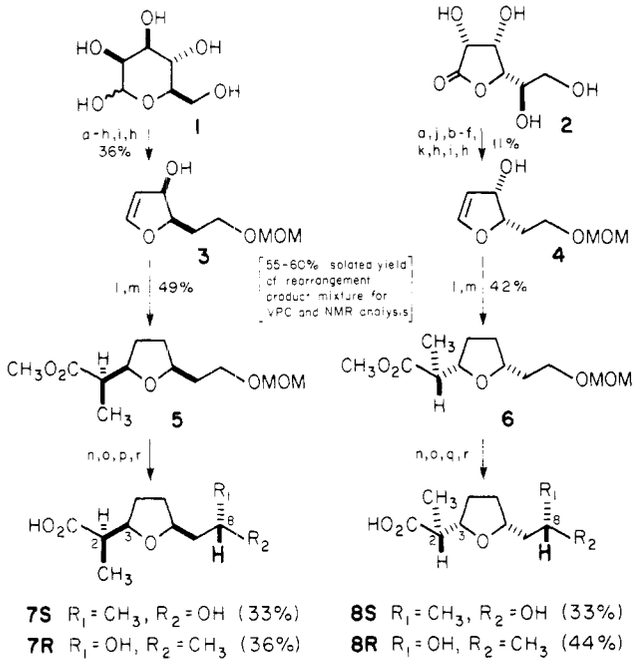
Scheme I. Synthesis[8] of (−)- and (+)-Nonactic Acids[a]

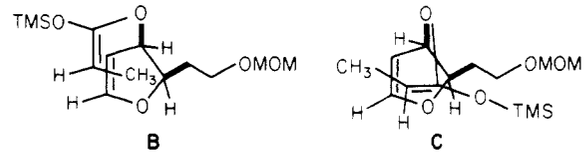


[a] a, CH_3COCH_3, H^+; b, NaH, $C_6H_5CH_2Cl$, DMF; c, concentrated HCl, CH_3OH; d, $(CH_3)_2NCH(OCH_3)_2$, CH_2Cl_2; e, $(CH_3CO)_2O$, 130 °C; f, 9-BBN, THF; H_2O_2, aqueous NaOH; g, KH, $ClCH_2OCH_3$; h, Li, NH_3; i, $(C_6H_5)_3P$, CCl_4; j, *i*-Bu_2AlH, Et_2O; k, $CH_2(OCH_3)_2$, P_2O_5; l, *n*-BuLi; C_2H_5COCl; LDA, THF; Me_4SiCl, room temp; H_2O, OH^-; CH_2N_2; m, H_2, Rh/C, THF; n, 2% HCl, CH_3OH; o, $(COCl)_2$, Me_2SO; Et_3N; p, $LiCu(CH_3)_2$, pentane; q, CH_3MgBr, Et_2O, −78 to −10 °C; r, 2 N KOH, H_2O.

85–90% of the mixture. This observation, coupled with the appropriate choice of a chiral carbohydrate precursor for the allylic alcohol portion of the diene system, uniquely defines the geometrical and stereochemical parameters of the rearrangement substrate. As a result, the stereochemistry of the single bond that is formed in the rearrangement will depend only on whether a chair-like or boat-like transition state is followed.

For the synthesis of (−)-nonactic acid (**7S**) (Scheme I) the furanoid glycal **3**, available[6] in 36% overall yield in ten steps from D-mannose (**1**), is the appropriate chiral precursor for definition of the allylic alcohol portion. Correspondingly, the glycal **4**, derived[6] from D-gulono-γ-lactone (**2**) in 11% overall yield in 11 stages, is required for the (+)-nonactic acid (**8R**) synthesis. When the labile[6] intermediate propionates of these enantiomeric glycals **3** and **4** are enolized with LDA in pure THF, previous work[7] shows that the *Z* enolate is the predominate geometrical isomer formed, and thereby the rearrangement substrate is defined. After the enolate is trapped with Me_3SiCl, rearrangement is allowed to occur, and the subsequent product mixture is further processed by esterification and then hydrogenation. Analysis (VPC and NMR) of the product mixtures[8] obtained in moderate yield from each of the glycals **3** and **4** showed that in each case one diastereomer of the esters **5** and **6** predominated in an 86–89/14–11 ratio. After separation by column chromatography, each of the major ester constituents was converted to the nonactic acid structure as shown (Scheme I). No stereochemical control was possible in the organometallic addition step of this sequence, and thus both epimers about C8 were obtained in approximately equal amounts. Comparison of the optical, physical, and spectral data[8] of these products with those published[4] for the nonactic acids and their C8 epimers established that the D-mannose derived glycal **3** had led to (−)-nonactic acid (**7S**) and its C8 epimer **7R**, while the D-gulano-γ-lactone glycal **4** had generated (+)-nonactic acid (**8R**) and its C8 epimer **8S**.

In addition to the completion of a new, chiral synthesis of the nonactic acids, these results serve to establish that in these heterocyclic systems (like in the cycloalkyl systems[9]) the Claisen rearrangement takes place through a boat-like transition state that probably resembles diagram B for the silyl ketene acetal from the glycal **3**, for instance. Rearrangement of this *E* silyl ketene acetal through a transition state like B will lead to the 2*R*,3*R* ester enantiomer **5** and thence to the (−)-nonactic acids (**7R**) and (**7S**).



Rearrangement of this *E* silyl ketene acetal through the alternate chair-like transition state C would have generated the 2*S*,3*R* diastereomer of the ester **5** and thence the 2-epinonactic acids. This definition of the pathway for these types of Claisen rearrangements is important to the scope of this useful reaction sequence.

Supplementary Material Available: Infrared and proton magnetic resonance spectra, optical rotations, physical constants, thin-layer chromatographic mobility, and elemental combustion analyses of compounds 3–8 and isolated intermediates (9 pages). Ordering information is given on any current masthead page.

(8) All isolated intermediates and synthetic (−)- and (+)-nonactic acids were characterized by appropriate physical, optical, and spectral (IR, NMR) data, thin-layer and vapor-phase chromatographic behavior and combustion analysis. For details, see the supplementary material.

(9) Lythgoe, B.; Cave, R. J.; Metcalfe, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1218–1228.

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A Direct Synthesis of *Z*-Trisubstituted Allylic Alcohols via the Wittig Reaction

Summary: The lithium-free modification of the Wittig reaction of unstabilized ylides and acyclic α-alkoxy ketones leads to protected trisubstituted allylic alcohols with high stereoselectivity for the *Z* isomer.

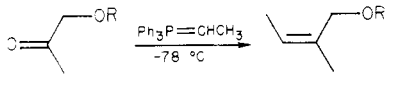
Sir: In the 25 or so years since its discovery, the Wittig reaction has served as a most powerful method for the regiocontrolled and, more recently, the stereocontrolled construction of carbon–carbon double bonds.[1] The latter aspect is of special significance and it is largely through publications of Schlosser and co-workers that highly ster-

(1) Reviews: A. W. Johnson, "Ylid Chemistry", Academic Press, New York, 1966; M. Schlosser, *Top. Stereochem.*, 5, 1 (1970); H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, CA, 1972, pp 682–709; M. Schlosser in "Methodicum Chimicum", Vol. 7, F. Korte, H. Zimmer, and K. Niedenzu, Eds., Thieme, Stuttgart, 1976, pp 529–552.

0022-3263/80/1945-4260$01.00/0

eoselective preparations of both cis and trans disubstituted olefins have become available.[2] Corresponding preparations of trisubstituted olefins from unstabilized ylides, however, have remained a problem. Although pertinent methodology based on electrophilic substitution of intermediate β-oxido ylides has been devised,[3] a direct Wittig route would be a desirable and convenient alternative. We have found that the lithium-free Wittig reaction of various α-alkoxy ketones with unstabilized ylides leads to protected trisubstituted allylic alcohols in which the *Z* isomer has been formed stereoselectively (e.g., **1** → **2**).

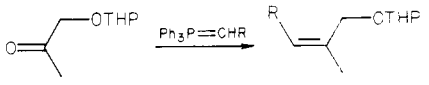
The system which we have studied most thoroughly is the simplest one imaginable: ethylidenetriphenylphosphorane and derivatives of hydroxyacetone. Given these reactants, stereoselectivity was examined as a function of the hydroxyl protecting group and the reaction medium. As summarized below, selectivity for the *Z* isomer was always observed and was highest with the tetrahydropyranyl group and with potassium hexamethyldisilazide in a basic solvent. Under these optimum conditions,[4] the angelic alcohol derivative **2** (R = THP) was produced in 83% isolated yield and with 97.5% stereoisomeric purity (VPC). Yields with the other protecting groups listed below ranged from 85–95%.[5]



1 **2**

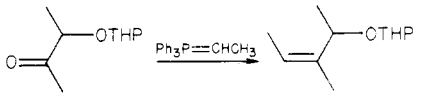
R	conditions	*Z*:*E*[6]
THP	10% HMPA/THP, $KN(SiMe_3)_2$	41:1
CMe_2OMe	10% HMPA/THF, $KN(SiMe_3)_2$	30:1
CPh_3	10% HMPA/THF, $KN(SiMe_3)_2$	18:1
$SiMe_2$-*t*-Bu	10% HMPA/THF, $KN(SiMe_3)_2$	14:1
CH_2Ph	10% HMPA/THF, $KN(SiMe_3)_2$	12:1
THP	THF, $KN(SiMe_3)_2$	29:1
THP	10% HMPA/THF, *n*-BuLi	28:1
THP	THF, *n*-BuLi	11:1
THP	Et_2O, *n*-BuLi	5:1

As shown by the examples which follow, this Wittig route to trisubstituted allylic alcohols has considerable potential for the construction of complex molecules. Thus certain additional substituents may be added to either of the reactants without any compromise in stereoselectivity or yield. The ylide, for example, may be substituted by various alkyl chains so long as the carbon β to phosphorus is not branched (eq 1). The carbonyl partner may also be substituted within limits. In general, substitutions at the α-carbon of an α-alkoxy ketone tend to improve stereoselectivity whereas α′-substitutions tend to diminish it (eq 2 and 3). Chemical yields are typically quite high provided that the atoms being joined are relatively unhindered. In systems where steric hindrance causes the coupling to proceed sluggishly, use of a less bulky protecting group (e.g., (benzyloxy)methyl) is often advantageous (eq 4, experiment performed by J. C. Barrish).



(1)

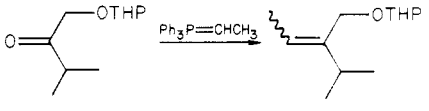
R	*Z*:*E*	yield
$CH_2CH_2CH_3$	60:1	87%
$CH(CH_3)_2$	6:1	45%



(2)

Z:*E*

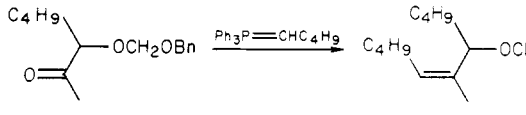
200:1 (>95%)



(3)

Z:*E*

1:1 (80%)

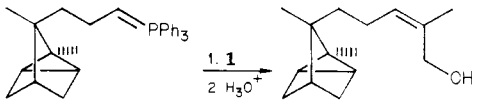


(4)

Z:*E*

>50:1 (>95%)

The Wittig synthesis of α-santalol shown below provides a simple illustration of the utility of this process.[3a] The ylide shown was prepared from the corresponding iodide[7] in the usual way and was reacted in tetrahydrofuran (with or without added HMPA) with [(2-methoxypropyl)oxy]-acetone (**1**, R = CMe_2OMe). The reaction product was not isolated but was hydrolyzed in situ with aqueous acetic acid to give α-santalol in approximately 85% yield with at least 99% stereoisomeric purity.[8]



As a final note, we might add that the stereoselectivity of these reactions may be marginally increased by using the phosphonium fluoborate instead of the more common phosphonium halide. Such a counterion exchange typically results in a 20–50% increase in selectivity for the *Z* isomer and is readily accomplished by mixing concentrated

(2) M. Schlosser and K. F. Christmann, *Angew. Chem., Int. Ed. Engl.*, **5**, 126 (1966); M. Schlosser, G. Müller, and K. F. Christmann, *ibid.*, **5**, 667 (1966).

(3) (a) E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 226 (1970); (b) M. Schlosser, K. F. Christmann, A. Priskala, and D. Coffinet, *Synthesis*, 29 (1971); (c) M. Schlosser and D. Coffinet, *ibid.*, 575 (1972); (d) E. J. Corey and A. Venkatesvarlu, *Tetrahedron Lett.*, 3231 (1977).

(4) A typical experimental procedure follows: To a suspension of 1.4 mmol of ethyltriphenylphosphonium bromide (or fluoborate) in 4.5 mL of anhydrous tetrahydrofuran and 0.5 mL of anhydrous hexamethylphosphoric triamide under nitrogen was added 1.3 mL of 1 M potassium hexamethyldisilazide in tetrahydrofuran (prepared from KH and $(Me_3Si)_2NH$). After being stirred for 10 min at 25 °C, the bright red solution was chilled to −78 °C and was treated with 1.0 mmol of the α-alkoxy ketone. The reaction mixture was allowd to warm to room temperature over a 60-min period and was worked up by partitioning between water and petroleum ether. Flash chromatography (W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978)) gave the pure allylic alcohol derivative. Products having significant water solubility (e.g., **2**, R = THP) were more effectively isolated by dilution of the reaction mixture with an equal volume of petroleum ether followed by direct application to a silica gel column for chromatography. For relatively large-scale preparations (>10 g), flash chromatography may be replaced by simple filtration through a thick pad of silica gel in a Büchner funnel with a solvent which moves the desired product on TLC to R_f ~0.25. The Wittig procedure using hexamethyldisilazide in tetrahydrofuran is taken largely from Bestmann and co-workers (cf. H. J. Bestmann, W. Stransky, and O. Vostrowsky, *Chem. Ber.*, **109**, 1694 (1976)).

(5) The starting α-alkoxyacetones were prepared either by direct protection of commercial hydroxyacetone (acetol) or by protection and ozonolysis of methallyl alcohol.

(6) These ratios were determined by ^1H NMR, VPC, and/or high-performance LC, with stereochemical assignments being made by comparison with authentic materials prepared from tiglic or angelic acids.

(7) The phosphonium salt was prepared from α-santalol by (1) O_3, MeOH; (2) $NaBH_4$; (3) *p*-TsCl, C_5H_5N; (4) NaI, CH_3COCH_3; (5) Ph_3P. We thank Dr. J. B. Hall of International Flavors and Fragrances for a generous sample of pure α-santalol.

(8) Product analysis was carried out by VPC and ^1H NMR comparisons with authentic samples of (*Z*)- and (*E*)-α-santalol.

aqueous solutions of sodium fluoborate and the phosphonium halide. The phosphonium fluoborate which precipitates may be dried under vacuum and converted to the ylide in the usual way.[9]

(9) This work was supported by grants from the Sloan Foundation and the National Science Foundation (CHE 78-01769).

(10) Fellow of the Alfred P. Sloan Foundation (1978-1980).

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Selective Reduction via Enolate Protection

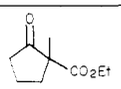
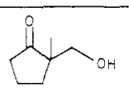
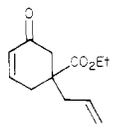
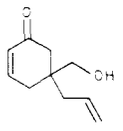
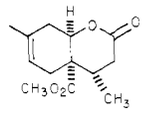
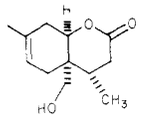
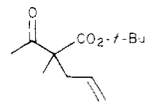
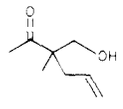
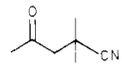
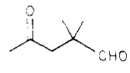
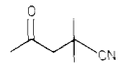
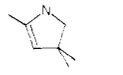
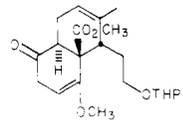
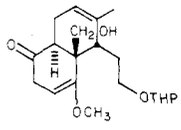
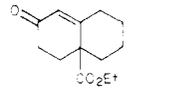
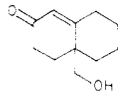
Summary: The use of enolate anions as protecting groups in order to effect the selective reduction of dicarbonyl compounds is studied.

Sir: Many procedures are available for the reduction of a ketone or aldehyde in the presence of an ester or lactone.[1] In order to achieve the complementary selectivity, a sequence involving protection, reduction, and deprotection must be employed. In addition to the obvious operational inconvenience, olefin isomerization and other acid-catalyzed rearrangements can occur during protection and deprotection. The concept of using selective enolate formation in combination with hydride reduction was first conceived by Barton[2] for the reduction of steroidal ketones. Both Schlessinger[3] and Goldsmith[4] have also used this method. However, aside from these interesting applications, no study of this reduction strategy has been reported. We now present an investigation of its scope and limitations.

Ketone deprotonation was effected with either lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide. These reagents are nonnucleophilic and capable of completely deprotonating ketones at low temperatures. The reducing agents employed included lithium aluminum hydride, diisobutylaluminum hydride, and lithium triethylborohydride. A variety of substituted dicarbonyl compounds was used. The results are illustrated in Table I.

This method is advantageous for the unambiguous synthesis of certain aldols, as evidenced by entries 1 and 4. Hirano and co-workers[5] have studied the acid-catalyzed aldol condensation between ketones and formaldehyde. Although the reaction of 2-methylcyclopentanone and formaldehyde affords a mixture of products, the major product is identical by NMR and IR with compound 1 prepared by our method. Reduction of the keto nitrile (entries 5 and 6) affords either a keto aldehyde or cyclic imine **2**, depending on the choice of reducing agents. The yields in both cases were somewhat reduced due to the volatility of the products. Imine **2** was identical by NMR with the compound produced by reduction of 4,4-dimethyl-5-nitro-2-pentanone.[6] The change in reaction conditions for entries 7 and 8 was necessitated by the extremely slow rate of reduction in tetrahydrofuran (incomplete after 48 h).

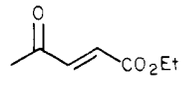
Table I. Selective Reductions

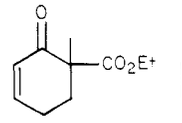
entry	reactant	reaction conditions	time, h	% yield	product[a]
1		A	1	76	 **1**
2		A	0.5	62	
3		A	0.5	65	
4		A	0.5	81	
5		B	2.0	46	
6		A	0.5	67	 **2**
7		C	8	95	
8		C	8	90	

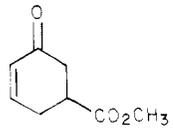
[a] All products exhibited satisfactory IR, ^{1}H NMR, ^{13}C NMR and mass spectral data and analytical analyses. See footnote 8 for experimental procedure.

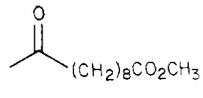
In contrast to the successful results in Table I, compounds I–IV failed to afford synthetically useful yields of the desired reduction products.

Thin-layer chromatography of the enolate solution[7]


I


III


IV


II

before the addition of the hydride reagent indicated, in the cases that failed, that new products have already begun to form. Thus, the failure was due to enolate anion instability. Such instability could arise from intramolecular

(1) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; Chapter 2.

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(7) TLC of enolate solutions in reactions which were successful showed only starting material. Aliquots for TLC could be either first quenched and then chromatographed or simply chromatographed directly.

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