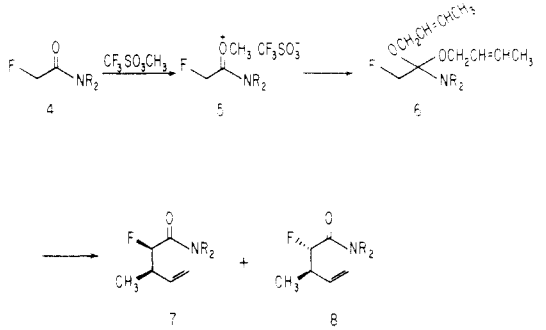
kylation of the fluoroacetamides with dimethyl sulfate[8] failed; presumably, fluorination diminishes the nucleophilicity of the carbonyl oxygen. Alkylation of **4a** with more reactive methyl triflate proceeded smoothly. In

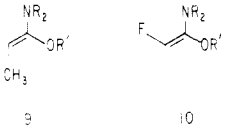


contrast to the ease with which **1a** formed the reactive N,O-ketene acetal, treatment of the O-methylated *N,N*-dimethylfluoroacetamide salt **5a** with 2 equiv of the lithium salt of (*E*)- or (*Z*)-2-buten-1-ol resulted in a 76% yield of the acetal **6a**. Heating this acetal at 80 °C for 7 h resulted in a nearly quantitative formation of the rearranged amides **7a** and **8a** but with poor diastereoselectivity. Reaction of **5a** with 3 equiv of the lithium salt of (*E*)- or (*Z*)-2-buten-1-ol (prepared by treatment of the alcohol with a slight excess of methyl lithium) resulted in the direct formation of **7a** and **8a** after 20 h at room temperature. The relative diastereoselectivity was determined by ^{19}F NMR in these cases.

In order to increase the steric demand of the *N*-alkyl substituents and therefore to increase the stereoselectivity of the N,O-ketene acetal formation, both pyrrolidinyl (**4b**) and diisopropyl fluoroacetamides (**4c**) were methylated with methyl triflate and were treated with the lithium alkoxides. In both cases the alkylated amides were converted into N,O-ketene acetals and rearranged in 12–70 h at room temperature directly to the amides **7** and **8** in good to fair yields with modest improvements in the diastereoselectivity. The acetals **6b** or **6c** were not isolated from the product mixture.

When the isolated amides were resubjected to the reaction conditions there was no change in the ratio of the diastereomers formed. The product amides were not further epimerized under the reaction conditions.[9]

The rearrangement products of both the (*E*)- and (*Z*)-2-buten-1-ol with **1b** were halolactonized with iodine in dimethoxyethane.[10] Characterization of the resultant iodolactones by ^{13}C NMR spectroscopy[11] confirmed the assignment of structures of the respective major products as **2b** and **3b**, the predicted products of the rearrangement of the thermodynamically favored *Z* N,O-ketene acetal **9**.



The amides formed on rearrangement of **5b** with (*E*)- and (*Z*)-2-buten-1-ol were iodolactonized under the same conditions. Comparison of the ^1H and ^{13}C NMR spectra of these products with previously determined spectra[4d,12] indicated the *E* N,O-ketene acetal **10** was being formed preferentially. The diminished steric demand of fluorine is apparently offset by stereoelectronic factors in the formation of the ketene acetal.

A comprehensive investigation of the effect of solvent and stoichiometry on the yield and diastereoselectivity of the rearrangement is in progress. The results of a study of the rearrangement of dissymmetric fluoroacetamides will be reported shortly.

Acknowledgment. Financial support of this work by the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Supplementary Material Available: Analytical and complete spectral data for all new compounds (8 pages). Ordering information is given on any current masthead page.

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(11) For the iodolactone from **2b**: ^{13}C NMR ($CDCl_3$) δ 178.36, 83.25, 38.00, 37.53, 13.51, 10.13, 5.45. For **3b**: ^{13}C NMR ($CDCl_3$) δ 178.18, 79.80, 40.83, 40.38, 13.74, 12.60, 1.81.

(12) For the iodolactone from **7b**: ^{13}C NMR ($CDCl_3$) δ 170.5 ($J_{C,F}$ = 22.2 Hz), 88.21 ($J_{C,F}$ = 201.5 Hz), 77.63 ($J_{C,F}$ = 7.0 Hz), 37.28 ($J_{C,F}$ = 18.1 Hz), 14.01, 5.17. For **8b**, ^{13}C NMR ($CDCl_3$) δ 169.63 ($J_{C,F}$ = 21.2 Hz), 91.29 ($J_{C,F}$ = 197.4 Hz), 79.85 ($J_{C,F}$ = 9.1 Hz), 43.07 ($J_{C,F}$ = 18.2 Hz), 13.99, 4.04.

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Z Stereoselective Wittig Olefination of 2-Oxygenated Cyclohexanones

Summary: Protected 2-hydroxy- and 2,3-epoxycyclohexanones provided (*Z*)-ethylidenecyclohexanes in a highly stereoselective manner upon their reactions with ethylidenetriphenylphosphorane in both the lithium base and the lithium-free conditions of the Wittig reaction.

Sir: Allylic alcohols, allylic epoxides and their equivalents are highly versatile intermediates to which numerous regio- and stereocontrolled methods can be applied for further synthetic manipulations.[1] Presumably the most obvious general synthetic route to these compounds would involve a direct Wittig reaction of the 2-oxygenated ketones. While Still[2] reported the synthesis of *Z* trisubstituted allylic alcohol systems using the Wittig reaction, this aspect of the Wittig reaction has not been well documented in the literature, especially for 2-oxygenated cyclic ketones. We wish to report that the lithium-free Wittig reaction of various 2-oxygenated cyclohexanones with ethylidenetriphenylphosphorane yields almost exclusively the trisubstituted allylic oxygenated olefins with *Z* stereochemistry.

The Wittig reaction of protected 2-hydroxycyclohexanones with ethylidenetriphenylphosphorane was examined with particular emphasis on the stereoselectivity of the reaction under both the lithium-base[3] and lithium-

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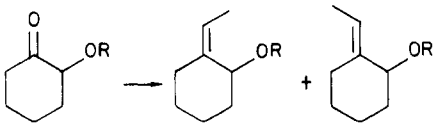
Table I



1 2 3

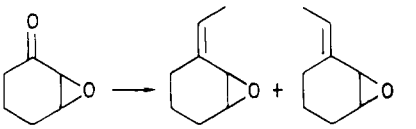
1, R	lithium-base Wittig[a] yield,[c] %	lithium-base Wittig[a] 2/3[d]	lithium-free Wittig[b] yield,[c] %	lithium-free Wittig[b] 2/3[d]
Ac[e]	*h*	*h*	67	6/1
Me[f]	50	2.6/1	76	8/1
Ph[e]	77	5/1	84	10/1
$SiMe_2$-*t*-Bu[g]	61	7.6/1	90	26/1
CH_2Ph[e]	55	1.1/1	86	36/1

[a] Reference 3. [b] Reference 4. [c] Yields are based on the chromatographically pure products (*Z*/*E* mixture). [d] The ratio of **2**/**3** or *Z*/*E* was determined on the crude products by using 360-MHz ^1H NMR and was identical, within the experimental error, with that obtained on the purified olefins in all cases. [e] Obtained by PCC oxidation from the corresponding monoprotected *trans*-1,2-cyclohexanediols (Ac, 95%, Ph, 80%; CH_2Ph, 87%). [f] Purchased from Aldrich Chem. Co. [g] Prepared in 85% yield by treating adipoin dimer with *tert*-butyldimethylchlorosilane and imidazole in DMF at 45 °C, overnight. [h] A complicated mixture of products was obtained.

free[4] conditions. The stereochemistry of the products was ascertained by direct comparison of the product mixture with the authentic *E* isomers except for the phenoxy series. The authentic *E* isomers were obtained by appropriate derivatization of (*E*)-1-hydroxy-2-ethylidenecyclohexane, which was prepared from (*E*)-2-ethylidenecyclohexanone by reduction with $NaBH_4/Ce^{3+}$.[5] The stereochemistry of 1-phenoxy-2-ethylidenecyclohexanes was assigned on the basis of the coupling pattern of the C-1 proton. Thus, the C-1 proton of the *Z* isomer showed a narrower doublet of doublets (J = 1.5 and 1.5 Hz) at 5.172 ppm over the C-1 proton of the *E* isomer (at 4.594 ppm with J = 4.7 and 4.5 Hz). This reflects the more equatorial-like orientation of the C-1 proton of the former in order to obviate the $A^{1,3}$ interaction between the methyl and the phenoxy groups. The same phenomenon was observed for all of the allylic systems studied herein.

The results of the Wittig reaction under the lithium-base and the lithium-free conditions are summarized in Table I. The use of the lithium-free conditions described by Still[2] proved to be superior in both yields and stereoselectivity over the conventional lithium-base method. There was observed a reasonably good correlation between the two methods in terms of a general trend in stereoselectivity with the exception of the benzyl protecting group. While 2-(benzyloxy)cyclohexanone gave the best stereoselectivity amongst those examined under the lithium-free conditions, it was totally nonstereoselective under the lithium-base conditions.

Table II



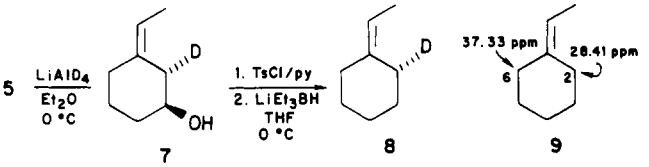
4 5 6

conditions	yield,[c] %	5/6[d]
lithium-base Wittig[a]	77	3.5/1
lithium-free Wittig[b]	65	6/1

[a] Reference 3. [b] Reference 4. [c] Yields are based on the purified products by distillation. [d] The ratio of **5**/**6** or *Z*/*E* was determined on the crude products by using 360-MHz ^1H NMR and was identical, within the experimental error, with that obtained on the purified epoxides by distillation.

The study was then extended to 2,3-epoxycyclohexanone (**4**) where the oxygen lone pairs of the C-2 substituent are conformationally fixed. Interestingly, the Wittig reaction of **4** with ethylidenetriphenylphosphorane showed similar *Z* stereoselectivity to other 2-oxygenated cyclohexanones (see Table II). Furthermore, purification using silica gel flash column chromatography[6] resulted in preferential decomposition of the minor *E* isomer, thus enriching the *Z* isomer at the expense of the yield. For example, purification by silica gel column chromatography of the product mixture of the allylic epoxides from the lithium-free conditions afforded the allylic epoxides **5** and **6** in 45% yield with a *Z*/*E* (or **5**/**6**) ratio of 20/1.

The stereochemical assignment of these allylic epoxides proved to be nontrivial. Since the NOE between the 2-H and the methyl group in **5** was observed to be too small (ca. 2%) to draw any conclusion, the following unequivocal assignment was undertaken. Treatment of the epoxide **5** with $LiAlD_4$ provided the trans alcohol **7** in 77% yield.



7 8 9

Deoxygenation of **7** tosylate[7] with $LiEt_3BH$[8] in THF at 0 °C yielded (*Z*)-2-deuterio-1-ethylidenecyclohexane (**8**) in 50% yield together with the elimination product (*Z*)-1-ethylidenecyclohex-2-ene (20%). Comparison of the ^{13}C NMR spectra (90.56 MHz) of **8** and ethylidenecyclohexane (**9**)[9] clearly indicated that the peak at 28.41 ppm in **9** (C-2) appeared as a triplet in **8** at 27.89 ppm ($^1J_{^{13}CD}$ = 19.9 Hz),[10]

(3) A typical procedure for the lithium-base Wittig reaction used in this study was as follows: To a suspension of 2.0 mmol of ethyltriphenylphosphonium bromide in anhydrous THF (10 mL less the volume of *n*-BuLi solution to be added) at −78 °C was added 2.1 mmol of *n*-BuLi (as a 1.2–1.7 M solution in hexane) under nitrogen. The solution was allowed to warm to room temperature and stirred for 20 min, after which it was recooled to −78 °C, and the ketone (1.0 mmol in 10 mL of anhydrous THF) was added slowly at that temperature. The reaction mixture was allowed to warm to room temperature over a 60-min period and was quenched with water and extracted with ether or pentane. The organic layer was washed with 3% H_2O_2 and saturated NaCl, dried over sodium sulfate and the solvent was removed under vacuum. Purification of the crude product by silica gel flash column chromatography afforded pure olefins.

(4) A typical procedure for the lithium-free Wittig reaction used in this study was as follows:[2] To 2.0 mmol of ethyltriphenylphosphonium bromide in 10 mL of THF was added 2.1 mmol of potassium hexamethyldisilazide (prepared from KH and hexamethyldisilazane) at −78 °C under nitrogen. The ketone (1.0 mmol) in 10 mL of 10% HMPT in THF was cooled to −40 °C (further cooling caused HMPT to solidify) and added by a transfer needle. The remainder of the reaction and workup were identical with those for the lithium-base Wittig reaction described in ref 3.

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(7) For **7** tosylate: 360-MHz ^1H NMR ($CDCl_3$) δ 1.3–2.1 (m, 7 H), 1.455 (d, 3 H, J = 6.8 Hz), 2.448 (br s, 3 H), 4.427 (ddd, 1 H, J = 4.0, 9.2, 9.2 Hz), 5.267 (br q, 1 H, J = 6.8 Hz), 7.339 (apparent d, 2 H, J = 8.2 Hz), 7.808 (apparent d, 2 H, J = 8.2 Hz); 90.56-MHz ^{13}C NMR ($CDCl_3$) δ 12.53, 21.51, 24.09, 32.55, 34.07 (t, $^1J_{^{13}CD}$ = 19.8 Hz), 35.13, 80.99, 119.68, 127.62, 129.73, 134.13, 135.07, 144.37.

(8) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064.

(9) The assignment of C-2 and C-6 chemical shifts was verified by using 2,2,6,6-tetradeuterio-1-ethylidenecyclohexane.

(10) For a recent comprehensive review on the isotope effect on nuclear shielding, see: Hansen, P. E. *Annu. Rep. NMR Spectrosc.* **1983**, *15*, 106.

thus defining the stereochemistry of 8 and accordingly of 5 as *Z*.

While the origin of the *Z* stereoselectivity of these Wittig reactions remains to be determined,[11] the remarkably high *Z* stereoselective synthesis of the allylic oxygenated olefins described herein should find general synthetic applications.

Acknowledgment. We are grateful to the National Institute of Health (Grant AM30025) for the support of this research and to the National Science Foundation for its contribution to the purchase of a Bruker 360-MHz NMR spectrometer.

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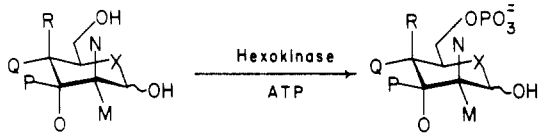
Chemoenzymatic Syntheses of Fluoro Sugar Phosphates and Analogues

Summary: Combined chemical and enzymatic procedures are described for the preparation of fluorinated sugar phosphates and analogues. These derivatives are useful for study of sugar metabolism and for synthesis of pharmacological probes in a number of enzymatic systems utilizing sugars.

Sir: This paper describes studies of a regioselective, enzyme-catalyzed phosphorylation of fluorinated sugars and sugar analogues with heteratoms in the pyranose rings (Scheme I) which provides a combined chemical and enzymatic route to potentially useful pharmacological probes in numerous enzyme systems.

Current studies indicate that fluorinated sugar phosphates or sugar nucleotides in which one of the hydroxyl groups is replaced with the fluorine group can be strong inhibitors of the nonfluorinated species and are of interest as potential pharmaceuticals or pharmacological probes.[1] The inhibitions are due to the difference of C–F and C–OH in reactivity and the similarity of both groups in polarity and bond length.[2] Despite the usefulness of this class of compounds, the synthesis, however, still depends on chemical procedures which require multiple protection and deprotection steps to overcome the problems of regioselectivity.[3] In particular, chemical phosphorylation of fluorinated sugars requires a different protection strategy from that of the nonfluorinated counterparts. As a part of our interest in developing enzymatic routes to this class of compounds, we have surveyed the substrate specificity of yeast hexokinase (E.C. 2.7.1.1) on a variety of fluorinated hexopyranoses and glucose analogues with S or NH in the ring (Scheme I).[4] As shown, each of compounds **a–j** can be accepted as a substrate for the enzyme. Although high specific activity of enzymes used as catalysts in large-scale organic synthesis permits the construction of efficient reactors, low specific activity of enzymes using weak substrates could also be valuable and practical provided the enzymes and the cofactor regeneration system used are inexpensive and stable. In order to illustrate the practicality of the enzymatic preparation of unnatural sugar phosphates using the ATP-requiring hexokinase reactions, we selected a weak substrate and a strong ATP regeneration system based on pyruvate kinase as a catalyst and phosphenolpyruvate as a phosphoryl donor which has excellent stability in solution.[5]

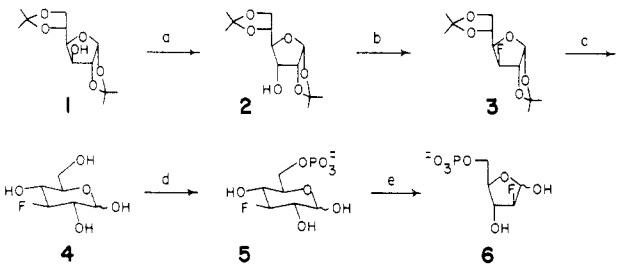
Scheme I[a]



Cmpd	M	N	O	P	Q	R	X	Km (mM)	Vmax (Umg^{-1})
a	OH	H	H	OH	OH	H	O	0.17	300
b	F							0.19	150
c	H	F						0.41	260
d	F	F						0.13	160
e			F	H				82	30
f				F				70	30
g					F			84	30
h					H	F		–	3
i							S	4	15
j							NH	1	30

[a] The substituents other than those for glucose (a) are indicated. 1 U = 1 μmol product formed per min.

Scheme II.[a] Synthesis of 2-Deoxy-2-fluoro-D-arabinose 5-Phosphate (6)



[a] (a) 1. pyridinium dichromate/acetic anhydride, 96%. 2. $NaBH_4$/70% aqueous ethanol, 92%. (b) DAST/CH_2Cl_2/pyridine, 88%. (c) Dowex 50 (H^+)/H_2O, 92%. (d) ATP/hexokinase/phosphoenolpyruvate/pyruvate kinase, 86%. (e) $Pb(OAc)_4/H^+$, 64%.

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(4) For the preparations and kinetic analyses of compounds **a–d** and **f–h**, see: Bessell, E. M.; Foster, A. B.; Westwood, J. H. *Biochem. J.* **1972**, *128*, 199. For that of compound **i**, see: Chen, M.; Whistler, R. L. *Arch. Biochem. Biophys.* **1975**, *169*, 392. Compound **e** was prepared by acid hydrolysis of methyl 3-deoxy-3-fluoro-6-trytil-β-D-allopyranoside prepared according to the procedures reported by Card (see ref 7). Compound **j** was prepared by following the procedures reported previously: Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125.

(5) Hirschbein, B. L.; Mazenod, F. P.; Whitesides, G. M. *J. Org. Chem.* **1982**, *47*, 3766.

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