Diastereoselective [2,3] Wittig Rearrangement of Tertiary Allylic Ethers

Summary: The [2,3] Wittig rearrangement of oxazoline ethers of α-alkoxy, tertiary allylic alcohols affords a diastereoselective entry to remotely functionalized trisubstituted olefins; the stereochemistry of the rearrangement is directed by a stereogenic center external to the sigmatropic framework.

Sir: The prominence of the [3,3] Claisen[1] and [2,3] Wittig[2] rearrangements among existing procedures for homologation of a functionalized allylic system can be attributed in part to the highly predictable stereochemical induction which can accompany these processes.[3] For sigmatropic substrates derived from primary and secondary allylic alcohols, the stereochemical consequences of the electrocyclic mechanism are well-documented and have been widely exploited for the stereocontrolled elaboration of synthetic targets possessing remote chiral elements. By comparison, the rearrangement of substrates derived from tertiary allylic alcohols has received little attention, due to practical difficulties associated with preparation of the requisite tertiary precursors and the unsatisfactory mixtures that result from rearrangement of tertiary systems through two or more conformations of comparable energy.[4,5] We now report that the [2,3] Wittig rearrangement of tertiary, α-alkoxy allylic ethers provides a direct and diastereoselective entry to highly functionalized, trisubstituted olefins (i.e., **3**), which incorporate key structural and stereochemical elements of biologically significant acyclic and macrocyclic systems.[6] Critical to the observed stereoselectivity in these tertiary systems is the role of a stereogenic center external to the sigmatropic framework, which controls the stereochemical course of the electrocyclic event.[7]

During the course of synthetic studies directed at the ansamycin macrolides, we required an effective procedure for the sigmatropic homologation of racemic alcohol **1**. Not surprisingly, all attempts to prepare a suitable substrate for Claisen rearrangement by acylation of **1** were unsuccessful; however, alkylation of **1** proceeded smoothly to give ether **2**. Subsequent [2,3] Wittig rearrangement of the derived α-allyloxy anion[8] afforded a 35:1 mixture of

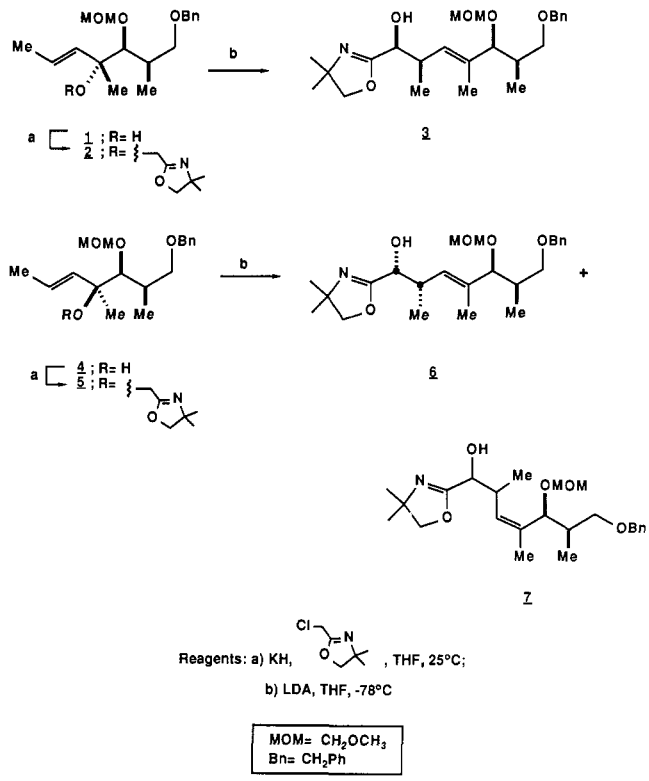

Figure 1.

Table I. [2,3] Wittig Rearrangement of Tertiary Ethers

entry	substrate	conditions[a]	product(s) (ratio)[b]	yield, %[c]
1	**2**	A	**3** (35:1)[d]	95
2	**8a**	B	**9a** (>100:1)[e]	82
3	**8b**	B	**9b** (68:1)[f]	87[h]
4	**8b**	C	**9b** (8.8:1)[f]	85[h]
5	**8c**	B	**9c** (>100:1)[e]	91
6	**5**	A	**6**:**7** (1.7:1)[g]	90[h]
7	**10a**	B	**11a**:**12a** (1.8:1)	95[h]
8	**10a**	D	**11a** (>100:1)[e]	20
9	**10b**	B	**11b**:**12b** (2.2:1)	87[h]
10	**10b**	C	**11b**:**12b** (1.2:1)	85[h]

[a] Conditions: (A) LDA, THF, −78 °C; (B) *n*-BuLi, THF, −78 °C; (C) *n*-BuLi, THF: 20% HMPA, −78 °C; (D) MeMgBr, THF, 0 °C. [b] Determined by capillary GC (detection limit, 100:1) except entries 1 and 6. [c] All yields are for isolated, chromatographically pure materials. [d] Determined by HPLC analysis of the *O*-methyl ether; stereochemistry of minor product not established. [e] Only product detected. [f] Minor product identified as *Z* olefin. [g] Determined by 300-MHz ^{1}H NMR spectroscopy. [h] Combined yield of major and minor products.

products in which crystalline oxazoline **3** predominates.[9-11] Of considerable interest was the analogous sequence starting from the *epimeric* alcohol **4**, which yielded a 1.7:1 mixture of two products, **6** and a *Z* olefin **7** (Figure 1).

Intrigued by this remarkable contrast in olefin selectivity, we have examined the [2,3] Wittig rearrangement of a series of optically active, tertiary ethers and report that the divergent stereoselectivity observed for **2** and **5** is paralleled in related tertiary systems. Oxazoline ether **8a**, prepared from (*S*)-(−)-methyl lactate,[12] was subjected to

(1) (a) Rhoads, S. J.; Raulins, N. R. In *Organic Reactions*; Wiley: New York, 1975; Vol. 22, p 1. (b) Bennett, G. B. *Synthesis* **1977**, 589.

(2) For a recent review, see: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

(3) (a) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic: New York, 1984; Vol. 3, p 503. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.

(4) See: (a) Chillous, S. E.; Hart, D. J.; Hutchinson, D. K. *J. Org. Chem.* **1982**, *47*, 5418. (b) Still, W. C.; Schneider, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 948. (c) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526.

(5) An example of the [2,3] Wittig rearrangement of a tertiary propargyl ether has been reported: Marshall, J. A.; Jenson, T. M. *J. Org. Chem.* **1984**, *49*, 1707.

(6) Burke and co-workers have reported an elegant approach to these systems via the enolate Claisen rearrangement of vinyl dioxanones. (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* **1986**, *42*, 2787. (b) Burke, S. D.; Armistead, D. M.; Fevig, J. M. *Tetrahedron Lett.* **1985**, *26*, 1163. (a) Burke, S. D.; Schoenen, F. J.; Murtiashaw, C. W. *Tetrahedron Lett.* **1986**, *27*, 449. (d) Burke, S. D.; Schoenen, F. J.; Nair, M. S. *Tetrahedron Lett.* **1987**, *28*, 4143.

(7) For recent examples of auxilliary directed asymmetric induction, see: (a) Denmark, S. E.; Marlin, J. E. *J. Org. Chem.* **1987**, *52*, 5743. (b) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1986**, *51*, 1152. (c) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1986**, *51*, 1377. (d) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 433. (e) Mikami, K.; Fujimoto, K.; Takashi, K.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 6011.

(8) Mikami, K.; Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* **1983**, *24*, 513.

(9) All new compounds have been fully characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopic or combustion analysis.

(10) Olefin geometries for [2,3] Wittig products were determined by ^{1}H NOE difference studies and (where applicable) comparison of ^{13}C chemical shifts. See: Nishino, C.; Bowers, W. S. *Tetrahedron* **1976**, *32*, 2875.

(11) The structure of **3** has been established by X-ray crystallography (C. E. Pfluger, Syracuse University, unpublished results).

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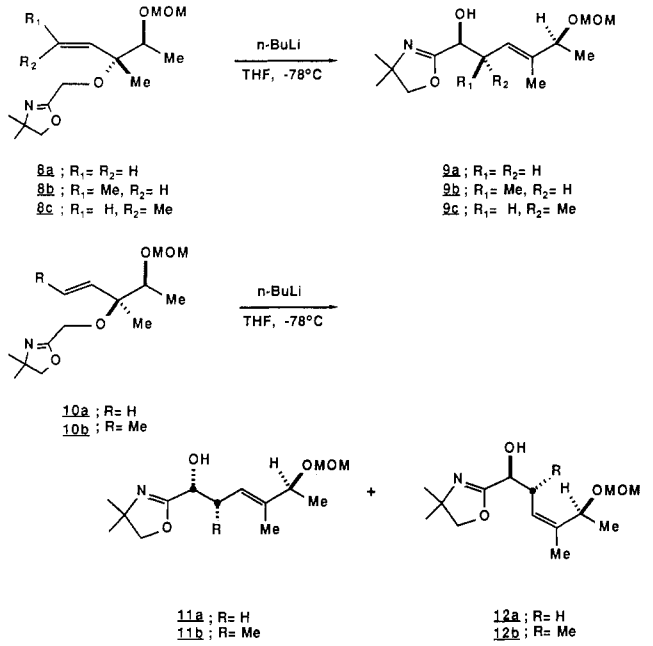

Figure 2.

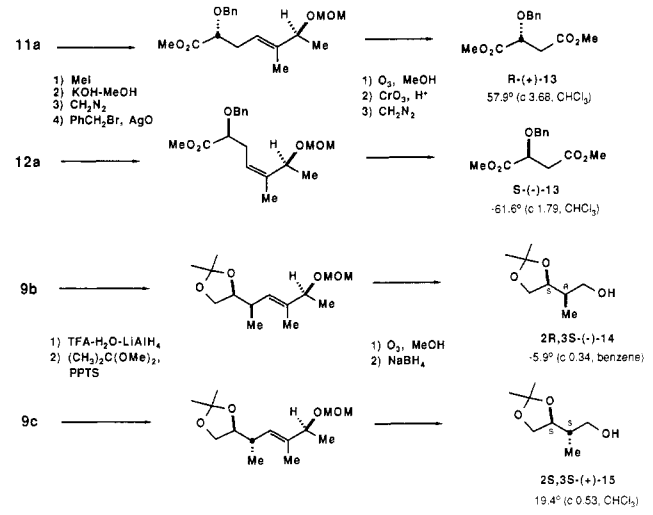

Figure 3.

[2,3] Wittig rearrangement[8] to give a single product, **9a**. Similarly, the chiral *E* and *Z* propenyloxazolines **8b** and **8c** undergo highly selective rearrangement to **9b** and **9c**, respectively.[13] Rearrangement of the *epimeric* substrates **10** was examined; in each case, the major products **11** are

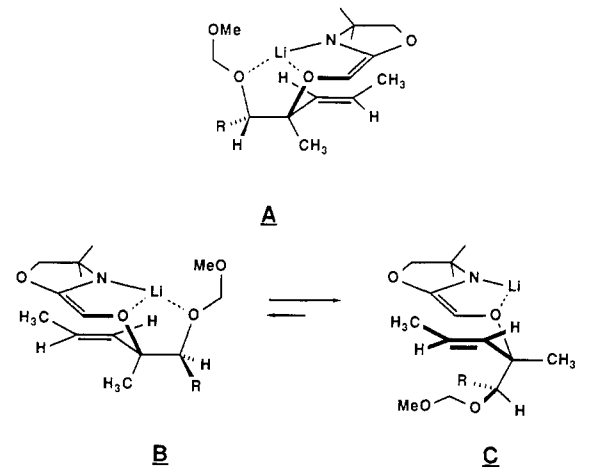

Figure 4.

accompanied by significant amounts of the *Z* olefinic products **12** (Figure 2). Rearrangement of ether **10a** yields a 1.8:1 mixture of **11a** and **12a**, while **10b** affords a 2.2:1 mixture of **11b** and **12b**. Remote stereochemistry of the [2,3] Wittig products in these examples has been unambiguously established by degradation to known optically active intermediates (Figure 3). Thus, oxazolines **11a** and **12a** were transformed to the *O*-benzyl maleic esters (*R*)-(+)-**13**[14] and (*S*)-(−)-**13**, while oxazolines **9b**, **9c**, and **11b** were transformed to ketals (2*R*,3*S*)-(−)-**14**, (2*S*,3*S*)-(+)-**15**, and (2*S*,3*R*)-(+)-**14**, respectively.[15]

These results demonstrate that the [2,3] Wittig rearrangement can indeed provide for the highly stereoselective sigmatropic homologation of tertiary allylic ethers and further indicate that the stereochemical outcome of the reaction is dramatically influenced by a stereocenter *external* to the electrocyclic arena.[7] The selectivity observed for the α-alkoxy-substituted systems is in striking contrast to that of simple alkyl analogues, which afford product mixtures in which *Z* olefinic products predominate.[16,17] The high diastereoselectivity and exclusive formation of *E* olefinic products observed for ethers **2** and **8** can be rationalized by rearrangement through a chelated species, A, which involves coordination of the α-methoxymethyl group to the cation. In this conformation, the MOM ether and oxazoline system are required to be proximal, resulting in formation of an *E* olefin. This model accommodates the diminished selectivity observed for substrates **5** and

(12) Oxazolines **8b** and **8c** were obtained from the tertiary alcohols, which, in turn, were prepared by chelation-mediated addition of methyl Grignard to the corresponding acetylenic ketone i followed by $LiAlH_4$ reduction or semihydrogenation. Alcohol precursors to oxazolines **10** were prepared by addition of the appropriate acetylenic or vinyl Grignard to methyl ketone ii. Both i and ii are readily available from (*S*)-(−)-methyl lactate (Aldrich, ee >95%). Optical purity of tertiary alcohols used in this study were determined in each case to be >95% by NMR analysis using the chiral shift reagent $Eu(DCM)_3$.

(13) A minor (<3%) product in observed in the rearrangement of **8b** has been identified as a *Z* olefin (stereochemistry undefined); we are unable to detect other diastereomers in the product mixture of this and related rearrangements, an observation consistent with the high internal diastereoselectivity, which has been established for the [2,3] Wittig rearrangement of oxazoline systems.[8]

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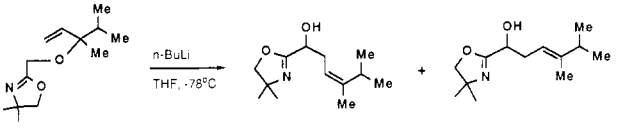
(16) For example, rearrangement of ether iii affords 2.6:1 ratios of *Z*:*E* olefins.



(17) (a) Evans has observed the rearrangement of tertiary allylic sulfoxides to the corresponding *E* trisubstituted olefins: Evans, D. A.; Andrews, G. C.; Fujimoto, T. T.; Wells, D. *Tetrahedron Lett.* **1973**, 1389. (b) Rearrangement of α-allyloxy carbanions gives predominantly *Z* olefins: Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. Still, W. C.; McDonald, J. H.; Collum, D. B.; Mitra, A. *Tetrahedron Lett.* **1979**, 593. (c) The [2,3] Wittig rearrangement of (secondary) zirconium enolates to give *Z* olefins has been reported: Uchikawa, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 4581.

10, where the eclipsing of the tertiary methyl group and the alkyl chain offsets the thermodynamic advantages of chelate formation, resulting in a partitioning of the rearrangement through conformations B and C (Figure 4). The observed sensitivity of the reaction to the nature of the cationic species provides evidence that supports the role of multidentate chelation in defining the transition state. Rearrangement of the magnesium enolate of **10a** is considerably more selective than that of the lithium species, affording only **11a**, although yields are significantly diminished. Also consistent with the proposed chelation model is the deterioration of selectivity observed in the presence of a cation-coordinating additive; for example, in 20% HMPA–THF, rearrangement of **8b** gives an mixture of **9b** and a *Z* olefinic product, while the rearrangement of **10b** becomes essentially nonselective.

The [2,3] Wittig rearrangement of **1** and related tertiary substrates represents a powerful entry to highly functionalized acyclic intermediates, which incorporate structural features not readily accessible by other linear protocols. In particular, the ability to develop a remote stereochemical relationship across a trisubstituted olefin of defined geometry should prove a valuable addition to existing methodology.[18] The availability of both the homoallylic hydroxyl and allylic alkoxy substituent as control elements should facilitate further stereoselective functionalization of the trisubstituted olefin, for example, by directed hydrogenation[19] or osmylation,[20] and we envision tertiary [2,3] Wittig products such as **3** as advanced precursors to a variety of functional arrays present in polyketide-derived natural products. Application to the synthesis of biologically significant targets is under way and will be the subject of future reports.

Acknowledgment. We thank the National Institutes of Health (Grant AI-19632) for partial support of this work. We wish to thank Professor Clarence Pfluger for obtaining the X-ray crystal structure of **3**.

Supplementary Material Available: Experimental Procedures and analytical data for all new compounds (7 pages). Ordering information is given on any current masthead page.

(18) Review of trisubstituted olefin synthesis: (a) Faulkner, D. J. *Synthesis* **1971**, 175. (b) Reucroft, J., Sammes, P. G. *Q. Rev. Chem. Soc.* **1971**, *25*, 135. See also ref 17b and references therein.

(19) (a) Evans, D. A.; Morrissey, M. M. *Tetrahedron Lett.* **1984**, *25*, 4637. (b) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005. (c) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. (d) Brown, J. M.; Naik, R. G. *J. Chem. Soc. Chem. Commun.* **1982**, 348. (e) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *24*, *105*, 1072.

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Changing Coenzymes Improves Oxidations Catalyzed by Alcohol Dehydrogenase[1]

Summary: Oxidation of alcohols to aldehydes catalyzed by HLADH proceeds more smoothly if the oxidant, NAD^+, is replaced by a stronger oxidant, e.g., thionicotinamide or 3-acetylpyridine adenine dinucleotide.

(1) Presented in part at the American Chemical Society Meeting, New Orleans, LA, September 1987. Abstract ORG 193.

Sir: One goal of current efforts in site-directed mutagenesis is to improve existing enzymes for use in synthesis by modification of the amino acid chain of an enzyme.[2] A complementary approach, described below, is to optimize the coenzymes to be used in such syntheses.

As an example reaction, we have examined the oxidation of ethanol with NAD^+ catalyzed by alcohol dehydrogenase from horse liver, EC 1.1.1.1 (eq 1). This oxidation, like

$$CH_3CH_2OH + NAD^+ \rightleftharpoons CH_3CHO + NADH + H^+ \quad (1)$$

$$K_{eq} = 0.0004 \text{ at pH } 7.0^3$$

other oxidations involving NAD^+, proceeds poorly due to inhibition by the product acetaldehyde (K_i(acetaldehyde) = 0.6 mM, noncompetitive).[4,5] Examination of 13 different analogues of NAD^+ identified thionicotinamide adenine dinucleotide ($SNAD^+$) and acetylpyridine adenine dinucleotide ($APAD^+$), both of which are stronger oxidants than NAD^+, as useful substitutes for NAD^+ because they show increased rates and yields of acetaldehyde. Similar substitutions in other oxidoreductases will allow the reevaluation of previously impractical reactions.[5]

Kinetic parameters of eq 1 were measured for two classes of NAD^+ analogues by steady-state kinetics (see Table I) under identical conditions. These values allow direct comparison of the different analogues and are consistent with values measured under similar conditions.[6-9]

The first class of NAD^+ analogues contain modifications only in the adenine portion, thus substitution of these analogues does not alter the equilibrium constant of eq 1. No significant changes in the inhibition constants for acetaldehyde were observed. The second class of analogues contain modifications in the carboxamide portion of the nicotinamide ring. The largest changes in the inhibition constant for acetaldehyde were observed with $SNAD^+$, $APAD^+$, and formylpyridine adenine dinucleotide which showed increases by factors of 10, 60, and 100, respectively. These three analogues are stronger oxidants than NAD^+ and shift the equilibrium constant of eq 1 toward aldehyde formation by factors of 15, 130, and 92, respectively. Several analogues that are weaker oxidants than NAD^+ were ineffective coenzymes.

The reactivity of two analogues that showed less product inhibition, $SNAD^+$ and $APAD^+$, was further investigated to determine whether they would be suitable for enzyme-catalyzed syntheses. Both analogues showed a V_{max} approximately twice that for NAD^+. Two procedures for regeneration of NAD^+—NH_4^+/2-oxoglutarate[10] and methylene blue/O_2[5]—could also be used to regenerate $SNAD^+$ and $APAD^+$. Oxidation of the reduced coenzymes (0.12 mM) by 2-oxoglutarate (14 mM) and ammonia (220 mM), catalyzed by glutamate dehydrogenase (bovine liver)

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(3) Calculated from redox potentials tablulated in Walsh, C. *Enzymatic Reaction Mechanisms*; W. H. Freeman: San Francisco, 1979; p 313.

(4) Jones, J. B. In *Enzymes in Organic Synthesis*; Ciba Foundation Symposium 111; Pitman: London, 1985; p 3. Whitesides, G. M. *Ibid.* p 76.

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