A Highly Stereoselective Preparation of a Novel Class of Vinyl Epoxides from α-Allenic Alcohols

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Summary: Treatment of α-allenic alcohols 1 with iodine provides a mixture of *Z*- and *E*-diiodides 2 and 3, respectively. When treated with base, the diiodides are efficiently converted in a highly diastereoselective manner into the *trans*-iodovinyl epoxides 4.

Vinyl epoxides (also called alkenyl epoxides (oxiranes) or α,β-unsaturated epoxides) are useful intermediates in organic synthesis because of the potential that exists for the selective reaction of one of the four contiguous functionalized carbon atoms with a given reagent.[1] A variety of reactivity patterns have been elucidated for this moiety including, for example, the nucleophilic addition of heteroatoms and carbon based nucleophiles, both in the presence and absence of transition-metal catalysts.[1] As a result, several methods for the synthesis of vinyl epoxides have been developed in order to utilize their potential synthetic versatility.[2]

In the course of our work on the cyclofunctionalization reactions of the derivatives of α-allenic alcohols 1 (H replaced by CONHX) in the presence of iodine,[3] we noted that the initial products in these reactions were those derived from the addition of iodine across the terminal double bond of the allene moiety.[3,4] We reasoned that if this were also the case with the free α-allenic alcohols 1, we could take advantage of the intermediate diiodides 2 and 3 to effect an intramolecular S_N2' displacement with the allylic oxygen atom (Scheme I). If successful, the resultant products 4/5 would be, as far as we are aware, a unique class of vinyl epoxides (or vinyl iodides, depending

Scheme I
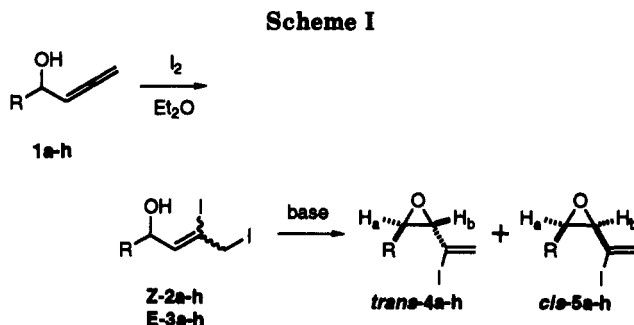
upon your point of view) and might exhibit unique and synthetically useful patterns of reactivity. Herein, we describe the highly diastereoselective preparation of this class of *trans*-iodovinyl epoxides.

Our initial experiments were carried out with alcohol 1a[5] (Scheme I). Treatment of an ethereal solution of 1a with iodine provided the somewhat unstable but isolable *Z*- and *E*-diiodides 2a and 3a, respectively, in a 7:1 ratio.[6] This mixture of diiodides was then treated under a variety of basic reaction conditions (NaOH/MeOH, NaH, LiN-(^{i}Pr)$_2$, NaN(TMS)$_2$, KN(TMS)$_2$, K$_2$CO$_3$, Ag$_2$CO$_3$; each in a variety of solvents), and the crude reaction mixtures were inspected by ^{1}H NMR in order to measure the ratio of diastereomeric epoxides 4a and 5a that were produced. Optimum results were obtained using NaN(TMS)$_2$ in ether.[7] The displacement reaction using this base was slow at −78 °C while, at 0 °C, the reaction was complete within 15 min and provided in an extremely clean fashion the *trans*-iodovinyl epoxide 4a ($J_{a,b}$ = 2.0 Hz).[8,9] Since an authentic sample of the cis diastereomer 5a ($J_{a,b}$ = 4.3 Hz)[8] was available from the reaction performed using NaOH/MeOH (diastereoselectivity, trans:cis = 15:1), we were able to confidently measure the diastereoselectivity of the reaction to be >100:1.[10] There was no evidence for the formation of dihydrofuran products resulting from S_N2 reactions. Thus, starting from a 7:1 mixture of diiodides 2a and 3a, the *trans*-iodovinyl epoxide 4a was

(1) For reviews of the reactions of vinyl epoxides, see: (a) Smith, J. G. *Synthesis* **1984**, 629. (b) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503. (c) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Section 8.1.4. In addition, see: (d) Trost, B. M.; Angle, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 6123. (e) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. (f) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933. (g) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931. (h) Kim, S.; Lee, S.; Koh, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 5106. (i) Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1991**, *56*, 2225. (j) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1992**, *33*, 6169.

(2) The following examples are illustrative. Addition of heteroatom-substituted allylic anions to carbonyl compounds, followed by conversion to epoxides: (a) Seebach, D.; Geiss, K.-H.; Pohmakotr, M. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 437. (b) Pohmakotr, M.; Geiss, K.-H.; Seebach, D. *Chem. Ber.* **1979**, *112*, 1420. (c) Ikeda, Y.; Furuta, K.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7663. (d) Furuta, K.; Ikeda, Y.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2781. (e) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1979**, 1279. Addition of α-seleno carbanions to α,β-unsaturated carbonyl compounds followed by conversion to epoxides: (f) Van Ende, D.; Krief, A. *Tetrahedron Lett.* **1976**, 457. Dimethylsulfonium methylide reaction with α,β-unsaturated carbonyls: (g) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. Vinyl sulfonium ylide reaction with carbonyls: (h) LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem.* **1971**, *36*, 1126. (i) Rosenberger, M.; Neukom, C.; Aig, E. R. *J. Am. Chem. Soc.* **1983**, *105*, 3656. Intramolecular S_N2/S_N2' displacement of allylic bromides: (j) Cookson, R. C.; Crumbie, R. L. *Tetrahedron Lett.* **1985**, *26*, 3377.

(3) (a) Friesen, R. W. *Tetrahedron Lett.* **1990**, *30*, 4249. (b) Friesen, R. W.; Kolaczewska, A. E. *J. Org. Chem.* **1991**, *56*, 4888. (c) Friesen, R. W.; Phipps, L. G. *Synlett* **1991**, 420.

(4) For other reports on the preparation of diiodides from allenes, see: (a) Shaw, R.; Anderson, M.; Gallagher, T. *Synlett* **1990**, 584. (b) Walkup, R. D.; Guan, L.; Kim, S. W.; Kim, Y. S. *Tetrahedron Lett.* **1992**, *33*, 3969.

(5) The α-allenic alcohols were prepared by the method of: Cowie, J. S.; Landor, P. D.; Landor, S. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 720.

(6) See ref 3a,b. The diiodides 2a/3a can be purified by column chromatography, but the diiodides used in these experiments were worked up and used immediately as crude reaction mixtures.

(7) Note that the reaction conditions reported here differ significantly from those reported in ref 2j since no crown ether is used: the reaction temperatures are lower (0 vs 20 °C) and the reaction times are shorter (15 min vs 12 h).

(8) Values of $J_{a,b}$ similar to those observed have been reported for analogous vinyl epoxides ($J_{cis} \approx 4$ Hz, $J_{trans} \approx 2$ Hz). See, for example, ref 2b,d.

(9) The relative stereochemistry about the epoxide was confirmed by difference NOE experiments (in acetone-d_6). Irradiation of the H$_b$ resonance (δ 3.08) resulted in enhancement of the resonance of the methylene protons (δ 1.55–1.65). Irradiation of the methylene protons (δ 1.55–1.65) resulted in enhancement of both the H$_a$ (δ 2.86) and H$_b$ resonances.

(10) Because the ^{1}H NMR spectrum of the crude reaction mixture was so clean, we could easily compare the integrated values of the vinyl proton resonances in 5a with those of the ^{13}C satellites of the vinyl proton resonances in 4a. This method indicated a ratio of 4a:5a of 135:1.

Table I. Preparation of *trans*-Iodovinyl Epoxides 4 from α-Allenic Alcohols 1

en-try	alcohol 1 (R)	ratio of 2:3[a]	product 4, yield[b] (%)	¹H NMR δ H$_a$, H$_b$ ($J_{a,b}$ (Hz))[c]
1	1a, R = n-heptyl	7:1	4a, 81	2.86, 3.08 (2.0)[d]
2	1b, R = BnOCH$_2$OC$_4$H$_8$	7:1	4b, 81	2.89, 3.09 (1.9)
3	1c, R = TIPSOC$_4$H$_8$	7.5:1	4c, 81	2.89, 3.09 (2.0)
4	1d, R = isobutyl	9:1	4d, 70	2.87, 3.07 (2.0)
5	1e, R = c-hexyl	7:1	4e, 93	2.66, 3.17 (2.0)
6	1f, R = 3,4-(OCH$_2$O)C$_6$H$_3$	e	4f, 65	3.82, 3.38 (1.8)
7	1g, R = 4-MeOC$_6$H$_4$	e	4g, 78	3.83, 3.39 (1.9)
8	1h, R = PhC$_2$H$_4$	7.5:1	4h, 88	2.93, 3.07 (2.0)

[a] From the integrated ¹H NMR spectrum of the crude reaction mixture (see ref 11). [b] Yield of isolated, purified product in a one-pot reaction from 1. These compounds were characterized by IR, ¹H and ¹³C NMR, and high-resolution mass spectroscopy. [c] Spectra obtained in acetone-d_6. [d] Minor cis isomer 5a: δ 3.17, 3.67 (4.3 Hz). [e] Could not be determined.

Scheme II
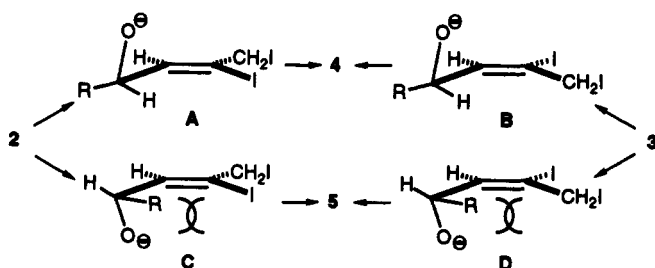
formed in an extremely clean reaction and with exceptionally high diastereoselectivity.

With this result in hand, we developed a one-pot procedure to effect the overall transformation from 1 to 4. An ethereal solution of the alcohol 1a (0.4 M) at room temperature was treated with solid iodine (1 equiv) periodically until the iodine color persisted (typically over 0.5–1 h). Ether was added to make the solution 0.3 M, and the mixture was then cooled to 0 °C. A 1 M solution of NaN(TMS)$_2$ in THF (1.2 equiv) was added dropwise. The mixture was stirred for 15 min at 0 °C and was then

worked up with water. Inspection of the crude reaction mixture by ¹H NMR was followed by flash chromatography to provide the *trans*-iodovinyl epoxide 4a in 81% yield.

The one-pot reaction sequence was then applied to a variety of α-allenic alcohols 1b–h,[5] and the results are summarized in Table I.[11] In each case, the *trans*-iodovinyl epoxide 4 was the major diastereomer produced (diastereoselectivity >100:1).[12] Most of the epoxides 4 are stable to silica gel flash chromatography and survive for extended periods of time if stored under argon in the freezer. However, the isolated yields in several cases are lower than we had expected based upon inspection of the ¹H NMR spectra of the crude reaction mixtures (entries 4 and 6) but we believe that this is due to the volatility and/or chromatographic instability of these particular compounds. As mentioned previously, the crude reaction mixtures are extremely clean with respect to the production of byproducts, and therefore, if these epoxides are to be used for subsequent reactions, the potentially problematic purification step can be omitted.

The diastereoselectivity of the overall reaction process can be explained by inspection of the interactions that are present in the S$_N$2′ transition states leading from the diiodide intermediates to the epoxide products (Scheme II). In the reaction transition states arising from conformers C and D, there is a severe steric interaction between the R group and either the iodine atom or the iodomethylene fragment, respectively. These steric interactions are absent in the transition states arising from conformers A and B. Thus, the latter S$_N$2′ pathways would be energetically more favorable and produce preferentially the *trans*-epoxides 4.

In any event, the overall process for the preparation of 4 from 1 is simple to carry out experimentally and is extremely diastereoselective. The limitation to the range of iodovinyl epoxides that are available by this method is presently under investigation. In addition, we are actively exploring the reactivity patterns of these novel compounds.

Supplementary Material Available: General experimental procedure, characterization data, and NMR spectra for 4a–h and 5a (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Note that separate experiments were performed in order to obtain the ratio of diiodides for each example.

(12) In each of these examples, we did not have access to the minor *cis*-epoxides 5 since they were produced in such small amounts. Instead, the integrated ¹H NMR spectrum of the crude reaction mixture was inspected in the vinyl proton region (δ 5.5–7.0 ppm). The largest minor resonances were compared to those of the ¹³C satellites of the vinyl protons in the major *trans*-epoxides 4 in order to obtain the diastereomeric ratios. All of these ratios were >100:1.