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A Mild Preparation of Vinyliodides from Vinylsilanes

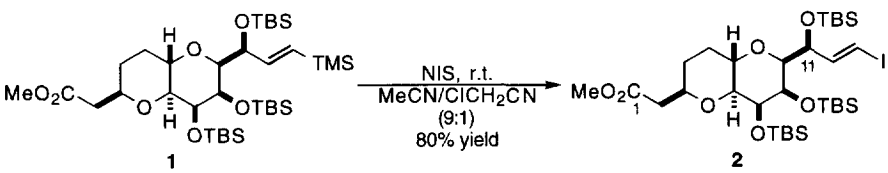
Dean P. Stamos, Andrew G. Taylor, and Yoshito Kishi*

Department of Chemistry and Chemical Biology, Harvard University
12 Oxford Street, Cambridge, MA 02138

Abstract: *A new method for the synthesis of vinyliodides from vinylsilanes is presented. Using N-iodiosuccinimide in acetonitrile or acetonitrile/monochloroacetonitrile, this transformation is cleanly effected at room temperature under virtually neutral conditions.* Copyright © 1996 Elsevier Science Ltd

During the course of our studies towards a practical and economical synthesis of the C.1-C.13 portion of halichondrin B,[1] an iododesilylation was needed to transform the C.13 vinylsilane **1** to the vinyliodide **2**[2] (Scheme 1). Though numerous methods are known for effecting such a transformation,[3] none gave promising results for this case; reactions either led to recovered starting material or decimation of the substrate by highly reactive iodinating reagents, e.g., ICl, IBr, and IBF_4. Clearly, a method which utilizes an electrophilic iodine source with high reactivity but does not generate too reactive intermediates was needed.

Scheme 1



1 **2**

After screening many reaction conditions, it was discovered that *N*-iodosuccinimide (NIS) in acetonitrile at room temperature for 8-10 hours cleanly effected the transformation of **1** to **2** in 90% yield. However, there seemed to be a curious relationship between the number of equivalents of NIS used and the stereochemical integrity of the C.11 stereocenter.[4] Using 10 equivalents of NIS resulted in significant epimerization of C.11 (15~30%), whereas using 25 equivalents of NIS resulted in no epimerization. Obviously, the use of 25 equivalents of NIS is impractical in terms of cost and ease of scaling such a reaction. However, this observation hinted at the possibility that the overall efficiency of this process might be significantly affected via the degree of the interaction of the initially formed iodonium species with a nucleophile (reagent or solvent) present in the reaction media.

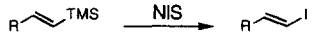
After investigating the effects of a number of additives in the reaction, it was discovered that using 5 equivalents of NIS in monochloroacetonitrile as solvent led to a large increase in the reaction rate (nearly a titration) with no epimerization at C.11. Using a 9:1 v/v mixture of acetonitrile/monochloroacetonitrile, this

effect on the stereochemical integrity at C.11 was also seen, giving 80% of the desired product **2** after 1.5 hours at room tmeprature on a multi-gram scale.

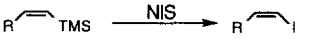
To investigate the generality of this reaction, a series of simple vinylsilanes[5-8] was subjected to similar reaction conditions (Table 1). In a typical procedure, the vinylsilane was dissolved in acetonitrile[9] at room temperature and treated with two equivalents of solid NIS in one portion. Once the reaction was judged to be complete by TLC (five minutes to two hours) the mixture was treated with saturated aqueous Na_2SO_3 and vigorously stirred until a clear colorless solution was obtained. The mixture was then diluted with a 1/1 (v/v) mixture of hexanes and ethyl acetate, the phases separated, the organic phase washed twice with 1.0 N NaOH, once with brine, and dried over Na_2SO_4. The crude extract was then filtered through a short pad of silica gel with the same hexanes/ethyl acetate solvent, concentrated by rotary evaporation at 25 °C, and then distilled or chromatographed to isolate the pure product.

Table 1[a,b]

A: Aliphatic vinylsilanes

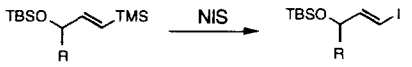


Entry:	R	Yield in MeCN (E/Z)	Yield in MeCN/ ClMeCN (E/Z)
1-*t*	*n*-hexyl	79% (2.8:1)	75% (2.8:1)
2-*t*	*i*-butyl	74% (1:0)	72% (1:0)
3-*t*	*t*-butyl	65% (1:0)	60% (1:0)
4-*t*	phenyl	95% (1:0)	95% (1:0)
5-*t*	4-formyl-phenyl	90% (1:0)	90% (1:0)

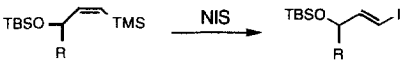


Entry:	R	Yield in MeCN (E/Z)	Yield in MeCN/ ClMeCN (E/Z)
1-*c*	*n*-hexyl	80% (1.2:1)	80% (1.2:1)
2-*c*	*i*-butyl	64% (1:12)	68% (1:12)
3-*c*	*t*-butyl	65% (0:1)	65% (0:1)
4-*c*	phenyl	95% (0:1)	95% (0:1)
5-*c*	4-formyl-phenyl	91% (0:1)	90% (0:1)

B: Silylated allylic alcohol-vinylsilanes

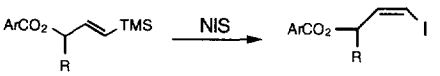


Entry:	R	Yield in MeCN (E/Z)	Yield in MeCN/ ClMeCN (E/Z)
6-*t*	H	80% (8:1)	78% (8:1)
7-*t*	*n*-$C_{12}H_{25}$	65% (1:0)	62% (1:0)

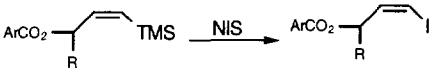


Entry:	R	Yield in MeCN (E/Z)	Yield in MeCN/ ClMeCN (E/Z)
6-*c*	H	73% (2:1)	78% (2:1)
7-*c*	*n*-$C_{12}H_{25}$	10% (1:0)	10% (1:0)

C: Acylated allylic alcohol-vinylsilanes



Entry:	Ar	Yield in MeCN (E/Z)	Yield in MeCN/ ClMeCN (E/Z)
8-*t*[c]	Ph	90% (1:9)	88% (1:9)
9-*t*[c]	4-MeO-Ph	60% (1:12)	57% (1:12)
10-*t*[c]	2,4-(MeO)$_2$-Ph	30% (1:20)	31% (1:20)
11-*t*[d]	4-MeO-Ph	65% (1:2.7)	62% (1:2.7)

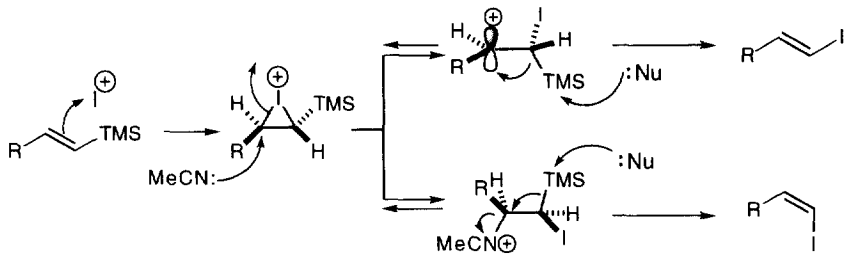


Entry:	Ar	Yield in MeCN (E/Z)	Yield in MeCN/ ClMeCN (E/Z)
8-*c*[c]	Ph	84% (1:2.5)	83% (1:2.5)
9-*c*[c]	4-MeO-Ph	30% (1:3.5)	33% (1:3.5)
10-*c*[c]	2,4-(MeO)$_2$-Ph	0% [e]	0% [e]
11-*c*[d]	4-MeO-Ph	40% (1:8)	38% (1:8)

a. Yields are of purified products and are unoptimized. b. E/Z ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. c. R = H. d. R = *n*-$C_{12}H_{25}$. e. Iodohydrin only isolable product.

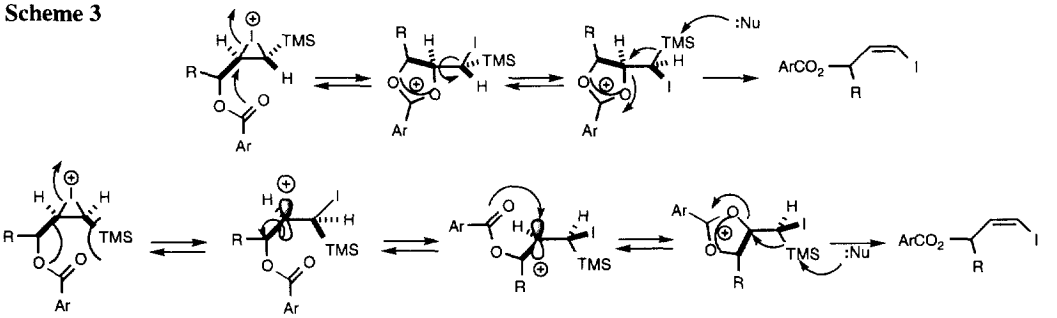
In the aliphatic series (Table 1A) a noticeable trend is observed; substrates with bulkier allylic carbons gave better overall retention of olefin geometry. This effect seems to be steric in nature since in both the *cis*- and *trans*-cases the 4-formylphenyl- and phenyl-substituted (4-*t* , 5-*t*, 4-*c*-, and 5-*c*) vinylsilanes gave the corresponding vinyliodides with complete retention of olefin geometry. In other cases (entries 1-*t*, 1-*c*, and 2-*c*) solvent participation may account for the product mixtures obtained (Scheme 2). Substrates with stereically tolerant allylic carbons may allow solvent to open the cyclic iodonium ion leading to inverted olefins. Sterically demanding allylic carbons block this pathway leading to retention of olefin geometry.

Scheme 2



In the silyl allyl ether series (Table 1B) trans selectivity is observed in all cases. For these substrates it appears that the presence of the carbon-oxygen bond electronically destabilizes the cyclic iodonium ion and forces equilibration favoring the *trans*-product. This effect is especially seen in the *cis*-secondary ether substrate (entry 7-*c*, Table 1B). Interestingly, entries 7-*c* and 7-*t* (Table 1B) were the only substrates which exhibited any noticeable rate enhancement upon the addition of monochloroacetonitrile, similar to the original halichondrin B case.

Scheme 3



In the acylated allylic alcohol series, a general cis selectivity was observed (Table 1C). For the *trans*-vinylsilane substrates, a mechanism involving intramolecular opening of the cyclic iodonium by the aroyl group leads to the inverted vinyliodides (Scheme 3). For the *cis*-vinylsilanes, steric destabilization may lead to opening of the cyclic iodonium ion and formation of the β-silicon stabilized cation. Aroyl participation may then occur in an *anti* mode to silicon, leading to overall retention of olefin geometry.

In conclusion, a new method to convert vinylsilanes to vinyliodides has been developed. The reaction conditions are very mild and lead to predictable olefin geometries.

Acknowledgments: Financial support from the National Institutes of Health (CA-22215) and Eisai Pharmaceutical Company is gratefully acknowledged.

References and Notes:

1. (a) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.;Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.*, **1992**, *114*, 3162-3164. (b) Duan, J. J.-W.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 7541-7544 and references cited therein.

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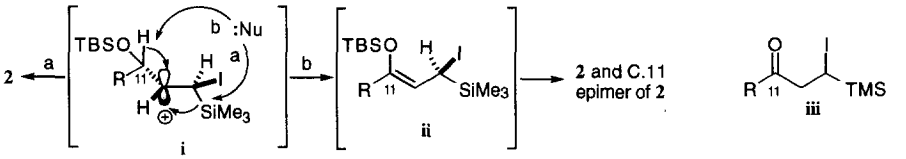
3. (a) Chan, T. H.; Lau, P. W. K.; Mychajlowskij, W. *Tetrahedron Lett.*, **1977**, *18*, 3317-3320. (b) Miller, R. B.; Reichenbach, J. *Tetrahedron Lett.*, **1974**, *15*, 543-546. (c) Miller, R. B.; McGarvey, G. *J. Org. Chem.*, **1978**, *43*, 4424-4431. (d) Huynh, C.; Linstrumelle, G. *Tetrahedron Lett.*, **1979**, *20*, 1073-1076. (e) Miller, R. B.; McGarvey, G. *Synth. Comm.*, **1978**, *8*, 291-293. (f) Chan, T. H.; Koumaglo, K. *Tetrahedron Lett.*, **1986**, *27*, 883-886. (g) Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.*, **1987**, *52*, 1100-1106. (h) Barluenga, J.; Alvarez-Garcia, L.J.; Gonzaléz, J. M. *Tetrahedron Lett.*, **1995**, *36*, 2153-2156. (i) Chan, T. H., Fleming, I. *Synthesis*, **1979**, 761-786.

4. The C.11 epimerization observed may be explained by an early intermediate such as **i** proceeding to either **2** (the path a) or a silyl enol ether **ii** (path b), which is then protodesilylated in a conjugate fashion to yield a mixture of **2** and its C.11 epimer. Monochlroacetonitrile might act as a quencher of the generated succinate anion via alkylation, thereby changing the profile of a nucleophile(s) affecting these steps. It is worthwhile noting that **iii** was isolated in 5~10% yield either with or without monochloroacetonitrile.



5. *trans*-Aliphatic vinylsilanes (Table 1A) were prepared via platinum catalyzed hydrosilylation of the parent alkyne as described in reference 3c.

6. *cis*-Aliphatic vinylsilanes (Table 1A) were prepared from the parent alkynylsilanes and were reduced via the method as described by Eisch, J. J.; Damasevitz, G. A. *J. Org. Chem.*, **1976**, *41*, 2214-2215.

7. Protected primary-alcohol *trans*-vinylsilanes (Table 1B, entry 6-*t*, and Table 1C, entries 8-*t*, 9-*t*, and 10-*t*) were prepared by standard methods, i.e., TBSCl/imidazole/DMF or aroyl chloride/triethylamine/DMAP/ CH_2Cl_2 from *trans*-1-trimethylsilyl-1-propene-3-ol. This alcohol was prepared by Red-Al reduction of 3-trimethylsilylpropargyl alcohol as described by Denmark, S. E.; Jones, T. K. *J. Org. Chem.*, **1982**, *47*, 4595-4597. Protected secondary-alcohol *trans*-vinylsilanes (Table 1B, entry 7-*t* and Table 1-*c*, entry 11-*t*) were prepared by oxidation using tetrapropylammonium perrhuthenate/4-methylmorpholine *N*-oxide in CH_2Cl_2 followed by treatment with dodecylmagnesium bromide in THF. The resulting alcohols were then protected as described above.

8. All protected primary- and secondary-alcohol *cis*-vinylsilanes (Tables 1B and 1C) were prepared as described in reference 6 from *cis*-1-trimethylsilyl-1-propene-3-ol which was prepared from the trimethylsilyl ether of 3-trimethylsilylpropargyl alcohol by hydroboration with dicyclohexyl borane followed by protonolysis with acetic acid.

9. For vinylsilanes that are not soluble in acetonitrile, propionitrile may be used either with or without monochloroacetonitrile without any adverse affects to the reaction (Table 1A, entry 1-*t* and 1-*c*, Table 1B, entry 7-*t* and 7-*c*).

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