Water as a Solvent for the Claisen Rearrangement: Practical Implications for Synthetic Organic Chemistry

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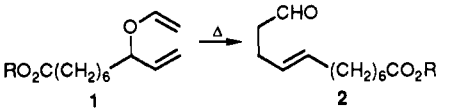
Summary: The accelerating influence of water as a solvent on the rate of the Claisen rearrangement has been demonstrated on several substrates, thus illustrating the enormous potential it holds for those engaged in the synthesis of natural and unnatural products. Claisen rearrangement products which hitherto were inaccessible due to decomposition at high temperatures or elimination can now be realized through the agency of water.

Sir: The accelerating influence of water as a solvent on the rate of the Claisen rearrangement[1] has been demonstrated in one instance by determining the first-order rate constants for the rearrangement of allyl vinyl ether **1** (R = Na, Me) in solvents ranging in polarity from cyclohexane to water.[2] We detail below the results of a study which clearly demonstrate the effectiveness of employing water as a solvent for the Claisen rearrangement and, more importantly, illustrates the enormous potential it holds for those engaged in the synthesis of natural and unnatural products. *Claisen rearrangement products which hitherto were inaccessible due to decomposition at high temperatures or elimination can now be realized through the agency of water.*

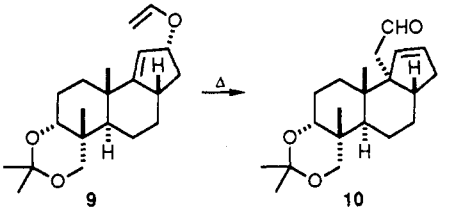


1 **2**

In our preliminary study, substrate **1** (R = Na) was shown to undergo [3,3]-sigmatropic rearrangement in water (0.01 M in **1** and 0.01 M in pyridine) at 60 °C, giving rise to aldehyde **2** (R = H) after 3.5 h in 85% isolated yield. Rearrangement of the corresponding ester **1** (R = Me) in water is equally facile and efficient at 60 °C, giving rise to **2** (R = Me) in comparable yield despite a heterogeneous reaction medium. In sharp contrast ester **1** (R = Me) in benzene requires 108 h at 60 °C in order to realize a 64% yield (85% based on recovered starting material) of aldehyde **2** (R = Me).

Similar results were observed with substrate **3** (Table I). Once again in the case of **3** the Claisen rearrangement is dramatically accelerated in water. Even more profound was the data obtained with substrate **5** (Table I). Note that after 5 h at 100 °C (bath temperature) an 80% isolated yield of aldehyde **6** was realized. In contrast, the results in toluene are disappointing. In the cases where the solubility of a substrate in water is negligible, one can employ cosolvents (see Table I) such as methanol, pyridine, and dimethyl sulfoxide, provided the amount of cosolvent is kept to a minimum. The effect of employing cosolvents is to decrease the rate of the Claisen rearrangement but not to the extent that reaction is no longer practical.

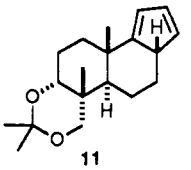
Several years ago, McMurry,[3] in connection with a synthesis of aphidicolin, had considerable difficulties finding conditions to bring about the Claisen rearrangement depicted in eq 1. Elimination of acetaldehyde was



(1)

9 **10**

the major reaction product obtained under the majority of reaction conditions studied both in the gas phase and in solution. For example gas-phase pyrolysis of allyl vinyl ether **9** at 360 °C in a base-washed silylated quartz tube resulted in a 20% yield of aldehyde **10** with the major product being cyclopentadiene **11**. After extensive ex-



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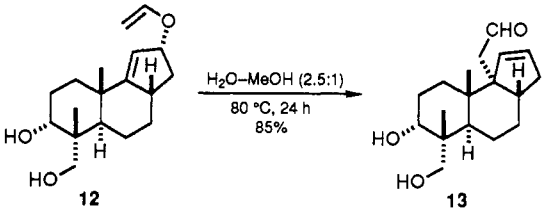
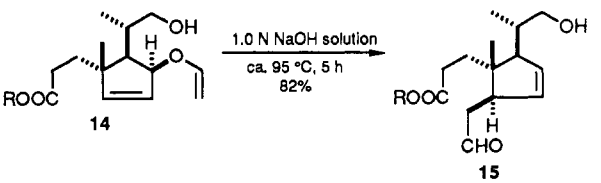
perimentation McMurry[3] found that **9** undergoes rearrangement at 220 °C in a base-washed silylated sealed glass tube containing toluene and sublimed sodium *tert*-pentoxide, giving rise to the desired aldehyde **10** in 60% yield. Remarkably, we find that the unprotected allyl vinyl ether **12**, 0.01 M in water–methanol (2.5:1) containing an equivalent of sodium hydroxide, smoothly undergoes rearrangement at ca. 80 °C, affording after 24 h an 85% isolated yield of aldehyde **13**.



12 **13**

Equally remarkable is the effect water had on the [3,3]-sigmatropic shift of allyl vinyl ether **14**, a key intermediate in a synthesis of the Inhoffen–Lythgoe diol.[4] The rearrangement of **14** (R = Na), presumably proceeding through a boat transition state, occurred in only 5 h at 95 °C in 1.0 N sodium hydroxide solution. Aldehyde **15** (R = H) was isolated in 82% yield. The corresponding ester **14** (R = Me) upon prolonged heating in decalin at 95 °C



14 **15**

(1) For general reviews on the Claisen rearrangement, see: (a) Ziegler, F. E. *Chem. Rev.*, **1988**, *88*, 1423. (b) Rhoads, S. J.; Raulins, N. R. *Org. react. (N.Y.)* **1975**, *22*, 1. (c) Also, see: Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170. Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160.

(2) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515.

(3) McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, M. A. *Tetrahedron* **1981**, *37* (Supplement No. 1), 319.

(4) Unpublished results of Ellen Brandes, Indiana University.

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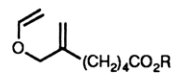
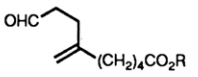
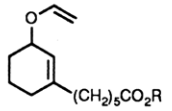
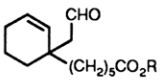
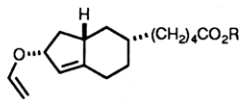
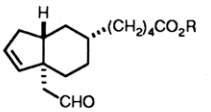
Table I. Solvent Effects on Claisen Rearrangements: Water versus Hydrocarbons

	R	solvent	temp, °C	time, h	product	% yield[a]
 3	Na	H_2O[b]	90	4	 4	82
	Me	PhH[c]	90	167		61 (91)
 5	Na	H_2O[d]	100	5	 6	80
	Me	$PhCH_3$[c]	100	95		12 (16)
 7	Na	H_2O[d]	80	1	 8	78
	Na	H_2O–Py (3:1)	85	1		82
	Me	H_2O–Py (3:1)	85	2		85
	Me	decalin[c]	180	2		44 (54)

[a] Numbers in parentheses refer to yields based on recovered starting material. [b] Reaction run in the presence of 0.1 equiv of sodium hydroxide. [c] Reaction run in the presence of 1.0 equiv of pyridine. [d] Reaction run in the presence of 1.0 equiv of sodium hydroxide.

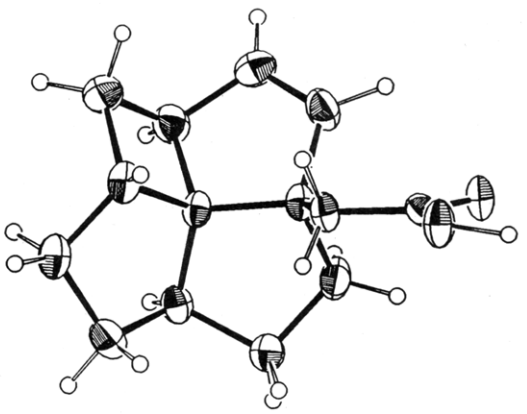
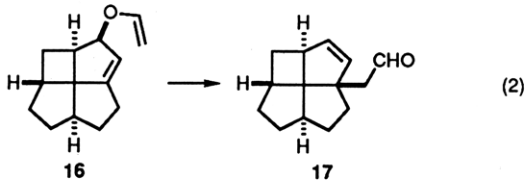


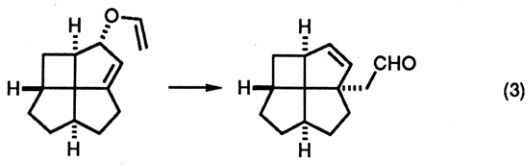
Figure 1. ORTEP view of compound **21**.

led only to recovered starting material. Previous attempts to carry out transformations of the type **14** → **15** have resorted to flash vacuum pyrolysis or temperatures in excess of 220 °C.[5] This example along with the aphidicolin case cited above clearly demonstrates the effectiveness of employing water as a solvent for the Claisen rearrangement, as well as its potential for application to natural products synthesis.

In an attempt to further probe the potential of aqueous Claisen rearrangements we set out to examine a system wherein, as a direct consequence of the [3,3]-sigmatropic process, significant torsional strain would be imparted to a molecule. In this regard we set out to study the Claisen rearrangements depicted in eq 2 and 3, which lead to the

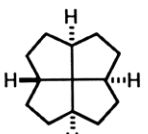


16 **17** (2)



18 **19** (3)

novel functionalized [4.5.5.5]fenestrenes **17** and **19**.[6] Note that **19** possesses a trans configuration between the two five-membered rings common to the acetaldehyde unit. It is interesting to note that all previous attempts to employ Claisen rearrangements within the carbon framework of the fenestrane system as well as all efforts to prepare a fenestrane wherein one of the ring fusions is trans, have met with no success. Keese's[7] attempts to prepare fenestranes possessing a trans ring fusion between adjacent rings have been unsuccessful to date [cf. (1α,4α,7α,10β)-[5.5.5.5]fenestrane, **20**].



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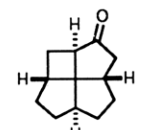
The Claisen rearrangement of allyl vinyl ether **16**[8] (eq 2) was conducted in water–pyridine (3:1) at 90 °C. After 36 h a 21% yield of aldehyde **17** was isolated. The structure of **17** (Figure 1) was confirmed by single-crystal X-ray analysis of the crystalline carboxylic acid **21**,[10] mp 100.0–101.5 °C, obtained by oxidation of the alcohol derived from **17**. Equally facile was the transformation of **18** into **19**, which gave rise to aldehyde **19** in 38% yield upon heating (80 °C, 18 h) a solution of **18** in water–pyridine (3:1). Aldehyde **19** was characterized as its carboxylic acid **22**, mp 107–109 °C.

(5) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378. Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380. Brandes, E.; Grieco, P. A.; Garner, P. *J. Chem. Soc., Chem. Commun.* **1988**, 500.

(6) For a review on Fenestranes, see: Venepalli, B. R.; Agosta, W. C. *Chem. Rev.* **1987**, *87*, 399.

(7) Luyten, M.; Keese, R. *Tetrahedron* **1986**, *42*, 1687.

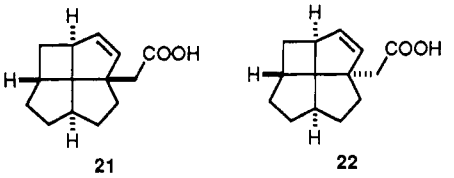
(8) Prepared in straightforward fusion from the known [4.5.5.5]fenestranone i.[9]



i

(9) Dauben, W. G.; Walker, D. M. *Tetrahedron Lett.* **1982**, *23*, 711.

(10) Compound **21** crystallizes in space group $P\bar{1}$ with cell dimensions of a = 7.251 (2) Å, b = 12.641 (4) Å, and c = 13.823 (4) Å; V = 1150.79 Å^3, ρ_{calcd} = 1.260 g cm^{-3} (Z = 4). A total of 4172 reflections were measured of which 2419 were determined to be observable, $F_o > 2.33\sigma(F)$. All atoms, including hydrogens, were located and refined to final residuals of $R(F)$ = 0.0680 and $R_w(F)$ = 0.0728.



21 22

The origin of the rate accelerations recorded above might be attributed to stabilization of a polar transition state by water, but it should be recognized that the rate response of **1** to polar solvents is far less than what might be anticipated for an S_N1 reaction.[2] Another factor, particularly the effect of solvent pressure on a reaction with a negative activation volume, appears to be important.

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Enantiospecific Synthesis of D-*myo*-Inositol 1,4,5-Trisphosphate from (−)-Quinic Acid

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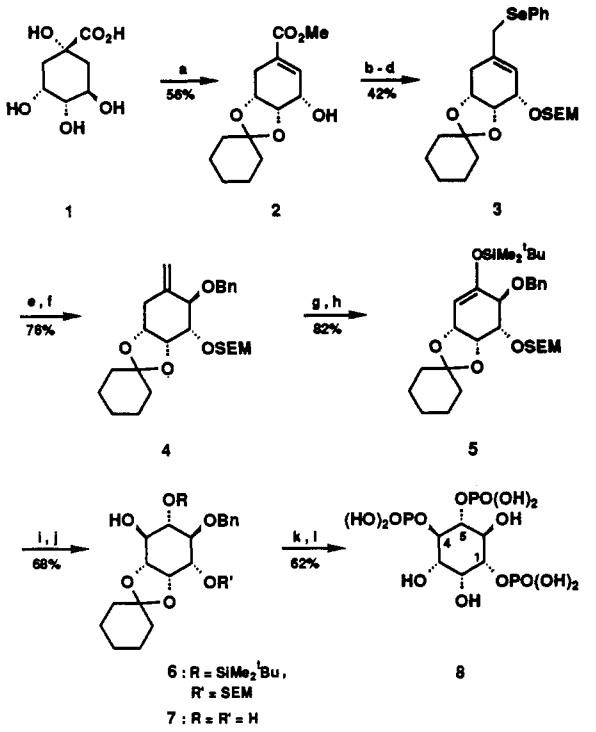
Summary: A versatile, enantiospecific approach to functionalized cyclitols from (−)-quinic acid is illustrated by a synthesis of D-*myo*-inositol 1,4,5-trisphosphate, the calcium-mobilizing intracellular second messenger of the phosphatidylinositol cycle.

Sir: In recognition of the physiologic role of the phosphatidylinositol cycle in receptor-mediated signal transduction[1] and the limited availability of its metabolites from natural sources, there has been a resurgence of interest in the chemical synthesis of inositol (poly)phosphates and analogues.[2] To date, the majority of preparative studies have exploited readily available *myo*-inositol as the initial precursor and relied upon protection/deprotection sequences to differentiate amongst this cyclitol's six hydroxyls.[3] Furthermore, since *myo*-inositol is meso, a resolution is required to obtain optically active products. Herein, we described an enantiospecific approach to functionalized cyclitols from commercial (−)-quinic acid and illustrate its versatility by a synthesis of the calcium mobilizing intracellular second messenger D-*myo*-inositol 1,4,5-trisphosphate (**8**).

(−)-Quinic acid (**1**) was converted to ester **2** (mp 75 °C) in four steps according to literature procedure[4,6] (Scheme I). Sequential protection of the C(1)-alcohol (inositol numbering) as its β-(trimethylsilyl)ethoxymethyl (SEM) ether,[7] diisobutylaluminum hydride (DIBAL-H) reduction of the ester, and selenylation[8] of the resultant primary alcohol furnished **3**. Rearrangement of the allylic selenoxide[9] derived from **3** and benzylation generated a single stereoisomer[10] identified as **4** by ^{1}H NMR analysis (250

Scheme I[a]



[a] (a) Four steps, ref 4; (b) SEM-Cl, *i*-Pr_2NEt, THF, 45 °C, 12 h; (c) DIBAL-H, $PhCH_3$, −78 °C, 3 h; (d) *N*-(phenylseleno)phthalimide, Bu_3P, THF, 0 °C, 45 min; (e) $NaIO_4$, pH 7 buffer, 1,4-dioxane/H_2O (1:1.6), 0 °C, 6 h; (f) KH, $PhCH_2Br$, THF, 12 h; (g) O_3, CH_2Cl_2/MeOH (4:1), −78 °C; Me_2S, −78 → 25 °C, 4 h; (h) *t*-$BuMe_2SiOTf$, Et_3N, CH_2Cl_2, 2 h; (i) BH_3, THF, 25 °C, 3 h; alk H_2O_2, 1 h; (j) *n*-Bu_4NF, HMPA, 4-Å MS, 100 °C, 1 h; (k) KH, $[(BnO)_2PO]_2O$, THF, 60 °C; (l) H_2, 10% Pd/C, 50 psig, 95% EtOH; AcOH/H_2O.

(1) Reviews: (a) Downes, C. P. *Biochem. Soc. Trans.* **1989**, *17*, 259–268. (b) Abdel-Latif, A. A. *Pharm. Rev.* **1986**, *38*, 227–272.

(2) Review: Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83–122. Ley, S. V.; Sternfeld, F. *Tetrahedron Lett.* **1988**, *29*, 5305–5308. Vacca, J. P.; deSolms, S. J.; Huff, J. R.; Billington, D. C.; Baker, R.; Kulagowski, J. J.; Mawer, I. M. *Tetrahedron* **1989**, *45*, 5679–5702.

(3) For recent significant exceptions using chiral precursors, see: (a) Ballou, C. E.; Tegge, W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 94–98. (b) Watanabe, Y.; Mitani, M.; Ozaki, S. *Chem. Lett.* **1987**, 123–126. (c) Kazikowski, A. P.; Fauq, A. H.; Rusnak, J. M. *Tetrahedron Lett.* **1989**, *30*, 3365–3368.

(4) The 3,4-O-cyclohexylidene ketal of quinic acid lactone (ref 5) was transformed to **2** by the method of Lesuisse, D.; Berchtold, G. A. *J. Org. Chem.* **1985**, *50*, 888–890.

(5) Mercier, D.; Leboul, J.; Cleophax, J.; Gero, S. D. *Carbohydr. Res.* **1971**, *20*, 299–304.

(6) Satisfactory spectral data and elemental analyses were obtained for all stable intermediates.

(7) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343–3346.

(8) Grieco, P. A.; Jaw, J. Y.; Claremon, D. A.; Nicolaou, K. C. *J. Org. Chem.* **1981**, *46*, 1215–1217.

(9) Alternatively, the phenyl sulfide analogue of **3** could be prepared in good yield from the corresponding alcohol using tributylphosphine and phenyl disulfide. Oxidation with 3-chloroperoxybenzoic acid gave a ca. 1:1 mixture of sulfoxides which rearranged (45 °C, $(MeO)_3P$, MeOH) to **4** only. The rearrangement of diastereomeric allylic sulfoxides to the same stereoisomeric alcohol in biased polycyclic systems has precedent: Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147–155.

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