A New [2 + 3] Annulation for Highly Functionalized Dihydrofurans via C–C Bond Formation[1a]

Tomas Hudlicky*,[1b] and Graciela Barbieri

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

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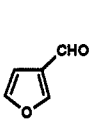
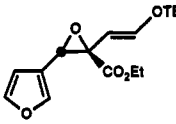
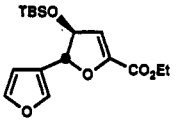
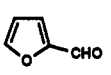
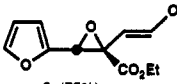
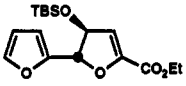
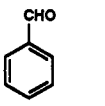
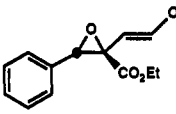
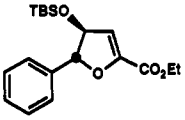
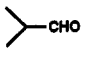
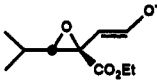
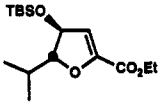
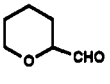
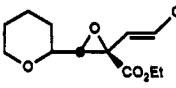
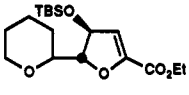
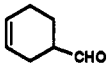
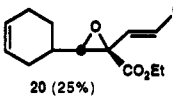
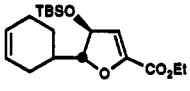
Summary: An unique low-temperature rearrangement of silyl enol ether terminated oxiranes, prepared by the addition of the dienolate anion of ethyl 2-bromo-4-siloxycrotonate to aldehydes, has been implemented for the synthesis of functionalized dihydrofurans.

The synthesis of substituted furans, dihydrofurans, and tetrahydrofurans continues to play a prominent role in the design of new methodologies for the preparation of naturally occurring compounds that contain such units.[2] In recent years several methods of synthesis for furanoid derivatives have been reported,[3] usually in the context of approaches to such compounds as monensin,[4] nigericin,[5] and other biologically significant targets.[6] Most recent tetrahydro- or dihydrofuran syntheses[7] feature C–O bond formation during the key reaction leading to ring closure. Exceptions to this strategy involving C–C bond formation have recently appeared.[7a,b] We report a simple, mild procedure (two steps) based on an unprecedented low-temperature rearrangement of silyl enol ether terminated oxiranes **2** to dihydrofurans of type **3** (Figure 1).

These compounds possess the necessary functionality patterns of several naturally occurring antibiotics and can be functionalized further to either furans or tetrahydrofurans. The methodology is designed, through the reduction of the ester in **3** to an aldehyde, to permit eventual iterative annulations of multiple furanoid subunits under extremely mild reaction conditions that tolerate sensitive functionalities.

The annulation relies on the addition of the lithium dienolate of **1**[8] to aldehydes at −90 °C in THF. The resulting vinyloxiranes were formed stereospecifically, regardless of the stereochemistry of the starting dienolate, in analogy with an aldol-type transition state invoked for similar stereospecificity reported for vinyloxiranes lacking the silyl enol ether moiety.[9] (All of the results reported in Table I were obtained using the *Z* isomer of **1**). The crude vinyloxiranes were suitably pure (~70% vide NMR)[10] and were immediately used in the rearrangement sequence because of their instability to silica gel or HPLC chromatography. The stereochemistry of the vinyloxiranes was assigned as *E* for the oxirane substitution and *E* for

Table I. Low-Temperature Rearrangement of Vinyloxiranes

aldehyde	vinyloxirane (% yield)[a]	dihydrofuran (% yield)[b] [% yield][c]
 4	 5 (70%)	 6a (65%) [40]
 7	 8 (75%)	 9a (71%) [44]
 10	 11 (80%)	 12a (70%) [42]
 13	 14 (50%)	 15a (47%) [90]
 16	 17 (50%)	 18 (26%)
 19	 20 (25%)	 21 (13%)

[a] Estimated by ^{1}H NMR. [b] Overall yield from aldehyde via low-temperature rearrangement. [c] Overall yield from aldehyde via thermolytic rearrangement, see ref 16.

(1) (a) Portions of this work have been presented: ACS 200th National Meeting, Washington, D.C., Aug. 26–31, 1990. Abstracted in part from the Ph.D. thesis of G.B., Virginia Tech, 1991. (b) Recipient of the NIH Research Career Development Award, 1984–1989 (AI-00564).

(2) For recent reviews, see: (a) Kishi, Y. In *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J. W., Ed.; Marcel Dekker: New York; 1982, Vol. II, Chapter 1. (b) Wierenga, W. In *The Total Synthesis of Natural Products*; Ap Simon, J., Ed.; Wiley: New York, 1981; Vol. IV, p 263. (c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(3) (a) Nicolau, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (b) Danishefsky, S. J.; De Ninno, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 2082. (c) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105. (d) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106. (e) Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894. (f) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100. (g) Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144. (h) Padwa, A.; Murphee, S. S.; Yeske, P. E. *J. Org. Chem.* **1990**, *55*, 4241. (i) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1990**, *55*, 2995.

(4) Still, W. C.; McDonald, J.; Collum, D. *J. Am. Chem. Soc.* **1980**, *102*, 2117.

(5) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933. Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.

(6) X 206 synthesis: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(7) (a) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438 and references therein. (b) Yamago, S.; Nakamura, E. *J. Org. Chem.* **1990**, *55*, 5553. Other recent furan or dihydrofuran syntheses: (c) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407. (d) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233. (e) Whang, K.; Cooke, R. J.; Okay, G.; Cha, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 8985. (f) Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995 and references therein.

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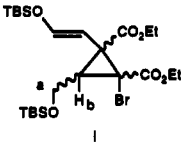
(9) Hudlicky, T.; Fleming, A.; Lovelace, T. C. *Tetrahedron* **1989**, *45*, 3021.

(10) The samples of crude vinyloxiranes were contaminated with recovered excess starting material (displaying a signal at 6.3 ppm), and its known dimer i[8a] (displaying two doublets at 6.5 and 5.0 ppm, corresponding to the protons of the E-olefin of the enol ether, and a multiplet at 3.7 ppm and triplet at 2.5 ppm, corresponding to protons a and b, respectively). Discounting of these signals in the NMR of vinyloxiranes lends credence to the argument that the diastereomeric (*Z*)-oxiranes were not present in the crude reaction mixtures.



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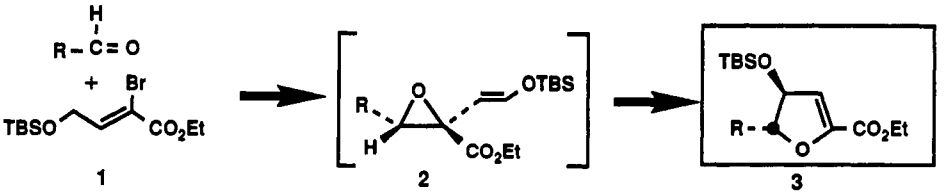


TBS = t-butyldimethylsilyl

Figure 1.

the enol ether moiety. The basis for this assignment followed from NMR studies (NOE difference) performed on the analogous vinyloxiranes lacking the enol ether group.[9] The syn relationship of the carbethoxy group and the proton was inferred by similarities in the chemical shifts of the vinyloxirane methines in the two series and the absence of NOE enhancement of vinyl protons upon irradiation of the vinyloxirane methines. The *E* geometry of the enol ether follows from the *J* value of the olefinic protons (15 Hz).

Treatment of vinyloxiranes with trimethylsilyl iodide (TMSI) and hexamethyldisilazane (HMDS) at −78 to −50 °C produced siloxydihydrofurans in good to excellent yields (with the exception of **14** and **17** where the yields of rearrangement were 50%) and with exclusive trans stereochemistry (Table I). This result was both unexpected and unprecedented as the topography of dihydrofurans obtained in this fashion was identical to that resulting from thermal rearrangement of vinyloxiranes. Chuche,[11] Eberbach,[12] and others[9,13a] have shown that at temperatures in the range of 400 °C simple vinyloxiranes rearrange via cleavage of C–C bond and the subsequent stereospecific closure of carbonyl ylides.[13b] Conversely, opening of such compounds with halogen nucleophiles proceeds with C–O bond cleavage and leads to halohydrins.[8a,14] We therefore expected the 2,3,5-regiochemistry found in **22**,[15] resulting from a C–O bond cleavage in stereoelectronic analogy with the reported opening of TMS enol ether terminated vinylcyclopropanes.[8,15,16] Previous attempts to prepare analogues such as **22** or its norsiloxy derivatives via nucleophilic cleavage of vinyloxiranes required additional steps and conditions to elicit dihydrofuran formation.[8a] It is remarkable that the presence of an enol ether on the vinyloxirane so alters the stereoelectronics of the system to create the operational difference between 400 and −78 °C to elicit the rearrangement. At the present time no mechanistic speculation is available concerning this rearrangement as there apparently is no parallel between the mechanism of the TMSI-mediated closure of silyl enol ether terminated vinylcyclopropanes and vinyloxiranes.[14-16]

For the purpose of comparison and precise identification of the topography of dihydrofurans, the flash vacuum pyrolysis was studied also and was shown to lead to both cis- and trans-substituted dihydrofurans, with the expected regiochemistry indicative of C–C cleavage and the six π electron closure of the carbonyl ylide (Table I).[16] Vinyloxiranes **5**, **8**, and **11** also rearranged to dihydrofurans and oxepines such as **25** (4:1 ratio in the case of **11**) at room temperature in dilute $CDCl_3$ solution with the rearrangement complete in 7 days. Exposure to silica gel on the other hand gave products such as **26**,[15] derived from C–O cleavage assisted by hydrolysis of the enol ether moiety. All compounds were characterized by NMR spectroscopy and mass spectral or combustion analysis. The stereochemistry of all dihydrofurans was also assigned on the basis of NMR studies and proton coupling constants.[18] The potential for synthetic applications was briefly investigated with compounds **16** and **19**. These vinyloxiranes were obtained in lower yields, presumably because of competing enolization. The dihydrofurans **18** and **21**, resembling furanoid units found in natural products, were formed as inseparable diastereomeric mixtures (2:1), which, in the case of **21**, converged to one isomer on hydrogenation. These transformations remain to be investigated in detail for optimization. Detailed mechanistic studies of

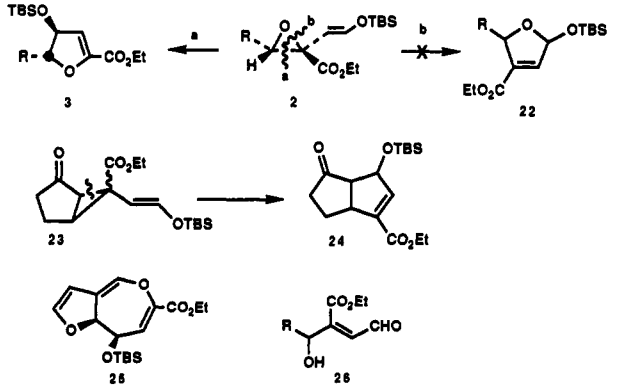
(11) Paladini, J. C.; Chuche, J. *Tetrahedron Lett.* **1971**, 4383.

(12) Eberbach, W.; Roser, J. *Tetrahedron Lett.* **1987**, *28*, 2685.

(13) (a) O'Sullivan, A.; Bischofberger, N.; Frei, B.; Jeger, O. *Helv. Chim. Acta* **1985**, *68*, 1089. For additional examples, see ref 9. (b) For an up-to-date review of such rearrangements see: Hudlicky, T.; Reed, J. W. Rearrangements of vinylcyclopropanes and related systems. In *Comprehensive Organic Chemistry*; Pergammon Press: New York, 1991; Vol. 5, Chapter 8.

(14) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259.

(15) The thermolysis and the TMSI-mediated rearrangements of **2** both proceeded via cleavage of bond a. The regioisomeric dihydrofuran **22** was not observed.

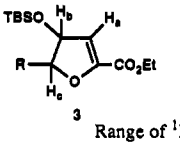


In the case of enol ether terminated vinylcyclopropanes **23** both sets of conditions also gave the diquinane **24** through the cleavage of the indicated bond. Oxepine **25** was identified in thermal and acid-catalyzed rearrangements of **5**, and aldehyde **26** was obtained in acid catalyzed rearrangements of **5**, **8**, and **11**. Details of mechanistic studies in this series and results of low-temperature NMR work will be disclosed at a later date (Hudlicky, T.; Heard, N.; Wild, C., unpublished observations).

(16) Slow evaporation of vinyloxiranes at 80 °C (Kugelrohr) led mostly to the trans isomers (series a), while evaporation at higher temperature (300 °C) gave mixtures of trans and cis (series b) compounds as well as fully aromatic furans (see the Supplementary material). The reversible formation of oxepine in one case occurred during thermolysis, consistent with the expected tendency of divinyloxiranes for such rearrangement.[9,17] Details will be disclosed in a full paper.

(17) Pommelet, J. C.; Manisse, N.; Chuche, J. *C. R. Acad. Sc. Paris C* **1970**, *270*, 1894. Paladini, J. C.; Chuche, J. *Bull. Soc. Chim. Fr.* **1974**, 197. Eberbach, W.; Burchardt, B. *Chem. Ber.* **1978**, *111*, 3665. Eberbach, W.; Trostmann, U. *Chem. Ber.* **1985**, *118*, 4035.

(18) Proton signals were assigned using the COSY experiment and the experimental J_{C-H} values compared nicely with those obtained by calculations using the MM2 method (QCPE-395, implemented by Chemical Design, U.K., 1989). The absence of NOE enhancement between H_b and H_c further confirmed the stereochemistry of the trans isomers.



	trans isomer			cis isomer		
proton	δ(ppm)	J(Hz)	proton	δ(ppm)	J(Hz)
Hb	5.7	0-1	Hb	4.9	6.8;2.8
Hc	6.2	0-1	Hc	5.3	6.6
Ha	6.7	0-1	Ha	6.0	2.8

Range of ^{1}H NMR J-values for dihydrofuran isomers

the unusual TMSI and Lewis acid catalyzed rearrangements and applications of this technology to natural product synthesis form the focus of our current endeavors and will be reported in due course.

Acknowledgment. We are grateful to the following agencies for the support of this work: NIH (AI-00564, GM-40648), the donors of the Petroleum Research Fund administered by the American Chemical Society, and the Jeffress Trust Fund.

Supplementary Material Available: Experimental Section with ^1H and ^{13}C NMR spectra (including 2D NMR for **9a**, **9b**, **12a**, and **25**) and the details of preparation of compounds **5**, **6a,b**, **8**, **9a,b**, **11**, **12a,b**, **14**, **15a,b**, **17**, **18**, **20**, **21**, **25** (41 pages). Ordering information is given on any current masthead page.

A Four-Step Synthesis of TIBO R82150

Kathlyn A. Parker* and Craig A. Coburn

Department of Chemistry, Brown University, Providence, Rhode Island 02912

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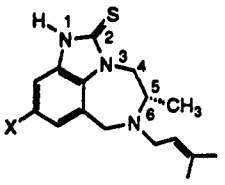
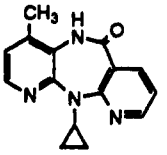
Summary: An efficient, four-step synthesis of the novel HIV-1 reverse transcriptase inhibitor TIBO R82150 is described.

The recently reported TIBO compounds, for example R82150 (**1a**) and R82913 (**1b**), are remarkably specific inhibitors of HIV-1 virion replication in T-cell cultures. Unlike AZT and the related nucleoside antiviral agents DDC and DDI, which are effective against both HIV-1 and HIV-2, the TIBO compounds do not inhibit replication of HIV-2, other RNA viruses, or DNA viruses. Several members of the TIBO series are active at nanomolar concentrations and TIBO **1b** has an inhibitory concentration equal to that of AZT. In preliminary tests in humans, TIBO **1a**, which has the best selectivity index (50% cytotoxic dose/50% inhibitory concentration) of the TIBO's reported, appears to be well tolerated.[1]



1a X=H, TIBO R82150
1b X=Cl, TIBO R82913

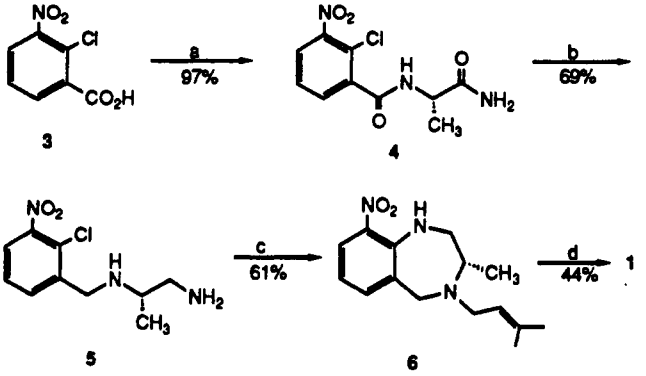


2, BI-RG-587

Since the discovery of the TIBO's, a second class of HIV-1 specific inhibitors, the dipyridodiazepinones (e.g. BI-RG-587, **2**) has been described.[2] The TIBO's and the dipyridodiazepinones inhibit HIV-1 reverse transcriptase; they do so by binding to a common site which is not a substrate binding site.[3] A third class of HIV-1-selective inhibitors appears to act by a different mechanism.[4]

The preparation of TIBO R82150 was originally reported to be an 11-step procedure with an overall yield of 4%.[1,5]

Scheme I. Synthesis of TIBO 1[a]



[a] (a) $(ClCO)_2$, PhMe, 50 °C; then L-alaninamide hydrochloride, K_2CO_3, PhMe/H_2O, 0 °C, 2 h; (b) 10 equiv of BH_3SMe_2, THF, reflux, 12 h; (c) DMF, K_2CO_3, 120 °C, 3-methyl-2-butenyl bromide; (d) H_2, 5% Pd(C), EtOH, 2 h, filter; then CS_2, 37 °C, 3 h.

Clearly, a shorter and more efficient synthesis of the TIBO structure was desirable for the preparation of analogues and essential for the anticipated manufacture of a drug in this series.

We are now pleased to report an efficient synthesis of TIBO R82150 in which the four structural components are incorporated into the desired TIBO product in only *four steps*. The synthesis uses only standard reagents, none of which is difficult to handle.

Straightforward retrosynthetic analysis of TIBO **1** strongly suggests precursors to three of its four structural components. Thus, the imidazothione ring would be elaborated by "capping" an aminodiazepine with a thiocarbonyl reagent; the C-4 to N-6 chain, containing the chiral center, would be derived from an L-alanine derivative; and the prenyl side chain would be introduced by alkylation of the benzylic nitrogen (N-6).

Recognition that commercially available 2-chloro-3-nitrobenzoic acid (**3**) might be a suitable precursor to the 1,2,3-trisubstituted benzene moiety led us to pursue a strategy in which the chloro substituent is displaced in an intramolecular nucleophilic aromatic substitution. Prep-

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