); 0.11 (9 H, s, $SiMe_3$).

***trans,trans*-3-(6-Hydroxyhexyl)-1,2-cyclohexanediol (7).** To the enol ether A (7.7 g; 22.5 mmol) was added BH_3·Me_2S (67 mL; 67 mmol; 1 M THF) at room temperature. The mixture was stirred for 3 days. Ethanol was added to destroy excess borane, and then NaOH (10 mL; 3 N) and H_2O_2 (10 mL; 30%) were added. The resulting mixture was stirred for 1 h, extracted with ether, washed with water, dried with magnesium sulfate, and evaporated. The crude oil was chromatographed on a silica gel column (AcOEt) to afford **7**, which crystallized spontaneously (3.4 g; yield: 63% from cyclohexenone). Mp: 64 °C. IR: 3640, 3620–3420 cm^{-1}. ^1H NMR (200 MHz) (+MeOD): δ 3.65 (2 H, t, J = 6.4 Hz, CH_2O); 3.38 (1 H, ddd, $J_{1,2}$ = 9.2 Hz, $J_{1,6}$ = 10.4 Hz $J_{1,6'}$ = 4.6 Hz, CHO); 3.02 (1 H, dd $J_{1,2}$ = $J_{2,3}$ = 9.2 Hz 2, C*H*O); 1.97 (2 H, m); 1.76 (2 H, m); 1.57 (2 H, m); 1.34 (10 H, m); 0.95 (1 H, m). Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.75; H, 11.33.

***trans,trans*-3-(6′-Bromohexyl)-1,2-cyclohexanediol (8).** To a suspension of triol **7** (1.08 g; 5.0 mmol) in CH_3CN (20 mL) were added CBr_4 (2.15 g; 6.5 mmol) and, portionwise at 0 °C, PPh_3 (1.70 g; 6.5 mmol). After 1 h the solvent was evaporated, ether was added, and the suspension was filtered. The filtrates were evaporated, and the crude oily bromide was purified by chromatography on silica gel column (5:5 AcOEt/hexane) (1.06 g; oil; yield: 84%). IR: 3620–3420 cm^{-1}. ^1H NMR (200 MHz) (+MeOD): δ 3.40 (2 H, t, J = 5.3 Hz, CH_2Br); 3.37 (1 H, ddd, $J_{1,2}$ = 9.2 Hz, $J_{1,6}$ = 10.4 Hz, $J_{1,6'}$ = 4.6 Hz, CH_2CHO); 2.98 (1 H, dd $J_{1,2}$ = $J_{2,3}$ = 9.2 Hz, C*H*OCH); 1.6–2.05 (6 H, m); 1–1.5 (10 H, m); 0.92 (1 H, m). Anal. Calcd for $C_{12}H_{23}O_2Br$: C, 51.62; H, 8.30. Found: C, 51.82; H, 8.41.

***trans,trans*-3-(6′-Bromohexyl)-1,2-bis[(dimethylthexylsilyl)oxy]cyclohexane (9).** To a solution of diol **8** (0.64 g; 2.3 mmol) and lutidine (1.1 mL; 9.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C thexyldimethylsilyl trifluoromethanesulfonate ($TfOSiMe_2Thx$) (1.66 g; 6.2 mmol; Thx = thexyl = 2,3-dimethyl-2-butyl, see: Wetter, H.; Oertle, K. *Tetrahedron Lett.* **1985**, 5515–5518). The mixture was stirred overnight at room temperature, quenched with 1 M $CuSO_4$ (10 mL), and extracted with ether (2 × 15 mL). The organic layer was dried and evaporated and the residue chromatographed (hexane) to yield the bis(silyl) ether **9** as an oil (yield: 95%). ^1H NMR (200 MHz): δ 3.62 (1 H, m, C*H*O); 3.47 (1 H, m, C*H*O); 3.41 (2 H, t J = 6.9 Hz, CH_2Br); 1.9–1.1 (19 H, m, CH_2 + C*H*); 0.90 (6 H, d, J = 6.9 Hz, Me_2CH); 0.89 (3 H, d, J = 6.9 Hz, *Me*CH); 0.88 (3 H, d, J = 6.9 Hz, *Me*CH); 0.84 (12 H, s, 2 Me_2CSi); 0.08 (6 H, s, Me_2Si); 0.07 (3 H, s, *Me*Si); 0.06 (3 H, s, *Me*Si). Anal. Calcd for $C_{28}H_{59}O_2Si_2Br$: C, 59.64; H, 10.55. Found: C, 59.83; H, 10.75.

[6′-(*trans,trans*-1″,2″-Bis((dimethylhexylsilyl)oxy)-3″-cyclohexyl)hexyl]triphenylphosphonium Bromide (3). A solution of bromide **9** (1.30 g; 2.3 mmol) and PPh_3 (0.59 g; 2.3 mmol) in CH_3CN (3 mL) was refluxed for 72 h. The mixture was cooled, the solvent was evaporated, and the crude phosphonium salt was chromatographed (7:10:3 AcOEt/CH_2Cl_2/EtOH) to yield pure phosphonium salt **3** as an amorphous solid (1.48 g; yield: 79% from bromo diol **8**). ^1H NMR (200 MHz): δ 7.92–7.65 (15 H, m, *Ph*); 3.84 (2 H, m, CH_2PPh_3); 3.58 (1 H, m, C*H*OSi); 3.40 (1 H, m, C*H*OSi); 1.64–1.17 (19 H, m, CH_2 + C*H*); 0.89 + 0.86 + 0.82 + 0.79 (24 H, 4 s, 8 *Me*); 0.55 (12 H, m, 2 $SiMe_2$).

4-Acetoxybutanal (2). Acetyl chloride (10.47 g; 133.4 mmol) was added dropwise at 0 °C under argon to a solution of butanediol (20.01 g; 222.3 mmol) and pyridine (10.54 g; 133.4 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred overnight and then evaporated and chromatographed (8:2 (Et_2O/hexane) to give the monoacetate of butanediol (21.72 g; 74% yield/AcCl).

A solution of the monoacetate (3.66 g; 27.7 mmol) in CH_2Cl_2 (15 mL) was rapidly added to a suspension of CrO_3 (16.67 g; 166.2 mmol) in CH_2Cl_2 (400 mL) containing pyridine (26.60 g; 322.4 mmol) at 25 °C. After being stirred for 15 min, the reaction mixture was filtered through silica gel (30 g), and the product was eluted with AcOEt (200 mL). The solvent was evaporated, and the crude liquid aldehyde was used without further purification. IR: 3600–3200, 1715 cm^{-1}. ^1H NMR: δ 9.80 (1 H, br s, C*H*O); 4.11 (2 H, t, J = 6 Hz, CH_2O); 2.50 (2 H, dt J_t = 6.6 Hz, J_d = 5 Hz, CH_2CHO); 2.06 (3 H, s, CH_3COO); 2.2–1.8 (2 H, m).

***trans,trans*-3-(10′-Acetoxy-6′-decenyl)-1,2-bis[(dimethylthexylsilyl)oxy]cyclohexane (10). Method A.** A solution of phosphonium salt **3** (0.20 g; 0.2 mmol) and aldehyde **2** (0.04 g; 0.3 mmol) in butene oxide (2 mL) was refluxed overnight.[11] The mixture was cooled and evaporated and the residue was chromatographed (2:98 AcOEt/hexane) to yield alkene **10** as an oil (0.10 g; yield: 72%).

Method B. A solution of $NaN(TMS)_2$ in THF (0.72 mL; 1 M) was added dropwise at 0 °C to a solution of phosphonium **3** (0.60 g; 0.7 mmol) in THF (1 mL). The mixture was refluxed for 90 min, cooled to −78 °C, and a solution of aldehyde **2** (0.03 g; 0.2 mmol) in THF (1 mL) was added. The mixture was stirred at −78 °C for 30 min and then at room temperature for 14 h. The reaction was quenched with HCl (1 mL; 0.5 M) and extracted with ether (3 × 5 mL). The organic layer was dried, evaporated and the residue chromatographed to give alkene **10** as an oil (0.31 g; yield: 75%). IR: 1740 cm^{-1}. ^1H NMR (200 MHz): δ 5.45–5.32 (2 H, m, C*H*=C*H*); 4.07 (2 H, t, J = 6.7 Hz, CH_2OAc); 3.62 (1 H m, C*H*O); 3.47 (1 H, m, C*H*O); 2.17–1.97 (4 H, m, 2 CH_2C=C); 2.06 (3 H, s, CH_3COO); 1.80–1.26 (21 H, m, CH_2 + C*H*); 0.90 (6 H, d, J = 6.9 Hz, Me_2CH); 0.89 (3 H, d, J = 6.9 Hz, *Me*CH); 0.88 (3 H, d J = 6.9 Hz, *Me*CH); 0.84 (12 H, s, 2 Me_2CSi); 0.08 (6 H, s, Me_2Si); 0.07 (3 H, s, *Me*Si); 0.06 (3 H, s, *Me*Si); [after decoupling

of the allylic protons] CH=CH cis AB δ 5.37, 5.35 (J = 10 Hz); no trans double bond could be detected. Anal. Calcd for $C_{34}H_{68}O_4Si_2$: C, 68.39; H, 11.48. Found: C, 68.37; H, 11.52.

***trans,trans*-3-(10′-Hydroxy-6′-decenyl)-1,2-bis[(dimethylthexylsilyl)oxy]cyclohexane (11).** A mixture of acetate **10** (0.32 g; 0.50 mmol) and K_2CO_3 (37.5 mg; 0.30 mmol) in MeOH (2 mL) was stirred for 90 min at room temperature. The suspension was filtered over silica gel (2 g), the filtrate was evaporated, and the residue was chromatographed (1:9 AcOEt/hexane) to afford alcohol **11** as an oil (0.29 g; yield: 99%). IR: 3620, 3600–3200 cm^{-1}. ^{1}H NMR (200 MHz): δ 5.44–5.36 (2 H, m, C*H*=C*H*); 3.67 (3 H, t, J = 6.5 Hz, CH_2O); 3.64 (1 H, m, C*H*OSi); 3.48 (1 H, m, C*H*OSi); 2.19–2.02 (4 H, m, 2 CH_2C=C); 1.72–1.29 (21 H, m, CH_2 + C*H*); 0.90 (6 H, d, J = 6.9, Me_2CH); 0.89 (3 H, d, J = 6.9 Hz, *Me*CH); 0.88 (3 H, d, J = 6.9 Hz, *Me*CH); 0.84 (12 H, s, 2 Me_2CSi); 0.08 (6 H, s, Me_2Si); 0.07 (3 H, s, *Me*Si); 0.06 (3 H, s, *Me*Si). Anal. Calcd $C_{32}H_{66}O_3Si_2$: C, 69.25; H, 11.99. Found: C, 69.07; H, 12.07.

***trans,trans*-3-(10′-Oxo-6′-decenyl)-1,2-bis[(dimethylthexylsilyl)oxy]cyclohexane (12).** DMSO (0.18 mL; 1.2 mmol) was added dropwise at −78 °C to a solution of $(COCl)_2$ (0.10 mL; 2.4 mmol) in CH_2Cl_2 (2 mL); after 3 min, a solution of alcohol **11** (0.33 g; 0.60 mmol) in CH_2Cl_2 (1 mL) was added, and the mixture was stirred for 15 min at −50 °C. The solution was allowed to warm to room temperature, quenched with 0.5 N HCl (2 mL), and extracted with ether (3 × 4 mL). The organic layer was washed with brine, dried with magnesium sulfate, and evaporated. The remaining oil was used without purification for the next step.

***trans,trans*-5-[9′-(2″,3″-Bis((dimethylthexylsilyl)oxy)-cyclohexyl)-3′-nonenyl]-3-methylenetetrahydro-2-furanone (14).** LAH (0.04 g; 1.2 mmol) was added portionwise at 0 °C to a suspension of $CrCl_3$ (0.34 g; 2.4 mmol) in THF (3 mL). The suspension was stirred at room temperature for 15 min, then a solution of crude aldehyde **12** (0.33 g) in THF (2 mL) was added in one portion, and a solution of ethyl 2-(bromomethyl)acrylate (**13**) (0.21 g; 1.2 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at room temperature overnight and quenched with 0.5 N HCl (4 mL). The usual workup was followed by a chromatography (1:9 AcOEt/hexane) to yield lactone **14** as an oil (0.28 g; yield: 83% from alcohol). IR: 3000, 1750 cm^{-1}. ^{1}H NMR (200-MHz): δ 6.24 (1 H, t, J = 3.0, C=C*H*); 5.63 (1 H, t, J = 2.6 Hz, C=C*H*); 5.45–5.32 (2 H, m, C*H*=C*H*); 4.53 (1 H, m, C*H*O); 3.62 (1 H, m, C*H*OSi); 3.47 (1 H, m, C*H*OSi); 3.08 (1 H, ddt, J_{AB} = 17.1 Hz, J_{AX} = 7.7 Hz, J_{AZ} = 3.0 Hz, J_{AY} = 2.6 Hz, CH_AC=CH_2); 2.58 (1 H, ddt, J_{AB} = 17.1 Hz, J_{BX} = 6.1 Hz, J_{BZ} = 3.0 Hz J_{BY} = 2.6 Hz, CH_BC=CH_2); 2.22–2.15 (2 H, m, CH_2C=C); 2.05–2.02 (2 H, m, CH_2C=C); 1.87–1.28 (19 H, m, CH_2 + C*H*); 0.90 (6 H, d, J = 698 Hz, Me_2CH); 0.89 (3 H, d, J = 6.8 Hz, *Me*CH); 0.88 (3 H, d J = 6.8 Hz, *Me*CH); 0.84 (12 H, s, 2 Me_2CSi); 0.08 (6 H, s, Me_2Si); 0.07 (3 H, s, *Me*Si); 0.06 (3 H, s, *Me*Si). Anal. Calcd $C_{35}H_{68}O_4Si_2$: C, 69.62; H, 11.03. Found: C, 69.47; H, 11.09.

***trans,trans*-5-[9′-(2″,3″-Dihydroxycyclohexyl)-3′-nonenyl]-3-methylenetetrahydro-2-furanone (1).** Lactone **14** (0.23 g; 0.4 mmol) was stirred for 8 days at room temperature in a solution of THF (2.5 mL) containing 2% concentrated HCl (50 μL). The mixture was then neutralized with solid K_2CO_3 and filtered over silica gel (2 g). The solvent was evaporated and the residue chromatographed (8:2 AcOEt/hexane) to give diol **1** as a hygroscopic oil (0.11 g; 82%). IR: 3620, 3600–3200, 1750 cm^{-1}. ^{1}H NMR (400-MHz, COSY) ($CDCl_3$ + MeOD): δ 6.24 (1 H, t, J = 2.4 Hz, C=C*H* syn); 5.64 (1 H, t, J = 2.4 Hz, C=C*H* anti); 5.50–5.39 (1 H, m, $H_{4'}$); 5.39–5.29 (1 H, m, $H_{3'}$); 4.54 (1 H, m, H_5); 3.40 (1 H, m, $H_{3''}$); 3.08 (1 H, ddt J_t = 2.4 Hz, $J_{4,5}$ = 7.8 Hz, $J_{4,4a}$ = 17.2 Hz, H_3); 3.03 (1 H, dd, J = 10.4 Hz, J = 9.2 Hz, $H_{2''}$); 2.60 (1 H, ddt, J_t = 2.4 Hz, $J_{4a,5}$ = 6.2 Hz, $J_{4,4a}$ = 17.2 Hz, H_{4a}); 2.21 (2 H, dt, J_t = 8 Hz, J_d = 6.5 Hz, $H_{2'}$ + $H_{2'a}$); 2.1–1.9 (2 H, m, H_5 + H_{5a}) 1.8–0.8 (21 H, m, CH_2 + C*H*); [after decoupling $H_{5,5a}$ and then $H_{2,2a}$] CH=CH cis, AB part of ABX_2Y_2 A δ 5.44, B δ 5.33 (J_{AB} = 10.8 Hz, J_{AX} = 6.5 Hz, J_{BY} = 6.5 Hz). No trans double bond could be detected. Anal. Calcd $C_{20}H_{32}O_4\cdot H_2O$: C, 67.76; H, 9.67. Found: C, 67.68; H, 9.64.

(5*R*)-5-(Bromomethyl)tetrahydro-2-furanone (16). (5*R*)-5-(Hydroxymethyl)-tetrahydro-2-furanone (**15**) was obtained as described in ref 17. To a solution of (5*R*)-(hydroxymethyl)-tetrahydro-2-furanone (**15**) (2.11 g; 18.2 mmol) and CBr_4 (7.25 g; 21.8 mmol) in CH_3CN (40 mL) was added at 0 °C portionwise PPh_3 (5.73 g; 21.8 mmol). The mixture was stirred overnight at room temperature and evaporated. The residue was taken up in ether (100 mL) and filtered. The filtrates were evaporated, and the remaining oil was chromatographed (3:7 AcOEt/hexane) to give **16** as an oil (2.77 g; yield: 85%). IR: 1780 cm^{-1}. ^{1}H NMR: δ 5.0–4.5 (1 H, m, C*H*O); 3.54 (2 H, d, J = 6, CH_2Br); 2.9–1.9 (4 H, m, CH_2CH_2COO). $[\alpha]^{20}_D$ −2° (c 2.73, $CHCl_3$). Anal. Calcd for $C_5H_7O_2Br$: C, 33.55; H, 3.94. Found: C, 33.80; H, 4.17.

(5*S*)-5-(3′-Butenyl)tetrahydro-2-furanone (18). A mixture of bromide **16** (2.70 g; 15.1 mmol), allyltributyltin (4.7 mL; 15.1 mmol), and azobisisobutyronitrile (AIBN) (one crystal) in toluene (10 mL) was refluxed for 30 h. After cooling, the solvent was evaporated, and the residue was chromatographed (first hexane, 1.5 L, and then 3:7 AcOEt/hexane) to yield **18** as an oil (1.48 g; yield: 70%). IR: 1770, 1170 cm^{-1}. ^{1}H NMR: δ 6.1–5.4 (1 H, m, C=C*H*); 5.3–4.8 (2 H, m, C=CH_2); 4.47 (1 H, m, C*H*O); 2.7–1.1 (8 H, m, CH_2). $[\alpha]^{20}_D$ −56° (c 1.88, $CHCl_3$). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.57.

(5*S*)-5-(3-Oxopropyl)tetrahydro-2-furanone (19). A solution of **18** (0.30 g; 2.1 mmol) in MeOH (6 mL) and CH_2Cl_2 (4 mL) was ozonolyzed at −78 °C. On completion of the reaction (TLC), nitrogen was bubbled through the solution, Me_2S (1 mL) was added, and the mixture was stirred at −78 °C for 1 h and warmed to room temperature. The solvent was evaporated, leaving the crude unstable aldehyde **19** as a liquid, which was used without further purification. ^{1}H NMR: δ 9.55 (1 H, br s, C*H*O); 4.30 (1 H, m, C*H*O); 2.5–1.5 (8 H, m, CH_2).

***trans,trans*-(5*S*)-5-[9′-(2″,3″-Bis((dimethylthexylsilyl)-oxy)cyclohexyl)-3′-nonenyl]-2,3-dihydrofuranone (20).** A mixture of phosphonium salt **3** (0.20 g; 0.2 mmol) and aldehyde **19** (0.04 g; 0.3 mmol) in butene oxide (2 mL) was refluxed for 40 h. After cooling, the solvent was evaporated, and the residue was chromatographed (1:9 AcOEt/hexane) to afford alkene **20** as an inseparable oily mixture of two diastereoisomers (0.09 g; yield: 57%). IR: 3000, 1770, 1400 cm^{-1}. ^{1}H NMR (200 MHz): δ 5.47–5.31 (2 H, m, C*H*=C*H*); 4.50 (1 H, m, C*H*O); 3.63 (1 H, m, C*H*OSi); 3.48 (1 H, m, C*H*OSi); 2.58–1.26 (27 H, m, 2CH_2C=C + CH_2 + C*H*); 0.90 (6 H, d, J = 6.9 Hz, Me_2CH); 0.89 (3 H, d, J = 6.9 Hz, *Me*CH); 0.88 (3 H, d, J = 6.9 Hz, *Me*CH); 0.84 (12 H, s, 2 Me_2CSi); 0.08 (6 H, s, Me_2Si); 0.07 (3 H, s, *Me*Si); 0.06 (3 H, s, *Me*Si); [after decoupling of the allylic protons] CH=CH cis, AB δ 5.38, 5.34 (J = 10 Hz); no trans double bond could be detected. Anal. Calcd for **20**: C, 69.02; H, 11.25. Found: C, 68.77; H, 11.42.

trans,trans*-(5*S*)-5-[9′-(2″,3″-Bis((dimethylthexylsilyl)-oxy)cyclohexyl)-3′-nonenyl]-3-methylenetetrahydro-2-furanone (14*).** A solution of lactone **20** (0.11 g; 0.2 mmol) in THF (1 mL) was added at −78 °C to a solution of lithium cyclohexylisopropylamide (LiICA), prepared as usual from cyclohexylisopropylamine (0.04 mL; 0.2 mmmol) and butyllithium (0.14 mL; 1.6 M hexane) in THF (1 mL). The mixture was stirred at −78 °C for 1 h, and *N,N*-dimethylmethyleneammonium iodide (Eschenmoser's salt) was added in one portion (0.05 g; 0.3 mmol). The resulting solution was stirred overnight at room temperature. The solvent was evaporated and the residue chromatographed (AcOEt). The resulting amine was dissolved in MeOH (10 mL) and treated with MeI (2 mL). After 20 h at room temperature, the solvent was evaporated, and the remaining crystals were washed with ether and suspended in CH_2Cl_2 (5 mL) and aqueous $NaHCO_3$ 10% (2 mL). As soon as the crystals were dissolved, the mixture was extracted with ether (3 × 5 mL). The organic layer was dried with magnesium sulfate and evaporated, and the remaining oil was chromatographed (1:9 AcOEt/hexane) to afford lactone **14 as an inseparable mixture of two diastereoisomers (0.08 g; yield: 70%). This mixture was identical in all respects with **14**: identical TLC (one spot only for a mixture of **14** and **14***) and the IR and NMR spectra were superimposable.

trans,trans*-(5*S*)-5-[9′-(2″,3″-dihydroxycyclohexyl)-3′-nonenyl]-3-methylenetetrahydro-2-furanone (1*).** This compound was prepared as an unseparable mixture of two diastereomers in 81% yield from **14 by the procedure used to synthesize **1** from **14**. **1*** was identical in all respects with **1**: a TLC of the mixture only gave one spot, and the IR and NMR spectra were superimposable.

Biological Assays. Albino Himalayan spotted Füllingsdorf (from Hoffmann La Roche, Basel) female guinea pigs weighing from 300 to 500 g were sensitized as described by Klecak (21): on alternate days, the hapten, emulsified in a 1:1 dispersion of saline–Freund's complete adjuvant (FCA), was injected intradermally (0.1 mL) on the shaved nuchal region of the animal (in all three injections). After 15 days of rest, the elicitation was conducted by an open epicutaneous test (OET): 25 μL of ethanolic solution of hapten was deposited on the shaved flank of the animal (on a 2-cm^2 surface delimited by a standard circular stamp). Tests were read at 24 h by using the following scale: 0 = no reaction; 0.5 = slight erythema not covering the whole test area; 1 = erythema covering the whole test area; 2 = erythema plus swelling covering the whole test area. Before starting sensitization (allergy induction), irritation thresholds (primary toxicity) were determined on FCA-injected controls (same procedure as above but without hapten and same elicitation procedure). None of the concentrations used were toxic in control animals. In each experiment eight controls (FCA treated but without the hapten). Results are collected in Table I. Student's t test was used to assess the significance of the skin reaction intensities. All the results were statistically significant.

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New Type of 1,3-Molecular Rearrangement of Substituted-Vinyl Alkoxymethyl Ethers and Its Application to Synthesis of 1(or 3)-Substituted 4-Alkoxybutan-2-ones

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A new type of molecular rearrangment of substituted-vinyl alkoxymethyl ethers is disclosed. A 1,3-cationotropic rearrangement mechanism via relatively stable alkoxymethyl cations is postulated. The intermediacy of transient alkoxymethyl cation ion pairs is indicated by a crossover experiment. A series of 1(or 3)-substituted 4-alkoxybutan-2-ones were synthesized in good yields by aluminum chloride catalyzed rearrangement of the corresponding 2(or 1,2)-substituted 3,5-dioxahex-1-enes.

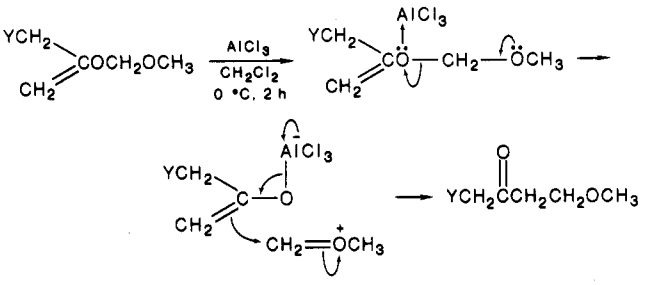
2-(Chloromethyl)-3,5-dioxahex-1-ene (**1a**) has been developed recently as an acetonylating reagent[1] which is very effective owing to the simplicity of its preparation and isolation, its stability on storage, and its high reactivity and versatility in allylation. During an investigation on the chemical reactivity of **1a** to extend its utility in organic synthesis, we found that **1a** and its derivatives undergo a new type of 1,3-migration of the methoxymethyl group in the presence of aluminum chloride to afford 1-chloro-4-methoxybutan-2-one and 1-substituted derivatives in good yields (Scheme I).

There is an extensive body of literature on molecular rearrangements such as the Claisen rearrangement which involves 3,3-sigmatropic rearrangement of vinyl allyl ethers,[2] the Fries rearrangement of phenolic esters, in which the acyl group migrates in a 1,3 manner,[3] 1,3-migration of an alkyl group by a free-radical path,[4] and so on.[5] In this paper, we disclose the results of studies on the mechanistic aspects of this new type of 1,3-molecular rearrangement of substituted-vinyl alkoxymethyl ethers and its utilization for the synthesis of a series of 1(or 3)-substituted 4-alkoxybutan-2-ones.

Results and Discussion

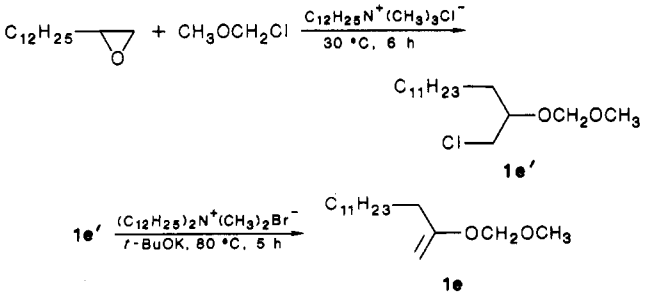
The 1,3-migration of an alkoxymethyl group in vinyl ethers **1** was first found when **1a** was treated with 1.0 equiv of aluminum chloride in dichloromethane at 0 °C for 2 h. In order to clarify the 1,3-migration mechanism, and to inspect the scope of migration reaction and the influence of the substituent, we examined several 2-substituted 3,5-dioxahex-1-enes (**1a,d–j**) and dioxaheptenes (**1b,c**). 2-Substituted 3,5-dioxahex-1-enes and dioxaheptenes

Scheme I[a]



[a] Y: Cl, RCOO, RO, RS, R_1R_2N, alkyl.

Scheme II



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