Claisen Rearrangements of Enol Phosphates

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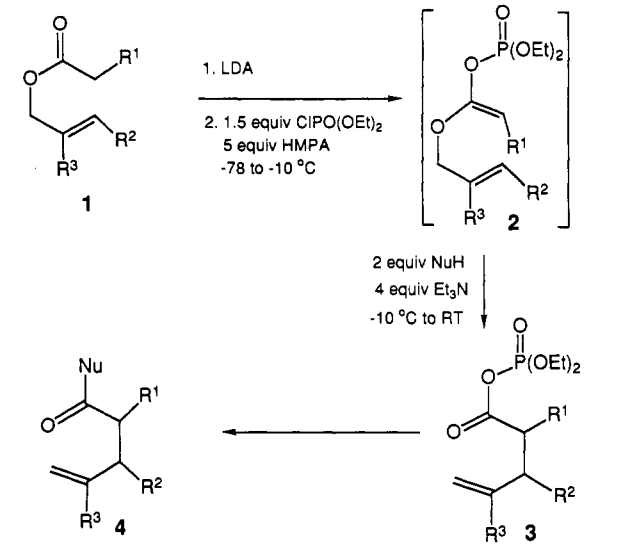
Since its introduction in 1972, the Ireland protocol[1] has remained preeminent among the numerous methods for effecting Claisen rearrangements.[2] The utility of this procedure stems largely from the availability of *O*-silyl ketene acetals, prepared from allyl ester or lactone enolates, and the facility of their rearrangement to silyl esters. We became interested in the possibility of replacing the trialkylsilyl group of *O*-silyl ketene acetals with other groups, primarily for the purpose of varying the degree of bond breaking and bond making in the transition state and thereby affecting the rate and, potentially, even the diastereoselectivity of the rearrangement.[3]

Initially, the Claisen rearrangements of enol phosphates[4] were selected in view of their well-precedented stabilities[5] and accessibilities from ester or lactone enolates.[6] Moreover, the anticipated rearrangement products, mixed carboxylic dialkylphosphoric anhydrides, are synthetically useful acylating agents.[7] Herein it is reported that the rearrangements of *dialkoxyphosphinyl* ketene acetals (1) are more facile than their trialkylsilyl counterparts, (2) provide direct access to a variety of carboxylic acid derivatives, and (3) can proceed with improved diastereoselectivity.

The various esters **1** that have been subjected to this new rearrangement procedure are collected in Table I. The derived enol phosphate **2** was not isolated for any of these examples since rearrangement took place either at the temperature required for phosphorylation (−78 to −10 °C) or upon warming of the solution to room temperature in the presence of an appropriate nucleophile. As expected, the intermediate mixed anhydrides[7] smoothly participated in acylation reactions with a variety of nucleophiles including *N*-methoxy-*N*-methylamine and ethanethiol, the products[8] of which can be easily converted to ketones[9a,b] and/or aldehydes.[9c] It should be noted that the products of entries 8 and 9 were obtained as an *erythro/threo* mixture of diastereomers in an 83:17 ratio that was identical to that obtained using the Ireland protocol (82:18), which indicates that the integrity of the enolate stereochemistry is preserved during phosphorylation as well as silylation.

Table I. Claisen Rearrangements of Enol Phosphates



entry	R^1	R^2	R^3	Nu	yield **4** (%)
1	H	H	H	OMe	78
2	H	H	Me	OMe	81
3	Me	H	Me	OMe	76
4	Me	H	Me	OPr	70
5	Me	H	Me	O*t*-Bu	54
6	Me	H	Me	SEt	79
7	Me	H	Me	N(OMe)Me	81
8	Me	Me	H	OMe	82
9	Me	Me	H	N(OMe)Me	84

Lactone **5** represents a useful substrate for evaluating the relative rates of rearrangement of trialkylsilyl ketene acetals vs dialkoxyphosphinyl ketene acetals (Scheme I). Previously, the half-life of the rearrangement of the *tert*-butyldimethylsilyl ketene acetal derivative of lactone **5** was determined to be 58 min at 65 °C in chloroform.[10] The enol phosphate **6** was prepared, purified by silica gel chromatography (77%), and rearranged ($CHCl_3$, 4 equiv of MeOH, 4 equiv of NEt_3, 65 °C) with a half-life of ca. 10 min to the chrysanthemate ester **7** (83%).[11] Additional examples examined in this laboratory, *vida infra*, support the conclusion that the rearrangements of phosphinyl ketene acetals are more facile than silyl ketene acetals. The factors responsible for this rate acceleration are not clear; however, the fact that the bis(trichloroethyl)phosphinyl ketene acetal analogous to **6** rearranges at or below room temperature is suggestive that these ketene acetals rearrange through a transition state with allyl cation/enolate anion character rather than one with allyl radical/oxallyl radical character, which has been proposed for silyl ketene acetal rearrangements.[12]

A final example, rearrangement of lactone **8**, serves to illustrate that the diastereoselectivity of an ester enolate rearrangement is

(1) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *Ibid.* **1976**, *98*, 2868.

(2) For a recent review, see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(3) Alternatively, replacement of the silyl group with a chiral moiety offers the possibility of an enantioselective preparation of substituted γ,δ-unsaturated carboxylic acids, following hydrolytic removal of the chiral auxiliary. Indeed, highly enantioselective Claisen rearrangements of achiral allylic esters via chiral boron enolates have been reported, see: Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026.

(4) In fact, one example of this type of rearrangement may be known. Treatment of *trans*-2-butenyl trichloroacetate with triethyl phosphite affords 2,2-dichloro-3-methyl-4-pentenoic acid. This transformation has been postulated to proceed through an intermediate enol phosphate via an initial Perkow reaction. However, rearrangement of an intermediate enolate cannot be excluded, see: Baldwin, J. W.; Walker, J. A. *J. Chem. Soc., Chem. Commun.* **1973**, 117.

(5) For a review, see: Lichtenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607.

(6) (a) Kane, V. V.; Doyle, D. L.; Ostrowski, P. C. *Tetrahedron Lett.* **1980**, *21*, 2643. (b) Greene, A. E.; Moyano, A.; Charbonnier, F. *J. Org. Chem.* **1987**, *52*, 2303. (c) Wiemer, D. F.; Hammond, G. B.; Jackson, J. A. *J. Org. Chem.* **1989**, *54*, 4750.

(7) For the reaction with thiols: (a) Yamada, S.; Yokoyama, Y.; Shioiri, T. J. *J. Org. Chem.* **1974**, *39*, 3303. (b) Masamune, S.; Kamata, S.; Diakur, J.; Sugihara, Y.; Bates, G. S. *Can. J. Chem.* **1975**, *53*, 3693. Amines: (c) Górecka, A.; Leplawy, M.; Zabrocki, J.; Zwierzak, A. *Synthesis* **1978**, 474. Sodium borohydride: (d) Koizumi, T.; Yamamoto, N.; Yoshii, E. *Chem. Pharm. Bull. Jpn.* **1973**, *21*, 312. For a review, see: Stelzel, P. Houbon-Weyl, In *Methoden der Organischen Chemie*, 4-Aufl; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1974; Vol XV/2, p 226.

(8) All new compounds reported herein exhibit satisfactory spectral (IR, NMR), analytical, and/or high-resolution mass spectral characteristics.

(9) (a) Weinreb, S. M.; Nahm, S. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Sibi, M. P. *Org. Prep. Proceed. Int.* **1993**, *25*, 18. (c) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

(10) Funk, R. L.; Munger, J. D., Jr. *J. Org. Chem.* **1985**, *50*, 707.

(11) The rate of rearrangement was measured by following the disappearance of the proton resonance at δ 1.44 for the methyl substituents on the allylic oxycarbon of **6** and the appearance of the proton resonances for the vinyl methyl substituents of **7** at δ 1.69 and 1.73.

(12) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733. Alternatively, ground-state destabilization may be responsible for this rate effect as proposed for a trifluoromethyl group at C(2) of allyl vinyl ether, see: Gajewski, J. J.; Gee, K. R.; Jurayj, J. *J. Org. Chem.* **1990**, *55*, 1813. However, the rate of the Claisen rearrangement is accelerated by a factor of only 73 over the parent system (allyl vinyl ether) when a trifluoromethyl group is present at C-2, in contrast to a factor of at least 10^6 for a C(2) dialkoxyphosphate.

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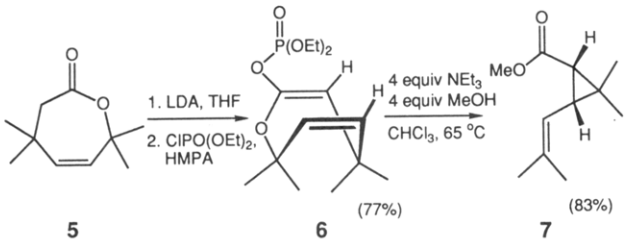
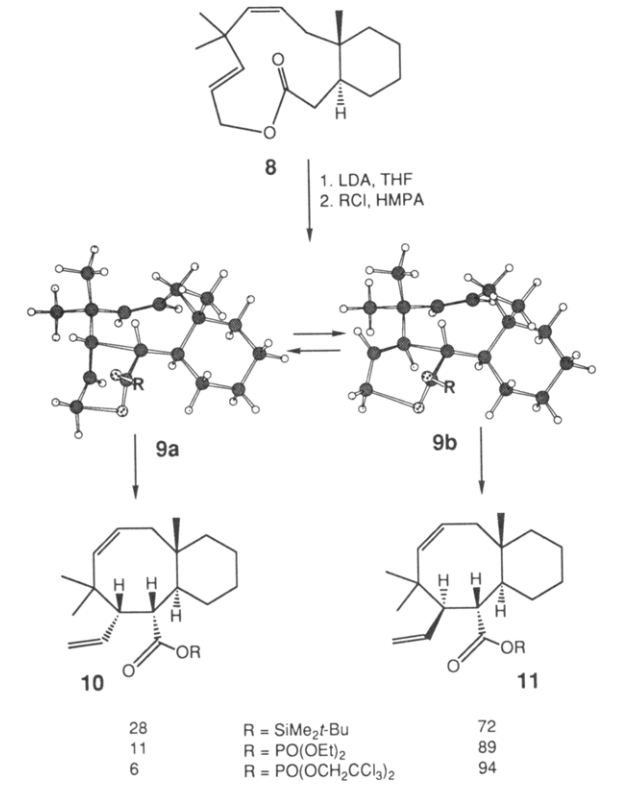
Scheme I



Scheme II



sensitive to the enolate oxygen substituent (Scheme II). Silylation of the enolate of lactone **8** gave a single silyl ketene acetal, presumably the (*E*) stereoisomer **9** (R = *t*-BuMe$_2$Si),[1] which rearranged upon thermolysis in toluene (100 °C, 10 h), preferentially through a boatlike transition state (**9b**) rather than the alternative chair-like transition state (**9a**). The resulting mixture of silyl esters was hydrolyzed (PPTS, MeOH, 45 °C, 12 h) and esterified (CH_2N_2) to provide a 72:28 mixture (57%) of methyl cyclooctenoates **11** and **10**, respectively.[13] In contrast, rearrangement of the enol phosphate **9** [R = PO(OEt)$_2$] proceeded *at room temperature* (THF, 4 equiv of NEt_3, 2 equiv of MeOH, 2 h) with improved stereoselectivity to provide an 89:11 mixture of diastereomers (R = Me, 65%). Moreover, additional stereocontrol (94:6) could be realized by rearranging the bis(trichloroethyl)phosphinyl ketene acetal **9** [R=PO(OCH$_2$CCl$_3$)$_2$, 70% yield] using conditions identical to those employed for the diethylphosphinyl ketene acetal. This trend suggests that electronic factors, as opposed to steric effects, are responsible for the markedly improved diastereoselectivity, especially since the ketene acetal bearing the larger bis(trichloroethyl)phosphinyl substituent prefers to rearrange through the presumably more sterically congested boatlike transition state.

In conclusion, the Claisen rearrangement of an ester or lactone enolate as the dialkoxyphosphinyl ketene acetal merits consideration when a derivative of the product γ,δ-unsaturated carboxylic acid is desired or when diastereotopic transition states are likely to compete and, consequently, are subject to this stereocontrol element.

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Supplementary Material Available: Experimental procedures for rearrangement of enol phosphates and spectral data for all rearrangement products (5 pages). Ordering information is given on any current masthead page.

(13) The stereochemical assignments are assigned on the basis of an observed C(1)–C(2) (taxane numbering) proton coupling constant of J = 11.03 Hz and a C(2)–C(3) proton coupling constant of J = 2.63 Hz for the major atropisomer of **11** (product conformer analogous to **9b**, 300 MHz, –40 °C), in agreement with the calculated values of J = 12.5 and 4.6 Hz, respectively. In addition, an NOE was observed for the C(9_β, 6%), the vinyl (3.5%), and two of the three methyl (3.9 and 2.3%) proton resonances upon irradiation of the C(2) proton resonance at δ 2.75. The observed broad singlet for the C(2) proton resonance for **10** (product conformer analogous to **9a**, 300 MHz, –40 °C) is in agreement with the calculated values of J = 1.22 and 3.45 Hz for the C(1)–C(2) and C(2)–C(3) proton coupling constants, respectively. In addition, an NOE was observed for the C(9_β, 9.8%), C(1, 7.1%) and two of the three methyl (8.9 and 5.5%) proton resonances upon irradiation of the C(2) proton resonance at δ 3.00.