isotope effect). The third factor, the solvation of the nucleophile, would, however, affect mainly the reaction rate and not the transition-state structure because the desolvation would be expected to occur prior to the transition state. This desolvation energy would be expected to be much greater for the oxygen nucleophiles than for the sulfur nucleophiles since stronger hydrogen bonds to oxygen are well known, apparently due to oxygen's small size and greater electron density. Therefore, this "deshielding" of an unshared pair of electrons on the nucleophile might be expected to retard the reactivity of the oxides much more than that of the thiooxides. This conclusion is supported by the data of others[9,10] where the solvent was varied and may explain why the relative reaction rates of oxygen- and sulfur-containing nucleophiles do not parallel the isotope effect data. The polarizability of the nucleophile would lead to a conclusion which does not fit the observed kinetic isotope effects, and this suggests that polarizability may not be a dominant factor in these reactions. Because the oxides are more basic than the corresponding thiooxides, however, we would predict that the oxides would be more nucleophilic, once desolvation has occurred. This explanation does fit the observed isotope effects. Our initial results, therefore, suggest that the great speed of many displacement reactions involving large atom nucleophiles in protic solvents may not be due so much to their polarizability as to their ease of desolvation, and that the leaving group isotope effects provide a probe for distinguishing between the two. These results are also consistent with the operation of a concerted transition state as opposed to an intermediate ion-pair mechanism such as proposed by Sneen and Larsen[11,12] for other reactants and solvents.

If these initial conclusions are substantiated by further experiments and are not found to be unduly complicated by the intervention of specific solvation of substituents,[13] specific solvation of the leaving group, or mass effects upon changing the nucleophile, the kinetic isotope effects of leaving groups may result in one of our more powerful yet subtle probes for transition-state geometry. We propose to explore these possible complications further.

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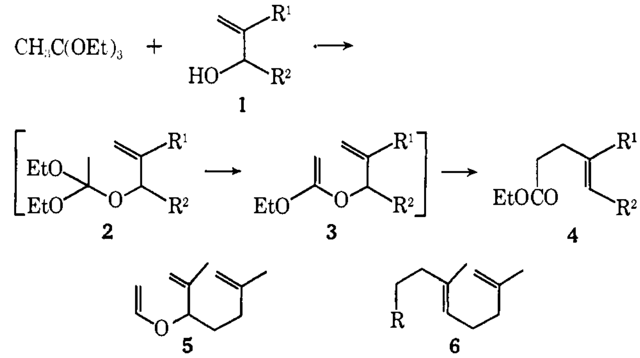
A Simple Stereoselective Version of the Claisen Rearrangement Leading to *trans*-Trisubstituted Olefinic Bonds. Synthesis of Squalene

Sir:

We wish to disclose a version of the Claisen rearrangement which is highly stereoselective and can be applied to the synthesis of *trans*-trisubstituted olefinic bonds. The method simply involves heating an allylic alcohol, **1**, with excess ethyl orthoacetate in the presence of a trace of weak (*e.g.*, propionic) acid. Evidently a mixed orthoester, **2**, is first formed and loses ethanol to form the ketene acetal **3** which rearranges to the olefinic ester **4**.[1]

As compared with the classical pyrolysis of simple vinyl ethers (**3** with H in place of EtO), this orthoester process is simpler to perform (one instead of two operations), and the overall yield as well as stereoselectivity is higher. The high stereoselectivity is probably attributable to nonbonded interactions between the ethoxy and R^2 groups (**3**) that develop only in the transition state leading to *cis* product.[2]



Thus the alcohol **1** (R^1 = Me, R^2 = $CH_2CH_2C(Me){=}CH_2$), on heating with 7 equiv of ethyl orthoacetate and 0.06 equiv of propionic acid at 138° for 1 hr under conditions for distillative removal of ethanol, was converted into the diene ester **4** (R^1 = Me; R^2 = $CH_2CH_2C(Me){=}CH_2$) in 92% yield (distilled[3] at <5 mm). Analysis by vpc indicated that this product consisted of >98% *trans* and <2% *cis* isomer. This result is to be compared with the vinyl ether approach: the alcohol **1** (R^1 = Me; R^2 = $CH_2CH_2C(Me){=}CH_2$) was converted by reaction with ethyl vinyl ether and mercuric acetate[4] into the vinyl ether **5** (60% yield after distillation[3] from sodium at 20 mm) which was heated at 83–98° for 61 hr, giving the aldehyde **6** (R = CHO) in 98% yield. Analysis by vpc indicated that this product contained 86% *trans* and 14% *cis* isomer. The essentially pure *trans* aldehyde **6** (R = CHO), on the other hand, can be obtained readily in 80% (distilled[3] at <0.5 mm) yield by reduction of the aforementioned diene ester with excess lithium aluminum hydride in ether at 0° (giving **6**, R = CH_2OH) followed by oxidation with 4 equiv of filtered Collins solution[5] in the presence of Drierite.

(1) We have found also that an analogous stereospecific reaction occurs on heating 1-dimethylamino-1,1-dimethoxyethane [A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, 47, 2425 (1964)] with an allylic alcohol giving the pure *trans* olefinic amide in practically quantitative yield, *e.g.*, 1 (R^1 = Me; R^2 = $CH_2CH_2C(Me){=}CH_2$) → 6 (R = $CONMe_2$). The amino acetal is a precursor of and is easier to prepare than 1-dimethylamino-1-methoxyethylene which has formerly been used for Claisen rearrangements [D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969)].
(2) *Cf.* C. L. Perrin and D. J. Faulkner, *Tetrahedron Letters*, 2783 (1969), and ref 3b,d,e, 4, and 5 cited therein.
(3) Evaporative bulb-to-bulb distillation using a Büchi kugelrohrofen.
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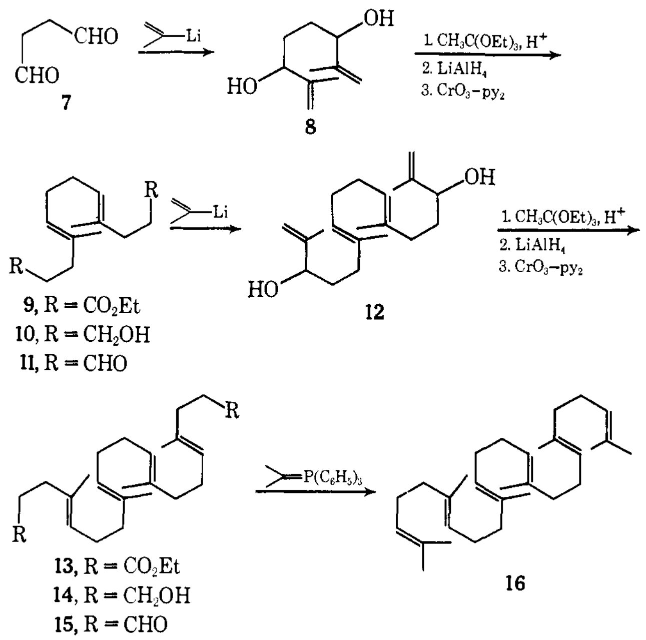
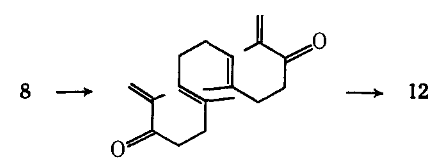
The orthoester Claisen reaction, like the methoxyisoprene method,[6] lends itself readily to the production of successive head-to-tail isoprene units with *trans*-olefinic bonds as they appear in many natural products. This synthetic sequence is exemplified by a total synthesis of all-*trans* squalene (**16**),[7] which is *ca.* 98% stereoselective for each double bond. This synthesis is described below.



Succinic dialdehyde (**7**), obtained readily in 56% yield by hydrolysis of commercially available 2,5-dimethoxytetrahydrofuran with 1 *N* phosphoric acid at 60° for 2.5 hr,[8] was treated with 2-propenyllithium at −15° giving (54% yield) the diene diol **8** as a crystalline mixture of *meso* and *dl* forms (one isomer, mp 91–92°, was isolated by crystallization from ether–hexane). The diene diol mixture, on treatment with ethyl orthoacetate and propionic acid for 3 hr at 138° followed by distillation[3] at 5×10^{-2} mm, was converted into the diene diester **9** (87% yield), which was estimated by vpc to be 97% pure with respect to a single isomer. The nmr spectrum showed absorption for six protons at δ 1.61 ppm corresponding to the two methyl groups of the two *trans*-trisubstituted olefinic bonds.[9] The diene dialdehyde **11** (75% yield from **9** after distillation[3] at 0.05 mm), obtained by treatment of the diene diester **9** with excess lithium aluminum hydride in ether at −5° followed by oxidation with Collins reagent[5] (5 equiv/OH 3 hr, 5° with added BaO), was submitted to the identical sequence of reactions described above, giving in turn the tetraene diol **12** (75% yield after chromatography on silica gel followed by distillation[3] at 0.5 mm), the tetraene diester **13** (obtained in 84% yield after chromatography on silica gel and containing 9% of stereoisomers other than all-*trans* as estimated by vpc), and the tetraene dialdehyde **15** (71% overall yield from **13**). In this second series the tetraene diol **14** fortunately was crystalline, mp *ca.* −8°, allowing for removal of a portion of the small amount of unwanted stereoisomers by a single crystallization (94% recovery) from ether–hexane. The crude tetraene dialdehyde, on treatment with 20% excess isopropylidenetriphenylphosphorane (from $(CH_3)_2CHP(C_6H_5)_3I$ and C_6H_5Li in THF), afforded squalene **16** which was separated in 36% yield by chromatography on Florisil. This product, which was 95% pure all-*trans* isomer as shown by vpc, had identical characteristics (nmr, ir, co-injection vpc, tlc) with those of natural squalene.

The use of 3-methoxyisoprene in the Claisen rearrangement[6] has been examined as an alternative method for effecting the transformation of **8** into **12**. Thus the diene diol mixture **8** was heated at 140° in xylene with excess 3-methoxyisoprene and catalytic amounts of hydroquinone and perchlorohomocubanecarboxylic acid[10] under nitrogen for a total of 25 hr. Chromatography of the crude product on neutral alumina gave the tetraene dione **17** which was reduced with excess sodium borohydride in methanol at 0°. The crude product obtained on evaporation of the solvent (57% yield from **8**) proved to be the tetraene diol **12** as ascertained by nmr and vpc comparison with the authentic material. At the present stage of development the orthoester and methoxyisoprene methods are comparably efficacious. The overall yields are similar, and while the orthoester approach involves more steps, they are very simple to perform and the reagents are commercially available.



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The orthoester Claisen rearrangement is also applicable to the stereoselective production of *trans*-disubstituted olefinic bonds. Thus the trienic alcohol **1** (R^1 = H; R^2 = $CH_2CH_2C(Me){=}CHCH_2CH_2C(Me){=}CH_2$), obtained by reaction of the *trans*-olefinic aldehyde **6** (R = CHO) with vinyllithium solution at −22° for 1 min, was converted by reaction with ethyl orthoacetate for 30 min into the *trans,trans* ester **4** (R^1 = H; R^2 = $CH_2CH_2C(Me){=}CHCH_2CH_2C(Me){=}CH_2$). The yield of this triene ester was 91% overall from **6** (R = CHO) after distillation[3] at <0.5 mm.

Acknowledgments. We wish to thank the U. S. Public Health Service, the National Science Foundation, and the donors of the Petroleum Research Fund

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Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Spectra of the Silver(I) Complexes of Cyclopentene and Cyclohexene[1]

Sir:

In recent years, proton magnetic resonance spectroscopy has been utilized to investigate the nature of the species arising when alkenes are dissolved in solutions containing either silver(I)[2] or mercury(II)[3] ions. We report here on the use of high-resolution nmr spectra of ^{13}C (cmr) in natural abundance[4] in examining such complexes.

The cmr spectra of cyclopentene and cyclohexene in aqueous silver nitrate solution[5] reveal that the unsaturated carbon resonances in both compounds are shifted to higher fields by 4.4 ppm, relative to those of the free cycloalkenes (see Table I). The remaining carbon resonances are shifted downfield slightly. These shifts seem best rationalized on the basis of a small increase in the σ character of the bonds at the unsaturated carbons,[6] although steric interactions[2c] with the silver ion cannot be definitely ruled out. As with the proton chemical shifts of silver-alkene complexes,[2b] there is no significant concentration effect on the ^{13}C chemical shifts.

The downfield shift of vinyl protons on formation of a silver(I) complex is usually explained as resulting from proton deshielding arising from π-electron donation from the alkene to the silver(I) ion.[2] Dewar[7] has proposed that the complexes are formed as the result of σ overlap between the bonding alkene π orbital with a vacant s or sp hybrid orbital on the silver(I) ion and π overlap of an occupied d orbital on the ion with an antibonding alkene π orbital. The net effect appears to be that the π-electron density decrease at carbon is not balanced by the d-electron contribution, thus making σ bonding more important than π bonding.[2c] Thus, an increase in the σ character of the bonds at the alkene carbons is expected and the ^{13}C results tend to bear this out. An increase in the σ character of the bonds to the unsaturated carbons would be expected to decrease the couplings between alkenic carbons and the directly attached hydrogens, but actually there is very little change upon complexation. The lack of appreciable change in the ^{13}C–H coupling constants suggests an alternative explanation of the chemical-shift changes, namely that the π-orbital energy of the alkene is reduced by coordination with silver ion, so as to produce small changes in the excitation energy.

Table I. Carbon Chemical Shifts of Cycloalkene–Silver Nitrate Complexes in Aqueous Solution at 15.1 MHz

	δ (CS_2)[a]	δ (CS_2)[a]	$\Delta\delta$
Cyclopentene		Cyclopentene–$AgNO_3$ Complex	
C1, C2	62.2	66.6	+4.4
C3, C5	160.2	158.3	−1.9
C4	169.7	168.3	−1.4
Cyclohexene		Cyclohexene–$AgNO_3$ Complex	
C1, C2	65.6	70.0	+4.4
C3, C6	167.3	165.8	−1.5
C4, C5	169.7	169.4	−0.3

[a] In parts per million relative to carbon disulfide.

With regard to interaction of mercury(II) ion with alkenes, evidence has been presented[3b,c] and challenged[3a] for direct observation of proton resonances of mercurinium ions. We have found that the cmr spectra of methanol solutions containing equimolar amounts of cyclopentene or cyclohexene and mercury(II) acetate gave no resonances corresponding to alkenic carbons and, indeed, were best explained as arising from 1-acetoxymercuri-2-methoxycyclopentane or 1-acetoxymercuri-2-methoxycyclohexane.

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(5) The samples were prepared by saturating either a 2 *M* or saturated silver nitrate solution with cycloalkene. Cyclopentene and cyclohexene were chosen for study because of their high solubility in silver nitrate solutions (H. J. Taufen, M. J. Murray, and F. F. Cleveland, *ibid.*, 63, 3500 (1941)).
(6) It is well known that there is a large chemical shift difference between sp^2- and sp^3-hybridized carbons, the sp^3 carbons being upfield by about 100 ppm (J. B. Stothers, *Quart. Rev.* (London), 19, 144 (1965)).
(7) M. J. S. Dewar, *Bull. Soc. Chim. Fr.*, **18**, C79 (1951).

Isoporphyrins

Sir:

The discovery of phlorins and the recognition of their stability prompted Woodward[1] to suggest that tautomeric structures of porphyrin with a saturated bridging carbon atom [isoporphyrin (**1**)] might exist. We report here the synthesis of a metalloisoporphyrin.

Controlled-potential oxidation of zinc *meso*-tetraphenylporphyrin (ZnTPP), at 1.1 V *vs.* sce, in dichloromethane–tetrapropylammonium perchlorate brings about two successive reversible one-electron oxidations. The first step generates a π cation radical[2] which is stable in nucleophilic solvents[3] and can be isolated in

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(2) R. H. Felton, D. Dolphin, D. C. Borg, and J. Fajer, *J. Amer. Chem. Soc.*, **91**, 196 (1969).
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